Title: Optimum frequency of exercise for bone health: randomised controlled trial of a high-impact unilateral intervention.

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ABSTRACT

Introduction: Exercise can increase bone strength, but to be effective in reducing fracture risk, exercise must be feasible enough to be adopted into daily life and influence potentially vulnerable skeletal sites such as the superolateral cortex of the femoral neck, where thinning is associated with increased fracture risk. Brief, high-impact exercise increases femoral neck bone density but the optimal frequency of such exercise and the location of bone accrual is unknown. This study thus examined 1) the effectiveness of different weekly frequencies of exercise on femoral neck BMD and 2) whether BMD change differed between hip sites using a high-impact, unilateral intervention.

Methods: Healthy premenopausal women were randomly assigned to exercise 0, 2, 4, or 7 d/week for 6 months. The exercise intervention incorporated 50 multidirectional hops on one randomly selected leg. BMD was measured by DXA at baseline and after six months of exercise. Changes in the exercise leg were compared between groups using ANCOVA, with change in the control leg and baseline BMD as covariates. RM-MANOVA was conducted to determine whether bone changes from exercise differed between sites.

Results: 61 women (age 33.6 ± 11.1 years) completed the intervention. Compliance amongst exercisers was 86.7±10.6%. Peak ground reaction forces during exercise increased from 2.5 to 2.8 times body weight. The change in femoral neck BMD in the exercise limb (adjusted for change in the control limb and baseline BMD) differed between groups (p=0.015), being -0.3 (-1.2-0.6), 0.0 (-1.0-1.0), 0.9 (-0.1-2.0) and 1.8 (0.8-2.8) % in those exercising 0, 2, 4 and 7 days per week respectively. When BMD changes at upper neck, lower neck and trochanter were compared using RM-MANOVA, a significant exercise effect was observed (p=0.048), but this did not differ significantly between sites (p=0.439) despite greatest mean increases at the upper femoral neck.

Conclusions: Brief, daily hopping exercises increased femoral neck BMD in premenopausal women but less frequent exercise was not effective. Brief high-impact exercise may have a role in reducing hip fragility, but may need to be performed frequently for optimal response.

KEY WORDS:

Bone mineral density

Femoral neck

Exercise

Osteoporosis prevention

Premenopausal women

INTRODUCTION

It is estimated that one in five men and one in two women in the U.K. over 50 years of age will suffer an osteoporosis-related fracture in their lifetime [1] and the annual cost for all fractures in the U.K. is £1.5 billion [2]. Regular exercise can improve bone mineral status and neuromuscular competency, thus reducing predisposition to falls and fractures [3]. However, not all exercise is effective, so a prescription in terms of optimal type, intensity, duration and frequency is required. Findings in animal models suggest that loading that is high in magnitude, rapidly applied and novel is most effective [4-6], whilst duration is less important beyond a threshold number of cycles [7, 8]. Studies comparing different athletic populations suggest that those who participate in high- or odd-impact sports have higher bone mineral density (BMD) [9, 10], whilst previous intervention studies have demonstrated that brief but regular impact exercise such as jumping can significantly increase hip BMD [11, 12]. As yet, no study has compared the effectiveness of different weekly frequencies of exercise for maximum bone accrual in humans. Given that the effectiveness of any exercise intervention is limited by compliance, it is of great public health importance to determine the effectiveness of a brief, accessible intervention and how often such a regime must be performed.

Bone strength and fracture risk depends not only upon BMD but also upon the distribution of bone. Section modulus (Z) and cross-sectional moment of inertia (CSMI), measures of bone strength in bending, may theoretically influence fracture risk and were lower in hip fracture cases than controls [13], although cortical thickness and BMD were more predictive of fracture risk [13]. Hip fracture patients have greatest deficits in infero-anterior to supero-posterior axis of the femoral neck [14, 15] and it has been suggested that bone loss in this region may reflect habitual loading patterns, with the activities that persist into older age (e.g. slower walking) loading the inferior rather than superior femoral neck [16, 17]. Cross-sectional studies have demonstrated that athletes who participate in “odd-impact” activities have greater areal BMD, cross-sectional area and section modulus [9] and cortical thickness [18] at the femoral neck. However, differences in athletes participating in different sports may arise from selection bias, so there is a need for intervention studies to determine whether exercise can influence bone at potentially vulnerable sites such as the upper femoral neck.

Studies on exercise effects on bone may be subject to confounding in that groups may differ or change in endocrine status, calcium or other dietary intakes or genotype. A unilateral intervention allows an exercise and a control limb, in which these potential confounders are matched, thus increasing the power of the study and reducing the necessary sample size. Unilateral jumping, i.e. hopping, may be at least as effective as jumping since loading is applied to one leg instead of being distributed between both legs and may thus provide a useful model for studying exercise effects on bone. Furthermore, multidirectional movement may provide the “odd” impacts proposed to thicken the cortex at vulnerable regions of the femoral neck [18].

The main aim of the present study was therefore to investigate the effectiveness of a high-impact, unilateral exercise program on hip BMD in premenopausal women and to determine whether hip BMD response differed according to weekly frequency of exercise. A second objective was to determine whether the exercise-related BMD change differed between different regions of the hip.

MATERIALS AND METHODS

Design

The study was a longitudinal, randomised controlled trial conducted in premenopausal women who were randomly divided (in blocks of 12) into the control group (C) or one of three exercise groups: exercising two (Ex2), four (Ex4) or seven (Ex7) days per week. The exercise program included 50 hops performed 2, 4, or 7 days per week, for 6 months. For logistic reasons it was not possible to blind participants or investigators to participant group assignation. Participants were requested to maintain their usual diet and lifestyle throughout the study. The study was approved by the institution's Ethics Advisory Committee and all participants provided written, informed consent. The primary outcome measure was femoral neck BMD. Secondary outcome measures were BMD, BMC and geometry at other hip sites, ground reaction force and height during both typical and maximal hops. Measurements were made on both sides of the body, where appropriate. To have an 80% power to detect a significant ($p<0.05$) 2.0% difference in response in femoral neck BMD between groups, with an assumed standard deviation of response of 2.0%, we estimated that 16 women were required in each group (64 in total).

Participants

Healthy premenopausal women, able to perform brief high-intensity exercise were recruited on the university campus and in the local community by word-of-mouth, e-mail, advertising posters, and press releases in local newspapers. Volunteers were screened to exclude those younger than 18 years or older than 45 years; those with a body mass index above 30 kg/m^2; those with current or recent (previous 12 months) participation in high-impact or weight-bearing exercise for more than 1h/week; those with current or recent (previous 12 months) medical or surgical problems likely to affect bone metabolism, history of lower limb or back problems; those with low calcium intake (i.e. those avoiding dairy products unless taking calcium supplements); and those who do not have 10-13 menstrual cycles per year (oral contraception use was permitted). Women were also excluded for pregnancy, recent childbirth (previous 12 months), or current or recent (previous 6 months) lactation. The sample size at each stage of the study is traced in the flow chart in Figure 1.

Bone mineral density and geometry

BMD and BMC at both proximal femurs were assessed using dual X-ray absorptiometry (DXA) (*Lunar Prodigy Advance*, GE Lunar). Specific regions of interest of the proximal femur were the femoral neck, upper neck and trochanter. Hip CSMI, minimum neck width and the distance from the centre of gravity to the lateral surface of the femoral neck (y) were estimated using the Advanced Hip Analysis program (version 10.10, *encore 2006* software). Section modulus (Z) was calculated from CSMI divided by y. All scanning and analyses for each participant were performed by the same operator.

Anthropometry

Standing height was measured using a wall-mounted stadiometer and body mass in light indoor clothing was measured using digital scales. Body mass index (BMI) was calculated by dividing body mass by height squared (kg/m^2). Participants were requested to avoid strenuous exercise, alcohol, and caffeine intake during the preceding 12 hours, as well as food and water for 4 hours beforehand, in order to control hydration status.

Ground reaction forces and hop height

Vertical ground reaction forces (GRF) were determined to provide a measure of impact forces during exercise as well as changes in neuromuscular function that may provide objective evidence of compliance. GRF were sampled using a force plate during two tests: a single, maximal, vertical hop and a set of 10 consecutive hops; both performed with countermovement (i.e. preceded by knee flexion). After a demonstration and practice attempt, the highest value from three maximal attempts for each leg was recorded as the test score. For submaximal hopping tests, participants were instructed to *“Hop 10 times as you would perform one set of hopping exercises at home”*.

Force plate data were also used to calculate time of flight. This was used to estimate the height of the hop from the following formula [19]:

$$\text{Height (m)} = 1.226 \times (\text{flight time (s)})^2$$

Questionnaires

At baseline, all participants completed a lifestyle questionnaire regarding calcium intake, menstruation, previous and current physical activity, alcohol consumption, family history of osteoporosis, past fractures, and whether or not they smoked. Dietary assessment involved a food frequency questionnaire (adapted from Yarnell et al. [20]), to assess frequency of consumption of food from a range of food groups; followed by a more specific food frequency questionnaire for calcium intake (adapted from Magkos et al. [21]). At 3 and 6 months exercisers completed an additional questionnaire regarding injury or experience of discomfort and subjective ratings of the intervention.

Exercise intervention

Each training session consisted of several minutes of gentle warm up and mobilisation exercises followed by 5 sets of 10 unilateral propulsive moves (hops) on one limb. The same (randomly assigned) limb was trained for the duration of the study. Hops were performed without shoes on, in a variety of directions: vertically; with anteroposterior movement; with mediolateral movement; and twisting hops (i.e. incorporating rotation). Sets were interspersed with approximately 15 s walking in place. Intensity of the hops progressively increased by encouraging participants to increase hop height and speed over time. Participants chose where and when to do the exercises, and were provided individual training logs to record the amount of exercise completed.

Reproducibility

The reproducibility of all methods described here was determined by repeating measurements on consecutive days in 10 healthy women (age 30.4±7.9 years) who met inclusion criteria but were not taking part in the study. Coefficients of variation (CVs) were calculated as described by Glüer et al. [22].

Statistical analysis

As the aim was to compare effectiveness of different weekly frequencies of exercise, data were analysed for those who completed the intervention, rather than using an intention-to-treat analysis. Differences between groups at baseline were detected using analysis of variance with post hoc Bonferroni tests. Changes in outcome measures were calculated as final value minus baseline value and expressed as a percentage of baseline value. Analysis of covariance (ANCOVA) was conducted to compare changes in bone density in the exercise leg (adjusted for change in control leg and baseline BMD) between groups of differing exercise frequency. To determine whether the exercise effect differed between hip regions of interest, repeated measures multivariate analysis of variance (RM-MANOVA) was conducted on BMD changes, with site (upper neck, lower neck and trochanter), leg (exercise and control) and group (C, Ex2, Ex4 and Ex7) as factors. Changes in GRF and hop height were analysed by repeated measures ANOVA to determine whether mean changes differed between groups or legs (exercise versus control), or whether there was any group x leg interaction. Differences were considered statistically significant at the 95% significance level (p<0.05). Data were analysed using SPSS (*SPSS 16.0 for Windows*, SPSS).

RESULTS

Reproducibility

CVs were 1.4%, 1.8%, 1.3% and 2.3% respectively for femoral neck, upper neck, lower neck and trochanter BMD respectively and 1.7, 2.1, 1.8 and 5.5% for BMC. Corresponding values for Z and minimum neck width were 4.1% and 1.4%. CVs for maximal and submaximal GRF were 23.0% and 8.7% whilst those for maximal and submaximal hop height were 16.5% and 24.6%.

Baseline characteristics, persistence, and compliance

Groups did not differ at baseline (Table 1). The exercise limb was the dominant limb in 38, 52, 61 and 45% of participants in groups C, Ex2, Ex4 and Ex7 respectively.

Persistence rates for C, Ex2, Ex4, and Ex7 were 95%, 76.2%, 59.1%, and 72.7%, respectively (Figure 1). Those who dropped out did not differ significantly from those who persisted in any of the characteristics listed in Table 1. The number of hops completed per week (mean ± SD) was 86±10, 189±23 and 312±37 in groups Ex2, Ex4 and Ex7 respectively, and differed significantly between groups (p<0.001). Compliance to the exercise programme did not differ between groups (*p*=0.25), being 84% (range 65%-100%), 90% (74%-100%), and 86% (65%-97%) for Ex2, Ex4, and Ex7, respectively.

Effects of the exercise intervention on bone variables

Changes in BMD are summarised in Table 2. The change in femoral neck BMD in the exercise limb (adjusted for change in the control limb and baseline BMD) differed significantly between groups in ANCOVA (*p*=0.015), being significantly higher in group Ex7 than in control or Ex2 groups (*p*= 0.003 and 0.015 respectively; Figure 2A). This difference between groups remained statistically significant (*p*<0.05) regardless of whether analyses were conducted on absolute or percentage changes, or with or without baseline BMD included as a covariate.

Of the other hip sites, the highest mean increase in daily exercisers was observed at the upper femoral neck (Table 2, Figure 2B). BMD at this sub region increased more in the exercise than the control leg in group Ex7 (Table 2) although changes in lower neck and trochanter BMD did not differ significantly between groups. When BMD changes were compared between sites by RM-MANOVA, an overall exercise effect was evident (significant leg x group interaction, *p*=0.048) but this exercise effect did not differ significantly according to site (leg x group x site interaction not significant; *p*=0.439).

Changes in femoral and upper neck BMC showed similar trends to those in BMD in Ex7 (there was an increase of 1.2% and 1.8% in the exercise leg vs. a decrease of 0.3% and 0.6% in the control leg in femoral neck and upper neck BMC, respectively).There were no changes in trochanter or lumbar spine BMD or BMC, Z or femoral neck width (Table 2).

Effects of the exercise intervention on body composition and neuromuscular function

Body mass and composition did not change significantly in any group with the mean changes (95% confidence intervals) in body mass being -1.9 (-4.2-0.5), -0.5 (-2.2-1.1), -0.4 (-2.7-1.9) and -0.4 (-2.1-1.4) kg respectively in groups C, Ex2, Ex4 and Ex7. There were some significant changes in hopping performance. The mean height of a set of 10 typical, consecutive hops increased by 44-94% in the exercise leg of exercise groups, with smaller increases in the control limb (22-26%) and control group (9%; Table 3). This change in hop height differed significantly between exercise and control legs ($p<0.001$) and this difference between legs differed between groups ($p=0.01$ for leg x group interaction). The change in *maximal* hop height also differed between legs ($p<0.001$) with increases in the exercise limb of 18-29% in groups Ex2, Ex4 and Ex7, again with no significant change in the control limb or in the control group (mean increases of 3-12 %; Table 3). The change in GRF during a set of 10 hops differed between groups ($p=0.03$) with increases in the exercise leg of around 15% in each of the exercise groups but smaller increases (3-7%) in the control group (Table 3).

DISCUSSION

Brief, high-impact exercise performed daily for 6 months increased BMD at the femoral neck in the exercise relative to the control leg. Less frequent exercise had no significant effect. Our findings are important as this is, to our knowledge, the first time the effects of different weekly frequencies of exercise have been compared in a randomised controlled trial.

Daily exercise increased femoral neck BMD by nearly 2%. This finding is consistent with previous studies where 5-6 months of brief, high-impact jumping exercises produced comparable gains in BMD in premenopausal women [11, 12]. The exercise-related BMD changes did not differ significantly between the hip sites assessed in this study, although the largest proportional change was observed at the upper femoral neck site. It is suggested that inadequate loading of the superior aspect of the femur during habitual activities may contribute to the cortical thinning in this region that is observed in hip fracture cases [17], so this region may be of particular importance. We did not detect any changes in the Z or femoral neck width that may be indicative of periosteal expansion, although the lower precision for Z may have again limited our statistical power to detect change in this variable and the duration of the study may have been too short for any detectable structural adaptation. Whilst exercise increased BMD, we have not found any structural adaptation in this study.

Although high-impact exercise may produce only modest gains in BMD in premenopausal women [23], research in rats has found that such small changes can accompany large increases in ultimate force and energy to failure [24], especially if the bone is added to sites that particularly contribute to bone strength. The intervention was feasible as the program was brief and can be conducted at home without specialist equipment. The majority (73%) of exercisers completed the intervention, completing 87% of the prescribed exercise volume, and it seems likely that bilateral exercise, which would confer greater health benefits, would be more acceptable. Jumping or hopping exercises performed on both legs could therefore have a role in osteoporosis prevention. It may be preferable to start the intervention more progressively as a higher proportion of daily exercisers withdrew citing discomfort during exercise early in the intervention. Furthermore, the high-impact nature of the intervention may need some modification for frail older people in whom there may be a higher risk of injury.

In this study, those randomised to daily exercise showed the greatest improvement in femoral neck and upper neck BMD. The change in femoral neck BMD of the exercise leg (adjusted for change in the control leg) was significantly greater in exercisers training daily than in those exercising twice a week or less. Our findings thus suggest that frequent exercise is most effective for increasing bone density. It is, however, not possible to conclusively determine whether the differences in response in BMD between groups are due to differences in exercise frequency or total volume. Since all exercisers performed the same number of hops per exercise session, the total volume of exercise varied 3.5 fold between daily and bi-weekly exercisers. However, standardising volume would require that some participants completed 175 hops in one session. This may have been unfeasible and would likely be associated with reduced intensity (i.e. lower hop height and hence impact force). Evidence suggests there is a threshold number of loading cycles beyond which there is little additional effect. Although such a threshold has not been determined in humans, the range seems to be between 4 and 36 loading cycles in turkey ulnae [25] and 10 to 20 jumps in rats [8]. As intensity of exercise is a major determinant of bone response [6], we attempted to standardise the intensity by controlling the number of hops per session, rather than standardising the volume by controlling total number of hops in the intervention.

Compliance (as determined by exercise diaries) was similar in the training groups, with mean compliance ranging between 84 and 90% of prescribed hops completed. It thus seems unlikely that differences in compliance between groups may have confounded comparisons of different exercise frequencies. Typical hop height increased from 5 to 7 cm in exercisers. GRF, sampled to provide indirect assessment of the intensity of the loading forces produced by a set of typical hops, were found to be around 2.5 times body weight at baseline, increasing to around 2.8 times body weight post intervention in exercisers, representing an increase of 15%. During a hop these forces are transferred through one leg rather than two, so this may be equivalent to 5-6 times body weight during jumping, equivalent to a drop jump or running at

13 km/h [26]. We could not measure internal strain in the proximal femur during hopping but compressive axial forces at the femur during a jump have been estimated as 2.6-2.9 times the GRF during take-off and 1.4-1.5 times the GRF during landing based on measurements using a femoral implant [27]. The increases in typical hop height and GRF provide objective evidence of compliance to the intervention, as increases were substantially greater in the exercise than control group. Furthermore, they demonstrate the progression of impact forces that is necessary for continued adaptation [3]. Increases in GRF were similar in groups training at different weekly frequencies thus confirming that only frequency and not intensity of exercise differed.

It is possible that greater bone response might have been seen with a longer duration of exercise, as it is suggested that even a year may be inadequate to assess the relationship between mechanical loading and BMD [28]. Since one *sigma* – the complete cycle of activation, resorption, and formation of bone – is approximately 3 to 4 months, the exercise needs to be continued through several sigmas in order to detect changes in BMD using DXA. However, prior high-impact exercise interventions have reported increases in BMD within 6 months in premenopausal women [11, 12] , whilst 12-18 month interventions did not produce significantly greater response [29, 30]. It is possible, however, that the skeletal response might have been slower in the less frequent exercisers (perhaps relating in part to slower progression of exercise intensity) and that effects of less frequent exercise on hip BMD might have been evident with a longer study duration.

The limitations of the study include that the exercise programme was not supervised. The measures of hop height and GRF had poor reproducibility. Groups differed in volume as well as frequency of exercise. The duration was only 6 months and the sample size was selected to detect a change of 2% in BMD, so any smaller magnitude or slower onset benefit of less frequent exercise may not have been detected in this study. Further research is thus needed to compare optimal frequencies of exercise over a longer duration. The major strength of the study is the use of a unilateral design, which reduces the likelihood that findings have been influenced by confounding factors such as changes in diet or habitual activity.

Our findings may have implications for the exercise prescription to optimise bone mass in premenopausal women. The American College of Sports Medicine recommends weight-bearing endurance activities 3–5 times per week and/or resistance exercise 2–3 times per week [3]. In the U.K., exercise that loads muscles and bones is recommended at least twice a week in children with no specific recommendation in adults [31]. Paradigms based on animal studies suggest that more frequent exercise should be more effective [32], and our findings are consistent with more frequent exercise being more beneficial in humans too. Recommendations to incorporate brief exercise that loads bones on most, if not all, days should therefore be considered in order to achieve optimal bone health in premenopausal women.

In conclusion, we have demonstrated that high-impact, unilateral exercise can be used to investigate the effects of exercise on bone. The unilateral design reduced confounding and allowed comparison of different exercise prescriptions in the same study. Brief, multi-directional, high-impact exercise is feasible in premenopausal women and when performed daily can increase BMD at the femoral neck, including the potentially vulnerable upper neck. Less frequent exercise had no significant effect over 6 months. Brief, feasible exercise interventions may thus reduce hip fragility, but may need to be performed frequently for optimal response.

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FIGURE LEGENDS

Figure 1: Diagram showing the flow of participants through each stage of the study

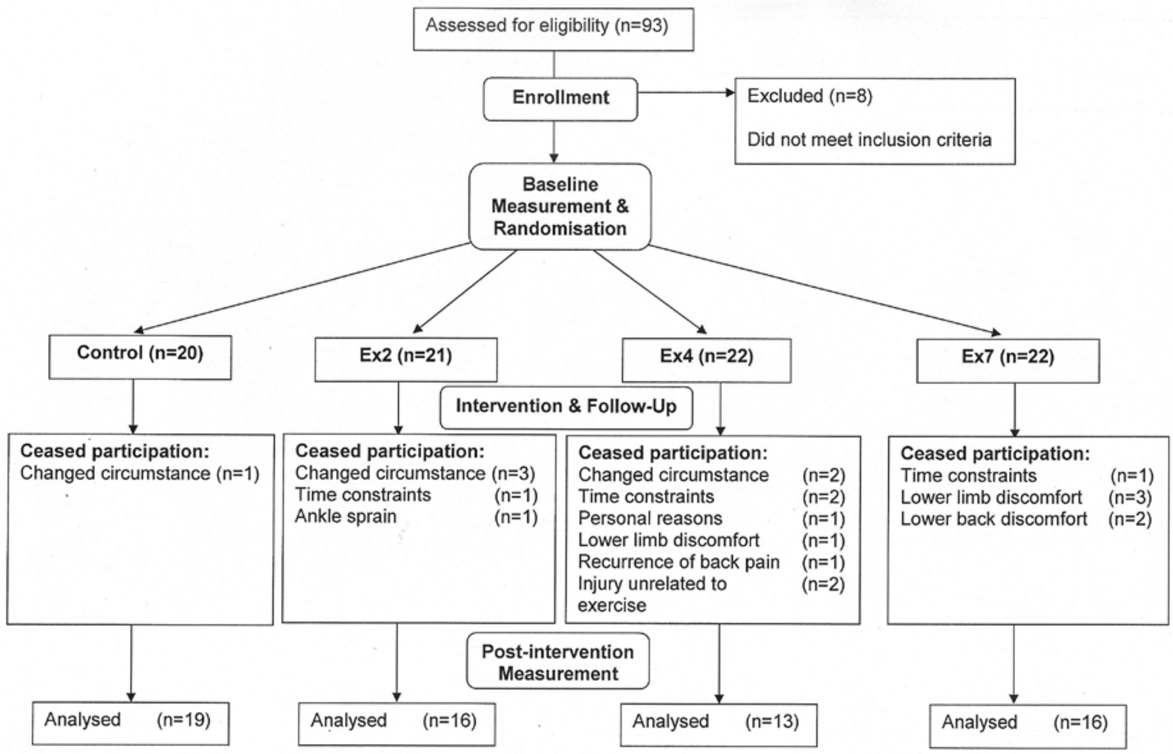
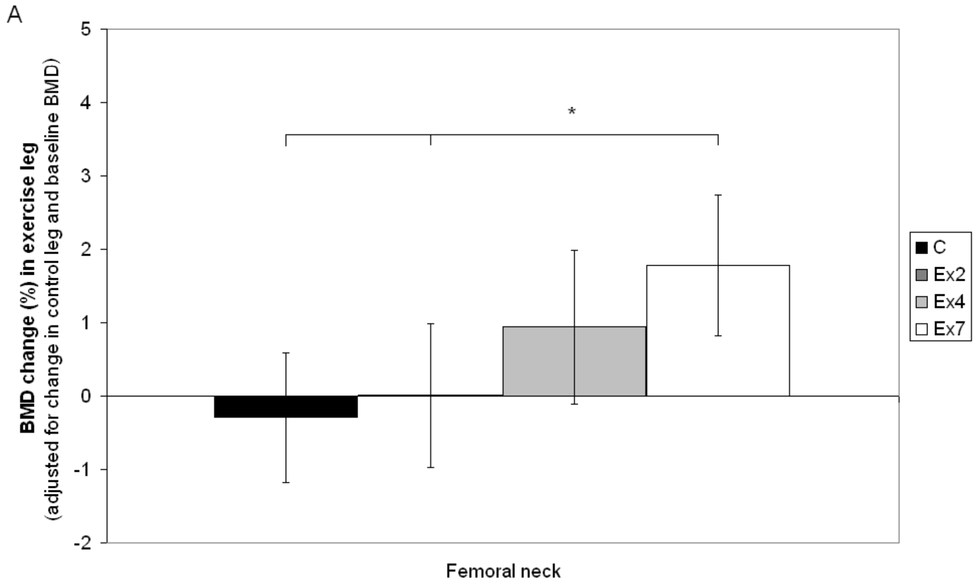


Figure 2: Changes in exercise leg BMD according to prescribed exercise frequency, adjusted for change in control leg and baseline BMD. A) Femoral neck, B) Upper and lower femoral neck and trochanter. Error bars show 95% confidence intervals.



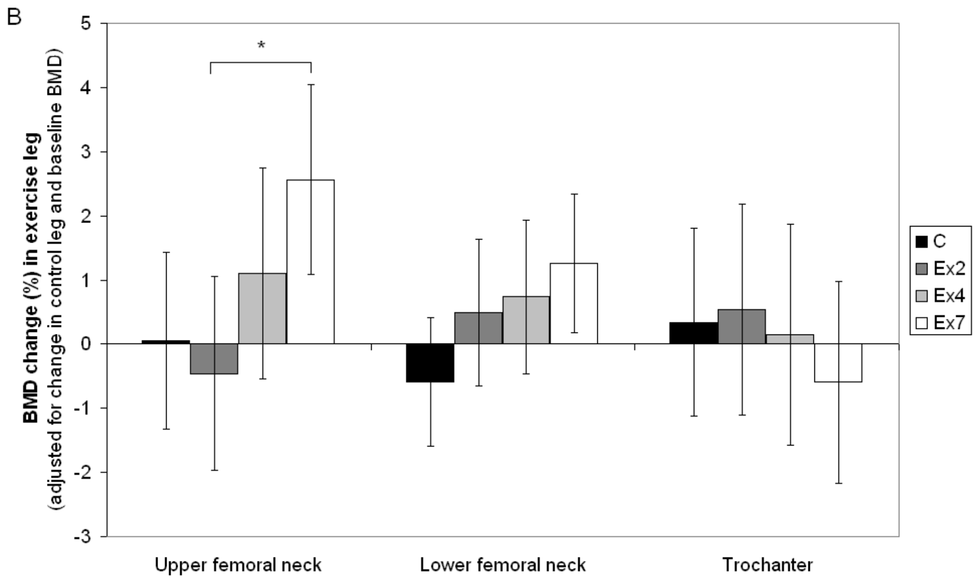


Table 1: Baseline characteristics of participants according to trial group, mean (SD) or proportion (%).

Variable	C (*n*=19)	Ex2 (*n*=16)	Ex4 (*n*=13)	Ex 7 (*n*=16)
Age (yrs)	32.9 (9.4)	30.7 (7.4)	32.2 (10.0)	34.6 (7.9)
Weight (kg)	62.6 (9.5)	58.1 (7.9)	60.3 (10.3)	60.7 (10.2)
Height (m)	1.62 (0.06)	1.64 (0.05)	1.64 (0.07)	1.63 (0.08)
BMI (kg/m²)	23.9 (3.5)	21.7 (3.0)	22.4 (3.3)	22.9 (3.2)
Body fat (%)	29.7 (5.0)	26.1 (6.5)	27.8 (6.2)	30.1 (6.1)
Age at menarche (yrs)	13.5 (2.3)	13.9 (2.5)	13.0 (1.7)	13.2 (1.2)
No. of dairy servings per day	3.2 (1.5)	2.4 (1.0)	2.7 (1.7)	2.7 (1.2)
Current physical activity duration (min/week)	139 (121)	126 (108)	186 (175)	183 (156)
Regular participation in extracurricular sports/ exercise during childhood/adolescence (%)	56	69	61	62
Proportion using hormonal contraception (%)	16	14	9	13
Mean peak landing GRF from 10 hops (xBW)				
Exercise leg	2.42 (0.26)	2.59 (0.44)	2.35 (0.30)	2.46 (0.35)
Control leg	2.57 (0.28)	2.37 (0.37)	2.43 (0.34)	2.42 (0.34)
Peak landing GRF from a maximal hop (xBW)				
Exercise leg	2.84 (0.46)	2.85 (0.63)	2.73 (0.64)	3.10 (1.03)
Control leg	2.90 (0.45)	3.23 (0.57)	2.88 (0.87)	2.73 (0.53)
Mean peak hop height from 10 hops (m)				
Exercise leg	0.053 (0.024)	0.059 (0.019)	0.045 (0.022)	0.052 (0.020)
Control leg	0.055 (0.021)	0.057 (0.016)	0.046 (0.022)	0.049 (0.018)
Peak hop height during a maximal hop (m)				
Exercise leg	0.112 (0.031)	0.128 (0.038)	0.104 (0.031)	0.100 (0.038)
Control leg	0.127 (0.052)	0.122 (0.033)	0.114 (0.043)	0.103 (0.033)
Femoral neck BMD (T-score)				
Exercise leg	0.3(1.1)	-0.1 (1.0)	0.3 (1.3)	0.0 (1.4)
Control leg	0.2 (1.1)	-0.1 (1.0)	0.5 (1.4)	0.0 (1.4)
Femoral neck Z (mm^3)				
Exercise leg	600 (121)	582 (97)	590 (88)	572 (117)
Control leg	604 (124)	593 (90)	602 (92)	551 (105)
Minimum femoral neck width (mm)				
Exercise leg	28.5 (3.0)	28.1 (1.7)	28.2 (1.7)	28.1 (2.4)
Control leg	28.7 (2.9)	28.5 (1.8)	28.5 (1.4)	27.9 (2.2)

GRF – Ground reaction force; BW – Body weight
No significant differences between groups or between exercise and control leg (p>0.05)

Table 2: Percentage changes in bone density and geometry values in exercise and control leg during a 6-month high impact, unilateral exercise intervention according to trial group, mean (95% confidence intervals)

Variable	Leg	Group				*p**
		C	**Ex2**	**Ex4**	**Ex7**	**group**
Femoral neck BMD (g/cm²)	Exercise	-0.3 (-1.2-0.5)	+0.2 (-0.8-1.2)	+0.9 (-0.2-2.0)	+1.7 (+0.7-2.7)	0.016
	Control	+0.4 (-0.6-1.4)	+0.9 (-0.4-2.1)	+0.7 (-0.6-2.0)	-0.6 (-1.8-0.5)	
Upper neck BMD (g/cm²)	Exercise	+0.1 (-1.3-1.5)	-0.5 (-2.2-1.1)	+1.5 (-0.3-3.3)	+2.2 (+0.6-3.8)	0.028
	Control	+0.1 (-1.7-1.9)	-0.2 (-1.8-1.4)	+1.0 (-0.7-2.8)	-0.9 (-2.5-0.6)	
Lower neck BMD (g/cm²)	Exercise	-0.7 (-1.7-0.4)	+0.8 (-0.4-1.9)	+0.5 (-0.7-1.7)	+1.3 (+0.2-2.4)	0.140
	Control	+0.6 (-0.6-1.9)	+1.7 (+0.6-3.1)	+0.4 (-1.0-1.9)	-0.4 (-1.7-0.9)	
Trochanter BMD (g/cm²)	Exercise	+0.2 (-1.2-1.6)	+0.9 (-0.8-2.5)	+0.1 (-1.6-1.9)	-0.8 (-2.4-0.8)	0.768
	Control	-0.7 (-2.2-0.7)	+1.3 (-0.6-3.2)	-0.1 (-2.1-1.9)	-1.6 (-3.4-0.2)	
Femur Z (mm^3)	Exercise	1.1 (-1.7-3.9)	-0.5 (-3.5-2.6)	0.7 (-2.6-3.9)	0.9 (-2.0-3.9)	0.917
	Control	1.2 (-1.8-4.1)	-1.3 (-4.5-2.0)	2.3 (-1.1-5.8)	1.1 (-2.0-4.2)	
Minimum femoral neck width (mm)	Exercise	+0.2 (-1.1-1.4)	+1.4 (+0.1-2.7)	-0.3 (-1.9-1.2)	+0.7 (-0.8-2.2)	0.356
	Control	+0.4 (-1.2-2.0)	+0.1 (-1.3-1.4)	-0.3 (-1.7-1.1)	+0.3 (-0.9-1.5)	

* *p* from ANCOVA comparing BMD change in the exercise leg between groups (with change in the control leg and baseline BMD as covariates).

Z – Section modulus

Table 3: Percentage changes in neuromuscular measures in exercise and control leg during a 6-month high impact, unilateral exercise intervention according to trial group, mean (95% confidence intervals).

Variable	Leg	Group				*p (from RM-ANOVA)*		
		C	**Ex2**	**Ex4**	**Ex7**	**group**	**leg**	**group*leg**
Mean peak hop height from 10 hops (m)	Exercise	+8.9 (-5.1-23.7)	+49.7 (8.4-90.9)	+94.5 (48.7-140.2)	+44.0 (2.8-85.2)	0.15	<0.001	0.01
	Control	+9.3 (-6.7-25.4)	+23.0 (-2.3-48.3)	+26.2 (-1.9-54.3)	+21.6 (-3.7-46.9)			
Peak hop height during a maximal hop (m)	Exercise	+7.8 (-2.5-18.9)	+18.3 (1.8-34.8)	+29.1 (10.8-47.5)	+27.9 (11.3-44.4)	0.67	<0.001	0.11
	Control	+4.1 (-14.5-22.7)	+11.6 (-1.4-24.5)	+3.0 (-11.3-17.3)	+2.8 (-11.6-17.2)			
Mean peak landing GRF from 10 hops (xBW)	Exercise	+7.7 (3.4-12.0)	+15.3 (6.1-24.6)	+15.3 (5.6-25.0)	+14.5 (5.5-23.5)	0.03	0.10	0.19
	Control	+3.4 (-1.0-7.8)	+18.7 (9.4-28.1)	+6.1 (2.1-10.0)	+11.4 (4.7-18.0)			
Peak landing GRF from a maximal hop (xBW)	Exercise	+15.1 (3.7-26.5)	+35.9 (-3.5-75.2)	+7.1 (-10.3-24.6)	-4.5 (-22.8-13.7)	0.28	0.03	0.09
	Control	+3.6 (-10.8-18.0)	-2.7 (-16.8-11.4)	-3.9 (-16.8-9.1)	+0.7 (-16.8-18.1)			

GRF – Ground reaction force; BW – Body weight