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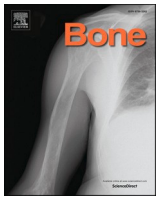

Full Length Article

Determinants of muscle density and clinical outcomes: Findings from the Hertfordshire Cohort Study

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ABSTRACT

Purpose: The age-related loss of skeletal muscle mass and strength is associated with adverse health outcomes. However, to date, peripheral quantitative computed tomography (pQCT)-derived muscle density has been little studied. We used a well characterised cohort of older adults to identify lifestyle and anthropometric determinants of pQCT-derived muscle density measured 11 years later, and to report relationships between pQCT-derived muscle density with history of falls and prevalent fractures.

Methods: A lifestyle questionnaire was administered to 197 men and 178 women, aged 59–70 at baseline. After a median of 11.5 (IQR 10.9, 12.3) years, pQCT (Stratec XCT2000) of the radius and tibia was performed to measure forearm muscle density (FMD) and calf muscle density (CMD). Presence of falls and fractures since the age of 45 were determined through participant recall; vertebral fractures were also ascertained through vertebral fracture assessment using iDXA. Total hip BMD (TH aBMD) was assessed using DXA. Baseline characteristics in relation to muscle density at follow-up were examined using linear regression; associations between muscle density and prior falls and fractures were investigated using logistic regression. All analyses were adjusted for sex and age.

Results: Mean (SD) age at muscle density measurement was 76.3 (2.6) years. Mean (SD) FMD was 79.9 (3.1) and 77.2 (3.2) among males and females, respectively; CMD was 80.7 (2.6) and 78.5 (2.6) among males and females, respectively. Significant sex-differences in muscle density were observed at each site ($p < 0.001$). Female sex, lower weight, and lower body mass index were associated ($p < 0.05$) with both lower FMD and CMD. Additional correlates of lower CMD included older age and shorter stature. Lifestyle measures were not associated with muscle density in this cohort. Lower FMD was related to increased risk of previous fracture (odds ratio (95 % CI) per SD lower FMD: 1.42 (1.07, 1.89), $p = 0.015$) but not after adjustment for TH aBMD ($p > 0.08$). No significant relationships were seen between muscle density and falls.

Conclusion: Female sex, older age, and lower BMI were associated with subsequent lower muscle density in older community-dwelling adults. Lower FMD was related to increased risk of previous fracture. Changes in muscle density over time might precede adverse outcomes such as falls and fractures and may be a long-term predictor of frailty. It could be also suggested that muscle density could be a more clinically meaningful surrogate of functional decline and disability than muscle size or mass, but more studies are needed to support this notion.

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1. Introduction

Sarcopenia is associated with a number of adverse health outcomes, including decreased quality of life, functional impairment, disability, increased risk of falls, hospitalisation, and increased mortality [1–7]. Muscle health can be assessed in many ways, and researchers have sought to identify muscle parameters, including muscle quality [8], which has been linked to muscle density [9,10]. Few studies have considered the demographic and lifestyle determinants of muscle density, which has been shown to decrease with age [11]. Furthermore lower muscle density may imply greater fatty infiltration within skeletal muscle and so might link to adiposity [7,12].

Muscle density represents an interesting muscle variable to study further as reduced leg muscle density increases the risk of mobility loss and has been associated with falls [13,14], which may increase future fracture risk. Muscle density has been shown to perform better than bone mineral density or muscle size in discriminating individuals with a history of hip fracture, and has been associated with an increased risk of hospitalisation [13,15–20].

Muscle density can be assessed by peripheral quantitative computed tomography (pQCT), a technique that was developed for bone density and bone strength estimation. This technique produces a cross-sectional image that permits quantification of three-dimensional tissue structure properties of a limb segment, enabling the cross-sectional area (CSA) of soft tissue and muscle density to be estimated. Since fat is calibrated to zero with pQCT, typical muscle density values range from 65 to 90 mg/cm^3 [21]. Recent studies have highlighted the link between muscle density assessed by pQCT, and fracture risk [22], but these data were collected in a large US study of older males only.

Assessment of muscle-bone relationships using pQCT-derived variables has been undertaken previously in the Hertfordshire Cohort Study; muscle size and grip strength were associated with bone size and strength, but relationships between gait speed and bone structure and strength were not apparent in this cohort, supporting a role for the muscle-bone unit [23]; in other work in Hertfordshire, we have shown positive associations between changes in muscle area and cortical area in both men and women [24].

Given the relative paucity of available research on muscle density, our aims were to use a prospective study of community-dwelling adults to: (1) identify determinants of peripheral muscle density (lifestyle and anthropometric characteristics); and (2) to relate peripheral muscle density measures to history of falls and prevalent fractures. In our study, participants had a mean age at baseline of 64.7 years. This is a stage in the lifecourse when identification of individuals at high risk of poor musculoskeletal outcomes later in life might be possible, and if evidence exists that lifestyle modification might be beneficial, this may result in substantial personal and societal benefit.

2. Methods

2.1. The Hertfordshire Cohort Study

The Hertfordshire Cohort Study (HCS) is a population-based cohort of older adults, consisting of 1579 males and 1418 females, born in Hertfordshire, UK, between 1931 and 1939 and still living in the county in 1998–2004. All participants were Caucasian. Following our initial contact in 1998–2004, participants completed a baseline home interview and attended a research clinic for detailed assessment of their socio-demographic, lifestyle and clinical characteristics; the study has previously been described in detail [25,26]. In 2004, of the 966 participants from East Hertfordshire who had a dual-energy X-ray absorptiometry (DXA) scan at the start of the study, 642 were recruited for a musculoskeletal follow-up study (8/966 had died, 74/966 could not be located and 242/966 declined to participate). In 2011–2012, 570/642 participants from East Hertfordshire were invited to take part in a further bone follow-up study which involved measurement of muscle density by peripheral quantitative computed tomography (pQCT); 376/570 agreed to participate.

2.2. Ascertainment of participant characteristics in 1998–2004

A lifestyle questionnaire was administered at the home interview to collect information on physical activity (Dallosso questionnaire [27]), smoking, and alcohol consumption. Participants completed a food-frequency questionnaire from which protein intake was ascertained, and a 'prudent diet' score was derived using principal components analysis; higher scores reflected healthier diets [28]. Social class was coded from the 1990 OPCS Standard Occupational Classification (SOC90) unit group for occupation [29]. Social class was ascertained from current or most recent full-time occupation for all men and also among women who never married, and only from husband's occupation for ever-married women. Details of all prescription and over-the-counter medications currently taken were coded according to the British National Formulary; the number of systems medicated was derived as a marker of comorbidity.

Investigations conducted at the baseline clinic included measurement of standing height (Harpenden pocket stadiometer, Chasmors Ltd, London, UK) and weight (SECA floor scale, Chasmors Ltd, London, UK) which were used to derive body mass index (BMI).

2.3. Ascertainment of characteristics at the 2011–2012 follow-up

Bone density measurements have been described in detail previously [30]. pQCT was performed using a Stratec XCT2000 instrument (software version 6.20, Stratec Medizintechnik, Pfrozheim, Germany); scans were acquired at the 4 and 66 % sites of the radius, and at the 4 and 38 % sites of the tibia. Muscle density was derived at the 66 % site on the non-dominant side using standard thresholds and calculated by dividing mass by volume; muscle mass was obtained by calculating total area at C1P2, threshold −50, 41 mg/cm^3 and muscle mass at a threshold of 100 mg/cm^3, filer F03F05. All scans were checked for motion artefact by a trained observer. Additionally, scans were excluded if extreme outliers were observed. Bone mineral density (BMD) of the total hip was assessed using DXA (Lunar Prodigy Advance DXA scanner GE Medical Systems, Waltham MA); the lowest value from the left and right side was used for analysis. Appendicular lean mass (ALM) was derived using the same DXA scanner and height was measured using a wall mounted SECA stadiometer; these measures were used to derive appendicular lean mass index (ALMi) as ALM (kg) divided by the square of height (m).

Grip strength (kg) was measured three times for each hand using a Jamar dynamometer (Promedics, Blackburn); the highest measurement was used for analysis. Mean customary gait speed in metres per second was calculated after two 8 ft. walking exercises.

Participants were asked the following through nurse-administered questionnaires: 'Have you had any falls since the age of 45 years?' and 'Have you broken any bones since the age of 45 years?'. Morphometric vertebral fractures were diagnosed from a lateral spine view imaged using the Prodigy DXA scanner and graded based on the Genant semi-quantitative method of vertebral fracture assessment by two trained independent observers [31]. Participants with a vertebral fracture or a self-reported fracture since age 45 years were regarded as having had a previous fracture.

2.4. Statistical analysis

Participant characteristics were described using summary statistics. Standard deviation (SD) scores were derived for continuous baseline characteristics and the muscle density measures to enable comparison of effect sizes. For each participant, follow-up time was calculated as the duration from the study baseline (1998–2004) to when the muscle density measures were ascertained at the 2011–2012 follow-up.

Baseline characteristics in relation to muscle density outcomes at

follow-up were examined separately using linear regression. Sex, baseline age and follow-up time were included as covariates in all models.

Pearson correlations were used to examine muscle density measures in relation to ALM index, grip strength, gait speed and total hip BMD.

Muscle density measures in relation to falls and fractures since age 45 years were examined using logistic regression with adjustment for sex and age and then additionally for total hip BMD.

Analyses were conducted using Stata, release 16.1 (StataCorp, College Station, Texas, USA). The analysis sample comprised the 375 participants who had values for forearm or calf muscle density. To maintain sample size, males and females were pooled for analyses (sex-interaction effects were examined) and analyses were adjusted for sex; $p < 0.05$ was regarded as statistically significant.

3. Results

3.1. Participant characteristics

Characteristics of the 375 participants (197 males, 178 females) who were included in the analysis are presented in Table 1. Mean (SD) age at baseline was 64.7 (2.7) years and median (lower quartile, upper quartile) follow-up time was 11.5 (10.9, 12.3) years. Mean (SD) muscle density values (mg/cm^3) were as follows: forearm [males 79.9 (3.1), females 77.2 (3.2)], calf [males 80.7 (2.6), females 78.5 (2.6)]. Pearson correlations between calf and forearm muscle density were 0.13 ($p = 0.070$) among men and 0.23 ($p = 0.002$) among women (data not shown).

Males, as expected, were taller at baseline (mean [SD] height: males 174.6 [6.7] cm, females 161.9 [5.4] cm) and heavier (mean [SD] weight was 79.9 [10.1] kg among males, 69.6 [12.2] kg among females). Over half of males (n = 115, 58.4 %) and a third of females (n = 62, 34.8 %) were identified as current or previous smokers. Only 48 (24.4 %) males and 3 (1.7 %) females had high alcohol consumption (>21 units per week for males or >14 units per week for females). 55.6 % (n = 105) of males and 56.7 % (n = 101) of females were of manual social class. On average, females had higher diet quality scores compared with males (mean prudent diet score 1.0 vs −0.6) and lower physical activity levels (mean Dallosso activity score was 65.6 in males and 62.1 in females). Overall, 117 (59.4 %) males and 83 (46.6 %) females had less than the recommended protein intake of 1.2 g/kg/day at the HCS baseline stage (1998–2004). This reflects dietary protein intake from food only.

46 (25.7 %) males and 51 (30.9 %) females self-reported fractures since the age of 45 years or had documented vertebral fractures. 103 (56.6 %) males and 119 (72.1 %) females self-reported falls since the age of 45 years.

Sex-interaction effects were not statistically significant in any of the regression models fitted; sex-adjusted analyses were therefore performed among the pooled sample of men and women.

Table 1
Characteristics of the 375 participants who were included in the analysis sample.

Participant characteristic	Mean (SD); median (lower quartile, upper quartile); or n (%)	
	Males (n = 197)	Females (n = 178)
Baseline (1998–2004)		
Age (years)	63.9 (2.5)	65.6 (2.6)
Height (cm)	174.6 (6.7)	161.9 (5.4)
Weight (kg)	79.9 (10.1)	69.6 (12.2)
BMI (kg/m^2)	26.2 (3.1)	26.5 (4.3)
Ever smoked	115 (58.4 %)	62 (34.8 %)
Weekly alcohol units (M: males; F: females)		
Very low (<1 M&F)	21 (10.7 %)	74 (41.6 %)
Low (1-10M, 1-7F)	78 (39.6 %)	81 (45.5 %)
Moderate (11-21M, 8-14F)	50 (25.4 %)	20 (11.2 %)
High (>21M, >14F)	48 (24.4 %)	3 (1.7 %)
Dallosso activity score	65.6 (13.6)	62.1 (13.7)
Prudent diet score	−0.6 (2.0)	1.0 (1.7)
Protein intake (g/day)	93.2 (16.6)	84.3 (19.5)
Occupational social class (manual)	105 (55.6 %)	101 (56.7 %)
Number of systems medicated	1.0 (0.0, 1.0)	1.0 (0.0, 2.0)
Follow-up (2011–2012)		
Age (years)	76.1 (2.5)	76.5 (2.6)
Follow-up time (years)	12.3 (11.8, 12.7)	10.8 (10.5, 11.2)
Calf muscle density (mg/cm^3)	80.7 (2.6)	78.5 (2.6)
Forearm muscle density (mg/cm^3)	79.9 (3.1)	77.2 (3.2)
Appendicular lean mass index (kg/m^2)	8.0 (0.7)	6.4 (0.7)
Grip strength (kg)	36.6 (7.5)	21.8 (6.2)
Gait speed (m/s)	0.79 (0.17)	0.74 (0.18)
Total hip BMD (g/cm^2)	1.03 (0.15)	0.88 (0.14)
Previous fall since age 45 years	103 (56.6 %)	119 (72.1 %)
Self-reported fracture since age 45 years	40 (22.3 %)	45 (27.1 %)
Vertebral fracture	11 (5.6 %)	14 (8.0 %)
Previous fracture since age 45 years	46 (25.7 %)	51 (30.9 %)

Previous fractures included self-reported and vertebral fractures.

3.2. Associations between baseline characteristics and muscle density

Associations between baseline characteristics and muscle density measures at follow-up are presented in Table 2. Sex, baseline age and follow-up time were included as covariates in all models. Female sex, lower weight, and lower BMI were associated with both lower forearm and calf muscle density. SD differences in calf muscle density for females compared to males, and per SD lower weight and BMI were −0.84 [95 % CI: −1.13, −0.54], −0.37 [−0.46, −0.27] and −0.31 [−0.40, −0.23] respectively. Additional correlates of lower calf muscle density included older age (SD difference per SD younger age: 0.20 [0.10, 0.30], $p < 0.001$) and shorter stature (SD difference per SD shorter height: −0.16

Table 2
SD difference in forearm and calf muscle density (2011/2012) per SD lower level of characteristic at HCS baseline (1998–2004).

Participant characteristic	Forearm muscle density		Calf muscle density	
	Estimate (95 % CI)	p-Value	Estimate (95 % CI)	p-Value
Age	0.09 (−0.01, 0.19)	0.082	*0.20 (0.10, 0.30)*	*<0.001*
Sex (female vs male)	*−1.04 (−1.33, −0.74)*	*<0.001*	*−0.84 (−1.13, −0.54)*	*<0.001*
Height	−0.11 (−0.24, 0.02)	0.109	*−0.16 (−0.30, −0.03)*	*0.018*
Weight	*−0.16 (−0.26, −0.06)*	*0.002*	*−0.37 (−0.46, −0.27)*	*<0.001*
BMI	*−0.12 (−0.21, −0.03)*	*0.012*	*−0.31 (−0.40, −0.23)*	*<0.001*
Smoking (ever vs never)	0.01 (−0.18, 0.20)	0.908	0.00 (−0.19, 0.19)	0.997
Alcohol consumption (per lower band)	0.05 (−0.06, 0.15)	0.374	0.04 (−0.07, 0.14)	0.507
Dallosso activity score	0.05 (−0.04, 0.14)	0.284	−0.04 (−0.13, 0.06)	0.469
Prudent diet score	0.03 (−0.07, 0.13)	0.612	−0.10 (−0.20, 0.00)	0.052
Protein intake	0.04 (−0.05, 0.14)	0.398	0.04 (−0.06, 0.13)	0.422
Social class (manual vs non-manual)	0.10 (−0.08, 0.28)	0.278	−0.03 (−0.22, 0.16)	0.743
Comorbidity (per fewer system medicated)	−0.00 (−0.08, 0.08)	0.983	0.06 (−0.02, 0.15)	0.139

SD: standard deviation.
CI: confidence interval.
Each regression model included the individual participant characteristic of interest along with sex, baseline age and follow-up time.
Significant associations ($p < 0.05$) are shown in italic.

[−0.30, −0.03], p = 0.018). Lifestyle factors, social class and comorbidity were not associated with either of the muscle density measures.

3.3. Muscle density in relation to musculoskeletal parameters and clinical outcomes

Forearm and calf muscle density were weakly correlated with total hip BMD (males: r = 0.13 (p = 0.089) and r = 0.20 (p = 0.006), females: r = 0.19 (p = 0.011) and r = 0.29 (p < 0.001) respectively) (Table 3). Calf muscle density was moderately correlated with ALM index among both males (r = 0.41, p < 0.001) and females (r = 0.38, p < 0.001); calf muscle density was also correlated with grip strength among males (r = 0.23, p = 0.002). In general, correlations between musculoskeletal parameters and forearm muscle density were weaker than the correlations with calf muscle density (Table 3).

After adjustment for sex and age, lower forearm muscle density was related to increased risk of previous fracture (odds ratio (95 % CI) per SD lower forearm muscle density: 1.42 (1.07, 1.89), p = 0.015) (Table 4). This association was attenuated after adjustment for total hip BMD (p > 0.08). By contrast, no significant relationships were seen between calf or forearm muscle density and previous falls. However, a trend was observed between lower calf muscle density and increased risk of previous fracture after adjustment for sex and age (odds ratio (95 % CI) per SD lower calf muscle density: 1.23 (0.94, 1.62), p = 0.131). Similarly, lower values of each muscle density measure were associated with greater risk of vertebral fracture after adjustment for sex and age, but these associations were not statistically significant.

4. Discussion

In this study we reported muscle density values for community-dwelling Caucasian UK males and females in older age, and explored the demographic, anthropometric and lifestyle determinants of muscle density. We also considered the relationships of muscle density measures to the clinical outcomes of falls and fractures. Our study demonstrated that demographic and anthropometric characteristics (female sex, older age, and lower adiposity), rather than lifestyle factors examined such as physical activity and diet, were associated with lower muscle density, approximately 11 years later. We have also demonstrated that forearm muscle density was associated with previous fracture, rather than falls history.

These findings complement earlier evidence linking lower muscle density/attenuation with adverse clinical outcomes including falls, fractures, poor physical performance, reduced muscle strength, frailty, and poor prognosis [10,18,19,32–45]. We found that only forearm, and not calf muscle density, was significantly associated with previous fracture in our cohort; we examined these associations with previous fractures at any site. Additional information on fractures since age 45 years, such as their type, date, and total number, was unavailable. However, it seems likely that a high proportion of fractures were upper limb distal forearm fractures, as the majority occurred in women in midlife. We suspect that the lack of association of calf muscle density with prior fracture reflects a health survivor bias in this cohort making calf muscle density less reflective of functional limitations, whereas forearm muscle density may be more reflective of general fragility contrary to lower limbs which are load bearing sites. In other studies, fat infiltration at mid femur, a measure of reduced muscle quality likely through reduction in force generating capacity through loss of type II fibers, was independently associated with a modest increase risk of incident clinical fracture in the Health, Aging, and Body Composition Study [46]. As lower extremity muscle attenuation and pQCT-derived muscle density is associated with poor physical performance, this might explain the relative higher reported risk of hip fractures in those individuals [20,32,34,47–49].

Table 3
Cross-sectional Pearson correlations between musculoskeletal parameters and muscle density at the forearm and calf (2011/2012) stratified by sex.

Parameter	Forearm muscle density	Calf muscle density
Males		
ALM index	r = 0.16 (p = 0.033)	r = 0.41 (p < 0.001)
Grip strength	r = 0.08 (p = 0.262)	r = 0.23 (p = 0.002)
Gait speed	r = 0.00 (p = 0.980)	r = 0.08 (p = 0.331)
Total hip BMD	r = 0.13 (p = 0.089)	r = 0.20 (p = 0.006)
Females		
ALM index	r = 0.14 (p = 0.073)	r = 0.38 (p < 0.001)
Grip strength	r = −0.02 (p = 0.832)	r = 0.04 (p = 0.603)
Gait speed	r = 0.02 (p = 0.845)	r = 0.07 (p = 0.369)
Total hip BMD	r = 0.19 (p = 0.011)	r = 0.29 (p < 0.001)

ALM index: appendicular lean mass index.
BMD: bone mineral density.

The lack of association between grip strength and forearm muscle density among both males and females was surprising. However, a possible reason for the lack of association is that muscle density was only assessed on the non-dominant side whereas the highest out of six grip strength measurements (three on each side) was used for analysis. We also reported no association between forearm or calf muscle density with falls which was somewhat unexpected. Muscle density has previously been shown to be associated with falls status, and this association is independent of functional mobility [13,34]. Again, this may reflect our use of retrospective questionnaires, which may be limited by recall bias.

Our other findings are certainly consistent with what is currently known. Older age was associated with lower calf muscle density in our cohort after adjustment for sex and follow-up time; this association was also robust when additionally adjusted for weight (data not shown). Skeletal muscle fibre changes have been reported in ageing humans [50], and changes in muscle fibre morphology, infiltration of fat and other non-contractile proteins, altered gene expression, and innervation can all affect muscle quality [51–53]. Previous cross sectional and longitudinal cohorts have suggested that muscle density changes over time are also age-related [10,54–56] supporting our findings, while female sex and poor quality of life (according to Health Assessment Questionnaire scores) were associated with declines in muscle density in a study of patients with rheumatoid arthritis [45]. Therefore, changes in muscle density over time might precede adverse outcomes such as falls and fractures and may be a long-term predictor of frailty. It could be also suggested that muscle density could be a more clinically meaningful surrogate of functional decline and disability than muscle size or mass but more studies are needed to support this notion [20,57].

In our cohort, lifestyle factors such as physical activity, diet, smoking, and alcohol consumption were not associated with future muscle density. Previous studies have examined the effect of smoking on muscle mass and strength in older adults, but not muscle density in the general population [58,59], though one study examining factors associated with declines in pQCT derived-muscle density in rheumatoid arthritis patients showed that active smoking was associated with lower muscle density [60]. In addition, the toxic effects of excess alcohol on skeletal muscle are recognised as important [61,62]; however, a recent meta-analysis did not show alcohol as a risk factor for sarcopenia [63] and studies examining the associations of alcohol specifically with muscle density are absent, so our observations here (where few participants drank to excess, or were current smokers) are perhaps unsurprising. Nutrition intake, specifically dietary protein, alone and/or resistance exercise are recognised as important for muscle health [64,65]. In contrast, dietary protein intake was not related to subsequent muscle density in our cohort possibly because the proportion of adults not consuming recommended levels was lower than in other samples [66]. Information on resistance exercises was not available in our cohort at baseline; however, carrying loads of 10 lb. more frequently was related (p = 0.038) to greater subsequent calf muscle density at follow-up after

Table 4
Odds ratios for previous falls and fractures since age 45 years per SD decrease in parameter in 2011/2012.

Parameter	Adjustments	Previous fall		Previous fracture		Previous vertebral fracture	
		Odds ratio (95 % CI)	p-Value	Odds ratio (95 % CI)	p-Value	Odds ratio (95 % CI)	p-Value
Forearm muscle density	Sex, age	0.90 (0.70, 1.17)	0.439	*1.42 (1.07, 1.89)*	*0.015*	1.44 (0.88, 2.37)	0.151
	Sex, age, total hip BMD	0.88 (0.67, 1.14)	0.330	1.30 (0.97, 1.75)	0.081	1.23 (0.73, 2.06)	0.431
Calf muscle density	Sex, age	1.01 (0.78, 1.30)	0.938	1.23 (0.94, 1.62)	0.131	1.53 (0.95, 2.44)	0.077
	Sex, age, total hip BMD	0.98 (0.75, 1.27)	0.866	1.10 (0.82, 1.47)	0.527	1.15 (0.70, 1.90)	0.574

Previous fractures include self-reported and vertebral fractures.
Significant associations ($p < 0.05$) are shown in italic.

adjustment for sex, age, and follow-up time (data not shown).

There are strengths and limitations of the current study, some of which have been discussed previously. The determinants of future muscle density have not been previously explored in a community or hospital-based cohort. The literature on pQCT analyses in older adults is limited and previous studies have focused on associations between pQCT derived muscle data and outcomes but not determinants of future muscle density [35,67–69]. Peripheral QCT is proving to be a useful tool for the measurement of muscle density and has been found to be highly correlated with MRI-derived measures of muscle cross-sectional area [70]. HCS is a well characterised cohort that has been extensively phenotyped according to strict protocols by highly-trained fieldworkers [26]. Individuals recruited were selected because they had been born in Hertfordshire and continued to live there in 1998–2004, as in previous studies. Although our cohort might be expected to demonstrate a healthy cohort effect (as evidenced by low rates of smoking and high dietary calcium intakes), we have previously demonstrated that the Hertfordshire population studied have similar smoking characteristics and bone density to national figures [25]. This healthy cohort effect might have contributed to the absence of associations between lifestyle factors and future muscle density in our cohort and the fairly high mean values of muscle density observed. Drop out at each stage of the study occurred due to participants moving away or becoming unwilling to participate in further studies; this has contributed to the relatively small number of participants examined. We also recognise the limitations associated with self-reported information, and the lack of phenotypic data around time spent participating in resistance exercises at baseline. Another limitation is the potential for recall bias from participants self-reporting previous fractures and falls which may have occurred decades ago. Furthermore, additional information on falls and fractures since age 45 years, such as their type, date and total number, was unavailable. A key limitation is that only falls and fractures ascertained prior to the muscle density measures were available; determining whether muscle density influences risk of adverse outcomes or vice versa is limited without also having incident outcomes assessed after the muscle density measures. Finally, the narrow age range of the analysis sample prevents a detailed characterisation of how muscle density varies over the lifecourse.

5. Conclusion

This study provides further insights into the determinants of future muscle density and the associations of muscle density with clinical outcomes such as falls and fractures in a well characterised community-dwelling cohort of older adults. pQCT-derived muscle density could provide a biomarker to further complement the musculoskeletal health assessment in older adults and further studies are now warranted.

CRediT authorship contribution statement

FL, NF, NCH, HPP, CC, KW and ED participated in the conception, design and conduct of the study. LW conducted the statistical analyses. FL drafted the first version of the manuscript. All authors read and approved the final manuscript.

Declaration of competing interest

ED declares consultancy and speaker fees from Viatris, Pfizer, UCB and Lilly.

CC has received lecture fees and honoraria from Amgen, Danone, Eli Lilly, GSK, Kyowa Kirin, Medtronic, Merck, Nestlé, Novartis, Pfizer, Roche, Servier, Shire, Takeda and UCB outside of the submitted work.

NF declares travel bursaries from Pfizer and Eli Lilly.

HPP has received lecture fees from Abbott, Pfizer, and HC-UK conferences outside of the submitted work.

The remaining authors declare that they have no conflicts of interest.

Data availability

Hertfordshire Cohort Study data are accessible via collaboration. Initial enquires should be made to CC (Principal Investigator). Potential collaborators will be sent a collaborators' pack and asked to submit a detailed study proposal to the HCS Steering Group.

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Ethical approval

All study participants provided written informed consent and ethical approval was obtained from the Hertfordshire Research Ethics Committee (reference 07/MRE01/30). The baseline Hertfordshire Cohort Study had ethical approval from the Hertfordshire and Bedfordshire Local Research Ethics Committee and the follow-up had ethical approval from the East and North Hertfordshire Ethical Committees.

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