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MUSCLE SIZE, STRENGTH AND PHYSICAL PERFORMANCE AND THEIR ASSOCIATIONS WITH BONE STRUCTURE IN THE HERTFORDSHIRE COHORT STUDY

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Abstract

Sarcopenia is associated with a greater fracture risk; this relationship was originally thought to be explained by an increased risk of falls in sarcopenic individuals. However, in addition, there is growing evidence of a functional muscle-bone unit in which bone health may be directly influenced by muscle function. Since a definition of sarcopenia encompasses muscle size, strength and physical performance, we investigated relationships for each of these with bone size, bone density and bone strength to interrogate these hypotheses further in participants from the Hertfordshire Cohort Study. 313 men and 318 women underwent baseline assessment of health and detailed anthropometric measurements. Muscle strength was measured by grip strength and physical performance was determined by gait speed. Peripheral quantitative computed tomography (pQCT) examination of the calf and forearm was performed to assess muscle cross-sectional area (mCSA) at the 66% level, and bone structure (radius and tibia, 4% and 66% levels). Muscle size was positively associated with bone size (distal radius total bone area =17.5mm²/SD [12.0, 22.9]) and strength (strength strain index (=23.3mm³/SD [18.2, 28.4]) amongst women (p<0.001). These associations were also seen in men and were maintained after adjustment for age, height, weight-adjusted-for-height, limb length-adjusted-for-height, social class, smoking status, alcohol consumption, calcium intake, physical activity, diabetes mellitus, and in women, years since menopause and estrogen replacement therapy. While grip strength showed similar associations with bone size and strength in both sexes, these were substantially attenuated after similar adjustment. Consistent relationships between gait speed and bone structure were not seen. We conclude that while muscle size and grip strength are associated with bone size and strength, relationships between gait speed and bone structure and strength were not apparent in this cohort, supporting a role for the muscle-bone unit.

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Keywords

Osteoporosis; Epidemiology; Sarcopenia; Peripheral Quantitative Computed Tomography (pQCT); Muscle

INTRODUCTION

Osteoporotic fractures are associated with considerable morbidity, mortality and economic costs (1,2). The propensity to fracture is dependent upon the mechanical strength of a bone balanced against the forces it must endure. Sarcopenia, the age related loss of muscle mass and function (3) may add to fracture risk by increasing falls risk (4). However, the mechanostat hypothesis suggests that bones adapt to mechanical loads generated by voluntary mechanical usage, including that of muscle contraction (5) implying the direct role of muscle on bone structure and strength. Genetic, developmental, endocrine and lifestyle factors, such as physical activity, have dual effects on both muscle and bone (6-9). While others have attempted to examine these relationships, previous studies have focused on associations between muscle measurements with bone mass and density (10-12) but not bone structure. Since mechanical loading preferentially increases bone size above mass and density (13), neglecting the assessment of bone structure in the association between sarcopenia and fracture risk may lead to an incomplete understanding. Furthermore, studies examining relationships between physical performance and bone structure are limited, and those investigating the effects of muscle size or strength often fail to adequately consider the role of potential confounding factors such as body size, diet and lifestyle (14-17). The Hertfordshire Cohort Study is well placed to examine this issue because of the wealth of phenotypic data available relating to body build, and musculoskeletal health.

We aimed to study associations between the three muscle components of sarcopenia (low muscle mass; low muscle function defined as low muscle strength or low physical performance) and measures of bone strength, as well as cortical and trabecular bone structure using peripheral quantitative computed tomography (pQCT).

METHODS

Study design

The Hertfordshire Cohort Study (HCS) is a population-based cohort study in the UK which was designed to examine the relationship between growth in infancy and the subsequent risk of adult disease, including osteoporosis. Study design and recruitment have been described in detail previously (11). Briefly, in conjunction with the National Health Service Central Registry and the Hertfordshire Family Health Service Association, we traced men and women who were born between 1931 and 1939 in Hertfordshire and still lived there during the period 1998–2003. In 2004–5, 437 men and 447 women from the geographical area of East Hertfordshire were invited for a follow up study. Of these, 322 men (65%) and 320 women (68%) agreed to participate,

Interviews and Examination

A detailed questionnaire was administered to obtain information on lifestyle, medical history, cigarette smoking and alcohol consumption. Details regarding physical activity, dietary calcium intake, socioeconomic status and, in women, years since menopause and use of estrogen replacement therapy had already been obtained from a questionnaire which was administered by trained nurses when the participants were initially recruited into the HCS (1998-2003). Physical activity was calculated as a standardised score ranging from 0–100

derived from frequency of gardening, housework, climbing stairs and carrying loads in a typical week. Higher scores indicated greater levels of activity (18). Dietary calcium intake was assessed using a food frequency questionnaire (19). Socioeconomic status was determined using own current or most recent occupation of the participant in men and single women, and of the husband in ever-married women based on the OPCS Standard Occupational Classification scheme for occupation and social class (20).

Anthropometry

Height was measured to the nearest 0.1 cm using a Harpenden pocket stadiometer (Chasmors Ltd, London, UK) and weight to the nearest 0.1 kg on a SECA floor scale (Chasmors Ltd, London, UK). Body mass index (BMI) was calculated as weight divided by height² (kg/m²). Grip strength was measured three times in each hand using a Jamar hand-held isokinetic dynamometer using a standardised protocol (21). The maximum value was used in analyses. Gait speed was quantified from the time taken to complete a 3 metre walk test.

Peripheral Quantitative Computed Tomography (pQCT)

Nine men and two women either declined or were unable to undergo pQCT. In total, 313 men and 318 women underwent scanning at the radius and tibia (non-dominant side) using a Stratec 2000XL pQCT scanner running software version 6.00. The radial length was measured from the distal end of the ulna styloid to the tip of the olecranon in millimetres (mm). The tibial length was measured from the prominence of the medial malleolus to the tibial plate (mm). Forearm and lower leg scout views identified measurement reference lines at the cortical end plates. Two slices were taken in the forearm scan: 4% distal radius and 66% radial mid-shaft and forearm cross-sectional area (CSA) of muscle. Three slices were taken for the lower leg scan: 4% distal tibia, 38% tibial midshaft and 66% calf CSA. Assessment of muscle size by pQCT has been found to be valid and reliable (22). Trabecular parameters were measured distally and cortical parameters were measured in the mid-shaft (radius, 66%; tibia, 38%). Measurements were taken from both the radius and tibia of distal total bone area (dTBA), trabecular bone mineral density (tBMD), cortical bone mineral density (cBMD), cortical bone area (cBA), and polar strength strain index (SSI). Mid-shaft periosteal circumference (PC) and mid-shaft endosteal circumference (EC) were then calculated assuming that the bone had a circular cross-section. Measurement precision error, expressed as a coefficient of variation, ranged from 0.88% (tibial total density, 4% slice) to 8.8% (total radial area, 66% slice), but was typically around 1-3%. These figures were obtained by 20 volunteers who were part of the study undergoing 2 scans on the same day, with limb repositioning between examinations.

For all scans a threshold of 280 mg/cm³ was used to separate the bone from the soft tissue background. Once separated, the default peeling algorithm was applied to the distal 4% scans to separate trabecular bone. With this peeling, 55% of the outer bone area was concentrically separated and defined as cortical and subcortical; the remaining 45% was defined as trabecular bone. For proximal scan locations the default threshold of 710 mg/cm³ was used to separate cortical bone. Muscle CSA at the forearm and calf was derived using the default analysis steps that utilize various threshold and edge tracking settings to segment muscle from subcutaneous fat. We chose to adopt this algorithm as it allowed better comparability for our work with other studies and as we hope to perform follow-up scans on this group, it will allow consistency in our approach. Those with significant movement artefact were excluded from analyses.

Ethical approval was granted from the Hertfordshire Research Ethics Committee and all participants gave written informed consent in accordance with the Declaration of Helsinki (23).

Statistical methods

Study participant characteristics for continuous variables were calculated as means (standard deviation, SD). Categorical and binary variables were summarized as numbers and percentages of the total study population. All data were visually inspected for normality and \log_e transformed as appropriate. Measures of sarcopenia for each individual were then converted to a standardized score that represented the number of standard deviations the value was from the mean of the study population. Primary analysis used linear regression to examine the associations between each of these standardized measures of sarcopenia; i) muscle size (forearm and calf muscle CSA), ii) muscle strength (grip strength) and iii) physical performance (gait speed), and pQCT bone parameters in the corresponding limb. For forearm muscle size and grip strength the corresponding limb was the radius, and for calf muscle size and gait speed it was the tibia. This analysis was repeated with and without adjustment for *a priori* confounders: age, height, weight-adjusted-for-height, limb length-adjusted-for-height, social class, smoking status, alcohol consumption, calcium intake, physical activity, diabetes mellitus, and in women, years since menopause and estrogen replacement therapy. EC was additionally adjusted for PC to take into consideration bone size.

As skeletal size is a key determinant of muscle and bone parameters consideration was taken of height, weight and limb length. To avoid over-adjustment, the latter two were adjusted for height before inclusion in the model. The model also included adjustment for diabetes (DM), which is known to influence both muscle and bone parameters (24-27). Bonferroni correction was retrospectively applied to each association to take account of multiple testing (28).

RESULTS

Participant characteristics

The mean age of men and women in the study was 69.2 and 69.5 years respectively (Table 1). All women were postmenopausal. Men were taller, heavier and had higher calcium intakes. Among men, 61.7% were current or ex-smokers compared with only 36.8% of women. Men were more likely to be heavy alcohol drinkers. Approximately 1 in 5 participants had fractured since the age of 45 years. Two fifths of men and three fifths of women reported falls since the age of 45 years. DM had been diagnosed in 15.7% of men and 12.7% of women. Men had bigger muscles in both their upper and lower limbs, stronger grip strength and walked faster than women (Table 2). As expected in both the radius and tibia, measures of bone size and density were higher in men than women.

Muscle size

Clear positive associations were seen between forearm muscle size and radial bone size (dTBA, cBA, PC) and bone strength (SSI) in men (Figure 1). However, no association was observed between forearm muscle size and radial bone mineral density (cBMD, tBMD). Similar patterns were found in the lower limb between calf muscle size and tibial bone parameters (Table 3). In women, as in men, muscle size in the forearm and calf was positively associated with both bone size (dTBA, cBA, PC) and bone strength (SSI) (Figure 2). However, in contrast to men, muscle size was also positively associated with tBMD, but not cBMD, in both upper and lower limbs.

In both sexes, after adjustment for age, height, weight-adjusted-for-height, limb length-adjusted-for-height, social class, smoking status, alcohol consumption, calcium intake, physical activity, DM, and in women, years since menopause and estrogen replacement therapy, positive associations between muscle size and both bone size (dTBA, cBA, PC) and bone strength (SSI) in the corresponding limb all persisted (Table 4).

We considered relationships between muscle size and the cortical and trabecular compartments. In general EC was inversely related with muscle size; this was most apparent in women (Table 4). Overall after adjustment for confounders, muscle size was independent of both cortical and trabecular BMD, with the exception of a persistent positive relationship between forearm muscle size and radial tBMD in women. After correction for multiple testing, the majority of associations between muscle size and bone structure were maintained, despite partial attenuation (data not shown).

Grip strength (Muscle strength)

Positive relationships were identified between grip strength and both radial bone size (dTBA, cBA, PC) and bone strength (SSI) in men (Figure 1). Similar relationships were seen in women, although associations with bone size were weaker (Figure 2). Although adjustment fully attenuated our observed associations between grip strength and bone strength, the associations with bone size persisted in both men and women (Table 4). In general BMD was independent of grip strength.

Gait speed (Physical performance)

In contrast to muscle size and grip strength, analyses found no evidence to support an association between gait speed and any of the tibial bone parameters in men (Figure 1) or women (Figure 2) that were robust to adjustment for multiple testing and confounders.

DISCUSSION

We have shown that muscle size is strongly associated with bone size and bone strength in both men and women and that these relationships remain robust after rigorous adjustment. By contrast, gait speed was not associated with measures of bone size, strength or density in this cohort of older adults. These data support the mechanostat hypothesis with associations between both muscle size and grip strength with bone size likely to arise through dynamic loading.

The associations of muscle size with both bone size and strength, that we have shown, are in keeping with published findings (16-17,29-31). However, in contrast to most previous studies, we were able to look not only at cBA but specifically at changes in periosteal and endosteal circumferences. In both weight-bearing and non weight-bearing limbs, we found greater muscle size was invariably associated with larger PC and bone size. Conversely, EC tended to decrease after adjustment for PC, in particular in women. This indicates that the greater cBA is likely to reflect contributions from increased PC and reduced EC. The greater effect in women than men might suggest a role for estrogen in this relationship.

The positive associations between tBMD and muscle size in weight-bearing and non weight-bearing limbs were attenuated after adjustment. This observation has previously only been made in children (29). We found no evidence to support an association between muscle size and cBMD which is consistent with animal studies that show cortical bone adapts its strength to mechanical loading by preferentially increasing bone size rather than BMD (13).

Positive associations were found between grip strength and both bone strength (SSI) and size (dTBA, cBA and PC) in men and women consistent with what has been found

previously (15,32). However, we were uniquely positioned to take account of potential covariates (14,17) and this may explain why we observed a greater attenuation after adjustment than had been previously demonstrated. Furthermore, the published literature describing grip strength and BMD relationships are heterogeneous in terms of ethnicity, exclusion criteria, assessment of confounders, study size and conclusions and fail to reach a consensus (14-15,33).

To our knowledge, the relationship between physical performance as measured by gait speed and bone structure has not been previously investigated. The STRAMBO study defined physical performance in terms of chair rises, static and dynamic balance (34), and found that those participants who failed on more than one of these tests had significantly lower BMD (trabecular, cortical and total) and cortical bone area as assessed by high resolution pQCT. While our definition of PP is different, it is also possible that our cohort was generally fitter than the participants from the STRAMBO study.

Associations between muscle and bone size could be explained in several ways. First, the mechanostat hypothesis (5) states that a muscle provides a direct mechanical stimulus to a bone during contraction to generate bending moments (35). Mechanotransduction of these forces subsequently occurs mainly through the function of osteocytes which sense strain and regulate sclerostin production in response. This allows deforming forces applied to bone to promote osteogenesis. This hypothesis forms a possible mechanism through which muscle and bone may be linked. Second, genetic and hormonal factors have pleiotropic effects on the musculoskeletal system and can, either directly or indirectly, impact on both muscle and bone growth (6-8,36-37). Third, exercise can affect both bone structure and muscle size and strength (38-40). Finally, in keeping with the developmental origins hypothesis, there is evidence supporting associations between birth weight and both bone health(41) and muscle function(42) in later life. Consequently, a common developmental contribution to both facets could partly explain associations seen.

The main strengths of our study are that the sample investigated is generally representative of the UK population as a whole(43) and that previous extensive phenotyping has allowed us to thoroughly adjust for potential confounding factors. However, there are also several limitations of this study. Firstly, the design was cross-sectional which prevents assessment of causality. Grip strength was taken as the highest of 6 measurements (3 on the dominant side and 3 on the non-dominant side) and so usually the maximum grip strength measurement was taken from the dominant side whilst bone parameters were assessed on the non-dominant side. This may attenuate associations seen between grip strength and bone parameters to a degree although the difference between dominant and non dominant limbs is usually small and relatively consistent (44). Furthermore, the pQCT assessment of bone strength provided is a theoretical estimate, rather than a measure of experimental failure. However, it has previously been shown to be related to in vitro breaking strength (45). Third, it is clear that the radius and tibia are not completely circular in cross-section. The manufacturer of the instrument recommends use of a circular ring model assumption in analysis of pQCT images; furthermore, images analyzed on this basis have been shown to be accurate at both skeletal sites(46-47). A potential alternative strategy would be use an iterative contour detection method which might provide a direct measurement, based on the true shape of the bone. However, this procedure fails to produce a measurement that can be utilized in an appreciable portion of individuals. As a consequence our main data were presented using a circular ring model assumption as suggested by the manufacturer. Finally, we also recognise the limitations associated with self-reported physical activity, dietary calcium, smoking status and alcohol consumption.

In conclusion, we have shown that muscle size and grip strength, but not gait speed, are associated with bone size and strength. Potential mechanisms explaining this relationship include the mechanostat hypothesis, developmental, genetic and hormonal factors. Further studies are needed to determine whether muscle size and grip strength have a deterministic relationship with bone structure and whether associations also exist between each of the muscle parameters and bone-related clinical outcomes such as fractures.

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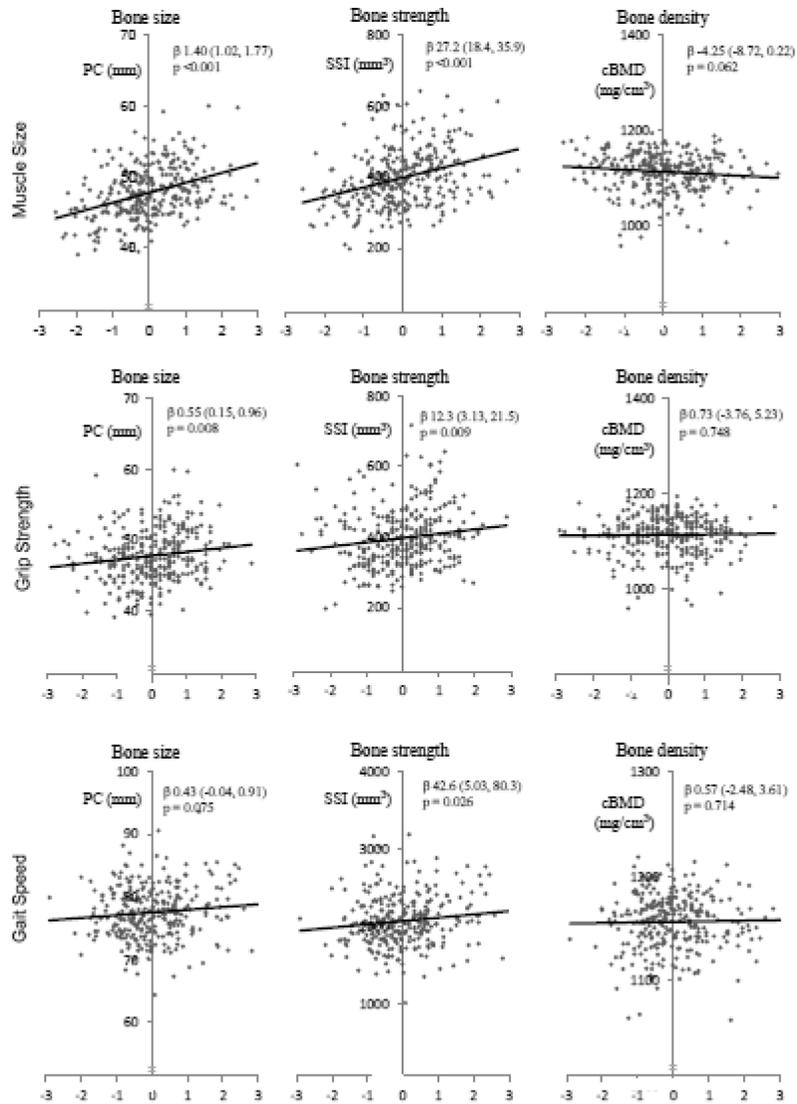
MHE, EMD and CC made substantial contributions to the conception and design of the study. EMD and CC were involved in data acquisition. MHE drafted the manuscript with input from CLG, ED, and CC. All authors contributed to the analysis and interpretation of the data, revised the manuscript critically for important intellectual content, and approved the final version of the submitted manuscript. MHE accepts responsibility for the integrity of the data analysis.

References

1. Johnell O, Kanis JA. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. *Osteoporos.Int.* Dec; 2006 17(12):1726–33. [PubMed: 16983459]
2. Burge R, Dawson-Hughes B, Solomon DH, Wong JB, King A, Tosteson A. Incidence and economic burden of osteoporosis-related fractures in the United States, 2005-2025. *J.Bone Miner.Res.* Mar; 2007 22(3):465–75. [PubMed: 17144789]
3. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, Martin FC, Michel JP, Rolland Y, Schneider SM, Topinkova E, Vandewoude M, Zamboni M, European Working Group on Sarcopenia in Older People. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. *Age Ageing.* Jul; 2010 39(4):412–23. [PubMed: 20392703]
4. Wickham C, Cooper C, Margetts BM, Barker DJ. Muscle strength, activity, housing and the risk of falls in elderly people. *Age Ageing.* Jan; 1989 18(1):47–51. [PubMed: 2565665]
5. Frost HM. Bone's mechanostat: a 2003 update. *Anat.Rec.A Discov.Mol.Cell Evol.Biol.* Dec; 2003 275(2):1081–101. [PubMed: 14613308]
6. Karasik D, Kiel DP. Genetics of the musculoskeletal system: a pleiotropic approach. *J Bone Miner Res.* Jun; 2008 23(6):788–802. [PubMed: 18269309]
7. Tritos NA, Biller BM. Growth hormone and bone. *Curr Opin Endocrinol Diabetes Obes.* Dec; 2009 16(6):415–22. [PubMed: 19770650]
8. Urban RJ. Growth hormone and testosterone: anabolic effects on muscle. *Horm Res Paediatr.* Jul; 2011 76(Suppl 1):81–3. [PubMed: 21778755]
9. Gomez-Cabello A, Ara I, Gonzalez-Aguero A, Casajus JA, Vicente-Rodriguez G. Effects of training on bone mass in older adults: a systematic review. *Sports Med.* Apr 1; 2012 42(4):301–25. [PubMed: 22376192]
10. Segal NA, Torner JC, Yang M, Curtis JR, Felson DT, Nevitt MC. Muscle mass is more strongly related to hip bone mineral density than is quadriceps strength or lower activity level in adults over age 50 year. *J Clin Densitom.* Oct; 2008 11(4):503–10. [PubMed: 18456530]
11. Blain H, Vuillemin A, Teissier A, Hanesse B, Guillemin F, Jeandel C. Influence of muscle strength and body weight and composition on regional bone mineral density in healthy women aged 60 years and over. *Gerontology.* Jul; 2001 47(4):207–12. [PubMed: 11408726]
12. Sirola J, Tuppurainen M, Honkanen R, Jurvelin JS, Kroger H. Associations between grip strength change and axial postmenopausal bone loss—a 10-year population-based follow-up study. *Osteoporos.Int.* Dec; 2005 16(12):1841–8. [PubMed: 16049626]

13. Robling AG, Castillo AB, Turner CH. Biomechanical and molecular regulation of bone remodeling. *Annu.Rev.Biomed.Eng.* Aug.2006 8:455–98. [PubMed: 16834564]
14. Cousins JM, Petit MA, Paudel ML, Taylor BC, Hughes JM, Cauley JA, Zmuda JM, Cawthon PM, Ensrud KE. Muscle power and physical activity are associated with bone strength in older men: The osteoporotic fractures in men study. *Bone.* Aug; 2010 47(2):205–11. [PubMed: 20466088]
15. Kaji H, Kosaka R, Yamauchi M, Kuno K, Chihara K, Sugimoto T. Effects of age, grip strength and smoking on forearm volumetric bone mineral density and bone geometry by peripheral quantitative computed tomography: comparisons between female and male. *Endocr.J.* Dec; 2005 52(6):659–66. [PubMed: 16410656]
16. Hasegawa Y, Schneider P, Reiners C. Age, sex, and grip strength determine architectural bone parameters assessed by peripheral quantitative computed tomography (pQCT) at the human radius. *J Biomech.* Apr; 2001 34(4):497–503. [PubMed: 11266673]
17. Frank AW, Lorbergs AL, Chilibeck PD, Farthing JP, Kontulainen SA. Muscle cross sectional area and grip torque contraction types are similarly related to pQCT derived bone strength indices in the radii of older healthy adults. *J Musculoskelet.Neurol.Interact.* Jun; 2010 10(2):136–41. [PubMed: 20516630]
18. Dallosso HM, Morgan K, Bassej EJ, Ebrahim SB, Fentem PH, Arie TH. Levels of customary physical activity among the old and the very old living at home. *J Epidemiol.Community Health.* Jun; 1988 42(2):121–7. [PubMed: 3221161]
19. Robinson SM, Jameson KA, Batelaan SF, Martin HJ, Syddall HE, Dennison EM, Cooper C, Sayer AA. Diet and its relationship with grip strength in community-dwelling older men and women: the Hertfordshire cohort study. *J Am Geriatr.Soc.* Jan; 2008 56(1):84–90. [PubMed: 18005355]
20. Office of Population Census and Surveys (OPCS). Standard occupational Classification. Vol. Volume 3. HMSO; London: 1991.
21. Roberts HC, Denison HJ, Martin HJ, Patel HP, Syddall H, Cooper C, Sayer AA. A review of the measurement of grip strength in clinical and epidemiological studies: towards a standardised approach. *Age Ageing.* Jul; 2011 40(4):423–9. [PubMed: 21624928]
22. Cramer JT, Palmer IJ, Ryan ED, Herda TJ, Bembem DA, Bembem MG, Stratemeyer PH. Validity and Reliability of a Peripheral Quantitative Computed Tomography Scanner for Measuring Muscle Cross-sectional Area. *Med Sci Sports Exerc.* May; 2007 39(5):S225–6.
23. Declaration of Helsinki. Ethical principles for medical research involving human subjects. *J Indian Med.Assoc.* Jun; 2009 107(6):403–5. [PubMed: 19886379]
24. Stenholm S, Tiainen K, Rantanen T, Sainio P, Heliovaara M, Impivaara O, Koskinen S. Long-term determinants of muscle strength decline: prospective evidence from the 22-year mini-Finland follow-up survey. *J Am Geriatr.Soc.* Jan; 2012 60(1):77–85. [PubMed: 22211568]
25. Atlantis E, Martin SA, Haren MT, Taylor AW, Wittert GA. Inverse associations between muscle mass, strength, and the metabolic syndrome. *Metabolism.* Jul; 2009 58(7):1013–22. [PubMed: 19394973]
26. Everson-Rose SA, Paudel M, Taylor BC, Dam T, Cawthon PM, Leblanc E, Strotmeyer ES, Cauley JA, Stefanick ML, Barrett-Connor E, Ensrud KE, Osteoporotic Fractures in Men Research Group. Metabolic syndrome and physical performance in elderly men: the osteoporotic fractures in men study. *J Am Geriatr.Soc.* Aug; 2011 59(8):1376–84. [PubMed: 21806561]
27. Leslie WD, Rubin MR, Schwartz AV, Kanis JA. Type 2 diabetes and bone. *J Bone Miner.Res.* Nov; 2012 27(11):2231–7. [PubMed: 23023946]
28. Bland JM, Altman DG. Multiple significance tests: the Bonferroni method. *BMJ.* Jan.1995 310(6973):170. [PubMed: 7833759]
29. Macdonald H, Kontulainen S, Petit M, Janssen P, McKay H. Bone strength and its determinants in pre- and early pubertal boys and girls. *Bone.* Sep; 2006 39(3):598–608. [PubMed: 16600704]
30. Rittweger J, Beller G, Ehrig J, Jung C, Koch U, Ramolla J, Schmidt F, Newitt D, Majumdar S, Schiessl H, Felsenberg D. Bone-muscle strength indices for the human lower leg. *Bone.* Aug; 2000 27(2):319–26. [PubMed: 10913929]
31. Dowthwaite JN, Kanaley JA, Spadaro JA, Hickman RM, Scerpella TA. Muscle indices do not fully account for enhanced upper extremity bone mass and strength in gymnasts. *J Musculoskelet.Neurol.Interact.* Jan; 2009 9(1):2–14. [PubMed: 19240362]

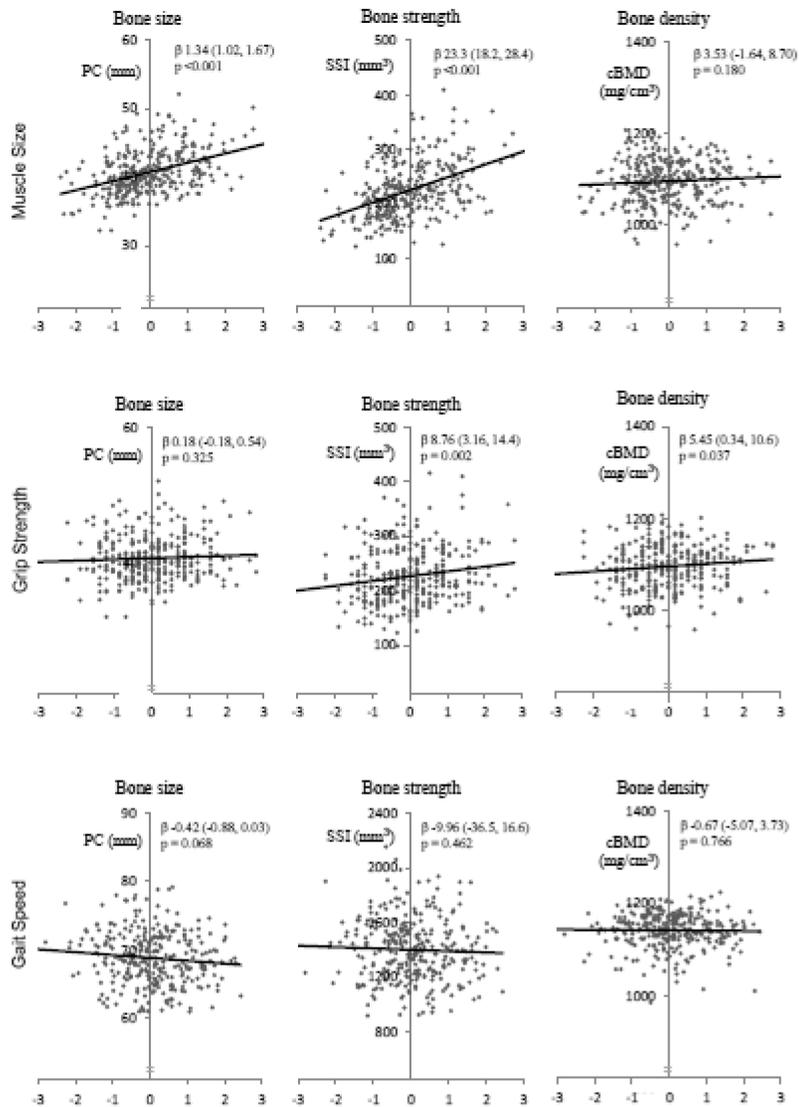
32. Wapniarz M, Lehmann R, Reincke M, Schonau E, Klein K, Allolio B. Determinants of radial bone density as measured by PQCT in pre- and postmenopausal women: the role of bone size. *J Bone Miner. Res.* Feb; 1997 12(2):248–54. [PubMed: 9041057]
33. Specker B, Binkley T, Fahrenwald N. Rural versus nonrural differences in BMC, volumetric BMD, and bone size: a population-based cross-sectional study. *Bone.* Dec; 2004 35(6):1389–98. [PubMed: 15589221]
34. Blaizot S, Boutroy S, Vilayphiou N, Boonen S, Chapurlat R, Szulc P. Poor bone microarchitecture in older men with impaired physical performance-the STRAMBO study. *Osteoporos.Int.* Jan 31.2012 [Epub ahead of print].
35. Lu TW, Taylor SJ, O'Connor JJ, Walker PS. Influence of muscle activity on the forces in the femur: an in vivo study. *J Biomech.* Nov; 1997 30(11-12):1101–6. [PubMed: 9456377]
36. Frost HM. Could some biomechanical effects of growth hormone help to explain its effects on bone formation and resorption? *Bone.* Nov; 1998 23(5):395–8. [PubMed: 9823444]
37. Hogler W, Briody J, Moore B, Lu PW, Cowell CT. Effect of growth hormone therapy and puberty on bone and body composition in children with idiopathic short stature and growth hormone deficiency. *Bone.* Nov; 2005 37(5):642–50. [PubMed: 16139578]
38. Specker BL. Influence of rapid growth on skeletal adaptation to exercise. *J Musculoskelet.Neurol.Interact.* Apr; 2006 6(2):147–53. [PubMed: 16849824]
39. Hamrick MW, Skedros JG, Pennington C, McNeil PL. Increased osteogenic response to exercise in metaphyseal versus diaphyseal cortical bone. *J Musculoskelet.Neurol.Interact.* Jul; 2006 6(3): 258–63. [PubMed: 17142947]
40. Hamilton CJ, Swan VJ, Jamal SA. The effects of exercise and physical activity participation on bone mass and geometry in postmenopausal women: a systematic review of pQCT studies. *Osteoporos.Int.* Jan; 2010 21(1):11–23. [PubMed: 19504035]
41. Baird J, Kurshid MA, Kim M, Harvey N, Dennison E, Cooper C. Does birthweight predict bone mass in adulthood? A systematic review and meta-analysis. *Osteoporos Int.* May; 2011 22(5): 1323–34. [PubMed: 20683711]
42. Dodds R, Denison HJ, Ntani G, Cooper R, Cooper C, Sayer AA, Baird J. Birth weight and muscle strength: a systematic review and meta-analysis. *J Nutr Health Aging.* Jul; 2012 16(7):609–15. [PubMed: 22836701]
43. Syddall HE, Aihie SA, Dennison EM, Martin HJ, Barker DJ, Cooper C. Cohort profile: the Hertfordshire cohort study. *Int.J Epidemiol.* Dec; 2005 34(6):1234–42. [PubMed: 15964908]
44. Bechtol CO. Grip test; the use of a dynamometer with adjustable handle spacings. *J Bone Joint Surg Am.* Jul.1954 36:820–4. [PubMed: 13174611]
45. Ferretti JL, Capozza RF, Zanchetta JR. Mechanical validation of a tomographic (pQCT) index for noninvasive estimation of rat femur bending strength. *Bone.* Feb; 1996 18(2):97–102. [PubMed: 8833202]



Key: PC, periosteal circumference; SSI, strength strain index; and cBMD, cortical bone mineral density.

Figure 1.

Scatter plots showing relationships between standardized forearm muscle size, muscle strength and physical performance, and bone size (PC), bone strength (SSI), and volumetric bone density (cBMD) in men.



Key: PC, periosteal circumference; SSI, strength strain index; and cBMD, cortical bone mineral density.

Figure 2. Scatter plots showing relationships between standardized forearm muscle size, muscle strength and physical performance, and bone size (PC), bone strength (SSI), and volumetric bone density (cBMD) in women.

Table 1
Summary characteristics of the study participants

	Total N	Men Mean (SD)	Total N	Women Mean (SD)	p value
Age (years)	313	69.2 (2.5)	318	69.5 (2.6)	0.111
Height (cm)	313	173.7 (6.5)	318	160.5 (6.1)	<0.001
Weight (kg)	313	82.0 (11.9)	318	71.8 (13.8)	<0.001
BMI (kg/m ²) ^{ab}	313	26.9 (1.14)	318	27.4 (1.19)	0.144
Radius length (mm)	304	263.3 (11.9)	316	239.1 (13.2)	<0.001
Tibia length (mm)	295	379.0 (21.5)	298	348.1 (19.9)	<0.001
Physical Activity Score	313	64.0 (14.2)	318	61.8 (14.3)	0.059
Calcium intake (mg/day) ^b	313	1208.4 (1.29)	318	1094.2 (1.30)	<0.001
	Total N	Men N (%)	Total N	Women N (%)	p value
1 Fall since age 45 years ^c	312	125 (40.1)	317	194 (61.2)	<0.001
Fracture since age 45 years ^d	305	56 (18.4)	316	68 (21.5)	0.325
Vitamin D status (nmol/l)					
<25	259	30 (11.6)	292	49 (16.8)	0.047
25-50		123 (47.5)		150 (51.4)	
>50		106 (40.9)		93 (31.8)	
Alcohol ^e					
Non-drinker	313	9 (2.8)	318	54 (17.0)	<0.001
<=recommended		234 (74.8)		256 (80.5)	
>recommended		70 (22.4)		8 (2.5)	
Smoking status					
Current	313	26 (8.3)	315	17 (5.4)	<0.001
Ex		167 (53.4)		99 (31.4)	
Never		120 (38.3)		199 (63.2)	
Social class					
I-IIIINM	297	128 (43.1)	318	136 (42.8)	0.934
IIIM-V		169 (56.9)		182 (57.2)	
Estrogen replacement					
Never	n/a	n/a	318	186 (58.5)	n/a
>5yrs ago				58 (18.2)	
<5yrs ago				20 (6.3)	
Current				54 (17.0)	
Years since menopause					

	Total N	Men Mean (SD)	Total N	Women Mean (SD)	p value
0-10	n/a	n/a	315	40 (12.7)	n/a
10-20				143 (45.4)	
>20				54 (17.1)	
Hysterectomy				78 (24.8)	

^aBMI: Body mass index,

^bGeometric mean,

^cSelf-reported falls,

^dAny site,

^eMaximum recommended units of alcohol per week are 21 in men and 14 in women.

Table 2
Summary of muscle parameters and bone structural parameters assessed by peripheral quantitative computed tomography

	Total N	Men (n=304) Mean (SD)	Total N	Women (n=316) Mean (SD)	p-value
Muscle					
Forearm Muscle CSA (mm ²)	304	4033.2 (517.6)	314	2554.9 (369.7)	<0.001
Calf Muscle CSA (mm ²) ^a	293	8035.2 (1203.6)	295	6212.2 (980.9)	<0.001
Grip strength (kg)	312	42.2 (7.6)	317	24.9 (5.8)	<0.001
Gait speed (m/s)	311	0.92 (0.17)	314	0.88 (0.16)	<0.001
Radial					
dTBA	304	493.8 (68.8)	316	371.3 (51.9)	<0.001
tBMD	304	211.6 (40.5)	316	173.1 (44.7)	<0.001
cBMD	304	1113.6 (39.7)	316	1095.5 (46.4)	<0.001
cBA	304	99.5 (13.7)	316	63.7 (12.1)	<0.001
PC	304	47.7 (3.6)	316	40.8 (3.3)	<0.001
EC	304	31.9 (4.7)	316	29.3 (4.3)	<0.001
SSI	304	397.5 (81.9)	316	226.1 (51.1)	<0.001
Tibial					
dTBA	295	1391.3 (163.4)	298	1129.8 (128.2)	<0.001
tBMD	295	241.9 (36.5)	298	220.6 (45.6)	<0.001
cBMD	295	1155.8 (26.4)	298	1141.1 (37.4)	<0.001
cBA	295	338.6 (39.9)	298	247.8 (32.2)	<0.001
PC	295	77.5 (4.2)	298	68.8 (3.9)	<0.001
EC	295	41.9 (4.8)	298	40.0 (5.4)	<0.001
SSI	295	2072.3 (328.2)	298	1400.7 (226.9)	<0.001

Key: dTBA, distal total bone area; tBMD, trabecular bone mineral density; cBA, cortical bone area; cBMD, cortical bone mineral density; SSI, strength strain index; EC, endosteal circumference; PC, periosteal circumference.

Table 3
Associations between muscle parameters and bone structure in the corresponding limb (unadjusted).

	Men (95%CI)	Women (95%CI)
Forearm Muscle CSA (muscle size) and radial bone structure		
dTBA	25.0 (17.7, 32.2) ***	17.5 (12.0, 22.9) ***
tBMD	2.34 (-2.24, 6.91)	10.1 (5.25, 14.9) ***
cBMD	-4.25 (-8.72, 0.22)	3.53 (-1.64, 8.70)
cBA	5.11 (3.68, 6.55) ***	5.91 (4.75, 7.08) ***
PC	1.40 (1.02, 1.77) ***	1.34 (1.02, 1.67) ***
EC ^d	-0.63 (-0.90, -0.35) ***	-1.05 (-1.32, -0.78) ***
SSI	27.2 (18.4, 35.9) ***	23.3 (18.2, 28.4) ***
Calf Muscle CSA (muscle size) and tibial bone structure		
dTBA	40.6 (22.4, 58.8) ***	37.3 (23.3, 51.4) ***
tBMD	3.84 (-0.35, 8.03)	10.2 (5.06, 15.3) ***
cBMD	-2.42 (-5.45, 0.62)	-0.71 (5.02, 3.60)
cBA	14.1 (9.88, 18.4) ***	15.7 (12.5, 19.0) ***
PC	1.58 (1.34, 2.02) ***	1.78 (1.39, 2.18) ***
EC ^d	-0.45 (-0.91, -0.01) *	-1.38 (-1.86, -0.90) ***
SSI	115 (80.0, 150) ***	112 (88.9, 134) ***
Grip Strength (muscle strength) and radial bone structure		
dTBA	12.4 (4.70, 20.1) **	9.52 (3.87, 15.2) **
tBMD	-1.26 (-5.85, 3.34)	0.35 (-4.61, 5.32)
cBMD	0.73 (-3.76, 5.23)	5.45 (0.34, 10.56) *
cBA	2.15 (0.62, 3.69) **	1.78 (0.45, 3.11) **
PC	0.55 (0.15, 0.96) **	0.18 (-0.18, 0.54)
EC ^d	-0.24 (-0.50, 0.20)	-0.31 (-0.57, -0.04) *
SSI	12.3 (3.13, 21.5) **	8.76 (3.16, 14.4) **
Gait Speed (physical performance) and tibial bone structure		
dTBA	15.5 (-3.32, 34.2)	-5.05 (-20.0, 9.87)
tBMD	-1.81 (-6.04, 2.42)	3.40 (-1.94, 8.75)
cBMD	0.57 (-2.48, 3.61)	-0.67 (-5.07, 3.73)
cBA	4.15 (-0.45, 8.76)	1.80 (-1.97, 5.58)
PC	0.43 (-0.04, 0.91)	-0.42 (-0.88, 0.03)
EC ^d	-0.14 (-0.57, 0.30)	-0.56 (-1.02, -0.11) *
SSI	42.7 (5.03, 80.3) *	-9.96 (-36.5, 16.6)

Key: dTBA, distal total bone area; tBMD, trabecular bone mineral density; cBMD, cortical bone mineral density; cBA, cortical bone area; PC, periosteal circumference; EC, endosteal circumference; SSI, strength strain index. NB Lower limb was corresponding limb for gait speed (physical performance).

^aAdjusted for PC.

*
p<0.05,

**
p<0.01,

p<0.001

Table 4
Associations between muscle parameters and bone structure in the corresponding limb after adjustment for age, height, weight-adjusted-for-height, limb length-adjusted-for-height, social class, smoking status, alcohol consumption, calcium intake, physical activity, diabetes, and in women, years since menopause and estrogen replacement therapy.

	Men (95%CI)	Women (95%CI)
Forearm Muscle CSA (muscle size) and radial bone structure		
dTBA	23.9 (14.6, 33.3) ***	16.8 (10.4, 23.1) ***
tBMD	2.63 (-3.33, 8.60)	8.09 (2.30, 13.9) **
cBMD	-2.38 (-8.08, 3.32)	-0.24 (-6.50, 6.01)
cBA	4.28 (2.36, 6.20) ***	5.25 (3.84, 6.66) ***
PC	1.20 (0.71, 1.69) ***	1.44 (1.05, 1.83) ***
EC ^a	-0.48 (-0.83, -0.13) **	-0.90 (-1.23, -0.58) ***
SSI	23.6 (12.2, 35.1) ***	24.6 (18.6, 30.6) ***
Calf Muscle CSA (muscle size) and tibial bone structure		
dTBA	22.8 (1.78, 43.9) *	19.5 (4.09, 34.9) *
tBMD	-0.35 (-5.61, 4.91)	3.65 (-2.60, 9.90)
cBMD	-1.39 (-5.42, 2.64)	-4.13 (-9.53, 1.27)
cBA	8.57 (3.20, 14.0) **	9.71 (5.97, 13.4) ***
PC	1.18 (0.65, 1.72) ***	1.32 (0.87, 1.77) ***
EC ^a	-0.04 (-0.61, 0.54)	-0.86 (-1.41, -0.32) **
SSI	78.2 (35.7, 121) ***	76.4 (51.3, 102) ***
Grip Strength (muscle strength) and radial bone structure		
dTBA	9.66 (0.84, 18.5) *	5.97 (0.19, 11.7) *
tBMD	-1.94 (-7.38, 3.50)	-0.30 (-5.46, 4.86)
cBMD	-0.68 (-5.86, 4.51)	2.80 (-2.64, 8.23)
cBA	1.43 (-0.38, 3.23)	0.78 (-0.57, 2.12)
PC	0.50 (0.04, 0.96) *	-0.04 (-0.41, 0.34)
EC ^a	-0.11 (-0.42, 0.21)	-0.15 (-0.43, 0.12)
SSI	8.59 (-2.10, 19.3)	4.17 (-1.64, 9.98)
Gait Speed (physical performance) and tibial bone structure		
dTBA	2.20 (-15.9, 20.3)	-3.63 (-16.9, 9.68)
tBMD	-0.21 (-4.65, 4.23)	3.88 (-1.41, 9.17)
cBMD	-1.30 (-4.69, 2.09)	-1.04 (-5.64, 3.56)
cBA	3.99 (-0.66, 8.64)	3.20 (-0.12, 6.51)
PC	0.40 (-0.07, 0.87)	-0.22 (-0.63, 0.19)
EC ^a	-0.15 (-0.62, 0.32)	-0.57 (-1.02, -0.13) *
SSI	37.1 (0.63, 73.5) *	0.96 (-22.0, 23.9)

Key: dTBA, distal total bone area; tBMD, trabecular bone mineral density; cBMD, cortical bone mineral density; cBA, cortical bone area; PC, periosteal circumference; EC, endosteal circumference; SSI, strength strain index. NB Lower limb was corresponding limb for gait speed (physical performance).

^a Additionally adjusted for PC.

*
p<0.05,

**
p<0.01,

p<0.001