

# BMJ Open The LIFTMOR-M (Lifting Intervention For Training Muscle and Osteoporosis Rehabilitation for Men) trial: protocol for a semirandomised controlled trial of supervised targeted exercise to reduce risk of osteoporotic fracture in older men with low bone mass

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## ABSTRACT

**Introduction** The primary aim of the proposed study is to examine the efficacy of an 8-month supervised, high-intensity progressive resistance training and impact loading programme in comparison with a supervised machine-based isometric exercise training programme using the bioDensity system in older men with low bone mass. We will also determine the safety and acceptability of each exercise training mode. Intervention group responses will be compared with those of a self-selected, non-randomised control sample of sex-matched and age-matched men who will follow their usual lifestyle activities for 8 months.

**Methods and analysis** Apparently healthy men over 50 years with low bone mass, screened for medical conditions and medications known to adversely affect bone health, will be recruited. Eligible participants will be randomly allocated to 8 months of either exercise programme with block randomisation based on presence or absence of osteoporosis medications. A twice-weekly, 30-minute, supervised exercise programme will be conducted for both groups. The primary outcome will be change in femoral neck areal bone mineral density determined by dual-energy X-ray absorptiometry (DXA). Secondary outcomes, assessed at baseline and 8 months, will include: DXA-derived whole-body, bilateral proximal femur and lumbar spine areal bone mineral density; proximal femur bone geometry and volumetric density extracted using three-dimensional hip analysis software; anthropometry; body composition; kyphosis; vertebral fracture assessment; physical function; safety (adverse events and injuries); and compliance. Intention-to-treat and per-protocol analyses will be conducted.

**Discussion** Whether a high-intensity, low-repetition progressive resistance training and impact loading programme or a machine-based isometric exercise programme can improve determinants of fracture risk, without causing injury, has not been examined in men. Determination of the efficacy, safety and acceptability of such programmes will facilitate formulation of future

## Strengths and limitations of this study

- To our knowledge, this will be the first trial to investigate the efficacy and safety of an 8-month supervised, high-intensity, progressive resistance training and impact loading programme on several determinants of fracture risk for older men with low bone mass, compared with a machine-based isometric exercise programme using the bioDensity system.
- There are few investigations into the effects of exercise on musculoskeletal health in older men; thus, the current unique focus on older men with poor bone health will address a notable gap in the literature.
- The engagement of a non-randomised control group of demographically matched men who have elected not to exercise for 8 months is a design limitation that was implemented for pragmatic reasons.
- Our study sample will include largely healthy older men, so our findings may not be applicable to men with comorbidities or other exclusion characteristics.

exercise guidelines for older men with low bone mass at risk of fragility fracture, a group who have previously been under-represented.

**Ethics and dissemination** Participant confidentiality will be maintained with publication of results. The study has been granted ethical approval from the Griffith University Human Research Ethics Committee (Protocol number AHS/07/14/HREC).

**Trial registration number** Australian New Zealand Clinical Trials Registry ([www.anzctr.org.au](http://www.anzctr.org.au)) ANZCTR12616000344493; Pre-results.

## INTRODUCTION

Epidemiological data indicate the global prevalence of osteoporosis to be over 200 million,<sup>1</sup>

with around 1.2 million Australians,<sup>2</sup> 10.2 million Americans<sup>3</sup> and 15 million European men and women over 50 years of age being affected.<sup>4</sup> It has been suggested that 285 000 Australian men aged over 50 will be diagnosed as osteoporotic, and a further 2.48 million older men will be diagnosed as osteopenic by 2022.<sup>5</sup> With the ageing of the population, there will undoubtedly be a corresponding increasing prevalence of low bone mass and consequent increase in the incidence of low trauma fracture.<sup>6</sup>

It is widely accepted that bone adapts to the mechanical loads it habitually experiences. Experimental data from animal models have revealed that the most influential loading characteristics for osteogenesis are magnitude,<sup>7,8</sup> rate<sup>9</sup> and frequency<sup>10–12</sup> of the engendered strain. Evidence also indicates that dynamic loading is more osteogenic than static loading.<sup>13</sup> The optimal exercise prescription for the prevention and management of osteopenia and osteoporosis would therefore ideally impose dynamic, high-magnitude loads applied at a rapid rate. High-intensity resistance training with high-impact jumping, the combination of which will elicit high strains and strain rates in bone, is thus theoretically the optimal exercise protocol for bone. Although such exercise is considered safe for healthy individuals with normal bone mass, it is unclear whether it will be safe for individuals with reduced bone mass who are at increased risk of fracture. Previous resistance exercise recommendations for individuals with low bone mass, particularly those who have experienced a low trauma fracture, include 8 to 12 repetitions, which represents a moderate level of intensity,<sup>14,15</sup> based on a lack of quality evidence that high-intensity resistance training is safe and effective.

Recently, a bone-targeted, high-intensity, progressive resistance training and impact loading (HiRIT) exercise programme was undertaken with postmenopausal women with low to very low bone mass at the hip or spine—the LIFTMOR (Lifting Intervention For Training Muscle and Osteoporosis Rehabilitation) trial. Interim results indicated the HiRIT protocol was well tolerated (no injuries sustained during supervised training sessions) and effective, exhibiting positive changes to musculoskeletal health in postmenopausal women at increased risk of fragility fracture.<sup>16</sup> Although the lifetime risk of fracture is greater in women over the age of 50 (one in three) than men of the same age (one in five), older men are more likely to suffer serious postfracture consequences.<sup>4,17</sup> The most devastating low-trauma fracture site for older men is the hip, with mortality exceeding that of similarly aged women within the first year postfracture.<sup>18</sup> In light of the fact that osteoporosis and low-trauma fractures affect men as well as women, it was necessary to replicate the protocol in older men to determine if it will be similarly effective.

Separately, but simultaneously with the LIFTMOR trial, an isometric device (the bioDensity system, Performance Health Systems, Northbrook, Illinois, USA) was developed in the USA to facilitate near-maximal isometric contractions against instrumented external resistance,

with a goal to increase bone mass. The developers are currently marketing the device on the grounds that short-duration, low-volume, high-intensity bioDensity training can enhance bone mass in individuals with osteoporosis: however, concrete evidence is lacking. To date, four studies examining the bioDensity training protocol have been published<sup>19–22</sup>; only one of which included bone outcome measures.<sup>22</sup> In the latter observational study, 70 postmenopausal women with low bone mass were invited by their general practitioner to take part in a 6-month bioDensity intervention (one training session per week) for which the primary outcome was maximal isometric muscle force production. A subgroup of nine participants underwent dual-energy X-ray absorptiometry (DXA) examinations for bone density. Those individuals reportedly sustained increases in bone mineral density (BMD) at the hip ( $14.9\% \pm 11.5\%$ ) and spine ( $16.6\% \pm 12.2\%$ )—responses that far exceed the BMD responses to previously reported exercise interventions. The lumbar spine T-score of one participant improved from  $-3.1$  to  $-0.10$ . As considerable methodological shortcomings were evident in the latter study design, including low sample size, no monitoring of dietary calcium intake or physical activity, lack of control group, lack of disclosure of simultaneous bone medications and the fact that follow-up DXA scans were conducted 60 days after the intervention was completed suggest that a more rigorous examination of efficacy of bioDensity training is indicated.

Short-duration (30 min), twice-weekly therapeutic exercise programmes for older men with low bone mass, such as the proposed HiRIT and bioDensity training protocols, provide an attractive alternative to more burdensome and time-consuming programmes typically recommended for osteoporosis. Indeed, trials examining the influence of progressive resistance training, hopping/jumping or multicomponent programmes on bone health in men have adopted session frequencies of three,<sup>23–28</sup> four<sup>29</sup> or even seven<sup>30</sup> per week. Hinton *et al.*<sup>28</sup> compared thrice-weekly sessions of jump training with twice-weekly sessions of periodised progressive resistance training; however, healthy physically active men aged 25 to 60 years were recruited. Whether high-load, low-volume training methods can safely improve bone strength in older men with low bone mass remains a knowledge gap. Thus, the Griffith University Bone Densitometry Research Laboratory has acquired a bioDensity device for the purposes of examining safety and efficacy alongside the HiRIT protocol in a semirandomised controlled trial design.

## METHODS AND ANALYSES

### Ethics and dissemination

The study has been granted ethical approval from the Griffith University Human Research Ethics Committee (GUHREC; Protocol number AHS/07/14/HREC), and all research activities will be conducted in accordance with the Declaration of Helsinki. The study is also registered

with the Australian New Zealand Clinical Trials Registry (Trial number ANZCTR12616000344493). Written informed consent will be obtained from all participants prior to testing by the investigator performing baseline assessments.

Pilot men's data (Protocol number AHS/07/14/HREC) and the LIFTMOR for women trial<sup>16</sup> (Protocol number AHS/07/14/HREC; Trial number ACTRN12616000475448) provide evidence of an extremely low risk of injuries from the current exercise protocols, with no severe injuries reported from a total of 7300 training sessions. Similar to the current protocol, ethical approval was granted by the GUHREC for both studies, and written informed consent was obtained from all participants. Strategies were in place to reduce the risk of injuries or adverse events occurring during the aforementioned trials and included: (1) full supervision of high-intensity resistance training sessions by a qualified exercise scientist, (2) small group sizes in the supervised training sessions, (3) an initial familiarisation period during which low-load exercise variants focused on proper lifting technique was implemented and (4) weight lifted that was progressively increased with training exposure. In order to monitor safety, participants were required to complete training diaries at every training session to record illnesses, falls, fractures, injuries and muscle soreness. Early termination of the trial is therefore exceedingly unlikely and, for this reason, a Data Safety Monitoring Board was not engaged. Instead, data will be monitored via compulsory annual progress reports to the GUHREC. Any adverse events which occur between annual reports will be reported independently to the GUHREC, in compliance with the Australian Code for the Responsible Conduct of Research developed by the National Health and Medical Research Council, and the University Code for the Responsible Conduct of Research. The GUHREC is a registered institution with the National Health and Medical Research Council (Registration number EC00162). For participants who are unaccustomed to physical activity, it is likely they will experience some degree of muscle soreness following any change in exercise exposure. In the unlikely event that a participant experiences significant intervention-related muscle soreness, or an injury occurs during the study period, consultations with a qualified Physiotherapist (external to the trial) at the Griffith University Allied Health Clinic will be available. If further treatment is required, they will be referred to an appropriate healthcare professional.

All participants will be supplied with a full summary of individual and overall study results to encourage retention for the duration of the study, and to comply with ethical requirements. The usual scientific reporting practices will take place, including presentations at discipline meetings and publication in peer-reviewed journals. There will be no interim analyses published prior to completion of the trial. Community and clinical talks will also be given as appropriate. Participant confidentiality will be maintained with publication of results.

### Study aims

The primary aim of the proposed study is to examine the efficacy of an 8-month supervised HiRIT programme in comparison to supervised bioDensity machine-based isometric exercise training, or no intervention (control), for improving femoral neck (FN) areal BMD (aBMD) in older men with low bone mass. The primary outcome measure was selected according to clinical relevance, in light of the large personal and economic impact of hip fracture. It is hypothesised that 8 months of twice-weekly HiRIT training will improve FN aBMD more than bioDensity training or control, and similar benefit will be observed in secondary outcome measures. Furthermore, we hypothesise that there will not be a higher rate of adverse events during 8 months of HiRIT compared with bioDensity training or control.

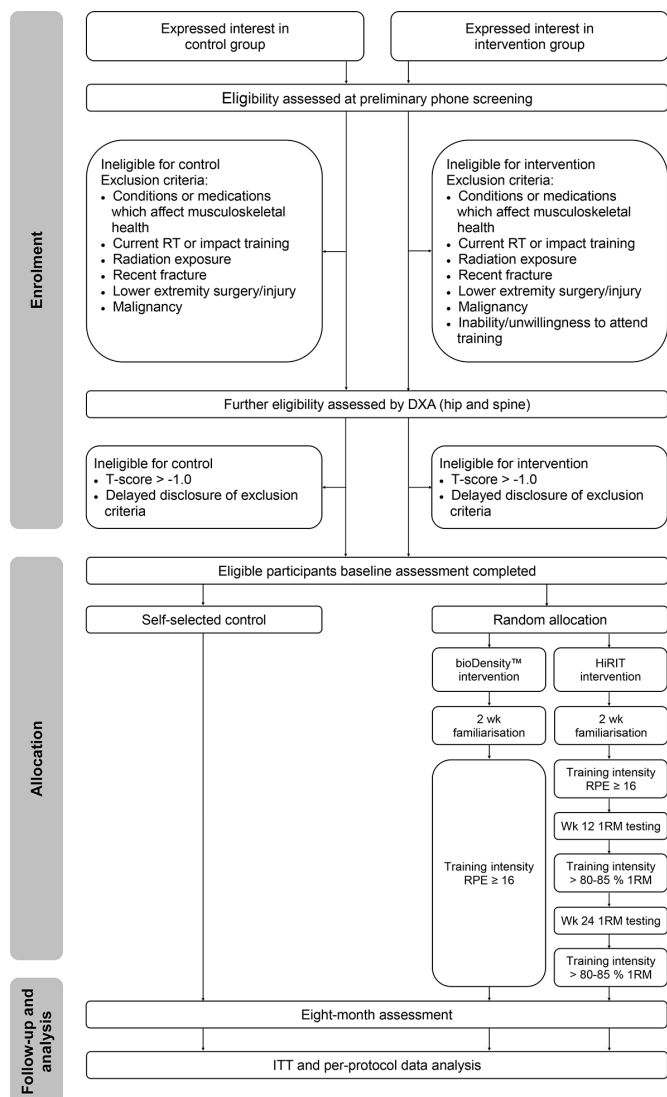
### Study design

The current project is a three-arm, 8-month, semirandomised, controlled exercise intervention trial. Proposed participant flow is outlined in figure 1. The 8-month exercise intervention period has been chosen as the minimum time frame in which notable changes in bone mass are likely to be detected from densitometry.<sup>31</sup> Eligible volunteers to the intervention arm will be randomly assigned to one of two exercise programmes, either supervised HiRIT or bioDensity training. The third arm will be a non-randomised control group of sex-matched and age-matched participants with lower than average bone mass recruited from the same community. The control group will follow their usual lifestyle for 8 months but undergo identical testing to the two exercise intervention groups at baseline and follow-up. We acknowledge that the somewhat unorthodox semirandomised design does not constitute the most rigorous clinical trial practice but adopt it out of necessity. Pilot testing conducted in our laboratory revealed that male study volunteers who expect to participate in an exercise trial, but are randomised to a conventional inactive control group, refuse to adhere to the requirement to refrain from exercise for 8 months. We also believe that it is unethical to withhold access to a potentially beneficial bone-targeted exercise programme for older men at increased risk of fragility fracture who are specifically seeking exercise therapy. For pragmatic reasons then, we will independently recruit a demographically matched sample of men who, for a variety of reasons (not including functional capacity), elect to remain sedentary for a minimum of 8 months.

### Sample size

Using the coefficient of variation for our device for FN aBMD (1.5%) to calculate least significant change ( $1.5\% \times 2.77 = 4.2\%$ ) and pilot (apparently healthy men over 50 years with low bone mass screened for identical inclusion and exclusion criteria to the current study) FN aBMD mean of  $0.790 \text{ g/cm}^2$  and SD of  $0.061 \text{ g/cm}^2$ , we determined that a sample size of 54 is required to detect the minimum change difference of  $0.033 \text{ g/cm}^2$  from a





**Figure 1** Proposed participant flow (CONSORT diagram) bioDensity, machine-based isometric exercise using the bioDensity system. DXA, dual-energy X-ray absorptiometry; HiRIT, high-intensity progressive resistance training and impact loading; ITT, intention to treat; RM, repetition maximum; RPE, rating of perceived exertion; RT, resistance training; Wk, week.

two-tailed test with a power of 80% and  $\alpha=0.05$ . Allowing for a 20% dropout, a total of 64 participants per group is required. The 20% dropout rate reflects that reported in previous bone-targeted exercise interventions in men,<sup>28–30</sup> and the dropout rate of randomised controlled intervention trials in adults (20.9%).<sup>32</sup> Recruitment for this study started in May 2016, and will continue until the planned sample size is achieved.

### Setting and recruitment

Baseline and follow-up assessments will be conducted in the Bone Densitometry Research Laboratory, School of Allied Health Sciences, Griffith University, Gold Coast campus, Queensland, Australia. All supervised training sessions will be conducted in the Strength Training Research Facility, co-located in the School of Allied

Health Sciences. Methods of recruitment include local media outlets (print media and radio), social media, official website ([www.liftmor.org](http://www.liftmor.org)), word of mouth, and notice board flyer advertisement at local lawn bowls clubs, golf clubs and senior citizens clubs.

### Eligibility and screening

Apparently healthy, able-bodied men over 50 years of age will be recruited. Volunteers are to be excluded if they have any of the following: uncontrolled cardiovascular or respiratory disease; disclosure of musculoskeletal or neurological conditions likely to affect their ability to perform exercise; medications known to affect bone metabolism (eg, corticosteroids, thyroxine, antiepileptic, and antiretroviral agents); medical conditions known to affect musculoskeletal health (eg, Paget's disease, hyperparathyroidism and thyrotoxicosis); current participation in high-intensity resistance or impact-type exercise; metal implants (eg, joint prostheses); recent radiation therapy or radiographic investigations; recent fracture or lower extremity surgery; or malignancy. Further exclusion for the exercise groups will be based on an inability or unwillingness to take part in 8 months of twice-weekly exercise training due to motivation, travel or work commitments. No upper age limit is stipulated. Potential participants who contact the investigator will initially undergo a preliminary phone screening for inclusion and exclusion criteria. If eligibility is established, prospective participants will be invited to attend the University research facility for BMD screening and, when relevant, to undergo baseline assessments. Potential exercise intervention participants and self-selected age-matched men will then undergo preliminary DXA scans. If osteopenia (T-score between  $-1.0$  and  $-2.5$ ) or osteoporosis (T-score  $<-2.5$ ) is detected at the lumbar spine and/or proximal femur, the individual will be eligible for inclusion and the full suite of scans. Participants will be discontinued if they: (1) withdraw consent, (2) cease to attend training sessions for longer than 3 weeks, (3) initiate or discontinue osteoporosis medications, or initiate medications known to affect bone metabolism, (4) become injured and unable to participate, (5) perform additional forms of exercise such as resistance training or impact-type exercise external to the trial and (6) are advised by their general practitioner to cease training.

### Randomisation and allocation

Allocation of eligible participants to the supervised HiRIT and bioDensity training groups will be achieved via block randomisation, stratified by the presence (more than 12 months exposure) or absence (lack of exposure) of osteoporosis medications, using a computer-generated randomisation sequence ([www.randomization.com](http://www.randomization.com), accessed 17 May 2016). To ensure concealment, the allocation sequence will be prepared in advance by an external source, and filed in sequentially numbered, sealed, opaque envelopes. On completion of baseline testing, those identified as eligible will be randomly

allocated to their exercise group and their supervised exercise training sessions will be scheduled.

### Exercise interventions

#### Progressive resistance training and impact loading exercise programme

The HiRIT group will perform approximately 30 min of supervised, high-intensity, free weight training and impact loading, twice-weekly, on non-consecutive days. Sessions will comprise three fundamental compound movement exercises (deadlift, squat and overhead press). During the initial 2 weeks, participants will perform low-load variants of each exercise focussing on technique for the purposes of familiarisation. During training weeks 3 to 12 participants will perform five sets of each exercise, lifting the maximum weight possible for five repetitions while maintaining correct form. The Rating of Perceived Exertion (RPE) scale will be used to subjectively select exercise intensity and guide weight progression prior to determining one repetition maximum. Participants will aim for an RPE  $\geq 16$  (6–20 point Borg scale<sup>33</sup>) to achieve a high-intensity equivalent before one repetition maximum testing. Maximal strength testing, to determine one repetition maximum for the deadlift and squat, will be performed at weeks 12 and 24. Briefly, the maximal strength test protocol will begin with a warm-up set of 5–10 repetitions at a relatively light load (approximately 50% of the heaviest weight they have previously lifted for five repetitions). After a 1 min rest, they will perform one set of three to five repetitions at 60%–80% of their perceived maximum. Gradually, the load will increase in 2.5 to 5.0 kg increments until a failed attempt (within three to six attempts), with each attempt interspersed with a 2 min rest. One repetition maximum is defined as the heaviest weight a participant can lift once with correct lifting technique. A similar one repetition maximum testing protocol was found to be reliable for untrained middle-aged adults (intraclass correlation coefficients  $>0.97$ ).<sup>34</sup> From training week 12 onwards, participants will perform five sets of five repetitions for each exercise, corresponding to an intensity of greater than 80%–85% of one repetition maximum. Load magnitude will be progressively increased in increments of 2.5 kg over the course of the intervention when they are able to easily complete seven repetitions at their current weight. In addition, five sets of five repetitions of jumping chin-ups (interspersed with rest) with a firm, flat-footed landing will be performed each session. Impact intensity will be gradually increased by moving towards achieving a stiff-legged landing as tolerated. Training will be fully supervised by a qualified exercise scientist. Weight progressions and RPE will be recorded in training diaries.

#### Machine-based isometric exercise programme

The supervised bioDensity group will exercise twice-weekly on non-consecutive days to match the HiRIT group protocol. Four exercises will be performed: chest press, leg press, core pull and vertical lift. The chest

press and leg press closely mirror conventional strength training equipment, the core pull movement combines an abdominal crunch with an underhand chin-up and the vertical lift simulates a high-hang deadlift position. During the initial 2 weeks, participants will perform a lower intensity repetition of each exercise focussing on technique. Following this familiarisation period, one self-initiated near-maximal 5 s isometric contraction will be performed for each of the four exercises (per manufacturer's recommendations). Integrated monitors provide real-time peak muscle force production feedback. Participants will provide an RPE with the aid of the 6–20 point Borg scale<sup>33</sup> for each exercise. They will be instructed to achieve a near-maximal 5 s isometric contraction at an intensity corresponding to greater than 80%–85% of one repetition maximum, translating to an RPE of greater than or equal to 16 on the 6–20 point Borg scale.<sup>35</sup> A single qualified trainer will supervise all sessions to operate the bioDensity system and ensure the exercises are performed correctly and safely. Peak force, average force and RPE will be recorded in participant training diaries.

#### Control group activities

The sex-matched and age-matched control group will be encouraged to maintain their customary physical activity and dietary patterns over the 8-month duration of the study. To monitor deviations from their usual lifestyle, diaries will be issued, in which they will be instructed to list variations to their physical activity level and diet on a fortnightly basis. Space is also provided to record any illnesses, falls, fractures, changes to their medical conditions and medications (inclusive of over-the-counter medications) and injuries other than muscle soreness. Diaries are to be returned at follow-up. Fortnightly emails will act as reminders to complete diary entries, with a monthly email requiring a reply to the investigator to prompt recording of any relevant changes. To detect change in bone-relevant physical activity or dietary calcium intake over the course of the 8-month study, participants will complete questionnaires (described below) at baseline and follow-up.

#### Outcome measures

All outcome measures will be performed at baseline and 8-month follow-up by a single investigator who is not blind to group allocation, using identical facilities, procedures and equipment. A summary of outcome measures is presented in [table 1](#).

#### Primary outcome

The primary outcome will be change in DXA-derived FN aBMD (Medix DR, Medilink, France).

#### Secondary outcomes

Secondary outcomes (described in more detail below) will include: changes in anthropometrics, as well as in whole-body and regional measures of bone, muscle and fat. Kyphosis will be examined in order to track angular

Table 1 Summary of outcome measures	
Variable	Data collection instrument
Primary outcome measure	
Femoral neck aBMD	Proximal femur DXA scan (Medix DR, Medilink, France)
Secondary outcome measures	
Other bone outcomes	
Whole body aBMD, BMC and bone area; lumbar spine aBMD, BMC and bone area; and proximal femur (trochanter and total hip regions) aBMD, BMC and bone area	DXA scans (Medix DR, Medilink, France)
Femoral neck (trabecular, cortical and total) BMC, vBMD and volume; total hip (trabecular, cortical and total) BMC, vBMD and volume	Proximal femur DXA scan (Medix DR, Medilink, France), 3D hip software (DMS Group, Mauguio, France)
Calcaneal broadband ultrasound attenuation, speed of sound and stiffness index	Calcaneal QUS (Lunar Achilles InSight, GE Healthcare, Wisconsin, USA)
Total content, vBMD and cross-sectional area; trabecular content, density and cross-sectional area; cortical content, vBMD, cross-sectional area and thickness; periosteal and endocortical circumference; total and trabecular bone strength indices; polar section modulus; polar strength strain index	Forearm 4% and 66% sites, and leg 4%, 14%, 38% and 66% sites pQCT scans (XCT-3000, Stratec Medizintechnik, Pforzheim, Germany)
Anthropometry	
Height	Wall-mounted stadiometer (Model 216; Seca, Hamburg, Germany)
Weight	Mechanical beam scale (Model 700; Seca, Hamburg, Germany)
Waist circumference	Steel tape (Model W606PM; Lufkin Executive Thinline, Apex, USA)
Body composition	
Lean mass, fat mass, appendicular lean mass and percent body fat	Whole-body DXA scan (Medix DR, Medilink, France)
Muscle cross-sectional area and muscle density	Forearm 66% site and leg 66% site pQCT scans (XCT-3000, Stratec Medizintechnik GmbH, Pforzheim, Germany)
Thoracic kyphosis	Plurimeter gravity referenced inclinometer (Australasian Medical & Therapeutic Instruments, Australia) Lateral decubitus thoracolumbar spine DXA (Medix DR, Medilink, France)
Vertebral fracture assessment	Lateral decubitus thoracolumbar spine DXA (Medix DR, Medilink, France)
Functional performance	
Timed up-and-go	Digital stopwatch (Fisher Scientific, USA)
Five times sit-to-stand	Digital stopwatch (Fisher Scientific, USA)
Functional reach	Perspex board with measurement grid lines
Muscle power	
Countermovement vertical jump	Load cell (Advanced Mechanical Technology, Watertown, Massachusetts, USA)
Isometric muscle strength	
Lower extremity strength	Leg platform dynamometer (TTM Muscle Meter, Tokyo, Japan)

Continued

**Table 1** Continued

Variable	Data collection instrument
Back extensor strength	Dynamometer (Lafayette Manual Muscle Testing Systems, USA)
Dietary calcium intake	AusCal questionnaire
Bone-specific physical activity	Bone-specific Physical Activity Questionnaire (BPAQ)
Barriers and facilitators	Physical Activity Enjoyment Scale (PACES) questionnaire Semistructured interviews
Quality of Life	WHO Quality of Life (WHOQOL) questionnaire
Safety (adverse events and injuries) and compliance	Purpose-designed lifestyle diaries and training diaries Trainer records

aBMD, areal bone mineral density; BMC, bone mineral content; DXA, dual-energy X-ray absorptiometry; pQCT, peripheral Quantitative CT; vBMD, volumetric bone mineral density.

changes of the spine with exercise exposure. Vertebral fracture assessment using the Genant semiquantitative approach<sup>36</sup> from lateral thoracolumbar spine imaging will be conducted preintervention and postintervention by DXA. A series of commonly utilised performance tasks will be employed to examine changes in lower extremity muscle force and power, dynamic balance and maximal trunk extensor strength in keeping with standard protocols. Standardised instructions will be provided for all performance tasks, with the best performance of three trials to be included in the analyses. Previously validated questionnaires will be used to estimate dietary calcium consumption, current and past bone-relevant physical activity, quality of life and exercise appeal. Participant safety (adverse events and injuries) and compliance will be monitored across the intervention period using training diaries.

### Bone strength indices

Whole body, bilateral proximal femur (trochanter and total hip regions) and lumbar spine aBMD, bone mineral content and bone area will also be determined by DXA. Parameters of proximal femur (FN and total hip regions) trabecular and cortical bone geometry and volumetric density will be extracted from standard DXA scans using three-dimensional hip analysis software (DMS Group, Maugeio, France). Quantitative ultrasonography will be used to evaluate changes in calcaneal bone quality (QUS; Lunar Achilles InSight, GE Healthcare, Wisconsin, USA). Volumetric BMD and geometric parameters contributing to bone strength at the tibia and radius will be determined from peripheral quantitative CT scans of the forearm and leg (pQCT; XCT-3000, Stratec Medizintechnik, Pforzheim, Germany; voxel size 0.5 mm, slice thickness 2.3 mm and scan speed 25 mm/s). Tibial length will be measured by means of palpation as the distance from the proximal border of the medial tibial plateau to the distal tip of the medial malleolus, and radial length measured from the proximal tip of the olecranon process to the distal tip of the ulnar styloid process. A planar scout view of the ankle joint line on the skeletally non-dominant leg will be acquired so the anatomical reference line can be adjusted to bisect the tibial endplate. A total of four image slices will be acquired at 4%, 14%, 38% and 66% sites proximal to the distal edge of the tibial endplate. For the distal tibia (4% site), contour mode 3 at 169 mg/cm<sup>3</sup> and peel mode 4 at 650 mg/cm<sup>3</sup>, with a 10% peel, will be used to determine total and trabecular content, total and trabecular volumetric bone mineral density, and total and trabecular cross-sectional area. At the midshaft of the tibia (38% site), cort mode 2 at 710 mg/cm<sup>3</sup> will be used to define cortical content, volumetric bone mineral density, area and thickness, and periosteal and endocortical circumference. Cort mode 2 at 480 mg/cm<sup>3</sup> will be used to determine polar section modulus and the polar strength strain index. A planar scout scan perpendicular to the long axis of the skeletally non-dominant forearm will be performed at the level of the ulnar head, with the



reference line positioned at the distal edge of the most horizontal portion of the radial cortical endplate. Two image slices will be acquired at the 4% and 66% sites proximal to the distal endplate of the radius. For the distal radius (4% site), contour mode 3 at 169 mg/cm<sup>3</sup> and peel mode 4 at 650 mg/cm<sup>3</sup>, with a 10% peel, will be used to determine total and trabecular content, total and trabecular volumetric bone mineral density, and total and trabecular cross-sectional area. At the proximal radius (66% site), cort mode 2 at 710 mg/cm<sup>3</sup> will be used to define cortical content, volumetric bone mineral density, area and thickness, and periosteal and endocortical circumference. Cort mode 2 at 480 mg/cm<sup>3</sup> will be used to determine polar section modulus and the polar strength strain index. pQCT-derived bone parameters will include: total content, density and cross-sectional area; trabecular content, density and cross-sectional area; cortical content, density, cross-sectional area and thickness; periosteal and endocortical circumference; and biomechanical strength indices calculated from density and area (total and trabecular bone strength indices, polar section modulus and polar strength strain index). All pQCT analyses will be conducted using host software V.6.20 (Stratec Medizintechnik GmbH, Pforzheim, Germany) with loop methods following the techniques of Bone Diagnostics Inc (Spring Branch, TX, USA).

#### Anthropometrics and body composition

Height will be measured via the stretch stature method with a wall-mounted stadiometer (Model 216; Seca, Hamburg, Germany). Weight will be measured using a mechanical beam scale without shoes and in light clothing (Model 700; Seca, Hamburg, Germany). Body mass index will be determined per the accepted method (body mass index = weight<sup>2</sup>/height<sup>2</sup>; kg/m<sup>2</sup>). Waist circumference, a predictor of visceral abdominal adiposity, will be measured using a steel tape following National Institute of Health guidelines (Model W606PM; Lufkin Executive Thinline, Apex, USA).<sup>37</sup> Briefly, the tape will be positioned on the horizontal plane at the level of the iliac crests on bare skin and recorded at the end of gentle expiration. Body composition parameters inclusive of lean mass, fat mass, appendicular lean mass and percentage body fat will be derived from whole-body DXA. Muscle cross-sectional area, an index of muscle size, and muscle density, an index of intramuscular fat, will be determined from pQCT scans of the forearm and leg at the 66% sites.

#### Thoracic kyphosis and vertebral fracture assessment

Thoracic kyphosis will be assessed in relaxed standing (neutral posture) and standing 'at attention' using a gravity-referenced inclinometer, following a procedure similar to MacIntyre *et al* (Plurimeter, Australasian Medical & Therapeutic Instruments, Australia).<sup>38</sup> The inclinometer will be zeroed at the 12th thoracic to first lumbar intervertebral space, and the angle at the seventh cervical to first thoracic intervertebral space recorded. Lateral thoracolumbar spine DXA will be performed in

the lateral decubitus position to calculate Cobb angle via two methods: (1) vertebral body endplates and (2) anterior vertebral body margins. The superior endplate of the fourth thoracic vertebra and the inferior endplate of the 12th thoracic vertebra will be manually digitised, perpendicular lines extended and the angle at their intersection measured.<sup>39</sup> To account for endplate angulation and tilt due to vertebral irregularity, the anterior margins will be digitised and the angle at their intersection measured.<sup>40</sup> In addition, lateral thoracolumbar spine DXA allows vertebral fracture identification using the Genant method.<sup>36</sup> The anterior, medial and posterior heights of the vertebral body are used to grade (mild, moderate or severe) wedge, biconcave or crush deformity.

#### Timed up-and-go

The timed up-and-go test is a measure of functional mobility and dynamic balance.<sup>41</sup> Participants will be instructed to rise from a seated position without using their hands for assistance, walk at a brisk pace to a mark on the floor a distance of 3 m away, pivot and return to assume the start position. Participants will be timed from the point at which their back no longer makes contact with the chair to when they return to the start and adopt the correct seated position.

#### Five-times sit-to-stand

The five-times sit-to-stand is a reliable assessment of the ability to rise unassisted from a seated position, with relevance to functional mobility, dynamic balance and lower extremity muscle strength.<sup>42</sup> Participants will be asked to move from a sitting to standing position, without the use of their arms, for five repetitions following the recommendations of Bohannon for assessing older adults.<sup>43</sup>

#### Functional reach

A modified version of the original functional reach test (that incorporated a yardstick) will be used to assess dynamic balance, which has been identified as an important component of falls risk.<sup>44</sup> Participants will stand with shoulders perpendicular to a Perspex board marked with vertical measurement lines, with the dominant arm located nearest the board and extended forwards to 90° shoulder flexion, with the hand forming a fist. The participant will be instructed to reach forward by flexing the trunk at the hip, maintaining a fixed base of support, without stepping or losing balance. If the participant makes contact with the Perspex board, takes a step or loses balance, the trial will be repeated. The start and finish positions of the third metacarpal in respect to the measurement lines will be recorded to determine displacement.

#### Muscle power

Lower extremity muscle power will be assessed by a countermovement vertical jump test. Participants will be instructed to perform a jump for maximum height, without arm swing, while positioned on a floor-mounted 900 mm x 600 mm load cell (Advanced Mechanical



Technology, Watertown, Massachusetts, USA). Impulse and impulse relative to body weight will be calculated from the vertical component of the ground reaction force of the loading and take-off phase according to the method described by Linthorne.<sup>45</sup>

#### Isometric muscle strength

Maximal isometric force of the lower extremity will be estimated using a leg strength platform dynamometer (TTM Muscle Meter, Tokyo, Japan). The participant will stand on the dynamometer platform assuming a semisquat position with knees flexed (knee angle of 115°, hip flexion angle of 65°), trunk extended and back flat against the wall. A straight bar handle is affixed to the dynamometer by a chain at a length so the arms are fully extended to grip it. After ensuring the chain is taut, the dynamometer is manually zeroed. Participants will be instructed to attempt to straighten their legs, while keeping their back fully in contact with the wall. This method has excellent validity against the 'gold standard' isokinetic dynamometry (Pearson's correlation coefficient  $r=0.84$ ,  $p<0.001$ ; test-retest reliability  $r=0.97$ ,  $p<0.001$ ) (Little A, Harding AT, Weeks BK, Horan SA, Watson SL, and Beck BR, 2016; unpublished data; conference abstract).

Maximal isometric back extensor muscle strength will be assessed in erect standing using a handheld dynamometer (Lafayette Manual Muscle Testing Systems, USA). The participant will be positioned midway between two vertical wall-mounted anchor rails, with their back and heels against the wall. An inelastic belt between the two rails will be fastened horizontally around the hips in order to restrain the pelvis. The padded transducer pressure plate will be positioned by the investigator between the wall and the seventh thoracic vertebral spinous process, until held securely against the wall by the pressure of the participant's back. Participants will be instructed to push back into the wall with their trunk, ensuring their feet remain flat with their heels in contact with the wall. This method has excellent validity against the 'gold standard' isokinetic dynamometry (Pearson's correlation coefficient  $r=0.85$ ,  $p<0.001$ ; test-retest reliability  $r=0.93$ ,  $p<0.001$ ).<sup>46</sup>

#### Dietary calcium intake

Calcium intake will be assessed using the AusCal, a calcium-focused food frequency questionnaire designed and validated for the Australian diet.<sup>47</sup> Frequency of consumption per day, week or month and approximate serving size will be recorded for each of the listed calcium-rich food and beverage items over the previous year. The AusCal will be investigator-administered. Questionnaire responses will be entered into customised FoodWorks analysis software to generate average daily calcium intake (V.7, Xyris Software, Brisbane, Australia).

#### Bone-specific physical activity

The Bone-specific Physical Activity Questionnaire (BPAQ)<sup>48</sup> will be used to quantify current and historical

physical activity of relevance to bone. Respondents will list all regular, structured physical activity and years of participation, with a minimum of investigator assistance. BPAQ scores will be calculated using an online, custom-designed analysis programme (<http://www.fithdysign.com/BPAQ/>). Mathematical algorithms in the calculator were developed using load ratings from vertical ground reaction forces of each activity, participation frequency, years of involvement and an age-weighting factor. High loading ratings represent high-impact activities, while the age-weighting factor reflects higher mechanosensitivity to physical activity during youth. Previous research has found that BPAQ scores are predictive of variance in DXA-derived bone strength parameters at clinically relevant sites in healthy middle-aged and older men.<sup>49</sup> This instrument has high reliability, with intraclass correlation coefficients of 0.92–0.97.<sup>50</sup>

#### Barriers and facilitators

The Physical Activity Enjoyment Scale (PACES), designed by Mullen *et al.*,<sup>51</sup> is a self-reported eight-item questionnaire which uses a 7-point Likert scale for each item. The respondent is required to circle the number corresponding to their current thoughts about physical activity. Higher PACES scores indicate a greater level of exercise appeal. Inclusion of this instrument was based on physical activity enjoyment being identified as a potential determinant of exercise adherence.<sup>52</sup> Semi-structured interviews to determine exercise appeal, barriers and facilitators to participation in HiRIT or bioDensity training programmes will be conducted within 1 month of completing the 8-month intervention by an independent investigator. Interviews will be tape-recorded with participant consent, and transcribed verbatim. Interview transcripts will be thematically coded using NVivo qualitative software (V.10, QRS International) to determine barriers and facilitators to participation in higher-intensity, bone-targeted exercise.

#### Quality of life

The WHO Quality of Life questionnaire was developed to assess four quality of life domains using a 5-point Likert interval scale.<sup>53</sup> Higher scores are indicative of higher quality of life. Participants will self-complete the questionnaire. Internal consistency across a large heterogeneous population from a field trial during its development showed each domain to have moderate to high Cronbach's  $\alpha$  levels; physical health ( $\alpha=0.82$ ), psychological health ( $\alpha=0.81$ ), social relationships ( $\alpha=0.68$ ) and environment ( $\alpha=0.80$ ).<sup>54</sup>

#### Safety and compliance

Prior to each training session, participants will rate their level of muscle soreness on a 10-point visual analogue scale, and note alterations to their diet, physical activity, health or medications since their previous session. Illnesses, falls, fractures and injuries other than muscle

soreness will be documented. Attendance will be entered to determine programme compliance, with 100% being defined as completion of 70 sessions over the course of 8 months. Adverse events will be fully documented by investigators and monitored across the intervention period.

### Data integrity

Participants will be allocated a unique study ID and data will be de-identified for analysis. After final data collection and cleaning, the data will be locked before analysis. Paper records will be stored securely at Griffith University in a laboratory with restricted swipe card access, and retained for a minimum of 15 years. Electronic data will be stored securely on password-protected University computers. Management, storage and retention of research data will be in line with Griffith University policy, the Griffith University Code for the Responsible Conduct of Research. There will be no contractual agreements limiting data set access. De-identified data will be shared for meta-analyses or other collaborations on a case-by-case basis. De-identified data will be made available to the bioDensity manufacturer, Performance Health Systems, after the final study results have been published.

### Blinding

The study will be single-blind; participants in the two exercise groups will only be aware of the details of their allocated exercise protocol. They will train separately, and will not be apprised of study hypotheses. The investigator performing baseline assessments will be blinded to the allocation sequence, which will be revealed to both investigator and participant only after baseline testing. As the assessor will also be training the participants, in order to maintain the highest level of test-retest reliability, follow-up testing will not be assessor blinded.

### Data analyses

Statistical analyses will be undertaken using SPSS V.24.0 (SPSS Inc., Chicago, IL, USA). The normality of the distribution of continuous outcome variables will be examined using the Kolomogorov-Smirnov test. Descriptive statistics of participant characteristics, biometric and dependent variables will be presented as means±SD and frequencies where appropriate. Between-group comparisons of descriptive statistics at baseline will be evaluated using analysis of variance (ANOVA) for normally distributed continuous data, non-parametric equivalents for non-normally distributed data (Kruskal-Wallis one-way ANOVA) and  $\chi^2$  for categorical data. Between-group comparisons for outcome measures will be examined using repeated measures analysis of covariance (RMANCOVA) for group, time and group-by-time interaction effects using raw baseline and follow-up data, adjusting for age, initial weight, calcium intake and baseline values. Secondary exploratory RMANCOVA analyses adjusting for age, initial weight, calcium intake, baseline values and training programme compliance will be performed. In accordance with the

principles of a classic intention-to-treat approach, all randomised participants will be included in the final analyses, regardless of withdrawal or compliance. In the case of missing follow-up data due to study withdrawal, imputation of the mean percentage change value for the specific group will be employed. Per-protocol exploratory analyses will be performed comparing outcome measures between the HiRIT, bioDensity and control groups for those with training programme compliance of greater than 70% to examine maximum treatment efficacy. Multiple linear regression analyses of absolute change from baseline will be employed to examine the relative influence of certain variables, found to significantly correlate with outcomes measures, on the bone response. Statistical significance will be set at  $p \leq 0.05$ .

### DISCUSSION

To our knowledge, this will be the first trial to investigate the efficacy and safety of an 8-month supervised HiRIT exercise programme on determinants of fracture risk for older men with low bone mass, compared with supervised bioDensity training or control. In the past, exercise prescription recommendations for individuals with osteoporosis have stipulated an emphasis on low to moderate intensity exercise,<sup>14 15</sup> with a goal to prevent falls; however, such exercises are unlikely to provide an adequate stimulus to elicit notable osteogenic adaptation. Both of the current HiRIT and bioDensity exercise programmes have been designed around key loading characteristics shown to be osteogenic in animal models, and adhere to the principle of progressive overload. The execution of the current trial is warranted in order to progress exercise recommendations for older men with low to very low bone mass, who are at increased risk of fracture.

Although some knowledge exists, exercise intervention studies targeting older men with low bone mass are yet to be conducted over an adequate time period to detect changes in bone with confidence. There is, however, evidence that high intensity (>80% to 85% of one repetition maximum) compound movement resistance training exercises can be safely tolerated (with no significant adverse events), and elicit positive effects on bone mass and muscle strength in older adults.<sup>16 24 26 55</sup> While the aforementioned studies suggest such high-intensity exercise prescription elicits bone and muscle strength changes, little is known about the response in men with low to very low bone mass, or men with low bone mass who have previously sustained a low-trauma fracture. The original high-intensity LIFTMOR trial<sup>16</sup> implemented in postmenopausal women with low to very low bone mass enhanced bone mass with a high level of safety. Maddalozzo and Snow<sup>24</sup> also examined the ability of high-intensity resistance training (functional standing free-weights programme) to enhance bone in older men and postmenopausal women, but as no baseline T-scores were reported, it is not clear if their participants were at increased risk of fracture. Kukuljan *et al*<sup>26</sup> examined the

influence of 12-months progressive resistance training and weight-bearing impact on musculoskeletal health in men over the age of 50 with normal to low bone mass. While positive changes were observed at the hip and spine, individuals with osteoporosis and/or a history of osteoporotic fracture were excluded from the intervention. A short (12 weeks) trial conducted by Mosti *et al*<sup>5</sup> randomly allocated postmenopausal women with osteopenia and osteoporosis to a supervised high-intensity hack squat programme or control. Four sets of three to five repetitions at 85% to 90% of one repetition maximum were performed thrice weekly. The significant increases in bone mineral content and area at the lumbar spine and FN observed in the exercise group must be interpreted with caution in light of the small sample (eight women in the strength training group completed the study) and the short study duration which is not normally considered long enough to detect BMD change from densitometry.

Evidence confirming the ability of high-intensity, low-volume, machine-based bioDensity training to improve bone health in older men with osteopenia or osteoporosis is essentially absent. The study will establish preliminary efficacy of two potentially beneficial exercise interventions and provides the opportunity to examine comparative efficacy. By examining the effects of two non-traditional exercise programmes on musculoskeletal health and risk factors for falls in a poorly researched population, our findings will contribute evidence towards developing efficacious non-pharmacological osteoporosis therapy.

### Limitations

Several limitations warrant discussion. First, due to the somewhat unorthodox semirandomised study design, there exists the possibility of self-selection bias. Pilot testing demonstrated a lack of feasibility for a fully randomised design based on an unwillingness of older male study volunteers to adhere to a control requirement to refrain from exercise for 8 months. When volunteering under the premise of receiving an exercise programme, we argue that there are also ethical issues of withholding exercise from individuals who wish to take it up. We have attempted to minimise the risk by applying uniform inclusion and exclusion criteria for all study participants, with the exception of a willingness to participate in an 8-month exercise intervention. The extent to which the self-selected control group differs from the intervention groups will be determined and reported in the course of descriptive analyses of baseline data. Any differences will be accounted for by adjusting for baseline values in the final analyses. Second, the current trial is not powered to detect significant differences in fractures as safety (adverse events and injuries) is a secondary outcome. Nevertheless, reporting adverse events and injuries is informative when determining if an exercise programme can be translated to clinical practice. Third, the outcome assessor will not be blind to group allocation, will deliver the intervention and will be responsible for documenting

adverse events and reporting to the GUHREC. Participants will be instructed to report even the slightest degree of discomfort/pain/muscle soreness or injury, and a protocol is in place for independent review by a qualified physiotherapist or general practitioner, as required. It is also an ethical requirement to report such events to the GUHREC, and harms or unintended events must be included when reporting randomised controlled trials (CONSORT guidelines). Failure to promptly report any adverse event would contravene both Institutional and National research ethics guidelines. A blinded outcome assessor is beyond the means of this unfunded project; therefore, our current study design has been adopted out of necessity.

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**Competing interests** None declared.

**Patient consent** Detail has been removed from this case description/these case descriptions to ensure anonymity. The editors and reviewers have seen the detailed information available and are satisfied that the information backs up the case the authors are making.

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