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Effects of a 12-month supervised, community-based, multi-modal exercise program followed by a 6-month research-to-practice transition on bone mineral density, trabecular micro-architecture and physical function in older adults: A randomised controlled trial

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Abstract

Multi-component exercise programs are recommended to reduce fracture risk, however their effectiveness in real world community settings remain uncertain. This 18-month randomized controlled trial investigated the effects of a 12-month, community-based, supervised multi-component exercise program followed by a 6-month *'research-to-practice'* transition, on areal BMD, trabecular bone microarchitecture, functional performance and falls in older adults at increased fracture risk. One-hundred and sixty-two adults aged ≥60 years with osteopenia or at increased falls risk were randomized to the *Osteo-cise: Strong Bones for Life* multi-component exercise program (n=81) or a control group (n=81). Exercise consisted of progressive resistance, weight-bearing impact and balance training (3-days/week) performed at community leisure centres. Overall 148 (91%) participants completed the trial, and mean exercise adherence was 59% after 12-months, and 45% during the final 6-months. After 12 months, there were significant net beneficial effects of exercise on lumbar spine and femoral neck BMD (1.0-1.1%, P<0.05), muscle strength (10-13%, P<0.05) and physical function (timed stair climb 5%; four-square step test 6%; sit-to-stand 16%, P ranging <0.05 to <0.001), which persisted following the 6-month transition. There were no significant effects of the 18-month intervention on distal femur or proximal tibia trabecular bone microarchitecture or falls incidence, but per protocol analysis (≥66% exercise adherence) revealed there was a significant net benefit of exercise [mean (95% confidence interval): 2.8% (0.2, 5,4)] on proximal tibia trabecular bone volume fraction [*Osteo-cise* 1.5% (-1.2, 4.2); controls -1.3% (-2.6, 0.1)] after 18-months, due to changes in trabecular number [*Osteo-cise* 1.7% (-0.9, 4.3); controls -1.1% (-2.4, 0.2)] and not trabecular thickness [*Osteo-cise* -0.2% (-0.5, 0.2); controls -0.2% (-0.4, 0.0)]. In conclusion, this study supports the effectiveness of the *Osteo-cise: Strong Bones for*

Life program as a real-world, pragmatic, evidence-based community exercise program to improve multiple musculoskeletal health outcomes in older adults at increased fracture risk.

Key words: exercise, bone mineral density, trabecular bone microarchitecture, randomized controlled trial, falls

Introduction

Osteoporosis is a growing public health concern worldwide through its association with low trauma fragility fractures. Pharmaceutical agents targeting bone mineral density (BMD) are used as a first-line treatment because they can reduce fracture risk by around 30% to 60%,[1,2] but they are limited to osteoporotic patients thus missing approximately 50% of fracture cases that occur in those with osteopenia [3] and have no effect on falls, a major contributor to fractures. Exercise is the only strategy that can improve multiple modifiable musculoskeletal fracture risk factors, but appropriate prescription and adherence is critical. Meta-analyses and systematic reviews of exercise intervention trials have reported that well controlled, supervised and structured programs involving multi-component exercise training, incorporating moderate-to-high intensity progressive resistance training (PRT) with short bouts of varied or diverse loading weight-bearing impact activities and challenging balance and mobility exercises, can improve or maintain BMD and multiple fall-related risk factors in older adults.[4-6] However, several real-world, translational studies examining the effects of exercise programs delivered to older people and those with osteoporosis in community settings have reported mixed findings on bone and muscle outcomes.[7,8] Thus, there remains a need for safe, effective, accessible, evidence-based exercise programs that can be widely adopted, implemented and maintained in the community for people with or at increased risk for fractures.

Another clinically important unanswered question is whether exercise delivered to older adults can improve other measures of whole bone strength beyond areal BMD, particularly trabecular bone microarchitecture. While there is some evidence to support a beneficial effect of exercise on tibial cortical and trabecular bone volumetric BMD and to a lesser extent cortical bone structure in older adults,[9-11] no long-term exercise interventions (>12 months) have quantified changes in trabecular

bone microarchitecture (trabecular number, thickness, connectivity) in older adults. This is important because trabecular bone loss starts earlier in life and occurs at a greater rate than cortical bone during ageing,[12,13] with some evidence that trabecular bone is more strongly associated with fracture risk than cortical bone.[14,15]

The primary aim of this 18-month RCT involving a 6-month '*research-to-practice'* translation phase, was to investigate whether a multi-faceted osteoporosis prevention program, termed *Osteo-cise: Strong Bones for Life*, incorporating a multi-modal resistance, weight-bearing impact and challenging balance training program implemented within community settings combined with theory-based behavioural support to enhance adherence and osteoporosis education to promote disease self-management, could improve BMD and functional muscle performance in older adults at increased risk for fracture. Since we have previously reported beneficial effects of the initial 12-month supervised and structured exercise phase on hip and spine BMD and functional muscle performance,[16] the aims of this study were to: i) evaluate whether the centre management at each community-based leisure centre could continue to deliver the exercise program independent of the research team and to assess if the initial musculoskeletal benefits were maintained at 18 month after the 6-month transition; and ii) assess the long-term effects (over 18 months) of the intervention on trabecular bone microarchitecture and falls incidence.

Materials and Methods

Study Design

Osteo-cise: Strong Bones for Life study was an 18-month community-based, multi-faceted RCT in which participants were randomly allocated (1:1) to: 1) a multi-component exercise, osteoporosis education and theory-based behavioural change program, or 2) a usual care control group.[16,17] All

exercise training took place within seven community-based health and fitness facilities. The 18-month intervention was divided into two phases: 1) a 12-month supervised and structured program in which the community-based exercise program and trainers delivering the program were closely monitored by the research team, and 2) a 6-month *'research-to-practice'* translational phase in which the centre management at each community leisure centre was asked to continue to implement the program independently of the research team. Participants in both groups were prescribed 1000 IU of vitamin D and 700 mg of elemental calcium as calcium phosphate daily (Blackmores) throughout the 18 months. The random allocation of participants to each study group was stratified by sex and performed by an independent staff member using a computer-generated random numbers table (Microsoft Excel) after completion of baseline testing. The assessment of all outcomes was performed by the same research staff at the Western Hospital, University of Melbourne, but those undertaking the strength and functional assessments were not blinded to the group allocation due to funding restrictions. Ethics approval was granted from the Melbourne Health Human Research Ethics Committee (HREC 2008.136) and the trial was registered with the Australian and New Zealand Clinical Trials Registry [ACTRN12609000100291].

Participants

Community-dwelling independently living men and women aged ≥60 years residing in the Western and surrounding regions of Melbourne, Australia were recruited into this study from January to October 2009 and all had completed the intervention by May 2011. Detailed information about the recruitment and three-step screening process has been previously outlined.[17] Briefly, participants were first screened over the telephone and excluded if they were: aged <60 years, had a BMI >40 kg/m^2, reported having osteoporosis (or a recent low trauma fracture in the past 6 months) or any

other medical conditions (including taking any medications) known to influence bone metabolism or fracture risk; reported participation in structured resistance or weight-bearing impact exercise more than once a week over the past three months, were a current smoker, had commenced taking vitamin D or calcium supplements in the preceding 6 months, were planning to undertake travel for >6 weeks throughout the intervention and, for women, were currently taking hormone replacement therapy (>0.625 mg/d premarin or equivalent estrogen) or had done so in the previous 6 months. Participants that passed the initial screening were then invited to have a DXA hip and spine areal bone mineral density (aBMD) scan and were included if osteopenic (T-score -1.0 to < -2.5 SD). Those with normal aBMD (greater than -1.0 SD) were included if they were classified as being an increased falls or fracture risk.[17] All participants who passed the aforementioned screening process needed to obtain approval from their general practitioner to confirm that they were clear of any contraindicated medical conditions to exercise as outlined in the American College of Sports Medicine (ACSM) guidelines.[18] A total of 696 participants were telephone screened, with 249 progressing to have a DXA aBMD scan and/or complete the falls and fracture risk assessment, of which 162 were randomized into either the *Osteo-cise* (n=81) or control (n=81) group.

Intervention

As reported previously,[17] *Osteo-cise: Strong Bones for Life* was a community-based, multi-faceted program that included four elements: 1) Osteo-*cise*: a multi-component exercise program specific to osteoporosis and falls prevention; ii) Osteo-*Adopt*: the incorporation of behavioural change strategies to encourage initial uptake and long-term adherence to exercise participation; iii) Osteo-*Ed*: a series of osteoporosis education and awareness seminars designed to enhance participants understanding of the risk factors for osteoporosis (session one), and the importance of exercise

(session two) and nutrition (session three) to enable them to actively take charge of their bone health, and iv) Osteo-*Instruct*: a 'train-the-trainers' workshop designed to educate exercise trainers on the objectives and structure of the program, ensure they were up-to-date on the latest osteoporosis prevention and management strategies and to instruct them on how to successfully implement the program at their training facility.

Participants allocated to the *Osteo-cise* program were assigned to one of seven leisure centres and instructed to train three non-consecutive days per week (~60 minutes sessions) for 12 months. Exercise sessions were supervised by certified exercise trainers who had completed the Osteo-*Instruct* training course. The initial 12-month program was divided into a four week 'adoption phase' followed by four discrete but increasingly challenging 12-week mesocycles. During the final 6-month *'research-to-practice'* phase, centre management at each leisure centre assumed responsibility for the program and organising the exercise sessions and trainers to deliver the program. All trainers were encouraged to continue to adhere to the same exercise prescription guidelines that were used during the initial 12 months.

Detailed information about the exercise training methods and progressions have been previously reported.[17] Briefly, all participants received individually-tailored programs using the key principles of specificity and progressive overload. Training incorporated high-velocity PRT together with moderate-intensity, multi-directional impact exercises and high-challenge balance and mobility activities. For PRT, a mixture of machine and free weights and pulleys were used and training intensity was monitored using the modified BORG (1 to 10) rating of Perceived Exertion (RPE) scale. In the 'adoption' training phase, participants performed two sets of 12-15 repetitions at 40-60% of one-repetition maximum (1-RM) (RPE 3-4 'moderate to somewhat hard'). Thereafter,

participants were prescribed two sets of 10-15 repetitions (RPE 3-4) for the first 4 weeks of each mesocycle followed by 8-12 repetitions (RPE 5-8 'hard to very hard') for each exercise for the remaining 8 weeks of each mesocycle. Core, postural and pelvic floor strengthening exercises were also included into each program. Weight-bearing impact exercises (3 sets, 10-20 repetitions, 2-3 exercises per session) included stationary movements (e.g. stomping); forward/backward movements (e.g. box step-ups); and lateral/multidirectional movements (e.g. side-to-side shuffle). The intensity of these exercises was progressively increased by increasing jump height or the rate of impact loading, by adding additional weight, or by incorporating multidirectional movement patterns to diversify the load distribution. High-challenge balance and mobility exercises were categorised into fit-ball exercises, standing balance and dynamic functional exercises. Participants performed two balance exercises at each session and each exercise was either maintained for up to 30 seconds or performed for a given number of repetitions.

Usual care (self-management) control group

Participants in the control group were asked to continue their usual self-care and were provided with general consumer material available from Osteoporosis Australia about osteoporosis to enable them to actively take charge of their own musculoskeletal health.[17]

Lifestyle characteristics, medical history and serum 25-hydroxyvitamin D

The Community Healthy Activities Model Program for Seniors (CHAMPS) physical activity questionnaire was used to assess current participation in weight-bearing and leisure-time physical activity (hours per week).[19] Details about medical, menstrual, medication use and smoking history and history of falls prior to the intervention (past year) were determined by questionnaire. Twenty-four-hour food diaries were used to estimate nutrient intakes and these were analysed using

Australia-specific dietary analysis software (Foodworks, Xyris Software, Highgate Hill, Australia). Serum 25-hydroxvitamin D was measured using the Liaison 25OH-vitamin D TOTAL (Liaison 25OHD) (DiaSorin Inc., Stillwater, MN, USA), a direct competitive chemiluminescent immunoassay.

Anthropometry, bone mineral density and body composition

Height to the nearest 0.1 cm and weight to the nearest 0.1 kg were measured using standard procedures. DXA (Hologic Discovery W, APEX Software v3.2, Hologic Inc. 1986-2010) was used to assess lumbar spine (L2-L4) and proximal femur areal BMD (g/cm^2), and total body lean mass (kg) and fat mass (kg). The CV for BMD and body composition ranged from 0.8-1.5% and 0.6-1.2%, respectively. A single investigator performed and analysed all DXA scans.

Trabecular bone microarchitecture

MRI scans of the left knee were performed at Sunshine Hospital (Melbourne) at baseline and 18 months on a 3.0T MR scanner (General Electric, Milwaukee, WI) using an eight-channel phased array knee coil (General Electric Medical Systems, WI) to assess trabecular bone microarchitecture. There is extensive research to support MRI as a validated technique to quantify trabecular bone microarchitecture.[20-23] Distal femur and proximal tibia images were attained with an axial 3D, phase cycled, fully balanced, steady-state coherent imaging pulse sequence (3D FIESTA-C) utilising the following scan parameters: repetition time ~11.8 ms, echo time 1.0 ms, flip angle 60 degrees, resolution 0.195 x 0.195, 512 x 384 matrix, a slice thickness 1 mm and a 10 cm field of view. For the assessment of trabecular bone microarchitecture, a standardized region of interest (ROI) was used at both the distal femur (35 mm) and the proximal tibia (15 mm), starting at 5 mm from the distal endplate of the femur and 5 mm from the proximal endplate of the tibia. The bone

within each MRI slice was semi-automatically masked (Bone J and Matlab), and then binarized using an established iterative histogram technique for segmentation.[24] This technique has been validated for MRI images.[25] Once binarized, trabecular apparent bone volume fraction (app.BV/TV), apparent trabecular number (app.Tb.N), apparent trabecular thickness (app.Tb.Th) and apparent trabecular spacing (app.Tb.Sp) were calculated for each slice using the plate model of bone structure and averaged for the entire ROI.[26] Overall, 115 participants (*Osteo-cise*, n=58; controls, n=57) had an MRI scan at baseline and 90 (*Osteo-cise*, n=45; controls, n=45) at the 18-month follow-up.

Muscle strength and functional performance

Detailed information on the muscle and functional tests used have been previously reported.[17] Briefly, maximum one-repetition (1-RM) lower limb muscle strength (bilateral leg press) and back strength (seated row) were predicted from 3-repetition maximum (3-RM) testing.[17] The timed stair climb test was used to determine functional stair climbing muscle power (Watts, W) which required participants to climb a flight of stairs (10 steps, 14 cm rise/step) as quickly as possible.[17] A battery of validated tests were used to assess functional muscle performance and included the 30 second sit-to-stand (sec), four square step test (sec), functional reach (cm) and the timed-up-and-go (TUG, sec) with a secondary cognitive task (counting backwards from 100 by 3's).[17]

Adherence, falls and adverse events

Adherence to the exercise program was determined from exercise cards that were completed by the participants during each training session, and reviewed regularly by the trainers to ensure accuracy and completeness. Adherence to the calcium and vitamin D supplements was calculated from a tablet count of all bottles returned at the testing appointments. Information related to falls (and

fractures) were derived from 'falls calendars' that were completed by participants and returned to study investigators (via reply-paid postage) on a monthly basis. In the event of fall(s), participants were contacted by the research staff to seek further details. A fall was defined as '*unintentionally coming to the ground or some lower level, other than as a consequence of a sudden onset of paralysis, epileptic seizure, or overwhelming external force'*.[27] Information on other adverse events (AE) or injuries was collected at each testing session and in addition, exercise trainers were asked to record AE on a *Osteo-cise* form kept in a dedicated folder at each training facility. An AE was defined as a musculoskeletal complaint requiring the participant to seek treatment such as icing, medication or review by a health professional, or modify their exercise program in any manner or withdraw from training.[17]

Statistical analysis

Expected mean differences between the groups for the change in the primary outcome measures of femoral neck BMD and functional muscle power (based on previous exercise trials) [28,29] were used for sample size calculations. As reported previously,[17] it was estimated that 60 participants in each group would provide 90% power to detect a 1.8% difference in femoral neck BMD (two-tailed, alpha of 0.05) assuming a standard deviation of 3.5. For functional muscle power, it was estimated that 24 participants per group would provide 90% power to detect a 15% net difference over time (two-tailed, alpha level of 0.05) assuming a standard deviation of 15%. With an anticipated 20% dropout rate, it was estimated that at least 72 participants per group (144 in total) was required.

Stata statistical software (version 15, Stata Corp, College Station, TX) was used to conduct all statistical analyses. As reported previously,[17] intention-to-treat basis was used to analyse the data and no results were imputed for the few participants with missing data. Per protocol analysis was

also conducted including participants with at least 66% adherence to the exercise program (equivalent to two sessions per week) over 18 months. All data was checked for normality and the following variables were log transformed prior to analysis: leg and back muscle strength, stair climbing power, sit-to-stand, four square step test and TUG. General Linear Mixed Models with random effects were used to assess time and group-by-time interactions, adjusting for sex. The incidence rate ratio for the number of falls in the *Osteo-cise* and control group was analysed using negative binomial regression, which allows for overdispersion.[16] To compare the relative risks of the number of participants with one or more falls and multiple falls in each group, log-binomial regression models were used.[16] Finally, any difference in time to first fall between groups was assessed using the Cox hazard-regression model. All analyses related to the falls outcomes were adjusting for age, sex and history of falls.[16] All data were presented as means ± SD or 95% CI unless stated with significance set at $P<0.05$.

Results

Baseline characteristics

The majority of participants were female (73%) and the mean age was 67.4 years (range 60-86 years) (Supplementary Table 1). A small proportion of women in each group were current users of HRT (~6%), and approximately 30% of participants in each group were ex-smokers. The average dietary calcium intake and serum 25-hydroyxvitamin D level was 808 mg/d and 61 nmol/L, respectively. Overall, 83% of the participants were classified as osteopenic (T-score -1.0 to <-2.5 SD) based on their baseline proximal femur and/or lumbar spine scan.

Study attrition and program adherence

A total of 14 participants (*Osteo-cise* n=4; control n=10) did not complete the 18-month follow-up leaving 148 participants (91%) for the final analysis. The reasons for attrition are shown in Figure 1. Mean (and median) adherence to the exercise program after 12 and 18 months was 59% (74%) and 55% (67%), respectively. Exercise adherence during the final 6 months was 45% (median 64%), despite the centre management of each leisure facility agreeing to continue to offer the program to all participants. Overall 25 (32%) of the participants did not complete any training session during the *'research-to-practice'* transition. For calcium and vitamin D supplements, mean compliance did not differ between groups during the intervention (calcium: *Osteo-cise* 87%; controls 88%; vitamin *D*: *Osteo-cise* 93%; controls 93%). For the three Osteo-*Ed* sessions, mean attendance by the *Osteo-cise* participants was 82%, 63% and 65% for sessions one, two and three, respectively.

Adverse events

Thirty-four of the 81 *Osteo-cise* participants reported a total of 40 musculoskeletal complaints during the initial 12 months, with half (50%) of all complaints related to hip or knee pain and linked to pre-existing injuries (53%) aggravated by participation in the program. Overall 67% of these complaints required some form of treatment (icing, medication, health professional consultation), but 28 (82%) of the participants continued to train with a modified program; 6 withdrew. During the final 6-months an additional seven musculoskeletal complaints were reported in seven of the 52 participants that continued training (rolled ankle n=1; heel pain/spur n=1; knee pain n=2; shoulder pain n=3), with five requiring treatment but all were able to complete the program.

Physical activity, diet and serum 25(OH)D

Habitual physical activity and diet did not change nor differ between the groups throughout the intervention (Supplementary Table 2), with the exception that the *Osteo-cise* group decreased their

total energy and carbohydrate intake and the control group increased their protein intake at 18 months relative to baseline. Serum 25(OH)D increased similarly after 12 and 18 months by an average of 24 and 29 nmol/L, respectively, in both groups.

DXA BMD

As shown in Table 1, the *Osteo-cise* group experienced a significant net 1.0% (P<0.05) benefit to FN BMD after 12 months relative to controls, which increased to 1.9% (P<0.001) after 18-months due largely to increased bone loss in the controls. For lumbar spine BMD, there was a significant 1.1% (P<0.05) greater gain in the *Osteo-cise* group after 12 months, but this significant difference did not persist after 18 months [net difference 0.7% (95% CI, -0.3, 1.8)]. There were no significant between-group differences for the change in total hip aBMD, despite significant within-group increases of 0.9% (P<0.001) and 0.6% (P<0.05) in the *Osteo-cise* group after 12 and 18 months.

MRI trabecular bone microarchitecture

There were no significant between group differences for the 18-month change in any trabecular bone microarchitecture measure at the distal femur (Table 2). Both groups experienced a significant 2.2% to 3.0% reduction in app.BV/TV at the distal femur, which was driven by a significant 2.2% to 2.9% loss in trabecular number (app.Tb.N) and a 3.6% to 5.2% increase in trabecular separation (app.Tb.Sp). At the proximal tibia, there was a trend (P=0.07) for a 1.8% net benefit in app.BV/TV in the *Osteo-cise* group relative to controls, which was due largely to a significant 1.3% loss in the controls (P<0.05). However, there were no between group differences for the change in any of the other trabecular microarchitecture measures, although controls did experience a significant reduction in proximal tibia app.Tb.Th (P<0.05) and increased Tb.Sp (P=0.051) after 18-months.

Body composition, muscle strength and function

For total body lean mass, there were no between group differences after 12 or 18 months, but the *Osteo-cise* group had a significant 0.5 kg ($P<0.05$) increase after 18-months (Table 1). Total body fat mass did not change in either group after 12-months, but both groups experienced a similar and significant ($P\leq0.001$) reduction (~0.9 kg) after 18-months. For measures of leg and back muscle strength, stair climbing power, 30 second sit-to-stand and the FSST functional test, the *Osteo-cise* group experienced significantly greater improvements after 6, 12 and 18 months relative to controls (Figure 2 and Supplementary Table 3). There was also a greater improvement in dual task TUG performance in the *Osteo-cise* relative to control group after 18-months ($P<0.05$).

Falls and fracture

Over 18 months, 59 falls were reported by 36 *Osteo-cise* participants while 53 falls were reported by 34 control participants. One participant reported a wrist fracture in the *Osteo-cise* group during the study which resulted from an accident during training. Falls incidence, the number of participants sustaining one or more falls or multiple falls (Table 3), and the time to first fall (hazard ratio [HR] = 1.15; 95% CI, 0.73, 1.83; P=0.54) did not differ between the groups.

Per protocol analysis

The per protocol analysis included 41 participants in the *Osteo-cise* group who achieved ≥66% exercise adherence over 18-months. All results remained unchanged, with the exception that there was a significant net 2.8% (95% CI, 0.2, 5.4) greater gain in proximal tibia app.BV/TV in the *Osteo-cise* compared with the control group (P=0.02). This was due to a 1.5% (95% CI, -1.2, 4.2) increase in the *Osteo-cise* group and a 1.3% (95% CI, -2.6, 0.1) loss in controls. This net benefit in proximal tibia app.BV/TV was driven by a trend (P=0.07) for a greater improvement [mean difference for the change: 2.8% (95% CI, 0.2, 5.3)] in app.Tb.N in *Osteo-cise* [1.7% (95% CI, -0.9,

4.3)] compared with controls [-1.1% (95% CI, -2.4, 0.2)] as both groups experienced a similar changes in app.Tb.Th [*Osteo-cise*, -0.2% (95% CI, -0.5, 0.2) versus controls, -0.2% (-0.4, 0.0)].

Discussion

The main finding from this 18-month community-based, multifaceted osteoporosis prevention exercise program was that the initial exercise-induced gains in femoral neck and lumbar spine aBMD, muscle strength and functional performance following the 12-month structured and supervised training period were effectively maintained during the 6-month *'research-to-practice'* transition. However, there was no significant effect of the 18-month intervention on falls incidence and only a trend for a positive effect of the intervention on proximal tibia trabecular bone microarchitecture in the intention-to-treat analysis. This is likely due in part to the fact that the study was not powered to evaluate the effects of the intervention on these outcomes, approximately one-third of participants did not continue to exercise during the final 6-month transition, and only a subset of participants had MRI scans to assess trabecular bone microarchitecture. Nevertheless, a noteworthy observation was that there was a significantly greater net improvement in proximal tibia trabecular bone volume fraction in the *Osteo-cise* relative to control group in the per protocol analysis (exercise adherence ≥66% over 18-months), which was driven largely by a change in trabecular number, but not trabecular thickness. This suggests that adherence to a twice weekly multimodal targeted bone and muscle exercise program may help to maintain trabecular bone microarchitecture in older adults.

The maintenance of the 12-month exercise-induced benefits to hip and spine aBMD, muscle strength and function, despite the modest adherence to training during the 6-month *'research-to-practice'* transition, suggests that a lower frequency of training over time may be effective to

maintain initial musculoskeletal benefits from a highly structured, supervised and targeted program. Several previous studies have also reported a preservation in hip and/or spine aBMD with continued training at a lower frequency and/or training dose.[30-32] Although questions still remain as to whether there is a minimum exercise frequency and/or dose to promote sustainability of any initial exercise related skeletal adaptations, retrospective analysis from a 16-year prospective study of a supervised high-intensity exercise program targeting bone and muscle outcomes in 55 older women reported that at least two exercise sessions per week was the minimum effective dose that is essential to relatively affect BMD.[33] There is also evidence that PRT-induced gains in muscle strength and to a lesser extent muscle mass (size) in older adults can be maintained with once weekly or reduced training doses (one-third or one-ninth of initial dose) after a period of intense training.[34,35] Given that long-term adherence to structured exercise programs remains an ongoing challenge for older people,[36] and that bone and muscle are rapidly lost following cessation of training,[37-39] our results provide some evidence to support the role of a lower frequency of training (1-2 sessions per week) to maintain initial exercise-induced muscle-bone benefits in older adults.

The lack of any further exercise-induced gains to BMD, muscle strength or function during the 6-month translation period may be explained by the training principle of diminished returns and/or a lack of progressive overload. That is, following any initial adaptations in response to loading, subsequent gains are likely to be modest with a similar loading regimen. Whether the training dose and/or exercises continued to be progressed incrementally is not known since exercise prescription during the final 6-months was performed by the trainers at each community leisure centre, and not closely monitored by the research staff. Nevertheless, our findings are consistent with several previous long-term (≥18 months), progressive multi-modal exercise trials in older adults which

demonstrated that the greatest gains in hip and/or spine aBMD, muscle mass, strength and function occurred during the first 6 to 12 months of training, with a maintenance thereafter.[29,40,41] Maintenance of exercise-induced benefits to BMD is clinically important as highlighted by the findings from a 16-year prospective study in postmenopausal osteopenic women which observed that a ~3.0-4.5% exercise-induced benefit to hip and spine BMD relative to controls after 4 years and maintained at the 16-year follow-up was associated with a 49% reduction in low trauma fractures [risk ratio 0.51 (95% confidence interval, 0.23-0.97), P=0.046].[42]

A novel feature of this study was the assessment of trabecular bone microarchitecture using MRI. While a number of previous exercise trials in older adults using (p)QCT have reported an exercise-related increase or maintenance in trabecular volumetric BMD at the lumbar spine [29,41] distal tibia [43] and proximal femur,[44] whether these benefits were due to changes in trabecular thickness and/or number has not been investigated. The findings from the current study revealed that there was a trend (P=0.07) for a 1.8% net beneficial effect of the multi-modal exercise program on proximal tibia trabecular bone volume fraction, which was due to a non-significant 0.5% increase in the *Osteo-cise* group and a significant 1.3% loss in controls. Subsequent per protocol analysis in those who achieved at least 66% exercise adherence revealed that there was a significant 2.8% net difference for the change in trabecular bone volume fraction in favour of the *Osteo-cise* group. Although the effects of the intervention on changes in trabecular number and thickness were statistically equivocal, the intention-to-treat and per protocol analysis revealed that there was a mean 1.6% and 2.8% net beneficial effect of the exercise intervention on trabecular number, with no evidence for any between-group difference in trabecular thickness. In line with our findings, a cross-sectional study in young men using high resolution pQCT reported a positive association

between trabecular bone volume fraction at the distal tibia and weight-bearing physical activity, which was attributed to an increase in trabecular number and not altered thickness.[45] An increase or preservation of trabecular number is clinically important as finite element modelling indicated that a reduction in trabecular number had a 2- to 5-fold greater effect on bone strength compared to a reduction in trabecular thickness that leads to a similar decrease in bone volume fraction.[46]

The strengths of this study include the successful delivery of an evidence-based, multi-modal exercise program into 'real-world' community-based leisure centres, the relatively long intervention period, high participant retention, comprehensive reporting of AE and the use of MRI to quantify trabecular bone microarchitecture. However, the findings must be considered in light of a number of limitations. First, mean adherence to the exercise training was modest over the final 6-month 'research-to-practice' transition (mean 45%), which likely attenuated the potential long-term effectiveness of the multi-modal exercise program on the musculoskeletal outcomes. However, this is consistent with the results from previous exercise intervention trials targeting BMD in adults which have reported lower exercise adherence with increased study duration.[33,47] In our study, the relatively poor mean adherence during the final 6 months is likely explained, at least in part, by the finding that 32% of participants did not complete any training during this phase. Indeed, median exercise adherence over the final 6 months was 64%, which is equivalent to approximately two training sessions per week. A previous systematic review of six studies in older people reported that mean adherence to community-based exercise programs of at least 6 months duration was 69%, but that there was considerable variability across studies (range 53-93%).[48] Based on these findings and our results, further research is needed to understand factors that influence participation in community-based exercise programs for older people. Second, this study was not powered to detect

an effect of the intervention on falls, and the majority (84%) of participants were included in the trial based on having osteopenia and thus were not at increased falls risk. Thus, the findings may not be generalizable to other groups, including those with osteoporosis. Third, only a subset of the participants agreed and had a pre- and post-intervention MRI scan which likely limited the power to detect significant between group differences in trabecular bone microarchitecture. In addition, this assessment was limited to the proximal femur and distal tibia, which are not common fracture sites. However, there is some evidence the MRI-derived bone microarchitectural parameters at these sites differs between women with fragility fractures and controls.[49,50] Fourth, detailed information was not recorded on the number of training sessions supervised by the exercise trainers nor the exercise progressions during the final 6 months transition. Finally, AE were not recorded in the controls, and thus it was not possible to determine what proportion of these participants relative to the exercise group may have experienced similar muscle or joint complaints over the 18-month period. It is also difficult to compare the number of AE in our study with other similar trials because many provide no or little information about AE and there is no consensus on the definition of an AE in trials involving exercise. This was highlighted in a review of AE from 121 PRT RCTs in older adults which found that 53 of the trials provided no comment about AE, 25 trials reported no AE, and of the 43 trials that did report some type of AE, the majority were musculoskeletal related problems such as muscle strain or joint pain,[51] consistent with the findings from our trial.

In conclusion, the findings from this 18-month randomized controlled trial including a 6-month *'research-to-practice'* transition demonstrates that the *'Osteo-cise: Strong Bones for Life'* multi-faceted osteoporosis prevention program, which includes an evidence-based, multi-component exercise program, can be successfully adopted and implemented within community-based leisure

centres as a real-world, pragmatic, exercise program for older adults at increased risk for fracture. This study also demonstrates that our *Osteo-cise* supervised and structured, multi-component exercise program can effectively improve multiple musculoskeletal and functional outcomes in older adults, and that these benefits can be sustained over a 6-month 'real-world' translation period with a lower frequency (1-2 sessions per week) of training. This is important because long-term adherence to exercise training remains one of the key challenges for many people. However, further long-term trials are still needed to ascertain if there is a minimum frequency and/or dose of exercise to retain any initial musculoskeletal benefits following well-controlled, structured and supervised exercise programs in older adults.

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Authors' roles: Study design: RMD, PRE, CAN, KS, KH. Study conduct: JG, CAB, RMD. Data collection: JG, CAB. MRI analysis: MK and RK. Data analysis: JG, CAB, RMD. Data interpretation: RMD JG, MK, CAB, PRE, CAN, RK, KS, KH. Drafting manuscript: RMD, JG.

Revising manuscript content: all authors. Approving final version of manuscript: all authors. RMD takes responsibility for the integrity of the data analysis.

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Figure 1: Study design and flow of participants.

Figure 2: Mean percentage changes with 95% confidence interval from baseline for leg muscle strength (panel A), back muscle strength (panel B), stair climbing power (panel C), four square step test (panel D), 30 second sit-to-stand (panel E) and dual task timed-up-and-go (TUG, panel F) in the *Osteo-cise* (black circles) and control group (open circles) during the 12 month supervised and structured training phase (shaded region) and 6 month translation phase. *$p<0.05$, † $p<0.01$, ‡ $p<0.001$ between-group difference for the change from baseline.

Table 1. Mean baseline values and within group changes in the *Osteo-cise* and control group for weight, total body fat mass and lean mass, total hip, femoral neck and lumbar spine bone mineral density after 12 and 18 months, and the net between group differences for the change relative to baseline.

Variable	Study Group				Intervention Effects	
	Osteo-cise		Control			
	Mean ± SD or 95% CI	***P-value***	***Mean ± SD or 95% CI***	***P-value***	***Net Difference***	***Group x Time (P)***
Weight					-	
Baseline, kg	73.3 ± 11.5		75.1 ± 14.9			
Δ 12 months	-0.17 (-0.74, 0.40)	*0.789*	-0.14 (-0.88, 0.59)	*0.676*	-0.03 (-0.95, 0.89)	*0.873*
Δ 18 months	-0.40 (-1.05, 0.24)	*0.185*	-0.51 (-1.36, 0.34)	*0.069*	0.11 (-0.94, 1.16)	*0.564*
Total body FM					-	
Baseline, kg	27.3 ± 8.0		28.3 ± 9.1			
Δ 12 months	-0.30 (-0.86, 0.25)	*0.292*	-0.36 (-0.97, 0.25)	*0.193*	0.06 (-0.76, 0.87)	*0.776*
Δ 18 months	-0.87 (-1.38, -0.37)	*<0.001*	-0.85 (-1.52, -0.18)	*0.001*	-0.02 (-0.85, 0.80)	*0.857*
Total body LM					-	
Baseline, kg	42.7 ± 7.9		43.6 ± 9.8			
Δ 12 months	0.26 (-0.19, 0.71)	*0.191*	0.09 (-0.34, 0.52)	*0.647*	0.17 (-0.45, 0.79)	*0.549*
Δ 18 months	0.48 (0.04, 0.92)	*0.019*	0.21 (-0.32, 0.73)	*0.342*	0.27 (-0.40, 0.95)	*0.359*
Total hip BMD					-	
Baseline, g/cm^2	0.899 ± 0.102		0.880 ± 0.105			
% Δ 12 months	0.90 (0.40, 1.40)	*<0.001*	0.52 (0.08, 0.96)	*0.025*	0.38 (-0.28, 1.04)	*0.301*
% Δ 18 months	0.61 (0.09, 1.14)	*0.015*	0.32 (-0.26, 0.91)	*0.250*	0.29 (-0.49, 1.07)	*0.345*
FN BMD					-	
Baseline, g/cm^2	0.730 ± 0.081		0.713 ± 0.082			
% Δ 12 months	0.63 (0.03, 1.22)	*0.057*	-0.40 (-0.98, 0.18)	*0.207*	1.03 (0.21, 1.86)	*0.025*
% Δ 18 months	0.60 (0.03, 1.16)	*0.058*	-1.33 (-2.00, -0.67)	*<0.001*	1.93 (1.07, 2.79)	*<0.001*

LS BMD					-	
Baseline, g/cm^2	0.971 ± 0.135		0.968 ± 0.146			
% Δ 12 months	1.45 (0.82, 2.08)	*<0.001*	0.31 (-0.34, 0.95)	*0.246*	1.14 (0.25, 2.03)	*0.042*
% Δ 18 months	1.49 (0.77, 2.21)	*<0.001*	0.76 (-0.03, 1.55)	*0.025*	0.73 (-0.33, 1.79)	*0.125*

FM, fat mass; LM, lean mass; FN, femoral neck, LS, lumbar spine. P, P-value. Baseline data represent means ± SD. Percentage change data represents means with 95% confidence intervals (95% CI). All statistical analyses were adjusted for sex.

Table 2. Mean baseline values and within group changes in the *Osteo-cise* and control group for MRI trabecular bone microarchitecture at the distal femur and proximal tibia after 18 months, and the net between group differences for the change relative to baseline.

	Study Group					
	Osteo-cise		**Control**		**Intervention Effects**	
Variable	***Mean ± SD or 95% CI***	***P-value***	***Mean ± SD or 95% CI***	***P-value***	***Net Difference***	***Group x Time (P)***

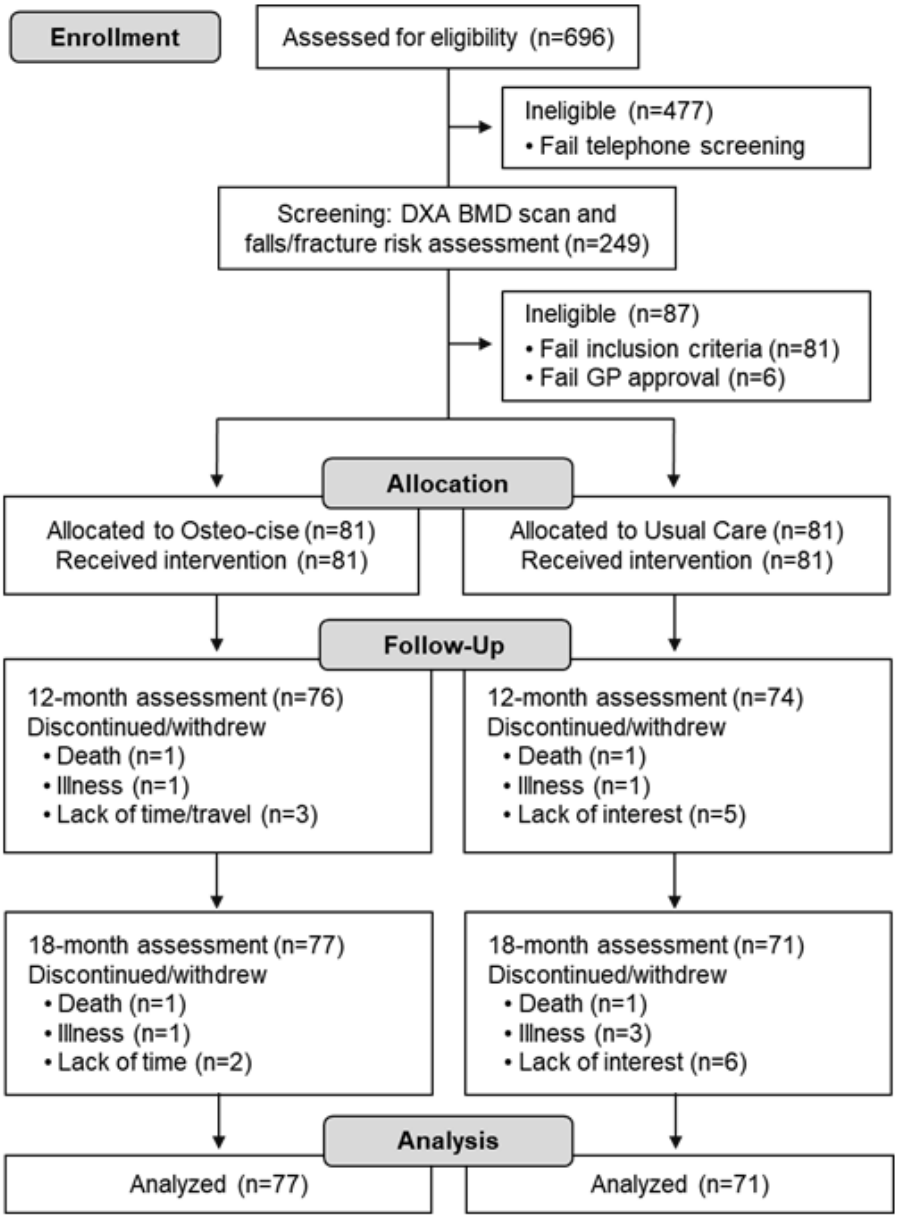
Distal Femur	app. BV/TV					
	Baseline, %	0.318 ± 0.042		0.329 ± 0.036		
	% Δ 18 months	-2.20 (-3.74, -0.67)	*0.002*	-3.02 (-4.34, -1.69)	*<0.001*	0.82
	app. Tb.N					
	Baseline, mm^{-1}	1.124 ± 0.150		1.163 ± 0.124		
	% Δ 18 months	-2.23 (-3.73, -0.73)	*0.002*	-2.89 (-4.21, -1.57)	*<0.001*	0.66
	app. Tb.Th					
	Baseline, μm^{-1}	0.283 ± 0.002		0.283 ± 0.002		
	% Δ 18 months	0.01 (-0.14, 0.17)	*0.679*	-0.13 (-0.27, 0.00)	*0.052*	0.14
	app. Tb.Sp					
	Baseline, μm^{-1}	0.748 ± 0.154		0.707 ± 0.134		
	% Δ 18 months	5.24 (1.93, 8.54)	*0.006*	3.61 (1.19, 6.04)	*0.003*	1.63
Proximal Tibia	app. BV/TV					
	Baseline, %	0.318 ± 0.042		0.323 ± 0.036		
	% Δ 18 months	0.46 (-1.25, 2.16)	*0.563*	-1.29 (-2.63, 0.05)	*0.044*	1.75
	app. Tb.N					
	Baseline, mm^{-1}	1.121 ± 0.145		1.136 ± 0.120		
	% Δ 18 months	0.57 (-1.14, 2.27)	*0.912*	-1.07 (-2.38, 0.24)	*0.091*	1.64
	app. Tb.Th					
	Baseline, μm^{-1}	0.284 ± 0.002		0.284 ± 0.003		
	% Δ 18 months	-0.11 (-0.34, 0.12)	*0.524*	-0.22 (-0.44, 0.00)	*0.046*	0.11
	app. Tb.Sp					
	Baseline, μm^{-1}	0.632 ± 0.137		0.615 ± 0.109		
	% Δ 18 months	0.66 (-1.25, 2.57)	*0.403*	2.18 (0.03, 4.33)	*0.051*	-1.52

app.BV/TV, trabecular bone volume fraction; app.Tb.N, trabecular number; app.Tb.Sp, trabecular separation; app.Tb.Th, trabecular thickness. P, P-value. Baseline data represent means ± SD. Percentage change data represents means with 95% confidence intervals (95% CI). All statistical analyses were adjusted for sex.

Table 3. Falls in the *Osteo-cise* and control groups during the 18 month intervention

Outcomes	*Osteo-cise*	Control	IRR [a] / RR [b] (95% CI)	P-value
Previous falls, n (%)	11 (13.6)	10 (12.4)	-	-
Falls, n (rate) [c]	59 (0.48)	53 (0.45)	1.08 (0.70, 1.67)[a]	0.74
≥ 1 fall, n (%)	37 (45.7)	35 (43.2)	1.07 (0.57, 2.00)[b]	0.84
≥ 2 falls, n (%)	15 (18.5)	10 (12.3)	1.59 (0.67, 3.81)[b]	0.29

[a] Incidence rate ratio (IRR) calculated for comparing the rate of falls between the groups; [b] Relative risk (RR) calculated for comparing the number of fallers in each group. [c] Fall rate = per 100-person years. All analyses were adjusted for age, sex and falls history.



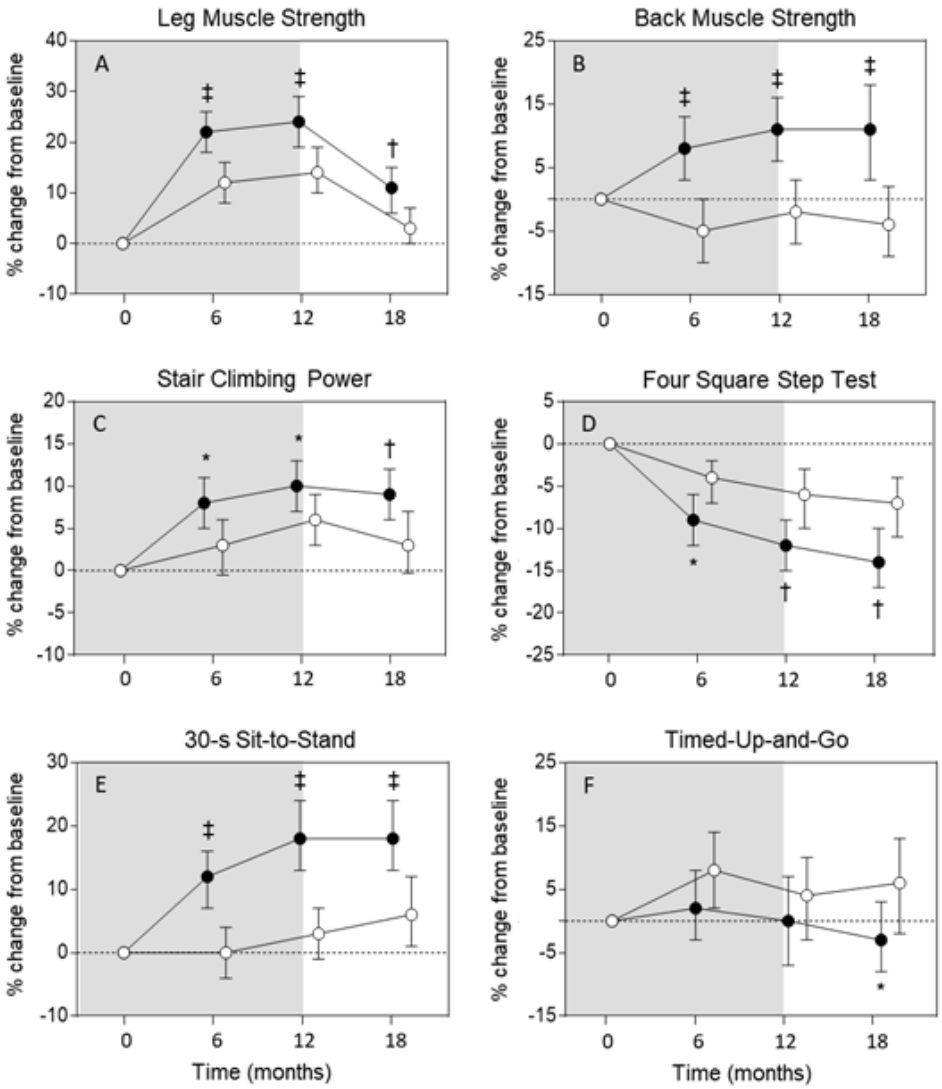


Table 1. Mean baseline values and within group changes in the *Osteo-cise* and control group for weight, total body fat mass and lean mass, total hip, femoral neck and lumbar spine bone mineral density after 12 and 18 months, and the net between group differences for the change relative to baseline.

Variable	Study Group				Intervention Effects	
	Osteo-cise		Control			
	Mean ± SD or 95% CI	***P-value***	***Mean ± SD or 95% CI***	***P-value***	***Net Difference***	***Group x Time (P)***
Weight					-	
Baseline, kg	73.3 ± 11.5		75.1 ± 14.9			
Δ 12 months	-0.17 (-0.74, 0.40)	*0.789*	-0.14 (-0.88, 0.59)	*0.676*	-0.03 (-0.95, 0.89)	*0.873*
Δ 18 months	-0.40 (-1.05, 0.24)	*0.185*	-0.51 (-1.36, 0.34)	*0.069*	0.11 (-0.94, 1.16)	*0.564*
Total body FM					-	
Baseline, kg	27.3 ± 8.0		28.3 ± 9.1			
Δ 12 months	-0.30 (-0.86, 0.25)	*0.292*	-0.36 (-0.97, 0.25)	*0.193*	0.06 (-0.76, 0.87)	*0.776*
Δ 18 months	-0.87 (-1.38, -0.37)	*<0.001*	-0.85 (-1.52, -0.18)	*0.001*	-0.02 (-0.85, 0.80)	*0.857*
Total body LM					-	
Baseline, kg	42.7 ± 7.9		43.6 ± 9.8			
Δ 12 months	0.26 (-0.19, 0.71)	*0.191*	0.09 (-0.34, 0.52)	*0.647*	0.17 (-0.45, 0.79)	*0.549*
Δ 18 months	0.48 (0.04, 0.92)	*0.019*	0.21 (-0.32, 0.73)	*0.342*	0.27 (-0.40, 0.95)	*0.359*
Total hip BMD					-	
Baseline, g/cm^2	0.899 ± 0.102		0.880 ± 0.105			
% Δ 12 months	0.90 (0.40, 1.40)	*<0.001*	0.52 (0.08, 0.96)	*0.025*	0.38 (-0.28, 1.04)	*0.301*
% Δ 18 months	0.61 (0.09, 1.14)	*0.015*	0.32 (-0.26, 0.91)	*0.250*	0.29 (-0.49, 1.07)	*0.345*
FN BMD					-	
Baseline, g/cm^2	0.730 ± 0.081		0.713 ± 0.082			
% Δ 12 months	0.63 (0.03, 1.22)	*0.057*	-0.40 (-0.98, 0.18)	*0.207*	1.03 (0.21, 1.86)	*0.025*
% Δ 18 months	0.60 (0.03, 1.16)	*0.058*	-1.33 (-2.00, -0.67)	*<0.001*	1.93 (1.07, 2.79)	*<0.001*
LS BMD					-	
Baseline, g/cm^2	0.971 ± 0.135		0.968 ± 0.146			
% Δ 12 months	1.45 (0.82, 2.08)	*<0.001*	0.31 (-0.34, 0.95)	*0.246*	1.14 (0.25, 2.03)	*0.042*
% Δ 18 months	1.49 (0.77, 2.21)	*<0.001*	0.76 (-0.03, 1.55)	*0.025*	0.73 (-0.33, 1.79)	*0.125*

FM, fat mass; LM, lean mass; FN, femoral neck, LS, lumbar spine. P, P-value. Baseline data represent means ± SD. Percentage change data represents means with 95% confidence intervals (95% CI). All statistical analyses were adjusted for sex.

Table 2. Mean baseline values and within group changes in the *Osteo-cise* and control group for MRI trabecular bone microarchitecture at the distal femur and proximal tibia after 18 months, and the net between group differences for the change relative to baseline.

		Study Group					
		Osteo-cise		Control		Intervention Effects	
	Variable	***Mean ± SD or 95% CI***	***P-value***	***Mean ± SD or 95% CI***	***P-value***	***Net Difference***	***Group x Time (P)***
Distal Femur	app. BV/TV					-	
	Baseline, %	0.318 ± 0.042		0.329 ± 0.036			
	% Δ 18 months	-2.20 (-3.74, -0.67)	*0.002*	-3.02 (-4.34, -1.69)	*<0.001*	0.82 (-1.19, 2.82)	*0.371*
	app. Tb.N					-	
	Baseline, mm^{-1}	1.124 ± 0.150		1.163 ± 0.124			
	% Δ 18 months	-2.23 (-3.73, -0.73)	*0.002*	-2.89 (-4.21, -1.57)	*<0.001*	0.66 (-1.31, 2.62)	*0.456*
	app. Tb.Th					-	
	Baseline, μm^{-1}	0.283 ± 0.002		0.283 ± 0.002			
	% Δ 18 months	0.01 (-0.14, 0.17)	*0.679*	-0.13 (-0.27, 0.00)	*0.052*	0.14 (-0.06, 0.35)	*0.132*
	app. Tb.Sp					-	
	Baseline, μm^{-1}	0.748 ± 0.154		0.707 ± 0.134			
	% Δ 18 months	5.24 (1.93, 8.54)	*0.006*	3.61 (1.19, 6.04)	*0.003*	1.63 (-2.42, 5.67)	*0.486*
Proximal Tibia	app. BV/TV					-	
	Baseline, %	0.318 ± 0.042		0.323 ± 0.036			
	% Δ 18 months	0.46 (-1.25, 2.16)	*0.563*	-1.29 (-2.63, 0.05)	*0.044*	1.75 (-0.39, 3.89)	*0.074*
	app. Tb.N					-	
	Baseline, mm^{-1}	1.121 ± 0.145		1.136 ± 0.120			
	% Δ 18 months	0.57 (-1.14, 2.27)	*0.912*	-1.07 (-2.38, 0.24)	*0.091*	1.64 (-0.48, 3.75)	*0.181*
	app. Tb.Th					-	
	Baseline, μm^{-1}	0.284 ± 0.002		0.284 ± 0.003			
	% Δ 18 months	-0.11 (-0.34, 0.12)	*0.524*	-0.22 (-0.44, 0.00)	*0.046*	0.11 (-0.20, 0.42)	*0.413*
	app. Tb.Sp					-	
	Baseline, μm^{-1}	0.632 ± 0.137		0.615 ± 0.109			
	% Δ 18 months	0.66 (-1.25, 2.57)	*0.403*	2.18 (0.03, 4.33)	*0.051*	-1.52 (-4.36, 1.32)	*0.354*

app.BV/TV, trabecular bone volume fraction; app.Tb.N, trabecular number; app.Tb.Sp, trabecular separation; app.Tb.Th, trabecular thickness. P, P-value. Baseline data represent means ± SD. Percentage change data represents means with 95% confidence intervals (95% CI). All statistical analyses were adjusted for sex.

Table 3. Falls in the *Osteo-cise* and control groups during the 18 month intervention

Outcomes	*Osteo-cise*	Control	IRR [a] / RR [b] (95% CI)	P-value
Previous falls, n (%)	11 (13.6)	10 (12.4)	-	-
Falls, n (rate) [c]	59 (0.48)	53 (0.45)	1.08 (0.70, 1.67)[a]	0.74
≥ 1 fall, n (%)	37 (45.7)	35 (43.2)	1.07 (0.57, 2.00)[b]	0.84
≥ 2 falls, n (%)	15 (18.5)	10 (12.3)	1.59 (0.67, 3.81)[b]	0.29

[a] Incidence rate ratio (IRR) calculated for comparing the rate of falls between the groups; [b] Relative risk (RR) calculated for comparing the number of fallers in each group. [c] Fall rate = per 100-person years. All analyses were adjusted for age, sex and falls history.