The Influence of High Impact Exercise on Cortical and Trabecular Bone Mineral Content and 3D Distribution across the Proximal Femur in Older Men: a Randomised Controlled Unilateral Intervention.

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Abstract (300/300 words)

Regular exercisers have lower fracture risk, despite modest effects of exercise on BMC. Exercise may produce localised cortical and trabecular bone changes that affect bone strength independently of BMC. We previously demonstrated that brief, daily unilateral hopping exercises increased femoral neck BMC in the exercise leg versus the control leg of older men. This study evaluated the effects of these exercises on cortical and trabecular bone and its 3D distribution across the proximal femur, using clinical computed tomography (CT).

Fifty healthy men had pelvic CT scans before and after the exercise intervention. We used hip QCT analysis to quantify BMC in traditional regions of interest and estimate biomechanical variables. Cortical bone mapping localised cortical mass surface density and endocortical trabecular density changes across each proximal femur, which involved registration to a canonical proximal femur model. Following statistical parametric mapping, we visualised and quantified statistically significant changes of variables over time in both legs, and significant differences between legs.

Thirty-four men aged 70 (4) years exercised for 12-months, attending 92% of prescribed sessions. In traditional ROIs, cortical and trabecular BMC increased over time in both legs. Cortical BMC at the trochanter increased more in the exercise than control leg, whilst femoral neck buckling ratio declined more in the exercise than control leg. Across the entire proximal femur, cortical mass surface density increased significantly with exercise (2.7%; $P<0.001$), with larger changes (>6%) at anterior and posterior aspects of the femoral neck and anterior shaft. Endocortical trabecular density also increased (6.4%; $P<0.001$), with localised changes of >12% at the anterior femoral neck, trochanter and inferior femoral head.

Odd impact exercise increased cortical mass surface density and endocortical trabecular density, at regions that may be important to structural integrity. These exercise-induced changes were localised rather than being evenly distributed across the proximal femur.

Introduction

Hip fractures are a major public health problem among older adults, incurring high economic and social costs (1). Low femoral neck areal bone mineral density (aBMD) is a strong predictor of hip fracture incidence (2-3), but the distribution of bone is also important in determining its strength and resistance to fracture (4-7). With increasing age, cortical thinning and trabecular loss may proceed at different rates, and differ in magnitude amongst localised regions of the proximal femur (8-12). Localised cortical thinning has been associated with an increased risk of hip fracture (13) and trabecular loss has been found in hip fracture cases (14). Consequently, interventions that target bone at regions susceptible to localised weakness may produce greater reductions in hip fracture incidence than could be expected from the changes in aBMD alone.

Exercise is a simple lifestyle approach that may produce localised adaptations in bone. In the femoral neck, simulations indicate that exercise can induce bone formation (15). In animal models, site-specific loading has been reported to stimulate large increases in bone strength despite small changes in BMC (16-19), which may suggest a redistribution of bone mineral to localised regions where mechanical demands are greatest. The distribution of cortical bone at the femoral neck differs between athletes from different sports (20) and clinical trials have demonstrated that exercise can differentially affect cortical and trabecular bone at the radius and tibia (21-22), although fractures at these skeletal sites are much less frequent and have fewer long-term consequences compared to the hip. One previous study of a short-term exercise intervention (~16 weeks) has quantified cortical and trabecular changes at the proximal femur using quantitative computed tomography (CT) in young adults (23).

It is particularly important to determine whether exercise can affect the amount and distribution of cortical and trabecular bone in older people, who may have already experienced the cortical thinning and trabecular loss that may predispose to hip fracture. The

Hip-Hop study (24) demonstrated that short bursts of daily hopping exercises increased DXA-derived aBMD and bone mineral content (BMC) at the femoral neck in a randomly assigned exercise leg compared to a control leg in older men. This hopping programme provides high- and odd- impact loading, with similar characteristics to the training associated with cortical thickening at the femoral neck in athletes (20). We now aim to discover the effects of this hopping exercise programme on BMC and 3D distribution of cortical and trabecular bone throughout the entire proximal femur. We hypothesised that the hopping exercises would increase cortical and trabecular bone mass with localised variation in bone gains across the proximal femur.

Methods

Study design

The study was designed as a randomised controlled trial of a 12-month unilateral exercise intervention, where changes in a randomly allocated exercise leg were compared to those in a control leg of the same participant (24). Leg allocation was randomised by the researcher who recruited participants and administered the exercise intervention using minimisation. Randomisation was conducted by participants selecting a card indicating the exercise leg (right or left side) from opaque sealed envelopes. Right and left sides were allocated, irrespective of limb dominance. All participants were asked to perform a programme of hopping exercises on their randomly assigned exercise leg only and to avoid any other changes to their physical activity or dietary habits during the trial. The primary outcome measure was integral BMC (g) and the secondary outcome measures were cortical and trabecular BMC (g) assessed by CT. Clinical CT scans were performed by radiographers blind to the leg allocation before (pre-intervention) and after (post-intervention) the exercise programme. CT scans were then analysed in a blind-to-treatment manner. A 7-day food diary,

and health and physical activity questionnaires, were completed pre-intervention. Anthropometric measurements, and body composition assessment by dual-energy x-ray absorptiometry (DXA), were taken pre-intervention and repeated post-intervention (24). The study was registered on a clinical trials database (clinicaltrials.gov; CTR number: NCT02007460) and the trial was approved by the National Research Ethics Service and the Loughborough University Ethical Advisory Committee.

Participants

Participants were healthy community dwelling men of white European origin, aged between 65 and 80 yrs, with no recent involvement in exercise (strength, power or weight-bearing endurance) for more than 1hr/wk and had no diagnosed or symptomatic diseases likely to influence bone, neuromuscular function or ability to perform exercises. Assuming a comparable effect size as seen in femoral neck aBMD in a previous unilateral hopping intervention study in premenopausal women (25) we estimated that a sample size of 30 participants would be needed to yield a statistical power of 80% at 95% significance levels. One hundred and twenty-five older men were screened via telephone, and of these, seventy-five men were excluded, as described previously (24). The men were recruited from the local community from the area around Loughborough, UK, from March to June 2010. All participants provided written informed consent. Pre-intervention measurements were conducted between June to September 2010 and post-intervention measurements between June to September 2011.

Prescribed exercise programme

All men were asked to participate in a home-based impact exercise intervention. "Impact exercise" may be defined as activities that take advantage of the body mass impacting the ground to generate gravitational and musculoskeletal loading. The unilateral impact exercises prescribed in this study elicited vertical ground reaction forces during landing of 2.7 body

weight, which increased to 3.0 times body weight after 6-months of exercise (24). A full description of the impact exercise programme has been reported previously (24). Briefly, each training session lasted approximately 10 minutes and consisted of short bursts (five sets of 10 hops, with 15 second rest between each set) of unilateral hopping exercises that were performed in a variety of directions (vertical, anterior-posterior, medio-lateral and rotational hops). Participants were asked to perform the hopping exercises as high and fast as they could on a hard, even surface in barefoot and when another person was nearby. This programme design was based on evidence originating from loading models in animals that demonstrate rapidly applied, high intensity unusually-distributed strains, interspersed with short regular rest periods, produce a maximal osteogenic response in bone at the site experiencing strain in a short duration (26-28). The multidirectional hopping exercises were intended to provide unusual and variably distributed strains (compression, bending, twisting) distributed across a greater proportion of the femoral neck than predominantly vertical high impact exercise such as vertical jumping. The progression of the 12-month impact exercise programme was individualised according to each participant's exercise tolerance and ability. To monitor progression and safety, participants were also asked to attend supervised training sessions at Loughborough University (in groups of five to six participants) each week for the first month of the training and every three months thereafter. The amount of training completed, occurrence of injuries and/or adverse events were noted in a training log book over the 12 month period.

CT image acquisition

Pre- and post-intervention scans were performed on a high resolution, 64 slice CT scanner (Aquilion^{TM}, Toshiba Medical Systems Corporation, Tokyo, Japan) at University Hospitals Leicester, UK. Scans were performed with a table height of 74 cm at 120 kV and with a tube

current of 70 to 200 mA, depending on the height and weight of participants. Participants were positioned supine on the scanner table, lying on top of a solid calibration phantom (Mindways) and bolus bags, which were placed from the lumbar vertebrae to the femoral shaft. To standardise placement of the proximal femur pre- and post-intervention, participants' knees were positioned with 10^{o} of knee flexion and their legs and feet were medially rotated by 15º and secured to a foot positioning block with Velcro straps, as used for DXA scan proximal femur positioning. All scans were acquired from 2 cm superior to the highest point of the acetabulum to 2 cm inferior to the lesser trochanter with a detector collimation of 64 x 0.5 mm and a gantry rotation time of 0.5 s in helical acquisition mode. The pitch was set at 0.828 (helical pitch 53) and the scan field of view was 500 mm with a 256 x 256 matrix. The helical image data was reconstructed at 2 mm slice thickness with 2 mm intervals, using the body reconstruction kernel FC13 for optimum spatial resolution and a 380 mm reconstructed field of view. Quality assurance (QA) scans were performed with a solid phantom (Mindways QA Model 3, Mindways Software Inc, Austin, USA) on each day when study measurements took place to monitor the CT scanner performance characteristics during the study period**.**

Cortical, trabecular and integral BMC and biomechanical variables

QCT-Pro Software Version 4.2.3 (Mindways Software Inc, Austin, USA) was used to analyse participant pelvic CT scans and the CTXA-Hip analysis estimated cortical, trabecular and integral mineral mass (BMC; g at traditional regions of interest within the proximal femur (femoral neck, trochanter and inter-trochanter sites). CTXA-Hip analysis was performed according to the QCT-Pro instruction manual (version 4.2.3) and involved the following automated steps, i) extraction of the proximal femur and ii) rotation and segmentation of bone voxels from soft tissue in three planes (axial, sagittal and coronal). Pre- and post-intervention scans were analysed together to ensure consistent positioning between scans. For each scan at

each time point, a fixed threshold (450 mg/cm^3) was used to delineate cortical from trabecular bone. QCT-Pro Bone Investigational Toolkit version 2 (Mindways Software Inc, Austin, USA) was then used to estimate biomechanical variables, including cross-sectional area (CSA; cm^2), the minimum and maximum cross-sectional moment of inertia (CSMImin and CSMImax; cm^4) and buckling ratio (BR) at the mid femoral neck, located where eccentricity (ratio of lengths of major and minor principal axes) was 1.4.

Distribution of cortical and trabecular bone across the proximal femur

Cortical Bone Mapping (29) was applied to each CT scan to display local, pointwise measurements of the thickness (mm) and mass surface density (the mass of bone per unit surface area at each point on the cortex; mg/cm^2) of cortical bone and the density (mg/cm^3) of endocortical trabecular bone, as a colour map over each participant's 3D bone surface, with several thousand independent measures across each proximal femur. A single value of average cortical density (mg/cm^3) was estimated for the whole proximal femur (29), by reference to the calibration standards in the Mindways phantom, converting Hounsfield Units into mg/cm^3 of bone. The process of measuring cortical thickness, mass surface density and endocortical trabecular density at every vertex on a 3D bone surface has been described in detail previously (29-32). In brief, this procedure involved segmentation of each femur using Stradwin software (Treece, Gee, Cambridge UK) to create a 3D surface rendered image, followed by registration of each proximal femur to an average right canonical proximal femur model. Each participant's map from the post-intervention scan was subtracted from his own pre-intervention bone map to give a difference map for each leg (EL and CL). Statistical parametric mapping was used to find and quantify where the cortical mass surface density, thickness and endocortical trabecular density differed pre and post-intervention.

Statistical analysis

Statistical analysis for anthropometric (height, body mass, BMI) and QCT-Pro derived variables was conducted using PASW Statistics (21.0; SPSS Inc, Chicago, IL, USA). Paired t-tests were used to determine differences pre and post-intervention for anthropometric variables. Two-way repeated measures analysis of variance (RM-ANOVA) was used to examine the influence of the hopping exercise programme on natural log transformed data for QCT-Pro derived variables over time (pre vs. post); between legs (exercise leg [EL] vs. control leg [CL]) and to detect leg × time interactions. Repeated measures multivariate analysis of variance (RM-MANOVA) was used to determine whether exercise effects differed according to hip site over time (leg × time × site [femoral neck, trochanter, inter-trochanter] interactions). For variables derived from Cortical Bone Mapping, Surfstat (http://math.mccgill.ca/keith/surfstat/33) was used to test whether the difference value at each vertex was significantly different from zero using a fixed-effects general linear model. Paired t-tests were calculated to test the significance of differences pre and post-intervention and any difference between legs. Results for cortical and endocortical trabecular bone mapping variables are expressed either as an absolute measure or as a percentage change of the pre-intervention value. For all statistical analysis, the significance level was set at $P<0.05$.

Results

Intervention adherence and physical characteristics

Fifty men completed pre-intervention assessments and commenced the intervention. Fourteen (28%) withdrew from the study because of health problems or injuries unrelated to the intervention (n=9), time commitments (n=2) or musculoskeletal discomfort during exercise (n=3) (24). Two participants' CT scans were affected by movement or other artefact and were

therefore excluded from further analysis. Data were analysed for the remaining thirty-four men, who completed 92% of prescribed sessions (mean (SD) 308 (30) sessions out of the 336 prescribed sessions). Pre-intervention, the men reported completing 1.9 (2.0) hrs/wk current physical activity, and consuming a dietary intake of 3.1 (1.7) µg/d dietary vitamin D and 1065.8 (261.8) mg/d calcium.

There were no significant changes pre- to post-intervention for height [175.0 (6.2) vs. 174.9 (6.1) cm, paired t-test, P=0.603), body mass [80.0 (8.2) vs. 79.8 (7.8) kg, paired t-test, P=0.667) or body mass index [26.1 (2.3) vs. 26.1 (2.2) kg/m^2, paired t-test, P=0.913). There were no significant differences between physical characteristics (height, body mass, BMI) for the men that withdrew from the study (n=16, including those missing CT scans) and those that completed the trial (n=34) (paired t-test, $0.145<P<0.365$).

Cortical, trabecular and integral BMC and biomechanical variables

At femoral neck, trochanter and intertrochanter sites, both cortical and trabecular BMC increased significantly over time in each leg, leading to a statistically significant increase in integral BMC at each region of the proximal femur (all $P<0.05$ for time factor in RM-ANOVA; Table 1, Figure 1).

At the trochanter, cortical BMC increased significantly more in the EL compared to CL (net benefit in exercise relative to control leg of 12.6%), although the increase in trabecular BMC did not differ significantly between legs (net benefit 1.2%). This contributed to a significant increase in integral BMC at the trochanter (net benefit of 4.0%; RM-ANOVA interaction; P=0.004; Table 1, Figure 1).

At the intertrochanter and femoral neck sites, the net benefits in the exercise relative to the control leg were smaller (changes in cortical, trabecular and integral bone mineral masses were +0.9, -2.1 and -0.1% at intertrochanter and +0.6, -1.3 and +0.5% at femoral neck) and

did not differ significantly between exercise and control legs (leg x time interaction $P>0.05$; Table 1, Figure 1).

When effects were compared between sites (femoral neck, trochanter, inter-trochanter) by RM-MANOVA, an overall exercise effect was evident for cortical BMC (significant leg x time interaction, $P=0.041$), which differed according to site (leg × time x site, $P=0.003$). There were no overall exercise effects for trabecular (leg × time, $P=0.455$), or integral BMC (leg ×, $P=0.185$) and consequently no effects between sites (leg x time x site, $P>0.05$).

The effects of the exercise intervention on biomechanical variables of femoral neck strength are shown in Table 1. Buckling ratio decreased significantly more in the EL (-8.3%) than the CL leg (-4.6%) (RM-ANOVA interaction, $P=0.014$; Table 1) and there were significant changes over time for all other biomechanical variables (Table 1). CSMImax, CSMImin and CSA increased by 2.4%, 1.7% and 2.0% in the EL and by 0.9%, 3.1% and 2.1% in the CL.

Distribution of cortical and trabecular bone across the proximal femur

Overall proximal femur averages for cortical mass surface density, cortical density and endocortical trabecular density increased significantly after the 12-month exercise programme in both legs. The average increase in cortical mass surface density across the entire proximal femur was 2.7% (+4.5(1.3) mg/cm^2, $P<0.001$) in the exercise leg and 1.6% in the control leg (+2.8(1.4) mg/cm^2, $P=0.002$), yielding a net benefit of 1.1% ($P=0.007$).

Statistically significant increases in regional cortical mass surface density were also apparent. The increases in cortical mass surface density varied across the proximal femur, with substantially larger increases (over +6%) evident at localised regions of the exercise leg: inferoanterior and superoposterior aspects of femoral neck and anterior aspect of intertrochanter region (Figure 2A). The control leg showed statistically significant increases in cortical mass surface density at the inferoanterior and posterior femoral neck, the anterior

aspect of the intertrochanter region and the lesser trochanter (Figure 2A), although changes were smaller in magnitude than those in the exercise leg.

Cortical density increased by 1.8% (P=0.0001) in the exercise leg and 1.6% (P=0.001) in the control leg, although the net benefit of 0.1% did not differ significantly between legs (P=0.776). Cortical thickness increased by 0.5% in the exercise leg and decreased by 0.2% in the control leg, although these changes were not statistically significant (P=0.24 and 0.57 respectively) and the net difference between legs (0.8%) was not statistically significant (P=0.127).

The average density of the endocortical trabecular layer increased across the entire proximal femur by 6.4% (+9.8(3.1) mg/cm^3, paired t-test, P<0.001) in the exercise leg and 4.5% (+6.5(paired t-test, P<0.001) in the control leg, with the net benefit of 1.9% being statistically significant (P=0.019).

The changes in endocortical trabecular density were also varied across the proximal femur in the exercise leg, up to 12% (Figure 2B). The largest relative percentage increases in endocortical trabecular density in the exercise leg (over +12%) were at the inferoanterior aspect of the femoral neck, the anterior aspect of the greater trochanter and the inferior of the femoral head, and increases of up to 6% were also evident at the lateral shaft (Figure 2B). The control leg also showed some statistically significant increases in endocortical trabecular density at similar regions, although these affected a much smaller proportion of the proximal femur (Figure 2B).

Discussion

This is the first randomised controlled trial using clinical CT to investigate the longitudinal effects of exercise on the mass and 3D distribution of cortical and trabecular bone across the proximal femur. We discovered that cortical and trabecular BMC increased at the trochanter, femoral neck and intertrochanter during the study. Cortical BMC at the trochanter increased

more in the exercise leg than control leg, whilst femoral neck buckling ratio declined more in the exercise than control leg. Across the entire proximal femur, cortical mass surface density and endocortical trabecular density increased significantly with exercise, with larger localised changes evident in some localised regions. We therefore demonstrated that 12-months of very brief (~3 minutes) hopping exercises produced varied and focal changes in cortical and trabecular bone throughout the proximal femur as well as changes in biomechanical properties of bone strength at the mid femoral neck.

Substantial cortical bone adaptation was evident during the hopping intervention. The relative magnitude of the exercise-induced increases in cortical BMC were proportionally greater than those found for trabecular BMC. Cortical and integral BMC at the trochanter, and across the proximal femur, increased significantly more in the exercise leg than the control leg, and cortical bone mass surface density responses differed substantially across the proximal femur. Since we did not detect significant changes in cortical thickness or cortical density, we cannot determine whether the increase in focal cortical mass was due to thickening of the cortex or by infilling of cortical pores. At the femoral neck, the increase in cortical mass surface density we found after 12 months of very brief exercise (over 6%) was of a similar magnitude to the increase previously reported following 36 months of treatment with Denosumab (4-5%) (28), suggesting that exercise could produce localised changes in cortical bone at key regions of proximal femur that are at least of comparable magnitude as pharmaceutical treatment.

We also found that buckling ratio decreased significantly more in the exercise than control leg at the femoral neck, although increases in cortical and trabecular masses and cross-sectional area did not differ significantly between legs. That buckling ratio should increase more in one leg than the other, when both showed similar increases in mass implies a redistribution of bone. Cross-sectional moment of inertia increased over time which may also

imply a redistribution of bone at the femoral neck and this finding is consistent with our findings from DXA (24). The cortical mass maps demonstrated that there was indeed substantial regional variation in cortical mass surface density. Our findings are important because previous studies using clinical CT have shown women with femoral neck fractures have a lower bending strength and higher buckling ratio than controls (34), so this redistribution of bone may reflect increased bone strength and reduced fracture risk.

There was substantial regional variation in bone changes following exercise. At the femoral neck, we discovered particularly large increases in cortical mass surface density and endocortical trabecular density at the inferoanterior aspect (over 6% and 12%, Figures 2) and the superoposterior aspect (over 6% and 10%, Figures 2). Clear visual differences between the exercise and control leg were also evident at these sub-regions (Figures 2). With ageing, substantial declines in cortical thickness and trabecular density occur in the superoposterior region (10-12) which compromises the femur's capacity to resist fracture in a sideways fall (35-36). Thinning of the superolateral cortex has been associated with femoral neck fracture (13) and trabecular weakness in the superior region has been reported in femoral neck fracture cases (14). Our findings suggest that these regional age-related effects may be counteracted by targeted exercise which could reduce risk of fracture.

After 12 months of exercise, we also found large focal increases in cortical mass surface density (over 5%) at the posteromedial conjunction of the femoral neck and shaft, i.e. the calcar femorale. This finding may potentially have clinical importance because the calcar femorale is a fundamental anatomical structure for the proximal femur that increases its mechanical strength (37) by bearing compression load and redistributing stress (38) and thus may also be important in fracture risk (39). Increased trabecular density was also evident at the inferior aspect of the femoral head, whose trabecular density contributed most strongly to hip fracture discrimination in vivo (40).

Most studies regarding hip fracture risk have focused on cortical bone in the femoral neck sub regions, but recent evidence has shown that trabecular bone loss in hip fracture patients occurs not only at femoral neck but also expanded to the intertrochanteric region (41-42) which is a region of the proximal femur that is rich in trabecular bone. We detected substantial changes in endocortical trabecular density in the lateral trochanteric region (between 10-13%) with exercise, but little change in cortical mass surface density at this site. Our demonstration of these endocortical trabecular responses to exercise suggests that exercise induced bone adaptations may reduce risk of trochanteric and femoral neck fractures.

Overall trabecular BMC changes (as assessed by analysis of trabecular BMD by Mindways software) did not differ significantly between legs, although the endocortical trabecular density (as assessed by cortical bone mapping) increased more in the exercise than the control leg. This discrepancy between the two trabecular bone measures most likely reflects the different volume assessed and may possibly suggest a redistribution of trabecular mass with exercise. The bone mapping demonstrated substantial variation in endocortical trabecular density changes. The greater cortical (and endocortical trabecular) response may reflect adaptation to increased strain distributed primarily through the cortex and endocortical layer of trabecular bone, or a shorter remodelling cycle in cortical bone (median of 120 days) (43) than in trabecular bone (up to 2 years).

Cortical and trabecular BMC increased at the trochanter, femoral neck and intertrochanter over time in both legs. The increase in the control leg was not detected by DXA (24) whereby there was no increase aBMD and BMC of the femoral neck, whilst increases in means at trochanter and total hip sites were not statistically significant. It is possible that CT provides greater power than DXA to detect localised changes in bone. The increases in control leg BMC may have been due to "cross-education"; a neurophysiological phenomenon whereby

muscular strength gains can occur in the opposite, untrained limb following unilateral training, which may have contributed to greater bone mass. However, there was no evidence of increased lean mass in either leg by DXA. Alternatively, training of one limb may have increased the impact forces imposed on the contralateral limb during habitual activities such as stair ascent/descent. A further explanation is that participants may have increased physical activity.

The response of bone to exercise is dependent upon the mechanical loads (i.e. strains) imposed upon it from the activity (44). The hopping exercises in our study incorporated a variety of multidirectional movements that were designed to distribute a variation of stresses and strains throughout the proximal femur. Large increases in cortical and trabecular bone were discovered in key locations throughout the proximal femur, suggesting that the multidirectional hopping exercise were effective at modulating the strain distributions more widely than in those regions (i.e. inferior femoral neck) which typically experience a high amount of loading during habitual activity such as walking. Noticeably, some of the localised gains coincided with attachment points (namely the lateral facet and anterior border of the greater trochanter and lesser trochanter) of the primary hip abductors (gluteus medius), extensors (gluteus minimums) and primary hip flexors (iliopsoas) and studies comparing impact exercises have shown that the gluteal muscles are most activated during multidirectional single legged hops (45). Therefore, compression and/or tensile stresses generated through skeletal muscle contraction as well as ground impact may have contributed to the localised bone gain on cortical and trabecular surfaces.

Individuals who take part in regular exercise have substantially reduced fracture risk (46), despite only modest effects of exercise on aBMD. Our findings of localised skeletal adaptations to exercise suggests that specific exercises designed to target regions important to structural integrity could increase bone strength disproportionately more than aBMD and

could further explain the lower fracture risk in exercisers. Thus, previous exercise studies using aBMD as the main outcome measurement may have underestimated the changes in bone strength that occurred with exercise. Current exercise guidance for bone health e.g. the American College of Sports Medicine (47) is based on findings from intervention studies that have measured aBMD. However, exercise that is most effective for increasing aBMD may not necessarily be the most effective exercise for targeting other important biomarkers of bone strength such as cortical and/or trabecular structures. Our findings highlight the importance of using 3D scanning technologies in future trials for identifying localised structural changes in both cortical and trabecular bone compartments, to determine the optimal training components (i.e. type, intensity, frequency and duration) of exercise for increasing bone strength and resistance to fracture. Application of modelling techniques such as finite element analysis to 3D CT data would add important information about the stresses and strain distributions (e.g. compression, tension) experienced on the proximal femur from exercise and ultimately help with this endeavour.

Currently the lack of persistence with exercise over a period of years is a major problem for exercise invention trials in bone health research. In older adults, exercise induced changes in bone mass and structure seem to be largely dependent on continued compliance and ability to maintain sufficient exercise intensity (48). In the current study, adherence to the exercise programme was 92% which suggests that short bursts of high intensity exercise (home-based) was not only effective for producing localised changes in cortical and trabecular bone compartments, but, importantly, was also feasible for this group of healthy older men to continue with in the longer term.

There are strengths and limitations to this work. A major strength was using 3D scanning technologies and computational anatomy techniques to provide a detailed delineation of exercise effects on the distribution of mass and cortical and trabecular bone throughout the

proximal femur; effects that would have otherwise been overlooked by DXA. A limitation is that we did not include an independent control group, as changes in a control leg did not differ significantly from changes in an independent control group in our previous study in premenopausal women (25); however increases in the control leg were evident in this study. A further limitation is that we did not objectively assess physical activity or estimate dietary habits after the intervention, so we are unable to quantify any changes in these factors but we requested that participants maintained their normal habits during the trial. The benefits of exercise in the control leg, the relatively small sample size and subsequent high variability may have confounded our ability to find some statistically significant changes in the exercise leg relative to control. The study was conducted in healthy older men so findings may be less generalizable to other groups, for whom the exercise prescription may need modification.

In conclusion, we discovered that short bursts of regular hopping exercises increased cortical mass surface density and endocortical trabecular density throughout the proximal femur (12 months). These exercise induced changes were varied across the proximal femur, but included some substantial localised adaptations at regions that may be important to structural integrity and hip fracture risk. Therefore, exercise that targets localised cortical and/or trabecular regions of the proximal femur could produce greater increases in bone strength and resistance to fracture than would be expected from areal BMD.

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Figure Legends

Figure 1 Changes in integral, trabecular and cortical bone mineral content of the exercise leg (EL) and control leg (CL) during the 12 month hopping intervention. Values are median±interquartile range.

* RM-ANOVA of log transformed data revealed a difference in response between legs for cortical BMC (significant leg x time interaction, *P*=0.041).

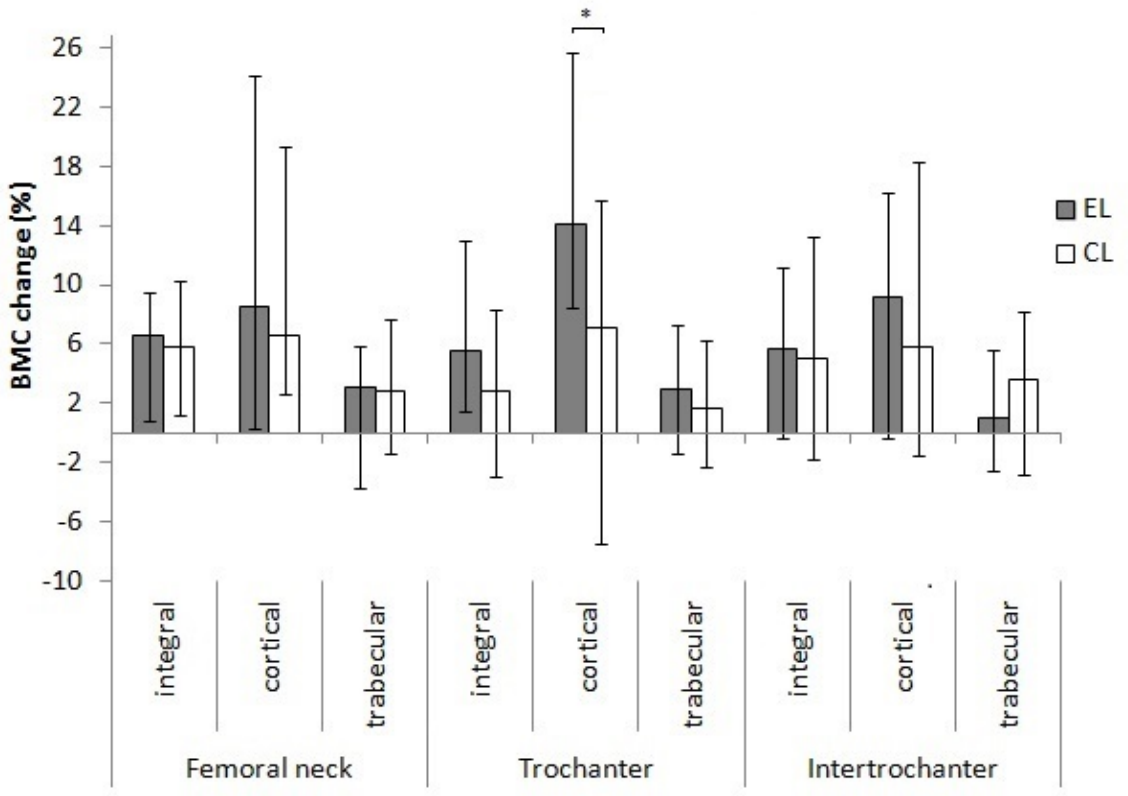

Figure 2 Changes in cortical surface mass density (A) and endocortical trabecular density (B) in the exercise leg and control leg. Data are expressed as a percentage change from pre-intervention values. 3D colour maps are displayed across an average right proximal femur in anterior, posterior and inferior anatomical views. Areas where there were no statistically significant changes are shown in the grey colour.

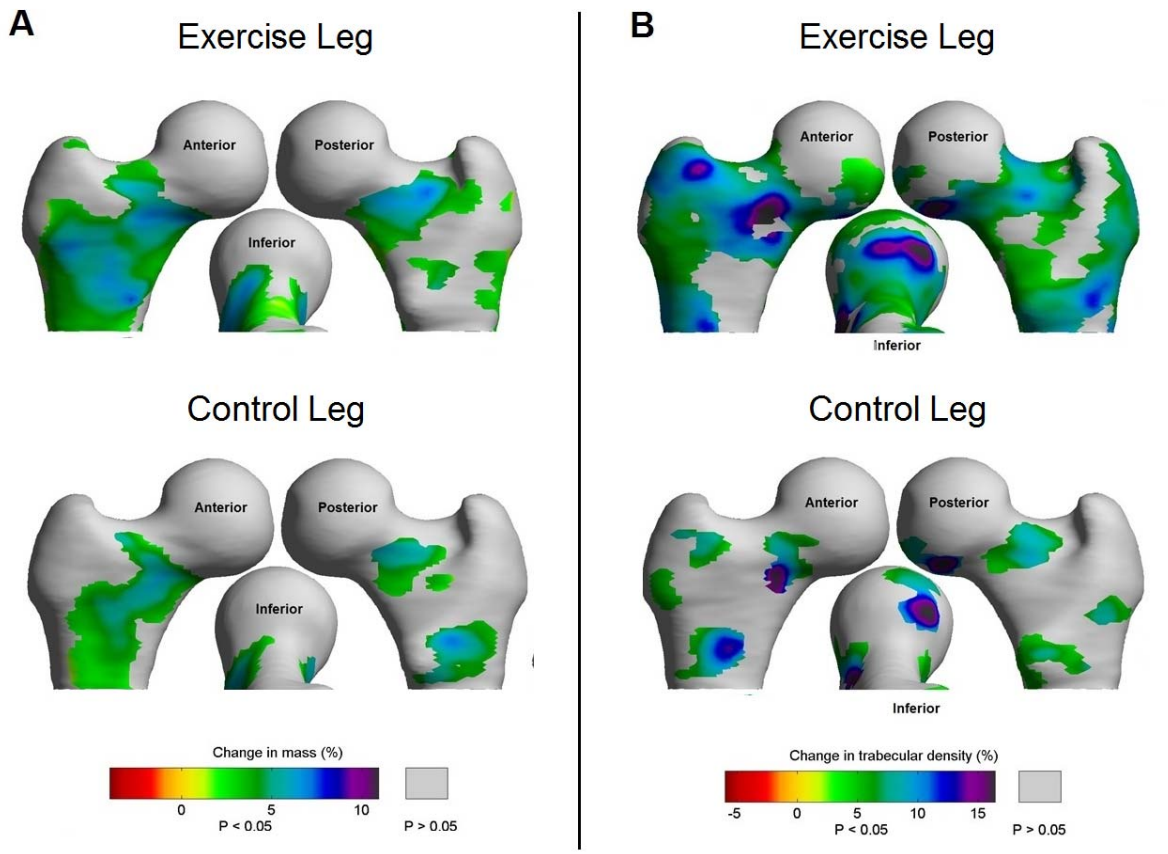

Table 1 Proximal femur cortical and trabecular bone mineral mass and biomechanical variables in the EL (n=34) and CL (n=34) before and after the exercise programme. Data are expressed as mean (95% CI).

	EL (n=34)		CL (n=34)		P value from RM-ANOVA		
	Pre	Post	Pre	Post	Time	Leg	Leg x Time
Trochanter							
Cortical BMC (g)	2.37 (2.01-2.80)	2.74 (2.32-3.24)	2.55 (2.18-2.98)	2.63 (2.20-3.14)	0.000	0.606	0.001
Trabecular BMC (g)	6.53 (6.19-6.89)	6.76 (6.38-7.17)	6.58 (6.21-6.98)	6.73 (6.29-7.21)	0.005	0.961	0.434
Integral BMC (g)	9.04 (8.40-9.72)	9.66 (8.93-10.45)	9.25 (8.58-9.98)	9.50 (868-10.40)	0.000	0.832	0.004
Intertrochanter							
Cortical BMC (g)	12.20 (11.06-13.46)	13.26 (12.00-14.65)	12.09 (11.00-13.29)	13.03 (11.88-14.29)	0.000	0.585	0.813
Trabecular BMC (g)	8.29 (7.83-8.77)	8.40 (7.91-8.93)	8.15 (7.64-8.70)	8.43 (7.89-9.00)	0.016	0.599	0.239
Integral BMC (g)	20.61 (19.14-22.19)	21.79 (20.15-23.57)	20.36 (18.87-21.96)	21.55 (19.97-23.27)	0.000	0.529	0.951
Femoral Neck							
Cortical BMC (g)	1.89 (1.72-2.08)	2.08 (1.86-2.33)	1.90 (1.71-2.11)	2.08 (1.87-2.33)	0.000	0.935	0.852
Trabecular BMC (g)	2.44 (2.31-.2.58)	2.49 (2.36-2.62)	2.40 (2.24-2.58)	2.48 (2.32-2.64)	0.001	0.588	0.565
Integral BMC (g)	4.37 (4.11-4.65)	4.63 (4.35-4.93)	4.37 (4.11-4.65)	4.61 (4.28-4.96)	0.000	0.826	0.705
Mid Femoral Neck Geometry							
BR	13.7 (12.4-15.1)	12.5 (11.3-13.9)	13.6 (12.3-15.0)	12.9 (11.6-14.4)	0.000	0.587	0.014
CSMImin cm^4)	12.8 (11.8-13.8)	13.0 (12.0-14.1)	12.5 (11.6-13.4)	12.8 (11.9-13.9)	0.004	0.326	0.251
CSMImax (cm^4)	15.9 (14.7-17.1)	16.3 (15.1-17.5)	16.2 (15.0-17.4)	16.3 (15.1-17.7)	0.037	0.616	0.154
CSA (cm^2)	12.4 (12.0-12.8)	12.6 (12.2-13.0)	12.4 (12.0-12.8)	12.6 (12.2-13.1)	0.000	0.999	0.819

EL (exercise leg), CL (control leg), BR (buckling ratio), CSMI (cross section moment of inertia), CSA (cross-section area)