BMJ Open

The influence of antiresorptive bone medication on the effect of high-intensity resistance and impact training on osteoporotic fracture risk in postmenopausal women with low bone mass: protocol for the MEDEX-OP randomised controlled trial

Melanie Fischbacher,[1] Benjamin K Weeks,[1] Belinda R Beck[1,2]

¹Menzies Health Institute Queensland and School of Allied Health Sciences, Griffith University, Gold Coast, Queensland, Australia
²The Bone Clinic, Brisbane, Queensland, Australia

Correspondence to
Dr Belinda R Beck;
b.beck@griffith.edu.au

ABSTRACT

Introduction Antiresorptive medications increase bone density and decrease vertebral fracture, while high-intensity resistance and impact training (HiRIT) increases balance, bone and muscle strength decreasing risk for falls and fractures. Medications are typically prescribed by doctors and exercise by exercise specialists, frequently in isolation.

Objective Our primary aim is to determine the effect of an 8-month HiRIT programme with or without osteoporosis medications on bone mineral density (BMD) of the spine and hip in postmenopausal women with low bone mass.

Methods and analysis One hundred and sixty postmenopausal women with low bone mass will be recruited from the community to participate in an 8-month randomised controlled trial. Participants will be on stable doses of antiresorptive bone medication for at least 12 months (n=80) or have not taken bone medications for at least 12 months (n=80). Participants will be block randomised, stratified by medication intake, to twice-weekly 40-min supervised sessions of HiRIT or a low-intensity exercise programme (control). Primary outcomes include change in lumbar spine and total hip areal bone mineral density. Secondary outcomes include whole body, femoral neck and forearm BMD, proximal femur bone geometry and volumetric density, vertebral morphology, body composition, anthropometry, physical function, posture, rate of falls, osteoarthritis symptoms, pelvic floor health, quality of life, physical activity enjoyment, resting blood pressure, safety and compliance. All outcomes will be assessed at baseline and 8 months and intention-to-treat and per-protocol analyses will be conducted. Repeated measure analysis of covariance will be used to determine intervention effects on outcome measures, controlling for initial values, compliance and other variables found to differ between groups at baseline.

Ethics and dissemination The study has been approved by Griffith University Human Research Ethics Committee (Ref: 2017/739). Results will be reported in peer-reviewed journals and at conferences.

Strengths and limitations of this study

► This will be the first trial to investigate whether bone medication enhances the efficacy of high-intensity resistance and impact training (HiRIT) on indices of fracture risk in healthy postmenopausal women with low to very low bone mass.

► The inclusion of three dimensional hip analyses derived from dual-energy X-ray absorptiometry scans will provide insight into the response of bone geometry to HiRIT, beyond standard areal bone mineral density measures.

► A single investigator will conduct data collection and participant training optimising measurement reliability and training fidelity.

► Group allocation will not be blind to investigators or participants.

► Our study sample is limited to relatively healthy postmenopausal women, as will be the conclusions.

INTRODUCTION

Osteoporosis is defined as 'a skeletal disorder characterised by compromised bone strength predisposing a person to an increased risk of fracture'.[1] It is estimated that there are ~9 million osteoporotic fractures annually and >60% occur in women. In fact, one in three women over the age of 50 years will experience an osteoporotic fracture and the lifetime risk of sustaining a hip, forearm or vertebral fracture is equivalent to the risk of being diagnosed with a cardiovascular disease.[2] Osteoporotic fractures lead to significantly increased mortality, particularly in the

first year following a fracture, and a global loss of almost 6 million disability-adjusted life years annually.[3 4] With the rapid increase in the proportion of seniors over 65 years of age,[5] there will be a commensurate increase in prevalence of osteoporosis and incident fractures,[6] imposing significant personal, societal and economic burden.

As bone responds to changes in habitual mechanical loading, exercise is an important strategy to build and maintain bone mass at any stage of life.[7 8] Animal research has shown that mechanical loads should be applied in short bouts,[9] at high rates[10] and frequencies[11] and induce high-magnitude bone strains[12 13] in order to stimulate bone formation. As falling is a major risk factor for osteoporotic fractures, a complete exercise programme for osteoporosis should include elements aiming to decrease the incidence of falls. Resistance and balance training programme are the most effective strategies to improve muscle function and strength,[14] gait performance[15] and balance[16] to reduce the risk of falling.[17] Safety, feasibility and efficacy of a high-intensity resistance and impact training (HiRIT) programme for postmenopausal women with low bone mass was recently established in the Lifting Intervention For Training Muscle and Osteoporosis Rehabilitation (LIFTMOR) trial.[18 19] In the latter trial, 8 months of HiRIT produced a net gain in bone density at the lumbar spine (LS) and femoral neck of 4.1% and 2.3%, respectively, compared with a very low-intensity exercise control . The programme also improved muscle strength, mobility and balance. Only one mild adverse event occurred during a training session, which was resolved within 1 week, and no fragility fractures occurred,[20] suggesting the programme was safe for otherwise healthy postmenopausal women with low bone mass.[18]

Pharmacological management of osteoporosis comprises anabolic and antiresorptive agents. The latter have most commonly included bisphosphonates (eg, alendronate, risedronate, zoledronic acid) and human monoclonal antibody (denosumab), which are recommended as first-line therapy for osteoporosis. Bisphosphonates and denosumab act on osteoclasts and slow bone resorption through slightly different pathways. Nitrogen containing bisphosphonates bind the mineral component of bone and disrupt the mevalonate pathway, thereby preventing the formation of metabolites that are essential for osteoclast function. As a result, osteoclasts undergo apoptosis and the process of bone resorption slows.[21] Denosumab on the other hand acts as a Receptor Activator of NK-kB ligand (RANKL) inhibitor in the Receptor Activator of NK-kB (RANK)/RANKL pathway to decrease osteoclast activity.[21] Both types of medication can result in increased bone mineral density (BMD), particularly at the spine, and reduce the risk for vertebral and other fractures.[22–24]

While the independent efficacy of drugs and exercise has been confirmed, they are typically applied in isolation; medications being prescribed by doctors, whereas targeted physical activity is prescribed by exercise specialists. In light of the different mechanisms of action of exercise and medication on bone, it is not unreasonable to hypothesise that the combination of bone-targeted exercise and antiresorptive medication may be an even more effective strategy to reduce osteoporotic fracture risk than either alone. Studies in ovariectomised rats have indeed found additive effects of exercise and bisphosphonate therapy for whole body and proximal femur BMD and bone mineral content.[25 26] By contrast, the two trials conducted in postmenopausal women report no such additive benefit in humans.[27 28] Shortcomings in trial design may account for the reported outcomes. Neither trial employed both impact and resistance training[27 28] and one study was clearly underpowered.[27] An adequately powered study examining the combined effect of osteoporosis drug therapy and resistance and impact training on bone fracture risk factors is therefore indicated.

METHODS AND ANALYSES
Study aims
The overall objective of the proposed study is to determine the influence of antiresorptive osteoporosis medication on the efficacy of a HiRIT programme to improve factors of risk for osteoporotic fracture in postmenopausal women with low bone mass.

The primary aim is to determine the effect of an 8-month, twice-weekly, bone-targeted, supervised HiRIT programme with or without osteoporosis medications compared with control, on areal bone mineral density (aBMD) of the LS and total hip (TH) in postmenopausal women with low bone mass. We hypothesise that following 8 months of twice-weekly training, the HiRIT group on medications will experience greater improvement in LS and TH aBMD compared with the HiRIT group not on medications or the control group (CON) on medications.

Secondary aims include the effect of a HiRIT programme with or without osteoporosis medications on bone mass and strength at the femoral neck, forearm and whole body, vertebral morphology, body composition, anthropometry, physical function, posture, rate of falls, osteoarthritis symptoms, pelvic floor health, health-related quality of life, physical activity enjoyment, resting blood pressure, safety and compliance.

Study design
MEDEX-OP is an 8-month, randomised, controlled exercise intervention trial. Proposed participant flow is illustrated in figure 1. Postmenopausal women with low bone mass, who have been on or off stable doses of antiresorptive bone medication for at least 12 months are to be recruited from the community and randomly allocated, stratified for presence or absence of medication intake, to HiRIT or CON. All participants will undergo baseline and 8-month testing, which will include measures of BMD, bone geometry, body composition, anthropometry, physical function, posture, previous falls and fractures, osteoarthritis symptoms, pelvic floor health, health-related
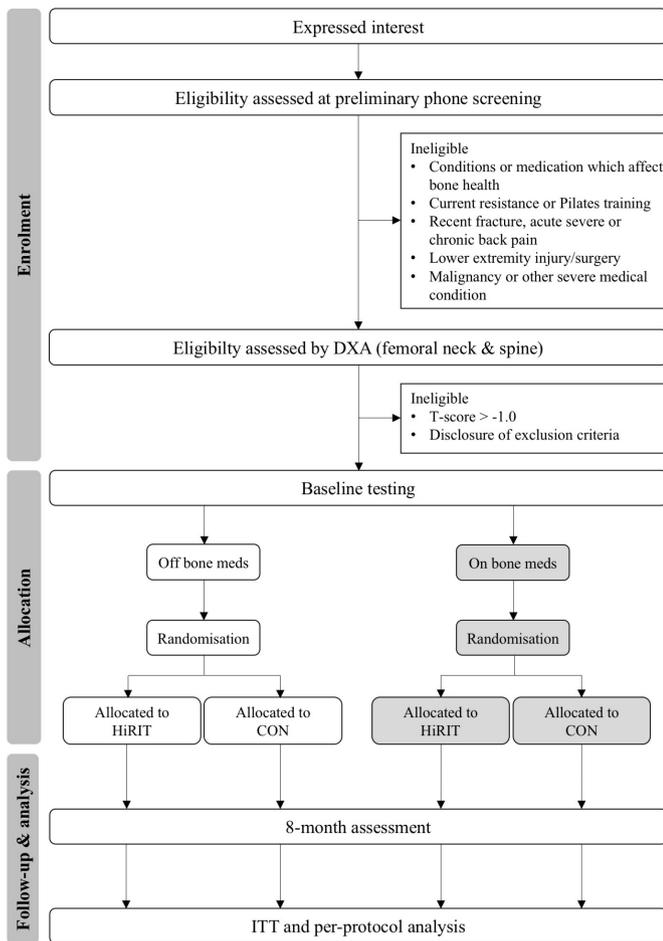
Figure 1 Proposed participant flow (consort diagram). CON, control group; DXA, dual-energy X-ray absorptiometry; HiRIT, high-intensity resistance and impact training; ITT, intention-to-treat.

quality of life, physical activity enjoyment and resting blood pressure.

Sample size

The sample size calculation was based on observations from the LIFTMOR trial, a recent study that observed a significant effect of the HiRIT programme on bone health in postmenopausal women with low bone mass.[18] To detect a 2.3% difference in hip BMD (Cohen's d=0.67), at α=0.05, for 80% power will require a group n of 39. To detect a 4.1% difference in LS BMD (Cohen's d=1.36), at α=0.05, for 80% power, a group n of 11 and a total N of 44 will be required.

Therefore, with a sample size of 160 women (n=40 per group), we will have 80% power to detect changes in hip BMD and 99% power to detect changes in LS BMD according to the condition on or off medication. Sample size calculations were conducted using an online calculator (https://www.stat.ubc.ca/~rollin/stats/ssize/n2.html). Recruitment began in March 2018 and will continue until the planned sample size is acquired.

Setting and recruitment

Participants will be recruited independently from the community through print media, social media, radio, bespoke website (www.medexop.org), word of mouth, posters and flyers, and presentations at local community groups and retirement villages. To achieve recruitment of participants who are currently taking antiresorptive bone medication, we will collaborate with local endocrinologists, radiology clinics and pharmacies, who will distribute study flyers and information to suitable clients. Prospective participants who express their interest in the study will be provided with a verbal description of the study and a three-page information package including the consent form. They will be given a minimum of 48 hours to study the document before being contacted again for a preliminary phone screening for eligibility and the opportunity to ask questions.

Eligibility and screening

Otherwise healthy postmenopausal women with low bone mass or osteoporosis (maximum T score −1.0 at hip or spine) will be recruited. Participants will be included if they are at least 5 years postmenopause, or 50 years or older if they had a hysterectomy, in good general health, ambulant without a walking aid, and willing and able to undertake activities of either of the two groups. They must have been taking antiresorptive bone medication (bisphosphonate or denosumab) for at least 12 months or not taking bone medication for at least 12 months, and not intending to alter that choice for the 8-month study period. Participants will be excluded if any of the following criteria apply: are or have been (12 months prior to enrolment) taking anabolic medication (eg, teriparatide), hormone replacement therapy or selective oestrogen receptor modulators (eg, raloxifene); have had a lower limb joint injury or surgery, recent fracture, localised back pain or malignancy; currently receiving chemotherapy or radiation therapy; have contraindications for participating in heavy physical activity; have conditions known to influence bone health (eg, thyrotoxicosis or hyperparathyroidism, Paget's disease, renal disease, diabetes, immobility); taking other medication known to influence bone health (eg, prolonged use of corticosteroids, thyroxine, thiazides or antiretroviral agents); have medical conditions or lifestyle plans that would prevent adoption of either of the two group activities for the intervention duration (eg, uncontrolled cardiovascular disease, nerve disorder, spinal cord injuries; longer than 3 weeks planned holiday in the next 8 months, planned weight loss); and/or are unable or unwilling to attend twice-weekly supervised exercise classes. Participants who have had more than two radiation-related exposures in the 12 months prior to enrolment may participate if they wish, but will be required to give specific informed written consent to undergoing further radiation-based scanning during the course of the trial.

Prospective participants who express interest in the study will undergo a preliminary phone screening for

eligibility. If eligible after preliminary screening, they will be invited to attend a BMD assessment and, if LS and/or femoral neck T-scores are less than −1.0, will be deemed eligible and will undergo all remaining baseline measures.

The following reasons could lead to early discontinuation of participation in the study: (1) withdrawal of consent, (2) initiation of or discontinuation of osteoporosis medications, or initiation of medication known to affect bone metabolism, (3) postenrolment detection or disclosure of exclusion criteria, (4) adverse event or injury external to trial activities restricting the ability to conduct group activities, (5) failure to present or ceasing contact with investigators (lost to follow-up) and (6) advice to cease training by a medical professional (eg, their general practitioner). In cases of early withdrawal, participants will nevertheless be encouraged to attend their 8-month testing session. If a participant is withdrawn because an exclusion criteria was not disclosed at baseline, that participant will be replaced. This includes participants who withdraw their consent after baseline testing, before commencing the exercise programme; the exclusion criterion being 'unwilling to attend twice-weekly supervised exercise classes'.

Randomisation, allocation and blinding

Randomisation to HiRIT or CON will be stratified for presence or absence of stable doses of osteoporosis medication for the previous 12 months, using a computer-generated randomisation sequence (www.randomization.com, accessed 26 September 2017). Randomisation of participants on medication will be further stratified by medication type (denosumab vs bisphosphonates). The allocation sequence will be sealed in sequentially numbered, opaque envelopes in advance. On completion of baseline testing, participants will be randomly allocated to a group. In this way, the investigator performing baseline assessments will be blinded to allocation sequence. Follow-up testing will be conducted by the same investigator as baseline testing to maintain the highest level of test–retest reliability. Study participants cannot be blinded to group allocation; however, they will be blinded to the study hypotheses being tested, in other words, which exercise group is considered to be the 'active control'.

Group allocations
High-intensity resistance and impact training

Participants in the HiRIT group will attend two training sessions of 30–40 min per week on non-consecutive days. The classes will be supervised by a qualified exercise scientist. The programme, based on the recently published LIFTMOR protocol,[18] consists of three fundamental free weight exercises (back squat, overhead press, deadlift) and one impact exercise (jumping chin-ups). In addition, participants will perform two balance exercises that will vary each session.

The first 2 weeks of the intervention will serve as familiarisation during which time only bodyweight variants of the lifting exercises will be performed. For the following 2 weeks, the four movements will be practiced with little to no weight (eg, wooden plates/broomstick) with the focus on correct lifting technique. Those 4 weeks serve as an accommodation period for participants who are new to resistance training, to minimise risk of injuries and consolidate technique. From week 5 onwards, participants will perform five sets of five repetitions for each exercise with the focus on progression of loading to 80%–85% of their one repetition maximum. Loads will be progressively increased in 2.5 kg increments for deadlifts and squats and 1–1.5 kg increments for overhead presses. The 6–20 point Borg scale will be used to monitor intensity and guide progression of the load. Participants will aim for a rating of perceived exertion (RPE) of ≥16 which represents 'very hard' or 'high' intensity. Five sets of five repetitions of jumping chin-ups with a flat-footed landing will be performed each session. During the 2-week familiarisation period, participants will perform only heel drops. The intensity of the impact will then be gradually increased, as tolerated, through landings with decreasingly bent knees and hips, ultimately aiming for a stiff-legged landing.

CON activities

Cognisant of the potential for drop out of CON participants who sign up for an exercise trial, the decision was made to include an active CON involving low-intensity loading that is unlikely to provide an osteogenic stimulus but provides an equivalent exposure to supervised exercise sessions.[29] The CON will therefore attend 40 min of a twice-weekly supervised mat Pilates programme on non-consecutive days, led by a certified instructor. The programme focuses on posture, breathing and strengthening core, back, hips and arms. Each class will start with a warm-up in a standing position, followed by Pilates movements on the mat. Mat Pilates exercises are conducted in a supine (eg, single leg stretch, the hundred), side-lying (eg, side leg lift, clam shells) prone (eg, single leg kick, grasshopper) and quadruped position (eg, four-point kneeling). The last 10 min of each session are performed in a standing, weight-bearing position and include balance, resistance (eg, squats, biceps curls) and impact exercises (eg, stomping). Small weights are used during that standing section. No equipment other than Pilates mats and dumbbells are used. All exercises can be simplified or progressed and targeted to the individual level. While the Pilates programme adopted as our active control condition is currently marketed as osteoporosis exercise therapy (Buff Bones), there is no evidence that loading of this low-intensity nature provides an osteogenic stimulus and considerable evidence to suggest otherwise.

The Pilates programme is specifically designed for people with low bone mass and safe movement for this population is emphasised. No exercises that include spine flexion and rotation will be performed. Each participant in the Pilates/CON will receive an introduction before the first session to familiarise them with the exercises, and explain and practice the fundamental concepts.

Outcome measures

All outcome measures will be examined at baseline and 8 months by a single investigator, blind to group allocation at baseline (table 1). Identical equipment and standardised procedures will be used for each testing session.

Primary outcome

The primary outcomes include change in LS aBMD and TH aBMD assessed by dual-energy X-ray absorptiometry (DXA; Medix DR, Medilink, Mauguio, France).

Secondary outcomes

Secondary outcomes, described in detail below, include changes in indices of bone strength of whole body, proximal femur, LS and radius; anthropometrics and body composition; vertebral morphology; muscle strength, balance, functional mobility and posture; rate of incident falls; quality of life related to osteoarthritis, pelvic floor health and general mental and physical health; and resting blood pressure; along with exercise enjoyment; safety and compliance with the two exercise programme.

Fracture incidence will be recorded as an exploratory outcome, cognisant of the likelihood of insufficient power for formal analysis.

Bone strength indices

aBMD and bone mineral content (BMC) of the whole body, bilateral proximal femur (TH, trochanter, femoral neck), anterior–posterior LS and non-dominant forearm will be determined by DXA (Medix DR, Medilink, Mauguio, France). Three-dimensional hip analysis software (DMS Group, Mauguio, France) will be used to extract bone geometry (cortical thickness and so on) and volumetric parameters of the femoral neck and TH regions from the proximal femur DXA scans.

Anthropometrics and body composition

Height will be measured using a wall-mounted stadiometer (Seca 216, Seca, Hamburg, Germany) and weight will be measured using a digital scale (Model MS 3200, Charder, Taichung City, Taiwan) without shoes and in light clothing. Body mass index (BMI) will be calculated (BMI=weight/height^2, kg/m^2). Waist circumference will be measured according to the guidelines of the National Institute of Health using a measuring tape, which will be positioned at the level of the iliac crest on bare skin.[30] Whole body DXA scans (Medix DR, Medilink, Mauguio, France) will be used to determine lean and fat mass, including total % body fat using standard manufacturer procedures and analysis software (V.4.5.9.0 or current version).

Posture

Kyphosis will be examined in a number of ways. Forward head displacement in relation to the body will be quantified by tragus-to-wall distance.[31] The participant will stand relaxed with buttocks and back against the wall and head in their natural position (eyes forward, chin not tucked in). A measure from the anterior-most part of the tragus

of the right ear to the wall will be taken. Thoracic kyphosis will be measured with participants standing in both their usual relaxed and erect postures using a gravity-referenced inclinometer (Australasian Medical & Therapeutic Instruments, Brendale, Australia). The spinous process of the 1st (T1) and 12th (T12) thoracic vertebrae will be identified as anatomical landmarks. The dial of the inclinometer will be set at zero at T1 and then placed at T12 to measure the measure the thoracic kyphosis angle.[32] The average of three measurements will be calculated and used for analyses. Kyphosis will also be evaluated based on a lateral thoracolumbar spine DXA scan (Medix DR, Medilink, Mauguio, France). The Cobb angle will be calculated by extending lines from the superior endplate of the 4th and inferior endplate of the 12th thoracic vertebra. The angle formed by the intersection of lines drawn perpendicular to the extended lines defines the Cobb angle for kyphosis.[33] The lateral spine scan will also be used for a digital vertebral assessment. Presence of deformation and fractures of the vertebral bodies from T5 to L4 will be identified using the semiquantitative Genant method.[34]

Mobility

Functional mobility will be assessed by the timed up-and-go and the five times sit-to-stand tests and by measuring gait speed.[35 36] For the timed up-and-go test, the participant will be asked to rise from a seated position without using their arms for assistance, walk a distance of 3 metres, turn at the indicated mark, walk back and sit down.[37] Participants will be asked to walk as fast as possible without running. The five times sit-to-stand test assesses functional lower limb muscle strength and mobility. Participants will be asked to stand up from a seated position to a fully upright position (knees and hips fully extended) and sit down five times as quickly as possible with their arms folded across their chest.[38] The timed up-and-go and the five-times sit-to-stand tests will be performed three times and the fastest attempt for each test will be used for analyses. Gait speed will be measured over a distance of 6 metres. The participant will walk a distance of 10 metres at their usual, preferred speed and time will be measured for the intermediate 6 metres to allow 2 metres for acceleration and 2 metres for deceleration.[39] An additional test will be performed at a fast walking speed where participants will walk the same 10 metres as fast as they can without running. Participants will complete three walks for both conditions, usual and fast walking, and the average time of the three attempts will be used to calculate gait speed.

Isometric strength

Back extensor muscle strength will be examined using a handheld dynamometer (Lafayette Manual Muscle Testing System, Lafayette, USA) which measures peak force in kilograms during isometric back extension.[40 41] The participant will stand with her back to the wall between two vertically oriented anchor rails, with a broad inelastic strap secured firmly 2 cm inferior to the

Table 1 Summary of outcome measures to be collected

Measure	Unit	Data collection method
Primary outcome measure		
Lumbar spine aBMD	g/cm^2	DXA (Medix DR, Medilink, Mauguio, France)
Total hip aBMD	g/cm^2	DXA (Medix DR, Medilink, Mauguio, France)
Secondary outcome measures		
Bone strength indices		
Lumbar spine BMC	g	DXA (Medix DR, Medilink, Mauguio, France)
Total hip trabecular, cortical and total BMC; vBMD; volume; cortical thickness	g; g/cm^3; cm^3; mm	Proximal femur DXA scan, 3D hip software (DMS group, Mauguio, France)
Femoral neck trabecular, cortical and total BMC; vBMD; volume; cortical thickness	g; g/cm^3; cm^3; mm	Proximal femur DXA scan, 3D hip software (DMS group, Mauguio, France)
Whole body aBMD; BMC	g/cm^2; g	DXA (Medix DR, Medilink, Mauguio, France)
Ultradistal, 33% and total radius aBMD; BMC	g/cm^2; g	DXA (Medix DR, Medilink, Mauguio, France)
Vertebral morphology		
Vertebral fractures, changes in vertebral morphology		DXA (Medix DR, Medilink, Mauguio, France)
Anthropometry		
Height	cm	Wall-mounted stadiometer (Seca 216, Seca, Hamburg, Germany)
Weight	kg	Digital scale (Model MS 3200 Charder, Taichung City, Taiwan)
Waist circumference	cm	Measuring tape
Body composition		
Whole body (lean mass; fat mass; body fat percentage)	g; g; %	DXA (Medix DR, Medilink, Mauguio, France)
Muscle strength		
Lower extremity isometric strength	kg	Leg dynamometer (TTM Muscle Meter, Tokyo, Japan)
Back extensor isometric strength	kg	Dynamometer (Lafayette Manual Muscle Testing Systems, Lafayette, USA)
Hand grip isometric strength	kg	Dynamometer (JAMAR Plus, Patterson Medical, Sammons Preston, Bolingbrook, Illinois, USA)
Mobility		
Timed up-and-go	s	Stop watch
Five times sit-to-stand	s	Stop watch
Gait speed	m/s	Stop watch
Balance		
Functional reach	cm	Functional reach board, ruler
Tandem walk	s	Stop watch
Posture		
Relaxed and erect kyphosis	°	Inclinometer (Australasian Medical & Therapeutic Instruments, Brendale, Australia)
Tragus to wall distance	cm	Ruler
Cobb angle of kyphosis	°	DXA (Medix, DR, Medilink, Mauguio, France)
Quality of life and physical activity enjoyment		
Mental and physical health	Scores	SF-36 questionnaire
Pelvic floor health	Scores	PFDI-20 and PFIQ-7 questionnaire
Osteoarthritis symptoms	Scores	WOMAC questionnaire

Table 1 Continued

Measure	Unit	Data collection method
Physical activity enjoyment	Score	PACES questionnaire
Safety and compliance		
Adverse events		Training diaries, investigator records
Compliance		Training diaries, instructor records
Exploratory outcome measures		
Incident number of falls		Training diaries, investigator records
Incident number of fractures		Training diaries, investigator records

aBMD, areal bone mineral density; BMC, bone mineral content; DXA, dual-energy X-ray absorptiometry; PACES, Physical Activity Enjoyment Scale; PFDI-20, Pelvic Floor Distress Inventory; PFIQ-7, Pelvic Floor Impact Questionnaire; SF-36, 36-item Short Form Health Survey; vBMD, volumetric bone mineral density; WOMAC, Western Ontario and McMaster Universities.

iliac crest to prevent movement away from the wall. The dynamometer will be placed on the back over the seventh thoracic spinous process while the participant flexes slightly at the trunk with arms crossed. The participant will then be instructed to push as hard as possible back into the instrument against the wall.

An isometric dynamometer platform (TTM Muscular Meter, Tokyo, Japan) will be used to measure maximal isometric strength of the lower extremities.[42 43] Participants will stand on the platform with their knees flexed to 115° and their back flat against the wall. A bar handle will be connected to the dynamometer by a chain at a length so the participants will have to fully extend the elbows to reach and grip it. They will be instructed to attempt to straighten their legs and slide up the wall, while keeping their back fully against the wall at all times[44] (Little *et al*, unpublished data, 2014).

Grip strength will be measured using an isometric hand-held dynamometer (JAMAR Plus, Patterson Medical, Sammons Preston, Bolingbrook, Illinois, USA).[45] Participants will sit upright in a chair without arm rests with feet touching the floor, knees and hips at 90°, their shoulder adducted by their side and neutrally rotated, elbow flexed to 90°, with the forearm and wrist in a neutral position. The dynamometer will then be handed to the participant who will be instructed to squeeze with maximum strength.[46] The grip size setting that is most comfortable for the participant will be used.[47]

Each of the strength tests will be performed three times and the maximum effort will be recorded for analysis.

Balance

The functional reach test measures the maximum distance a person can reach forward while standing, thereby assessing dynamic balance during an internally generated perturbation.[48] The test will be conducted according to the original published protocol with the exception that a functional reach board will be used instead of a yardstick.[49] The participant will stand in the starting position with shoulders perpendicular to the wall, their right side closest to the board and their right upper extremity in 90° shoulder flexion with a closed fist (starting position).

The location of the third metacarpal head on the functional reach board in the starting position will be noted. The participant will then reach forward as far as possible without taking a step or losing balance and the end position (third metacarpal head) in relation to the functional reach board will be noted. The horizontal distance in cm between the end and start locations will be recorded. The greatest distance from three trials will be used for analysis.

Dynamic balance will be assessed using the tandem walk test.[36 48] The tandem walk test is a 6-metre heel-to-toe walk wherein participants are asked to walk along a line on the floor by alternately placing one foot directly in front of the other with no gaps in between.[50] Time to complete the 6-metre distance will be recorded and mistakes during the walk will be counted. Mistakes will include gaps left between feet or misplacement of a foot off the line. The time of the attempt with the least mistakes or, if no or an equal number of mistakes occur in each attempt, the fastest time will be recorded.

Quality of life

The 36-item Short Form Health Survey (SF-36) is a self-reported quality of life measure, assessing physical and mental health and well-being. The SF-36 consists of eight sections (general health, physical and social function, role limitations due to physical and emotional problems, mental health, vitality and pain) and each of the eight sections has good test–retest reliability.[51] The SF-36 has been used previously in osteoporosis studies[52 53] and scores significantly correlate with those from an osteoporosis-specific quality of life instrument, the quality of life questionnaire of the European Foundation for Osteoporosis 41/QUALEFFO 41.[54] The SF-36 will be self-administered using the RAND SF-36 iPad app which directly calculates physical and mental health scores.

Pelvic floor health

The short forms of the Pelvic Floor Distress Inventory (PFDI-20) and Pelvic Floor Impact Questionnaire (PFIQ-7) will be used to assess the impact of pelvic floor health on quality of life.[55] The PFDI-20 short form consists of 20 items and three scales (Urinary Distress Inventory,

Pelvic Organ Prolapse Distress Inventory and Colorectal-Anal Distress Inventory) while the PFIQ-7 short form includes seven items rated against three domains (bladder or urine, bowel or rectum, vagina or pelvis). All scales of the short forms correlate significantly with their long form counterparts.[56] Both questionnaires will be self-administered. Scores for each subscale and composite scores will be calculated for each questionnaire, following the official scoring rules for PFIQ-7 and PFDI-20.

Osteoarthritis symptoms
The Western Ontario and McMaster Universities Osteoarthritis Index is a widely used questionnaire to evaluate pain, stiffness and physical functioning of the joints.[57] It consists of 24 items (5 for pain, 2 for stiffness and 17 for physical function) that are rated on a 5-point Likert scale (none, mild, moderate, severe, extreme). Scores are calculated for each subscale and the three scores are summed for a composite score. Higher scores indicate worse pain and stiffness and more limitation in function.[58] The questionnaire will be self-administered.

Physical activity enjoyment
Physical activity enjoyment will be evaluated using the Physical Activity Enjoyment Scale (PACES).[59] The PACES is a self-reported questionnaire and participants will be asked to rate each of the eight items on a 7-point bipolar rating scale. Higher scores reflect greater levels of exercise enjoyment. PACES will be administered after 4 months in addition to baseline and 8-month visits as a new exercise routine may change physical activity enjoyment over time.

Illness/injuries and adverse events
Participants will record any new health events or diagnoses including illness, falls and fractures in their training diary and report them to the research team. Changes in medication intake will also be recorded. Prior to each session, participants will rate their current muscle soreness on a 10-point visual analogue scale. For any conditions related to the study interventions, beyond regular muscle soreness, an injury report will be completed and the injury will be reported to the ethics committee. Adverse events associated with HiRIT and CON activities will be closely monitored and recorded by the investigators including details of severity and outcomes.

Circumstances and consequences of each fall and fracture will be ascertained by a questionnaire specifically designed for the study. Falling will be defined as unintentionally coming to rest on the ground, floor or other lower level.[60 61] Low-trauma fractures will be defined as fractures that result from minor or moderate trauma such as falling from a standing height or minimal impact fractures (eg, coughing, sneezing). High-trauma fractures will be those that result from high impact such as falling from a height or being hit by an object (eg, car).[60]

Compliance
Participants in both exercise groups will record attendance at exercise sessions in their training diaries. In addition,

the instructor will document attendance on a spreadsheet after every class. Compliance to the programme will be based on the percentage of classes attended during the intervention period in relation to total possible sessions, with 100% compliance defined as completion of two sessions per week for 8 months or 70 sessions.

Lifestyle behaviours
Average daily calcium intake and historical bone-relevant physical activity will be assessed at baseline and 8 months for comprehensive characterisation of lifestyle behaviours with the potential to influence bone outcomes in order to adjust for any between group differences.

Daily calcium intake
Average daily calcium intake will be estimated using the AusCal, a food frequency questionnaire specific to the Australian diet. It assesses frequency (per day, week or month) of consumption of calcium-rich foods and beverages and any calcium supplementation.[62] The questionnaire will be tester-administered and analysed using an online calculator to estimate daily intake from diet and supplements (mg) (http://calciumcalculator.com.au/).

Historical bone-relevant physical activity
The Bone-specific Physical Activity Questionnaire (BPAQ) is an instrument designed to quantify historical bone-relevant physical activity participation.[63] Participants will be asked to record all sports and physical activities they have participated in at least weekly over the last 12 months. For all activities they have engaged in for at least one sporting season throughout their lifetime, they will be asked to record their age and the number of years/seasons of participation. BPAQ scores will be calculated using custom-designed software (http://www.fithdysign.com/BPAQ/).

Data integrity
To ensure participant confidentiality, all will be allocated a study ID and data will be deidentified for analyses and publications. Hard copy records will be stored in a locked filing cabinet and electronic data will be securely stored on a password-protected computer and backed up regularly onto a secure hard drive. The Griffith University Code for the Responsible Conduct of Research will be followed for management, storage and retention of research data. Deidentified data may be shared on a case-by-case basis for meta-analyses or other collaborations. Test results, such as the reports from DXA scans, may be shared with a participant's general practitioner if the participant explicitly requests it or has given consent.

Data analyses
All statistical analyses will be conducted in SPSS statistical software (v24.0 or most current version).

Normality of the distribution will be tested using Kolmogorov-Smirnov test. Baseline descriptive characteristics of participants will be compared based on treatment assignment and medication intake (yes/no) and

presented as means±SD. Differences in baseline characteristics between groups will be evaluated with T-tests for continuous variables and χ^2 tests for categorical variables.

Comparison of mean change in primary and secondary outcomes between HiRIT and CON will be examined by repeated measures analysis of covariance, adjusting for initial values and compliance and any other variable found to differ between groups at baseline. Duration of medication exposure will be included as a covariate for the groups on medication. The intention-to-treat (ITT) approach will be adopted. All participants who were randomised to receive treatment will be included in ITT analyses, regardless of compliance or discontinuation of the intervention. For drop outs where 8-month follow-up data are missing, mean percentage change values for the specific treatment group will be imputed. Per-protocol analyses will include participants who underwent both the baseline and 8-month follow-up assessments and who completed at least 70% of exercise intervention sessions.

Multiple linear regression analyses of absolute change from baseline will be employed to examine the relative influence of certain variables on outcome measures. It is recognised that duration and nature (bisphosphonates vs denosumab) of therapeutic exposure will influence bone response. Statistical significance level will be set at 5% for analyses (α=0.05, two-sided).

Ethics and dissemination

The trial has been registered with the Australian and New Zealand Clinical Trial Registry (ANZCTR). Written informed consent will be obtained from all participants at baseline, prior to testing by the investigator.

The LIFTMOR trial, which has previously examined a HiRIT programme in postmenopausal women with low bone mass, reported a very low risk for injuries and only one mild adverse event from the exercise protocol which provides preliminary evidence for the safety of the intervention.[18] Early termination of the study is therefore unlikely and the engagement of a data safety monitoring board was not deemed necessary in addition to GriffithUniversity Human Research Ethics Committee (GUHREC) monitoring processes. Safety will be monitored through compulsory annual progress reports to the GUHREC and 24hours reporting of adverse events for GUHREC review.

The results of the study will be disseminated through the usual scientific reporting channels, including presentation at discipline-specific conferences and publication in peer-reviewed journals. All study participants will be provided with a summary of their individual results and a lay summary of the findings after completion of the trial.

Patient and public involvement

Participants will be drawn from the general community but have not been consulted on the design, conduct and reporting of the research.

DISCUSSION

The current study will be the first adequately powered trial to investigate the effect of HiRIT in combination with antiresorptive bone medication intake on indices of osteoporotic fracture risk in healthy postmenopausal women with low to very low bone mass. The goal is to examine the combined effect of two therapeutic strategies that have typically been prescribed in isolation. Findings from the study will help to bridge the gap between healthcare providers and offer a novel pragmatic approach to osteoporosis management.

Only two studies have previously examined the question of an interaction between exercise and bisphosphonate therapy on BMD in postmenopausal women and both suggested there is no additive benefit.[27 28] One trial examined the independent and combined effect of 12 months of a thrice-weekly, progressive jumping exercise and/or 5 mg of alendronate daily compared with placebo and no exercise in 159 postmenopausal women.[28] A second study used the same design, study population and intervention period to examine the independent and combined effect of a thrice-weekly, moderate-intensity resistance training and/or intermittent cyclical etidronate (400 mg/day of etidronate for 14 day followed by 76 day of 500 mg/day of calcium carbonate) in 57 postmenopausal women.[27] The first study examined the effect of only impact exercises, while the other employed only resistance training. The combination of both, resistance and impact training has been suggested to be more effective than either intervention alone.[64] The small sample size in the second study suggests a lack of statistical power may have contributed to the absence of reported effects.[27]

There are several limitations of the current study. First, the investigator assessing the outcomes and adverse events will not be blinded to group allocation at the time of follow-up testing as they will also be the instructor of the exercise classes. The employment of an independent blinded outcome assessor was beyond the resources of the project. The high intratester reliability achieved by a single assessor at baseline and follow-up goes someway to offset this limitation. Second, for reasons of participant retention after randomisation, we elected to adopt a positive CON such that our CON will not be entirely exercise naïve. While this situation has the potential to reduce the sensitivity of our measures to detect a difference between groups, we note the same study design was used successfully in the LIFTMOR trial with no such limitations to outcomes. We adopted a Pilates programme as our control in light of the evidence that similarly low-intensity exercise is unlikely to be osteogenic.[29] Furthermore, the design facilitates the dispensing of an equivalent degree of supervised exercise exposure between groups. Third, our study sample is limited to relatively healthy ambulant women with low bone mass at least 5years postmenopause, which has the potential to limit the generalisability of our findings to a somewhat healthy ageing demographic.

In conclusion, the proposed study is expected to advance recommendations to manage osteoporosis by

determining whether commonly prescribed antiresorptive bone medication enhances the efficacy of a known effective exercise stimulus.

REFERENCES

1. NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy. Osteoporosis prevention, diagnosis, and therapy. *JAMA* 2001;285:785–95.
2. Kanis JA. Diagnosis of osteoporosis and assessment of fracture risk. *The Lancet* 2002;359:1929–36.
3. Johnell O, Kanis JA. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. *Osteoporos Int* 2006;17:1726–33.
4. Teng GG, Curtis JR, Saag KG. Mortality and osteoporotic fractures: is the link causal, and is it modifiable? *Clin Exp Rheumatol* 2008;26(5 Suppl 51):S125–37.
5. Kevin K, Wan H, World: AA. *An aging world: 2008*. Washington DC: Us government printing office, 2009.
6. Reginster J-Y, Burlet N. Osteoporosis: a still increasing prevalence. *Bone* 2006;38:4–9.
7. Hernandez CJ, Beaupré GS, Carter DR. A theoretical analysis of the relative influences of peak BMD, age-related bone loss and menopause on the development of osteoporosis. *Osteoporos Int* 2003;14:843–7.
8. Beck BR. Exercise for bone in Childhood—Hitting the sweet spot. *Pediatr Exerc Sci* 2017;29:440–9.
9. Robling AG, Burr DB, Turner CH. Recovery periods restore mechanosensitivity to dynamically loaded bone. *J Exp Biol* 2001;204:3389–99.
10. O'Connor JA, Lanyon LE, MacFie H. The influence of strain rate on adaptive bone remodelling. *J Biomech* 1982;15:767–81.
11. Hsieh Y-F, Turner CH. Effects of loading frequency on mechanically induced bone formation. *J Bone Miner Res* 2001;16:918–24.
12. Rubin CT, Lanyon LE. Regulation of bone mass by mechanical strain magnitude. *Calcif Tissue Int* 1985;37:411–7.
13. Mosley JR, March BM, Lynch J, *et al*. Strain magnitude related changes in whole bone architecture in growing rats. *Bone* 1997;20:191–8.
14. Liu C-ju, Latham NK. Progressive resistance strength training for improving physical function in older adults. *Cochrane Database Syst Rev* 2009;(3).
15. Van Abbema R, De Greef M, Crajé C, *et al*. What type, or combination of exercise can improve preferred gait speed in older adults? A meta-analysis. *BMC Geriatr* 2015;15:72.
16. Lesinski M, Hortobágyi T, Muehlbauer T, *et al*. Effects of balance training on balance performance in healthy older adults: a systematic review and meta-analysis. *Sports Med* 2015;45:1721–38.
17. Gillespie LD, Robertson MC, Gillespie WJ, *et al*. Interventions for preventing falls in older people living in the community. *Cochrane Database Syst Rev* 2012;85.
18. Watson SL, Weeks BK, Weis LJ, *et al*. High-Intensity resistance and impact training improves bone mineral density and physical function in postmenopausal women with osteopenia and osteoporosis: the LIFTMOR randomized controlled trial. *J Bone Miner Res* 2018;33:211–20.
19. Watson SL, Weeks BK, Weis LJ, *et al*. Heavy resistance training is safe and improves bone, function, and stature in postmenopausal women with low to very low bone mass: novel early findings from the LIFTMOR trial. *Osteoporos Int* 2015;26:2889–94.
20. Watson SL, Weeks BK, Weis LJ, *et al*. High-Intensity exercise did not cause vertebral fractures and improves thoracic kyphosis in postmenopausal women with low to very low bone mass: the LIFTMOR trial. *Osteoporos Int* 2019;30:957–64.
21. Baron R, Ferrari S, Russell RGG. Denosumab and bisphosphonates: different mechanisms of action and effects. *Bone* 2011;48:677–92.
22. Beaudoin C, Jean S, Bessette L, *et al*. Denosumab compared to other treatments to prevent or treat osteoporosis in individuals at risk of fracture: a systematic review and meta-analysis. *Osteoporos Int* 2016;27:2835–44.
23. Cummings SR, Martin JS, McClung MR, *et al*. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *N Engl J Med* 2009;361:756–65.
24. Serrano AJ, Begoña L, Anitua E, *et al*. Systematic review and meta-analysis of the efficacy and safety of alendronate and zoledronate for the treatment of postmenopausal osteoporosis. *Gynecological Endocrinology* 2013;29:1005–14.
25. Fuchs RK, Shea M, Durski SL, *et al*. Individual and combined effects of exercise and alendronate on bone mass and strength in ovariectomized rats. *Bone* 2007;41:290–6.
26. Tamaki H, Akamine T, Goshi N, *et al*. Effects of exercise training and etidronate treatment on bone mineral density and trabecular bone in ovariectomized rats. *Bone* 1998;23:147–53.10.1016/S8756-3282(98)00075-1
27. Chilibeck PD, Davison KS, Whiting SJ, *et al*. The effect of strength training combined with bisphosphonate (etidronate) therapy on bone mineral, lean tissue, and fat mass in postmenopausal women. *Can J Physiol Pharmacol* 2002;80:941–50.10.1139/y02-126
28. Uusi-Rasi K, Kannus P, Cheng S, *et al*. Effect of alendronate and exercise on bone and physical performance of postmenopausal women: a randomized controlled trial. *Bone* 2003;33:132–43.
29. Smidt GL, Lin S-YU, O'DWYER KD, *et al*. The effect of high-intensity trunk exercise on bone mineral density of postmenopausal women. *Spine* 1992;17:280–5.
30. Janssen I, Katzmarzyk PT, Ross R, *et al*. Waist circumference, and health risk: evidence in support of current National Institutes of health guidelines. *Arch Intern Med* 2002;162:2074–9.
31. Shipe NK, Billek-Sawhney B, Canter TA, *et al*. The intra- and inter-rater reliability of the tragus wall distance (TWD) measurement in non-pathological participants ages 18-34. *Physiother Theory Pract* 2013;29:328–34.
32. Mika A, Unnithan VB, Mika P. Differences in thoracic kyphosis and in back muscle strength in women with bone loss due to osteoporosis. *Spine* 2005;30:241–6.
33. Kado DM, Christianson L, Palermo L, *et al*. Comparing a supine radiologic versus standing clinical measurement of kyphosis in older women: the fracture intervention trial. *Spine* 2006;31:463–7.
34. Genant HK, Wu CY, van Kuijk C, *et al*. Vertebral fracture assessment using a semiquantitative technique. *J Bone Miner Res* 1993;8:1137–48.
35. Lundin H, Sääf M, Strender L-E, *et al*. Gait speed and one-leg standing time each add to the predictive ability of FRAX. *Osteoporos Int* 2017;28:179–87.
36. Dargent-Molina P, Favier F, Grandjean H, *et al*. Fall-Related factors and risk of hip fracture: the EPIDOS prospective study. *The Lancet* 1996;348:145–9.
37. Podsiadlo D, Richardson S. The Timed "Up & Go": A Test of Basic Functional Mobility for Frail Elderly Persons. *J Am Geriatr Soc* 1991;39:142–8.
38. Bohannon RW, Bubela DJ, Magasi SR, *et al*. Sit-to-stand test: performance and determinants across the age-span. *Isokinet Exerc Sci* 2010;18:235–40.
39. Steffen TM, Hacker TA, Mollinger L. Age- and Gender-Related Test Performance in Community-Dwelling Elderly People: Six-Minute Walk Test, Berg Balance Scale, Timed Up & Go Test, and Gait Speeds. *Phys Ther* 2002;82:128–37.

40. Harding AT, Weeks BK, Horan SA, *et al*. Validity and test–retest reliability of a novel simple back extensor muscle strength test. *SAGE Open Med* 2017;5.

41. Zhou Z, Zheng L, Wei D, *et al*. Muscular strength measurements indicate bone mineral density loss in postmenopausal women. *Clin Interv Aging* 2013;8:1451–9.

42. Elhakeem A, Hartley A, Luo Y, *et al*. Lean mass and lower limb muscle function in relation to hip strength, geometry and fracture risk indices in community-dwelling older women. *Osteoporos Int* 2019;30:211–20.

43. Wolfson L, Judge J, Whipple R, *et al*. Strength is a major factor in balance, gait, and the occurrence of falls. *J Gerontol A Biol Sci Med Sci* 1995;50 Spec No:64–7.

44. Scott D, Blizzard L, Fell J, *et al*. Statin therapy, muscle function and falls risk in community-dwelling older adults. *QJM* 2009;102:625–33.

45. Kärkkäinen M, Rikkonen T, Kröger H, *et al*. Association between functional capacity tests and fractures: an eight-year prospective population-based cohort study. *Osteoporos Int* 2008;19:1203–10.

46. Roberts HC, Denison HJ, Martin HJ, *et al*. A review of the measurement of grip strength in clinical and epidemiological studies: towards a standardised approach. *Age Ageing* 2011;40:423–9.

47. Trampisch US, Franke J, Jedamzik N, *et al*. Optimal Jamar dynamometer handle position to assess maximal isometric hand grip strength in epidemiological studies. *J Hand Surg Am* 2012;37:2368–73.

48. Najafi DA, Dahlberg LE, Hansson EE. A combination of clinical balance measures and FRAX® to improve identification of high-risk fallers. *BMC Geriatr* 2016;16:94.

49. Duncan PW, Weiner DK, Chandler J, *et al*. Functional reach: a new clinical measure of balance. *J Gerontol* 1990;45:M192–M197.

50. Lark SD, Pasupuleti S. Validity of a functional dynamic walking test for the elderly. *Arch Phys Med Rehabil* 2009;90:470–4.

51. Brazier JE, Harper R, Jones NM, *et al*. Validating the SF-36 health survey questionnaire: new outcome measure for primary care. *BMJ* 1992;305:160–4.

52. Miyakoshi N, Kudo D, Hongo M, *et al*. Comparison of spinal alignment, muscular strength, and quality of life between women with postmenopausal osteoporosis and healthy volunteers. *Osteoporos Int* 2017;28:3153–60.

53. Hopman WM, Towheed T, Anastassiades T, *et al*. Canadian normative data for the SF-36 health survey. Canadian multicentre osteoporosis study Research Group. *CMAJ* 2000;163:265–71.

54. de Oliveira Ferreira N, Arthuso M, da Silva R, *et al*. Quality of life in women with postmenopausal osteoporosis: correlation between QUALEFFO 41 and SF-36. *Maturitas* 2009;62:85–90.

55. Barber MD, Kuchibhatla MN, Pieper CF, *et al*. Psychometric evaluation of 2 comprehensive condition-specific quality of life instruments for women with pelvic floor disorders. *Am J Obstet Gynecol* 2001;185:1388–95.

56. Barber MD, Walters MD, Bump RC. Short forms of two condition-specific quality-of-life questionnaires for women with pelvic floor disorders (PFDI-20 and PFIQ-7). *Am J Obstet Gynecol* 2005;193:103–13.

57. Bellamy N, Buchanan WW, Goldsmith CH, *et al*. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. *J Rheumatol* 1988;15:1833–40.

58. Bellamy N, Campbell J, Hill J, *et al*. A comparative study of telephone versus onsite completion of the WOMAC 3.0 osteoarthritis index. *J Rheumatol* 2002;29:783–6.

59. Mullen SP, Olson EA, Phillips SM, *et al*. Measuring enjoyment of physical activity in older adults: invariance of the physical activity enjoyment scale (paces) across groups and time. *Int J Behav Nutr Phys Act* 2011;8.

60. Warriner AH, Patkar NM, Yun H, *et al*. Minor, major, low-trauma, and high-trauma fractures: what are the subsequent fracture risks and how do they vary? *Curr Osteoporos Rep* 2011;9:122–8.

61. Buchner DM, Hornbrook MC, Kutner NG, *et al*. Development of the common data base for the FICSIT trials. *J Am Geriatr Soc* 1993;41:297–308.

62. Beck BR, Weeks BK, Norling TL. A novel Australian calcium-specific diet questionnaire: validity and reliability. *Osteoporos Int* 2011;22:S626–S7.

63. Weeks BK, Beck BR. The BPAQ: a bone-specific physical activity assessment instrument. *Osteoporos Int* 2008;19:1567–77.

64. Zhao R, Zhao M, Xu Z. The effects of differing resistance training modes on the preservation of bone mineral density in postmenopausal women: a meta-analysis. *Osteoporos Int* 2015;26:1605–18.