Mid-calf skeletal muscle density and its associations with physical activity, bone health and incident 12-month falls in older adults: The Healthy Ageing Initiative

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Highlights

- Lower mid-calf muscle density was associated with increased likelihood for multiple incident falls over 12 months
- Muscle density was inconsistently associated with bone parameters at the hip, lumbar spine and proximal and distal radius
- Muscle density was consistently positively associated with tibial bone parameters suggesting local effects on bone health
- Moderate/vigorous physical activity was positively associated with mid-calf muscle density

Abstract

Background: Lower skeletal muscle density, indicating greater infiltration of adipose tissue into muscles, is associated with higher fracture risk in older adults. We aimed to determine whether mid-calf muscle density is associated with falls risk and bone health in community-dwelling older adults.

Methods: 2,214 community-dwelling men and women who participated in the Healthy Ageing Initiative (Sweden) study at age 70 were included in this analysis. Mid-calf muscle density (mg/cm^3) at the proximal tibia, and volumetric bone mineral density (vBMD) and architecture at the distal and proximal tibia and radius, were assessed by peripheral quantitative computed tomography. Whole-body lean and fat mass, lumbar spine and total hip areal bone mineral density (aBMD) were assessed by dual-energy X-ray absorptiometry. Participants completed seven-day accelerometer measurements of physical activity intensity, and self-reported falls data were collected 6 and 12 months later.

Results: 302 (13.5%) participants reported a fall at the 6- or 12-month interview, and 29 (1.3%) reported a fall at both interviews. After adjustment for confounders, each standard deviation decrease in mid-calf muscle density was associated with a trend towards greater likelihood of a fall (OR 1.13; 95% CI 1.00, 1.29) and significantly greater likelihood of multiple falls (1.61; 1.16, 2.23). Muscle density was not associated with total hip aBMD, and was associated with lower lumbar spine aBMD (B=-0.003; 95% CI -0.005, -0.001 per mg/cm^3) and higher proximal cortical vBMD (0.74; 0.20, 1.28) at the radius. At the tibia, muscle density was positively associated with distal total and trabecular vBMD, and proximal total and cortical vBMD, cortical thickness, cortical area and stress-strain index (all $P<0.05$). Only moderate/vigorous intensity physical activity, not sedentary time or light activity, was associated with higher mid-calf muscle density (0.086; 0.034, 0.138).

Conclusions: Lower mid-calf muscle density is independently associated with higher likelihood for multiple incident falls and appears to have localised negative effects on bone structure in older adults.

Keywords: muscle density, falls, bone density, osteoporosis, sarcopenia, physical activity

1.0 Introduction

Low lower-limb skeletal muscle density has been associated with higher risk of fractures in older adults (1-5). Low muscle density is an indicator of higher amounts of intra- and intermuscular adipose tissue (IMAT) and can be assessed at the mid-calf in older adults using peripheral quantitative computed tomography (pQCT) (6). The relationship of low muscle density with greater risk of fractures is likely to be explained, at least in part, by its associations with poor physical performance (7-10), and also with higher likelihood of falls as reported in retrospective studies (11-13). However, there is currently a lack of prospective data on the contribution of low muscle density to incident fall risk in older adults.

Another mechanism by which low skeletal muscle density may influence fracture risk in older adults is through its associations with bone health. Lower gluteus maximus and abductor muscle densities are associated with lower hip areal bone mineral density (aBMD) in hip fracture patients (14), and measures of ‘bone qualities’, such as peripheral volumetric BMD (vBMD) and bone geometry (15), also appear to be poorer in those with lower muscle density. Indeed, we recently reported that lower mid-calf muscle density is associated with lower proximal tibial cortical vBMD and area in older adults (16), and high relative lower-leg intra-muscular fat has also been associated with lower tibial bone content and area (17). The findings of these studies suggest a potential negative localised effect of lower skeletal muscle density on bone health in older adults, but no study has reported associations between muscle density and bone density and architecture at multiple anatomical sites.

Interventions which increase physical activity have been successful in reducing IMAT (18, 19), and low self-reported physical activity levels are associated with higher levels of IMAT in multiple patient populations (20-22). However self-reported estimates of physical activity are subject to recall bias (23). Accelerometers provide objective estimates of sedentary behaviour and intensity of physical activity but it is currently unclear whether objectively-determined physical activity of different intensities have similar associations with mid-calf skeletal muscle density in older adults.

The primary aim of this analysis of a community-dwelling population of Swedish older adults was to determine the associations of mid-calf skeletal muscle density with 12-month incident falls. The secondary aims were to determine cross-sectional associations of mid-calf muscle density with bone density and architecture at different anatomical sites, and with accelerometer-determined physical activity intensity.

2.0 Materials and Methods

2.1 Study design and participants

This was an analysis of the Healthy Ageing Initiative (HAI) cohort study; an ongoing observational study of 70-year-old adults in the Umeå municipality in northern Sweden. The objectives of HAI are to investigate traditional and potentially novel risk factors for cardiovascular disease and injurious falls and fractures in 70-year-old men and women. Two eligibility criteria were applied: 1) Residence in the Umeå municipal area and, 2) 70 years of age at the time of testing. Using contact information drawn from population registers, all eligible individuals were sent written information about the study. A subsequent phone call was made, where individuals either accepted or declined to participate. The HAI participation rate was 69.5%. The study was approved by the Umeå University Research Ethics Committee and complied with the World Medical Association's Declaration of Helsinki. All participants provided written informed consent. The current analysis included the first 2,214 participants with complete data for demographics, body composition and bone parameter, accelerometer-determined physical activity, and 12-month incident falls.

Participants attended the attended a hospital clinic near Umeå University for a baseline clinic appointment where they completed assessments detailed below and also had fasting blood tests from which plasma glucose (P-glucose) was analysed. Height and weight were assessed by stadiometer (Holtain Limited, Crymych, Dyfed, UK) and scales (Avery Berkel HL 120, Taiwan), respectively, and body mass index (BMI; kg/m^2) was calculated. Participants also completed a questionnaire which assessed demographics, lifestyle and medical history characteristics, including past falls and fractures. Participants were asked if they had experienced a fracture any time in their life. If they answered yes, they were asked to explain the circumstances. A fracture was registered only if it was low-energy in nature, such as a fall, and not due to trauma such as high speed collisions. The timed up-and-go

(TUG) test assessed physical performance; participants were asked to rise unaided from an armchair and walk forward 3 meters, then to turn around and return to a seated position in the chair. Research nurses provided instructions and measured TUG time using a stopwatch.

2.2 Bone parameters and body composition

aBMD (g/cm^2) was measured at the lumbar spine (L1–L4) and non-dominant (determined by asking the participant if they considered themselves to be left- or right-handed) total hip and femoral neck, and T-scores were estimated, using a Lunar iDXA (GE Healthcare Lunar, Madison, WI, USA). Whole-body soft-tissue composition (total fat and lean mass) was assessed using the same machine. The machine was calibrated using a phantom each morning before measurements were obtained. Coefficients of variation (CVs) for in-vivo measurements of the iDXA are 0.4% for the lumbar spine and 1.4% for the femoral neck (24).

A peripheral quantitative computed tomography (pQCT) device (XCT-2000; Stratec Medizintechnik, Pforzheim, Germany) was used to measure total, cortical and trabecular vBMD (mg/cm^3) and area (mm^2), cortical thickness (mm), periosteal and endosteal circumferences (mm), and stress-strain index (SSI polar) of the non-dominant tibia and radius. Slice thickness was set at 2.0 mm, with a voxel size of 0.5 mm. Total and trabecular vBMD and area were measured at scan sites in the metaphysis located at 4% (distal site) of total tibial bone length in the distal–proximal direction, and cortical vBMD, area, thickness, periosteal and endosteal circumferences, and SSI polar were measured at diaphyseal scan sites located at 66% (proximal site) of total bone length in the same trajectory.

Mid-calf skeletal muscle density (mg/cm^3; density of tissue within the muscle compartment after removal of subcutaneous fat and bone areas) was determined from the scan performed at the proximal tibia, which is the region with the largest outer calf diameter with small variability across individuals (25). All mid-calf images were first checked by the operator and repeated in the event of any motion artefacts. The manufacturer's software was used to apply a filter (F03F05) to mid-calf images, and to perform automatic threshold-based iterative edge-detection-guided segmentation (3). Muscle was segmented from bone at a density threshold of 280 mg/cm3 (contour mode 1 and peel mode 2), and from subcutaneous fat at a threshold of 40 mg/cm3 (contour mode 3 and peel mode 1). Reported CVs for the Stratec XCT-2000 pQCT device are 1.6% for trabecular density and 0.3% for cortical density, measured in-vivo (26).

2.3 Accelerometer-determined physical activity

Participants wore a triaxial accelerometer (GT3X+; Actigraph, Pensacola, FL, USA) for seven days following the clinic appointment as described previously (27). This solid-state accelerometer measures acceleration with a dynamic range of ± 6*g* in the anterior–posterior (z), mediolateral (x), and vertical (y) axes. Participants were instructed to wear the accelerometer on their non-dominant hip and to remove it only when showering, swimming or in bed at night. They were also instructed to be normally active in accordance with their current lifestyle, to obtain representative accelerometer measurements. Participants who did not provide at least 4 days of at least 10 hours per day of valid measurements had accelerometer data excluded.

Accelerometer data were collected at a frequency of 30 Hz and data were transformed into "counts" of movement with an activity threshold of 100 counts per min (CPM). Collected data were downloaded using ActiLife 6.11.2 software (Actigraph, Pensacola, FL, USA) in epoch lengths of 60 seconds with subsequent wear time validation performed. Periods ≥60 min characterized by zero activity were marked as non-wear time, facilitating the exclusion of sleep time from further analyses. Sedentary time was classified as 1 to 99 CPM, while physical activity was classified as light (100 to1951 cpm), moderate

(1952 to 5724 cpm), or vigorous (≥5725 cpm), as proposed by Freedson, et al. (28). Due to low amounts of vigorous intensity activity, moderate and vigorous intensity physical activity (MVPA) were combined into a single variable. Percentages of sedentary time, light activity and MVPA were calculated by dividing each value by total accelerometer wear time.

2.4 Incident falls assessment

Participants were contacted by a research nurse six and 12 months after the clinical appointment to determine incident falls since the appointment (29). Participants were asked: “During the past 6 months, have you experienced a fall at the same level?” This question was further clarified by explaining that qualifying falls were low energy, where the participant had unexpectedly come to rest on the ground by him/herself.

2.5 Statistical Analyses

Descriptive data were presented as mean ± SD for continuous variables or frequencies for categorical variables. We initially compared differences in participant characteristics at baseline for included and excluded participants, and amongst included participants, by incident faller status (non-faller, single faller and multiple faller) at 12 months, using one-way ANOVA (continuous variables) and Chi-square tests (categorical variables) with Bonferroni post-hoc tests and column proportion Z-tests, respectively, to determine between group differences. Scatterplots and Spearman correlations assessed associations between percentages of sedentary time, light activity and MVPA with mid-calf muscle density. Additionally, multivariable linear regression analyses investigated the independent associations of sedentary time, light activity and MVPA with muscle density after adjustment for confounders including sex, P-glucose, smoking status, TUG time and total fat mass.

Multivariable linear regression analyses, and binary logistic regression analyses, explored associations of mid-calf muscle density with bone density and geometry parameters, and incident falls, respectively. These analyses were adjusted for sex, fasting P-glucose, average daily MVPA, and total lean mass at baseline, and odds ratios for incident falls were presented per SD decrease in mid-calf muscle density. We further adjusted incident falls analyses for timed up-and-go scores to determine whether associations of mid-calf muscle density with falls were independent of physical performance. All statistical analyses were performed using SPSS Version 24 (IBM, USA) and P-values <0.05 or 95% confidence intervals (95% CI) not including the null point were considered statistically significant.

3.0 Results

Of 3,633 participants recruited for this study, 14 and 573 did not complete DXA and pQCT at baseline, respectively. A further 195 participants did not provide complete accelerometer data, and 632 had incomplete falls reports over 12 months. Additionally, inspection of mid-calf muscle density box-plots identified 5 participants as extreme outliers (muscle density ≤50 or ≥100 mg/cm^3) and these participants were also excluded from the analysis. Thus, a total of 2,214 participants were included in this analysis. Compared with excluded participants, included participants had lower BMI (27.1 ± 4.8 vs 26.2 ± 3.9 kg/m^2; P<0.001) and timed up-and-go times (10.3 ± 3.0 vs 9.8 ± 2.1 s; P<0.001). There were no differences between included and excluded participants for mean mid-calf muscle density, daily MVPA, or total hip BMD (all P>0.05), and there were similar sex proportions (49.3 vs 50.7% women; P=0.52). A total of 302 (13.5%) included participants reported a fall at the 6-month or 12-month interview, while 29 participants reported a fall at both interviews. Table 1 presents baseline characteristics for participants classified as non-fallers, single fallers or multiple fallers over 12 months. Multiple fallers were significantly more likely to be women than non-fallers, and had higher BMI and total fat mass, lower MVPA and slower TUG times compared with both non- and single fallers (all P<0.05).

Figure 1 presents individual scatterplots and Spearman correlations between physical activity intensity levels and mid-calf muscle density. Percentage of time spent in sedentary behaviour was negatively correlated with mid-calf muscle density, whereas percentages of light activity and MVPA demonstrated positive correlations with muscle density, with almost twice the magnitude of correlation observed for MVPA compared with light activity.

These findings were supported by multivariable regression analyses reported in Table 2. After adjustment for sex (Model 1), sedentary time was negatively associated with muscle density, and light activity and MVPA demonstrated significant positive associations with mid-calf muscle density. After further adjustment for fasting P-glucose, smoking status, TUG time and total body fat (Model 2), the associations of sedentary time and light activity with mid-calf muscle density were not significant. MVPA remained positively associated with mid-calf muscle density although the association was attenuated.

Table 3 reports multivariable linear regression coefficients for the association between mid-calf muscle density and bone parameters assessed by DXA at the hip and lumbar spine, and by pQCT at the proximal and distal tibia and radius. Mid-calf muscle density was negatively associated with lumbar spine aBMD but not associated with femoral neck or total hip aBMD. Amongst pQCT measures at the radius, muscle density was positively associated with cortical vBMD, but negatively associated with endosteal circumference, at the proximal site. For the distal tibia, muscle density was positively associated with total and trabecular density, although negative trends were observed for total and trabecular area (both P=0.056). Similarly, at the proximal tibia, muscle density was negatively associated with total area, and periosteal and endosteal circumferences, but positively associated with total and cortical vBMD, cortical area and thickness, and SSI polar.

Table 4 reports associations between mid-calf muscle density (per SD lower) and likelihood of falls over 12 months. Muscle density was not associated with likelihood of reporting a fall at six months, but in the fully adjusted model, a trend (P=0.053) was observed for higher likelihood of reporting a fall at 12 months with lower muscle density. Moreover, in unadjusted and adjusted models, each SD lower muscle density was associated with 68% and 61%, respectively, higher likelihood of reporting a fall at both six and 12 months. Furthermore, the association of lower muscle density with multiple falls over 12 months remained significant after further adjustment for timed up-and-go time (odds ratio: 1.44; 95% CI 1.01, 2.05).

4.0 Discussion

In this cohort of community-dwelling Swedish older adults, lower mid-calf muscle density was independently associated with higher likelihood for multiple incident falls and appeared to have localised negative effects on bone structure at the tibia. Prospective studies are required to determine whether these associations explain previously observed effects of lower-limb skeletal muscle density on higher risk of fractures in older adults (1-5).

A cross-sectional study of 147 Canadian women aged 60 years and older with 12-month retrospective falls data reported that women with one or more falls had mid-calf muscle density around 2 mg/cm^3 lower than non-fallers, whereas muscle area and TUG time were not associated with falls (11). This is consistent with the present study where we observed a trend approaching significance for increased likelihood of a fall over 12 months, and a significant increased likelihood of multiple falls over 12 months, after adjustments for confounders including lean mass and TUG. Similarly, a separate study of older men and women by Frank-Wilson et al., reported that higher mid-calf muscle density was independently associated with reduced likelihood of falls (odds ratio: 0.83; 95% CI 0.69-0.99) in the past 12-months after adjustment for TUG (12). These studies suggest that increased falls risk in older adults with low muscle density are not wholly explained by poor physical performance. However, further research is required to determine whether the associations are mediated by other components of physical function, such as lower-limb power or balance.

We observed that associations for mid-calf muscle density with bone health were most consistent at the tibia, as opposed to the radius, hip or lumbar spine. This finding suggests a potential localised effect of muscle density on bone and previous studies have indicated that higher fat infiltration of the mid-calf is associated with poorer tibial bone health. A previous small study of older women reported that higher relative lower-limb intra-muscular fat was generally negatively associated with bone content and area tibial sites (r =-0.31 to -0.03), although these associations failed to reach significance (17). We also observed in obese older women that mid-calf muscle density was positively associated with proximal tibial cortical vBMD and area (B=2.91 mg/cm^3; 95% CI 0.02, 5.80 and 2.71 mm^2; 0.06, 5.33, per mg/cm^3 higher muscle density, respectively) (16). A study of 178 osteoporotic women with hip fractures has further demonstrated that gluteus maximus (r=0.230) and abductor (r=0.221) muscle densities are positively correlated with hip BMD (14). It should be noted that the apparent effect sizes for associations between mid-calf muscle density and tibial bone parameters, whilst significant, were small in the present study; for example, the mean cortical vBMD value at the proximal tibia was 1089 mg/cm^3, and a 1 mg/cm^3 higher muscle density was associated with only 1.4 mg/cm^3 higher cortical vBMD. This is consistent with the modest effects observed for physical activity on bone parameters in older adults (27). Therefore, the potential benefit of improvements in muscle density to local bone health need to be determined in further research.

It might be expected that age-related fat infiltration of muscle would be consistent throughout the musculature, and therefore the deleterious associations observed at the tibia should similarly be observed at other anatomical sites. However, IMAT at the lower-leg and thigh regions have been demonstrated to be only marginally correlated (15). Individual lower-limb muscles also differ with the gluteus maximus demonstrating the lowest, and rectus femoris the highest, muscle density amongst older adult fallers and non-fallers (13). This may explain why muscle density at the mid-calf region was most consistently associated with tibial bone health, and not other sites, in the present study.

Interestingly however, muscle density was negatively associated with proximal tibia total area, endosteal circumference at the proximal radius, and both periosteal and endosteal circumferences at the proximal tibia. The association of lower muscle density with greater proximal tibial total area and periosteal circumference, but poorer cortical density, is consistent with the concept of periosteal apposition as a response to bone loss; it may be that cortical bone area declines at a faster rate in older adults with lower muscle density, resulting in greater loading being applied to the bone periphery and stimulating subperiosteal bone formation which increases total bone area (30).

There are a number of mechanisms by which increasing IMAT may contribute to falls and poor bone health. IMAT is associated with increased lipotoxicity and local inflammation (31) which may compromise bone and muscle quality. Higher IMAT is linked with mitochondrial dysfunction (32) and impaired muscle blood flow (6), both of which may reduce muscle function. Furthermore, high levels of IMAT reduce muscle contractile tissue area and alter muscle fibre orientation and force capacity (33), and resulting reductions in contractile force may contribute to bone loss. Nevertheless, as described above, associations of low muscle density with falls were significant after adjustment for physical performance suggesting other factors may influence this relationship.

We also examined relationships between objectively-determined physical activity intensities and mid-calf muscle density. We observed that sedentary time was negatively correlated, while both light activity and MVPA were positively correlated, with muscle density. However, only MVPA remained significantly associated with mid-calf muscle density after adjustment for potential confounders. A previous study of 384 adults with peripheral arterial disease assessed self-reported walking speed outside the home and total sedentary hours per day. Slower walking speed (perhaps a surrogate for MVPA) was associated with faster annual declines in calf muscle density, whereas no associations were observed between sedentary time and muscle density (22). Previous studies which have examined accelerometer-determined physical activity in older adults have consistently reported associations of MVPA with reduced body fat, and increased muscle mass and function (34-36). Future studies should explore whether increasing MVPA in particular is the most effective strategy for improving muscle density. Exercise, combined with nutrition, interventions have been effective in reducing IMAT in older adult populations. In obese older women, six months of dietary restriction plus exercise reduced lower-limb IMAT, with decreases in the calf, but not thigh, IMAT associated with improvements in walking speed (18). In mobility-limited older adults, a nutritional supplement combined with a physical activity program for six months also improved thigh muscle density (37).

The strengths of this study include the large, well-defined cohort with objective assessment of physical activity, measurement of aBMD, vBMD and bone architecture at multiple sites and prospective follow-up of falls. However, several limitations should be acknowledged. Some muscle density values may have been influenced by motion streaks in pQCT images, although scans were re-acquired if substantial movement was observed, and motion streaks have been previously reported to have no influence on associations of muscle density with fractures (38). The associations described for muscle density with physical activity and bone health are cross-sectional only, and so causality cannot be determined. Moreover, there were relatively few fallers and multiple fallers in this study compared with other older adult cohorts internationally. This may be explained in part by the fact that our definition of falls included only low-energy falls resulting in coming to rest at ground level, rather than ground or other lower level as commonly defined in other studies. Lower likelihood of falls in 70-year olds residing in Umeå in the HAI study may also be related to high levels of physical activity and fitness; average accelerometer-determined MVPA was approximately 33 minutes per day for HAI participants, while older Australians achieve only around 16 minutes per day of MVPA (34). In this regard, the findings of the study may only be generalisable to relatively healthy 70-year olds.

5.0 Conclusions

Lower mid-calf muscle density is independently associated with higher likelihood for multiple incident falls over 12 months and may have localised negative effects on bone structure at the tibia. Further studies are required to determine whether these associations persist over the long-term, and potentially contribute to the greater fracture risk previously observed in older adults with low muscle density.

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Conflicts of Interest

None to declare.

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Figure legend

Figure 1. Spearman correlations for accelerometer-determined sedentary time, light activity and moderate/vigorous physical activity with mid-calf muscle density.

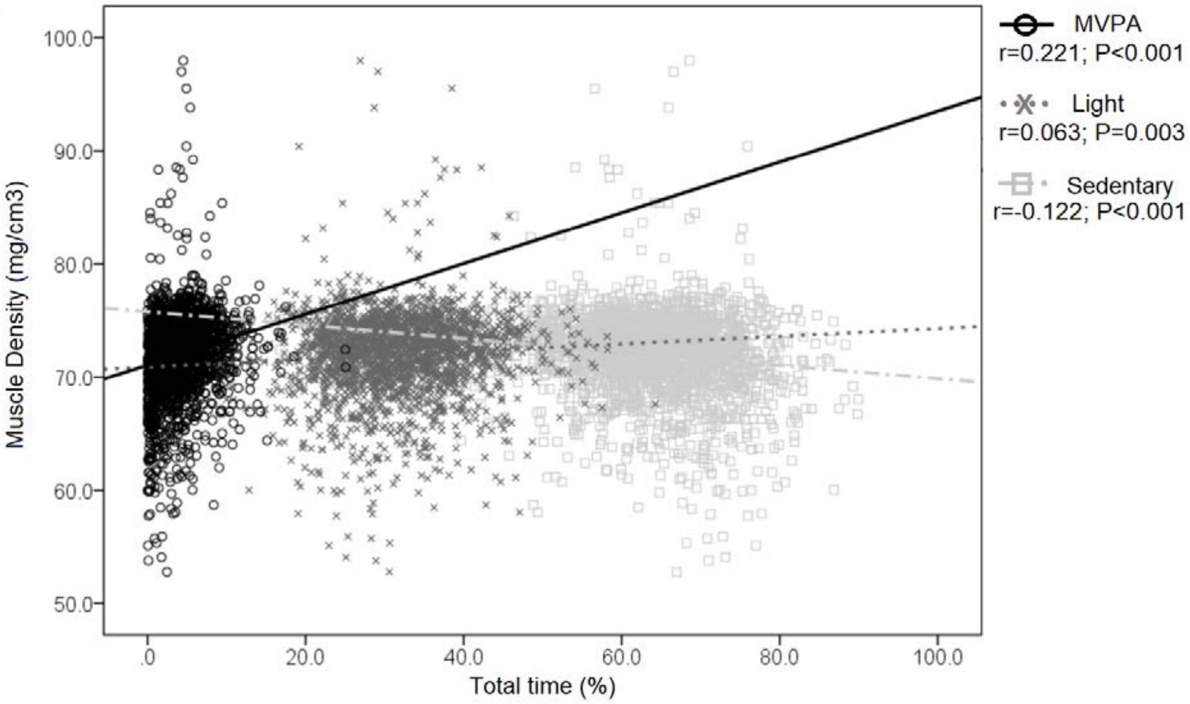

Table 1. Baseline characteristics for participants classified as fallers and non-fallers at 12 months.

	Non-faller (N=1912)	Single Faller (N=273)	Multiple Faller (N=29)	P-value for trend
Age (years)	70.0±0.1	70.00±0.1	70.0±0.0	0.726
Women (%)*	49.8[c]	54.5	75.9[a]	**0.009**
Current smoker (%)*	6.3	6.9	0	0.348
Blood pressure medication (%)*	55.6	53.5	66.7	0.416
Diabetes (%)*	7.6	9.5	13.8	0.301
History of fracture (%)*	14.0	16.0	11.1	0.846
Fasting P-glucose (mmol/L)	5.6±1.2	5.6±1.1	5.4±1.0	0.502
BMI (kg/m^2)	26.1±3.9[c]	26.6±4.0[c]	28.5±4.9[a,b]	**0.001**
Total fat mass (kg)	26.7±8.3[c]	27.8±8.3[c]	32.3±10.7[a,b]	**<0.001**
Total lean mass (kg)	46.4±9.0	45.8±8.9	44.2±8.4	0.329
Mid-calf muscle density (mg/cm^3)	72.0±3.8	71.8±4.2	69.5±4.6	**0.002**
Total hip aBMD (g/cm^2)	0.94±0.15	0.94±0.15	0.94±0.15	0.953
Lumbar spine aBMD (g/cm^2)	1.14±0.21	1.15±0.22	1.15±0.25	0.979

MVPA/day (mins)	33.4±25.4^{c}	34.7±27.2^{c}	21.7±20.8^{a,b}	**0.035**
Timed up-and-go (s)	9.8±2.0^{c}	9.9±2.2^{c}	11.7±4.8^{a,b}	**<0.001**

*Note: ± standard deviation; all tests are one-way ANOVA, except * (Chi-square tests).* ^{a}*denotes significantly different to non-fallers;* ^{b}*denotes significantly different to single fallers;* ^{c}*denotes significantly different to multiple fallers (Bonferroni post-hoc tests). Abbreviations: P-glucose; plasma glucose, BMI; body mass index, aBMD; areal bone mineral density, MVPA; moderate/vigorous physical activity.*

Table 2. Multivariable linear regression coefficients for associations between accelerometer-determined activity levels (percentages) and mid-calf muscle density.

	Model 1		**Model 2**	
	B (95% CI)	**Adjusted R^2**	**B (95% CI)**	**Adjusted R^2**
Sedentary time	**-0.056 (-0.076, -0.037)**	0.019	-0.010 (-0.029, 0.008)	0.169
Light activity	**0.029 (0.008, 0.051)**	0.008	-0.001 (-0.020, 0.019)	0.169
MVPA	**0.234 (0.181, 0.286)**	0.037	**0.086 (0.034, 0.138)**	0.173

Note: Bold values are significant. Adjusted R^2 is for the overall model. Model 1 adjusted for sex. Model 2 adjusted for sex, fasting P-glucose, timed up-and-go time, smoking status and total fat mass. Abbreviations: MVPA; moderate/vigorous physical activity.

Table 3. Multivariable linear regression coefficients for associations between mid-calf muscle density and bone health parameters.

Outcome	**B (95% CI)***
DXA	
Lumbar spine	
L1-L4 aBMD (g/cm^2)	**-0.003 (-0.005, -0.001)**
Hip	
Femoral neck aBMD (g/cm^2)	0.001 (-0.002, 0.001)
Total hip aBMD (g/cm^2)	0.001 (-0.002, 0.001)
pQCT - Radius	
4% site	
Total area (mm^2)	0.21 (-0.48, 0.91)
Total vBMD (mg/cm^3)	0.51 (-0.04, 1.06)
Trabecular area (mm^2)	0.10 (-0.22, 0.41)
Trabecular vBMD (mg/cm^3)	0.35 (-0.08, 0.77)
66% site	
Total area (mm^2)	-0.24 (-0.56, 0.09)
Total vBMD (mg/cm^3)	0.98 (-1.55, 2.12)
Cortical area (mm^2)	0.09 (-0.07, 0.25)
Cortical vBMD (mg/cm^3)	**0.74 (0.20, 1.28)**
Cortical thickness (mm)	0.01 (-0.01, 0.01)
SSI polar (mm^3)	0.70 (-0.22, 1.62)
Periosteal circumference (mm)	-0.03 (-0.07, 0.01)
Endosteal circumference (mm)	**-0.06 (-0.11, -0.01)**

pQCT – Tibia	
4% site	
Total area (mm^2)	-1.80 (-3.64, 0.05)
Total vBMD (mg/cm^3)	**0.88 (0.42, 1.34)**
Trabecular area (mm^2)	-0.81 (-1.64, 0.02)
Trabecular vBMD (mg/cm^3)	**0.76 (0.32, 1.20)**
66% site	
Total area (mm^2)	**-2.25 (-3.28, -1.22)**
Total vBMD (mg/cm^3)	**2.30 (1.32, 3.28)**
Cortical area (mm^2)	**0.48 (0.01, 0.95)**
Cortical vBMD (mg/cm^3)	**1.35 (0.94, 1.76)**
Cortical thickness (mm)	**0.02 (0.01, 0.02)**
SSI polar (mm^3)	**5.79 (0.80, 10.78)**
Periosteal circumference (mm)	**-0.15 (-0.23, -0.08)**
Endosteal circumference (mm)	**-0.25 (-0.35, -0.15)**

*Note: *Adjusted for sex, fasting P-glucose, percentage MVPA, and total lean mass at baseline. Abbreviations: aBMD; areal bone mineral density, vBMD; volumetric bone mineral density; SSI; stress-strain index*

Table 4. Odds ratios (95% CI) for falls per SD lower mid-calf muscle density.

	Faller in next six months	Faller in next 12 months	Multiple faller in next 12 months
Unadjusted	1.03 (0.88, 1.21)	1.12 (1.00, 1.27)	**1.68 (1.26, 2.26)**
Adjusted*	1.03 (0.87, 1.22)	1.13 (1.00, 1.29)	**1.61 (1.16, 2.23)**

*Note: *Adjusted for sex, fasting P-glucose, percentage MVPA, and total lean mass at baseline.*