



## **LIFTMOR: Lifting Intervention For Training Muscle and Osteoporosis Rehabilitation**

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# LIFTMOR: Lifting Intervention For Training Muscle and Osteoporosis Rehabilitation

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Doctor of Philosophy

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LIFTMOR: Lifting Intervention For  
Training Muscle and Osteoporosis  
Rehabilitation

## **Abstract**

Osteoporosis is defined by critically low bone mass or a fragility fracture. Physical activity has been proposed as a necessary lifestyle contributor to bone health, however, few exercise programs have demonstrated an ability to notably increase bone mass. The bone response to exercise is highly dependent on the nature of applied mechanical loads. The most osteogenic activities are those that induce high magnitude strains at high rates or frequencies in bone. Under such conditions, only brief loading bouts are required to stimulate a response. Such strains are typically induced by weight bearing impact loading and high-intensity progressive resistance training. To date, high intensity resistance and impact training has not been investigated in postmenopausal women due to a perceived risk of fracture and/or injury. Consequently, the primary aim of the current work was to develop a novel bone specific high intensity resistance and impact training program (HiRIT) for postmenopausal women to improve bone, physical function and risk factors for fracture.

The thesis comprises of four publications, presented as three published manuscripts and prepared for submission. In the first manuscript (Chapter 4), the preliminary bone and physical performance findings of the Lifting Intervention For Training Muscle and Osteoporosis Rehabilitation (LIFTMOR) trial are presented. In the subsequent manuscript (Chapter 5), the final findings of bone and physical function from the LIFTMOR trial are presented. The LIFTMOR trial was an 8-month exercise intervention of twice-weekly, 30-minute, supervised HiRIT (5 sets of 5 repetitions, > 85% of 1 repetition maximum) program. A home-based, low intensity exercise program served as a positive control (CON). Postmenopausal women with low bone mass were recruited and randomized, stratified on presence or absence of osteoporosis medication

use. Pre and post intervention testing included lumbar spine and proximal femur bone mineral density and geometry, and measures of functional performance. We found that 8 months of twice-weekly HiRIT improved lumbar spine and femoral neck bone mineral density and geometry and all physical performance measures compared to losses or minimal change in the low intensity home based exercise program.

Manuscript three (Chapter 6) presents changes in kyphosis and vertebral morphology over the period of the LIFTMOR trial. We found that 8 months of twice-weekly, 30-minute, supervised HiRIT improved thoracic kyphosis more than the low-intensity control exercise program. Furthermore, HiRIT did not induce new vertebral fractures or worsen existing vertebral deformities. The findings of manuscript three challenge traditional concerns that high-intensity exercise loading presents an unacceptable level of risk to postmenopausal women susceptible to fragility fractures from osteoporosis.

The final manuscript (Chapter 7) was a mixed methods qualitative analysis of LIFTMOR participant experiences and perceptions of the HiRIT and CON exercise programs. We observed that 8 months of supervised HiRIT improved physical activity enjoyment and quality of life. The qualitative analysis revealed that HiRIT was received positively, with participants reporting a sense of achievement, enjoyment of the group nature of training sessions and feeling stronger. Furthermore, HiRIT group participants were more likely to participate in the LIFTMOR trial again given the opportunity, to continue HiRIT after trial completion and would recommend HiRIT to a friend.

In summary, the current thesis reports the positive effects of a bone-targeted HiRIT exercise program on bone, kyphosis and physical function. Furthermore, the HiRIT exercise program was enjoyable. Based on these findings, we conclude HiRIT has the

potential to be a safe, efficacious and appealing exercise program for the management of osteoporosis in postmenopausal women.

## **Statement of Originality**

This work has not previously been submitted for a degree or diploma in any university.

To the best of my knowledge and belief, the thesis contains no material previously published or written by another person except where due reference is made in the thesis itself.

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Steven L. Watson

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## **Keywords**

Bone; Bone geometry; Bone loading; Bone mineral density; Cobb angle; Combined training; Dual-energy x-ray absorptiometry; Exercise; Flexicurve; Fracture; Fracture prevention; Functional performance; High intensity; High impact; Impact training; Inclinator; Kyphosis; Lateral vertebral assessment; Lumbar spine; Osteopenia; Osteoporosis; Physical activity; Proximal femur; Quantitative ultrasound; Resistance training; Vertebral fracture; Vertebral morphology; Weights; Weight training

## Abbreviations

25OHD	25-hydroxycholecalciferol
2D	Two-dimensional
3D	Three-dimensional
aBMD	Areal bone mineral density
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
ANZBMS	Australia and New Zealand Bone and Mineral Society
ARPANSA	Australian Radiation Protection and Nuclear Safety Agency
AUD	Australian dollar
AusCal	Australian calcium-specific diet questionnaire
BES	Back extensor strength
BI	Bioelectrical impedance
BMC	Bone mineral content
BMD	Bone mineral density
BMI	Body mass index
BPAQ	Bone-specific physical activity questionnaire
BUA	Broadband ultrasound attenuation
C7	Seventh cervical vertebra
cBPAQ	Current bone-specific physical activity questionnaire
CI	Confidence interval
CON	Control group
CTR	Clinical trials registration
DALYS	Disability adjusted life years

DXA	Dual energy x-ray absorptiometry
FN	Femoral neck
FRT	Functional reach test
FTSTS	Five times sit-to-stand test
HiRIT	High-intensity resistance and impact training
HIRT	High-intensity resistance training
HIWB	High-intensity weight bearing exercise
HREC	Human research ethics committee
HT	Hormone therapy
ITT	Intention to treat analysis
LES	Leg extensor strength
LIFTMOR	Lifting Intervention For Training Muscle and Osteoporosis Rehabilitation
LIRT	Low-intensity resistance training
LIWB	Low-intensity weight bearing exercise
LS	Lumbar spine
LSD	Least significant difference
LVA	Lateral vertebral assessment
MIRT	Moderate intensity resistance training
MRI	Magnetic resonance imaging
PACES	Physical activity enjoyment scale questionnaire
pBPAQ	Past bone-specific physical activity questionnaire score
pQCT	Peripheral quantitative computed tomography
PP	Per protocol analysis

PRT	Progressive resistance training
QCT	Quantitative computed tomography
QUS	Quantitative ultrasound
RCT	Randomized controlled trial
RM	Repetition maximum
SEM	Standard error of the mean
SI	Stiffness index
SOS	Speed of sound
SPSS	Statistical Package for the Social Sciences
tBPAQ	Total bone-specific physical activity questionnaire score
T4	Fourth thoracic vertebra
T12	Twelfth thoracic vertebra
TH	Total hip
TUGT	Timed up-and-go test
vBMD	Volumetric bone mineral density
VJ	Vertical Jump
WB	Whole body
WHOQOL	World Health Organization Quality of Life questionnaire

## Thesis Organisation

- **Chapter 1** of the thesis provides a general introduction to the LIFTMOR trial, including a brief background, objectives, aims and hypotheses.
- **Chapter 2** presents a review of scientific literature essential to the development and implementation of the LIFTMOR trial. It begins with a review of bone biology, bone response to mechanical loading, determinants of bone strength and an overview of osteoporosis. Next, the effect of exercise and aging is reviewed, with a focus on the different exercise modalities proposed for the management of osteoporosis and factors influencing participation. Finally, a review of the effect of kyphosis on older individuals and potential exercise programs for improving kyphosis is presented.
- **Chapter 3** details the methods of the LIFTMOR trial, including study design, recruitment, descriptions of the intervention and control exercise programs, data collection, analysis and statistical analyses.
- **Chapters 4, 5, 6 and 7** comprise the individual papers generated from the LIFTMOR trial. Each paper is complete with its own introduction, methods, results and discussion section; however, references are presented together at the end of the thesis.
- **Chapter 8** summarises the findings of the LIFTMOR trial, their significance and possible directions for future research.

## List of Publications

### *Papers included in this Thesis*

Included in this thesis are papers in chapters four, five and six which are co-authored with the other researchers. My contribution to each co-authored paper is outlined at the front of the relevant chapter. The bibliographic details for these papers including all authors, are:

**Watson, S.L;** Weeks, B.K; Weis, L; Horan, S.A. and Beck, B.R. (2015) 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. *Osteoporosis International*, 26(12):2889-94

**Watson, S.L;** Weeks, B.K; Weis, L; Harding, A; Horan, S.A. and Beck B.R. (2017) High intensity resistance and impact training improves bone and physical function in postmenopausal women with osteopenia and osteoporosis: The LIFTMOR trial. *Journal of Bone and Mineral Research*, 33(2):211-220

**Watson, S.L;** Weeks, B.K; Weis, L; Harding, A; Horan, S.A. and Beck B.R. High intensity progressive resistance and impact training is safe and improves thoracic kyphosis in postmenopausal women with low to very low bone mass: The LIFTMOR trial. *Osteoporosis International*, DOI:10.1007/s00198-018-04829-z

***Papers related to this thesis***

Beck, B.R; **Watson, S.L**; Weis, L; Horan, S.A; and Weeks, B.K. (2016) Response to Giangregorio et al.: “Intensity is a subjective construct”. *Osteoporosis International*, 27(7):2393-2395

**Watson, S.L**; Weeks, B.K; Weis, L; Harding, A; Horan, S.A. and Beck B.R. Erratum: 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. *Journal of Bone and Mineral Research*, accepted

***Papers not directly supporting this thesis***

Harding, A.T; Weeks, B.K; Horan, S.A; Little, A; **Watson, S.L**. and Beck, B.R. (2017) Validity and reliability of a novel simple back extensor muscle strength test. *SAGE Open Medicine*, DOI: 10.1177/2050312116688842

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Lambert, C; Beck, B.R; Harding, A; **Watson, S.L**. and Weeks, B.K. (2017) A protocol for a randomised controlled trial of the bone response to impact loading or resistance

training in young women with lower than average bone mass: The OPTIMA-Ex trial.  
*BMJ Open*, 7(9):e016983

***Oral presentations***

**Watson, S.L;** Horan, S.A; Weeks, B.K and Beck, B.R. (2014) LIFTMOR – Lifting Intervention For Training Muscle and Osteoporosis Rehabilitation. Australian Physiotherapy Association QLD symposium: *Early career research showcase*, Gold Coast, 13th November

**Watson, S.L;** Weeks, B.K; Horan, S.A. and Beck, B.R. (2015) High intensity progressive resistance training for postmenopausal women with low bone mass: Early findings from the LIFTMOR trial. *Sports Medicine Australia National Conference*, Gold Coast, 21-24<sup>th</sup> October

**Watson, S.L;** Weeks, B.K; Horan, S.A. and Beck, B.R. (2015) Efficacy of high intensity progressive resistance training for improving bone mineral density and body composition in postmenopausal women: Early findings from the LIFTMOR trial. *Sports Medicine Australia Queensland Branch Conference*, Brisbane, 16th May

**Watson, S.L;** Weeks, B.K; Weis, L; Harding, A; Horan, S.A. and Beck B.R. (2016) Breaking the rules in exercise therapy for osteoporosis: The LIFTMOR trial. *Gold Coast Health and Medical Research Conference*, Gold Coast 1-2nd December

**Watson, S.L;** Weeks, B.K; Weis, L; Harding, A; Horan, S.A. and Beck B.R. (2016) High intensity progressive resistance training is safe and effective for postmenopausal

women with low to very low bone mass: The LIFTMOR Trial. *Joint ESA, SRB and ANZBMS Annual Scientific Meeting*, Gold Coast 21-24<sup>th</sup> August

***Poster presentations***

**Watson, S.L;** Horan, S.A; Weeks, B.K and Beck, B.R. (2014) LIFTMOR: Lifting intervention for training muscle and osteoporosis: an RCT study protocol. *Gold Coast Health and Medical Research Conference*, Gold Coast, 4-5<sup>th</sup> December

**Watson, S.L;** Weeks, B.K; Weis, L; Horan, S.A; Harding, A and Beck B.R. (2015) Relationship of lean and fat mass to bone health, function and physical activity enjoyment in postmenopausal women. *Gold Coast Health and Medical Research Conference*, Gold Coast 3-5<sup>th</sup> December

**Watson, S.L;** Weeks, B.K; Weis, L; Harding, A; Horan, S.A and Beck B.R. (2016) High Intensity Progressive Resistance Training for Postmenopausal Women with Low to Very Low Bone Mass: The LIFTMOR Trial. *American Society for Bone and Mineral Research*, Atlanta, Georgia, USA, 16-19<sup>th</sup> September

**Watson, S.L;** Weeks, B.K; Weis, L; Harding, A; Horan, S.A. and Beck B.R. (2018) Supervised high intensity resistance and impact training does not cause vertebral crush fractures and improves thoracic kyphosis in postmenopausal women with low to very low bone mass: The LIFTMOR Trial. *American Society for Bone and Mineral Research*, Montreal, Quebec, Canada, 28<sup>th</sup> September-1<sup>st</sup> October



# Chapter 1: General Introduction

## 1.1 Overview

Osteoporosis is defined by critically low bone mass or a fragility fracture [330]. In Australia, approximately one in four women over 50 years of age and one in two women over 80 years of age have osteoporosis [131]. This is a major concern given those with osteoporosis have a greater risk of fracture, with approximately 8.9 million osteoporosis-related fractures worldwide each year, equating to a fracture every three seconds [146]. Regular exercise is a safe and effective strategy to prevent or minimise age-related bone loss [136], however few exercise programs have demonstrated an ability to notably increase bone mass.

The bone response to exercise is highly dependent on the nature of applied mechanical loads. The most osteogenic activities are those that induce high magnitude strains [258] at high rates [228, 305], or high frequencies [259, 304] in bone. Observational studies demonstrate that athletes participating in high-intensity weight bearing sports such as gymnastics and running have greater bone mass than athletes of non-weight bearing sports such as swimming, or untrained controls [35, 92, 194]. Similarly, high-intensity weight bearing exercise interventions which generate high strains and/or strain rates in bone tissue are required to stimulate positive adaptive changes in bone [44], while low-intensity activities such as walking are largely ineffective [235]. Paradoxically, it is widely held that high-intensity exercise should not be attempted by individuals with osteoporosis, owing to a potential increased risk of fracturing fragile bone [111, 176, 209]. The latter notion has led to the development of osteoporosis prevention programs that incorporate predominantly low to moderate-intensity exercises, which have been shown to yield only modest improvements in bone strength indices. In postmenopausal women, those gains represent a 1-2% increase in

bone mineral density [168, 191, 214, 218]. The examination of the safety and efficacy of less conservative bone-targeted exercise is overdue. The primary aim of the current project then was to determine the safety and efficacy of a supervised high-intensity resistance and impact training program for postmenopausal women with low to very low bone mass on known risk factors for osteoporotic fracture, including, bone mass and strength, physical function, and risk factors for falls.

## **1.2 Aims and objectives**

### *1.2.1 Aim*

The aim of the study was to examine the influence of supervised high-intensity resistance and impact training on parameters of musculoskeletal health in postmenopausal women with low to very low bone mass. Specifically, we examined the effect of an 8-month, twice-weekly, high-intensity resistance and impact training intervention on indices of bone strength at the lumbar spine and hip, and physical performance. A home-based resistance exercise program served as a positive control. The acceptability, safety and feasibility of the intervention was examined in terms of participant satisfaction, adverse events, and compliance.

### *1.2.2 Objectives*

The objectives of the study were to:

1. determine the effect of an 8-month, twice-weekly, supervised high-intensity resistance and impact training program on indices of bone strength, including areal bone mass and area at the spine and hip (DXA), volumetric BMD and geometric parameters at the femoral neck (3D-DXA), and calcaneal bone quality

- (QUS) in healthy postmenopausal women with low to very low bone mass in comparison with a very low-intensity, twice-weekly, home exercise program.
2. determine the effect of an 8-month, twice-weekly, supervised high-intensity resistance and impact training program on physical performance measures and falls risk factors (i.e. back extensor strength, leg extensor strength, functional reach test, timed up-and-go test, five times sit-to-stand, and vertical jump) in healthy postmenopausal women with low to very low bone mass in comparison with a very low intensity twice-weekly home exercise program.
  3. determine the effect of an 8-month, twice weekly, supervised high-intensity resistance and impact training program on kyphosis (Cobb angle, Flexicurve and inclinometer) in healthy postmenopausal women with low to very low bone mass in comparison with a very low-intensity, twice-weekly, home exercise program.
  4. determine participant satisfaction (PACES), compliance (session attendance), experiences (semi-structured interviews) and safety (adverse events) of an 8-month, twice weekly supervised high intensity resistance and impact training program in healthy postmenopausal women with low to very low bone mass in comparison with a very low-intensity, twice-weekly, home exercise program.

### 1.3 Hypotheses

#### Objective 1

Null: There will be no differences in indices of bone strength following an 8-month, twice-weekly, supervised high-intensity resistance and impact training intervention compared with a very low-intensity home exercise program in healthy postmenopausal women with low to very low bone mass.

Alternative: There will be differences in indices of bone strength following an 8-month, twice-weekly, supervised high-intensity resistance and impact training intervention compared with a very low-intensity home exercise program in healthy postmenopausal women with low to very low bone mass.

#### Objective 2

Null: There will be no differences in muscle strength or physical performance following an 8-month, twice-weekly, supervised high-intensity resistance and impact training intervention compared with a very low-intensity home exercise program in healthy postmenopausal women with low to very low bone mass.

Alternative: There will be differences in muscle strength or physical performance following an 8-month, twice-weekly, supervised high-intensity resistance and impact training intervention compared with a very low-intensity home exercise program in healthy postmenopausal women with low to very low bone mass.

#### Objective 3

Null: There will be no differences in kyphosis or changes in vertebral morphology following an 8-month, twice-weekly, supervised high-intensity resistance

and impact training intervention compared with a very low-intensity home exercise program in healthy postmenopausal women with low to very low bone mass.

Alternative: There will be differences in kyphosis or changes in vertebral morphology following an 8-month, twice-weekly, supervised high-intensity resistance and impact training intervention compared with a very low-intensity home exercise program in healthy postmenopausal women with low to very low bone mass.

#### **Objective 4**

Null: There will be no differences in participant satisfaction following an 8-month, twice-weekly, supervised high intensity resistance and impact training intervention compared with a very low intensity home exercise program in healthy postmenopausal women with low to very low bone mass.

Alternative: There will be differences in participant satisfaction following an 8-month, twice-weekly, supervised high intensity resistance and impact training intervention compared with a very low intensity home exercise program in healthy postmenopausal women with low to very low bone mass.



## Chapter 2: Literature Review

## 2.1 Ageing and health

The increase in health care costs and rising pressure on the healthcare system associated with an ageing population is of great concern [10]. In 2016-17, Australian healthcare expenditure was AUD \$181 billion and is increasing approximately 7% per annum [12]. In the older population, chronic diseases are the leading cause of illness, disability and death, accounting for approximately 90% of all deaths in 2011 [11]. The most common and costly chronic conditions include arthritis, asthma, cancer, cardiovascular disease, diabetes, dementia and osteoporosis [11]. Seventy-seven percent of older individuals have at least one chronic condition, and 80% of these are afflicted by three or more [60]. Chronic disease can have broad-ranging detrimental effects on an individual, including physiological and psychological consequences. In combination, such changes may increase the risk of other significant health events, such as fall-related fractures [205].

After motor vehicle accident-related health care costs, falls are the second largest contributor to injuries overall and account for the majority of traumatic injuries in older individuals [82]. Of all injuries sustained by individuals in Australia, 8.5% are sustained by older adults [319]. This proportion is incongruent with actual direct health care costs, where 22% of all trauma-related health care expenditure is spent on older Australians [319]. Fracture is a common consequence of a fall in older adults, with the direct cost of fractures reported to be between AUD \$4,386 and \$33,576 depending on the site of fracture [320]. The greater cost associated with older patients who fall is related to co-morbidities that tend to increase recovery time and lengthen hospital stays [331].

## 2.2 Osteoporosis

Osteoporosis, a common chronic condition associated with aging, is defined as a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture [225]. Diagnosis of osteoporosis is based on dual-energy x-ray absorptiometry (DXA) estimates of areal bone mineral density (aBMD). The two clinically relevant sites typically measured are the hip and lumbar spine. The relative risk of fracture is increased by 1.5-fold for every standard deviation below the aBMD mean of the reference population [183]. Osteopenia can be defined as a bone mineral density (BMD) T-score between -1.0 and -2.5 standard deviations below the young (20 year-old) race- and sex-matched mean [330], while osteoporosis may be defined as a BMD T-score more than 2.5 standard deviations below that mean [244, 330]. The 2014 National Bone Health Alliance Working Group proposed that the definition of osteoporosis should extend beyond BMD alone. They recommend that those with the presence of a low-trauma hip fracture, or with osteopenia plus a low-trauma vertebral, proximal humerus, pelvis, or, in some cases, distal forearm fracture should also be classified as having osteoporosis [280].

### 2.2.1 Epidemiology

Osteoporosis is estimated to affect over 200 million people worldwide [74, 248], and in the year 2000 there were an estimated 9 million osteoporosis-related fractures [146]. Of the 9 million fractures, there were a total of 1.6 million hip fractures and 70% of these fractures occurred in women [146]. In Australia, it is estimated that 66% of people over 50 years of age have osteopenia or osteoporosis [320]. In 2011, it was estimated that 1.2 million Australians suffered from osteoporosis, with a further 6.3

million suffering from osteopenia and this is only expected to rise with the ageing of the population [88, 131]. In 2012, there were over 140,000 fractures in Australia associated with osteoporosis and osteopenia [320].

### *2.2.2 Osteoporosis and osteopenia burden of disease*

An estimated 5.8 million disability adjusted life years (DALYS) are lost annually to osteoporotic fractures globally, with hip fractures accounting for 41% of the global burden of osteoporosis [146]. Hip fractures have major health consequences and are directly responsible for a 20-30% increase in mortality in the first year post-fracture [145]. Beyond the individual cost of osteoporosis, the financial cost of osteoporosis and osteopenia in Australians over the age of 50 years was AUD \$2.75 billion in 2012, and the total direct and indirect costs of osteoporosis, osteopenia and associated fracture over the subsequent 10 years was estimated at AUD \$33.6 billion [320].

## **2.3 Bone biology**

### *2.3.1 Basic bone biology*

Bone is a dynamic tissue which can adapt to mechanical loading. The primary functions of bone include: 1) structural support; 2) storage of minerals such as calcium and phosphorous; 3) blood cell production in bone marrow; 4) protection of organs; and 5) leverage and attachment for muscles to facilitate movement [199].

Bone is typically comprised of an outer dense cortical layer and an inner lattice-like trabecular structure. Dense cortical bone predominates in the shafts (i.e. diaphyses) of long bones but forms a thin shell around short and irregular bones. Trabecular bone is found predominantly in the bodies of short bones and the ends (i.e. epiphyses) of long

bones. The majority of bone tissue is made up of bone matrix and mineral, with only approximately 10% of bone volume comprising bone cells [53].

Bone contains four types of cells that are important to its function and properties, including: osteoclasts; osteoblasts; osteocytes; and bone lining cells. Osteoclasts are large, multinucleated cells that secrete acids and proteinases onto the bone surface to break down bone matrix in a process known as resorption. Osteoclasts originate from hematopoietic stem cells, whereas osteoblasts, bone lining cells and osteocytes originate from mesenchymal stem cells and differ from each other based on their phase of lifespan and activity.

Bone lining cells are found on the surface of bone, and when activated transform into osteoblasts that secrete a substance called osteoid onto the bone surface. Osteoid later mineralises to form new bone. Osteoblasts have three potential endpoints [54]. Firstly, they can become less active and become a bone lining cell. Secondly, during the bone formation process, they can become trapped in the new bone matrix and are considered osteocytes thereafter. Lastly, given the large number of osteoblasts that do not become osteocytes, the majority migrate away from the site of bone formation [54].

The most abundant cell type in bone is the osteocyte, making up over 90% of all bone cells [54]. Osteocytes reside in cavities in bone tissue known as lacunae and are connected to each other by dendritic processes that pass through an extensive network of small channels called canaliculi [53]. Osteocyte communication via canaliculi is thought to be important in the process of mechanotransduction (i.e. a process where mechanical loads are converted to physiological signals) and regulating bone formation and resorption.

### 2.3.2 *Bone remodelling*

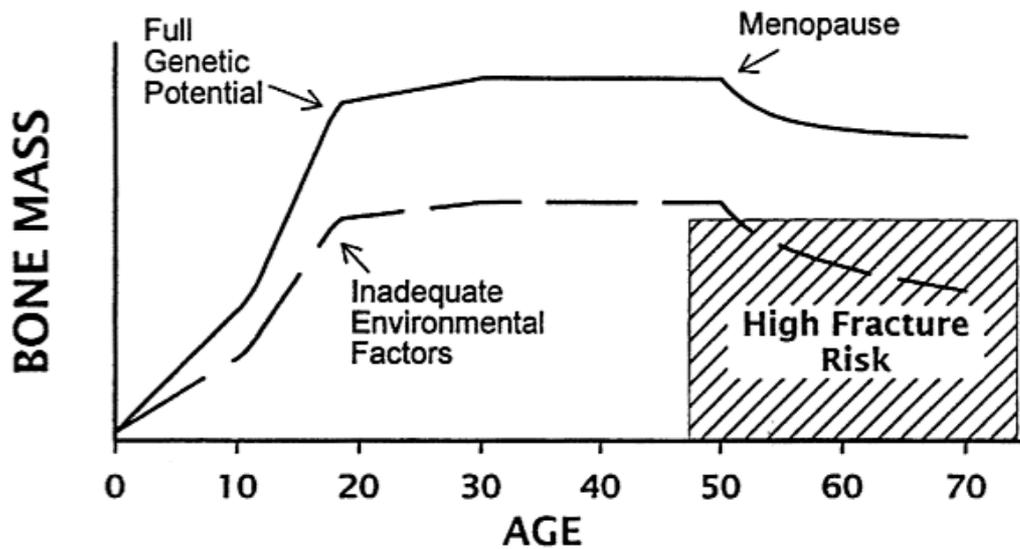
Throughout life, bone mass is continually resorbed and replaced in a process known as remodelling. In fact, approximately 10% of our skeleton is remodelled each year [237]. The process is characterized by the co-ordinated and coupled action of osteoclasts and osteoblasts to remove older bone (osteoclasts) and form new bone (osteoblasts), with no net change in bone size or shape.

### 2.3.3 *Bone modelling*

Bone modelling is the result of the uncoupled action of osteoclasts and osteoblasts, which brings about a change in bone size and shape. While bone modelling occurs throughout life, it is a particularly important process during growth to alter the length, width and shape of long bones and allow expansion of flat bones.

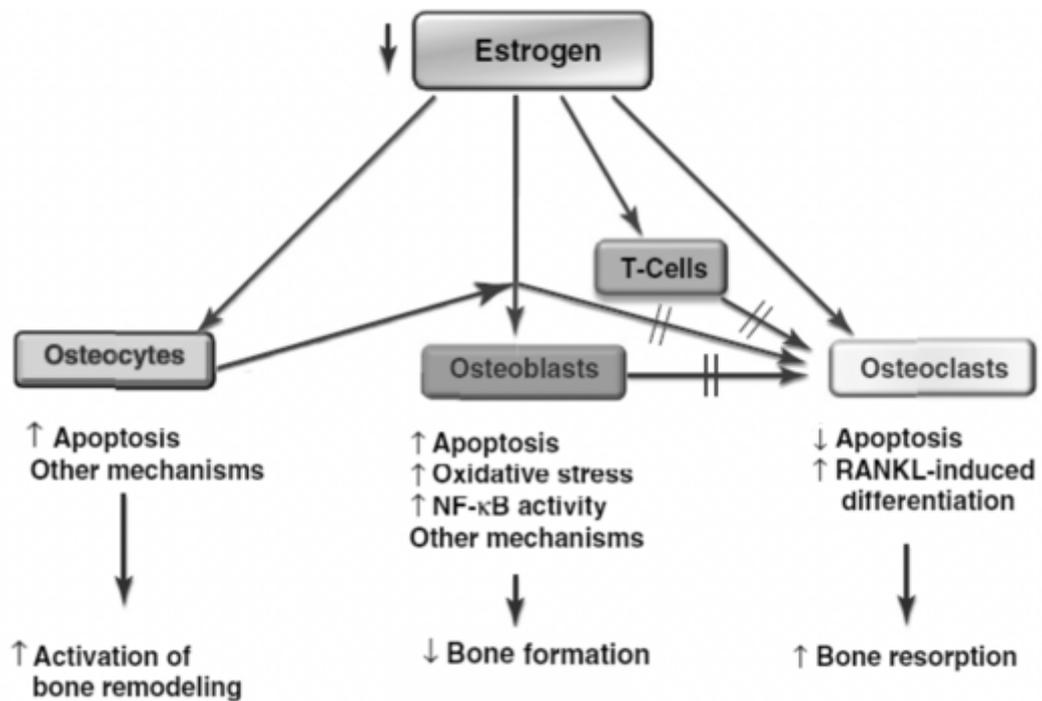
### 2.3.4 *Age-related decline in bone*

Bone mass increases rapidly in the first two decades of life, such that by 18 years of age approximately 90% of peak bone mass has been achieved [202]. Peak bone mass is reached between 25 and 30 years of age, followed by a gradual decline of approximately 3% per decade for cortical bone, and 7-11% per decade for trabecular bone [95, 98, 251] (Figure 1).



**Figure 1:** Bone mass across the lifespan and contributing factors [130]

Bone mass changes differently over the lifespan in men and women. In women, bone mass temporarily declines at a greater rate around the age of menopause due to the decline in circulating estrogen, resulting in a 10% decline over a five-year period (Figure 1) [231]. As circulating estrogen declines, there is a decrease in osteoblast activity due to an increase in osteoblast apoptosis. This is coupled with an increase in osteoclast activity due to reduced osteoclast apoptosis and increased osteoclast differentiation. The overall effect is net bone loss (Figure 2) [231]. Estrogen-related bone loss is associated with a four-fold greater prevalence of osteoporosis in women compared to men over 50 years [196], with one in three women having osteoporosis and more than half of women aged over 50 years having osteopenia [196].



**Figure 2:** A flow diagram of the protective effect of estrogens in bone metabolism and regulation (adapted from [231])

As bone mass declines, fractures become an increasing concern, with fragility hip fracture rates of around 1% in the older population [255]. In Australia, there has been a gradual decline in the incidence of falls, decreasing from 370 to 295 per 100,000 persons from 1997-2007 [75]. Despite the reduction in falls incidence, the absolute number of hip fractures has actually increased from 14,769 to 16,412 due to the expanding population [75].

### 2.3.5 Measuring bone

A number of different methods exist for the measurement of bone quantity and quality, such as DXA and quantitative ultrasound (QUS) [9]. DXA is widely used and is

the current gold standard for bone mass estimation through the measurement of two-dimensional (areal) BMD ( $\text{g}/\text{cm}^2$ ). Whole body scans are less common for the purpose of measuring bone quantity, however they can be used for monitoring systemic changes in bone, muscle, and fat and are often utilised in the fields of nutrition and sports performance [9]. While DXA is considered the gold standard for the clinical estimation of bone mass, it does have limitations. The primary limitation is that two-dimensional areal BMD does not reflect three-dimensional geometric properties or the microstructure of bone [68]. These important determinants of bone strength are independent of bone mass and their omission therefore limits the ability of DXA to detect potentially-relevant bone adaptations to an intervention [68, 282]. For this reason, DXA-derived BMD should be considered with other musculoskeletal outcomes when interpreting the efficacy of the intervention [282].

QUS provides an estimate of bone quality by quantifying the changes in shape, intensity and speed of sound waves from one side of bone to the other; most commonly the calcaneus [19, 226]. The most frequently reported parameter for QUS is broadband ultrasound attenuation (BUA,  $\text{dB}/\text{MHz}$ ), which is the regression slope of attenuation against a broad range of frequencies. While QUS has relatively high precision error and is therefore not typically recommended as a diagnostic measure for osteoporosis [137], it is a simple, quick, inexpensive and portable technique that is thought to provide unique information about bone quality not derived from DXA, such as trabecular spacing and connectivity [226].

### 2.3.6 *Determinants of bone strength*

The strength of bone and its ability to withstand the stresses placed upon it are influenced by a number of factors. Up to 60-70% of bone strength is accounted for by tissue mass, with the remainder derived from morphology and intrinsic microstructure [66]. The shape and size of a bone has important implications for its strength. For instance, the diameter of a long bone is exponentially related to its resistance to bending loads [66]. In fact, diameter alone can predict up to 55% of the variation in bone bending strength [66]. Cortical thickness also influences load resistance, although to a lesser extent than that of both bone mass or periosteal diameter [66]. Consequently, in order to obtain a proper estimate of bone strength, measures of both bone mass and geometry must be considered.

Many factors influence bone mass and therefore strength; with 50-80% of bone mass variance accounted for by genetic factors [76, 130, 203, 269]. Beyond genetics, nutrition and physical activity participation are important influential factors.

Vitamin D and calcium are arguably the most influential dietary factors affecting bone and when deficient, are associated with osteoporosis [201, 289]. Vitamin D is ingested or synthesized in the skin from sun exposure and is required for calcium absorption across the intestinal wall and osteoclast activity [289]. Calcium is a critical component in bone mineralisation. In conjunction with phosphorus, calcium forms hydroxyapatite; the major mineral component of bone [138]. Dietary intake of calcium is important for calcium homeostasis. If calcium deficiency exists, bone resorption occurs by the indirect activation of osteoclasts by parathyroid hormone to increase the bioavailable calcium in the blood, leading to a decrease in bone mass.

## 2.4 Bone adaptation to mechanical load

Bone tissue is responsive to mechanical stimuli. Mechanotransduction is the process by which mechanical loads are detected and converted (i.e. transduced) into biological signals that consequently modulate adaptive cellular activity. The process is complex and is comprised of four fundamental phases: 1) mechanocoupling; 2) biochemical coupling; 3) transmission of the signal from the sensor cell to the effector cell; and 4) the effector cell response [306]. This is thought to occur when mechanical loads are applied to bone causing tissue deformation, leading to the formation of pressure gradients and resultant shear forces on osteocytes from fluid flow within canaliculi. Shear force in combination with cell membrane and extracellular protein deformation ultimately leads to the recruitment of osteoblasts (effector cell) from bone lining cells and pre-osteoblasts [288, 306].

Bone modelling can have both a protective and a detrimental effect, depending on the characteristics of loads applied. For instance, bone loss of approximately 1-2% per month is experienced by astronauts exposed to microgravity due to net resorption [181]. In contrast, chronically increased mechanical loading can increase bone mass due to net formation [307]. Bone loss can occur if a formation-inducing stimulus is subsequently removed [35, 92, 140, 194]. Factors that influence the adaptive response to bone are strain magnitude, rate, frequency and the number of loading cycles, as described below.

### 2.4.1 *Strain magnitude*

Strain is the deformation of bone in response to an external load. Strain magnitude is represented as the percentage shortening of the bone, with 0.08%

shortening equivalent to 800 microstrain ( $\mu\epsilon$ ) [103]. Bones adapt to chronic changes in habitual strain; both increases and decreases. Chronically increased strain induces increased bone mass and/or altered morphology that will enhance resistance to the provoking strain [258]. Using a turkey ulna model, Rubin and Lanyon [258] observed a dose-related adaptive response to the application of a variety of load magnitudes 100 times per day for 8 weeks. They found strains less than  $1000\mu\epsilon$  were associated with bone loss, whereas strains greater than  $1000\mu\epsilon$  provoked a dose-dependent increase in periosteal bone formation. Similarly, peak strain magnitudes have shown a dose-dependent increase in periosteal bone area in growing rats [213].

#### 2.4.2 *Strain frequency*

Strain frequency refers to the number of tissue deformations that occur in one second (Hertz [Hz]), and is directly related to loading frequency (measured in cycles per second). It is also an important determinant of the bone adaptive response to mechanical loading in a complex relationship with strain magnitude [303]. Rubin and McLeod [259] used a turkey model to investigate the application of  $150\mu\epsilon$  magnitude for 100 seconds, daily, for 8 weeks at 1Hz or 20Hz. They found that 20Hz (69%) induced the greatest ingrowth of bone compared to 1Hz (28%) and non-loaded (-8%) ulnae. Similarly, a dose-response relationship between frequency and bone formation has been shown in rats, with no bone formation in frequencies below 0.5Hz (0.05-0.2Hz) and increased bone formation above 0.5Hz (0.5-2Hz) [304].

### 2.4.3 *Strain rate*

Strain rate is the speed at which bone deformation occurs, and is therefore closely positively associated with strain frequency. As with strain frequency, higher strain rates induce bone formation more than low [113, 303]. Using an ovine model, O'Connor and colleagues [228] demonstrated that 68-81% of the variance in bone formation could be explained by strain rate. Turner and colleagues [305] similarly found that high strain rates are necessary to stimulate new bone formation, with higher strain rates resulting in greater bone formation than low, when strain magnitude was constant.

### 2.4.4 *Dynamic versus static loading*

Static loads appear to have negligible effect on bone formation; indeed dynamic loads are required to stimulate bone adaptation [180, 188]. The seminal observations in this regard of Hert and colleagues from rabbit studies have since been supported by results of studies in rats and turkeys [180, 252]. For instance, Robling and colleagues [252] applied both static and dynamic forces (17N) to rat ulnae for 10 minutes per day, with the rats otherwise free to ambulate. They found that after two weeks, dynamic loads increased bone formation, whereas static loads had an inhibitory effect.

### 2.4.5 *Loading cycles*

Bone adaptation to mechanical loading can occur in response to a small number of loading cycles, with minimal benefit from additional loading cycles [257]. In a rooster model, Rubin and colleagues [257] demonstrated the effects of loading cycles on bone formation. Specifically, a similar mechanical load was applied at 0.5Hz for 0.95 seconds for either 0, 4, 36, 360, or 1800 cycles per day for six weeks. They discovered

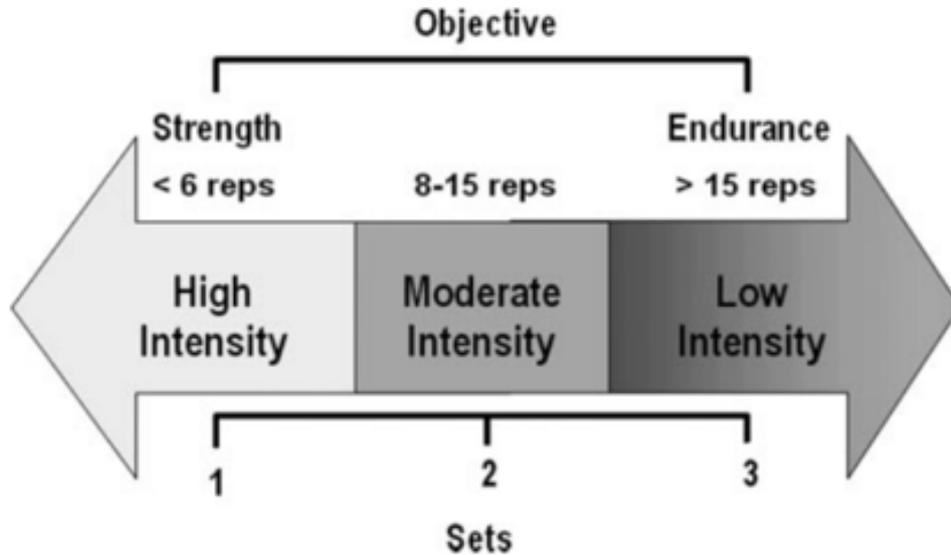
that there was a saturation effect, with 36 cycles being sufficient to stimulate bone formation and no additive benefit for either 360 or 1800 cycles a day. A similar saturation profile was observed in a rat model, with 5 jumps per day being sufficient to increase bone formation, while little added benefit was gained by performing 10-100 jumps per day [308].

## **2.5 Exercise for bone**

The following summary of exercise programs for bone has been derived using the following process. PubMed, Cochrane Library and the Medline databases were searched using the terms “elderly”, “exercise”, “bone”, “BMD”, “older”, “osteopenia”, “osteoporosis”, “resistance training”, “physical activity”, “postmenopausal”, “post menopausal”, “post-menopausal”, “weight lifting” and “weight training”. The searches were conducted in June 2014, and again in January 2019. Although not a formal systematic review, articles were only included if they examined either LS or FN BMD as an outcome measure, and could isolate the effect of exercise from other interventions and involved older women not affected by notable comorbidities. They were subsequently classified on type and intensity specific to the exercise modality.

The translation of the aforementioned characteristics of optimal loading for bone adaptation into practical exercise prescription has not been well executed. Current exercise recommendations for older adults with osteoporosis advise twice-weekly resistance training of 8 repetitions at 80-85% 1 repetition maximum for each large muscle group plus moderate-high impact (2-3 times bodyweight) training 4-7 times per week [28]. While these guidelines appear to reflect the basic loading principles derived from the animal research, the recommended exercise intensity may be insufficient to

promote optimum bone adaptation. In fact, the interpretation of exercise intensity in almost all of the prior bone literature has been problematic. This has resulted in inconsistent findings on the effects of exercise for bone, although when meta-analysed, small overall beneficial effects of 0.85% at the spine and 0.08% at the femoral neck are evident [136]. Resistance training repetition ranges of 8-12 are routinely described as high-intensity in bone exercise trials, despite the true classification of high intensity resistance training (as defined by the American Heart Association) involving fewer than 6 repetitions (Figure 3) [327]. In fact, when studies are classified according to the intensity standard defined by the American Heart Association, only one true high intensity exercise trial has been conducted, and it was of insufficient duration for bone adaptation to be detected [214].



**Figure 3:** American Heart Association scheme for the classification of resistance training intensity according to number of repetitions and sets [327]

### 2.5.1 *Low-impact weight-bearing exercise*

Low impact weight bearing exercise is considered to be an exercise program that applies less than 2 times bodyweight on the musculoskeletal system. Many forms of low-impact exercise have been examined with inconsistent outcomes for their potential therapeutic effect on bone health (Table 1) [62, 69, 89, 121, 294, 322]. The proposed benefits of low impact weight bearing exercises are that they are easy to perform, require limited equipment and are typically safe. A low impact exercise program frequently undertaken by older individuals is Tai Chi. Some preliminary evidence has indicated that it may have a protective effect on BMD and reduce risk of falls, although studies are limited in quantity and quality [62, 108, 294, 322]. One limitation of findings from Tai Chi trial are small sample sizes, however when combined in meta-analysis there appears to be a slight increase in BMD of 0.03 g/cm<sup>2</sup> (95% CI 0.01 to 0.06) at the spine [294]. The effects of non-weightbearing and low-impact exercise such as walking, swimming and cycling have also been investigated, with findings suggesting none provide sufficient loading to stimulate positive effects on bone [69, 80, 121, 136, 172, 178, 234]. Interestingly, walking has been shown to increase the cumulative risk of falls in postmenopausal women with osteoporosis, thus increasing fracture risk [89]. The limited osteogenic benefit of low impact exercise such as walking is not surprising given that bone adapts preferentially to novel loading of high magnitude. Additionally, the non-progressive nature of many forms of low-impact weight-bearing exercise may further limit their efficacy for bone [80]. Nonetheless, low-impact activities retain a role in maintaining and improving balance, in some cases reducing the risk of falling, and weight management and thus, should be considered important elements of a well-balanced exercise program [178].

### 2.5.2 *Moderate and high-impact weight-bearing exercise*

Moderate-impact weight-bearing exercise is defined as an activity that exerts forces 2-3 times bodyweight on the skeletal system, whereas high-impact exercises apply greater than 4 times bodyweight [28, 301]. High-impact weight-bearing exercise in the form of jumping has been shown to improve bone mass in young and middle-aged adults [159, 173, 186, 245]. Currently, moderate-impact exercises are recommended for older adults with low bone mass, as it has been proposed that high-impact activities are not suitable due to the risk of injury [28, 106]. In premenopausal women, high-impact exercises have been shown to be beneficial to bone health, however, conflicting results exist for postmenopausal women (Table 1) [23, 64, 65, 121, 177, 221, 264, 285]. Variations in exercise selection and the corresponding variety in magnitude of mechanical loading is a likely reason for the range of outcomes [23, 64, 264]. With the high forces produced during jumping being favourable for bone health, it is interesting to note that the normalised peak ground reaction force during a jumping task is greater for postmenopausal women when compared to premenopausal women [23, 64]. Moreover, the higher ground reaction forces experienced with jumping have the potential to have a greater effect on bone mass in older adults, as high impact loads are novel in that demographic. While high impact forces may be beneficial to the musculoskeletal system, safety concerns exist with high-impact weightbearing exercise for those at risk of fracture.

**Table 1:** Summary of weight bearing exercise trials for femoral neck and lumbar spine bone mineral density in postmenopausal women

Study	Sex	Groups	Age	Intervention	Within group results	Between group results
<i>Grove et al (1992) [121]</i>	F	MIWB (n=5)	54.0±1.9	Jumping, landing forces >2x bodyweight, 3/week for 12 months	NS LS BMD	Both MIWB and LIWB > controls for LS BMD
		LIWB (n=5)	56.6±4.3	Low impact walking and heel lifts, landing forces <1.5x bodyweight, 3/week for 12 months	NS LS BMD	
		Control (n=5)	56.0±4.5	Usual activities	↓6.0% LS BMD	
<i>Martin et al (1993) [198]</i>	F	LIWB (n=20)	60.3±7.8	Treadmill at 70-85 heart rate maximum, 30 mins 3/week for 12 months	NS LS BMD	NS LS BMD change between groups
		LIWB (n=16)	57.8±7.1	Treadmill at 70-85 heart rate maximum, 45 mins 3/week for 12 months	NS LS BMD	
		Control (n=19)	56.7±6.9	Usual activities	NS LS BMD	
<i>Kohrt et al (1995) [177]</i>	F	MIWB (32 in total, no information on groups sizes)	66±3	Walking, jogging and stair climbing (45 mins) ≥3/week for 11 months	↑ in both FN BMD and LS BMD, no values given	MIWB>control for LS and FN BMD
		Control	65±5	Usual activities	NS FN BMD; NS LS BMD	
<i>Ebrahim et al (1997)[89]</i>	F	LIWB (n=49)	66.4±7.8	Brisk walking, 40 mins 3/week for 24 months	NS FN BMD; NS LS BMD	NS LS BMD, LIWB> controls for FN BMD
		Control (n=48)	68.1±7.8	Upper limb exercises	NS FN BMD; NS LS BMD	
<i>Bassey et al (1998) [23]</i>	F	HIWB: Postmenopausal (n=45)	55.8±4.2	50 jumps, 6/week for 12 months	↓1.5% FN BMD; NS LS BMD	NS FN and LS BMD change between groups
		Control: Premenopausal (n=32)	54.9±4.1	Usual activities	NS FN BMD; NS LS BMD	
<i>Chein et al (2000) [65]</i>	F	LIWB (n=84)	57.1±8.6	Walking and step-ups with 20cm step, 3/week, 6 months	↑6.8% FN BMD; NS LS BMD	LIWB>control for LS and FN BMD
		Control (n=76)	57.0±5.4	Usual activities	NS FN BMD; ↓2.3% LS BMD	
<i>Kersch-Schindl et al (2000) [172]</i>	F	LIWB (n=19)	65.3±5.6	Calisthenics, no frequency reported, length of exercise participation ranged from 7-12 years	NS FN BMD; NS LS BMD	NS FN and LS BMD change between groups
		Control (n=6)	60.4±4.6	Usual activities	NS FN BMD; NS LS BMD	
<i>Snow et al (2000) [285]</i>	F	HIWB (n=9)	66.4±1.7	Weighted vest jumping exercises, 3/week for 60 months	NS FN BMD	HIWB>control for FN BMD
		Controls (n=9)	61.8±2.5	Usual activities	↓4.4% FN BMD	

Table 1 (continued)

Study	Sex	Groups	Age	Intervention	Within group results	Between group results
<i>Iwamoto et al (2001) [140]</i>	F	LIWB (n=8)	65.3±4.7	Walking (increasing daily step count by 30%) and twice daily bodyweight exercises for 24 months	↑4.33% LS BMD at 12 months and ↑4.29% LS BMD at 24 months	LIWB>control for LS BMD; LIWB + detraining NS LS BMD
		LIWB + detraining (n=7)	64.3±3.0	Walking (increasing daily step count by 30%) and twice daily bodyweight exercises for 12 months followed by 12 months detraining	↑4.5% LS BMD at 12 months and NS LS BMD after 12 months of detraining	
		Control (n=20)	64.9±5.7	Usual activities	NS LS BMD	
<i>Chan et al (2004) [62]</i>	F	LIWB (n=67)	54.4±3.3	Tai chi, 5/week for 12 months	NS FN BMD; NS LS BMD	NS FN and LS BMD change between groups
		Control (n=65)	53.6±3.2	Usual activities	↓1.8% FN BMD; NS LS BMD	
<i>Newstead et al (2004)[221]</i>	F	MIWB (n=23)	56.7±3.2	Multidimensional jumping (25-200 jumps per session), 2/week for 12 months	NS FN BMD; NS LS BMD	NS FN and LS BMD change between groups
		Control (n=27)	56.6±4.1	Usual activities	NS FN BMD; NS LS BMD	
<i>Chubak et al (2006) [69]</i>	F	LIWB (n=87)	60.7±6.7	Bike and treadmill, 45 mins 2/week for 12 months	NS FN BMD; NS LS BMD	NS FN and LS BMD change between groups
		Control (n=86)	60.6±6.8	Stretching, 45 mins, 1/week for 12 months	NS FN BMD; NS LS BMD	
<i>Korpelainen et al (2006) [178]</i>	F	MIWB (n=84)	72.9±1.1	Jumping and bodyweight exercises, 7/week, 30 months	NS FN BMD	NS FN BMD change between groups
		Control (n=76)	72.8±1.2	Usual activities	↓1.1% FN BMD	
<i>Woo et al (2007) [328]</i>	F	LIWB (n=28)	69.7±2.8	Tai Chi, 3/week for 12 months	NS LS BMD	NS LS BMD change between groups
		LIRT (n=30)	69.6±3.2	TheraBand exercises, 30 reps, 3/week for 12 months	NS LS BMD	
		CON (n=30)	69.3±3.0	Usual activities	NS LS BMD	
<i>Sakai et al (2010) [262]</i>	F	LIWB (n=49)	68.2±0.5	Unipedal standing, 3 x 6 minutes daily for 6 months	NS FN BMD	NS FN BMD change between groups
		Control (n=45)	68.3±0.8	Usual activities	NS FN BMD	
<i>Song et al (2010) [286]</i>	F	LIWB (n=30)	63.0±7.3	Tai Chi, 1 hr, 1-2 /week plus 20 minutes daily at home for 6 months	Results presented as T-score, ↑9% for FN in LIWB compared to controls	LIWB>control for FN BMD
		Control (n=35)	61.2±8.0	Usual activities		
<i>Wayne et al (2012) [321]</i>		LIWB (n=43)	58.8±5.6	Tai Chi, minimum 30 mins, 3/week for 9 months	NS FN BMD; NS LS BMD	LIWB>control for FN BMD, NS LS BMD between groups
		CON (n=43)	60.4±5.3	Usual activities	NS FN BMD; NS LS BMD	

Table 1 (continued)

Study	Sex	Groups	Age	Intervention	Within group results	Between group results
<i>Wang et al (2015) [316]</i>	F	LIWB (n=40)	58.5±3.4	Tai Chi resistance training, 1 hr 4/week for 12 months	NS FN BMD; ↑ LS BMD (% not reported)	NS FN and LS BMD change between groups
		LIWB (n=40)	58.5±3.4	Traditional Tai Chi, 1 hr 4/week for 12 months	NS FN BMD; NS LS BMD	
<i>Duckham et al (2015) [84]</i>	M & F	CON (n=39)	58.0±3.2	Usual activities	↓ FN BMD (% not reported)	NS FN and LS BMD change between groups
		LIWB (n=88)	71.4±4.9	Home based walking, balance and ankle weight exercises 30 mins, 3/week for 6 months	NS FN BMD; NS LS BMD	
		LIWB (n=105)	71.8±5.5	Community based walking, TheraBand, Tai Chi and ankle weight exercises 1x60 and 4x30 mins, 5/week for 6 months	NS FN BMD; NS LS BMD	
		CON (n=126)	72.2±5.5	Usual activities	NS FN BMD; NS LS BMD	

**Abbreviations:** HIWB = high intensity weight bearing exercise; MIWB = moderate intensity weight bearing exercise; LIWB = low

intensity weight bearing exercise; FN = femoral neck; LS = lumbar spine; BMD = bone mineral density

**Summary:** As illustrated in Table 1, many weight bearing exercise modalities exist, although they appear limited in their effect for bone as the majority involve low-impact. Exercises that confer the greatest benefit are those which induce high impact (>4x bodyweight), although limited evidence exists in postmenopausal women, especially in those at risk of fracture.

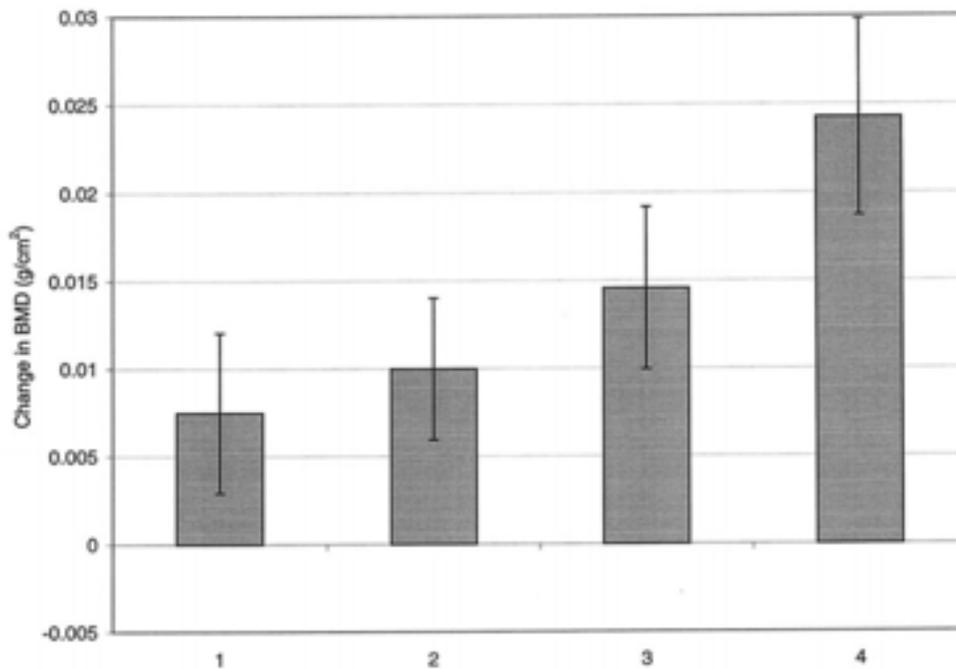
### 2.5.3 *Low-intensity progressive resistance training*

Low-intensity resistance training regimes (i.e. <67% 1RM or greater than 12 reps per set) have been tested for their effect on bone health with inconsistent results (Table 2) [32, 178]. The varied results may in part be due to the variety of resistance exercises examined. Programs that have utilised body weight exercises such as step ups and unloaded squats as part of a resistance training program have shown no benefit to bone [178]. Likewise, programs consisting of greater than 12 repetitions per set have shown to be no benefit to bone [32, 33, 49, 171]. The poor effect of low intensity resistance training to show an effect on bone may be a consequence of the low loads required to perform 12 or more repetitions, which provide insufficient mechanical loading for bone in older adults with osteoporosis. While no effect has been shown for bone, lower load resistance training in untrained postmenopausal women has, on occasion, induced improvements in muscle strength comparable to that of high intensity resistance training [32, 33, 49]. Those changes may have important implications for falls prevention.

### 2.5.4 *Moderate and high-intensity progressive resistance training*

The current Exercise and Sports Science Australia (ESSA) position statement on exercise prescription for osteoporosis recommends that “high” intensity resistance training be conducted twice-weekly at 8 repetitions (80% 1RM) for each large muscle group for older adults with osteoporosis [28]. Unfortunately, the moderate loads required to be able to perform 8 repetitions are unlikely to be sufficient to stimulate notable bone adaptation and according to the American Heart Association classification, are more accurately described as moderate-intensity resistance training [192]. Not

surprisingly, such moderate-intensity resistance training studies have produced only modest improvements in bone [45, 136, 200, 335]. Meta-analysis demonstrates the effect of moderate intensity resistance trainings is estimated as an improvement of 0.86% (95% CI 0.58 to 1.13) at the spine and 1.03% (95% CI 0.24 to 1.82%) at the femoral neck, with evidence that the benefits are dose dependent (Figure 4) [77, 123, 136, 170, 171, 264].



**Figure 4:** Change in trochanteric BMD by quartiles of weight lifted during squats in postmenopausal women [77]

Of the studies that have been conducted, moderate intensity loading has more efficacy than low intensity resistance training programs [77, 123, 170, 171, 264] (Table 2). Previously, moderate-intensity resistance training programs have used machine-based or isolated free weight exercises [33, 42, 49, 66, 70, 218, 242, 250]. Such

exercises are typically highly site specific and therefore may not replicate clinically relevant movement patterns or adequately stimulate clinically relevant bone sites. Multi-joint compound movements, such as the squat and deadlift, at high-intensity (>85% 1RM, <6 repetitions) have the potential to stimulate improvements in bone health due to the associated high magnitude of loading, but have not previously been tested due to safety concerns.

**Table 2:** Summary of resistance training exercise trials for femoral neck and lumbar spine bone mineral density in postmenopausal women

Study	Sex	Groups	Age	Intervention	Within group results	Between group results																																																																										
<i>Pruitt et al (1992) [241]</i>	F	MIRT (n=17)	53.6±1.0	Machine and free weight RT (2x10-15 reps), 3/week for 9 months	Within group data not presented	NS FN BMD; MIRT>controls for LS BMD																																																																										
		Control (n=10)	55.6±0.9	Usual activities			<i>Smidt et al (1992)[283]</i>	F	MIRT (n=27)	56.6±6.6	Prone extensions, sit up and leg raises (3x10), 3-4/week for 12 months	NS FN BMD; NS LS BMD	NS FN and LS BMD change between groups	Control (n=22)	55.4±8.0	Usual activities	NS FN BMD; ↓2.3% LS BMD	<i>Nelson et al (1994) [218]</i>	F	MIRT (n=20)	61.1±3.7	Machine based RT (3x8 reps), 2/week for 12 months	↑0.9% FN BMD; ↑1% LS BMD	MIRT>control for LS and FN BMD	Control (n=19)	57.3±6.3	Usual activities	↓2.5% FN BMD; ↓1.8% LS BMD	<i>Pruitt et al (1995)[242]</i>	F	MIRT (n=15)	67.0±0.5	Machine based RT (2x7 reps), 3/week for 12 months	NS FN BMD; NS LS BMD	NS FN and LS BMD change between groups	MIRT (n=13)	67.6±1.4	Machine based RT (3x14 reps), 3/week for 12 months	NS FN BMD; NS LS BMD	Control (n=12)	69.6±4.2	Usual activities	NS FN BMD; NS LS BMD	<i>Kerr et al (1996) [171]</i>	F	MIRT (n=28)	58.4±3.7	Machine and free weight RT on one upper and lower limb with the other serving as control (3 x8 reps), 3/week for 12 months	NS FN BMD	NS FN BMD change between groups	LIRT (n=28)	55.7±4.7	Machine and free weight RT on one upper and lower limb with the other serving as control (3x20 reps), 3/week for 12 months	NS FN BMD	Control: Non-exercising limb		Non-exercising control limb		<i>Adami et al (1999) [2]</i>	F	LIRT (n=118)	65±6	LIRT upper limbs only, 70 mins 2/week plus a further 30 mins/day at home for 6 months	NS FN BMD; NS LS BMD	NS FN and LS BMD change between groups	Control (n=116)	63±7	Usual activities	NS FN BMD; NS LS BMD	<i>Bemben et al (2000)[33]</i>	F	MIRT (n=10)	50.5±2.0	Machine based RT (3x8 reps), 3/week for 6 months	NS FN BMD; NS LS BMD	NS FN and LS BMD change between groups	LIRT (n=7)	51.9±2.3	Machine based RT (3x16 reps), 3/week for 6 months	NS FN BMD; NS LS BMD
<i>Smidt et al (1992)[283]</i>	F	MIRT (n=27)	56.6±6.6	Prone extensions, sit up and leg raises (3x10), 3-4/week for 12 months	NS FN BMD; NS LS BMD	NS FN and LS BMD change between groups																																																																										
		Control (n=22)	55.4±8.0	Usual activities	NS FN BMD; ↓2.3% LS BMD		<i>Nelson et al (1994) [218]</i>	F	MIRT (n=20)	61.1±3.7	Machine based RT (3x8 reps), 2/week for 12 months	↑0.9% FN BMD; ↑1% LS BMD	MIRT>control for LS and FN BMD	Control (n=19)	57.3±6.3	Usual activities	↓2.5% FN BMD; ↓1.8% LS BMD	<i>Pruitt et al (1995)[242]</i>	F	MIRT (n=15)	67.0±0.5	Machine based RT (2x7 reps), 3/week for 12 months	NS FN BMD; NS LS BMD	NS FN and LS BMD change between groups	MIRT (n=13)	67.6±1.4	Machine based RT (3x14 reps), 3/week for 12 months	NS FN BMD; NS LS BMD			Control (n=12)	69.6±4.2	Usual activities	NS FN BMD; NS LS BMD		<i>Kerr et al (1996) [171]</i>	F	MIRT (n=28)	58.4±3.7	Machine and free weight RT on one upper and lower limb with the other serving as control (3 x8 reps), 3/week for 12 months	NS FN BMD	NS FN BMD change between groups	LIRT (n=28)			55.7±4.7	Machine and free weight RT on one upper and lower limb with the other serving as control (3x20 reps), 3/week for 12 months	NS FN BMD	Control: Non-exercising limb			Non-exercising control limb		<i>Adami et al (1999) [2]</i>	F	LIRT (n=118)	65±6	LIRT upper limbs only, 70 mins 2/week plus a further 30 mins/day at home for 6 months	NS FN BMD; NS LS BMD	NS FN and LS BMD change between groups	Control (n=116)	63±7	Usual activities	NS FN BMD; NS LS BMD	<i>Bemben et al (2000)[33]</i>	F	MIRT (n=10)	50.5±2.0	Machine based RT (3x8 reps), 3/week for 6 months			NS FN BMD; NS LS BMD	NS FN and LS BMD change between groups	LIRT (n=7)	51.9±2.3		Machine based RT (3x16 reps), 3/week for 6 months	NS FN BMD; NS LS BMD	Control (n=8)	52.3±1.4
<i>Nelson et al (1994) [218]</i>	F	MIRT (n=20)	61.1±3.7	Machine based RT (3x8 reps), 2/week for 12 months	↑0.9% FN BMD; ↑1% LS BMD	MIRT>control for LS and FN BMD																																																																										
		Control (n=19)	57.3±6.3	Usual activities	↓2.5% FN BMD; ↓1.8% LS BMD		<i>Pruitt et al (1995)[242]</i>	F	MIRT (n=15)	67.0±0.5	Machine based RT (2x7 reps), 3/week for 12 months	NS FN BMD; NS LS BMD	NS FN and LS BMD change between groups	MIRT (n=13)	67.6±1.4	Machine based RT (3x14 reps), 3/week for 12 months	NS FN BMD; NS LS BMD			Control (n=12)	69.6±4.2	Usual activities	NS FN BMD; NS LS BMD		<i>Kerr et al (1996) [171]</i>	F	MIRT (n=28)	58.4±3.7	Machine and free weight RT on one upper and lower limb with the other serving as control (3 x8 reps), 3/week for 12 months	NS FN BMD	NS FN BMD change between groups	LIRT (n=28)	55.7±4.7	Machine and free weight RT on one upper and lower limb with the other serving as control (3x20 reps), 3/week for 12 months	NS FN BMD			Control: Non-exercising limb		Non-exercising control limb			<i>Adami et al (1999) [2]</i>	F	LIRT (n=118)	65±6	LIRT upper limbs only, 70 mins 2/week plus a further 30 mins/day at home for 6 months	NS FN BMD; NS LS BMD	NS FN and LS BMD change between groups	Control (n=116)	63±7	Usual activities	NS FN BMD; NS LS BMD	<i>Bemben et al (2000)[33]</i>	F	MIRT (n=10)	50.5±2.0	Machine based RT (3x8 reps), 3/week for 6 months	NS FN BMD; NS LS BMD	NS FN and LS BMD change between groups	LIRT (n=7)	51.9±2.3	Machine based RT (3x16 reps), 3/week for 6 months	NS FN BMD; NS LS BMD			Control (n=8)	52.3±1.4	Usual activities	NS FN BMD; NS LS BMD										
<i>Pruitt et al (1995)[242]</i>	F	MIRT (n=15)	67.0±0.5	Machine based RT (2x7 reps), 3/week for 12 months	NS FN BMD; NS LS BMD	NS FN and LS BMD change between groups																																																																										
		MIRT (n=13)	67.6±1.4	Machine based RT (3x14 reps), 3/week for 12 months	NS FN BMD; NS LS BMD																																																																											
		Control (n=12)	69.6±4.2	Usual activities	NS FN BMD; NS LS BMD																																																																											
<i>Kerr et al (1996) [171]</i>	F	MIRT (n=28)	58.4±3.7	Machine and free weight RT on one upper and lower limb with the other serving as control (3 x8 reps), 3/week for 12 months	NS FN BMD	NS FN BMD change between groups																																																																										
		LIRT (n=28)	55.7±4.7	Machine and free weight RT on one upper and lower limb with the other serving as control (3x20 reps), 3/week for 12 months	NS FN BMD																																																																											
		Control: Non-exercising limb		Non-exercising control limb																																																																												
<i>Adami et al (1999) [2]</i>	F	LIRT (n=118)	65±6	LIRT upper limbs only, 70 mins 2/week plus a further 30 mins/day at home for 6 months	NS FN BMD; NS LS BMD	NS FN and LS BMD change between groups																																																																										
		Control (n=116)	63±7	Usual activities	NS FN BMD; NS LS BMD																																																																											
<i>Bemben et al (2000)[33]</i>	F	MIRT (n=10)	50.5±2.0	Machine based RT (3x8 reps), 3/week for 6 months	NS FN BMD; NS LS BMD	NS FN and LS BMD change between groups																																																																										
		LIRT (n=7)	51.9±2.3	Machine based RT (3x16 reps), 3/week for 6 months	NS FN BMD; NS LS BMD																																																																											
		Control (n=8)	52.3±1.4	Usual activities	NS FN BMD; NS LS BMD																																																																											

Table 2 (continued)

Study	Sex	Groups	Age	Intervention	Within group results	Between group results
<i>Rhodes et al (2000)</i> [250]	F	MIRT (n=20)	68.8±3.2	Machine based and free weight RT (3x8 reps), 3/week for 12 months	NS FN BMD; NS LS BMD	NS FN and LS BMD changes between groups
		Controls (n=18)	68.2±3.5	Usual activities	NS FN BMD; NS LS BMD	
<i>Kerr et al (2001)</i> [170]	F	MIRT (n=42)	60±5	Machine and free weight RT (3x8 reps), 3/week for 24 months	NS FN BMD; NS LS BMD	NS FN and LS BMD change between groups
		LIRT (n=42)	59±5	Machine and free weight RT with no increase in load throughout program, 3/week for 24 months	NS FN BMD; NS LS BMD	
		Control (n=42)	62±6	Non-exercising control limb	NS FN BMD; NS LS BMD	
<i>Chilibeck et al (2002)</i> [66]	F	MIRT (n=10)	56.8±6.3	Machine and free weights RT (2x8-10 reps), 3/week for 12 months	NS FN BMD; NS LS BMD	NS FN and LS BMD change between groups
<i>Verschueren et al (2004)</i> [310]	F	Control (n=12)	58.8±5.7	Usual activities	NS FN BMD; NS LS BMD	NS LS BMD change between groups
		MIRT (n=22)	63.9±3.8	Machine based lower limb RT (3x8-12 reps), 3/week for 6 months	NS LS BMD	
		LIWB (n=25)	64.6±3.3	Bodyweight exercises on whole body vibration unit, 3/week for 6 months	NS LS BMD	
<i>Maddalozzo et al (2007)</i> [191]	F	MIRT (n=35)	52.3±3.3	Free weight RT, back squat and deadlift (3x8-12 reps), 2/week for 12 months	NS FN BMD; ↑0.4% LS BMD	MIRT>control for FN and LS BMD
		Control (n=34)	52.5±3.0	Usual activities	↓3.9% FN BMD; ↓3.6% LS BMD	
<i>Woo et al (2007)</i> [328]	F	LIWB (n=28)	69.7±2.8	Tai Chi, 3/week for 12 months	NS LS BMD	NS LS BMD change between groups
		LIRT (n=30)	69.6±3.2	TheraBand exercises, 30 reps, 3/week for 12 months	NS LS BMD	
		CON (n=30)	69.3±3.0	Usual activities	NS LS BMD	
<i>Brentano et al (2008)</i> [49]	F	MIRT (n=14)	Postmenopausal	Machine and free weights RT (2-4 sets, 6-20 reps), 3/week for 6 months	NS FN BMD; NS LS BMD	NS FN and LS BMD change between groups
		LIRT (n=9)	No age reported	Machine and free weights RT (2-3 sets, 10-20 reps), 3/week for 6 months	NS FN BMD; NS LS BMD	
		Control (n=9)		Usual activities	NS FN BMD; NS LS BMD	

Table 2 (continued)

Study	Sex	Groups	Age	Intervention	Within group results	Between group results
<i>Bocalini et al (2009)[42]</i>	F	MIRT (n=15)	69.0±9.0	Machine based RT (3x10 reps) 3/week, 60 min for 6 months	NS FN BMD; NS LS BMD	MIRT>control for FN and LS BMD
<i>Chuin et al (2009) [70]</i>	F	Control (n=10)	67.0±8.0	Usual activities	↓1.6% FN BMD; ↓1.0% LS BMD	NS FN BMD change between groups; MIRT>control for LS BMD
		MIRT (n=11)	65.4±3.5	Machine and bodyweight RT (3x8 reps), 3/week for 6 months	NS FN BMD; NS LS BMD	
<i>de Mantos et al (2009)[81]</i>	F	Control (n=7)	67.4±3.8	Usual activities	NS FN BMD; ↓1.0% LS BMD	NS FN BMD change between groups; MIRT>control for LS BMD
		MIRT (n=30)	57.5±5.1	Machine and bodyweight RT (3x10-15 reps), for 12 months, no frequency was reported	NS FN BMD; NS LS BMD	
<i>Bemben (2011) [32]</i>	M & F	Control (n=29)	56.6±4.6	Usual activities	NS FN BMD; ↓2.3% LS BMD	NS FN and LS BMD change between groups
		MIRT – 2/week (n=39)	55-74 yrs	Machine based RT (3 x8 reps), 2/week for 9 months	NS FN BMD; ↑~1.5% LS BMD	
		MIRT – 3/week (n=41)		Machine based RT (3x8 reps), 3/week for 9 months	NS FN BMD; ↑~1.1% LS BMD	
		LIRT – 2/week (n=34)		Machine based RT (3x16 reps), 2/week for 9 months	NS FN BMD; ↑~0.75% LS BMD	
<i>Marques et al (2011) [197]</i>	F	LIRT – 3/week (n=46)		Machine based RT (3x16 reps), 3/week for 9 months	NS FN BMD; ↑0.5% LS BMD	NS FN BMD change between groups
		MIRT (n=23)	67.3±5.2	Free weight RT (3 x8-12 reps), 3/week for 8 months	NS FN BMD	
		LIWB (n=24)	70.3±5.5	Stretching and dynamic aerobic exercises, 60 min, 3/week for 8 months	NS FN BMD	
<i>Chilibeck et al (2013)[67]</i>	F	Control (n=24)	67.9±5.9	Usual activities	NS FN BMD	NS FN and LS BMD change between groups
		MIRT (n=71)	55.3±6.3	Machine and free weights RT (2x8-10 reps), 2/week plus walking 20 min 4 days for 12 months	NS FN BMD; NS LS BMD	
<i>Mosti et al (2013)[214]</i>	F	Control (n=62)	56.4±7.1	Hone based stretching program	NS FN BMD; NS LS BMD	NS FN and LS BMD change between groups
		HIRT (n=8)	61.9±5.0	Hack squat machine (4 x3-5reps), 3/week for 3 months	NS FN BMD; NS LS BMD	
		Control (n=8)	66.7±7.4	Usual activities	NS FN BMD; NS LS BMD	NS FN and LS BMD change between groups

Table 2 (continued)

Study	Sex	Groups	Age	Intervention	Within group results	Between group results
<i>Novaes et al (2013)</i> [227]	F	MIRT (n=14)	66.9±6.1	Free weights (3x8-12 reps), 3/week for 6 months	↑4.2% FN BMD; ↑5.6 LS BMD	MIRT>control for FN and LS BMD
		Controls (n=17)		Aquatic exercises, 3/week for 6 months	NS FN BMD; NS LS BMD	
<i>Shanb et al (2014)</i> [270]	M & F	LIRT (n = 20)	63.8±3.1	Non-weightbearing resistance training (25% 1RM) 1 hr, 2week, 6 months	↓3.1% FN BMD; ↓3.3 LS BMD	Weightbearing LIRT > Non-weightbearing LIRT for FN and LS BMD
		LIRT (n = 20)	64.5±3.4	Weightbearing resistance training (25% 1RM) 1 hr, 2week, 6 months	↓2.8% FN BMD; ↓2.9 LS BMD	
<i>Raastad et al (2015)</i>	F	MIRT (n = 22) No control	68.3±6.7	Machine weights (progressed from 8-12 to 4-8 reps), 3/week for 3 months	NS FN BMD; NS LS BMD	NA
<i>Bacelar et al (2015)</i> [13]	F	MIRT (n = 18) No control	64±3	Machine weights (3 x 10 reps), 2/week for 10 weeks	NS FN BMD; NS LS BMD	NA
<i>Nicholson et al (2015)</i> [223]	F	LIRT (n = 24)	66.0±4.1	Free weights (>60 rep, <30% 1RM), 2/week, 6 months	NS FN BMD; NS LS BMD	LIRT>control for LS BMD, NS LS BMD
		Control (n = 26)	65.5±4.7	Usual activities	NS FN BMD; ↓2.1% LS BMD	

**Abbreviations:** HIRT = “high” intensity resistance training; MIRT = moderate intensity resistance training; LIRT = low intensity resistance training; FN = femoral neck; LS = lumbar spine; BMD = bone mineral density

**Summary:** As illustrated in Table 2, LIRT appears to confer no benefit to bone, whilst there appears to be some evidence for moderate efficacy of MIRT, particularly for improving LS BMD. Notably, there is a lack of true HIRT programs in postmenopausal women, despite its osteogenic potential.

### 2.5.5 *Combined training*

With the greatest improvements in bone health observed for programs that contain both higher intensity resistance training and impact exercises [123, 315, 334] (Table 3), it is not surprising that programs that combine the benefits of both training methods have the greatest effects [111, 136, 158]. Combined exercise programs incorporating moderate-intensity resistance training and high-impact weight-bearing exercise have resulted in improvements in bone mass, and significant reductions in the frequency and intensity of spinal pain [93, 165]. This mode of training should, therefore, be the focus of future research, with programs combining high-impact jumping tasks with a true high-intensity resistance training program.

**Table 3:** Summary of combined training exercise trials for femoral neck and lumbar spine bone mineral density in postmenopausal women

Study	Sex	Groups	Age	Intervention	Within group results	Between group results
<i>Metcalf et al (2001)</i>	F	Combined training (n=71)	55.8±4.7	Machine and free weight MIRT (3x6-8reps), LIWB-MIWB (walking/hopping) and balance exercises, 3/week for 12 months	NS LS BMD	NS LS BMD change between groups
<i>Going et al (2003) [111]</i>	F	Control (n=59)	57.1±5.0	Usual activities	NS LS BMD	NS FN and LS BMD change between groups
		Combined training (n=71)	55.8±4.7	Machine and free weight MIRT (3x6-8reps), LIWB-MWB (walking/hopping) and balance exercises, 3/week for 12 months	NS FN BMD; NS LS BMD	
<i>Jessup et al (2003) [143]</i>	F	Control (n=59)	57.1±5.0	Usual activities	NS FN BMD; NS LS BMD	When corrected for initial BMD values, Combined>control for FN BMD; NS LS BMD change between groups
		Combined training (n=9)	69.1±2.8	Machine based MIRT (3x8-10 reps), 3/week plus LIWB (walking, stair-climbing and balance training) for 8 months	↑11% FN BMD; NS LS BMD	
<i>Kemmler et al (2003) [164]</i>	F	Control (n=9)	69.4±4.2	Usual activities	NS FN BMD; NS LS BMD	NS FN change between groups; Combined>controls for LS BMD
		Combined training (n=86)	55.1±3.3	Free weight LIRT (2-4 x 3-20 reps), jumping and stretching exercises, 2/week plus 2 home sessions of TheraBand exercises and skipping for 14 months	↓0.8% FN BMD; ↑1.3% LS BMD	
<i>Milliken et al (2003) [209]</i>	F	Control (n=51)	55.8±3.1	Usual activities	↓1.8% FN BMD; ↓1.2% LS BMD	Combined>controls for FN and LS BMD
		Combined training (n=26)	56.9±4.6	Machine and free weight MIRT (2 x 6-8 reps), jumping and skipping with vests, 3/week for 12 months	NS FN BMD; NS LS BMD	
<i>Papaioannou et al (2003) [236]</i>	F	Control (n=30)		Usual activities	NS FN BMD; NS LS BMD	NS FN and LS BMD change between groups
		Combined training (n=71)	71.6±7.3	Home program of LIRT (TheraBand), walking and stretching 3/week for 12 months	NS FN BMD; NS LS BMD	
<i>Kemmler et al (2004) [165]</i>	F	Control (n=59)	72.2±8.0	Usual activities	NS FN BMD; NS LS BMD	Combined>controls for FN and LS BMD
		Combined training (n=50)	55.5±3.2	Machine and free weight LIRT (2-4x 3-20 reps), jumping and stretching exercises, 2/week plus 2 home sessions of Theraband exercises and skipping for 24 months	NS FN BMD; NS LS BMD	
<i>Englund et al (2005) [94]</i>	F	Control (n=33)	55.8±3.1	Usual activities	↓3% FN BMD; ↓2% LS BMD	NS FN and LS BMD change between groups
		Combined training (n=24)	72.8±3.6	Free weight MIRT (3x8-12 reps), LIWB (walking) and balance exercises, 2/week for 12 months	NS FN BMD; ↑3.1% LS BMD	
		Control (n=24)	73.2±4.9	Usual activities	NS FN BMD; NS LS BMD	

Table 3 (continued)

Study	Sex	Groups	Age	Intervention	Within group results	Between group results
<i>Kemmler et al (2005) [169]</i>	F	Combined training (n=48)	55.2±3.3	Machine and free weight LIRT (2-4x 3-20 reps), jumping and stretching exercises, 2/week plus 2 home sessions of TheraBand exercises and skipping for 38 months	↓0.7 FN BMD; NS LS BMD	Combined>controls for FN and LS BMD
<i>Stengel et al (2005) [290]</i>	F	Control (n=30)	55.5±3.0	Usual activities	↓2.6% FN BMD; ↓3% LS BMD	NS FN BMD; Power RT > than strength RT (↓1.2%) for LS BMD
		Combined training - Strength RT (n=16)	57.6±3.0	Machine based RT and jumping, 1/week plus home session of skipping, stretching and resistance band exercises for 12 months		
<i>Engelke et al (2006) [93]</i>	F	Control (n=30)	57.7±3.2	Machine based RT at high velocities and jumping, 1/week plus home session of skipping, stretching and resistance band exercises for 12 months	Within group differences not presented	NS FN BMD; Power RT > than strength RT (↓1.2%) for LS BMD
		Combined training - Power RT (n=18)	57.7±3.2	Machine based RT at high velocities and jumping, 1/week plus home session of skipping, stretching and resistance band exercises for 12 months		
<i>Engelke et al (2006) [93]</i>	F	Combined training (n=48)	55.1±3.3	Machine based LIRT (3x8-20 reps), 3/week plus jumping and running games plus 2 home sessions of weighted vest and skipping exercises for 38 months	NS LS BMD	Combined>controls for LS BMD
<i>Bergstrom et al (2008) [39]</i>	F	Control (n=30)	55.8±3.1	Usual activities	↓3.3% LS BMD	NS LS BMD change between groups
		Combined training (n=48)	58.9±4.3	LIWB walking 3/week for 30 mins plus 25 mins of RT (subject selected intensity) 2/week for 12 months	NS LS BMD	
<i>von Stengel et al (2011)[313]</i>	F	Control (n=44)	59.6±3.6	Usual activities	NS LS BMD	Combined>control for LS BMD; NS LS BMD change between combined + WBV and control group
		Combined training (n=47)	68.6±3.0	LIRT (3x15 reps) plus multidirectional impact loading 2/week plus home program of stretching and LIRT 2/week for 18 months	↑2.1% LS BMD	
<i>Bolton et al (2012) [45]</i>	F	Control (n=48)	68.8±3.6	LIRT (3x15 reps), whole body vibration plus multidirectional impact loading 2/week plus home program of stretching and LIRT 2/week for 18 months	↑1.5% LS BMD	NS LS BMD change between groups
		Combined training plus whole-body vibration (n=46)	68.8±3.6	LIRT (3x15 reps), whole body vibration plus multidirectional impact loading 2/week plus home program of stretching and LIRT 2/week for 18 months	↑1.5% LS BMD	
<i>Karakirious et al (2012) [157]</i>	F	Control (n=48)	68.1±2.7	Usual activities	NS LS BMD	Between group not reported
		Combined training (n=19)	60.3±5.6	Machine based MIRT (3x8 reps), 3/week for 40 mins plus 3x10 jumps daily for 12 months	NS LS BMD	
<i>Karakirious et al (2012) [157]</i>	F	Control (n=20)	56.3±4.7	Usual activities	NS LS BMD	Between group not reported
		Combined training (n=10)	53.4±0.9	MIRT (10-12 reps) 2/week plus aerobic exercise 1/week for 6 months	↑1.2% LS BMD	
		LIWB (n=13)	53.4±1.1	Whole body vibration 3/week for 6 months	NS LS BMD	
		Control (n=9)	53.0±1.4	Usual activities	↓1.6% LS BMD	

Table 3 (continued)

Study	Sex	Groups	Age	Intervention	Within group results	Between group results
<i>Bello et al (2014)[31]</i>	F	Combined training (n=10)	61.3±6.0	Multicomponent, including walking, LIWB, LIRT and aquatic exercise. 3/week for 32 weeks	NS FN BMD	NS FN BMD change between groups
<i>Gianoudis et al (2014) [107]</i>	M & F	Control (n=10)		Usual activities	NS FN BMD	Combined>controls for LS and FN BMD
		Combined training (n=81)	67.7±6.5	MIRT (2x8-12 reps) plus HIWB jumping exercises 3/week for 12 months	NS FN BMD; ↑1.5% LS BMD	
<i>Kemmler et al (2014) [166]</i>	F	Control (n=81)	67.2±5.5	Usual activities	NS FN BMD; NS LS BMD	Combined training >2/week > control for LS BMD, NS LS BMD change between combined, 2/week and control group
		Combined training >2/week (n=25)	55.4±3.1	Machine and free weight RT (2-4x 3-20 reps), jumping and stretching exercises, plus home sessions of TheraBand exercises and skipping more than 2 sessions per week for 144 months	NS LS BMD	
		Combined training <2/week (n=16)	53.9±3.8	Machine and free weight RT (2-4x 3-20 reps), jumping and stretching exercises, plus home sessions of TheraBand exercises and skipping less than 2 sessions per week for 144 months	↓4.1% LS BMD	
<i>Murtezani et al (2014) [216]</i>	F	Control (n=44)	55.8±3.1	Usual activities	↓4.2% LS BMD	Combined>controls for LS BMD
		Combined training (n = 33)	60.73±7.6	LIRT (3/week), stretching, balance and aerobic weight bearing exercise with weighted vest (30% 1RM for 6-8 reps), 10 months	↑5.5% LS BMD	
		Control (n = 31)	59.8±6.0	Aquatic exercise, 35 min, 3/week for 10 months.	NS LS BMD	

**Abbreviations:** MIRT = Moderate intensity resistance training; LIRT = low intensity resistance training; HIWB= high intensity weight bearing exercise; LIWB = low intensity weight bearing exercise; FN = femoral neck; LS = lumbar spine; BMD = bone mineral density

**Summary:** As illustrated in Table 3, although comparisons are hard to make given the large variations in exercises tested, combined exercise programs may have the potential to improve bone similar to that seen in resistance training programs independently.

## 2.6 Spinal deformity

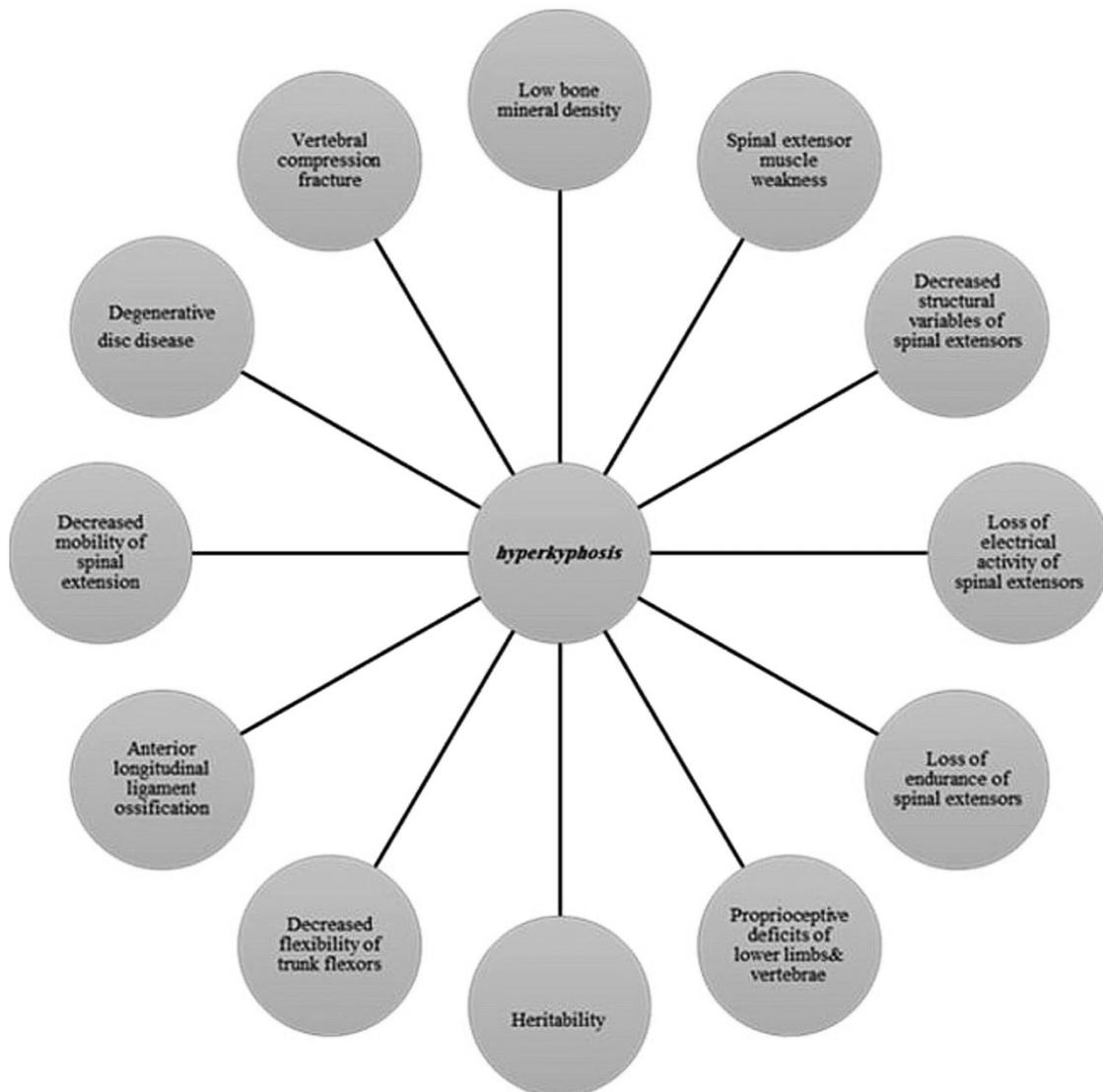
### 2.6.1 *Kyphosis and ageing*

Kyphosis is the natural primary curvature of the thoracic spine [254]. This anterior concavity of the thoracic spine increases with age, at approximately 3-5 degrees per decade in older adults [99, 150, 175]. There is no uniformly well-accepted threshold to delineate hyperkyphosis, defined as an excess of kyphosis [154]. It has been proposed that a kyphosis greater than 40 degrees in young adults should be classified as hyperkyphosis [163], although both 40 and 50 degrees have been applied as normal limits for kyphosis in older adults [22, 118, 233]. Notwithstanding the lack of a unified definition, it is estimated that incidence of hyperkyphosis is 20-40% in adults [149, 154, 260, 297]. The impact of hyperkyphosis on an individual can be profound. Hyperkyphosis has been associated with reduced lung function [129], pain [239], reduced physical capacity [17, 233, 260], fall-related injuries [151], and increased mortality [149, 152].

### 2.6.2 *Determinants of kyphosis*

The cause and progression of kyphosis are multifactorial. Contrary to common belief, increases in kyphosis are not exclusively caused by vertebral fractures, as anterior wedge fractures explain less than 50% of the variation in kyphosis [211]. Furthermore, approximately 60-70% of adults with severe kyphosis do not show signs of vertebral fractures [254]. It is proposed that degenerative disk disease, vertebral fractures, muscle weakness, ligamentous degeneration, and genetic predisposition may all be significant factors relating to changes in kyphosis (Figure 5) [154, 254]. While many of the determinants of kyphosis presented in Figure 5 are predetermined, many

factors are modifiable, including BMD, mobility of spinal extension, loss of muscle endurance and strength. When considering the aforementioned modifiable determinants of kyphosis, an important relationship exists. The age-related decline in back extensor strength that has been associated with increased kyphosis in postmenopausal women is the typical focus of current non-pharmacological management strategies [279].



**Figure 5:** Postulated causes of age-related hyperkyphosis [254]

### 2.6.3 *Vertebral fractures and ageing*

Vertebral fractures are present in approximately 20% of osteoporotic women, with approximately half being asymptomatic [87]. History of a prior fracture is strong predictor of future fracture [174]. The most common location of vertebral fractures is the thoracolumbar region (T11-L1) [51, 156], which corresponds to the area of maximal loads during lifting tasks [220]. Loading patterns of the vertebral column change with kyphosis, and hyperkyphosis has been associated with an increased risk of vertebral fracture [161]. Additionally, vertebral fractures commonly occur with twisting, flexion, or a combination of those movements, especially when performed under high external loads [112]. Individuals with osteoporosis have a particularly high risk of vertebral fracture, with BMD predicting 70-90% of the failure loads of vertebrae [212, 217]. Collectively, these factors contribute to the increased risk of vertebral fracture in postmenopausal women with osteoporosis and require careful consideration when developing a high-intensity resistance training program for bone.

### 2.6.4 *Measuring spinal deformities*

The gold standard measure of spinal deformities is lateral erect radiograph. When measuring kyphosis, quantification of the Cobb angle is the conventional approach [50]. Measuring the Cobb angle is performed by extending the endplates of the vertebral bodies to the point of intersection. Global thoracic Cobb angle is the concavity between the first and twelfth thoracic vertebrae endplates using the aforementioned method. Due to overlying skeletal structures obstructing vertebrae identification on lateral radiograph, image quality is the major limiting factor for global kyphosis Cobb angle quantification [109]. This has led to the use of regional measures

of kyphosis, with the fourth to twelfth thoracic vertebrae commonly used [50, 110]. The use of Cobb angle as a measure of kyphosis has been further criticized, as it has been suggested it may only reflect endplate tilt of the reference vertebrae, and may not reflect global curvature of the thoracic region [22, 50, 109, 128]. Despite limitations, Cobb angle remains the gold standard for the quantification of thoracic kyphosis.

The diagnosis of vertebral fracture is generally accepted as a 20% loss in vertebral body height relative to normal looking adjacent vertebra or expected vertebral height [119]. Quantitative vertebral morphology is a common approach performed on lateral radiographs for reporting vertebral deformities and fractures [97]. It is performed by comparing vertebral height ratios to the normal mean of the population, with greater than 3 standard deviations away from the population mean being classified as a deformity. Limitations of quantitative vertebral morphology include the lack of specificity for vertebral fractures and its time-consuming nature. The use of a semiquantitative approach based on deformities proposed by Genant and colleagues [105] appears to be a more practical method to measure vertebral morphology clinically and is easy to perform with excellent inter-reader reliability [119, 266]. In recent times, DXA has been used to perform vertebral morphology assessment. DXA has a few advantages over radiography. It can produce images of near-radiographic quality at a fraction of the radiation dose, is less expensive and can be easily performed at the same time as bone densitometry [97, 265]. Importantly, DXA has shown moderate sensitivity and high specificity for detecting vertebral fractures compared to radiography [182].

A wide variety of alternative non-invasive clinical and research measures of kyphosis have been developed, including cervical depth [15], Debrunner Kyphometer [230], C7 to wall [260], Flexicurve [20, 211, 333], manual and digital inclinometers

[78, 184, 207], postural board [15], tragus to wall [160], and spinal mouse [195].

Importantly, clinical measures have shown reasonable agreement with radiographic kyphosis measures [148]. The difficulty with many clinical measures is accurate spinal landmark palpation, as vertebral identification by clinicians has poor intertester and high intratester reliability [41]. Flexicurve has been proposed as the most practicable clinical measure of kyphosis, as it is inexpensive, easy to use and has high reliability and validity [22]. Similar to Flexicurve, manual inclinometer has been shown to have excellent reliability and affords the added benefit of immediate analysis [184]. All of the clinical measures have certain advantages, and most only require equipment common to the clinical environment.

#### *2.6.5 Exercise for kyphosis*

Exercise has been proposed as a potential management strategy and has been shown to reduce age-related increases in kyphosis [15]. Exercise programs have focused on improving back extensor strength through low-intensity postural and isolated back extension exercises [15, 139, 207, 275, 278], as increasing extensor muscle strength can improve thoracic kyphosis in as little as eight weeks (Table 4) [25, 141, 160, 162]. Improvements in kyphosis from 12 weeks of spinal extensor strengthening, flexibility exercises, and integrated spinal proprioception training showed continued improvement at 12 months post exercise cessation [160, 238]. To date there has been no targeted high-intensity resistance training program to improve bone and kyphosis. The use of high-intensity training has the potential to significantly improve back extensor strength, and in turn, improve thoracic kyphosis.

While high-intensity resistance training may have the potential to improve kyphosis, care needs to be taken when implementing an exercise program with individuals with marked kyphosis, as flexion-based movement may increase the risk of vertebral fractures [28, 275]. There have been few reports of exercise in the presence of vertebral fracture. Some recommend proprioceptive dynamic posture training to decrease both kyphosis and pain [86, 239]. Kyphosis progression has been associated with non-vertebral osteoporotic fractures, and it has been suggested that treating kyphosis may help reduce the risk of these non-vertebral fractures [153].

**Table 4:** Summary of exercise interventions for kyphosis in older adults

Study	Sex	Groups	Age	Intervention	Outcome measure	Within group results	Between group results
<i>Greendale et al (2002) [118]</i>	F	Intervention (n=21)	65	Yoga poses focusing on erector spinae, 60 mins, 2/week for 12 weeks	Height Tragus to wall Debrunner kyphometer	NS ↓ 2 cm NS	NA
<i>Katzman et al (2007) [160]</i>	F	Intervention (n=25)	72±4.2	Daily postural exercises, resistance exercises with dumbbells and TheraBand (3x8 reps) 12 weeks	Height Relaxed standing Debrunner kyphometer Standing tall Debrunner kyphometer Tragus-to-wall	NS ↓6° ↓5° NS	NA
<i>Ball et al (2008) [15]</i>	F	Intervention (compliant) (n=35) Control (non-compliant) (n=46)	53.2±2.1 54.8±0.6	Nine postural and TheraBand exercises to improve erector muscle groups. Considered compliant if they performed exercises >3/week, 12 months	Cervical depth Postural board AUC  Cervical depth Postural board AUC	↓ 0.9 cm ↓ 12.0 cm  NS ↑ 7.3 cm	Compliant > non-compliant for improvements in cervical depth and postural board AUC
<i>Benedetti et al (2008) [34]</i>	M & F	Intervention (n=15) Control (n=13)	71.5±4.3 71.5±4.9	Postural extensor muscle exercises Non-specific postural exercises	Occiput-to-wall Occiput-to-wall	↓1.4 cm NS	NA
<i>Greendale et al (2009) [117]</i>	M & F	Intervention (n=58) Control (n=60)	74.5±7.6 76.5±7.2	Yoga, 60 min, 3/week for 24 weeks Usual activities	Height Debrunner kyphometer Kyphosis index (Flexicurve) Flexicurve angle  Height Debrunner kyphometer Kyphosis index (Flexicurve) Flexicurve angle	NS NS NS NS  NS NS NS NS	Kyphosis index and Flexicurve angle improved in intervention compared to control. Other measures NS

Table 4 (continued)

Study	Sex	Groups	Age	Intervention	Outcome measure	Within group results	Between group results
<i>Bautmans et al (2010)</i> [25]	F	Intervention (n=29)	75.2±1.3	Physiotherapy, taping and daily postural and LIRT exercises for erector spinae muscles	Spinal Mouse device	↓3.4°	Intervention > control for thoracic kyphosis
		Control (n=19)	77.6±1.6	Usual activities	Spinal Mouse device	NS	
<i>Bennell et al (2010)</i> [36]	M & F	Intervention (n=11)	66.2±8.0	Physiotherapy, postural exercises and LIRT, 45 min, 10 weeks	Dual-inclinometer	NS	NS
		Control (n=9)	66.3±11.8	Usual activities	Dual-inclinometer	NS	
<i>Bergstrom et al (2011)</i> [38]	F	Intervention (n=20)	74.1±6.0	LIRT (bodyweight or TheraBand) focusing on erector spinae ,60 mins, 2/week for 4 months	Height Kyphometer C7-to-wall	NS NS NS	NS
		Control (n=16)	73.2±8.9	Usual activities	Height Kyphometer C7-to-wall	NS NS NS	
<i>Abreu et al (2012)</i> [1]	F	Intervention (n=10)	No age reported	Resistance training (intensity not reported) 2/week, 3 months	Flexicurve	NS	NS
		Control (n=10)		Usual activities	Flexicurve	↑ 1.65	
<i>Jang et al (2015)</i> [141]	F	Intervention (n=20)	73.7±5.6	Postural correction exercises, 60 minutes, 2/week for 8 weeks. Plus, daily stability and mobility exercise program	Dual inclinometer (relaxed) Dual inclinometer Tragus to wall (relaxed) Tragus to wall	↓3.4° ↓3.5° ↓1.7 cm ↓1.7 cm	Intervention > control for all kyphosis measures
		Control (n=21)	76.4±6.6	Same daily exercise program as intervention	Dual inclinometer (relaxed) Dual inclinometer (standing tall) Tragus to wall (relaxed) Tragus to wall (standing tall)	↓1.7° NS NS NS	
<i>Katzman et al (2017)</i> [162]	M & W	Intervention (n=51)	71.0±6.5	Postural training, erector spinae strengthening for 6 months, followed by home program	Cobb angle (lateral radiographs) Debrunner Kyphometer	↓3.3° ↓3.8°	Intervention > control for Cobb angle and Debrunner kyphometer
		Control (n=48)	70.2±5.7	Education sessions, inactive	Cobb angle (lateral radiographs) Debrunner Kyphometer	NS NS	

**Abbreviations:** LIRT = low intensity resistance training (based on American Heart Association classification)

**Summary:** As illustrated in Table 4, the majority of exercise programs for kyphosis focus on isolated back extensor strengthening and mobility exercises and have been associated with reduced kyphosis. No bone-focused high-intensity exercise program has been implemented for both improving bone and reducing kyphosis in postmenopausal women.

## 2.7 Muscle

### 2.7.1 *Skeletal muscle and ageing*

Skeletal muscle is the largest component of fat free body mass and has six primary functions, including: 1) production of skeletal movement; 2) maintenance of posture and body position; 3) support of soft tissue; 4) protection of entrances and exits; 5) maintenance of body temperature; and 6) storage of nutrients [199]. The ability of skeletal muscle to produce force is complex but is largely related to its physiological cross sectional area. Other influences include age, gender, intramuscular fat, and training status [147]. Muscle physiological cross-sectional area is important to muscle function as it directly relates to the number of muscle fibres arranged in parallel, and thus the ability to produce force.

Skeletal muscle mass peaks at approximately 25 years of age, is maintained until approximately 45 years of age, and typically declines thereafter [56, 142]. The loss of skeletal muscle mass is strongly related to deterioration in muscle strength, which occurs at a rate of approximately 1-2% per annum.

### 2.7.2 *Measuring muscle*

A number of methods exist for measuring skeletal muscle mass, including magnetic resonance imaging (MRI), dual-energy x-ray absorptiometry (DXA), peripheral quantitative computed tomography (pQCT), underwater weighing, 3D ultrasound and bioelectrical impedance (BI) [9]. MRI is considered the gold standard for regional measurements of skeletal muscle mass due to a high sensitivity and three-dimensionality [298]. The use of MRI, however, is limited by speed of measurement (i.e. 45-60 minutes), expense, and availability [263]. DXA on the other hand is a two-

dimensional measure widely used for quantifying skeletal muscle mass as it measures whole body composition quickly, is readily available, and shows excellent validity with MRI measures (correlation coefficient of 0.96) [312]. pQCT is also a valid estimate of skeletal muscle [242], but is limited to the assessment of limbs. It differs from DXA in that it is a three-dimensional measure, which allows measurement of both muscle cross sectional area and muscle density. BI is a common alternative for the estimation of skeletal muscle mass. It is simple, and relatively inexpensive and while associations with DXA are high (correlation coefficient of 0.84) [331], it varies greatly with hydration status, and is generally reserved for field-based testing, or when DXA or MRI are not available or affordable. While MRI is the preferred method for regional skeletal muscle assessment, both DXA and pQCT are valid and reliable measures of both whole body and regional measures of skeletal muscle [9].

### *2.7.3 Progressive resistance training and muscle*

The effects of resistance training on muscle size and strength are well understood [8, 111, 209]. In postmenopausal women, improvements in muscle strength from 11-150% have been observed in resistance training programs as short as 12 weeks in duration [59, 164, 169, 191, 214, 218]. Strength gains have generally been paralleled by increases in lean mass, with studies reporting increases of 3.9-4.6% [191, 218]. Resistance training in postmenopausal women has not only shown improvements in lean muscle and physical performance, it is associated with few injuries, highlighting that resistance training can be safe when conducted in a supervised environment [59, 191, 214, 218].

## 2.8 Physical activity and physical function

Physical activity participation is important for maintaining a healthy musculoskeletal system and is associated with benefits to physical performance [24, 37, 115, 189, 190, 292, 296, 309, 311] and psychosocial factors [206, 219]. With increasing age, a decrease in physical activity participation is associated with poorer health [224]. For older people who are able to maintain high levels of physical activity, positive health outcomes are achievable, such as a decreased cardiovascular disease and mortality [179, 332]. These benefits are not only applicable to those who maintain high levels of physical activity as they get older, but also late adopters who take up exercise in the more advanced stages of life [59, 191, 214, 218, 272].

### 2.8.1 *Physical activity and falls*

Falls are a common and serious issue facing older adults. In the USA, there has been a disproportionate increase in incidence of falls, which may be associated with an ageing population that is unhealthier and less functionally capable than those of the past [5]. Physical activity participation has the potential to reduce the increasing incidence of falls, and has been shown reduce the overall risk of falling by 17% [272]. The reduction of falls through physical activity participation is through improvements in gait, balance, coordination, proprioception, reaction time, and muscle strength, which are all modifiable risk factors for falls [5, 155]. Programs that confer the greatest benefits are those which include challenging balance training, high dosage and do not include walking [272].

### 2.8.2 *Barriers and facilitators to physical activity*

Despite the potential positive effects of exercise, particularly in older individuals, physical activity participation remains low and ranges from 20% to 60% in older individuals [293]. Poor physical activity participation may be a function of barriers preventing participation, with 87% of older persons reporting at least one barrier to physical activity participation [229]. These potential barriers to physical activity participation in older adults include lack of time, co-morbid conditions, lack of knowledge, lack of physician advice, cost, body image concerns, and low perceived benefits of physical activity [232, 267]. Additionally, older adults perceive the normal sweating and delayed muscle soreness responses to exercise negatively, which further impedes physical activity participation [267]. There is a complex interaction between barriers to physical activity participation and motivators, with deteriorating health serving as both a motivator and barrier to participation [72, 267]. Furthermore, poor health has been reported as an important barrier to physical activity participation in women [72]. Social interactions such as group classes, strong self-efficacy, encouragement and support, and professional instruction are perceived as important factors for older persons performing physical activity [102, 232, 267].

### 2.8.3 *Measuring physical activity*

Physical activity participation can be quantified in a variety of ways, using pedometers [73], accelerometers [40], multi-sensor devices (e.g. armbands) [40, 73], portable metabolic systems [40, 73, 104], doubly-labelled water (water labelled with the heavy, non-radioactive isotope) [40, 73, 193], physical activity diaries [73], and physical activity questionnaires [73, 193]. The latter measures typically quantify generic

physical activity exposure, but do not discriminate the critical characteristic of relevance to bone health, that is the magnitude and rate of mechanical loading of the skeleton. An instrument that was specifically designed to take account of loading of relevance to bone is the Bone-specific Physical Activity Questionnaire (BPAQ) [324]. The BPAQ has excellent validity and reliability for the determination of bone-relevant loading [323] and provides participation scores for current (i.e. previous 12-month period) and past activities (i.e. birth to current date), thereby accounting for whole of life loading.

#### *2.8.4 Measuring physical performance*

Many measures of physical performance exist, from laboratory-based measures to clinical measures of functional performance and activities of daily living. Isokinetic dynamometers are widely used in research laboratories to assess muscle force and rate of force development [57, 144, 255, 295]. While the accuracy of isokinetic dynamometers is excellent, they are rarely found in the clinical setting. Functionally-based surrogate measures of strength and power that are indicative of performance in everyday activities are typically used. Measuring functional performance in the clinical setting is important, as it can identify individuals who are at risk of injury and determine their ability to independently perform activities of daily living. Many clinical tests exist that incorporate everyday physical activities, including measures of walking, stair climbing and standing from a chair [189, 291, 296, 312]. The timed up-and-go test, functional reach test, and five times sit-to-stand have been reported widely in the investigations of older populations and are predictive of falls and fracture [61, 115, 243,

255]. In combination, these tests allow for the measurement of muscle strength, power and balance within a clinical setting with relevance to common daily movements.

The vertical jump is another simple validated measure of lower limb neuromuscular performance in adults [7, 114]. Vertical jump performance accounts for additional physical factors not captured by simple dynamometry as it involves not only power production, but also proprioception, co-ordination and balance. Whilst jumping is not necessarily a daily activity for postmenopausal women, vertical jump tasks have been used to examine the relationships between bone strength and neuromuscular performance in this demographic [246, 247].

## **2.9 Summary**

The development of a targeted, safe, effective, high-intensity resistance and impact training program to prevent osteoporotic fracture would be paradigm-shifting, as current therapeutic recommendations of low to moderate intensity exercise for individuals with established osteoporosis do not notably improve bone mass. Instead, the current recommendations take a conservative approach to fracture prevention by way of reducing falls. Pilot data from a commercial gym suggests higher magnitude loading than has previously been tested can be applied safely to women with low to very low bone mass. The current work extends those findings by utilising an RCT design with adequate statistical power to determine the safety and efficacy of a supervised high-intensity resistance and impact training program targeted to reduce risk of osteoporotic fracture in postmenopausal women with low bone mass with the aim of changing current recommendations.



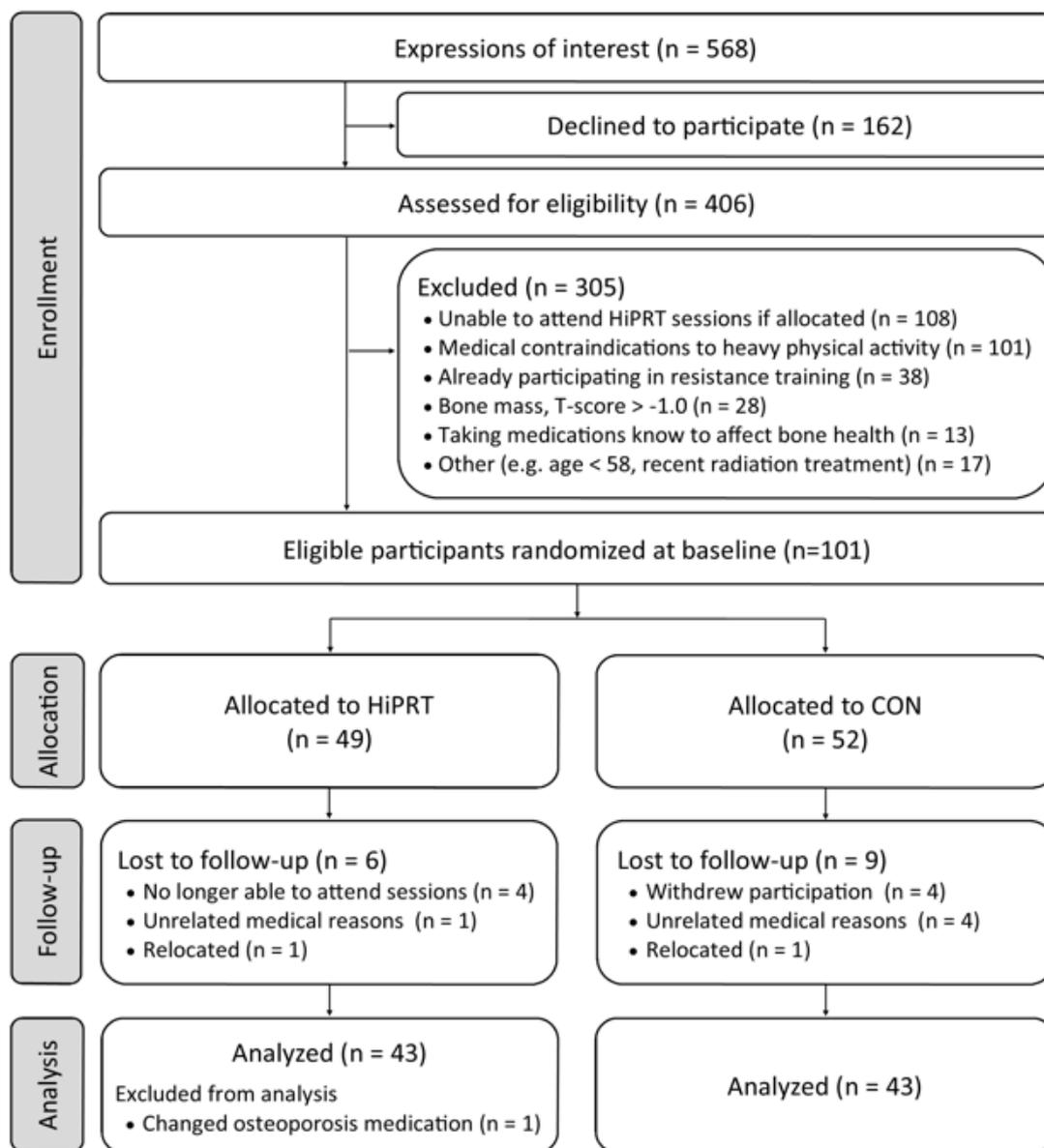
## Chapter 3: Methods

### **3.1 Introduction**

This chapter outlines the methods used to complete each study in the thesis including: 1) preliminary findings of the LIFTMOR trial; 2) bone and physical performance results from the LIFTMOR trial; 3) kyphosis, vertebral morphology and stature results for the LIFTMOR trial; and 4) Physical activity enjoyment, quality of life and other qualitative outcomes of the LIFTMOR trial. Methods will be presented as a single chapter rather than separated into individual chapters/sections, as all data was collected over the duration of the LIFTMOR study.

### **3.2 Study design**

A single-blind stratified randomized controlled trial was undertaken to test the efficacy of an 8-month supervised HiRIT program to improve indices of bone strength and falls risk in postmenopausal women. One-hundred and one postmenopausal women over 58 years of age with low bone mass (screened for conditions and medications that influence bone and physical function) were recruited from the community. Eligible participants were randomized to either twice-weekly, supervised HiRIT or a home-based program of low-intensity exercise (CON) (Figure 6). Comparisons at baseline (T0) and 8 months (T1) included validated measures of: historical bone-relevant physical activity, dietary calcium, quality of life, physical activity enjoyment, functional performance and falls risk factors, whole body and regional bone, muscle and fat mass, kyphosis, compliance and safety.



**Figure 6:** CONSORT diagram of participant flow in the LIFTMOR trial (n = 101)

### 3.3 Participants

One-hundred and one healthy postmenopausal women (>58 years) from the Gold Coast and Brisbane regions with low bone mass were recruited. Participants must have been willing to undertake an 8-month exercise program and were randomly

allocated to either HiRIT or CON groups. Participants were blinded to group activities they were not allocated to.

### **3.4 Participant recruitment strategy**

Recruitment was achieved by television, newspaper reports, radio interviews, a project website (<http://www.liftmor.org/>), word of mouth, and poster advertisements in the community. Individuals who contacted investigators by phone were provided further details and were screened for suitability for inclusion. Those volunteers who registered their interest via the project website were automatically emailed an information package (Appendix A) and were subsequently contacted via telephone for screening and scheduled for an initial testing session. In either case, each volunteer was provided with an information sheet, verbal description of the study, and an opportunity to have questions answered by the investigators before providing written informed consent (Appendix B). Participation was voluntary, and all participants were free to withdraw from the study at any time without penalty. If a potential participant was eligible to enrol in the LIFTMOR trial, a convenient time to attend baseline testing at Griffith University Gold Coast campus was arranged.

### **3.5 Informed consent**

The trial was granted ethical approval by the Griffith University Human Research Ethics Committee (Protocol number: AHS/07/14/HREC) (Appendix C). Before the commencement of initial testing and screening, each volunteer was provided an information package and was given time to ask any questions regarding the project before completing the written consent form.

### 3.6 Inclusion criteria

Participants were included if they:

- were postmenopausal (> 5 years post menopause);
- were over 58 years of age;
- had low bone mass (femoral neck or lumbar spine T-score < -1);
- were community ambulant without a walking aid;
- were in good general health; and
- consented to participate

### 3.7 Exclusion criteria

Participants were excluded if any of the following applied:

- lower limb joint surgery or injury;
- recent fracture or localized back pain;
- less than five years post menopause;
- malignancy;
- uncontrolled cardiovascular disease;
- cognitive impairment;
- recent x-ray or radiation treatment;
- contraindications for participating in heavy physical activity;
- conditions known to influence bone health (e.g. thyrotoxicosis or hyperparathyroidism, Paget's disease, renal disease, diabetes, or immobility); or

- taking medications known to influence bone (e.g. prolonged use of corticosteroids, thyroxine, thiazides or antiretroviral agents)
- planning to alter their bone medication status in the following 8 months

### **3.8 Location**

Initial (T0) and follow up (T1) testing was conducted at the Bone Densitometry Research Laboratory, Clinical Sciences I, Room 2.08, Griffith University, Gold Coast campus. The HiRIT program sessions were conducted at three locations – one on the Gold Coast and two in Brisbane. The Gold Coast location was room 2.34 in the Clinical Science I building at Griffith University’s Gold Coast campus in Southport, while Brisbane sites were located at Barbelles gym on Bothwick Avenue in Murarrie and The Bone Clinic on Turbo Drive in Coorparoo.

### **3.9 Participant randomisation**

Eligible participants were randomized to either HiRIT or CON. Randomization was stratified based on the existence or absence of established (12 months exposure or lack of exposure) osteoporosis medication. Randomization was performed at the conclusion of baseline testing (T0). A random number generator (Microsoft Excel, Microsoft, Redmond, WA, USA) was used to assign either a 0 or 1 to correspond with CON and HiRIT, respectively. Once a potential participant was deemed eligible for participation, random group allocation was achieved by asking the participant to open the next sequentially numbered opaque envelope stratified on osteoporosis medication use. The randomisation sequence was sealed in an envelope by a person outside of the

research team to ensure blinding and then locked in a cabinet where the initial testing session took place.

### **3.10 High intensity progressive resistance and impact training program**

Participants allocated to the intervention group attended twice-weekly instructor-led HiRIT at a private exercise facility in either Brisbane or the Gold Coast. Each session was approximately 30 minutes in duration and performed on non-consecutive days. A minimum trainer-to-participant ratio of 1:8 was maintained at all sessions.

To ensure a safe transition into the program for those who were unaccustomed to resistance training, the first month of the intervention served as familiarization (See appendix D for an example of the participant training log for a session within the familiarization phase). Bodyweight and low-load exercise variants with a focus on slow controlled movements were undertaken to ensure that participants were safely trained with correct lifting technique. This progression served to avoid loading the spine in flexed postures and other technical errors known to increase the risk of injury. Exercises performed in the initial familiarization period included:

- ‘Good mornings’: Participant stands upright with a weight plate held across their chest. Participant then flexes at the hip as far as possible, while maintaining natural lumbar and thoracic curvature and keeping legs straight before returning to the starting position.
- Half squat: Participant stands with feet shoulder width apart, arms folded across their chest with elbows pointed forward at 90 degrees. The participant starts the movement by moving their hips backwards and then down to achieve

45 degrees flexion at the hips and knees before returning to the starting position.

- Bent over row: Participant stands with 45 degrees of hip flexion, natural lumbar and thoracic curvature, arms extended towards the ground holding weight plate. Keeping elbows adducted, the participant is then instructed to lift the plate toward their chest while maintaining trunk position.
- Overhead press: Participant stands in an upright position holding a weight plate with both hands, with elbows flexed so that the plate is vertical in front of the chest. Keeping the plate vertical, the participant pushes the plate above their head, while keeping their elbows pointing forward and achieving full shoulder flexion and elbow extension. Once the weight reaches directly above their head they return to the starting position.
- Plate jumps with toe walks: Participant stands on a 10 kg weight plate (laid flat on the floor), with feet slightly apart. Participant then jumps off the plate, ensuring that they land on their toes; feet shoulder width apart and absorbs the landing through flexed knees. Once landed, the participant takes 10 steps while on their toes before they turn 180 degrees and walk back to the starting position.
- Crawling plank: Participant starts in a four-point kneeling position, i.e. knees, shoulders and hips all flexed at 90 degrees, ankles fully dorsiflexed with toes touching the ground. Participant is then instructed to keep their hands and knees positioned directly underneath their shoulders and hips respectively. The participant then lifts their knees off the ground approximately 1 inch while maintaining knee, hip and shoulder flexion at 90 degrees.

From months 2-8, there was a focus on the progression of exercises and weight utilized, such that by two months, participants were able to comfortably perform the four fundamental exercises of the program with correct technique. The exercises included three resistance (back squat, deadlift and overhead press) and one impact exercise (jumping chin ups). The resistance exercises were selected as they are compound movements that allow the application of large magnitude loads to the skeleton. The jumping chin ups were selected as an exercise modality involving high loading rates. The resistance exercises were performed throughout the remainder of the intervention period with progressively increasing weight to maintain a minimum of 80% 1RM for 5 sets of 5 repetitions (see appendix E for an example of the participant training log). The four fundamental exercises of the LIFTMOR trial were:

- Back squat: Participant stands with feet shoulder width apart, bar placed across their back just superior to the spine of the scapula and held firmly with arms abducted and elbows flexed. The participant commences the squat by moving their hips backwards as if they were to sit on a chair such that their thighs become parallel with the floor, before returning to the starting position.
- Jumping chin ups: The participant stands with shoulders and elbows flexed, holding a fixed bar just above their head with hands shoulder width apart and palms facing towards them. The participant then jumps using both their legs and arms, aiming to get their chin above the bar, before landing with as much impact as can be comfortably tolerated. To achieve this, participants were instructed to “land as heavy as possible” with a gradual increase in intensity.

- Overhead press: The participant stands in an upright position holding an Olympic bar with palms facing away from their body, arms adducted, and elbows flexed so that the bar is horizontal and across their chest at the level of the suprasternal notch. Keeping the bar horizontal, the participant pushes the bar above their head, with emphasis on maintaining the elbows pointing forward and achieving full shoulder flexion and elbow extension, and the bar directly above the participants head before returning to the starting position.
- Deadlift: The participant stands with shins touching the bar with feet just narrower than shoulder width. The participant then reaches down and holds the bar with an overhand grip and hands shoulder width apart. In this position, the participant is instructed to maintain neutral spine curvatures with the torso aligned parallel to the ground. The participant then lifts the bar to a fully upright position while maintaining full elbow extension, normal spinal curvatures and avoiding pulling through their arms. The bar is then lowered by flexing at the hips, maintaining a neutral spine, and allowing the bar to slide down the thigh and past the knees. Once the bar passes the knees, the participant bends their knees to return to the starting position.

### **3.11 Control program**

Participants randomized to CON undertook a low-intensity home-based exercise program which served as a positive control to HiRIT. The regime included two 30-minute sessions per week, comprising of four stretches and four low-intensity resistance exercises, with a focus on flexibility, lower limb muscle endurance and balance. The resistance exercises were a standard inclusion for the duration of the program, although

the intensity increased progressively through the use of hand weights (maximum 3 kg) and increasing repetitions. The regime also incorporated a 10-minute walking warm-up and 5-minute walking cool-down (Appendix F). The exercises for the home-based program were:

- Neck mobility exercise: The participant stands in an upright standing position. The participant then flexes, extends and laterally flexes their neck in a slow controlled movement to end of available range of motion.
- Shoulder stretch: Participant stands in an upright standing position, then flexes their shoulder to 90 degrees, so that it is parallel to the ground. From this position, the participant then horizontally flexes their arm across their body and uses the other arm to place pressure on the posterior aspect of the elbow of the adducted arm to achieve a stretching sensation.
- Lumbar spine mobility exercise: Participant stands in an upright position, with arms by their side with palms facing towards their thighs. The participant then flexes laterally at the lumbar and thoracic spine allowing their arm to slide down their lateral thigh. This motion is repeated in both left and right lateral flexion, ensuring the participant performs the motion in a controlled manner, and to full available range of motion.
- Calf stretch: Participant stands in an upright lunge position, with one foot placed approximately one metre in front of the other. To perform the stretch, the back leg is kept straight with their heel on the ground, and the front knee is flexed to ensure a stretch was achieved in the calf of the back leg.
- Sit to stand: Participant starts by sitting in a chair with their back against the backrest and arms folded across their chest. The participant then stands,

ensuring they fully extend their knees and hips. The participant then sits back down and to count as a repetition the participant must ensure that their back touches the backrest upon returning to the seated position.

- Bilateral calf raise: Participant stands in an upright position, feet shoulder width apart, heels on the ground and holding onto a stable surface at waist height with both hands. The participant then plantarflexes, coming up onto their toes, ensuring their heels are raised off the ground as far as possible. The participant then slowly lowers their heels back to the starting position.
- Lunge: Participant starts in a stride stance position with feet placed approximately 1 metre apart, so that one foot is in front of the participant and the other behind. The participant then flexes the back knee, so that it lowers to the ground. Once the knee makes contact with the ground, the participant returns to the starting position. During the lunge, the participant keeps their trunk upright, looking forward and does not let their front knee progress over their toes. If required, the participant is allowed to hold a stable surface to provide support for balance.
- Single leg balance: Participant starts in an upright position, feet shoulder width apart, heels on the ground and holding onto a stable surface in front of them at waist height with both hands. The participant then lifts one foot off the ground, then if able, they take their hands off the stable surface. The single leg stance position is held for 30 seconds, then the exercise is repeated on the opposite lower limb.
- Toe walk: Participant starts in an upright position, with a space of approximately 10 m clear of obstruction in front of them. The participant then

completes a bilateral calf raise, so that they are on their toes. Maintaining this position, the participant takes ten steps forward, before turning around and returning to their starting point.

- Shrug: Participant stands upright, with arms by their sides and holding onto the prescribed weight. The participant then elevates each shoulder simultaneously towards their ears, ensuring their shoulders are elevated as high as possible. The participant then lowers their shoulders to the starting position, with their shoulders relaxed and arms by their side.
- Standing forward arm raise: Participant stands in an upright position with hands by their side with the prescribed weight. The participant then flexes their shoulders to 90 degrees, while keeping elbows at full extension. The participant then returns their arms slowly to the starting position.

### **3.12 Data collection**

Data collection occurred at baseline (T0) and on completion of the exercise programs (T1). The majority of testing was conducted at the Griffith University Bone Densitometry Research Laboratory. The functional performance tasks required additional equipment and space and were conducted in the Griffith University Biomechanics Laboratory. The same investigator performed all tests to maximise measurement reliability. Data collection included:

1. Medical history
2. Anthropometric measures - Height, weight, waist circumference, and body mass index (BMI)
3. Blood pressure

4. Physical activity participation - Bone-specific physical activity questionnaire (BPAQ)
5. Dietary calcium intake - Australian calcium-specific diet questionnaire (AusCal)
6. Quality of life - World Health Organization quality of life questionnaire (WHOQOL-BREF)
7. Physical activity enjoyment - Physical activity enjoyment scale questionnaire (PACES-8)
8. Functional performance and falls risk factors - Vertical jump (VJ), timed up-and-go test (TUGT), five times sit-to-stand test (FTSTS), functional reach test (FRT), back extensor strength (BES) and leg extensor strength (LES) test.
9. Whole body and regional bone, muscle and fat mass and density (DXA and QUS)
10. Kyphosis (DXA, inclinometer and Flexicurve)
11. Compliance and adverse effects

### *3.12.1 Testing protocol*

On arrival at the Bone Densitometry Research Laboratory, personal details and informed consent were obtained and recorded. Age, handedness, ethnic background, lifestyle, and medical history including medications were recorded on a case report form (Appendix G). Participants then underwent anthropometric and body composition measures before undertaking the physical performance tasks in the Biomechanics Laboratory. All measures were repeated at the completion of the intervention (T1) and recorded on a modified case report form (Appendix H).

### 3.12.2 Anthropometrics

Height and body mass were measured using a wall-mounted stadiometer (Seca 216, Ecomed Trading Pty Ltd, Seven Hills, Australia), and mechanical balance scales (Seca 700, Ecomed Trading Pty Ltd, Seven Hills, Australia). Body mass index (BMI) was calculated per the standard formula ( $BMI = \text{weight}/\text{height}^2$ , kg/m<sup>2</sup>).

The process for measuring height began by instructing the participant to remove their shoes, stand with back against the wall with feet together and look directly forward. Head position was then visually examined to ensure positioning in the Frankfort plane. Due to the limitations in participant and laboratory availability, the time of day that height was measured was not standardised. We were therefore unable to account for diurnal variations in height.

### 3.12.3 Physical activity participation

Participants completed a self-report questionnaire on lifetime bone-relevant physical activity participation using the BPAQ (Appendix I). The BPAQ is quick and simple to complete and comprises a single double-sided page to record whole of life activity participation using a checklist format. On the first page, participants were asked to record activities they had participated in for a year or more throughout their lifetime, while on the second page they listed all activities they had engaged in regularly over the previous 12 months. Participants were required to list all activities they had performed, including occupational and recreational. Questionnaires were scored using a custom-designed Microsoft Visual Basic executable program to generate a bone-specific score from algorithms that rank and weight activities based on rates and magnitudes of loading (<http://www.fithdysign.com/BPAQ/>) [324]. The BPAQ generated scores for

current activities (i.e. last 12 months; cBPAQ), past activities (i.e. lifelong; pBPAQ), and an overall score (tBPAQ).

#### *3.12.4 Dietary calcium intake*

Dietary calcium intake, including supplementation, was estimated with the AusCal (Appendix J) [30]. The AusCal is a validated Australian calcium-specific diet questionnaire comprising two double-sided pages. It records dietary intake by participant reported consumption frequency and serving size of a broad range of calcium-containing foods and supplements. Questionnaires were scored using food specific dietary software (Foodworks 2007 Version 7, Xyris, Brisbane, Australia) by inputting serving size and frequency of consumption, allowing the calculation of average daily calcium intake (mg) which was controlled in the final analysis of all bone outcome measures.

#### *3.12.5 Quality of life*

The WHOQOL-BREF (Appendix K) was completed by each participant to record quality of life (QOL). The WHOQOL-BREF questionnaire comprises 26 questions across four domains, including physical health, psychological health, social relationships, and environment. Each question was rated on a scale from 1-5 based on the participant's thoughts over the past four weeks. A final score for each domain was then calculated by multiplying the mean score for each domain by 4. This transformation of scores to a 4-20 scale allows comparisons to the WHOQOL-100 [329].

### 3.12.6 *Physical activity enjoyment*

Participants' perceptions of physical activity participation and enjoyment were recorded using the Physical Activity Enjoyment Scale (PACES-8) (Appendix L) developed by Mullen et al [215]. The questionnaire is a single-sided page consisting of 8 questions. Each question is scored on a 1-7 rating scale, with a higher score indicating a greater level of perceived enjoyment. The sum of scores from each of the 8 questions was calculated.

### 3.12.7 *Functional performance*

Functional performance was measured with the BES, LES, TUGT, FRT, FTSTS and maximal vertical jump test. A physiotherapist conducted all physical performance testing and closely supervised participants for safety. Participants completed the performance testing activities in the following order: strength tests (BES and LES); clinical measures (i.e. TUGT, FRT, and FTSTS); a five-minute warm-up on a cycle ergometer (Ergomedic 818E, Monark, Sweden) at 50 watts; and a maximal vertical jump test.

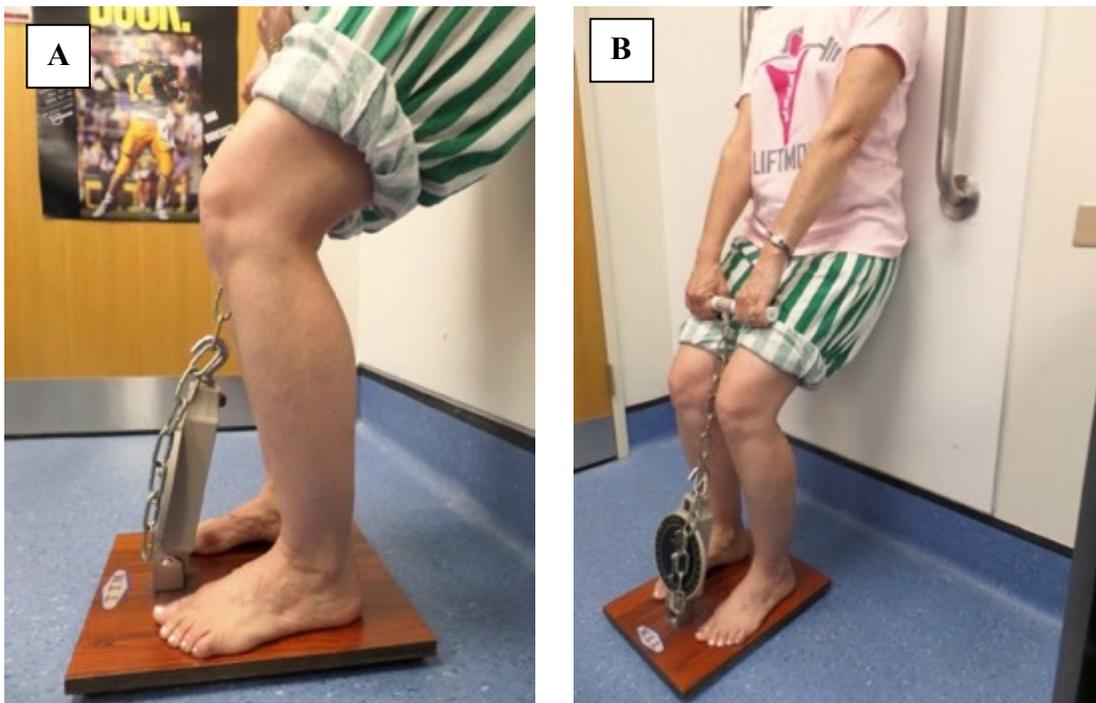
The validated BES test was performed as previously described [126], using a handheld dynamometer (Lafayette Manual Muscle Testing Systems, USA), which provided a digital readout of peak force in kilograms. We have demonstrated this novel BES measure has both excellent short- and long-term reliability within our laboratory (ICC 0.90-0.98) [126]. The participant was positioned with their back to the wall midway between two designated anchor points (Figure 7A). An inelastic strap was then firmly secured across the pelvis approximately 1 cm below the anterior superior iliac spine and pulled tight to prevent movement away from the wall during the trial. To

perform the task, the participant folded their arms across their chest, flexing the trunk slightly to allow placement of the hand-held dynamometer over the T7 vertebra (Figure 7B). The participant then pushed back as hard as possible for a period of 3 seconds and the peak force in kilograms across the three trials was used for analysis. To standardise motivation, the phrase “push, push, push” was used for all participants.



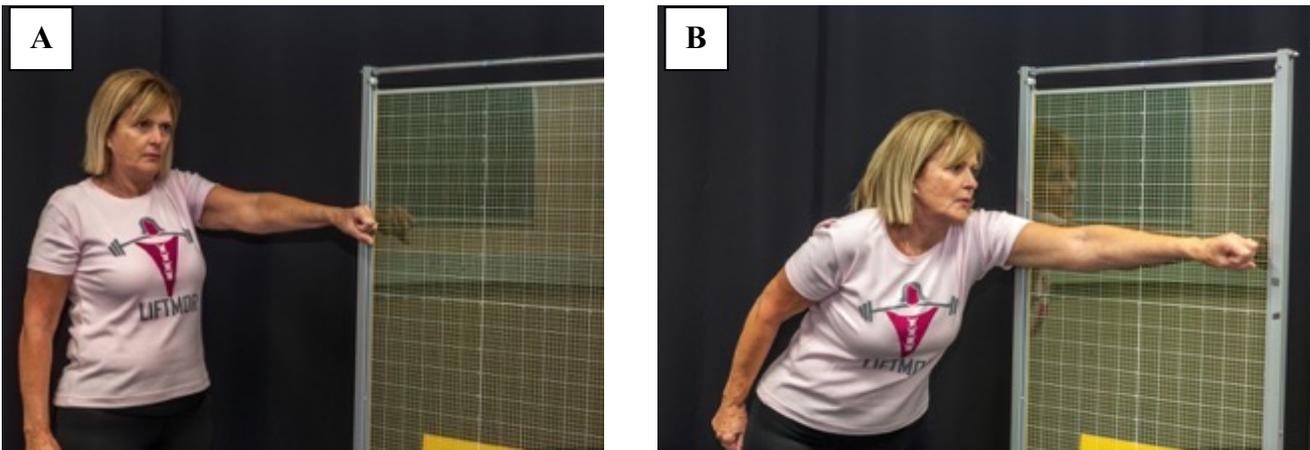
**Figure 7:** The back extensor strength test showing (A) participant position and (B) hand held dynamometer position during the test

Lower limb strength was measured using an isometric dynamometer (TTM Muscular Meter, Tokyo, Japan), which we have demonstrated to have excellent short- and long-term reliability (ICC 0.990-0.984) [325]. Participants were instructed to stand on a platform with their knees flexed to approximately 115° (Figure 8A) and their whole back against the wall (Figure 8B). Participants then grasped a bar connected by a chain to the platform with arms fully extended and attempted to move up the wall by pushing only with their legs, keeping their back and neck vertical against the wall and arms straight. To standardise motivation, the phrase “pull, pull, pull” was used for all participants. The maximum force in kilograms across the three trials was used for analysis.



**Figure 8:** The lower limb strength test showing (A) example of knee flexion angle (approximately 115 degrees) maintained during the test and (B) participant starting position

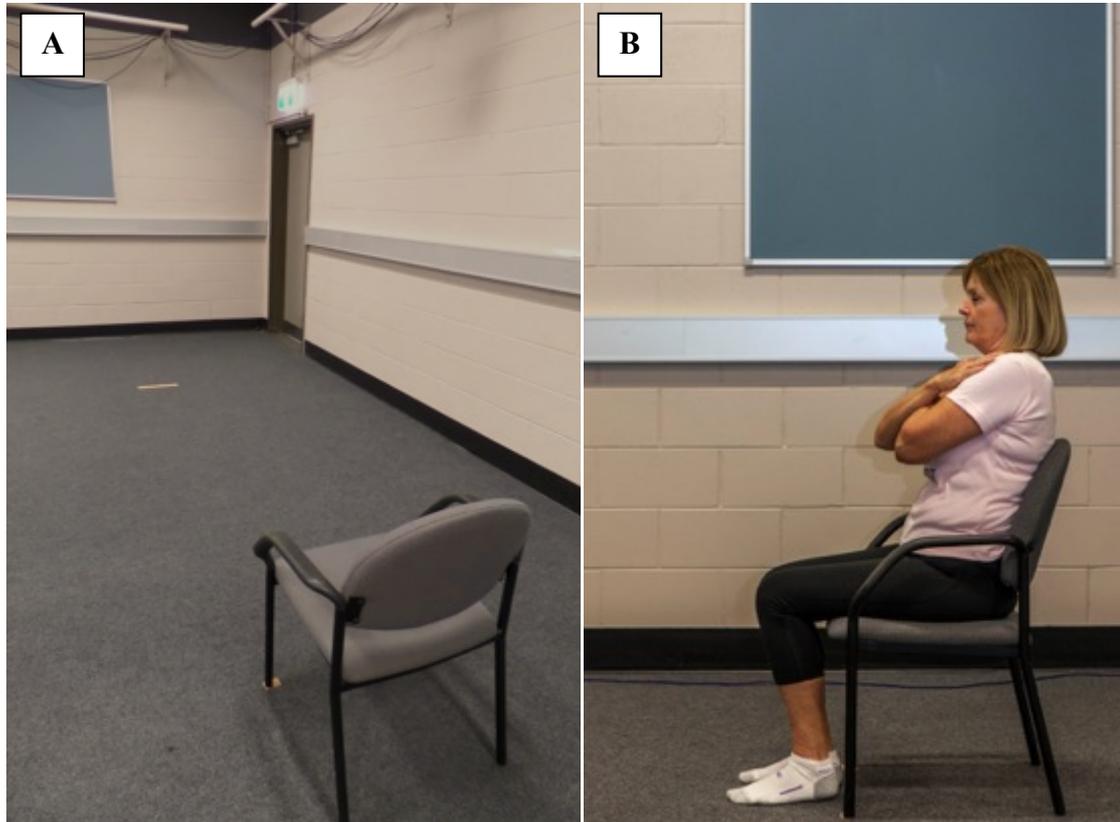
The FRT was performed as described by Duncan and colleagues [85] with the use of a custom-made portable vertical Perspex board, and has been shown to have good reliability (ICC 0.81) [85]. Participants stood with their feet shoulder width apart in a relaxed posture, the shoulder of their preferred arm flexed at 90 degrees, while making a fist with the same hand (starting position) (Figure 9A). Participants were then instructed to reach forward as far as possible without losing balance or taking a step, and the horizontal displacement (cm) of the head of the third metacarpal from the starting position was recorded (Figure 9B). Participants performed a total of three attempts and were allowed further attempts if they lost their balance or took a step. The maximum horizontal distance in cm of three attempts was recorded.



**Figure 9:** Participant (A) starting position and (B) forward flexion during the functional reach test

The TUGT was performed using a standard size seat (height: 46 cm) with armrests and has shown to have excellent reliability in older adults [222, 240]. Participants began seated with their back touching the backrest before standing, walking three metres as quickly as possible [240], turning 180 degrees, walking back to the chair, and sitting down to assume the starting position (Figure 10). The time taken to

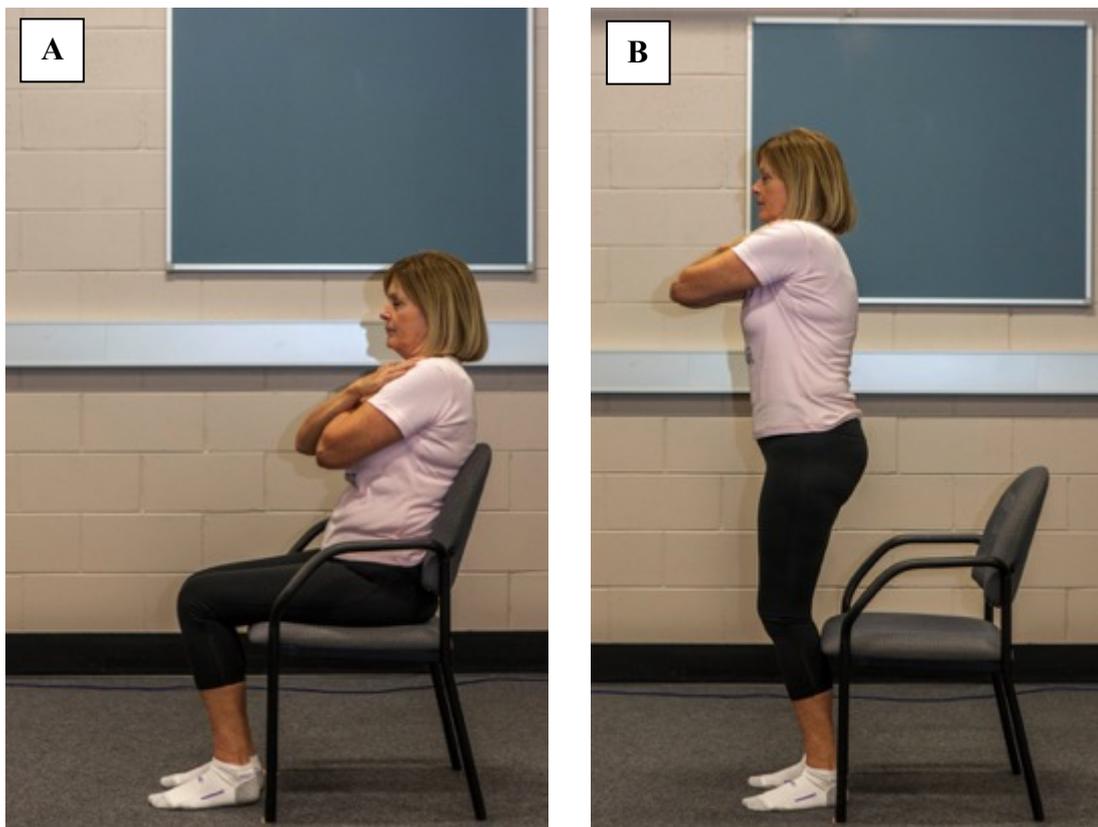
complete the task (in seconds) was recorded for each of three attempts and the mean was used for analysis.



**Figure 10:** Timed up-and-go test showing (A) equipment set up with tape marking at 3 metres and (B) starting position for the test

The FTSTS was performed in the same chair used for the TUGT and has been shown to have excellent reliability (ICC 0.89-0.96) in older adults [43, 300]. The participant was instructed to sit with their back against the backrest with arms folded across their chest (Figure 11A). The participant was then instructed to stand and sit five times as quickly as possible. Participants must have fully extended their knees and hips on rising and ensure that their back touched the backrest on sitting to be a valid test

(Figure 11B). The time taken to complete the task (in seconds) was recorded for each of three attempts and the shortest time to complete the test across the three trials was used for analysis.



**Figure 11:** Participant demonstrating (A) the starting position and (B) standing movement for the five times sit-to-stand test

The maximal vertical jump test was performed on a force plate (AMTI, Watertown, MA), where three-dimensional ground reaction forces were captured at 1000 Hz using Vicon Nexus software version 1.8 (Vicon, Oxford Metrics, Oxford, UK). The participant performed 4 maximal vertical jumps, with a 30-second rest between trials. Participants were instructed to perform a maximal countermovement vertical

jump without arm swing. This was achieved by positioning the participant in the centre of the force plate with their dominant upper limb raised and non-dominant upper limb by their side. The participant was instructed to squat down and jump as high as possible (Figure 12), ensuring they kept their dominant arm vertical and the non-dominant arm by their side throughout the manoeuvre. After the first attempt, the pegs of a vertical jump measuring device (Yardstick, Swift Sports, Aspley, Australia) were positioned approximately 10 cm out of reach of the jumping participant directly above the force plate to establish a target and maximize (and standardize) motivation.



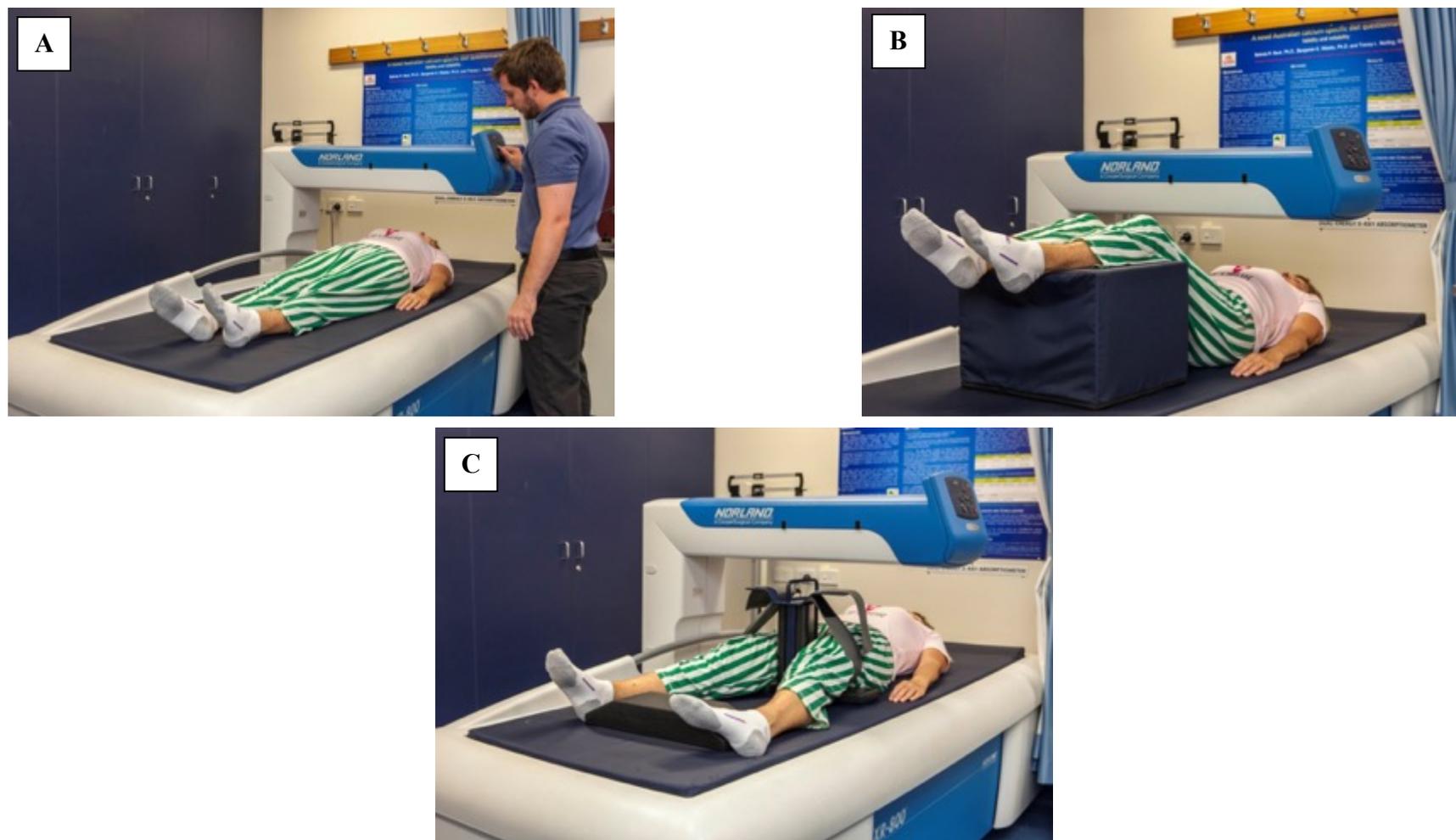
**Figure 12:** Participant performing a maximal vertical jump on the force plate

### 3.12.8 *Body composition measures*

Body composition was determined using dual-energy x-ray absorptiometry (DXA) (Norland XR-800, Norland Medical Systems, Inc., USA; Medix DR, Medilink, France) (Approved Procedure Register: Griffith University Ref No: PES/19/09/HREC),

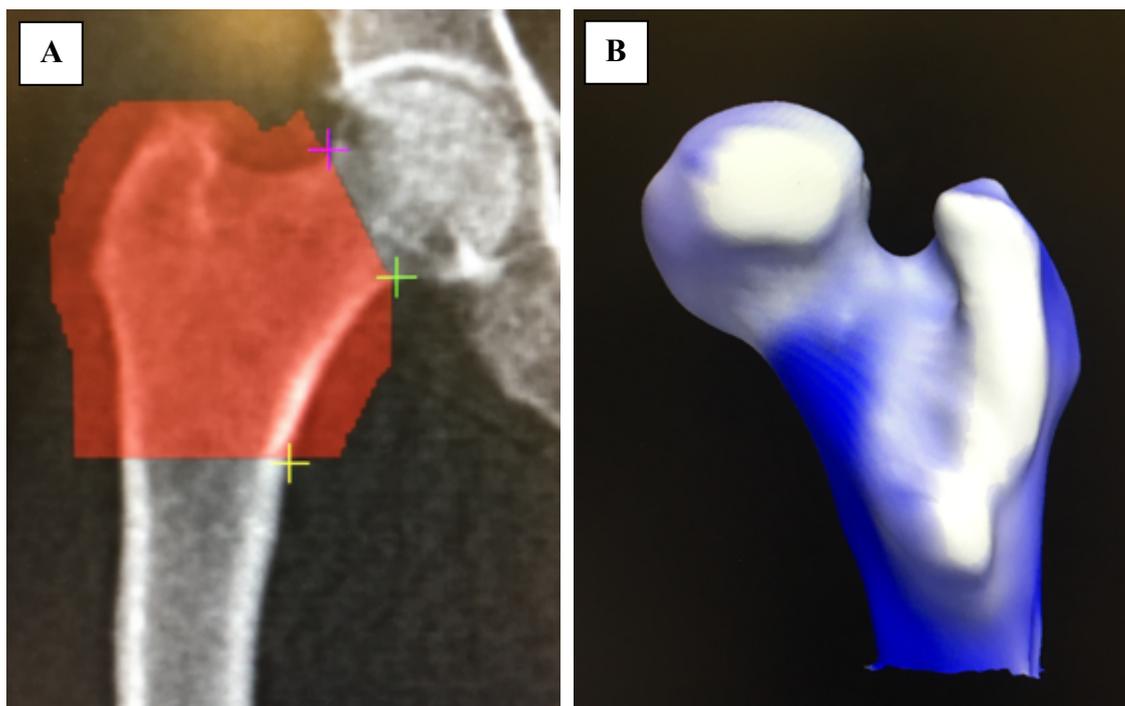
including whole body (WB), lumbar spine (LS) and femoral neck scans (FN). DXA was chosen as the outcome measure for bone for a number of reasons. Alternative measures of bone such as clinical QCT were not feasible due to financial constraints. But importantly, DXA remains the clinical gold standard for bone mass estimation through the measurement of two-dimensional (areal) BMD (g/cm<sup>2</sup>). This broad recognition facilitates the interpretation of findings within the clinical community. DXA replacement occurred during the course of the trial such that two DXA devices were used for data collection, with the first 50 participants tested on the Norland XR-800 and the final 51 participants being tested on the Medix DR. The procedure of participant placement was the same for both devices, and each participant was scanned on the same device at baseline and follow-up. The whole-body scan was performed by instructing the participant to lie supine, with their arms by their sides, palms flat on the scanning bed, and legs extended with feet slightly separated (Figure 13A). The lumbar spine scan required the participant to be lying on their back, with hips flexed 60-90 degrees, and legs supported by a high-density foam block (Figure 13B).

For the femoral neck scans, the participant was positioned on their back with feet separated and test hip internally rotated to approximately 20 degrees using the manufacturer's hip sling (Figure 13C). This process was repeated for the contralateral limb, as both proximal femora were measured. All scans were accomplished through automated procedures initiated by the investigator from a designated computer console. Short-term measurement reliability for FN and LS DXA scans in our lab is 1.1% and 0.4%, and 1.7% and 1.0% for the Norland and Medix DR devices, respectively.



**Figure 13:** Participant positioning for (A) whole body (B) lumbar spine and (C) femoral neck scans on the Norland XR-800 densitometer

Proximal femur scans for the final 51 participants captured on the Medix DR device underwent an additional analysis using 3D Hip software (DMS Group, Manguio, France). The 3D Hip software was used to reconstruct a 3D representation of the proximal femur in order to derive FN trabecular and cortical volume, trabecular and cortical bone mineral content (BMC), trabecular and cortical volumetric BMD, and FN cortical thickness. 3D parameters were derived according to manufacturer guidelines. Markers were placed on the standard 2D image using the cursor at the distal edge of the lesser trochanter and the superior and inferior junctions of the FN and head of the femur (Figure 14A). The 3D Hip software then automatically reconstructed the femur based on both shape and BMD distribution of the standard 2D image (Figure 14B).



**Figure 14:** (A) Marker placement for 3D reconstruction of 2D proximal femur DXA scan and (B) example of 3D reconstruction of 2D proximal femur DXA scan from 3D Hip software (DMS Group, Manguio, France)

Quantitative ultrasound (QUS) was used to assess calcaneal bone quality. Testing was undertaken in accordance with the approved protocol (Approved Procedure Register: Griffith University Ref No: PES/11/09/HREC). Both heels were examined independently to obtain calcaneal broadband ultrasound attenuation (BUA) ( $\text{db}\cdot\text{MHz}^{-1}$ ), speed of sound (SOS) ( $\text{m}\cdot\text{s}^{-1}$ ) and stiffness index (SI) (unitless) using a calcaneal ultrasonometer (Lunar Achilles TM Insight, GE). Participants were asked to sit upright in a chair, knee flexed approximately 90 degrees with the hip neither abducted nor adducted (Figure 15). The lateral aspects of the participant's heel and transducer membranes were sprayed with 70% ethanol solution before placement in the device well. A scout image was conducted to ensure correct placement of the scan location before the measurement was undertaken.



**Figure 15:** Quantitative ultrasound examination using the calcaneal ultrasonometer (Lunar Achilles TM Insight, GE)

All devices were calibrated each testing day and quality control procedures were undertaken as per ANZBMS and Australian Radiation Protection and Nuclear Safety Agency (ARPANSA) guidelines to ensure accurate and repeatable results. The same technician performed all scans. Participants were required to remain as still as possible for the duration of each scan to avoid movement artefact.

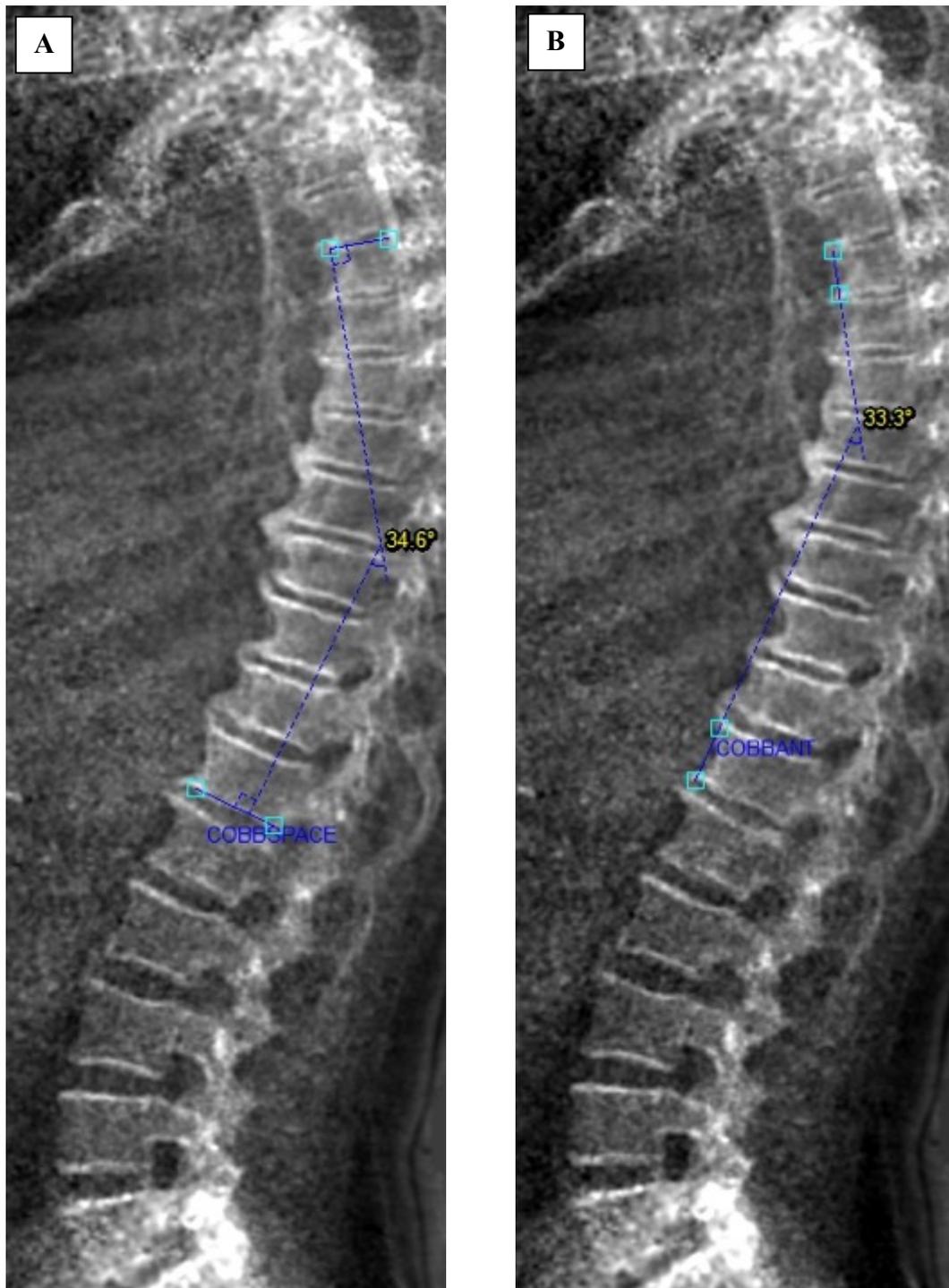
### *3.12.9 Kyphosis measures*

The magnitude of thoracic kyphosis for the last 51 participants was measured by both imaging (DXA) and clinical techniques (inclinometer and Flexicurve). Only the final 51 participants were recorded as these participants were scanned with the Medix DR DXA. The Medix has the ability to perform a lateral vertebral assessment, whereas the Norland DXA does not possess this function. To determine the magnitude of kyphosis, a lateral thoracolumbar DXA scan was performed in the lateral decubitus position (Figure 16), which allowed for both lateral vertebral assessment (LVA) and Cobb angle measurements. To perform the LVA, participants were asked to lie on their right side, with knees and hips flexed to 90 degrees. A foam block was then placed under the participant's head to maintain neutral spinal alignment between the thoracic and cervical regions. To reduce spinal rotation and to preserve a participant's natural kyphosis, shoulders, and hips were aligned vertically. To obtain vertical alignment of a participant's shoulders, their left arm was placed on top of the foam block as demonstrated in Figure 16 and was visually confirmed by the investigator. Similarly, the hips were aligned vertically by placing a foam block between the participant's knees.



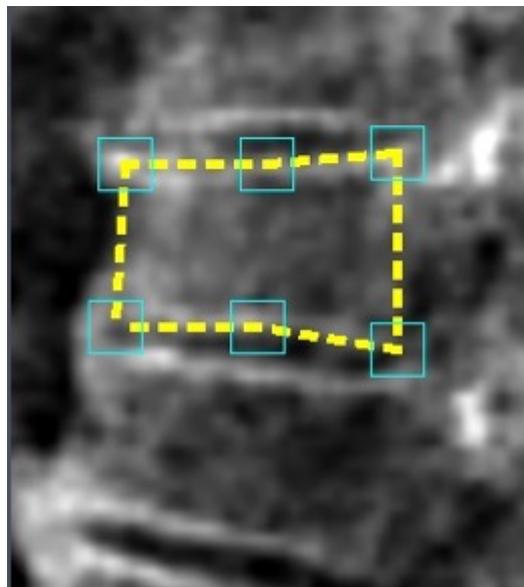
**Figure 16:** Participant position for lateral thoracolumbar DXA on the Medix DR densitometer

Cobb angle calculations were performed using two approaches: (1) using 4<sup>th</sup> and 12<sup>th</sup> thoracic vertebral body endplates (Figure 17A), and (2) using the anterior vertebral body margins of the 4<sup>th</sup> and 12<sup>th</sup> thoracic vertebrae (Figure 17B). The endplate Cobb angle analysis was performed by manually digitizing the superior endplate of the 4<sup>th</sup> thoracic vertebrae (T4) and the inferior endplate of the 12<sup>th</sup> thoracic vertebrae (T12); lines perpendicular to each endplate were computer generated and converged to create the Cobb angle as previously described [148]. The anterior body Cobb angle measure was undertaken to eliminate the effect of a dramatic vertebral deformity at T4 or T12 influencing overall Cobb measure. To complete the measure, the anterior margins of the vertebral bodies of T4 and T12 were digitized and extended until they converged to create the Cobb angle as previously described [50].



**Figure 17:** Cobb angle measurement using both (A) vertebral body endplates and (B) anterior vertebral body methods

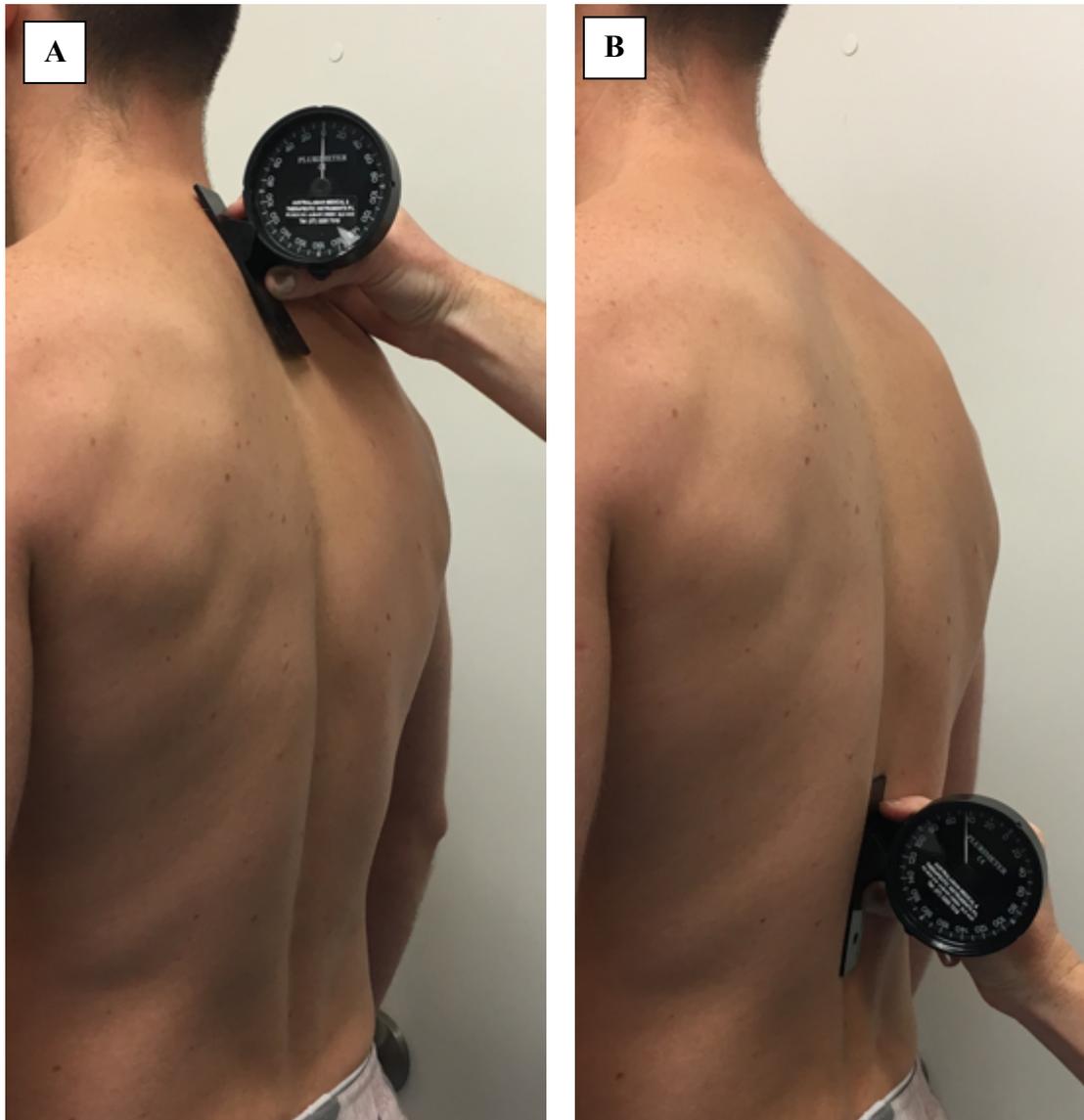
The lateral DXA scans on the Medix DR device allowed the assessment of vertebral bodies from T5 through L4 for the presence of fracture utilizing the semi-quantitative Genant method [105]. This method involves manual placement of digital markers on both superior and inferior endplates of each vertebral body, with three markers being placed at the most anterior, middle and most posterior points of each endplate (Figure 18).



**Figure 18:** Digital marker positioning for vertebral body assessment

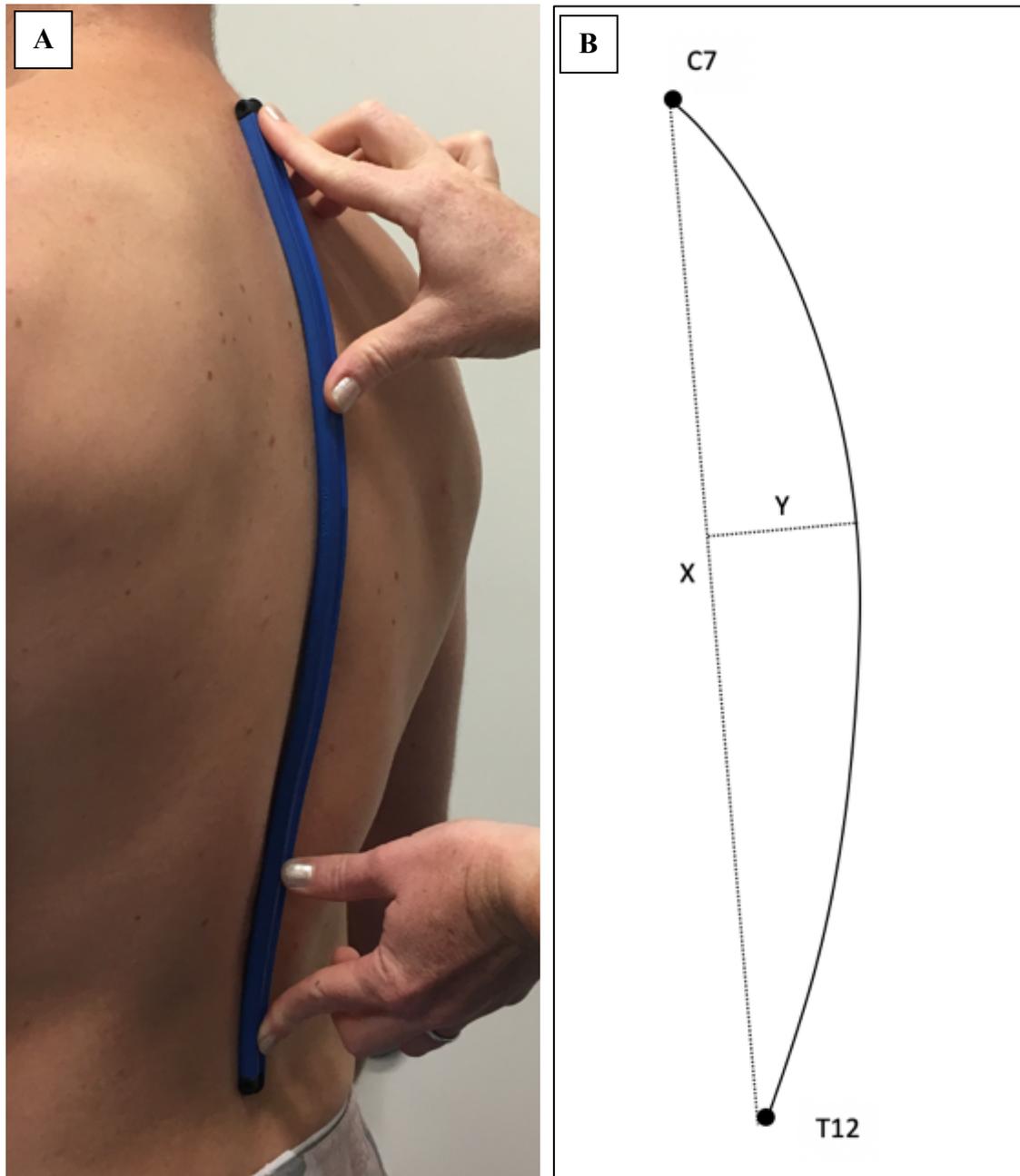
Two manual clinical measures of thoracic kyphosis were performed including gravity-referenced inclinometer (Plurimeter, Australasian Medical & Therapeutic Instruments, Australia) and Flexicurve (Staedtler Flexible Curve 400 mm, Nurnberg, Germany). To perform both measurements, participants were asked to remove their shirt and shoes. The following bony landmarks were palpated and marked: (1) the spinous process of the 7<sup>th</sup> cervical vertebra (C7), and (2) the 12<sup>th</sup> thoracic vertebra (T12). To identify C7, participants were instructed to flex their neck, so their chin was on their

chest, and the first prominent spinous process when palpating inferiorly from the occiput was marked as C7. To identify T12, the investigators fingers were placed on the participants iliac crests with thumbs approximated centrally over the participants spine. The first vertebra palpated superior to the iliac crests was identified as L4, and spinous processes were palpated superiorly until T12 was identified. After identification of anatomical landmarks, the inclinometer was zeroed at the 7<sup>th</sup> cervical and 1<sup>st</sup> thoracic intervertebral space as previously described [207] (Figure 19A). The inclinometer was then placed at the 11<sup>th</sup> to 12<sup>th</sup> thoracic intervertebral space to measure the thoracic kyphosis angle (degrees) (Figure 19B). The inclinometer method was conducted in both a ‘relaxed standing’ (neutral posture) and ‘standing tall’ posture. Our inclinometer measures exhibited excellent short term intra-rater reliability for kyphosis, both in relaxed (ICC=0.968 (95% CI, 0.954–0.977),  $p < 0.001$ ) and standing tall (ICC=0.974 (95% CI, 0.963–0.982),  $p < 0.001$ ) positions, which mirror the findings of others [21]. For the ‘relaxed standing’ posture, the participant was instructed to stand with feet shoulder width apart with equal weight distribution, arms relaxed by their sides and to take two deep breaths. The ‘standing tall’ posture was undertaken with feet shoulder width apart, arms relaxed by their sides, and the participant was instructed to ‘stand as tall as possible’. Two measures were performed for each posture and the average used for analysis.



**Figure 19:** Inclinometer placement at (A) 7th cervical and 1st thoracic intervertebral and (B) 11th to 12th thoracic intervertebral space for quantification of kyphosis

The C7 and T12 markings used for the inclinometer measures were then used to perform the Flexicurve thoracic kyphosis measure in a relaxed standing position. The end of the Flexicurve was placed on the C7 marking and then moulded to the participants spinal curvature caudally to the T12 marking which was recorded/marked on the Flexicurve (Figure 20A). The moulded Flexicurve was then transferred to paper and the thoracic curvature was traced (Figure 20B). A straight line was then drawn from the points coinciding with the C7 to T12 vertebrae, and the length of the line recorded (X). A perpendicular line was drawn from the C7-T12 line to the point of maximal curvature, and the length of that line also recorded (Y). The kyphosis index was then calculated by dividing the width of curvature by the height of the thoracic region and multiplying the result by 100 ( $Y/X \times 100$ ) [20, 333]. Flexicurve measures have excellent reliability (ICC 0.92-0.94), even in novice users [21, 134].



**Figure 20:** (A) Flexicurve placement and (B) digitization of Flexicurve tracing with markings for quantification of kyphosis

### *3.12.10 Exit survey*

A 13-item questionnaire (Appendix M) was developed to assess participant perception of the LIFTMOR trial. The questionnaire was designed to provide an objective measure of a participant's experiences of the LIFTMOR trial, including their group allocation, perception of the exercises they performed, how they felt during and after sessions and if they would enroll in the trial again if given the opportunity. To complete the questionnaire, participants were instructed to read each statement and select the most appropriate answer on a 5-point Likert scale (1 = strongly disagree, 3 = neutral, 5 = strongly agree) based on their participation in the LIFTMOR trial.

### *3.12.11 Semi-structured interviews*

A sub-group of HiRIT group participants who filled-out the exit survey were also invited to undertake a semi-structured interview. Similar to the exit survey, the semi-structured interviews were developed to investigate a participant's experiences of the HiRIT exercise program. The use of semi-structured interviews allowed additional information not captured in the exit survey to be obtained, as a face-to-face discussion allowed elaboration of both experiences during and perceptions of the LIFTMOR trial. The semi-structured interviews were conducted at the beginning of the follow-up (T1) testing session. Holding interviews at the beginning of the follow-up testing session was intended to limit the impact of individual results on participant responses to questions. Fourteen HiRIT participants were asked a series of 10 questions (Table 5) by an interviewer who was unknown to participants. The questions were developed to explore participant's motivation for participation, previous physical activity participation, experiences during and after the HiRIT sessions, whether they planned to continue

HiRIT after the LIFTMOR trial, and if they would recommend the program to a friend. For each question, the interviewer prompted the participant for an explanation of their answer using non-leading phrases, such as “can you be more specific”, “can you please explain further” and “what was it about ... that made you feel like ...”.

**Table 5:** Semi-structured interview questions for the LIFTMOR trial

Question
1. What was your motivation for your participation in the trial?
2. Have you ever participated in resistance training prior to the trial?
3. What were your experiences related to the study exercises during the course of the study?
4. Do you have any comments about the exercises or structure of the exercise sessions?
5. How did you feel during and after the exercise sessions?
6. Have you noticed any changes as a result of the exercise sessions?
7. Do you intend to continue regular resistance training?
8. What, if any, changes would you make to the exercise sessions?
9. Do you have any other feedback/anything else you would like to say?
10. Would you recommend this program to a friend?

### 3.13 Data analysis

Data analysis for the vertical jump was performed using the captured ground reaction force data from the point of stationary standing pre-jump ( $t_i$ ) to the point of take-off ( $t_{io}$ ). Utilising custom written Matlab software (Matlab version 7.8.0, The MathWorks, Natick, MA),  $t_i$ , was determined by identifying a horizontal line during stationary standing on a ground reaction force graph. To account for natural fluctuations in ground reaction force during stationary standing, the horizontal line was identified as the midpoint between the minimum and maximum ground reaction force during this

phase. The point of take-off ( $t_{to}$ ) was identified as the point where the ground reaction force was equal to zero immediately following lower limb force production. Applying these time points, impulse was calculated using the impulse momentum method described by Linthorne [187]:

$$\int_{t_i}^{t_{to}} (F_{GRF} - mg) dt = m v_{to}.$$

Abbreviations:  $t$  time;  $F$  force;  $GRF$  ground reach force;  $m$  mass;  $g$  gravity;  $v$  velocity

Data analysis for DXA scans was undertaken with host software provided by the manufacturer (XR-800 Norland Cooper Surgical, Fort Atkinson, WI, USA, Illuminatus software V.4.2.4; Medix DR, Medilink, France). Analysis was undertaken for whole body, lumbar spine and femoral neck to determine bone mineral content (g), bone area ( $\text{cm}^2$ ) and areal bone mineral density ( $\text{g}/\text{cm}^2$ ). Lean mass (g), fat mass (g), percent fat mass, and regional measures were obtained from the whole body scan analysis.

Data collected during semi-structured interviews were analysed with Leximancer software (Version 4.50.27; Leximancer Pty Ltd, Brisbane, Australia). Leximancer analysis was performed by first transcribing participant interviews, then collating responses for each of the 10 questions into a single word document. Once collated, responses for each question were uploaded and automatically analysed based on conceptual content to identify main themes and concepts [284]. During the analysis process, words with little semantic meaning (if, we, probably) were excluded as potential concepts or themes. Additionally, words with similar meaning were grouped

into a single theme/concept. Visual concept maps and statistical outputs were generated for each question to assist in the identification and interpretation of relationships between themes and concepts.

### 3.14 Statistical analysis

Statistical analyses were undertaken using SPSS statistical software (Version 22; SPSS Inc., Chicago, IL). Descriptive statistics were generated for subject characteristics, biometrics, and all dependent measures. One-way analysis of variance (ANOVA) was used to determine baseline differences in outcome measures between the HiRIT and CON groups. Both per protocol and intention to treat (ITT, mean values imputed) analysis were adopted with repeated measures analysis of covariance (ANCOVA) to test our hypotheses. Initial values, age, and compliance were applied as covariates for all analyses, with the addition of physical activity participation and dietary calcium as covariates for bone analyses. For all ordinal variables (PACES, WHOQOL-BREF, exit survey), Kruskal-Wallis test was used to examine HiRIT and CON between-group differences at baseline and follow-up, and Friedman's test was used to examine between group differences for PACES-8 and WHOQOL-BREF. All statistical analyses were conducted using a *P*-value of 0.05 to determine statistical significance.

Based on a previous similar high-intensity resistance training intervention trial in postmenopausal women [218], to achieve 80% power to detect between-group differences of 2.7% with a standard deviation of 4.5% for femoral neck BMD and 3.5% with a standard deviation of 3.6% for lumbar spine, a total of 68 and 52 participants

were required. To account for approximately 20% participant dropout and to maximise power for secondary outcome measures, a minimum of 100 participants were required.

### 3.15 List of equipment

A number of resources were required to undertake the LIFTMOR trial. For baseline and follow-up testing, all required equipment was available within the School of Allied Health Sciences or was purchased. The equipment included:

- Dual-energy x-ray absorptiometer (DXA, Norland XR-800 bone densitometer, Cooper Surgical Norland, USA)
- Dual-energy x-ray absorptiometer (Medix DR, Medilink, France)
- Quantitative ultrasound (QUS, Lunar Achilles™ Insight, GE)
- Stadiometer (HART Sport and Leisure, Australia)
- Mechanical balance scales (Seca 700, Economed Trading Pty Ltd, NSW)
- Sphygmomanometer (Standby Baumanometer, Baum Co. Inc, Copiague, New York, USA)
- Stethoscope (Littman classic, 3M, St. Paul, Minnesota, USA)
- Standardised chair for TUGT and FTSTS
- Stop watch for TUGT and FTSTS
- Metal tape measure (Lufkin, Sparks, Maryland, USA)
- Custom Perspex screen for Functional Reach Test (FRT)
- Handheld digital dynamometer (Lafayette Manual Muscle Testing Systems, USA) for back extensor strength
- Lower limb isometric dynamometer (TTM Muscular Meter, Tokyo, Japan)
- Training intervention recording booklets

- Inclinator (Plurimeter, Australasian Medical & Therapeutic Instruments, Australia)
- Flexicurve (Staedtler Flexible Curve 400 mm, Nurnberg, Germany)
- SPSS version 22 for Windows (IBM, Chicago, IL)

A number of resources were also required for each exercise program. The home-based exercise program required 50 sets of 2 x 1 kg, 2 x 2 kg and 2 x 3 kg dumbbells. The HiRIT group required weight plates, squat racks and Olympic bars. To implement both the HiRIT and CON exercise programs, the following items were acquired:

- 50 x 12 kg Vinyl dumbbell sets (HART Sport, Aspley, Australia)
- 1 x Squat rack (Revolution Half Rack, Revolution Fitness, Australia)
- 1 x Squat stand (Revolution Squat Rack, Revolution Fitness, Australia)
- 4 x Olympic bars (Force USA, Draper, UT, USA)
- Weight plates (Force USA, Draper, UT, USA)
  - 8 x 1.25 kg
  - 8 x 2.5 kg
  - 6 x 5 kg
  - 4 x 10 kg
  - 4 x 20 kg

A number of participants from the HiRIT required the use of an off-campus gym facility in the Brisbane region. Commercial training facilities were sourced. Two commercial sites in Brisbane (Barbells and The Bone Clinic) were made available free of charge and gained exposure via acknowledgement on the LIFTMOR website,

presentations and publications. The facilities had all the required equipment to implement the HiRIT program and staff with the requisite expertise to supervise the program.

### **3.16 Data management**

All data is kept in the possession of the investigators, de-identified and stored on password protected university computers. All hard copy forms are stored in a locked filing cabinet in a lab with restricted swipe card access for a minimum of five years. For all publications and presentations, participants have not been identified by name.

### **3.17 Communication of results**

A summary of the project findings in lay terms has been provided to all participants. In addition, each participant was provided copies of their DXA results for LS, FN and WB at each time point for interpretation by their General Practitioner. Project findings have also been reported at national and international conferences, or in peer-reviewed scientific journals.



## Chapter 4: Publication One

**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**

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**Statement of contribution to co-authored published paper**

For this co-authored manuscript, the candidate conceived and designed the experiment in consultation with co-authors, recruited participants, performed data acquisition, implemented the intervention, analysed the data, interpreted results, and prepared the manuscript.

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Steven Watson | *Candidate*

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Professor Belinda Beck | *Principal supervisor and corresponding author*

#### 4.1 Abstract

*Summary:* The aim of the LIFTMOR trial is to determine the safety and efficacy of brief, bone-targeted, high-intensity resistance and impact training (HiRIT) for postmenopausal women with low bone mass. Preliminary findings indicate the LIFTMOR program is safe and effective. *Introduction:* Despite a lack of notable efficacy, exercise guidelines for osteoporosis typically recommend moderate-intensity exercises, owing to a perceived risk of fracture from high-intensity loading. Indeed, safety concerns alone have prevented the well-recognised preferential response of bone tissue to high-intensity loads from being applied to those who stand to benefit the most. To progress from this therapeutic stalemate, a challenge to conventional wisdom was required. Our goal was to examine safety and efficacy of HiRIT for risk factors for osteoporotic fracture in postmenopausal women with low to very low bone mass.

*Methods:* Participants have been randomized to either eight months of twice-weekly, 30 minutes supervised HiRIT, or a low-intensity home-based exercise program of the same duration and dose. Testing at baseline and follow up has included anthropometry, bone, muscle and fat mass, and functional performance. *Results:* Twenty-eight women ( $66.1 \pm 4.8$  yrs, mean lumbar spine T-score  $-2.15 \pm 0.72$ ) have completed the study. HiRIT ( $n = 12$ ) improved height ( $0.4 \pm 0.2$  cm vs  $-0.3 \pm 0.1$  cm,  $p = 0.003$ ), femoral neck bone mineral density ( $0.3 \pm 0.5\%$  vs  $-2.5 \pm 0.8\%$ ,  $p = 0.016$ ), lumbar spine bone mineral density ( $1.6 \pm 0.9\%$  vs  $-1.7 \pm 0.6\%$ ,  $p = 0.005$ ), and functional performance ( $p < 0.05$ ), compared to controls ( $n = 16$ ). Compliance has been  $>87\%$ . There have been no injuries. *Conclusions:* Brief supervised HiRIT is safe and effective exercise therapy for postmenopausal women with low to very low bone mass.

## 4.2 Introduction

The bone response to exercise is highly dependent on the nature of applied mechanical loads. The most osteogenic activities are those that induce high magnitude strains [258] at high rates [228] or frequencies in bone [259]. Under such conditions, only brief loading bouts are required to stimulate a response [257]. Such strains are typically induced by weight bearing impact loading and high-intensity progressive resistance training or power training [42, 191, 218, 314]. Paradoxically, it is widely held that high-intensity exercises should not be attempted by individuals with established osteoporosis, owing to a potentially increased risk of fracture [106, 176].

In spite of an absence of documented evidence that high-intensity resistance and impact training (HiRIT) will cause fractures in individuals with osteoporosis, this prevailing concern has led to the development of more conservative exercise recommendations for osteoporosis. For example, walking is frequently prescribed for osteoporosis, despite representing very low intensity loading and being largely ineffective for bone [235]. In fact, walking has been associated with an increased risk of falls in the frail elderly [271], suggesting it is not an innocuous alternative. A recent consensus panel erred on the side of caution for older adults with vertebral osteoporosis, ultimately recommending a moderate intensity progressive resistance training protocol of 8-12 repetitions at 67-80% 1RM [42, 106, 191]. Such resistance training intensity however, is likely to confer modest benefit to bone at best [136], albeit increasing as loads increase [77]. For many practitioners, the standard exercise prescription for osteoporosis is even more conservative, targeting falls prevention rather than bone strengthening.

To designate a therapeutic standard on the basis of a hypothetical safety concern is counter to the principles of evidence-based medicine. The scientific approach would be to test high intensity training in individuals with osteoporosis to determine true safety and efficacy; however scientists have been understandably reluctant to do so. As a consequence, the field has stagnated in recent years, with advances in exercise recommendations for osteoporosis constrained by a perceived risk of injury. Clearly, a “leap of faith” trial was necessary to reignite progress in the field. Such a study would require concerted efforts to minimise risk, including close attention to exercise technique, gradual progressions, and supervision by suitably qualified clinical staff.

The purpose of the LIFTMOR project (Lifting Intervention For Training Muscle and Osteoporosis Rehabilitation) was to conduct such a trial. More specifically, our aim was to determine the safety and efficacy of brief, bone-targeted HiRIT for postmenopausal women with low to very low bone mass on risk factors for osteoporotic fracture, including BMD, lean mass, and physical function. While data collection is not yet complete on our full sample, our significant and novel early findings warrant rapid dissemination.

## **4.3 Methods**

### *4.3.1 Study design*

The LIFTMOR study is a single-blind randomized controlled exercise intervention trial. Eligible participants are block randomized to either eight months of 30 minutes, twice-weekly, supervised HiRIT, or an unsupervised low-intensity home-based exercise program of similar duration. Block randomisation is based on existence or absence of established (twelve months exposure or lack of exposure) osteoporosis

medication. Ethical approval was obtained from the Griffith University Human Research Ethics Committee (Approval number: AHS/07/14/HREC). Written informed consent has been obtained from each volunteer.

#### *4.3.2 Participants*

One hundred postmenopausal women over 60 years of age with low bone mass (T-score < -1.0 at hip and/or spine) but otherwise in good general health are being recruited from the community. The current report includes preliminary findings from the first group of participants who have completed the study (n = 28). Potential participants have been excluded if they had any of the following: lower limb joint surgery or injury; recent fracture or localized back pain; less than five years post menopause; malignancy; uncontrolled cardiovascular disease; cognitive impairment; recent x-ray or radiation treatment; contraindications for participating in heavy physical activity; conditions known to influence bone health (e.g. thyrotoxicosis or hyperparathyroidism, Paget's disease, renal disease, diabetes, or immobility); or taking drugs (other than osteoporosis medications) known to influence bone (e.g. prolonged use of corticosteroids, thyroxine, thiazides or antiretroviral agents).

#### *4.3.3 Intervention exercise program*

Intervention group activities include twice-weekly, 30-minute, supervised HiRIT in small groups with a maximum of eight participants per session. Bodyweight and low-load exercise variants with a focus on controlled movement are undertaken for the initial two to four weeks of training to ensure that participants are fully trained with correct lifting technique. For example, participants are trained to avoid loading the spine

in a flexed posture. Loaded exercises are then introduced and intensity progressed, so that all participants are able to comfortably perform the four exercises of the program (deadlift, squat, jumping chin ups/drop landings and overhead press) by the end of month two. The three resistance exercises (deadlift, squat and overhead press) are then performed in 5 sets of 5 repetitions for the remainder of the intervention, progressively increasing weight to maintain an intensity of 80-85% 1RM. Impact loading is applied by jumping chin ups with drop landings. Participants start by reaching up to an overhead bar and gripping in an underhand, narrow grip chin up position. Participants then jump as high as possible while simultaneously pulling themselves towards or above the bar using their arms. At the height of the jump, the bar is released so that participants drop to the floor. Five sets of 5 repetitions of the action are performed for the duration of the intervention. Progression of impact intensity is achieved by natural training-related increases in height of the jump and chin up, by raising the bar, and by gradually increasing the intensity of the impact landing from a shock-absorbing flexed lower limb position to a more stiff-legged landing. Participants perform 2 sets of 5 deadlifts at 50-70% 1RM to serve as a warm up as required. Training is fully supervised by an exercise scientist who is also a physiotherapist.

#### *4.3.4 Control exercise program*

Control group (CON) activities include a very low load home-based exercise program primarily designed for the purposes of participant retention, with the potential to reduce risk of falling (the latter for ethical reasons to address a duty of care to individuals who may be at increased risk of fracture). The CON regime was similarly comprised of two 30-minute sessions per week, consisting of a 10-minute walking

warm-up, four stretches and four low-resistance exercises (lunges, calf raises, standing forward raise and shrugs), with a focus on flexibility, lower limb muscle endurance and balance, followed by a 5-minute warm down walk. The intensity of the resistance exercises is mildly increased by progressively adding hand weights (to a maximum of 3 kg) and increasing repetitions.

#### 4.3.5 *Outcome measures*

Anthropometrics, whole body and regional measures of bone, muscle and fat, and functional performance measures have been performed at baseline and follow up by a single investigator.

Whole body (WB), non-dominant femoral neck (FN), and lumbar spine (LS) bone mineral density (BMD, g/cm<sup>3</sup>), fat and lean mass were obtained using dual-energy x-ray absorptiometry (Norland XR-800, Norland Medical Systems, Inc., Trumbull, CT, USA). Short-term measurement precision for WB, FN and LS DXA scans with repositioning from this device is 0.9%, 1.1% and 0.4%, respectively.

Physical performance was determined from both muscle strength testing and validated functional performance measures. Back extensor strength (BES) was measured isometrically in standing using a handheld dynamometer (Lafayette Manual Muscle Testing Systems, USA)[125]. Functional performance was measured using the standard protocols of the timed up-and-go test (TUGT) [240], five times sit-to-stand test (FTSTS) [122], and functional reach test (FRT) [85]. For all functional performance measures, the best performance of three attempts was used for analysis.

Participant safety and compliance is monitored via training diaries, with participants recording any injuries or illnesses, delayed onset muscle soreness (10-point

visual analogue scale), and any adverse events before every training session. CON participants are contacted either by telephone or email weekly to maintain investigator contact, maximise compliance and minimise attrition. One hundred percent compliance is deemed to be the completion of 70 sessions.

#### *4.3.6 Statistical analysis*

Statistical analysis was undertaken using SPSS version 22.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were generated for subject characteristics, biometrics, and all dependent measures. A per protocol analysis was adopted for this preliminary analysis with repeated measures ANOVA to test our hypotheses. All statistical analyses have been conducted using a *p*-value of 0.05 to determine statistical significance.

### **4.4 Results**

#### *4.4.1 Participant characteristics*

A total of 354 postmenopausal women have consented to participate in the LIFTMOR trial to date. Seventy-two individuals have met the inclusion criteria, completed baseline testing and been block randomised (based on medication status) to either HiRIT (n = 36) or CON (n = 36). Of those, 28 women have completed their active trial period and are included in these preliminary findings. The LS and FN T-scores of the women included in these preliminary findings have ranged from -0.6 to -3.31, with 13 and 15 women classified as osteoporotic and osteopenic respectively. The main reasons for participant exclusion are medical contraindications for exercise (n = 36), unable to attend training sessions (n = 28), currently conducting resistance or

impact training (n = 23), and not having osteopenia or osteoporosis (n = 10). There were no differences in baseline participant characteristics between the HiRIT and CON groups for anthropometric, body composition measures or physical performance (Table 6).

**Table 6:** Baseline participant characteristics (n = 28)

Parameter	HiRIT (n = 12)	CON (n = 16)	<i>p</i>
Age (years)	65.3 ± 3.9	66.7 ± 5.4	0.451
Weight (kg)	61.8 ± 8.9	63.4 ± 11.4	0.707
Height (cm)	163.4 ± 6.2	163.0 ± 5.5	0.879
BMI (kg/m <sup>2</sup> )	23.2 ± 3.4	23.8 ± 3.9	0.681
LS BMD (g/cm <sup>2</sup> )	0.784 ± 0.092	0.850 ± 0.091	0.074
LS T-score	-1.87 ± 0.68	-2.37 ± 0.69	0.073
FN BMD (g/cm <sup>2</sup> )	0.697 ± 0.082	0.684 ± 0.055	0.622
FN T-score	-2.01 ± 0.58	-2.11 ± 0.45	0.615
BES (kg)	26.6 ± 9.2	32.3 ± 8.1	0.154
TUGT (s)	6.04 ± 0.60	5.98 ± 0.67	0.784
FTSTS (s)	9.25 ± 1.00	10.10 ± 1.31	0.073
FRT (cm)	41.2 ± 5.5	42.2 ± 5.7	0.646

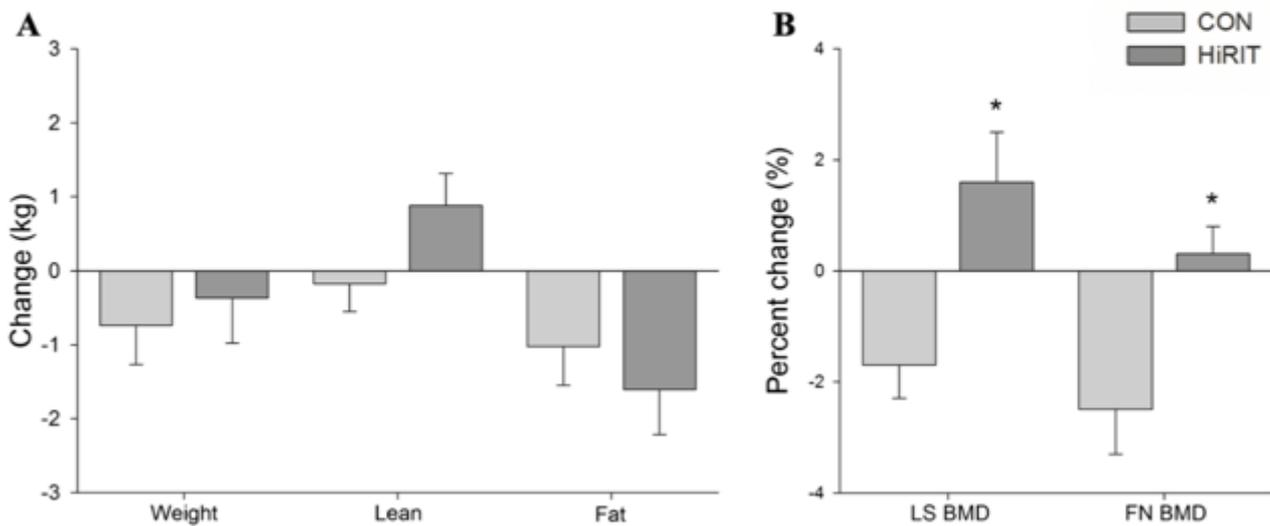
Abbreviations: *HiRIT* high-intensity resistance and impact training; *CON* control group; *BMI* body mass index; *LS* lumbar spine; *BMD* bone mineral density; *FN* femoral neck; *BES* back extensor strength; *TUGT* timed up-and-go test; *FTSTS* five times sit-to-stand; *FRT* functional reach test

#### 4.4.2 Anthropometrics

The HiRIT group have exhibited an increase in height ( $0.4 \pm 0.2$  cm vs  $-0.3 \pm 0.1$  cm,  $p = 0.003$ ) compared to a loss in CON. There were no significant between-group differences in BMI or weight (Figure 21A).

#### 4.4.3 BMD and body composition

The HiRIT group have improved FN BMD ( $0.3 \pm 0.5\%$  vs  $-2.5 \pm 0.8\%$ ,  $p = 0.016$ ) and LS BMD ( $1.6 \pm 0.9\%$  vs  $-1.7 \pm 0.6\%$ ,  $p = 0.005$ ) compared to losses in CON (Figure 21B). An improvement in lean mass in the HiRIT group and a loss in the CON group approached significance for the between group comparison ( $0.879 \pm 0.422$  kg vs  $-0.127 \pm 0.378$  kg,  $p = 0.094$ ) (Figure 21A). There was no between-group difference in change in fat mass ( $p = 0.475$ ) as both groups lost, however, a within group improvement reached significance for the HiRIT group ( $-1.608 \pm 0.666$ kg,  $p = 0.013$ ) (Figure 21A). There were no significant between-group differences in WB BMD between HiPRT/impacting loading and CON ( $-0.5 \pm 0.4\%$  vs  $-0.8 \pm 0.5\%$ ,  $p = 0.694$ ).



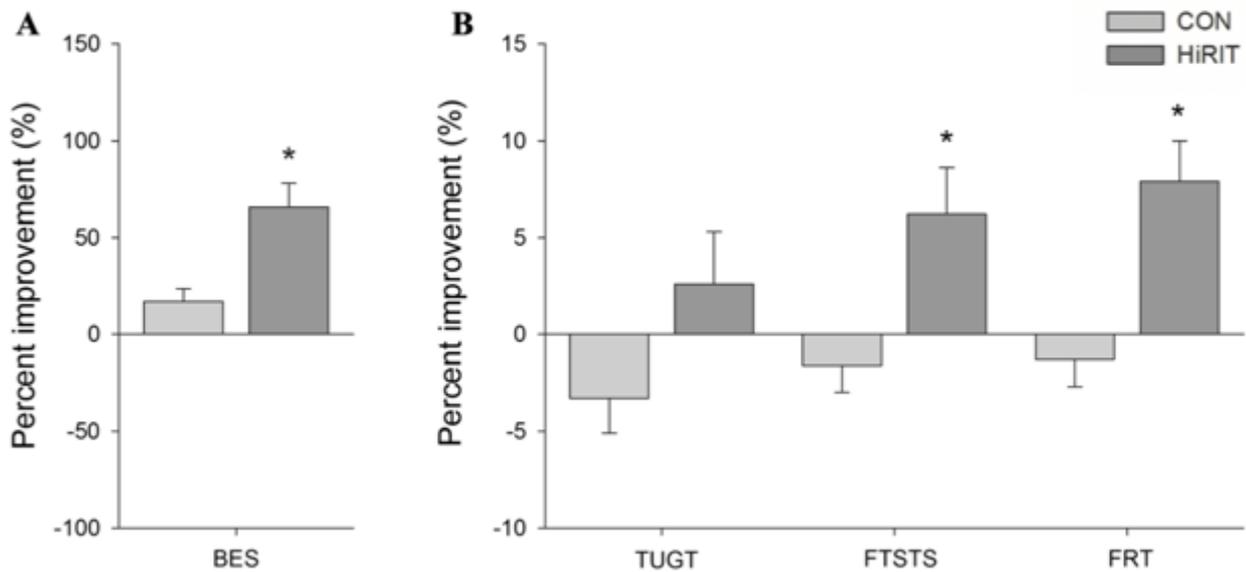
**Figure 21:** Change in (A) weight, lean mass, and fat mass and (B) FN and LS BMD for HiRIT and CON groups following an eight-month exercise intervention (n = 28)

Abbreviations: *FN* femoral neck; *LS* lumbar spine; *BMD* bone mineral density; *HiRIT* high-intensity resistance and impact training; *CON* control group.

\*  $p < 0.05$

#### 4.4.4 Physical performance

At follow-up, the HiRIT group exhibited substantial gains in BES; significantly greater than CON ( $65.7 \pm 12.2\%$  vs  $17.0 \pm 6.6\%$ ,  $p = 0.001$ ) (Figure 22A). FTSTS ( $6.2 \pm 2.4\%$  vs  $-1.6 \pm 1.4\%$ ,  $p = 0.007$ ) and FRT ( $7.9 \pm 2.1\%$  vs  $-1.3 \pm 1.4\%$ ,  $p = 0.001$ ) performance also improved in HiRIT, whereas the CON group declined in performance (Figure 22B). An improvement in TUGT in the HiRIT group and a loss in the CON group approached significance ( $2.6 \pm 2.7\%$  vs  $-3.3 \pm 1.8\%$ ,  $p = 0.07$ ).



**Figure 22:** Improvements in (A) back extensor strength, and (B) functional performance for HiRIT and CON groups following an eight-month exercise intervention ( $n = 28$ )

Abbreviations: *HiRIT* high-intensity resistance and impact training; *CON* control group; *BES* back extensor strength; *TUGT* timed up-and-go test; *FTSTS* five times sit-to-stand; *FRT* functional reach test

\*  $p < 0.05$

#### 4.4.5 Safety and compliance

No adverse events have been recorded as a result of either the HiRIT group or CON exercise programs. One participant in the HiRIT group missed a total of four sessions due to an injury unrelated to the training program. Of the 72 participants who have completed baseline testing, four participants (2 HiRIT, 2 CON) have withdrawn

their participation as a result of unrelated illness ( $n = 2$ ), inability to attend exercise sessions ( $n = 1$ ), or family reasons ( $n = 1$ ). Compliance has been high for both the HiRIT and CON programs, with no significant between-group difference ( $87.2 \pm 3.9\%$  vs  $92.7 \pm 3.8\%$ , respectively;  $p = 0.330$ )

#### **4.5 Discussion**

The aim of the LIFTMOR trial is to determine the safety and efficacy of an eight-month, brief, bone-targeted HiRIT exercise program for postmenopausal women with low to very low bone mass for BMD, lean and fat mass and physical function. Early findings clearly indicate that HiRIT is not only safe, but sufficient to improve bone mass, and to markedly improve physical function in this cohort. A highly novel observation is the net benefit of 0.7 cm in height in the HiRIT group which reflects an evident reduction in kyphosis and resultant increased stature [26].

The traditionally perceived increased risk of fracture from HiRIT for individuals with osteoporosis has prevented its application for the management of the condition. Some prior evidence has been reported that HiRIT can be implemented safely in this population [214]. A 12-week intervention of squat machine exercises, three times per week, at high intensity (4 sets, 3-5 repetitions,  $>85\%$  1RM) in postmenopausal women with low bone mass incurred no adverse events with a high compliance rate of 87%. In the current study, we have similarly observed no adverse events and have experienced the identical compliance rate of 87%, lending further support that the perceived safety concern is not justified when HiRIT is performed in a supervised and controlled environment.

Numerous studies have demonstrated that progressive resistance training can improve lean and fat mass in postmenopausal women [42, 191, 218]. The relationship is less clear for indices of bone strength, with a number of moderate-intensity progressive resistance training interventions (8-12 repetitions at 67-80% 1RM) showing only modest benefits for bone [42, 191, 218, 314]. In light of what is known about the optimal adaptive stimulus for bone it is possible to speculate that those modest improvements in BMD were a result of inadequate load intensity. The study that applied a high-intensity training stimulus is not instructive as twelve weeks of exercise is insufficient to observe changes in bone. Our findings then are the first to show a less conservative approach to exercise therapy, such as the LIFTMOR protocol is both safe and efficacious for enhancing indices of bone strength and fracture risk for postmenopausal women at increased risk of low trauma fracture. Furthermore, the benefits were achieved with only two 30-minute training sessions per week, suggesting the LIFTMOR program is a highly efficient training approach that could easily be added to an existing exercise regime for other body systems (e.g. cardiovascular fitness).

Increased back extensor strength has been associated with a reduced risk of vertebral fractures [277] and decreased thoracic kyphosis [139]. The marked improvements in BES in the HiRIT group coincide with a net benefit in stature of 7 mm for the HiRIT compared to CON. Equally, HiRIT invoked benefits in physical performance, with significant improvements observed in most functional tests compared with CON. Together, enhanced bone, lean and fat mass, physical function and posture are likely to reduce risk of osteoporotic fracture and enhance quality of life in this demographic.

We acknowledge the preliminary nature of our findings, but note the strength of the data is reflected in the early observation of strong statistical significance of treatment effects. Secondly, we recognise it will be important to account for confounding factors such as prior or concurrent physical activity and calcium consumption. Those data have been collected and will be controlled in the final analysis. Finally, our findings are applicable only to generally healthy postmenopausal women with low to very low bone mass. Another trial is under way to examine the effect of HiRIT in older men with low bone mass.

In summary, a novel, eight-month, twice-weekly, 30-minute supervised HiRIT program was safe and efficacious for bone, lean, fat, physical function and stature in postmenopausal women with low to very low bone mass. Despite a common perception of increased risk of HiRIT in people with osteoporosis, the LIFTMOR intervention has induced no adverse events. Although preliminary, findings suggest that the use of HiRIT is a very time efficient, safe and effective therapeutic option for postmenopausal women with low to very low bone mass.



## Chapter 5: Publication Two

**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**

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**Statement of contribution to co-authored published paper**

For this co-authored manuscript, the candidate conceived and designed the experiment in consultation with co-authors, recruited participants, performed data acquisition, implemented the intervention, analysed the data, interpreted results, and prepared the manuscript.

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Steven Watson | *Candidate*

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Professor Belinda Beck | *Principal supervisor and corresponding author*

## 5.1 Abstract

Optimal osteogenic mechanical loading requires the application of high-magnitude strains at high rates. High intensity resistance and impact training (HiRIT) applies such loads, but is not traditionally recommended for individuals with osteoporosis owing to a perceived high risk of fracture. The purpose of the LIFTMOR trial was to determine the efficacy and to monitor adverse events of HiRIT to reduce parameters of risk for fracture in postmenopausal women with low bone mass. Postmenopausal women with low bone mass (T-score < -1.0, screened for conditions and medications that influence bone and physical function) were recruited and randomized to either 8 months of twice-weekly, 30-minute, supervised HiRIT (5 sets of 5 repetitions, > 85% 1 repetition maximum) or a home-based, low intensity exercise program (CON). Pre and post intervention testing included lumbar spine and proximal femur BMD and measures of functional performance (timed up-and-go, functional reach, 5 times sit-to-stand, back and leg strength). One hundred and one women ( $65 \pm 5$  years,  $161.8 \pm 5.9$  cm,  $63.1 \pm 10.4$  kg) participated in the trial. HiRIT ( $n = 49$ ) effects were superior to CON ( $n = 52$ ) for LS BMD ( $2.9 \pm 2.8\%$  vs  $-1.2 \pm 2.8\%$ ,  $p < 0.001$ ), FN BMD ( $0.3 \pm 2.6\%$  vs  $-1.9 \pm 2.6\%$ ,  $p = 0.004$ ), FN cortical thickness ( $13.6 \pm 16.6\%$  vs  $6.3 \pm 16.6\%$ ,  $p = 0.014$ ), height ( $0.2 \pm 0.5$  cm vs  $-0.2 \pm 0.5$  cm,  $p = 0.004$ ) and all functional performance measures ( $p < 0.001$ ). Compliance was high (HiRIT  $92 \pm 11\%$ ; CON  $85 \pm 24\%$ ) in both groups, with only one adverse event reported (HiRIT: minor lower back spasm, 2/70 missed training sessions). Our novel, brief HiRIT programme enhances indices of bone strength and functional performance in postmenopausal women with low bone mass. Contrary to current opinion, HiRIT was efficacious and

induced no adverse events under highly supervised conditions for our sample of otherwise healthy postmenopausal women with low to very low bone mass.

## 5.2 Introduction

Exercise has been proposed as a potential strategy to manage osteoporosis [136], however, the magnitude of benefit of exercise intervention is traditionally perceived as modest at best [100, 136, 335]. It is known that bone responds preferentially to mechanical loads that induce high magnitude strains [258] at high rates [228] or frequencies [259] and that weight bearing loading is vital [177]. High intensity, progressive resistance and impact weight bearing training (HiRIT) can be employed to generate such loads, but have not been routinely prescribed by healthcare professionals in the absence of evidence to support its efficacy and safety. Instead, osteoporosis exercise guidelines typically recommend only moderate intensity exercises (70% - 80% 1 repetition maximum [RM], 8 - 15 repetitions) for individual muscle groups that are unlikely to generate the requisite skeletal strain to stimulate an osteogenic response [106]. It is therefore unsurprising that previous exercise programs have produced modest, if any, improvements in indices of bone strength [335].

By contrast, large multi-joint compound exercises such as the squat and deadlift that are conducted in weight bearing positions and involve extensive muscle recruitment have the potential to apply large loads at clinically-relevant bone sites such as the spine and hip [58, 116]. Few studies have investigated the effects of heavy lifting programs or large multi-joint compound movements on osteoporosis. A small 12-week intervention of high intensity (85% - 90% 1 repetition maximum) machine-based squats for postmenopausal women with low bone mass was found to be safe, but did not enhance

bone mineral density at the femoral neck (FN) or lumbar spine (LS) [214]. This finding must be interpreted with caution however, in light of the inadequate duration of the trial to detect changes in bone mass, as well as the very small sample size. A 12-month study of squats and deadlifts at moderate intensity modified LS and FN BMD by 0.4% and -1.2%, respectively in early postmenopausal women [191]. Thus a knowledge gap of whether an adequate duration program of high intensity weight bearing loading is efficacious and safe for the bones of people with osteoporosis remained.

The primary aim of the Lifting Intervention For Training Muscle and Osteoporosis Rehabilitation (LIFTMOR) trial was to determine the efficacy of brief, bone-targeted HiRIT for improving FN and LS BMD in postmenopausal women with low to very low bone mass. The secondary aims were to determine if HiRIT improves bone geometry, improves physical function and is safe in postmenopausal women with low bone mass. We hypothesized that (1) HiRIT training would induce greater improvements in bone and physical function than a low intensity exercise control program, and (2) HiRIT would not cause more injuries than a low intensity exercise control program for postmenopausal women with low to very low bone mass.

### **5.3 Materials and methods**

#### *5.3.1 Study design*

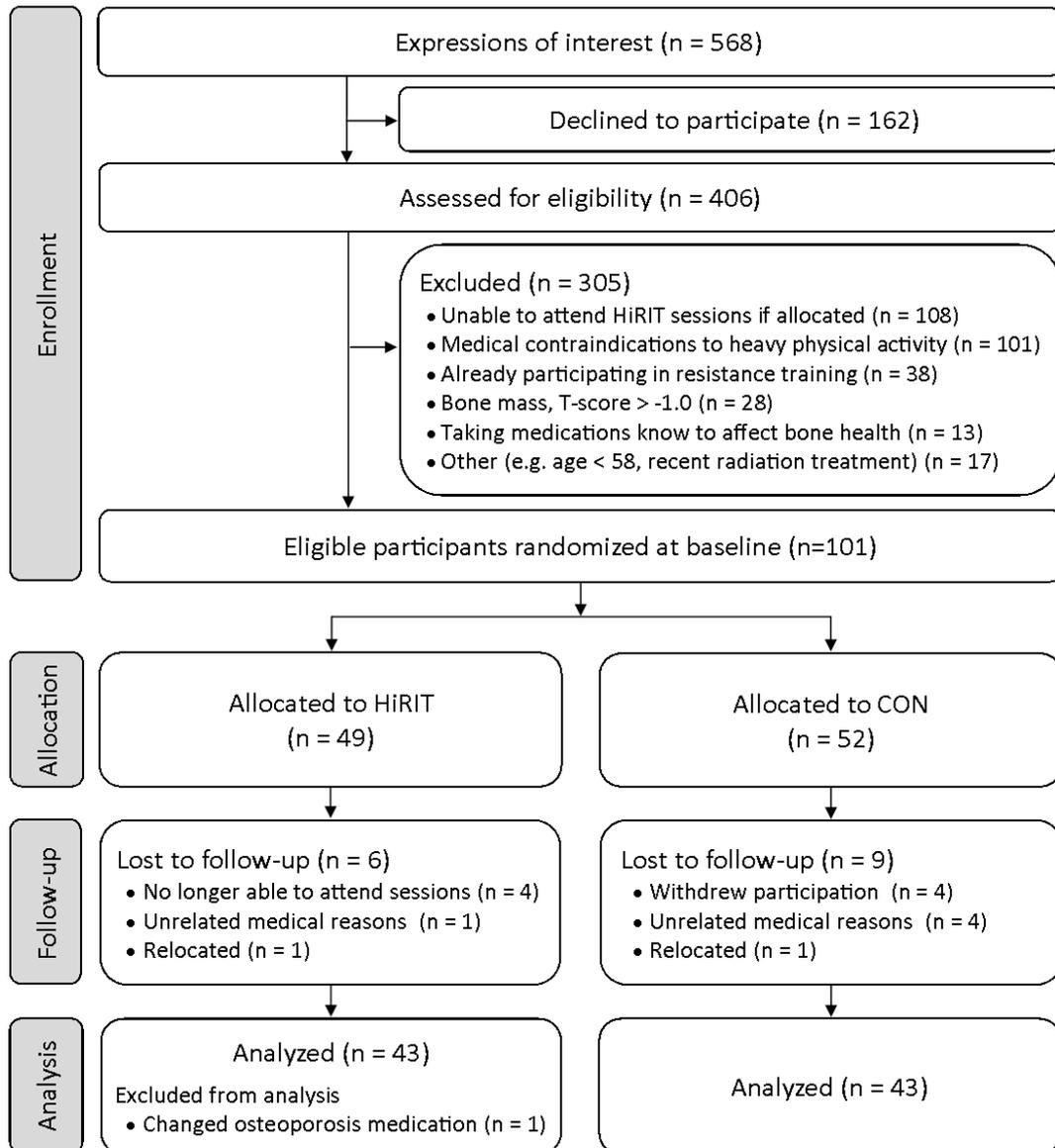
The LIFTMOR study was a single-blind, randomized, controlled, exercise intervention trial. Eligible participants were stratified randomized to 8 months of 30 minutes, twice-weekly, supervised HiRIT, or unsupervised low-intensity home-based exercise (CON), with an allocation ratio of 1:1 (Figure 23). The 8-month trial period was selected as the requisite duration for bone adaptation and mineralization to be

sufficiently detectable on DXA. While the duration of a bone remodelling cycle is approximately 4 months, there is a degree of lag before new bone can be detected radiologically as the osteoid mineralises [71]. Although BMD changes have previously been observed from DXA after only 6 months of intense physical intervention [91], we chose to extend the intervention period a further 2 months to maximize the opportunity to detect a treatment effect in our primary BMD outcome measures. Stratified randomisation was based on existence or absence of established (12 months exposure or lack of exposure) osteoporosis medication. At the completion of baseline testing, participants were stratified randomized, based on current presence or absence of osteoporotic medication, utilizing sequentially numbered opaque envelopes. The randomization sequence was produced by an external investigator via a random number generator (Microsoft Excel, Microsoft, Redmond, WA, USA) to generate either a 0 or 1, corresponding with CON or HiRIT respectively. Once a potential participant was deemed eligible for participation, random group allocation was performed by a study investigator (SW) asking the participant to open the next sequentially numbered opaque envelope stratified on osteoporosis medication use. The trial was registered on the Australian and New Zealand Clinical Trials Registry ([anzctr.org.au](http://anzctr.org.au); CTR number: ACTRN12616000475448) and ethical approval was granted by the Griffith University Human Research Ethics Committee (Approval number: AHS/07/14/HREC). Following trial registration, a minor change was made to the inclusion criteria with the minimum age of eligibility reduced to 58 years from the originally stipulated '60 years of age'. The current manuscript reports a subset of data collected in the LIFTMOR trial. Remaining data is to be published in a subsequent manuscript. A full list of primary and

secondary outcomes can be found at the Australian and New Zealand Clinical Trials Registry. Written informed consent was obtained from every study participant.

### 5.3.2 *Participants*

Postmenopausal women over 58 years of age with low bone mass (T-score < -1.0 at the hip and/or spine) were recruited from the community via posters, radio, newspaper, television and word-of-mouth from May 2014 to November 2015 and all had completed the intervention by August 2016. Potential participants were screened for eligibility, and excluded if they had any of the following: lower limb joint injury or surgery; recent fracture (within the last 12 months) or localized back pain; less than five years post menopause; malignancy; uncontrolled cardiovascular disease; cognitive impairment; recent x-ray or radiation treatment; contraindications for participating in heavy physical activity; conditions known to influence bone health (e.g. thyrotoxicosis or hyperparathyroidism, Paget's disease, renal disease, diabetes, or immobility); taking drugs (other than osteoporosis medications) known to influence bone (e.g. prolonged use of corticosteroids, thyroxine, thiazides or antiretroviral agents), or unable to attend the supervised training program if so assigned (Figure 23).



**Figure 23:** CONSORT diagram of participant flow (n = 101)

### 5.3.3 *Intervention exercise program*

Participants allocated to the intervention group participated in an 8-month, twice weekly, 30 minute, supervised HiRIT program at Griffith University, Gold Coast, Australia or The Bone Clinic, Brisbane, Australia. To ensure safe transition to high intensity exercise, the first month of the intervention comprised bodyweight and low-load exercise variants, with a focus on progressively learning the movement patterns of the HiRIT exercises. All participants were able to perform the 4 fundamental exercises of the intervention within 2 months. Resistance exercises (deadlift, overhead press and back squat) were performed for the remainder of the intervention period in 5 sets of 5 repetitions, maintaining an intensity of > 80-85% 1 RM. Participants performed up to 2 sets of deadlifts at 50-70% of 1RM to serve as a warm up, as required. Impact loading was applied via jumping chin ups with drop landings. Participants were instructed to grasp an overhead bar with their shoulders and elbows flexed to 90 degrees, and their hands shoulder width apart with an underhand grip. The participant then jumped as high as possible while simultaneously pulling themselves as high as possible with their arms. At the peak of the jump, the participant dropped to the floor, focussing on landing as heavily as comfortably possible. Each exercise session was performed in small groups with a maximum of 8 participants per instructor, who was an exercise scientist and physiotherapist.

### 5.3.4 *Control exercise program*

The goal of a positive control group (CON) was to maximize participant retention. Participants allocated to CON undertook an 8-month, twice weekly, 30 minute, home-based, low intensity (10-15 repetitions at < 60% 1RM) exercise program

designed to improve balance and mobility but provide minimal stimulus to bone. The CON program consisted of walking for warm up (10 minutes) and cool down (5 minutes), low load resistance training (lunges, calf raises, standing forward raise, and shrugs) and stretches (side to side neck stretch, static calf stretch, shoulder stretch, and side to side lumbar spine stretch). The intensity of resistance exercises was progressed from bodyweight to a maximum of 3 kg hand weights for the final month of the program.

#### 5.3.5 *Data collection*

Participants were required to attend a two-hour testing session at the Griffith University Gold Coast campus at baseline (T0) and follow-up (T8). Outcomes included anthropometrics, regional measures of bone, dietary calcium, physical activity, and functional performance. All measures were performed by a single unblinded investigator, however, to limit observer-expectancy bias, BMD outcome measures were verified by a blinded investigator.

#### 5.3.6 *Anthropometrics*

Height and body mass were measured using a wall-mounted stadiometer (Seca 216, Ecomed Trading Pty Ltd, Seven Hills, Australia), and mechanical balance scales (Seca 700, Ecomed Trading Pty Ltd, Seven Hills, Australia), respectively. Body mass index (BMI) was calculated per the accepted formula ( $BMI = \text{weight}/\text{height}^2$ , kg/m<sup>2</sup>).

### 5.3.7 *Lifestyle characteristics*

Bone-relevant lifetime (tBPAQ) and current (cBPAQ) physical activity participation scores were derived from the Bone-Specific Physical Activity Questionnaire (BPAQ) [324], using a custom-designed Microsoft Visual Basic executable program ([www.fithdysign.com/BPAQ/](http://www.fithdysign.com/BPAQ/)). Participants were instructed to record all physical activity undertaken during their lifetime (for a season or more on a weekly basis), and all activities engaged in over the past 12 months, to determine tBPAQ and cBPAQ respectively.

Daily calcium intake was estimated using an Australian calcium-specific questionnaire (AusCal) [30]. Participants recorded consumption frequency and serving size of common calcium-containing foods and supplements, and data were analysed using recognised dietary software (Foodworks 2007 Version 7, Xyris, Brisbane, Australia) to determine average daily calcium intake in milligrams.

### 5.3.8 *Bone measures*

Skeletally non-dominant FN and LS BMD ( $\text{g}/\text{cm}^2$ ) were obtained using dual-energy x-ray absorptiometry (DXA). During the trial period a change in DXA model was necessary, such that, the first 50 participants (Norland XR-800, Norland Medical Systems, Inc., Trumbull, CT, USA) and the final 51 (Medix DR, Medilink, France) were measured on different devices. Each individual participant, however, was measured on the same DXA at baseline and follow-up. Short-term measurement reliability for FN and LS DXA scans was 1.1% and 0.4%, and 1.7% and 1.0% for the Norland and Medix DR devices, respectively.

Non-dominant proximal femur DXA scans for the final 51 participants (HiRIT,  $n = 25$ ; CON  $n = 26$ ), that were conducted on the Medix DR, were additionally analysed using 3D Hip software (DMS Group, France), to derive FN trabecular and cortical volume, trabecular and cortical BMC, trabecular and cortical volumetric BMD, and FN cortical thickness. 3D parameters were determined according to manufacturer guidelines. Markers were placed on the standard 2D image using the cursor at the distal edge of the lesser trochanter and the superior and inferior junctions of the FN and head of the femur. The 3D Hip software then automatically reconstructed the femur based on both shape and BMD distribution of the standard 2D image. Reconstructions were performed by comparing individual 2D DXA scans to a reference set of proximal QCT scans for similarities to determine the reference scan of best fit. Once a reference scan was identified, the surface mesh of the reference scan was transformed to maximize similarities to the 2D DXA image. Finally, 2D BMD was transformed to match the shape model based on bone surface points to maintain BMD spacial distribution [326].

Quantitative ultrasound (QUS) (Lunar Achilles TM Insight, GE) was used to assess both skeletally dominant and non-dominant heels, to obtain calcaneal broadband ultrasound attenuation (BUA) (db/MHz), speed of sound (SOS) (m/s) and stiffness index (SI) (unitless).

### 5.3.9 *Physical performance*

Physical performance was determined from functional, muscle strength and neuromuscular performance measures. All were performed in the same sequence at T0 and T8, and by the same investigator, with standardised instructions, to maximize uniformity between participants. Maximal isometric muscle force was determined for

both lower limb and back extensor muscles. Lower limb extensor strength (LES) was determined using an isometric dynamometer (TTM Muscular Meter, Tokyo, Japan) [268]. Back extensor strength (BES) was measured using the Manual Muscle Testing System dynamometer (Lafayette, Indiana, USA) [318]. Three trials were performed for both strength tests, and the highest force in kg across the 3 trials was used for analysis. Functional performance was determined using the timed up-and-go test (TUGT) [240], 5 times sit-to-stand test (FTSTS) [122], and functional reach test (FRT) [85]. Three trials were performed for each functional performance test, with the best performance used for analysis.

Lower limb neuromuscular performance was determined from the maximal vertical jump test on a force plate (AMTI, Watertown, MA). Ground reaction forces were captured at 1000 Hz using Vicon Nexus software version 1.8 (Vicon, Oxford Metrics, Oxford, UK). The participant performed 4 maximal vertical jump trials without arm swing, with a 30-second rest interval between trials as previously described [318]. Vertical ground reaction forces were analysed from the point of stationary standing to the point of landing to determine impulse using custom-written software in Matlab version 7.8.0 (The MathWorks, Natick, MA, USA). All impulse measures were normalized to body mass and expressed as relative impulse (N·s/kg). The trial with the greatest relative impulse was used for analysis.

#### *5.3.10 Safety and compliance*

Participant safety and compliance was determined at training sessions and from individual training diaries. One-hundred percent compliance was deemed to be the completion of 70 sessions over a period of 8 calendar months. Before each HiRIT

exercise session, participants were asked to record any injuries, falls, changes to their diet, medications, wellbeing or physical activity participation, and to rate their muscle soreness (ten-point visual analogue scale). Investigators contacted CON participants weekly, either by telephone or email, to obtain the same information and to remind participants to complete their training diaries.

### 5.3.11 Statistical analysis

Statistical analysis was undertaken using SPSS statistical software (Version 22; IBM Inc., Chicago, IL). Descriptive statistics were generated for participant characteristics, biometrics, and all dependent variables. Both per protocol and intention to treat (mean values imputed) analyses were conducted. One-way ANOVA was used to examine differences between HiRIT and CON at baseline, while repeated measures ANCOVA was used to determine main effects for dependent variables. Initial values, age and compliance were applied as covariates for all analyses, with the addition of physical activity participation and dietary calcium as covariates for bone analyses. All statistical outcomes were examined against a *p*-value of 0.05 to determine statistical significance. To adjust for multiple comparisons, Fisher's LSD method was applied.

An *a priori* sample size calculation was conducted based on effect size data reported in a similar machine based HiRIT (80% 1RM) trial of postmenopausal women [218]. One-hundred participants were required to achieve a minimum of 80% statistical power to detect between-group differences of  $2.7 \pm 4.5\%$  for FN BMD and  $3.5 \pm 3.6\%$  for LS BMD, accounting for a dropout rate of 20%.

## 5.4 Results

### 5.4.1 Participant characteristics at baseline

A total of 406 postmenopausal women consented to participate in the LIFTMOR trial, of whom 101 met the inclusion criteria, completed initial testing and were randomized to either HiRIT ( $n = 49$ ) or CON ( $n = 52$ ). The LS and FN T-scores of the participants included in the trial ranged from 0.0 to -3.9, with 44 (43.6%) (CON 21, HiRIT 23) participants being classified as osteoporotic and the remaining 57 being osteopenic at one or other of the sites. Twenty-seven participants (28%) reported an osteoporotic fracture within the last 10 years, 11 (41%) of which were a consequence of a fall. Participant 5 year risk of hip or other osteoporotic fracture was  $4 \pm 6\%$  and  $8 \pm 10\%$  respectively, and  $12 \pm 8.4\%$  and  $23 \pm 14\%$  for 10 year fracture risk, from the Garvan fracture risk calculator (<https://www.garvan.org.au/promotions/bone-fracture-risk/calculator/>). Of those excluded, the common reasons were: unable to attend session locations or times ( $n = 108$ ), medical contraindications to heavy physical training ( $n = 101$ ) (which included current musculoskeletal injury/condition [ $n = 63$ ], uncontrolled cardiovascular disease [ $n = 11$ ], undergoing treatment for cancer [ $n = 10$ ], neurological condition that limited exercise capacity or exposed the individual to risk of injury [ $n = 6$ ], ongoing surgical management for chronic medical condition [ $n = 5$ ] and undisclosed medical reasons [ $n = 6$ ]), and already undertaking resistance training ( $n = 38$ ) (Figure 23). CON ( $n = 10$ ) and HiPRT ( $n = 10$ ) had similar distribution of participants on osteoporosis medication. The only significant between-group difference at baseline was for the TUGT, on which HiRIT performed more slowly (Table 7).

**Table 7:** Baseline participant characteristics (n = 101)

Parameter	CON (n = 52)	HiRIT (n = 49)	p
Age (years)	65 ± 5	65 ± 5	0.993
Weight (kg)	62.2 ± 9.5	63.9 ± 11.3	0.415
Height (cm)	161.9 ± 6.4	161.6 ± 5.4	0.810
BMI (kg/m <sup>2</sup> )	23.7 ± 3.2	24.5 ± 4.6	0.302
Osteoporosis medication			
<i>Bisphosphonate</i>	5	6	
<i>Denosumab</i>	3	4	
<i>HT</i>	2	0	
LS BMD (g/cm <sup>3</sup> )	0.820 ± 0.107	0.821 ± 0.106	0.950
LS T-score	-2.1 ± 0.8	-2.1 ± 0.8	0.914
FN BMD (g/cm <sup>3</sup> )	0.681 ± 0.62	0.698 ± 0.082	0.258
FN T-score	-2.1 ± 0.5	-1.9 ± 0.7	0.208
BUA (dB/MHz)	97.1 ± 11.3	100.5 ± 19.1	0.268
SOS (m/s)	1536.0 ± 26.6	1538.6 ± 25.6	0.606
SI	74.8 ± 13.3	76.2 ± 12.9	0.590
BES (kg)	32.2 ± 9.5	31.6 ± 11.1	0.784
LES (kg)	60.3 ± 14.7	60.3 ± 17.6	1.000
TUGT (sec)	5.9 ± 0.6	6.3 ± 0.7	0.008*
FTSTS (sec)	9.9 ± 1.5	9.9 ± 1.2	0.939
FRT (cm)	41.1 ± 4.7	40.0 ± 5.9	0.291
Vertical jump (N·s/kg)	1.30 ± 0.32	1.28 ± 0.25	0.228
tBPAQ	16.5 ± 17.5	12.4 ± 11.3	0.172
cBPAQ	0.74 ± 1.24	0.71 ± 1.24	0.907
Dietary calcium (mg)	1006 ± 596	892 ± 457	0.286

Abbreviations: BMI = body mass index; HT = hormone therapy; LS = lumbar spine; BMD = bone mineral density; FN = femoral neck; BUA = Broadband ultrasound attenuation; SI = stiffness index; SOS = speed of sound; LES = leg extensor strength; BES = back extensor strength; TUGT = timed up-and-go test; FTSTS = five times sit-to-stand; FRT = functional reach test; cBPAQ = current bone-specific physical activity questionnaire score; tBPAQ = total bone-specific physical activity questionnaire score.

\* indicates between-group difference ( $p < 0.05$ )

#### 5.4.2 *Eight-month change in anthropometrics and lifestyle characteristics*

The HiRIT group exhibited an increase in height ( $0.2 \pm 0.5$  cm vs  $-0.2 \pm 0.5$  cm,  $p = 0.004$ ; 95% CI 0.0 to 0.3% vs. 0 to -0.3%) compared to the CON group (ITT).

Similar to the ITT analyses, per protocol analyses indicated preferential improvements in height for HiRIT compared to CON (Table 8). There were no significant between-group differences in change for weight, cBPAQ, or daily calcium intake.

**Table 8:** Baseline and eight-month measures ( $\pm$  SD) with adjusted change in anthropometrics and lifestyle characteristics following an eight-month exercise intervention in postmenopausal women with low bone mass (per protocol data,  $n = 86$ )

Parameter	CON ( $n = 43$ )			HiRIT ( $n = 43$ )			$p$
	Baseline	Follow-up	Change	Baseline	Follow-up	Change	
Weight (kg)	62.4 $\pm$ 9.2	62.2 $\pm$ 9.4	0.0 $\pm$ 2.3	63.5 $\pm$ 10.0	63.5 $\pm$ 10.1	-0.1 $\pm$ 2.2	0.860
Height (cm)	162.0 $\pm$ 6.0	161.8 $\pm$ 6.0	-0.2 $\pm$ 0.6	161.4 $\pm$ 5.5	161.6 $\pm$ 5.5 <sup>†</sup>	0.2 $\pm$ 0.6	0.006*
BMI (kg/m <sup>2</sup> )	23.7 $\pm$ 3.1	23.7 $\pm$ 3.0	-0.0 $\pm$ 0.9	24.5 $\pm$ 4.4	24.4 $\pm$ 4.3	-0.1 $\pm$ 0.9	0.863
cBPAQ	0.61 $\pm$ 0.97	0.62 $\pm$ 1.0	0.01 $\pm$ 0.51	0.61 $\pm$ 0.75	0.54 $\pm$ 0.80	-0.08 $\pm$ 0.85	0.579
Daily calcium intake (mg)	1026 $\pm$ 636	972 $\pm$ 615	-53 $\pm$ 369	972 $\pm$ 615	897 $\pm$ 438	-10 $\pm$ 282	0.364

Abbreviations: BMI = body mass index; cBPAQ = current bone-specific physical activity questionnaire score.

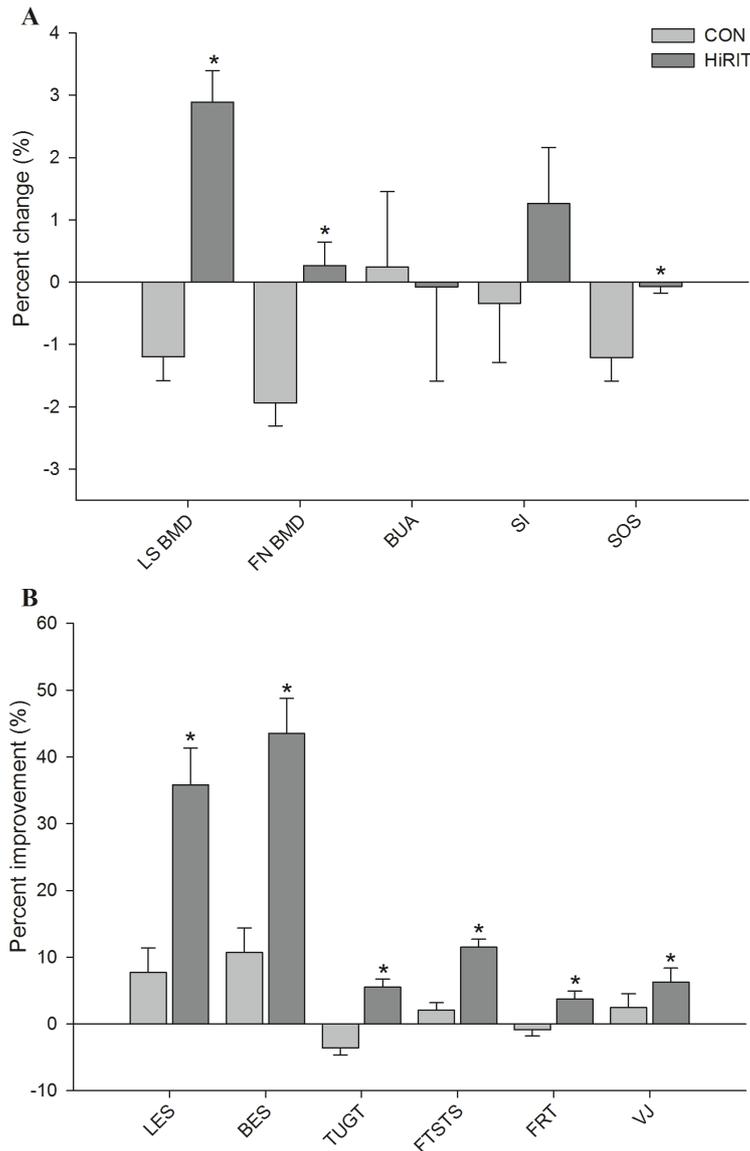
\* indicates between-group difference based on adjusted percent change ( $p < 0.05$ )

† indicates within-group difference ( $p < 0.05$ )

### 5.4.3 Eight-month change in body composition

Eight-month change in body composition is presented in Table 9 (per protocol). Percent change in LS BMD ranged from -3.4 to 12.4% for HiRIT, with only 8/43 (18.6%) participants having a reduction in LS BMD at follow up compared to -6.9 to 5.8%, and 31/43 (72.1%) of participants having a reduction in LS BMD for in CON. Participants in the HiRIT group exhibited FN BMD percent changes ranging from -6.0 to +6.8%, with 15/52 (28.8%) experiencing a reduction at follow up compared to -8.5 to 3.9%, and 27/43 (62.8%) of participants having a reduction in FN BMD for CON. Unadjusted ITT analyses produced similar findings, with the HiRIT effect being superior to CON for LS BMD ( $2.9 \pm 3.0\%$  vs  $-1.2 \pm 2.3\%$ ,  $p < 0.001$ ; 95% CI 2.1 to 3.6% vs. -1.9 to -0.4%) and FN BMD ( $0.1 \pm 2.7\%$  vs  $-1.8 \pm 2.6\%$ ,  $p = 0.001$ ; 95% CI -0.7 to 0.8% vs. -2.5 to -1.0%), with non-significant change in QUS SOS ( $0.3 \pm 1.0\%$  vs  $0.2 \pm 1.1\%$ ,  $p = 0.951$ ; 95% CI -0.0 to 0.6% vs. -0.1 to -0.5%). When adjusting for covariates, QUS SOS was significantly higher for HiRIT than CON ( $0.3 \pm 1.0\%$  vs  $0.2 \pm 1.0\%$ ,  $p = 0.009$ ; 95% CI 0.0 to 0.6% vs. -0.1 to -0.5%). Similar to the unadjusted, HiRIT effect was superior to CON for LS BMD ( $2.9 \pm 2.8\%$  vs  $-1.2 \pm 2.8\%$ ,  $p < 0.001$ ; 95% CI 2.1 to 3.7% vs. -1.9 to -0.4%), and FN BMD ( $0.3 \pm 2.6\%$  vs  $-1.9 \pm 2.6\%$ ,  $p = 0.004$ ; 95% CI -0.5 to 1.0% vs. -2.7 to -1.2%). There were no significant between-group differences in change between HiRIT and CON for QUS stiffness index or BUA (Figure 24A), or based on the use of osteoporosis medication for either LS or FN BMD. Subgroup analyses were undertaken to determine differences in response between those on and off osteoporosis medication. No between-group differences were observed between participants taking or not taking osteoporosis medications for either LS (CON:  $-0.2 \pm 3.4\%$  vs  $-1.4 \pm 2.2\%$ ,  $p = 0.192$ ; HiRIT:  $2.4 \pm 3.1\%$  vs  $3.0 \pm 3.4\%$ ,  $p = 0.631$ )

or FN BMD (CON:  $-1.9 \pm 3.4\%$  vs  $-1.7 \pm 2.8\%$ ,  $p = 0.835$ ; HiRIT:  $1.5 \pm 2.2\%$  vs  $-0.3 \pm 3.0\%$ ,  $p = 0.119$ ) in either the CON or HiRIT groups.



**Figure 24:** Eight-month change ( $\pm$  SEM) in A) bone and B) physical performance for HiRIT and CON following an eight-month exercise intervention in postmenopausal women with low bone mass ( $n = 101$ ).

Abbreviations: LS = lumbar spine; BMD = bone mineral density; FN = femoral neck; BUA = Broadband ultrasound attenuation; SI = stiffness index; SOS = speed of sound; LES = leg extensor strength; BES = back extensor strength; TUGT = timed up-and-go test; FTSTS = five times sit-to-stand; FRT = functional reach test; VJ = vertical jump.

\* indicates between-group difference ( $p < 0.05$ )

**Table 9:** Baseline and eight-month measures ( $\pm$  SD) with adjusted percent change in DXA and QUS-derived measures of body composition following an eight-month exercise intervention in postmenopausal women with low bone mass (per protocol data,  $n = 86$ )

Parameter	CON ( $n = 43$ )			HiRIT ( $n = 43$ )			$p$
	Baseline	Follow-up	% change	Baseline	Follow-up	% change	
LS BMD ( $\text{g}/\text{cm}^2$ )	$0.816 \pm 0.097$	$0.807 \pm 0.098^\dagger$	$-1.2 \pm 3.1$	$0.823 \pm 0.108$	$0.846 \pm 0.116^\dagger$	$2.9 \pm 3.1$	$<0.001^*$
FN BMD ( $\text{g}/\text{cm}^2$ )	$0.682 \pm 0.059$	$0.670 \pm 0.059^\dagger$	$-2.0 \pm 3.0$	$0.699 \pm 0.086$	$0.700 \pm 0.084$	$0.3 \pm 3.0$	$0.025^*$
BUA ( $\text{dB}/\text{MHz}$ )	$97.7 \pm 11.8$	$98.4 \pm 11.3$	$0.8 \pm 7.6$	$98.0 \pm 10.6$	$99.0 \pm 13.2$	$1.0 \pm 7.6$	$0.534$
SI	$74.9 \pm 13.5$	$76.1 \pm 12.5$	$2.0 \pm 6.8$	$75.7 \pm 12.7$	$77.7 \pm 13.6$	$2.7 \pm 6.8$	$0.200$
SOS ( $\text{m}/\text{s}$ )	$1535 \pm 26$	$1538 \pm 28$	$0.2 \pm 1.1$	$1538 \pm 25$	$1542 \pm 27.5$	$0.3 \pm 1.1$	$0.006^*$

Abbreviations: LS = lumbar spine; BMD = bone mineral density; FN = femoral neck; WB = whole body; BUA = Broadband ultrasound attenuation; SI = stiffness index; SOS = speed of sound.

\* indicates between-group difference based on adjusted percent change ( $p < 0.05$ )

† indicates within-group difference ( $p < 0.05$ )

Eight-month change in proximal hip geometry parameters are presented in Table 10. The HiRIT group was superior to CON for FN cortical BMC ( $7.7 \pm 21.3\%$  vs  $6.2 \pm 21.3\%$ ,  $p = 0.028$ ; 95% CI -1.7 to 17.0% vs. -2.6 to 15.2%) and FN cortical thickness ( $13.6 \pm 16.6\%$  vs  $6.3 \pm 16.6\%$ ,  $p = 0.027$ ; 95% CI 6.2 to 20.9% vs. -0.8 to 13.3%) (ITT). Furthermore, there was a within-group increase in FN cortical volume for HiRIT ( $9.8 \pm 16.7\%$ ,  $p = 0.024$ ). No other between-group differences were observed for parameters of FN geometry.

**Table 10:** Baseline and eight-month measures ( $\pm$  SD) with adjusted percent change in skeletally non-dominant proximal femur geometry derived from 3D DXA following an eight-month exercise intervention in postmenopausal women with low bone mass (per protocol data,  $n = 44$ )

Parameter	CON ( $n = 23$ )			HiRIT ( $n = 21$ )			$p$
	Baseline	Follow-up	% change	Baseline	Follow-up	% change	
FN trabecular volume (cm <sup>3</sup> )	11.18 $\pm$ 1.80	10.82 $\pm$ 1.63	-0.8 $\pm$ 11.9	10.91 $\pm$ 1.60	10.65 $\pm$ 1.88	-2.9 $\pm$ 12.0	0.963
FN cortical volume (cm <sup>3</sup> )	1.59 $\pm$ 0.31	1.68 $\pm$ 0.30	5.1 $\pm$ 16.7	1.59 $\pm$ 0.30	1.71 $\pm$ 0.35 <sup>†</sup>	9.8 $\pm$ 16.7	0.492
FN total volume (cm <sup>3</sup> )	12.77 $\pm$ 1.93	12.51 $\pm$ 1.80	-0.2 $\pm$ 10.8	12.51 $\pm$ 1.66	12.36 $\pm$ 2.00	-1.4 $\pm$ 10.7	0.987
FN trabecular BMC (g)	2.01 $\pm$ 0.49	1.88 $\pm$ 0.43	-2.9 $\pm$ 29.5	2.10 $\pm$ 0.55	2.02 $\pm$ 0.57	-0.3 $\pm$ 29.6	0.159
FN cortical BMC (g)	1.10 $\pm$ 0.23	1.15 $\pm$ 0.20	6.2 $\pm$ 21.3	1.10 $\pm$ 0.27	1.15 $\pm$ 0.25	7.7 $\pm$ 21.3	0.028*
FN total BMC (g)	3.11 $\pm$ 0.61	3.03 $\pm$ 0.54	-0.2 $\pm$ 23.6	3.20 $\pm$ 0.76	3.17 $\pm$ 0.74	1.7 $\pm$ 23.7	0.077
FN trabecular vBMD (g/cm <sup>3</sup> )	0.181 $\pm$ 0.038	0.176 $\pm$ 0.041	-2.5 $\pm$ 28.8	0.194 $\pm$ 0.500	0.196 $\pm$ 0.074	2.4 $\pm$ 28.9	0.798
FN cortical vBMD (g/cm <sup>3</sup> )	0.697 $\pm$ 0.121	0.689 $\pm$ 0.107	0.8 $\pm$ 15.0	0.698 $\pm$ 0.162	0.692 $\pm$ 0.189	-1.9 $\pm$ 15.1	0.310
FN total vBMD (g/cm <sup>3</sup> )	0.244 $\pm$ 0.037	0.244 $\pm$ 0.044	-0.3 $\pm$ 24.3	0.258 $\pm$ 0.6	0.265 $\pm$ 0.093	3.7 $\pm$ 24.3	0.830
FN cortical thickness (mm)	0.90 $\pm$ 0.16	0.97 $\pm$ 0.16	6.3 $\pm$ 16.6	0.92 $\pm$ 0.19	1.00 $\pm$ 0.18 <sup>†</sup>	13.6 $\pm$ 16.6	0.027*

Abbreviations: FN = femoral neck; vBMD = volumetric bone mineral density; TH = total hip.

\* indicates between-group difference based on adjusted percent change ( $p < 0.05$ )

<sup>†</sup> indicates within-group difference ( $p < 0.05$ )

#### 5.4.4 Eight-month change in physical performance

Eight-month change in physical performance measures is presented in Table 11 (per protocol). In ITT analyses, HiRIT improved LES ( $35.2 \pm 19.8\%$  vs  $8.1 \pm 20.7\%$ ,  $p < 0.001$ ; 95% CI 29.1 to 41.2% vs. 2.1 to 14.1%), BES ( $36.0 \pm 22.4\%$  vs  $11.0 \pm 22.4\%$ ,  $p < 0.001$ ; 95% CI 29.3 to 42.8% vs. 4.5 to 17.5%), TUGT ( $4.4 \pm 6.0\%$  vs  $-1.7 \pm 6.0\%$ ,  $p < 0.001$ ; 95% CI 6.0 to 2.7% vs. -0.3 to -3.3%), FTSTS ( $11.6 \pm 7.5\%$  vs  $1.7 \pm 7.5\%$ ,  $p < 0.001$ ; 95% CI 13.7 to 9.5% vs. 3.9 to -0.3%), FRT ( $5.4 \pm 7.2\%$  vs  $0.1 \pm 7.2\%$ ,  $p < 0.001$ ; 95% CI 3.4 to 7.5% vs. -1.8 to 2.1%) and VJ ( $6.2 \pm 14.5\%$  vs  $2.5 \pm 14.6\%$ ,  $p < 0.001$ ) compared to CON (Figure 24B).

**Table 11:** Baseline and eight-month measures ( $\pm$  SD) with adjusted percent improvement in functional performance following an eight-month exercise intervention in postmenopausal women with low bone mass (per protocol data,  $n = 86$ )

Parameter	CON ( $n = 43$ )			HiRIT ( $n = 43$ )			$p$
	Baseline	Follow-up	% change	Baseline	Follow-up	% change	
Leg extensor strength (kg)	59.2 $\pm$ 14.7	61.4 $\pm$ 13.7	5.1 $\pm$ 23.1	62.5 $\pm$ 16.3	80.7 $\pm$ 13.9 <sup>†</sup>	37.1 $\pm$ 20.3	<0.001*
Back extensor strength (kg)	32.5 $\pm$ 9.3	34.2 $\pm$ 10.3	10.9 $\pm$ 25.1	32.8 $\pm$ 10.3	42.6 $\pm$ 8.7 <sup>†</sup>	36.3 $\pm$ 24.1	<0.001*
Timed up-and-go (sec)	5.9 $\pm$ 0.6	6.1 $\pm$ 0.6 <sup>†</sup>	-2.2 $\pm$ 6.3	6.2 $\pm$ 0.7	5.8 $\pm$ 0.5 <sup>†</sup>	4.3 $\pm$ 6.0	<0.001*
Five times sit-to-stand (sec)	9.8 $\pm$ 1.4	9.6 $\pm$ 1.2	1.7 $\pm$ 8.1	9.8 $\pm$ 1.2	8.6 $\pm$ 1.1 <sup>†</sup>	11.6 $\pm$ 7.9	<0.001*
Functional reach test (cm)	40.9 $\pm$ 4.9	40.8 $\pm$ 4.7	0.1 $\pm$ 8.0	40.3 $\pm$ 5.5	42.4 $\pm$ 5.3 <sup>†</sup>	5.5 $\pm$ 7.6	<0.001*
Vertical jump (N·s/kg)	1.34 $\pm$ 0.24	1.35 $\pm$ 0.26	3.6 $\pm$ 16.0	1.24 $\pm$ 0.26	1.31 $\pm$ 0.28	5.1 $\pm$ 16.0	<0.001*

\* indicates between-group difference based on adjusted percent change ( $p < 0.05$ )

<sup>†</sup> indicates within-group difference ( $p < 0.05$ )

#### 5.4.5 Safety and compliance

Of the 101 participants who commenced the trial, 6 and 9 participants were lost to follow up for HiRIT and CON, respectively. The main reason for drop out was the inability to attend training times due to work ( $n = 3$ ), or family ( $n = 2$ ) commitments for the HiRIT group, and unrelated medical conditions ( $n = 4$ ) and lack of interest ( $n = 3$ ) for the CON group (Figure 23). One participant in the HiRIT was excluded from the analysis after follow-up testing due to revealing a previously undisclosed change in bone medication during the trial period. Compliance was slightly higher for HiRIT ( $92 \pm 11\%$ ) compared to CON ( $85 \pm 24\%$ ), but the difference was not statistically significant ( $p = 0.112$ ). A single adverse event occurred in the HiRIT group from over 2600 training sessions. At week 28, the participant experienced a mild low back muscle strain on a final repetition of the last deadlift set. She missed the following 2 training sessions (1 week) before being able to recommence training with nil concerns thereafter and was able to complete the intervention as prescribed. Falls data was also collected throughout the trial, with 7 participants (CON,  $n = 2$ ; HiRIT,  $n = 5$ ) experiencing a fall over the trial period, none of which resulted in an injury to the participant and all took place outside of trial exercise sessions.

## 5.5 Discussion

The aim of the LIFTMOR trial was to determine the efficacy and to monitor adverse events of an 8-month, brief, supervised HiRIT program for bone and functional outcomes for postmenopausal women with low to very low bone mass. HiRIT was superior to CON for bone mass, FN geometry and physical function, compared to a low intensity home exercise program serving as a positive control. Importantly, no fractures

or major adverse events were observed, suggesting HiRIT may be safe for postmenopausal women with low to very low bone mass, despite previous safety concerns.

Myriad exercise trials to improve bone health of postmenopausal women have been conducted with varying results. The majority of resistance training studies have implemented moderate intensity programs (8-12 repetitions at 67-80% 1RM) that have induced only modest benefits to BMD at the hip or spine, with a mean treatment effect of 0.3% at both sites [335]. A 12-month randomized controlled trial in early postmenopausal women utilizing large compound exercises similar to the LIFTMOR trial has previously been conducted, but only at a moderate loading intensity. The latter study reported 12-month changes of 0.4% and -1.2% for LS and FN BMD, respectively [191]. To our knowledge there has been no trial of adequate size and/or duration ( $\geq 8$  months) to determine the efficacy of high intensity loading to improve bone mass in postmenopausal women with low to very low bone mass, thus our findings are novel. Our observed improvements in BMD surpass previous reports from reputable exercise interventions; an observation that could be considered intuitive in light of the well-known positive relationship between load magnitude and bone adaptation [77, 171]. The limiting feature of high intensity resistance training in this demographic has traditionally been the perceived increased risk of fracturing fragile bone with heavy loading. We believe this overly conservative approach has contributed to an unnecessary stagnation in the field. The evidence from the LIFTMOR trial that high intensity loading can indeed be tolerated by postmenopausal women with low to very low bone mass justifies a quantum change in attitude in this regard. The graduated introduction of loading, close ongoing supervision, and focus on correct technique were

key to the evident safety of the protocol, and the ability of the LIFTMOR participants to tolerate the program. We do not recommend individuals with low bone mass undertake the LIFTMOR protocol in an unsupervised environment, even after notable training, as it is not possible to self-monitor technique.

The use of the Medix DR DXA and 3D Hip software that has been validated against QCT [326] provided the novel opportunity to examine the response of parameters of proximal femur geometry that are known to be associated with structural strength [6, 47, 135]. While the FN BMD response to HiRIT was modest (reflecting essentially a maintenance effect), we observed superior results for FN BMC, cortical thickness, and volume in the HiRIT group compared to CON. Although trabecular changes were not observed, the increase in cortical mass is particularly important, as cortical bone is the predominant contributor to FN compressive strength (> 90%) [135]. That is, cortical thickness is strongly associated with femoral neck failure loads [47], highlighting the relevance of optimising cortical elements of bone geometry to protect against hip fractures.

Exercise is recognised to be an effective and feasible treatment modality to prevent falls [90]. Falls prevention exercise programs are generally multimodal, including balance, functional and resistance training, and can effect a 61% reduction in falls resulting in fracture [90]. Whilst the current intervention did not have sufficient power to examine falls, improvements were nevertheless observed in characteristics that reduce the risk of falling, namely muscle strength, and functional and neuromuscular performance. The improvements observed in lower limb strength are similar to those reported previously following resistance training; in the realm of a 25% to 35% [191, 250], and parallel the increase in all functional and neuromuscular performance

measures (TUGT, FRT, VJ and FTSTS). Similar functional performance improvements have been observed in previous studies [96, 132, 133, 287]. TUG, FTSTS, and functional reach scores have previously been shown to be related to balance and incident falls [52, 85, 273]. Improvements in those functional performance scores therefore suggest HiRIT may not only reduce the risk of fracture by enhancing parameters of bone strength, but by preventing falls in postmenopausal women with low bone mass.

As safety concerns around high intensity loading for women with low bone mass have previously discouraged others from recommending (or even testing) it as a therapy for osteoporosis, adverse events were an important outcome measure in the LIFTMOR trial. A modicum of evidence had previously been reported for the safety of HiRIT in postmenopausal women with low bone mass, albeit limited by small sample size and short duration [214]. Our study similarly provides preliminary evidence for the feasibility and safety of a HiRIT exercise program for otherwise healthy postmenopausal women with low to very low bone mass, as no serious or chronic injuries related to the intervention were sustained. Further research is required to confirm safety of HiRIT exercise for individuals with comorbidities. The single minor low back muscle strain limited training for 1 week, after which time training load was progressively increased over 2 weeks such that the remainder of the program could be completed as prescribed without any further concern. While we observed no serious adverse events in the LIFTMOR trial, we were not adequately powered to assess safety as an outcome. Furthermore, our sample was relatively healthy, as volunteers with underlying musculoskeletal or serious cardiovascular co-morbidities were excluded. We therefore recommend circumspection when applying our findings beyond the sample

demographic and appropriate screening for contraindications to high intensity resistance and impact training. The 92% compliance rate of the HiRIT group in the current study compares favourably to that of previous resistance training studies that range from 59% to 92% for 6-12 months of training [107, 170, 191, 197, 218]. Adherence was also high for both groups, with dropout rates of 12% and 17% for HiRIT and CON, respectively. The main reason for dropout was the inability to attend supervised sessions as a consequence of work or family commitments (Figure 1). Lack of time is a common barrier to exercise, with adherence being as low as 50% in the first 6 months of some exercise programs [191, 253]. The high compliance and adherence rates observed in the LIFTMOR trial suggest that HiRIT is feasible and sufficiently appealing to postmenopausal women to be successfully implemented more broadly.

Although not originally a primary outcome measure, we observed that HiRIT improved stature compared to CON. The observed improvement in stature following HiRIT is likely to be a consequence of increased BES, as BES is inversely associated with magnitude of kyphosis [276]. Our results add support to the findings of other exercise intervention studies that have demonstrated improvements in BES by 21% and corresponding kyphosis reductions of 5-6° in postmenopausal hyperkyphotic women [160]. Notably, improvements in BES and kyphosis have been associated with a decreased incidence of vertebral fracture [277] and are therefore highly clinically significant.

Several study limitations warrant acknowledgement. Firstly, a change of DXA device was necessary during the trial period. To reduce the impact of this change, every participant was scanned at baseline and follow up on the same DXA scanner. Furthermore, statistical comparisons of the magnitude of treatment effects detected by

the Norland and the Medix revealed no differences (data not reported). Secondly, we were unable to examine bone biomarkers, serum 25OHD or circulating hormones and are therefore unable to account for the effects of those factors or their interactions on the study outcomes. While unable to control for serum 25OHD, ensuring all participants were at least 5 years post menopause reduced the influence of fluctuations in oestrogen during the study period. Thirdly, our data represents a composite of study participants on and off osteoporosis medications. In order to control for this highly influential variable, we stratified randomised on the basis of medication. Ultimately, 10 participants were randomised to each group, and no within-group differences in treatment effect were observed for our primary outcomes of FN or LS BMD from exploratory analyses of the medication-based subgroups. It is also important to note that preliminary findings were published [318]. The unblinding of data has the potential to result in observer-expectancy bias. To minimize the effect of a lack of the assessor blinding to group allocation at follow up, and the potential for observer-expectancy bias, BMD analyses were independently verified by an investigator who was blind to group allocation. Finally, while the use of 3D hip software may provide insight into changes in geometry of the proximal femur, the software is very new and the association of geometric parameters to hip fracture is unknown.

In conclusion, the LIFTMOR trial is the first to show that a brief, supervised, twice weekly HiRIT exercise intervention was efficacious and superior to previous programs for enhancing bone at clinically relevant sites, as well as stature and functional performance of relevance to falls in postmenopausal women with low to very low bone mass. Further, that no fractures or other serious injuries were sustained by any participant in our study suggests that HiRIT does not pose a significant risk for

postmenopausal women with low bone mass when closely supervised, despite a common misconception to the contrary. In light of the very positive bone, function, safety and feasibility outcomes of the LIFTMOR trial we believe HiRIT to be a highly appealing therapeutic option for the management of osteoporosis in postmenopausal women with low to very low bone mass.



## Chapter 6: Publication Three

**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**

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**Statement of contribution to co-authored published paper**

For this co-authored manuscript, the candidate conceived and designed the experiment in consultation with co-authors, recruited participants, performed data acquisition, implemented the intervention, analysed the data, interpreted results, and prepared the manuscript.

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Steven Watson | *Candidate*

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## 6.1 Abstract

*Introduction:* The LIFTMOR trial demonstrated a novel, HiRIT program notably improved bone mass in postmenopausal women with osteopenia and osteoporosis. While no clinical signs or symptoms of vertebral crush fracture were evident during the trial, anecdotal feedback suggests concerns about safety of HiRIT in the osteoporosis demographic remain. The aim of the current work was to assess vertebral body morphology, Cobb angle and clinical measures of thoracic kyphosis in participants in the LIFTMOR trial for evidence of vertebral fracture following 8 months of supervised high-intensity, resistance and impact training (HiRIT). *Methods:* Participants were randomized to either 8 months of 30-minute, twice-weekly supervised HiRIT or unsupervised, low-intensity, home-based exercise (CON). Lateral thoracolumbar DXA scans (Medix DR, Medilink, France) were performed at baseline and follow up. Cobb angle was determined and vertebral fracture identification was performed using the semi-quantitative Genant method. Clinical kyphosis measures were performed in relaxed standing (neutral posture) and standing tall using an inclinometer and a Flexicurve. *Results:* The HiRIT group exhibited a reduction in inclinometer-determined standing tall thoracic kyphosis compared to CON ( $-6.7 \pm 8.2^\circ$  vs  $-1.6 \pm 8.1^\circ$ ,  $p = 0.031$ ). Both the HiRIT and CON groups exhibited within-group improvement in kyphosis in relaxed standing as measured by both inclinometer and Flexicurve ( $p < 0.05$ ). There were no changes in vertebral fracture classification in the HiRIT group post-intervention. A single, new, wedge deformity was observed for CON. *Conclusions:* Supervised HiRIT was not associated with an increased risk of vertebral fracture in postmenopausal women with low bone mass. Indeed, a clinically-relevant improvement in thoracic kyphosis was observed following 8 months of supervised HiRIT, further

supporting its efficacy as an osteoporosis intervention for postmenopausal women with low to very low bone mass.

## **6.2 Introduction**

While exercise is a positive strategy to improve bone mass, some clinicians have worried that exercises known to stimulate bone may cause fragility fractures in those most at risk of osteoporosis [55, 136, 167]. Vertebral fractures (present in approximately 20% of osteoporotic women and accounting for 48% of kyphosis in postmenopausal women [16, 87, 210]), commonly occur with spine twisting, flexion, or a combination of those movements, especially when performed quickly and/or with high external loads [112]. As a consequence, exercise programs for individuals with osteoporosis have traditionally been recommended at only low to moderate-intensity [136]. Paradoxically, it is well known that mechanical loading has the greatest potential for bone adaptation when it induces high magnitude strain in [258] or is applied at high rates to bone [228, 259]. Recently an exercise program employing those osteogenic principles in an 8-month exercise trial for postmenopausal women with low to very low bone mass (the LIFTMOR trial) demonstrated highly positive bone adaptations with no associated fracture symptoms [317]. An objective assessment of changes in vertebral morphology attributable to fracture during the latter trial has not previously been reported. Other high-intensity exercise trials have been conducted in postmenopausal women with low bone mass but, similarly, measures of vertebral fracture have not been reported [191, 214, 218]. It was therefore not known if osteogenic exercise causes vertebral fractures in individuals at increased risk of fragility fracture.

The overall aim of the Lifting Intervention For Training Muscle and Osteoporosis Rehabilitation (LIFTMOR) trial was to determine the efficacy and safety of brief, bone-targeted, high-intensity, progressive resistance and impact weight bearing training (HiRIT) for postmenopausal women with low to very low bone mass. We hypothesized that (1) participants in both the HiRIT training group and the low-intensity exercise control group would experience no change in vertebral morphology over the 8-month intervention period, and (2) participants in both the HiRIT training group and the low-intensity exercise control group would experience no change in measures of thoracic kyphosis over the 8-month intervention period.

### **6.3 Materials and methods**

#### *6.3.1 Study design*

The current report comprises the findings of a sub-analysis of a larger RCT, the LIFTMOR trial [317]. The LIFTMOR trial was a single-blind, randomized, controlled, exercise intervention trial. Eligible participants were block-randomized to supervised HiRIT or unsupervised low-intensity home-based exercise (CON). The primary outcome of the LIFTMOR trial was femoral neck (FN) and lumbar spine (LS) bone mineral density (BMD). Eligible participants were block-randomized based on existence or absence of established (12 months exposure or lack of exposure) osteoporosis medications, utilizing sequentially numbered, sealed, opaque envelopes. The randomization sequence was produced by an external investigator using a computer-generated randomisation sequence (Microsoft Excel, Microsoft, Redmond, WA, USA) to generate either a 0 or 1, corresponding with CON or HiRIT, respectively. The LIFTMOR trial was registered on the Australian and New Zealand Clinical Trials

Registry (anzctr.org.au; CTR number: ACTRN12616000475448) and ethical approval was granted by the Griffith University Human Research Ethics Committee (approval number: AHS/07/14/HREC). Written informed consent was obtained from all study participants.

### 6.3.2 *Participants*

The current report includes observations from the final 51 participants of the original 101 participants of the LIFTMOR trial [317]. Those participants were included in this analysis as they were scanned on a DXA machine (Medix DR, Medilink, France) with lateral vertebral assessment (LVA) functionality, and host software enabled Cobb angle quantification from lateral thoracolumbar scans. As the first 50 LIFTMOR participants were examined on a Norland XR-800 DXA (Norland Medical Systems, Inc., Trumbull, CT, USA) which does not perform LVA, we were unable to include the full LIFTMOR sample in the current analysis. A comparison between the first and second half of the cohort revealed no differences in characteristics, with the exception of a slightly older age in the group included in the current work ( $64.1 \pm 4.1$  years vs  $66.3 \pm 5.1$  years,  $p = 0.021$ ). No clinical signs of vertebral fracture were observed in the initial 50 participants. The inclusion criteria for the LIFTMOR trial were postmenopausal women over 60 years of age with low bone mass (T-score less than -1.0 at the hip and/or lumbar spine), but otherwise in good general health. Women with established osteoporosis and a history of vertebral fracture were included. Participants were excluded if they had any of the following: recent lower limb joint surgery or injury; recent fracture or localized back pain; less than five years post menopause; malignancy; uncontrolled cardiovascular disease; cognitive impairment; recent x-ray or

radiation treatment; contraindications for participating in heavy physical activity; conditions known to influence bone health (e.g. thyrotoxicosis or hyperparathyroidism, Paget's disease, renal disease, diabetes, or immobility); or taking medications (other than osteoporosis medications, and calcium and vitamin D supplementation) known to influence bone (e.g. prolonged use of corticosteroids, thyroxine, thiazides or antiretroviral agents).

### *6.3.3 Exercise intervention*

The HiRIT group attended twice-weekly, 30-minute, supervised exercise sessions comprising progressive resistance training and impact loading exercises on non-consecutive days. The first two to four weeks comprised of low-load exercises (bodyweight) to ensure proper lifting technique and familiarization to the exercise program. From week four, exercise intensity was increased so that by the end of the second month each participant was able to comfortably perform the three fundamental compound movement exercises (deadlift, squat, and overhead press) at 80-85% of one repetition maximum (1RM) for 5 sets of 5 repetitions. Those exercises were then performed for the remainder of the exercise intervention, with loads gradually increasing to ensure participants remained within the high-intensity domain ( $\geq 80-85\%$  1RM). The impact-loading component of the exercise program was 5 sets of 5 repetitions of jumping chin-ups with drop landings, progressing to a firm, flat-footed landing. Each training session was supervised by an exercise scientist who is also a physiotherapist.

#### 6.3.4 *Control program*

A positive control (CON) was implemented for the purpose of participant retention. The CON exercise program was a low load (10-15 repetitions at < 60% of 1RM) unsupervised, home-based program, consisting of two 30-minute sessions per week, including a 10-minute walking warm-up, four stretches (side to side neck stretch, static calf stretch, shoulder stretch, and side to side lumbar spine stretch) and four low-resistance exercises (lunges, calf raises, standing forward raise, and shrugs), followed by a 5-minute cool-down walk. The CON program utilized light handheld weights (1, 2 and 3 kg dumbbells). The intensity of the resistance exercises increased progressively to a maximum of 3 kg for each exercise for the final 4 weeks of the program.

#### 6.3.5 *Outcome measures*

All outcome measures were performed at baseline and eight-months by a single unblinded investigator at the Bone Densitometry Research Laboratory at the Griffith University, Gold Coast campus. In this single blind RCT, participants were blinded to which exercise program was the bone focused intervention (HiRIT), or control (CON) exercise program. Height was measured using a wall-mounted stadiometer (Seca 216, Ecomed Trading Pty Ltd, Seven Hills, Australia). Weight was measured using a mechanical beam balance scale (Seca 700, Ecomed Trading Pty Ltd, Seven Hills, Australia).

The magnitude of kyphosis was measured using both imaging (DXA) and manual (inclinometer and Flexicurve) techniques. Lateral thoracolumbar DXA scans were performed in the lateral decubitus position for lateral vertebral assessment (LVA) and Cobb angle measurement. Calculation of the Cobb angle was performed using two

approaches: 1. using the 4<sup>th</sup> and 12<sup>th</sup> thoracic vertebral body endplates, and 2. using the anterior vertebral body margins of the 4<sup>th</sup> and 12<sup>th</sup> thoracic vertebrae. The endplate Cobb angle analysis was performed by manually digitizing the superior endplate of the 4<sup>th</sup> thoracic vertebrae (T4) and the inferior endplate of the 12<sup>th</sup> thoracic vertebrae (T12); lines parallel and adjacent with each endplate were then converged to create the Cobb angle as previously described [148]. The anterior body Cobb angle measure was undertaken to eliminate the effect of a dramatic vertebral deformity at T4 or T12 influencing overall Cobb measure. To complete the measure, the anterior margins of the vertebral bodies of T4 and T12 were digitized and extended until they converged to calculate the Cobb angle as previously described [50]. The lateral DXA scans allowed the assessment of vertebral bodies T5 through L4 for the presence of fracture utilizing the semi-quantitative Genant method [105]. All vertebral analyses (Cobb and LVA) were performed by the same technician and systematically cross-checked by another member of the research team for accuracy.

Two manual clinical measures of thoracic kyphosis were performed (gravity-referenced inclinometer and Flexicurve). Participants were asked to remove their shirt or blouse and shoes. The following bony landmarks were palpated and marked: (1) the spinous process of the 7<sup>th</sup> cervical vertebra (C7), and (2) the 12<sup>th</sup> thoracic vertebra (T12). After identification of anatomical landmarks, the inclinometer was zeroed at the 7<sup>th</sup> cervical and 1<sup>st</sup> thoracic intervertebral space as previously described [207]. The inclinometer was then placed at the 11<sup>th</sup> to 12<sup>th</sup> thoracic intervertebral space to measure the thoracic kyphosis angle (degrees). The inclinometer method was conducted in both a ‘relaxed standing’ (neutral posture) and ‘standing tall’ posture. For the ‘relaxed standing’ posture, the participant was instructed to stand with feet shoulder width apart

with equal weight distribution, arms relaxed by their sides and to take two deep breaths. The 'standing tall' posture was undertaken with feet shoulder width apart, arms relaxed by their sides, and the participant was instructed to 'stand as tall as possible'. Two measures were performed for each posture and the average used for analysis. Our inclinometer measures exhibited excellent short term intra-rater reliability for kyphosis, both in relaxed (ICC=0.968 (95% CI, 0.954–0.977),  $p<0.001$ ) and standing tall (ICC=0.974 (95% CI, 0.963–0.982),  $p<0.001$ ) positions, which mirror the findings of others [21]. The C7 and T12 markings used for the inclinometer measures were then used to perform the Flexicurve thoracic kyphosis measure in a relaxed standing position. The end of the Flexicurve was placed on the C7 marking and then moulded to the participants spinal curvature caudally to the T12 marking. The moulded Flexicurve was then transferred to paper and the thoracic curvature was carefully traced. A straight line was then drawn from the points coinciding with the C7 to T12 vertebrae, and the length of the line recorded (X). A perpendicular line was drawn from the C7-T12 line to the point of maximal curvature, and the length of that line also recorded (Y). The Kyphosis index was then calculated by dividing the width of curvature by the height of the thoracic region and multiplying the result by 100 ( $Y/X \times 100$ ) [20, 333]. Flexicurve measures have excellent reliability (ICC 0.92-0.94) even in novice users [21, 134].

#### 6.3.6 *Statistical analysis*

Statistical analysis was undertaken using SPSS version 22.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were generated for subject characteristics, biometrics, and all dependent measures. Intention-to-treat (ITT) and per protocol (PP) analyses were performed with repeated measures ANOVA to test the hypotheses related

to vertebral morphology. All statistical analyses were conducted using a  $p$ -value of 0.05 to determine statistical significance.

## **6.4 Results**

### *6.4.1 Participant characteristics at baseline*

A total of 51 participants were included in the current analysis. Of those, 6 were classified as hyperkyphotic (kyphosis  $>60$  degrees in relaxed standing); 4 in the HiRIT group and 2 in the CON group. The only significant between-group differences at baseline were for the relaxed and standing tall inclinometer measures; both showing the HiRIT group had greater thoracic kyphosis (Table 12).

**Table 12:** Baseline participant characteristics (n = 51)

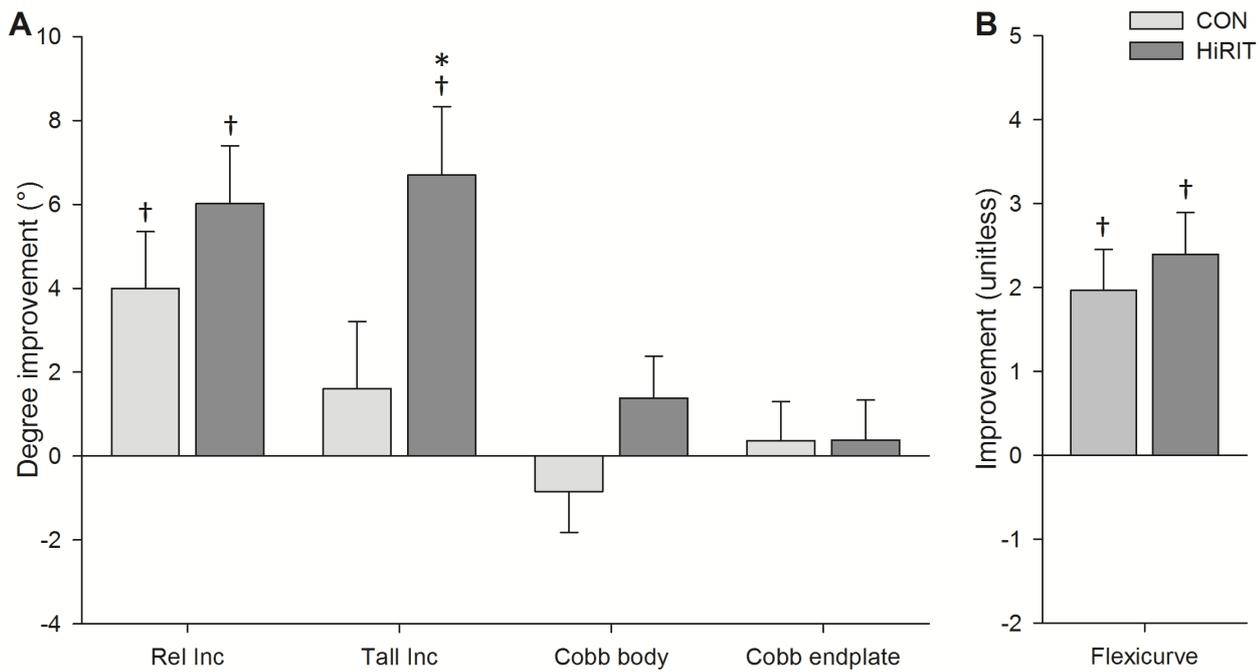
Parameter	CON (n = 26)	HiRIT (n = 25)	p
Age (years)	64 ± 5	64 ± 4	0.631
Weight (kg)	62.7 ± 8.7	64.7 ± 12.0	0.494
Height (cm)	161.9 ± 5.8	161.2 ± 6.2	0.636
BMI (kg/m <sup>2</sup> )	23.8 ± 2.8	25.0 ± 5.0	0.319
Inclinometer relaxed standing thoracic kyphosis (degrees)	44.8 ± 9.2	50.3 ± 8.5	0.035*
Inclinometer standing tall thoracic kyphosis (degrees)	35.4 ± 9.6	43.8 ± 9.3	0.004*
Flexicurve Kyphotic Index (unitless)	10.8 ± 2.6	11.3 ± 2.8	0.482
Cobb endplate angle (degrees)	31.2 ± 10.8	30.0 ± 9.2	0.672
Cobb body angle (degrees)	33.1 ± 11.6	32.5 ± 9.5	0.852
Compliance (%)	89 ± 13	92 ± 14	0.481

Abbreviations: BMI = body mass index; CON = control; HiRIT = high-intensity resistance and impact training; Cobb body = Cobb angle measured from lateral thoracolumbar DXA using anterior vertebral body method; Cobb endplate = Cobb angle measured from lateral thoracolumbar DXA using vertebral endplate method

\*Between-group difference ( $p < 0.05$ )

#### 6.4.2 Eight-month change in thoracic kyphosis

Following the 8-month intervention the HiRIT group exhibited a greater reduction in inclinometer-determined thoracic kyphosis in the standing tall posture ( $-6.7 \pm 8.2^\circ$  vs  $-1.6 \pm 8.1^\circ$ ,  $p = 0.031$ ; 95% CI  $-10.0$  to  $-3.4^\circ$  vs.  $-4.8$  to  $1.6^\circ$ ) than the CON group (ITT) (Figure 25A). Both the HiRIT and CON groups had within-group improvements in kyphosis in a relaxed standing posture as measured by inclinometer (HiRIT:  $-6.0 \pm 6.9^\circ$ ,  $p < 0.001$ , 95% CI  $-8.8$  to  $-3.3^\circ$ ; CON:  $-4.0 \pm 6.9^\circ$ ,  $p = 0.005$ , 95% CI  $-6.7$  to  $-1.3^\circ$ ) (Figure 25A) and Flexicurve (HiRIT:  $-2.4 \pm 2.5$ ,  $p < 0.001$ , 95% CI  $-3.4$  to  $-1.4$ ; CON:  $-2.0 \pm 2.4$ ,  $p < 0.001$ , 95% CI  $-2.9$  to  $-1.0$ ) (ITT) (Figure 25B). Adjusting for baseline differences in inclinometer-measured kyphosis did not change between-group significance. Similar to the ITT analyses, per protocol analyses indicated greater improvements in standing tall posture for HiRIT (Table 13). No within- or between-group differences were observed for Cobb angle using either the vertebral endplate or anterior vertebral body methods.



**Figure 25:** Eight-month change ( $\pm$ SEM) in (A) thoracic kyphosis angle in degrees and (B) Flexicurve Kyphosis index for HiRIT and CON after an eight-month exercise intervention in postmenopausal women with low bone mass ( $n = 51$ )

Abbreviations: Cobb body = Cobb angle measured from lateral thoracolumbar DXA using anterior vertebral body method; Cobb endplate = Cobb angle measured from lateral thoracolumbar DXA using vertebral endplate method; CON = control; HiRIT = high-intensity resistance and impact training; Rel Inc = Inclinator in relaxed standing; Tall Inc = Inclinator in standing tall

\*Between-group difference ( $p < 0.05$ )

† Within-group difference ( $p < 0.05$ )

**Table 13:** Baseline and eight-month measures ( $\pm$  SD) with absolute change in height and kyphosis measures following an eight-month exercise intervention in postmenopausal women with low bone mass (per protocol data,  $n = 43$ )

Parameter	CON ( $n = 23$ )			HiRIT ( $n = 20$ )			<i>p</i>
	Baseline	Follow-up	Change	Baseline	Follow-up	Change	
Height (cm)	161.6 $\pm$ 6.0	161.5 $\pm$ 5.7	-0.1 $\pm$ 0.6	160.2 $\pm$ 6.2	160.4 $\pm$ 6.3	0.2 $\pm$ 0.6	0.140
Inclinometer relaxed standing thoracic kyphosis (degrees)	44.5 $\pm$ 9.5	40.3 $\pm$ 6.2	-4.2 $\pm$ 6.7	49.6 $\pm$ 8.6	44.9 $\pm$ 7.6	-4.7 $\pm$ 6.3	0.779
Inclinometer standing tall thoracic kyphosis (degrees)	35.0 $\pm$ 10.2	33.0 $\pm$ 7.1	-2.0 $\pm$ 8.1	43.1 $\pm$ 9.0	37.8 $\pm$ 8.8	-5.3 $\pm$ 7.1 <sup>†</sup>	0.167
Flexicurve Kyphotic Index (unitless)	10.6 $\pm$ 2.6	8.7 $\pm$ 2.4	-1.9 $\pm$ 2.4	11.0 $\pm$ 2.8	8.9 $\pm$ 2.4	-2.1 $\pm$ 2.2 <sup>†</sup>	0.819
Cobb endplate angle (degrees)	31.5 $\pm$ 11.4	30.8 $\pm$ 10.1	-0.6 $\pm$ 4.3	29.6 $\pm$ 9.6	29.6 $\pm$ 9.1	0.0 $\pm$ 4.4	0.631
Cobb body angle (degrees)	33.4 $\pm$ 12.3	33.9 $\pm$ 11.3	0.5 $\pm$ 4.5	32.2 $\pm$ 9.2	31.1 $\pm$ 10.5	-1.0 $\pm$ 4.5	0.276

Abbreviations: CON = control; HiRIT = high-intensity resistance and impact training; Cobb body = Cobb angle measured from lateral thoracolumbar DXA using anterior vertebral body method; Cobb endplate = Cobb angle measured from lateral thoracolumbar DXA using vertebral endplate method

<sup>†</sup> Within-group difference ( $p < 0.05$ )

### 6.4.3 *Eight-month change in lateral vertebral assessment and vertebral body morphology*

At baseline, 17 participants (33%) had detectable vertebral fracture/s (HiRIT = 6; CON = 11), common locations were T7 (5/18), T8 (3/18) and L4 (3/18). Wedge-form morphology was most common (12/18), followed by biconcave morphology (3/18) and crush fractures (3/18). Eleven fractures were classified as Grade 1 (HiRIT = 3; CON = 8), while 7 were Grade 2 (HiRIT = 4; CON = 3). One new fracture was identified post intervention in the CON group (Grade 1 wedge fracture at T7) and no new fractures were identified in the HiRIT group (Table 14). Two fractures in the CON group progressed from Grade 1 to Grade 2, and one progressed from Grade 2 to Grade 3. There were no changes in vertebral fracture classification in the HiRIT group post 8-month exercise intervention. No between-group differences were observed for change in either anterior, middle or posterior vertebral body height.

**Table 14:** Baseline and 8-month vertebral fracture locations following an eight-month exercise intervention in postmenopausal women with low bone mass (per protocol data,  $n = 43$ )

Vertebrae	CON ( $n = 23$ )		HiRIT ( $n = 20$ )	
	Baseline	Follow-up	Baseline	Follow-up
T5	0	0	0	0
T6	2	2	0	0
T7	2	3	3	3
T8	3	3	0	0
T9	0	0	0	0
T10	1	1	0	0
T11	0	0	0	0
T12	0	0	1	1
L1	0	0	0	0
L2	1	1	1	1
L3	0	0	0	0
L4	2	2	1	1

Abbreviations: CON = control; HiRIT = high-intensity resistance and impact training

## 6.5 Discussion

The overarching aim of the LIFTMOR trial was to determine the effect of brief, bone-targeted, supervised HiRIT for postmenopausal women with low to very low bone mass on parameters of bone strength and vertebral safety. While the LIFTMOR program efficacy has been reported elsewhere [317], the current manuscript reports outcomes of vertebral and spine morphology related to osteoporotic fracture. We observed that 8 months of supervised HiRIT improved thoracic kyphosis more than a very low-intensity control exercise program. Furthermore, HiRIT did not induce new vertebral fractures or worsen existing vertebral deformities. We therefore conclude that

supervised, bone-targeted HiRIT does not increase risk of vertebral fracture in postmenopausal women with low to very low bone mass.

As no direct measures of the vertebral loads experienced during targeted exercise have ever been collected, the precise relationship of exercise intensity to fracture is not known. Musculoskeletal modelling has estimated the compressive load exerted on the vertebral column lifting 10 kg from the floor to be 900-1700 N. Maximal loads appear to occur at the thoracolumbar region (T11-L1) [51], which corresponds to the most common location of vertebral fractures [220]. Such loads are not dissimilar to the average QCT estimated or cadaveric compressive failure loads of thoracolumbar vertebrae of 500-5000 N [3, 120, 212]. Importantly, 70-90% of the failure load variance is explained by BMD alone [212, 217]. As such, an increase in BMD can be expected to be protective against fracture, but the balance between osteogenic loading and fracture threshold is unknown. The aetiology of thoracic kyphosis is multifactorial; having been associated with age, wedge deformities, decreased spinal mobility, dehydration of intervertebral disks and poor back extensor strength [18, 160, 163]. Those associations have propagated a variety of manual therapy and exercise interventions. Exercise interventions have generally focused on improving back extensor strength and spinal mobility through resistance training and mobility exercises [18]. Our results support the findings of previous back extension exercise trials that have shown both improvements in thoracic kyphosis of approximately 3° to 6° and a reduction in Kyphosis index in postmenopausal women [18, 25, 117, 139, 160]. The improvements in kyphosis seen in both HiRIT and CON groups in the current trial may stem from a combination of both enhanced spinal mobility and back extensor isometric strength (HiRIT: 33 ± 31%; CON 6 ± 26%). Interestingly, while participants had an average increase of 157% in deadlift

weight lifted over the intervention period and all other measures of physical performance improved [317], no functional outcome was significantly related to change in any kyphosis variable. Thus, the improvements in kyphosis observed in the LIFTMOR trial not only supports the safety of HiRIT as an effective bone intervention for postmenopausal women with low bone mass, but as an effective mechanism for postural change with highly positive implications for quality of life.

The latter observed improvements in kyphosis were derived from inclinometer-based and Flexicurve measures of thoracic kyphosis in an erect weight-bearing posture. Conversely, no significant changes were observed from measures of Cobb angle, although a trend favouring HiRIT is evident. It is possible the lack of observed change in Cobb angle is a result of our method of determination from the non-weight bearing lateral decubitus DXA scan position. A standard Cobb angle is traditionally measured using a standing lateral thoracic x-ray which allows for the natural weight bearing posture to be assumed. In the lateral decubitus DXA scan position, it is possible the participant is not truly positioned in the natural posture of the weight bearing spine. We acknowledge there is no recognised precedent for determining Cobb angle from lateral DXA scans and concede our results suggest it may not be a valid technique to do so. We note the primary purpose of conducting the lateral DXA scan was to facilitate the determination of vertebral body morphology quantification using the Genant method – a technique which does not rely on spine posture.

The assessment of individual vertebral body morphology allowed us to objectively assess evidence of vertebral fracture following 8 months of supervised HiRIT. Importantly, no HiRIT participant reported any clinical symptom of vertebral fracture throughout the trial period, nor were any new or progressing vertebral

deformities detected from image analysis. The lack of either clinical or morphological indicators of vertebral fracture further support the contention that supervised HiRIT did not incur crush fractures in postmenopausal women with low to very low bone mass. By contrast, study participants in the control group suffered progression and development of new vertebral deformities during the course of the trial suggesting either the very low-intensity control exercise program increased the risk of vertebral fracture (which is unlikely), or more likely, the low-intensity exercise program was insufficient to prevent further vertebral deterioration over the course of the trial. The higher incidence of vertebral deformities at baseline in the CON group than HiRIT may also explain the greater numbers of new or deteriorating vertebral deformities in CON during the trial as previous fracture increases the risk of a subsequent vertebral fracture 5-fold in postmenopausal women [256].

Several limitations warrant acknowledgement. First, vertebral fracture was not a primary outcome measure of the LIFTMOR trial, and the trial was not powered to examine it. Thus, despite our very promising observations, a larger trial is required to definitively examine the question of fracture risk during HiRIT. Secondly, as noted previously, lateral DXA scans were utilised for Cobb angle quantification. Despite having excellent inter-rater reliability [302], we recognise that lateral weight-bearing radiographs would have been a more acceptable method to determine Cobb angle. For this reason, we focussed our conclusions relating to kyphosis primarily on inclinometer-based measures.

In conclusion, observations from the LIFTMOR trial indicate that brief, twice-weekly, supervised HiRIT exercise for 8 months did not cause fragility fractures and improved thoracic kyphosis in postmenopausal women with low to very low bone mass.

Findings run counter to traditional concerns that high-intensity exercise loading represents an unacceptable level of risk to older women at risk of fragility fractures from osteoporosis. The evidence clearly suggests those concerns are overly conservative.



## Chapter 7: Publication Four

**Physical activity enjoyment improves with high intensity resistance and impact training in postmenopausal women with osteopenia and osteoporosis: The LIFTMOR trial**

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## 7.1 Abstract

*Introduction:* The LIFTMOR trial was efficacious for its primary outcome of improving bone in postmenopausal women with low to very low bone mass. As there is no guarantee an efficacious exercise program will be acceptable to a target population in ‘real life’, the question of participant enjoyment was fundamental to a comprehensive evaluation of its true potential as a public health intervention. Therefore, the aim of the current work was to assess physical activity enjoyment, quality of life, and participant perception of the high-intensity progressive resistance and impact training (HiRIT) program and the LIFTMOR trial. *Methods:* Participants were randomized to either 8 months of 30-minute, twice-weekly supervised HiRIT or unsupervised, low-intensity, home-based exercise (CON). At baseline and follow-up testing sessions, all participants completed physical activity enjoyment (PACES-8) and quality of life (WHOQOL-BREF) questionnaires. At follow-up, 32 participants completed an exit survey relating to their experiences of the trial. Of the those, 14 were in the HiRIT program and went on to participate in semi-structured interviews with questions related to physical activity and their experiences undertaking the HiRIT program. *Results:* Participants who undertook the HiRIT program reported greater physical activity enjoyment, were happier with their group allocation and were more enthusiastic about undertaking training prior to each session than the CON participants. Thematic analysis revealed current bone health status as the most common motivator for enrolling in the LIFTMOR trial, time was an important barrier to previous physical activity participation, supervised group exercise sessions were perceived as being positive, and tiredness, but not soreness, was common after the sessions. Lastly, all HiRIT participants would recommend the program to a friend. *Conclusion:* Supervised HiRIT was superior to a

low-intensity home exercise program in terms level of physical activity enjoyment. The combination of the highly osteogenic nature of the LIFTMOR program and high levels of acceptability, suggest supervised HiRIT is an effective and appealing management approach for postmenopausal women with low to very low bone mass.

## **7.2 Introduction**

With increasing age, there is typically a decrease in physical activity participation that is associated with poorer health outcomes [224]. For older adults who are able to maintain high levels of physical activity, positive health outcomes such as a decreased cardiovascular disease and mortality are achievable [79, 179, 332]. Barriers for exercise participation for older adults include perceived lack of time, co-morbid conditions, financial cost, body image concerns and low perceived benefits [232, 253]. While group classes are viewed positively, as they facilitate social interaction, encouragement, and support, professional instruction is also considered to be an important motivator for older adults undertaking physical activity [102, 232, 253]. Given physical activity participation has the potential for profound health benefits for older adults, it is important that such factors are considered when developing exercise programs if adherence and sustained participation is to be achieved.

The LIFTMOR trial was an 8-month bone targeted exercise trial recently conducted with postmenopausal women with low to very low bone mass. Results for the primary outcome measures of interest, revealed that the intervention program was effective in improving bone mineral density at the lumbar spine and femoral neck [317]. Whether participants enjoyed the program and were likely to undertake resistance training in the future, was also an important outcome of interest for the purposes of

determining feasibility of the program as a public health intervention. Program acceptability has not previously been reported in postmenopausal women undertaking a high-intensity resistance and impact training (HiRIT) program. Furthermore, the identification of specific barriers and motivating factors related to the implementation of HiRIT as an efficacious exercise program for bone is paramount for the translation of the program into the wider community.

The aim of the current work was to explore participant experiences of HiRIT and the LIFTMOR trial, to identify important motivators and barriers to participation. We hypothesized that (1) participants in the HiRIT training group would experience greater improvements in physical activity enjoyment over the 8-month intervention period compared to those in the low-intensity home exercise control group (CON), (2) participants in the HiRIT training group would experience greater improvements in quality of life over the 8-month intervention period compared to participants in the low-intensity home exercise control group, and (3) HiRIT would be considered positively by postmenopausal women with low to very low bone mass.

### **7.3 Materials and methods**

#### *7.3.1 Study design*

A grounded theory mixed-methods approach using both questionnaires and semi-structured interviews was undertaken to investigate the enjoyment and acceptability of HiRIT and the LIFTMOR trial. The LIFTMOR trial was a single-blind, randomized, controlled, exercise intervention trial. Eligible participants were stratified randomized based on the use of osteoporosis medication to either a supervised HiRIT, or unsupervised low-intensity home-based exercise (CON). The trial was registered on

the Australian and New Zealand Clinical Trials Registry (anzctr.org.au; CTR number: ACTRN12616000475448) and ethical approval was granted by the Griffith University Human Research Ethics Committee (Approval number: AHS/07/14/HREC). Written informed consent was obtained from every study participant.

### *7.3.2 Participants*

Generally healthy and ambulatory postmenopausal women (>58 years of age) with low bone mass (T-score < -1.0 at the hip and/or spine) were recruited for the LIFTMOR trial. The inclusion and exclusion criteria for the LIFTMOR trial has been reported previously [317].

### *7.3.3 Intervention exercise program*

Participants randomized to the HiRIT group attended supervised exercise sessions twice-weekly for 30-minutes, comprising progressive resistance training and impact loading exercises on non-consecutive days. The program consisted of three resistance exercises (deadlift, overhead press and back squat) and one impact loading exercise (jumping chin ups with drop landings). The resistance exercises were introduced as low load variants of the fundamental exercises, to ensure participant safety and instruction of correct technique for each exercise. At the completion of the second month of the intervention, each participant was able to perform the three fundamental resistance training exercises. For the remainder of the intervention period the resistance exercises were performed at 5 sets of 5 repetitions, maintaining an intensity of > 80-85% 1 repetition maximum.

#### 7.3.4 *Control exercise program*

Participants randomised to the CON group undertook two 30-minute sessions per week, performing low intensity (10-15 repetitions at < 60% of 1RM) unsupervised, home-based exercises. The CON exercise program included: 10-minute walking warm-up, four stretches (side to side neck stretch, static calf stretch, shoulder stretch, and side to side lumbar spine stretch) and four low-resistance exercises (lunges, calf raises, standing forward raise, and shrugs), followed by a 5-minute cool-down walk. The intensity of the CON exercise program was modified by handheld weights (1, 2 and 3 kg dumbbells), where the load was increased progressively to a maximum of 3 kg for each exercise for the final month of the program.

#### 7.3.5 *Data collection*

At baseline (T0) and follow-up (T1), each participant was required to attend a two-hour testing session at the Bone Densitometry Research Laboratory at the Griffith University, Gold Coast campus where all bone and functional measures were taken.

#### 7.3.6 *Physical activity enjoyment*

Physical activity enjoyment was assessed at both baseline (T0) and follow-up (T1) using the 8-item version of the physical activity enjoyment scale (PACES-8) [215]. Participants were asked to circle the most appropriate number relating to their thoughts of physical activity participation on a 7-point Likert scale (1 = unpleasurable; 7 = pleasurable), with a higher number indicating greater enjoyment of physical activity.

### 7.3.7 *Quality of life*

Quality of life (QOL) was assessed at baseline (T0) and follow-up (T1) by the WHOQOL-BREF questionnaire. For each of the 24 items of the WHOQOL-BREF questionnaire, participants were asked to circle the most appropriate answer on a 5-point Likert scale based on their quality of life over the last four weeks. The raw scores were then transformed to a 4-20 range based on the four dimensions of quality of life measured by the WHOQOL-BREF: physical health, psychological health, social relationships, and the environment. A higher score represents a greater quality of life.

### 7.3.8 *Exit survey*

A custom-designed 13-item survey was developed to examine participant perception of the LIFTMOR trial (Table 15). Participants were instructed to read each statement and select the most appropriate answer on a 5-point Likert scale (1 = strongly disagree, 3 = neutral, 5 = strongly agree) based on their participation in the LIFTMOR trial.

**Table 15:** Items contained in the exit survey of the LIFTMOR trial

Question
1. I was enthusiastic to commence the exercise program in the LIFTMOR study
2. I was familiar with resistance training exercises before I joined the study
3. I was happy with my allocation to the home/supervised exercise program (please circle)
4. I was enthusiastic to do each exercise session during the LIFTMOR study
5. found it easy to learn and perform the LIFTMOR study exercises
6. I found the LIFTMOR exercises physically challenging throughout the study
7. I did not feel any physical discomfort (some level of pain) as a result of the LIFTMOR study
8. I did not feel that muscle soreness as a result of the LIFTMOR affected my daily life
9. I felt safe from injury while undertaking my exercise program
10. I noticed changes to my bodily appearance as a result of the LIFTMOR program
11. I noticed changes to my physical ability as a result of the LIFTMOR program
12. I plan to continue/take up resistance training at the end of my involvement in the LIFTMOR study
13. I would participate in the LIFTMOR study again if I had the chance

### 7.3.9 *Semi-structured interviews*

The final 14 HiRIT participants were invited to undertake a semi-structured interview where they were asked a series of 10 questions (Table 16). The semi-structured interviews were conducted at the beginning of the follow-up (T1) testing session by an interviewer independent of the study and unknown to the participants. Interviews were conducted at the beginning of the follow-up testing session to limit the impact of individual trial results on participant responses. The questions were developed to explore participants motivation for participation, previous physical activity participation, experiences during and after the HiRIT sessions, if they planned to continue HiRIT following completion of the LIFTMOR trial, and if they would

recommend the program to others. For each question, the interviewer prompted participants using phrases such as “can you be more specific”, “can you please explain further” and “what was it about ... which made you feel like ...”.

**Table 16:** Semi-structured interview questions for HiRIT participants of the LIFTMOR trial

Question
1. What was your motivation for your participation in the trial?
2. Have you ever participated in resistance training prior to the trial?
3. What were your experiences related to the study exercises during the course of the study?
4. Do you have any comments about the exercises or structure of the exercise sessions?
5. How did you feel during and after the exercise sessions?
6. Have you noticed any changes as a result of the exercise sessions?
7. Do you intend to continue regular resistance training?
8. What, if any, changes would you make to the exercise sessions?
9. Do you have any other feedback/anything else you would like to say?
10. Would you recommend this program to a friend?

### 7.3.10 Data analysis

Data collected during the semi-structured interviews were analyzed using Leximancer software (Version 4.50.27; Leximancer Pty Ltd, Brisbane, Australia). Thematic analysis was performed by first transcribing participant interviews, then responses for each of the 10 questions were collated. Once collated, responses for each question were uploaded and automatically analyzed based on conceptual content to identify main themes and concepts [284]. During the analysis process, words with little

semantic meaning (e.g. ‘if’, ‘we’, ‘probably’) were excluded as potential concepts or themes. Secondly, the automated content analysis was repeated and appraised, which enabled adjustments of software settings to amalgamate common themes and to identify major themes and concepts for each question. Visual concept maps and statistical outputs were generated to assist in identifying, and interpreting relationships between themes and concepts.

### *7.3.11 Statistical analysis*

Statistical analysis was undertaken using SPSS statistical software (Version 22; IBM Inc., Chicago, IL). Descriptive statistics were generated for participant characteristics, and all dependent variables. For all ordinal variables (PACES, WHOQOL-BREF, exit survey), the Kruskal-Wallis test was used to examine between-group (HiRIT and CON) differences at baseline for outcome measures and the exit survey, and Friedman’s test was used to examine between-group differences for PACES-8 and WHOQOL-BREF. For continuous data (i.e. anthropometrics), a one-way ANCOVA was used to examine differences between HiRIT and CON at baseline, while repeated measures ANCOVA was used to determine between-group differences. Initial values and compliance were used as covariates for all statistical analyses. All statistical outcomes were examined against a *p*-value of 0.05 to determine statistical significance.

## **7.4 Results**

### *7.4.1 Participant characteristics at baseline*

A total of 101 postmenopausal women participated in the LIFTMOR trial and were randomized to either HiRIT (*n* = 49) or CON (*n* = 52). There was no difference

between CON and HiRIT at baseline for anthropometrics, physical activity enjoyment and quality of life ( $p > 0.05$ ) (Table 17). Similarly, no baseline differences were observed between groups involved in the exit survey sub-analyses ( $n = 32$ ).

**Table 17:** Baseline participant characteristics ( $n = 101$ )

Parameter	CON ( $n = 52$ )	HiRIT ( $n = 49$ )	$p$
Age (years)	$65 \pm 5$	$65 \pm 5$	0.993
Weight (kg)	$62.2 \pm 9.5$	$63.9 \pm 11.3$	0.415
Height (cm)	$161.9 \pm 6.4$	$161.6 \pm 5.4$	0.810
PACES-8 Sum	$46.4 \pm 7.9$	$45.8 \pm 6.9$	0.654
I find it pleasurable; I find it unpleasurable	$5.2 \pm 1.1$	$5.4 \pm 1.1$	0.068
It's a lot of fun; It's no fun at all	$5.6 \pm 1.2$	$5.4 \pm 1.2$	0.270
It's very pleasant; It's very unpleasant	$5.6 \pm 1.2$	$5.5 \pm 1.0$	0.414
It's very invigorating; It's not at all invigorating	$5.9 \pm 1.2$	$6.0 \pm 0.9$	0.783
It's very gratifying; It's not at all gratifying	$6.0 \pm 1.1$	$6.0 \pm 0.8$	0.363
It's very exhilarating; It's not at all exhilarating	$5.7 \pm 1.1$	$5.8 \pm 0.9$	0.994
It's very stimulating; It's not at all stimulating	$5.9 \pm 1.1$	$5.9 \pm 0.9$	0.753
It's very refreshing; It's not at all refreshing	$5.9 \pm 1.0$	$5.8 \pm 1.1$	0.426
WHOQOL-BREF			
Question 1 (Global QOL)	$4.4 \pm 0.6$	$4.4 \pm 0.5$	0.822
Question 2 (Health QOL)	$4.0 \pm 0.7$	$3.7 \pm 0.8$	0.107
Physical (Domain 1)	$17.5 \pm 1.9$	$17.0 \pm 1.6$	0.198
Psychological (Domain 2)	$16.1 \pm 2.1$	$15.7 \pm 1.7$	0.354
Social relationships (Domain 3)	$15.9 \pm 2.7$	$16.1 \pm 2.9$	0.742
Environment (Domain 4)	$17.5 \pm 1.6$	$17.2 \pm 1.7$	0.468

Abbreviations: CON = control; HiRIT = high-intensity resistance and impact training

#### 7.4.2 *Eight-month change in physical activity enjoyment*

Eight-month change in PACES-8 is presented in Table 18. HiRIT had greater physical activity enjoyment after the completion of the LIFTMOR trial compared to CON (Sum of PACES-8). Specifically, for the items contained in the PACES-8, participants in the HiRIT group demonstrated greater improvements in physical activity enjoyment for 7 out of 8 items after completion of the LIFTMOR trial when compared to the CON group ( $p < 0.05$ ).

**Table 18:** Baseline and eight-month measures ( $\pm$  SD) with absolute change in PACES-8 after an eight-month exercise intervention in postmenopausal women with low bone mass (Per protocol data,  $n = 86$ ).

Parameter	CON ( $n = 43$ )			HiRIT ( $n = 43$ )			$p$
	Baseline	Follow-up	Change	Baseline	Follow-up	Change	
Sum of PACES-8 items	45.5 $\pm$ 7.5	43.86 $\pm$ 7.3	-1.6 $\pm$ 0.9	45.5 $\pm$ 7.5	48.8 $\pm$ 7.3	3.3 $\pm$ 1.0	<0.001*
I find it pleasurable; I find it unpleasurable	5.7 $\pm$ 1.2	5.4 $\pm$ 1.2	-0.3 $\pm$ 1.0	5.4 $\pm$ 1.1	6.0 $\pm$ 1.0	0.6 $\pm$ 1.2	<0.001*
It's a lot of fun; It's no fun at all	5.4 $\pm$ 1.3	5.0 $\pm$ 1.5	-0.4 $\pm$ 1.2	5.3 $\pm$ 1.2	6.0 $\pm$ 1.0	0.7 $\pm$ 1.1	<0.001*
It's very pleasant; It's very unpleasant	5.5 $\pm$ 1.3	5.3 $\pm$ 1.4	-0.2 $\pm$ 1.4	5.5 $\pm$ 1.0	6.1 $\pm$ 1.0	0.5 $\pm$ 1.1	0.002*
It's very invigorating; It's not at all invigorating	5.8 $\pm$ 1.3	5.8 $\pm$ 1.1	-0.0 $\pm$ 1.2	6.0 $\pm$ 0.9	6.1 $\pm$ 1.1	0.1 $\pm$ 1.1	0.225
It's very gratifying; It's not at all gratifying	6.0 $\pm$ 1.1	5.8 $\pm$ 1.0	-0.1 $\pm$ 1.1	6.0 $\pm$ 0.8	6.4 $\pm$ 0.8	0.4 $\pm$ 0.8	0.009*
It's very exhilarating; It's not at all exhilarating	5.6 $\pm$ 1.2	5.3 $\pm$ 1.2	-0.2 $\pm$ 1.1	5.7 $\pm$ 0.9	5.9 $\pm$ 1.0	0.2 $\pm$ 0.9	0.049*
It's very stimulating; It's not at all stimulating	5.8 $\pm$ 1.2	5.8 $\pm$ 1.2	-0.1 $\pm$ 1.1	5.9 $\pm$ 0.9	6.3 $\pm$ 0.8	0.4 $\pm$ 0.9	0.046*
It's very refreshing; It's not at all refreshing	5.8 $\pm$ 1.1	5.5 $\pm$ 1.2	-0.4 $\pm$ 1.3	5.7 $\pm$ 1.1	6.2 $\pm$ 0.8	0.5 $\pm$ 1.1	0.001*

Abbreviations: CON = control; HiRIT = high-intensity resistance and impact training

\*  $p < 0.05$

### 7.4.3 *Eight-month change in quality of life*

Eight-month change in WHOQOL-BREF is presented in Table 19. HiRIT had a within-group improvement in self-reported health QOL (Question 2) on the WHOQOL-BREF ( $p = 0.003$ ). No other between-group or within-group differences were observed for self-reported WHOQOL domains or questions.

**Table 19:** Baseline and eight-month measures ( $\pm$  SD) with absolute change in WHOQOL-BREF after an eight-month exercise intervention in postmenopausal women with low bone mass (Per protocol data,  $n = 86$ )

Parameter	CON ( $n = 43$ )			HiRIT ( $n = 43$ )			$p$
	Baseline	Follow-up	Change	Baseline	Follow-up	Change	
WHOQOL							
Global QOL	4.4 $\pm$ 0.6	4.3 $\pm$ 0.6	0.0 $\pm$ 0.1	4.5 $\pm$ 0.6	4.5 $\pm$ 0.6	0.1 $\pm$ 0.1	0.350
Health QOL	4.0 $\pm$ 0.9	4.1 $\pm$ 0.7	0.1 $\pm$ 0.1	3.8 $\pm$ 0.9	4.2 $\pm$ 0.7 <sup>†</sup>	0.4 $\pm$ 0.1	0.144
Physical domain	17.3 $\pm$ 1.8	17.2 $\pm$ 1.9	-0.1 $\pm$ 0.3	17.2 $\pm$ 1.8	17.2 $\pm$ 1.9	0.1 $\pm$ 0.3	0.901
Psychological domain	15.9 $\pm$ 2.0	16.0 $\pm$ 2.0	0.1 $\pm$ 0.2	15.8 $\pm$ 2.0	16.2 $\pm$ 2.0	0.4 $\pm$ 0.2	0.271
Social domain	15.7 $\pm$ 2.9	16.1 $\pm$ 2.6	0.4 $\pm$ 0.4	16.1 $\pm$ 2.9	16.5 $\pm$ 2.6	0.5 $\pm$ 0.4	0.948
Environment domain	17.4 $\pm$ 1.7	17.6 $\pm$ 1.5	0.2 $\pm$ 0.2	17.3 $\pm$ 1.7	17.6 $\pm$ 1.5	0.2 $\pm$ 0.2	0.952

Abbreviations: CON = control; HiRIT = high-intensity resistance and impact training

<sup>†</sup>  $p < 0.05$

#### 7.4.4 *Exit survey*

HiRIT participants reported being happier with their group allocation, more enthusiastic to perform each training session, noticed positive body appearance changes and were more likely to participate in the LIFTMOR trial again if given the chance compared to participants in the CON group ( $p < 0.05$ ) (Table 20). No between-group differences were observed for any of the other questions on the exit survey.

**Table 20:** Exit survey scores ( $\pm$  SD) after an eight-month exercise intervention in postmenopausal women with low bone mass (Per protocol data,  $n = 32$ )

Question	CON ( $n = 15$ )	HiRIT ( $n = 17$ )	$p$
1. I was enthusiastic to commence the exercise program in the LIFTMOR study	4.7 $\pm$ 0.5	4.8 $\pm$ 0.5	0.344
2. I was familiar with resistance training exercises before I joined the study	3.3 $\pm$ 1.1	2.7 $\pm$ 1.1	0.099
3. I was happy with my allocation to the home/supervised exercise program	4.0 $\pm$ 1.2	4.8 $\pm$ 0.6	0.030*
4. I was enthusiastic to do each exercise session during the LIFTMOR study	3.7 $\pm$ 1.1	4.4 $\pm$ 0.5	0.030*
5. found it easy to learn and perform the LIFTMOR study exercises	4.3 $\pm$ 1.0	4.2 $\pm$ 0.8	0.325
6. I found the LIFTMOR exercises physically challenging throughout the study	3.8 $\pm$ 0.9	4.2 $\pm$ 0.8	0.193
7. I did not feel any physical discomfort (some level of pain) as a result of the LIFTMOR study	3.3 $\pm$ 1.0	3.8 $\pm$ 1.1	0.149
8. I did not feel that muscle soreness as a result of the LIFTMOR affected my daily life	4.0 $\pm$ 0.9	4.2 $\pm$ 0.7	0.535
9. I felt safe from injury while undertaking my exercise program	4.2 $\pm$ 0.9	4.5 $\pm$ 0.8	0.169
10. I noticed changes to my bodily appearance as a result of the LIFTMOR program	2.9 $\pm$ 1.3	3.8 $\pm$ 0.9	0.018*
11. I noticed changes to my physical ability as a result of the LIFTMOR program	2.9 $\pm$ 1.3	3.8 $\pm$ 0.9	0.088
12. I plan to continue/take up resistance training at the end of my involvement in the LIFTMOR study	2.9 $\pm$ 1.3	3.8 $\pm$ 0.9	0.081
13. I would participate in the LIFTMOR study again if I had the chance	2.9 $\pm$ 1.3	3.8 $\pm$ 0.9	0.028*

\*  $p < 0.05$

#### 7.4.5 Interview findings

##### 7.4.5.1 Motivators, barriers and previous resistance training participation

The major theme identified for a participant's motivation for registering in the LIFTMOR trial was their *bone* health status (hits = 42), followed by wanting to participate in *exercise* (hits = 5) and age-related muscle weakness (hits = 3). The major theme of *bone* was related to concepts of already knowing they had low bone mass (concepts of density, doctor, osteoporosis and osteopenia) and wanting to try the program given the prospect of gaining bone health benefits:

*“I don't like taking medication, so I spoke to the doctor and said I'd like to try this program and if it works out, maybe I wouldn't need medication for bones”*

When asked about past participation in resistance training, the major theme of *training* was identified (question 2, hits = 39). Training was related to other forms of exercise they had undertaken in the past, most commonly squash, tennis, light hand weights or walking, as no participant had performed higher intensity forms of resistance training. Training was followed by *time* as a theme (hits = 31), with concepts related to barriers to previous resistance training participation, such as:

*“I didn't have time to be running off to gyms”*

*“it was just simply time”*

The theme *weights* (hits = 16) for question 2 was related to concepts of participation in lighter resistance training, and not “heavy” resistance training like they experienced during the LIFTMOR trial. Lastly, the theme of *Pilates* (hits = 6) was identified, as 4 of the 14 interviewees (29%) had participated in Pilates prior to the trial, further reinforcing the lack of previous participation in resistance training:

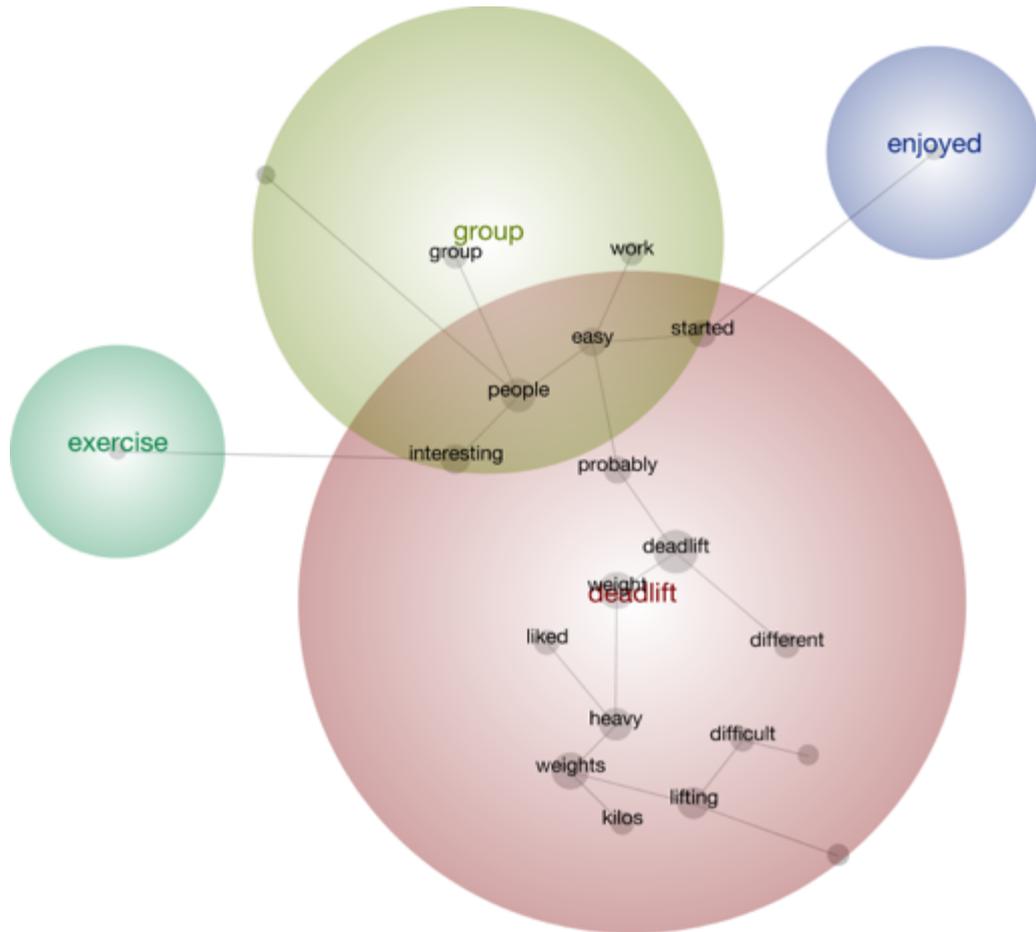
*“Just a little bit of Pilates and yoga”*

*“Not so much resistance training I wouldn't say. You know, I've done yoga and Pilates classes”*

#### 7.4.5.2 Participant experiences related to the HiRIT intervention

The dominant theme associated with a participant’s experience of HiRIT exercise was *deadlift* (question 3, hits = 76) (Figure 26). Deadlift as a theme was related to the concepts of weight, heavy, different and difficult, as participants were not expecting to perform deadlifts or lift such heavy weights:

*“I could see people who are my size doing heavy weights with deadlift. it's interesting to see and wonder why they were able to do that”*



**Figure 26:** Thematic concept map of participant experiences of HiRIT exercises in the LIFTMOR trial (n = 14)

*Group* (hits = 20) was the next theme identified for question 3 and was related to the group atmosphere and supervision provided during training sessions (Figure 26). Additionally, the group setting for HiRIT was perceived positively in response to questioning about the structure of the exercise sessions (question 4; hits = 64), and was a source of motivation to attend and challenge themselves at each training session:

*“Not wanting to let the group down or the program down was motivation to get there”*

*“The comradery of the group and the fact that you were challenging yourself each time”*

*Enjoyed* (question 3, hits = 9) was also identified as a theme, with 5/14 (36%) using this term in their first sentence when asked about their experiences of the study exercises. When asked to provide any additional feedback (question 9), participants reiterated their enjoyment of the group atmosphere and the motivation they drew from lifting with others. The theme of *encouraging* (hits = 3) was also related to other participants and instructors, where participants remarked on the positive nature of the group dynamics during the HiRIT program:

*“Well the fact that you're chatting and laughing about things, that sort of takes your mind off what you are doing. It was good and people encouraging you, which is a big thing too”*

*“I mean because a lot of the ladies were there, they were there with the same sort of positive attitude. So it was a very encouraging, optimistic, positive sort of environment”*

The instructors were identified again under the concept of *safe* and the theme of *people* when asked to provide additional feedback about the HiRIT program. Seventy-one percent (10/14) of participants took this opportunity to comment about the instructors who made them feel safe when performing the exercises.

The theme of *time* (question 4, hits = 9) was identified for two reasons in response to the structure of the HiRIT program, the first being the issue of peak hour traffic as a barrier for attending exercises sessions:

*“I guess the only sort of problem being around peak hour traffic, but I was lucky I lived in Helensvale, so I just came straight in and out”*

Secondly, *time* was related to the duration of the sessions, with the short duration being viewed positively. *Time* (question 8, hits = 24) was also identified when asked about any changes they would make to the program, with 6 participants (43%) noting their support for the twice weekly 30-minute time commitment. *Time* was also identified as a concept under the theme *longer* (question 8), with three participants explicitly stating that the program does not need to be longer, contrasting the single participant who advocated for longer sessions. The benefits of short training sessions were further supported when participants were given the opportunity to provide any further feedback (question 9, hits = 4):

*“one of the positives of it, was that it was short and sharp”*

*“Everyone could afford that time”*

Figure 27 displays common themes and concepts of how participants felt during and after the HiRIT sessions in the LIFTMOR trial (question 5). The dominant theme of

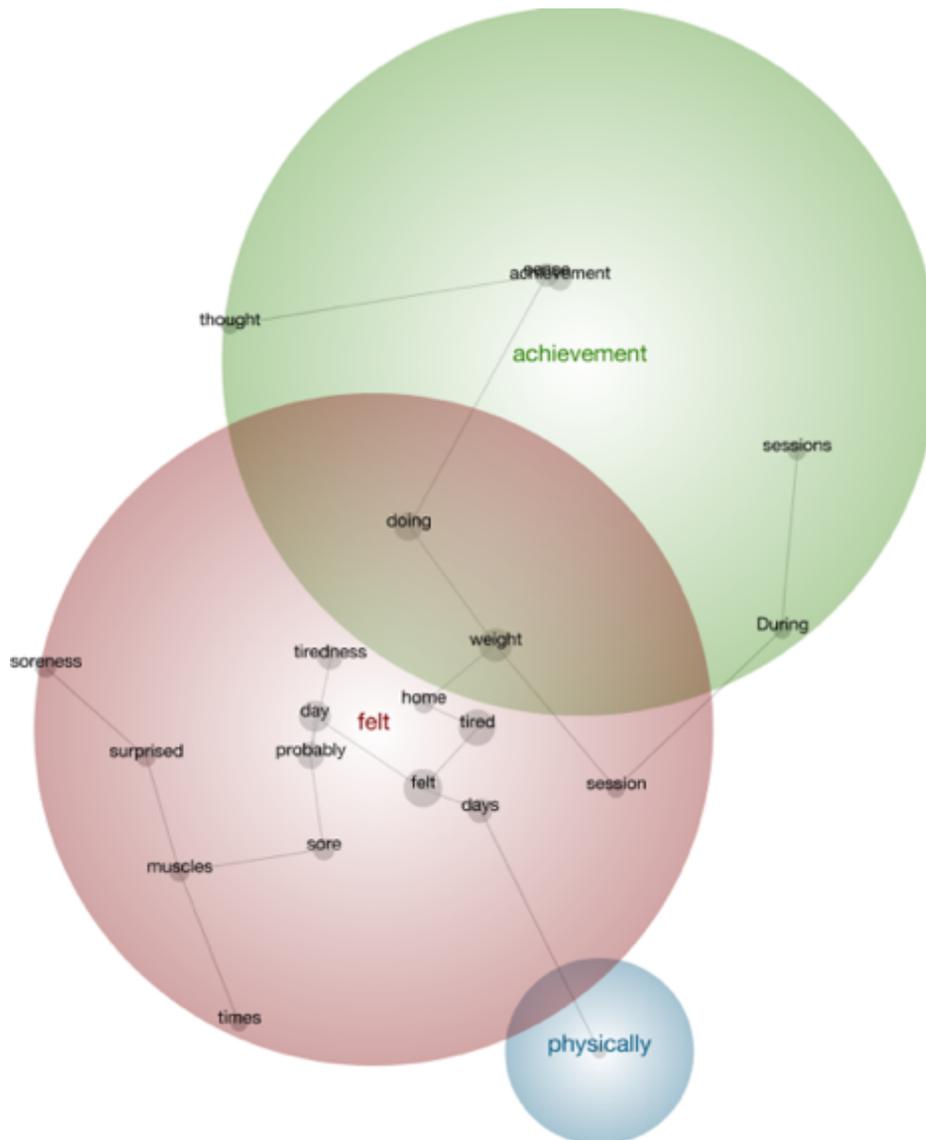
*felt* (hits = 51) was identified, and was related to the concepts of tiredness, tired and sore. Half of all participants (7/14) commented on the sense of tiredness they felt after the completion of HiRIT sessions. The concept of soreness, however, was not related to muscle soreness or pain after the session. Nonetheless, participants generally anticipated such tiredness, accepting that the tiredness was transient and that it gradually improved over the duration of the intervention. Participants commented:

*“Especially once you had an understanding of why it was there, so you thought it was good and you didn't mind you don't mind that sort of tiredness”*

*“And then afterwards I've noticed interestingly I've felt, sort of feel more energized after and then maybe tired the next day. I mean occasionally when I go home it's a bit of an effort to walk up the stairs”*

*Achievement* (hits = 18) was identified as a theme during the exercise sessions (question 5) and was associated with the concepts of *doing*, *sessions*, *during* and *weight*, where participants had a sense of achievement at the end of a session, or when they were able to lift a heavy weight:

*“We were always able to complete the class, even if it was hard. So there was a good sense of achievement”*



**Figure 27:** Thematic concept map of how HiRIT participants felt during and after the exercise sessions in the LIFTMOR trial (n = 14)

Figure 28 displays common themes and concepts related to changes noticed by participants as a result of HiRIT sessions in the LIFTMOR trial (question 6). The dominant theme of *better* (hits = 46) was identified, and was related to the concepts of *shape, stronger, muscle, body* and *mental*. Participant responses were often related to

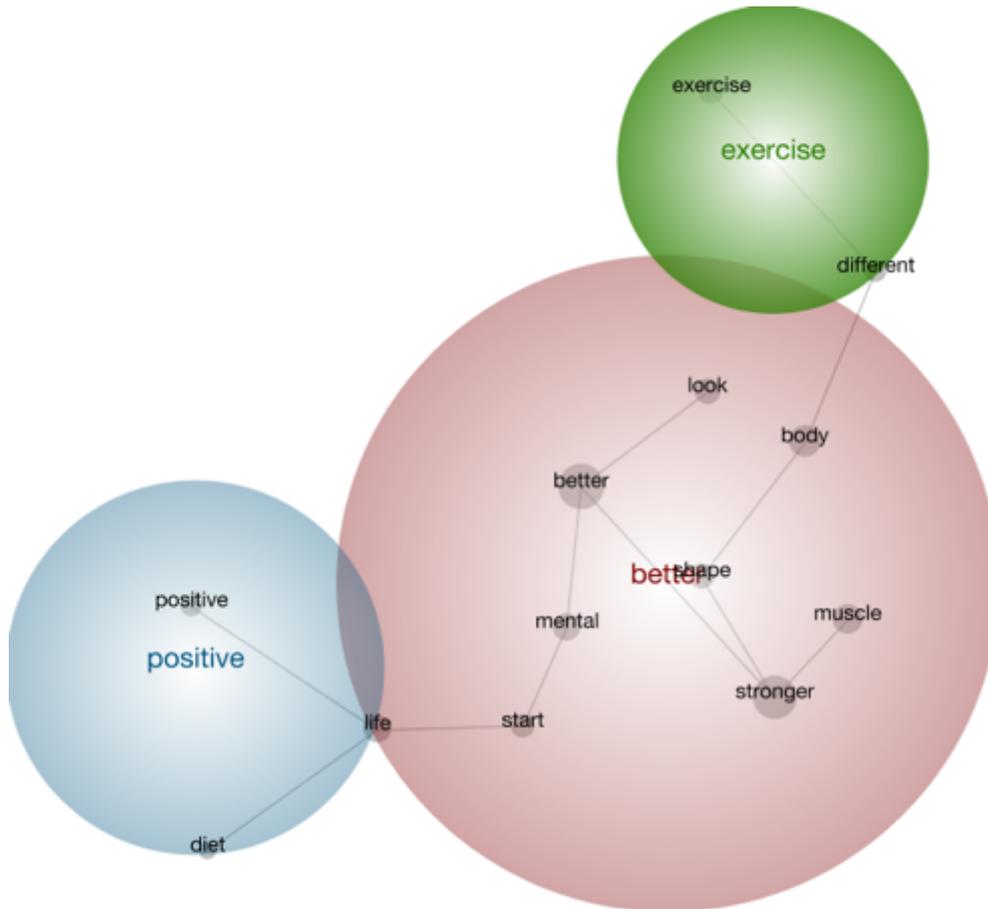
how they felt stronger, positive body composition changes, and how they noticed positive mental changes related to HiRIT:

*“I feel better in myself. I feel stronger in myself”*

*“I’m moving better, I’m feeling stronger generally”*

The themes *exercise* and *positive* were both identified with 10 hits each (question 6). The theme *exercise* was represented when participants explained the positive changes associated with the HiRIT exercise sessions and its positive effects on both the body and mind. Similarly, the term *positive* was also used when describing the benefits of HiRIT on strength, body image and mental state:

*“You know if your body feels better, you know your mental attitude improves significantly.”*



**Figure 28:** Thematic concept map of changes noticed by HiRIT participants as a result of LIFTMOR trial (n = 14)

#### 7.4.5.3 Future considerations and recommendations

When participants were asked if they intend to continue regular resistance training, the dominant theme of *gym* (hits = 40) was identified. The majority of participants (10/14) mentioned attending a local gym as a potential option for continued resistance training participation. The next two themes identified, *program* (hits = 9) and *classes* (hits = 5), were associated with commercial facilities that run a similar HiRIT program as a potential option for continuing resistance training. All participants

expressed an intent to continue resistance training after they completed the LIFTMOR trial.

When asked if they would make any changes to the HiRIT program, the term *exercises* (question 8, hits = 40) was identified as a major theme. The theme exercise was used in the context of not being an expert in exercise prescription and participants conceded their lack of knowledge and/or expertise (5/14) in suggesting changes. Upon further encouragement, three participants (21%) suggested the addition of balance exercises may be beneficial.

All participants stated that they would recommend the LIFTMOR trial (question 10), with half of participants (7/14) stating they have already recommended the program to a friend. The theme *absolutely* (hits = 6) was also identified when participants were asked if they would recommend the LIFTMOR trial. When asked why, the theme of *doing* (hits = 32) was identified. The theme of doing was linked to concepts of the positive participation experience and the benefits gained, such as becoming stronger. Furthermore, *benefits* was identified as a theme (hits = 4) and was also associated with the concept of *strength* and the beneficial experience being a factor for recommending the program to a friend. One participant commented:

*“Yes, I definitely would. I think of the all of the benefits I've talked about. You know, the social, the physical, the mental, ... the benefits far outweigh any of the negatives”*

## **7.5 Discussion**

The primary aim of the LIFTMOR trial was to determine the effect of brief, bone-targeted, supervised HiRIT for postmenopausal women with low to very low bone

mass on parameters of bone. While the LIFTMOR program efficacy for improving bone has been reported elsewhere [317], the current work comprises a report of secondary outcomes of physical activity enjoyment, quality of life and participant experiences of HiRIT and the LIFTMOR trial. We observed that 8 months of supervised HiRIT improved physical activity enjoyment and HiRIT participants were happier with their group allocation compared to a low intensity home-based exercise program.

Furthermore, HiRIT improved participant-rated health quality of life. The qualitative analysis of HiRIT participant interview responses revealed that HiRIT was received favorably, with participants reporting a sense of achievement, enjoyment in the group nature of the exercise sessions and feeling stronger. All HiRIT participants intended to continue the program after the trial period and would recommend the program to a friend.

The diagnosis of osteopenia or osteoporosis has been shown to be a strong motivator for undertaking physical activity [14]. Our data support previous findings, with a participant's bone status being the major theme related to a participant's interest in joining in the LIFTMOR trial. Furthermore, the use of physical activity as an alternative to medications was a motivator for some participants, which further supports interest in physical activity as a desirable management strategy in those with osteoporosis [14, 274]. Upon acceptance to the LIFTMOR trial and randomization, participants allocated to HiRIT were happier with their initial group allocation. This may have had a positive impact upon physical activity enjoyment and their increased enthusiasm for each session. It is important to consider that this question was answered after the intervention period, so the impact of physical activity enjoyment during the trial may influence a participant's retrospective happiness with their initial group

allocation. At initial randomization, participants understood that they may receive either a resistance training program at home or a supervised program in a group setting at one of two facilities. While we are unable to accurately determine their reasons for allocation happiness retrospectively, it is possible that participants view exercise in a group session more favorable to exercising at home independently. Finally, although there were differences in reported happiness with allocation, there were no differences in compliance or drop-out between HiRIT and CON (reported previously) [317]. Therefore, retrospective participant happiness with initial allocation or changes in physical activity enjoyment were not associated with compliance or drop-out in the LIFTMOR trial. This finding likely reflects an ethical commitment made by participants to the study irrespective of satisfaction with group allocation.

Higher levels of physical activity enjoyment are associated with increased exercise participation [249]. The increase in physical activity enjoyment in the HiRIT group may be multifactorial, and it is difficult to distinguish whether the improvements are a result of the exercises themselves, exercise instructors, or the group atmosphere. The influence of exercise instructors and group dynamics were identified as themes and concepts when participants were asked about their HiRIT program experiences. Both instructor and group dynamics are known to be influential factors in improving physical activity enjoyment, albeit in a younger sample [14, 101]. A study of older individuals showed that increased levels of social support from a group setting was instrumental in the perceived enjoyment of exercise [204]. The lack of social support may also explain the reduction in physical activity enjoyment of low-intensity home program participants. Indeed, exercising alone has been identified as an interpersonal barrier to exercise adherence in osteoporosis sufferers [14].

The social influence of group training sessions was also a theme identified by participants that related to their experiences of the exercises and the structure of the program. Beyond enjoyment, group exercise programs have been shown to increase motivation and adherence [14, 124] – an effect which may have played out in HiRIT participants. Seeing other participants lift heavy weights appeared to generate a level of competition between participants, which was identified as a concept under the theme of people. In fact, others have shown that older adults (>60 years) exhibit greater satisfaction from exercise when physically challenged [208] and may provide a catalyst for progression of weights during resistance training.

It is noteworthy that not all older individuals exhibit satisfaction when physically challenged, instead exhibiting fear when faced with the prospect of lifting heavy weights due to a perceived risk of fracture [336]. Supervision by a qualified exercise instructor, however, is known to reduce fear, create a safe environment, and increase physical ability [208]. Indeed, the idea of feeling safe was expressed by participants of the LIFTMOR trial, with participants reporting that the instructors made them feel safe when lifting heavier weights. Thus, our data further emphasizes the importance of appropriate exercise supervision to not only increase an individual's physical ability, but also increase adherence and enjoyment [14, 101, 124, 336].

Older adults perceive the time to commute, perform exercise and the associated hygiene practices associated with physical activity as very time consuming [63, 267]. Perceived lack of time is possibly the greatest barrier to physical activity participation and was highlighted by HiRIT participants as a barrier to previous resistance training participation [14, 253]. The theme of time was identified in responses to four of the interview questions, with the majority of positive comments related to the time-efficient

nature of the HiRIT training program. Participants were surprised that the program only required two half hour sessions each week and were encouraged by its brevity. The favorably small time commitment may help explain the high compliance (>90%) observed for the HiRIT participants who suggested that two half hour sessions each week were “doable” and do not need to be any longer. This has implications for the development of efficacious exercise programs and exercise recommendations, as effective programs must minimize time commitment in order to facilitate the greatest uptake.

Exercise has been shown to improve the physical, pain and vitality domains of quality of life [185, 299]. Contrary to these findings, we did not observe an increase in physical quality of life for either exercise group. The lack of quality of life findings may relate to the use of the WHOQOL-BREF as our chosen measure. Improvements in quality of life have been observed when the Quality of Life Questionnaire of the European Foundation for Osteoporosis (QUALEFFO) and Short Form 36 (SF36) questionnaires were collated in a meta-analysis [185]. While there were no increases in physical quality of life measured by the WHOQOL-BREF, interviews identified the concepts of shape, stronger, muscle, body and mental under the theme of better for HiRIT participants and body changes were reported in the exit survey. These self-reported improvements in physical aptitude support the physical and neuromuscular performance improvements reported for HiRIT previously [317].

Not all responses to HiRIT were positive. Half of HiRIT participants reported a sense of tiredness for one to two days after each training session. Participants clarified that this tiredness was not related to muscle soreness. This concept of whole body tiredness has been reported previously in older adults undertaking resistance training

[83, 261]. Contrary to the current findings, participants in both studies reported the tiredness as positive. The feeling of tiredness was associated with increased strength and health [83], or calmness [261]. HiRIT participants reported this sense of tiredness as negative, although the tiredness was short lived and generally accepted as a known effect of the training.

When combining the data gathered from questionnaires and interviews, the overall participant perception of the HiRIT program is positive. Importantly, when asked if they would participate in the trial again if given the opportunity, HiRIT were more likely to participate than CON. This sentiment was reinforced by interview responses, where all participants would recommend the program to a friend and many had already sought out local gyms where they could continue training after completion of the trial. When asked why they would recommend the program, the responses were focused on the improvements they have noticed, despite not knowing their study results at the time of the interview. This positive reaction to an efficacious exercise program for improving bone suggests that HiRIT is both an effective and appealing, and therefore a realistic strategy for managing osteoporosis in postmenopausal women in the ‘real world’.

Several limitations warrant acknowledgement. Firstly, the semi-structured interviews were conducted on only a subset of LIFTMOR trial participants. This small number of participants, and the lack of interviews for the low intensity home based control program limit the exploration of differences between the different exercise delivery methods. Secondly, as the exit survey and interviews were conducted at follow-up only, participants who dropped out were not included. However, no participant disclosed lack of appeal of either the HiRIT or control program as the reason

for discontinuing participation in the trial. Lastly, the study population was a convenience sample, meaning only individuals who were interested in participating in an exercise program were recruited. This limits the generalizability of findings to only those who already wish to undertake exercise, and does not provide information pertaining to barriers, experiences and motivators for those who are reluctant to undertake physical activity or are in the earlier stages of contemplation.

In conclusion, participation in supervised HiRIT was associated with increased physical activity enjoyment and was predominantly perceived as a positive experience. We therefore surmise that, not only is HiRIT efficacious for improving bone and physical function, it is an appealing exercise program for postmenopausal women with low bone mass. Positive aspects of the program included the group atmosphere, expert supervision, and short duration. When combined, the findings of the current work further support HiRIT as a potential real-world management option for postmenopausal women with low to very low bone mass.



## Chapter 8: General Discussion

## 8.1 Summary of the LIFTMOR trial

In Australia, it is estimated that 1 in 3 people over 50 years of age have osteopenia or osteoporosis [320]. In the year 2011, it was estimated that 1.2 million Australians suffered from osteoporosis and this is only expected to rise with an ageing population [88, 131]. Certain medications can increase bone mass and prevent fractures, but many individuals refuse to take them. Current non-pharmacological management recommendations for osteoporosis can be expected to confer little benefit to bone as they include exercise interventions of insufficient intensity.

High intensity, progressive resistance and impact weight bearing training (HiRIT) has not been routinely prescribed by healthcare professionals for osteoporosis in the absence of evidence to support its efficacy and safety. Our primary goal was to test a novel brief, bone-targeted, high-intensity resistance and impact training program for musculoskeletal health in postmenopausal women with low to very low bone mass. The specific aims of the project were to determine the effects of supervised HiRIT on 1) indices of bone strength; 2) physical performance measures and falls risk factors; 3) kyphosis and vertebral fracture; and 4) enjoyment, quality of life and exercise perception in healthy postmenopausal women with low to very low bone mass.

To address our aims, we developed the Lifting Intervention For Training Muscle and Osteoporosis Rehabilitation (LIFTMOR) trial. The LIFTMOR trial was a randomized controlled trial comparing supervised HiRIT and a low load home-based falls prevention program (CON). HiRIT comprised of high intensity resistance training in the form of deadlifts, squats and overhead press, and high intensity weight bearing exercise through jumping chin-ups. The following discussion presents a synthesis of the findings of the four publications arising from the LIFTMOR trial; which address the

aforementioned aims. The clinical significance of the research is highlighted, and future directions are proposed.

### *8.1.1 Publications one and two*

Exercise has been proposed as a potential strategy to manage osteoporosis [136], however the efficacy of exercise interventions are traditionally perceived as modest at best [100, 136, 335]. The most osteogenic activities are those that induce high magnitude strains [258] at high rates [228] or frequencies in bone [259]. High intensity, progressive resistance and impact weight bearing training (HiRIT) can be employed to generate such loads, although it is widely held that high-intensity exercises should not be attempted by individuals with established osteoporosis, owing to a potentially increased risk of fracture [106, 176]. Thus, it was not known if a bone focussed HiRIT program would be efficacious for improving risk factors for fracture in postmenopausal women.

The primary aim of publications one and two was to report the efficacy of bone-targeted HiRIT for improving FN and LS BMD in postmenopausal women with low to very low bone mass. The secondary aims were to determine if HiRIT improves bone geometry and physical function, and is safe for postmenopausal women with low bone mass. One hundred and one postmenopausal women with low to very low bone mass participated in the LIFTMOR trial. Pre and post intervention testing included lumbar spine and proximal femur DXA scans and measures of functional performance (timed up-and-go, functional reach, 5 times sit-to-stand, back and leg strength). HiRIT was superior to a home-based low intensity control exercise program for lumbar spine ( $2.9 \pm 2.8\%$  vs  $-1.2 \pm 2.8\%$ ,  $p < 0.001$ ) and femoral neck ( $0.3 \pm 2.6\%$  vs  $-1.9 \pm 2.6\%$ ,  $p =$

0.004) BMD, and all functional performance measures. Compliance was high in both exercise groups (HiRIT  $92 \pm 11\%$ ; CON  $85 \pm 24\%$ ), and only one adverse event was reported for HiRIT. The adverse event was an episode of low back pain where the participant missed two weeks of the intervention, before recommencing the HiRIT program and completing the trial successfully.

### *8.1.2 Publication three*

While exercise is a positive strategy to improve bone mass, some clinicians have worried that exercises known to stimulate bone may cause fragility fractures in those most at risk of osteoporosis [55, 136, 167]. Vertebral fractures commonly occur with spine twisting, flexion, or a combination of those movements, especially when performed quickly and/or with high external loads [112]. While no clinical signs or symptoms of vertebral fracture were evident during the LIFTMOR trial, more tangible evidence was required. An objective assessment of changes in vertebral morphology attributable to fracture following exercise in postmenopausal women at risk of fracture has not previously been reported. Furthermore, as HiRIT has the potential to substantially improve back extensor strength, it was possible that improvements in kyphosis would be observed.

The primary aim of publication three then was to determine the effect of a bone-targeted HiRIT program on vertebral morphology and kyphosis in postmenopausal women with low to very low bone mass. Lateral thoracolumbar DXA scans (Medix DR, Medilink, France) were performed at baseline and follow up. Cobb angle was determined, and vertebral fracture identification was performed using the semi-quantitative Genant method. Clinical kyphosis measures were performed in relaxed and

standing tall postures using an inclinometer and Flexicurve. Both CON and HiRIT exercise was efficacious in reducing thoracic kyphosis, however the greatest effect was observed following HiRIT (Standing tall inclinometer:  $-6.7 \pm 8.2^\circ$ ). Importantly, despite concerns, there were no changes in vertebral morphology in the HiRIT participants indicating no crush or wedge fractures were caused.

### 8.1.3 *Publication four*

Physical activity participation in older adults is generally low which is associated with poorer health [224, 293]. Barriers for exercise participation in older adults include lack of time, co-morbid conditions, financial cost, body image concerns and low perceived benefits of physical activity [232, 253]. Social interactions such as group classes, encouragement and support, and professional instruction are perceived as important motivating factors for older adults performing physical activity [102, 232, 253]. Given physical activity participation has the potential to have a profound effect on older adults, it is important that all psychosocial factors are considered when developing an exercise program to maximize participation and potential benefits.

The aim of publication four was to examine physical activity enjoyment, quality of life, and participant perception of HiRIT in the LIFTMOR trial. At baseline and follow-up testing sessions, participants completed physical activity enjoyment (PACES-8) and quality of life (WHOQOL-BREF) questionnaires. At follow-up, the final 32 participants completed an exit survey relating to their experiences of the trial. HiRIT participants who completed the exit survey also underwent semi-structured interviews with questions related to physical activity and their HiRIT experience. Participants in the HiRIT group exhibited greater physical activity enjoyment and were more

enthusiastic for each session than participants in the CON group. Qualitative analysis of semi-structured interviews of HiRIT participants identified bone health status as the most common motivator for enrolling in the LIFTMOR trial, time was an important barrier to physical activity participation, and supervised group exercise sessions were perceived as being positive.

## **8.2 Synthesis and significance of findings**

The work presented in this thesis contributes to current knowledge on the effects of exercise for improving musculoskeletal health in postmenopausal women. The LIFTMOR trial provides paradigm shifting evidence that high intensity resistance and impact training can be both safe and efficacious for improving bone in postmenopausal women with low to very low bone mass. This evidence is contrary to previous opinions that high intensity exercise is harmful to all postmenopausal women at risk of fracture.

### *8.2.1 New insights into exercise prescription*

Exercise prescription has endless possibilities, as exercise can be implemented via numerous modalities and intensities. When applying current knowledge, it is important to be consistent in defining and describing interventions, so as to allow comparisons between clinical fields and trials [281]. Exercise prescription for postmenopausal women has erred on the side of caution when recommending exercise interventions, a practice which has limited the effect of exercise programs for improving bone. The term high-intensity resistance training has been applied previously to describe exercises performed for 8-12 repetitions which, according to guidelines, actually defines moderate intensity resistance training [29]. A true high intensity

resistance training program requires loads that are >85% of an individual's one-repetition maximum and as a result can only be lifted for 6 or fewer repetitions before failure [4]. Inconsistency in defining exercise intensity may provide insight into the lack of response of bone to previous 'pseudo' high intensity resistance training programs for postmenopausal women.

Similarly, few studies have examined truly high intensity impact loading (>4 x BW) in postmenopausal women, with most being low-moderate intensity due to an anticipated risk of injury [28, 106]. The incorporation of high loading rate through jumping chin ups was a novel strategy to apply a combination of the two most osteogenic parameters into a single exercise for low bone mass (high load magnitude and rate). Importantly, this strategy did not result in increased injuries.

The LIFTMOR trial was the first to implement a true high intensity resistance and impact training program in postmenopausal women with low bone mass. Results confirmed our hypotheses that a program of supervised high intensity resistance and impact training confer greater benefits to bone than a low intensity exercise intervention for postmenopausal women.

### *8.2.2 Benefits of high intensity resistance and impact training*

Physical activity participation is important for maintaining a healthy musculoskeletal system and is associated with benefits to physical performance [24, 37, 115, 189, 190, 292, 296, 309, 311], body composition [48], and psychosocial factors [206, 219]. The improvements in many facets of the musculoskeletal system observed in the LIFTMOR trial support these findings. Our observed improvements in BMD surpass previous reports from reputable exercise interventions; an observation that

could be considered intuitive in light of the well-known positive relationship between load magnitude and bone adaptation [77, 171]. Importantly, improvements in those functional performance outcomes suggest that supervised HiRIT may not only reduce the risk of fracture by enhancing parameters of bone strength, but by preventing falls. The improvements in strength may extend further than functional performance. Exercise interventions for kyphosis focus on improving back extensor strength and spinal mobility [18]. Our results support previous findings, as we observed both improvements in back extensor strength and kyphosis [18, 25, 117, 139, 160]. Combined, the benefits of HiRIT in the LIFTMOR trial appear to be multifactorial, from improving bone and function, to reducing risk for fracture through falls prevention. The benefits of HiRIT for the prevention of osteoporotic fracture are multifactorial, from improving the resistance of bone to failure under sudden insult by increasing mass, to reducing the risk of sudden insult through falls prevention. Additional well-recognised benefits from high intensity resistance training include improvements in lipid profile, cognition, quality of life and aerobic exercise capacity [46].

### *8.2.3 High intensity resistance and impact training enjoyment*

Physical activity enjoyment is an important motivating factor for exercise participation [249]. It is therefore an important factor to consider when developing viable efficacious exercise programs, as low compliance will hamper the potential benefits a program may offer. The LIFTMOR trial exhibited high compliance and improvements in exercise enjoyment. The 92% compliance rate of the HiRIT group compares favourably to that of previous resistance training studies [107, 170, 191, 197, 218]. All HiRIT participants indicated an intention to continue the program beyond the

trial. This positive reaction emphasises that HiRIT may be an efficacious and feasible non-pharmacological management option for osteoporosis in postmenopausal women.

The causes for the positive response to HiRIT may be multifactorial. A study of older adults showed that increased levels of social support from a group setting was instrumental in the perceived enjoyment of exercise [204]. Furthermore, lack of time is a common barrier to exercise, with adherence being as low as 50% in the first 6 months of some exercise programs [191, 253]. The minimal time commitment and group nature of the LIFTMOR HiRIT program were clearly positive aspects.

#### *8.2.4 Safety of high intensity resistance and impact training*

Safety concerns exist for exercises known to stimulate bone, due to a perceived risk of fragility fracture [55, 136, 167]. The LIFTMOR trial supports the findings of a small previous trial, which reported no major adverse events for a high intensity resistance training intervention in postmenopausal women [214]. As flexion-based movements with high loads are known to cause fracture in weak spines, exercise programs for osteoporosis must avoid flexion moments when loading [28, 275]. The average estimated compressive failure loads of thoracolumbar vertebrae are not dissimilar to the loads experienced during lifting tasks [3, 120, 212, 220]. To address this concern, objective individual vertebral body morphology was assessed in the LIFTMOR participants. Contrary to concerns, no signs of vertebral fractures were observed either clinically or on lateral assessment of vertebral morphology.

While promising, the LIFTMOR trial does not provide unequivocal evidence of HiRIT safety. We express caution when implementing HiRIT in those who have co-morbidities, as the LIFTMOR sample included relatively healthy, ambulant

postmenopausal women who were screened for numerous risk factors that may impede HiRIT implementation or pose a risk to a potential participant. To minimise risk, graduated loading, close supervision, and a focus on technique were implemented in the LIFTMOR trial and may account for the lack of serious adverse events observed. Therefore, we do not recommend individuals undertake HiRIT without prior screening or in an unsupervised environment, even after notable training, as it is difficult to self-monitor technique.

### **8.3 Future directions**

The LIFTMOR trial was the first to examine the effects of high intensity resistance and impact training for bone in postmenopausal women. Therefore, further investigation into the long-term safety, efficacy and potential for reducing fracture is required. The participants from the LIFTMOR trial have been invited for follow-up testing at approximately 2 years since completion of the trial. In doing so, we wish to determine if participants are still undertaking exercise, if the benefits of the supervised HiRIT intervention are maintained, and if the effect is related to persistence with the program. The collection of this follow-up data is almost complete and will be analysed and disseminated in the coming year. A program similar to the LIFTMOR program has also been translated into practice, with long term follow-up data currently being collected in a clinical setting. The Bone Clinic in Brisbane, Australia, has successfully implemented a similar HiRIT intervention and has been reporting similar effects on bone and functional performance [27]. Importantly, their observations include data from three years of operation, providing initial translational evidence into the long-term

feasibility of HiRIT as an efficacious non-pharmacological management option for postmenopausal women.

Given the success of the LIFTMOR trial in healthy postmenopausal women, HiRIT warrants investigation in different patient populations. A variety of trials are currently underway implementing either the LIFTMOR HiRIT intervention, or a very similar program. The LIFTMOR-M trial ([anzctr.org.au](http://anzctr.org.au), CTR number: ACTRN12616000344493) in progress is investigating HiRIT for improving bone in older men with low bone mass [127]. The MEDEX-OP trial ([anzctr.org.au](http://anzctr.org.au), CTR number: ACTRN12617001511325) is investigating the effects of HiRIT in combination with pharmacological management in postmenopausal women with low bone mass. Lastly, the VIBMOR study is investigating HiRIT and whole body vibration in postmenopausal women with low bone mass. Therefore, studies to determine the efficacy of HiRIT are in progress, and will help inform evidence-based exercise prescription for musculoskeletal health more broadly. Large scale trials investigating HiRIT for common co-morbid conditions such as osteoarthritis, vertebral fracture, and low back pain are required.

#### **8.4 Conclusion**

The main aim of this doctoral work was to develop a novel, brief, bone-focussed high intensity resistance and impact training program for the management of osteoporosis in postmenopausal women at risk of low trauma fracture. Our novel intervention was safe, enjoyable and efficacious for improving bone, physical function and kyphosis in postmenopausal women with low to very low bone mass. Contrary to traditional clinical opinion, high intensity resistance training did not cause harm to

participants, with no serious adverse events or fractures occurring. Based on the findings of the LIFTMOR trial, we conclude HiRIT is a potentially appealing and efficacious non-pharmacological management strategy for osteoporosis in postmenopausal women with low to very low bone mass.



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## Appendix A: Information form



**Griffith**  
UNIVERSITY  
INFORMATION SHEET

**Project Title**

***“LIFTMOR: Lifting Intervention For Training Muscle and Osteoporosis Rehabilitation”***

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**Background**

As a person ages there is a gradual decline in bone health and an increased risk of falling which, when combined, increases the risk of fractures. This study will help to determine if high-load resistance training or a home-based exercise program are safe and effective strategies for improving bone strength, body composition and physical function in post-menopausal women.

**Method**

Who:

- Healthy women over 60 years of age

What:

- You will be *randomly* assigned to either a high-load resistance training program or a home-based exercise program.
- The exercise program will occur twice a week for 8 months.
- Before and after the 8-month exercise period you will be asked to complete:
  - Questionnaires regarding your health, diet and the amount of exercise you undertake
  - Measurement of height, weight and waist circumference to determine body composition;
  - Physical tasks including: standing jump, back extensor strength, reaching and walking tasks
  - Body composition using a dual-energy x-ray absorptiometer (DXA) and quantitative ultrasound (QUS) and a peripheral quantitative computed tomographer (pQCT) scans. Those tests are painless and non-invasive but involve either sitting beside or lying still on special scanners for between 3-10 minutes per scan.
- The total time for each testing session will be approximately 2 hours.
- We may video or photograph some activities, but you may opt out of those if you would prefer.

Where:

- For the high-load resistance training program, training will take place at either Burleigh (Gold Coast), Hendra (Brisbane) or Murarrie (Brisbane), whichever is most convenient for you.
- Testing will occur at Griffith University’s Gold Coast campus (Southport) in the School of Allied Health Sciences.

**Inclusion Criteria**

You may be eligible to participate in this study if you are over the age of 60 and have low bone mass (we can tell you if you do) and are willing to undertake an 8-month exercise program comprised of two exercise sessions per week.

**Exclusion Criteria**

You may be excluded if any of the following apply to you:

- Musculoskeletal condition/s preventing physical activity
- Reasons why you cannot participate in vigorous physical activity (i.e. uncontrolled cardiovascular disease)

- Metallic implants (e.g. Staples, joint replacement) or foreign bodies (e.g. shrapnel)
- More than two x-ray examinations in the past year or radiation treatment
- Malignancy
- Mental impairment
- Certain current physical activity
- Medications and/or conditions known to influence bone health (e.g. Paget's Disease)

### **Risks**

The risks associated with the project are relatively minor. For those unaccustomed to physical activity, it is likely that you will experience muscle soreness following any change in exercise exposure. There is also a risk of injury during exercise. Such injuries are uncommon but may include low back pain, joint sprains, or muscle strains. All physical testing and high-load resistance training will be closely supervised by the investigators to help reduce those risks. If you have low bone mass, you are at greater risk of fracture during heavy lifting exercises than people with higher bone mass. It will be important to perform the exercises as instructed by your trainer to make sure you are doing them safely. Should an injury occur during a study training session, three of the project investigators are physiotherapists who will provide an initial consult and one follow-up consult free of charge at the Griffith University *Physiotherapy and Active Health Centre*. If further treatment is required, investigators can refer you to an appropriate healthcare professional. The *Physiotherapy and Active Health Centre* has undertaken to provide discounted rates to physiotherapy patients referred by study investigators.

There are also slight risks associated with some of our tests. DXA and pQCT scans are non-invasive and painless, but they do involve exposure to small quantities of ionising radiation. The amount of radiation exposure during a chest x-ray is 8 times greater than that for either pQCT or DXA tests. The radiation exposure for DXA and pQCT scans is less than 0.01 mSv. For comparison, natural background radiation to which individuals living in developed countries are exposed is estimated to be around 2.4 mSv per year. The exposure to radiation during plane travel is approximately 0.005 mSv per hour, thus a 14 hour international flight from Australia to Los Angeles would expose an individual to approximately 0.07 mSv, or 28 times the radiation from a single DXA scan.

### **Benefits**

- Each participant will receive a free 8-month exercise training program Each participant will receive free bone, muscle and fat scans and an estimate of calcium consumption
- Your involvement in this study will help contribute to the understanding of exercise as a treatment strategy for bone health, which will help countless individuals suffering from osteoporosis.

### **Confidentiality**

Results will be kept as confidential as is possible by law and will not be disclosed to third parties without your consent, except to meet government, legal or other regulatory authority requirements. All data will be kept in the possession of the investigators. The information collected is confidential and a de-identified copy of this data may be used for other research purposes. You will not be referred to by name during research reports or study discussions. All records will be stored in a locked filing cabinet with restricted access for a minimum of five years in a private office. All computer records will be restricted by password. For further information consult the University's Privacy Plan at <http://www.griffith.edu.au/privacy-plan> or telephone (07) 3735 4375.

### **Use of video recordings and photography**

You have an option to consent to being videoed or photographed during the study. Those images or recordings could be used for presentations, media coverage and/or publication of research findings. All material will be stored in a locked file on a password protected computer for a minimum of 5 years.

### **Contacting the Investigators**

We are happy to answer any questions you may have. For general inquiries please contact Mr Steven Watson (student researcher), at [steven.watson3@griffithuni.edu.au](mailto:steven.watson3@griffithuni.edu.au) or on 5552 8281. If you have any concerns with the study, please do not hesitate to contact Dr Benjamin Weeks, on (07) 5552 9336, Dr Sean Horan on (07) 5552 8038, or Assoc Prof Belinda Beck on (07) 5552 8793.

### **Feedback**

Following completion of data collection and analysis, you will be presented with a brief summary of your individual results and, if you're interested, the overall study findings.

### **Voluntary Participation**

Whether you decide to participate in this study or not, your decision will not prejudice you in any way. If you do decide to participate, you are free to withdraw your consent and discontinue your involvement at any time.

### **Complaints Mechanism**

The University requires that all participants be informed that if they have any complaints concerning the manner in which a research project is conducted they may be given to the researcher, or, if an independent person is preferred: The Manager, Research Ethics, Office for Research, Room 3.60, Science, Engineering and Architecture (G39), Griffith University, Gold Coast campus, Q 4222, Phone: 373 54375 or [research-ethics@griffith.edu.au](mailto:research-ethics@griffith.edu.au)



## **Appendix B: Consent form**

## Consent Form

### Project Title

**“LIFTMOR: Lifting Intervention For Training Muscle and Osteoporosis Rehabilitation”**

### Investigators

**Mr Steven Watson**

BExSc(Hons), MPhy  
 PhD Candidate  
 School of Allied Health Sciences  
 Griffith University, Gold Coast  
 Mob:0401 491 414  
 Ph: (07)5552 8281  
 Email:  
[steven.watson3@griffithuni.edu.au](mailto:steven.watson3@griffithuni.edu.au)

**Dr Benjamin Weeks**

BPhy(Hons), BExSc, GCertHigherEd,  
 PhD  
 Supervisor  
 Senior Lecturer  
 School of Allied Health Sciences  
 Griffith University, Gold Coast  
 Ph: (07) 5552 9336  
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**Dr Sean Horan**

BExSc, MPhy, GCertHigherEd.  
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 Griffith University, Gold Coast  
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**Assoc. Prof Belinda Beck**

BHMS(Ed), MS, PhD  
 Associate Professor  
 Supervisor  
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 Griffith University, Gold Coast  
 Ph: (07) 5552 8793  
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**Ms Lisa Weis**

BIT, MBA  
 Director  
 Barbelles, Brisbane  
 Ph: (07) 3899 2966  
 Email: [lisa@barbelles.net.au](mailto:lisa@barbelles.net.au)

### Consent Statement

By signing below, I confirm that I have read and understood the information package and in particular have noted that:

- I understand that I will be asked to undertake an 8-month exercise program, consisting of 2 sessions per week.
- I understand that will I be *randomly* assigned to either a home-based exercise program or a high-load resistance training program I understand that there will be a testing session approximately 2 hours in duration both before and after the 8-month exercise period
- I understand that I will undergo dual-energy x-ray absorptiometer (DXA), quantitative ultrasound (QUS) and peripheral quantitative computed tomographer (pQCT) scans and measurement of height, weight and waist circumference to determine body composition;
- I understand that I will be asked to complete several questionnaires relating to physical activity, quality of life, evaluation of the exercise program and diet;
- I understand that I will be asked to perform a series of physical tasks including: standing jump, back extensor strength, walking and reaching tasks;
- I have had any questions answered to my satisfaction;
- I understand the risks involved;
- I understand the benefits of my participation in this research;
- I understand that my participation in this research is voluntary;
- I understand that if I have any additional questions I can contact the research team;
- I understand that I am free to withdraw at any time, without comment or penalty;
- I understand that I can contact the Manager, Research Ethics, on 373 54375 (or [research-ethics@griffith.edu.au](mailto:research-ethics@griffith.edu.au)) if I have any concerns about the ethical conduct of the project; and
- I agree to participate in the project.

\_\_\_\_\_  
 (Participant)

\_\_\_\_\_  
 (Participant signature)

\_\_\_\_\_  
 (Date)

### **Optional video and photography consent:**

- I agree to be video recorded while performing the physical activities to be used during presentations, media coverage and publication of research findings.
- I agree to be photographed while performing the physical activities to be used during presentations, media coverage and publication of research findings.



# Appendix C: Ethics approval

## HUMAN RESEARCH ETHICS COMMITTEE

### ETHICAL CLEARANCE CERTIFICATE

This certificate generated on 22-12-2014.

This certificate confirms that protocol 'LIFTMOR: Lifting Intervention For Training Muscle and Osteoporosis Rehabilitation' (GU Protocol Number AHS/07/14/HREC) has ethical clearance from the Griffith University Human Research Ethics Committee (HREC) and has been issued with authorisation to be commenced.

The ethical clearance for this protocol runs from 01-04-2014 to 17-02-2018.

The named members of the research team for this protocol are:

APro Belinda Beck

Dr Benjamin Weeks

Dr Sean Horan

Mr Steven Watson

The research team has been sent correspondence that lists the standard conditions of ethical clearance that apply to Griffith University protocols.

The HREC is established in accordance with the *National Statement on Ethical Conduct on Research Involving Humans*. The operation of this Committee is outlined in the HREC Standard Operating Procedure, which is available from [www.gu.edu.au/or/ethics](http://www.gu.edu.au/or/ethics).

Please do not hesitate to contact me if you have any further queries about this matter.

Rick Williams

Manager, Research Ethics

Office for Research

Bray Centre, N54 Room 0.15 Nathan Campus

Griffith University

Phone: 07 3735 4375

Facsimile: 07 373 57994

Email: [rick.williams@griffith.edu.au](mailto:rick.williams@griffith.edu.au)



## Appendix D: Example of HiRIT first month training log





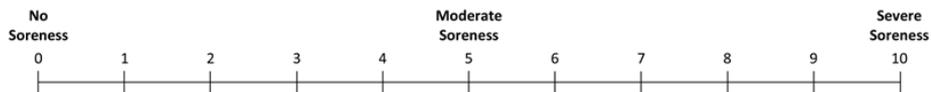
## Appendix E: Example of HiRIT training log for months 2-8

## Week 5: Familiarisation Period (Training plates)

Session 2	Date:										Tick if Completed
Warm-up											<input type="checkbox"/>
Program	Set 1		Set 2		Set 3		Set 4		Set 5		
	Weight	Reps									
Squat											
Deadlift											
Press											
Chin-ups											
Cool down											<input type="checkbox"/>

Comments: \_\_\_\_\_  
 \_\_\_\_\_  
 \_\_\_\_\_

### Muscle soreness rating:



Please answer and provide details if any of the below factors have changed since your initial testing session:

Have you had a fall? \_\_\_\_\_

Has your diet changed? \_\_\_\_\_

Have you changed your medications? \_\_\_\_\_

Have you changed your physical activity levels? \_\_\_\_\_

Have you had any injuries? (other than muscle soreness) \_\_\_\_\_

Have you been sick/ unwell since last session? \_\_\_\_\_



## Appendix F: Example of control program training log

**Week 1:**

Session 2	Date:				Tick if Completed																						
<b>Warm up</b>	10 minute walk				<input type="checkbox"/>																						
Stretches	Exercise	Duration	Reps																								
	Neck stretch	10 each side	2		<input type="checkbox"/>																						
	Shoulder stretch	60 s each side	2		<input type="checkbox"/>																						
	Side to side stretch	10 each side	2		<input type="checkbox"/>																						
	Calf stretch	60 s each side	2		<input type="checkbox"/>																						
Program	Exercises	Weight	Sets	Reps																							
	Toe walks	-	3	10	<input type="checkbox"/>																						
	Single leg balance	-	2 each leg	20 s	<input type="checkbox"/>																						
	Shrugs	1 kg	3	10	<input type="checkbox"/>																						
	Standing forward raise	1 kg	3	10	<input type="checkbox"/>																						
<b>Cool down</b>	5 minute walk				<input type="checkbox"/>																						
<b>Comments:</b>																											
<b>Muscle soreness rating:</b>																											
<table style="width:100%; border:none;"> <tr> <td style="text-align:left;">No Soreness</td> <td></td> <td></td> <td></td> <td></td> <td style="text-align:center;">Moderate Soreness</td> <td></td> <td></td> <td></td> <td></td> <td style="text-align:right;">Severe Soreness</td> </tr> <tr> <td>0</td> <td>1</td> <td>2</td> <td>3</td> <td>4</td> <td>5</td> <td>6</td> <td>7</td> <td>8</td> <td>9</td> <td>10</td> </tr> </table>						No Soreness					Moderate Soreness					Severe Soreness	0	1	2	3	4	5	6	7	8	9	10
No Soreness					Moderate Soreness					Severe Soreness																	
0	1	2	3	4	5	6	7	8	9	10																	

**Please answer and provide details if any of the below factors have changed since your initial testing session:**

Have you had a fall? \_\_\_\_\_

Has your diet changed? \_\_\_\_\_

Have you changed your medications? \_\_\_\_\_

Have you changed your physical activity levels? \_\_\_\_\_

Have you had any injuries? (other than muscle soreness) \_\_\_\_\_

Have you been sick/ unwell since last session? \_\_\_\_\_



## **Appendix G: Initial case report form**

# Case Report Form – Initial

## LIFTMOR – Lifting Intervention For Training Muscle and Osteoporosis Rehabilitation

**Participant Details:**

Participant ID: \_\_\_\_\_

Date: \_\_\_\_\_

Informed Consent:

Name: \_\_\_\_\_ DOB: \_\_\_\_\_

Address: \_\_\_\_\_

Phone: \_\_\_\_\_ Mobile: \_\_\_\_\_

Email: \_\_\_\_\_

**Race:**

- Caucasian
- African
- Other,
- Asian
- Middle Eastern
- Specify: \_\_\_\_\_

**Smoking status:**

- Current smoker, average number of cigarettes/day \_\_\_\_\_ for \_\_\_\_\_ yrs
- Ex-smoker, average number of cigarettes/day \_\_\_\_\_ for \_\_\_\_\_ yrs
- Never smoked

**Education Level (select the highest level attended):**

- Primary school
- High school – yr 10
- High school – yr 12
- Trade/technical college
- Other \_\_\_\_\_
- University - certificate
- University – bachelor’s degree
- University – master’s degree
- University - doctoral

**Marital/partner status:**

- Single
- Married
- Unmarried partnership
- Divorced
- Widowed
- Other

**Dominance**

- Handedness:  Right  Left  Ambidextrous
- Footedness:  Right  Left  Ambidextrous

**Medical History:**

Participant ID:
Date:

Please list current medical conditions (if applicable):

---

---

---

---

Please list any surgery you have had (if applicable):

---

---

---

---

Please list any medications you're currently taking (if applicable):

---

---

---

---

Are you currently participating in physical activity?

---

---

Have you had any falls?

Yes/No      If yes, how many \_\_\_\_\_, when was your last? \_\_\_\_\_ (approximate date)

Have you had any fractures?

Yes/No      Details (Including age): \_\_\_\_\_  
\_\_\_\_\_

Since the age of 40, have you had any hospital admissions? If yes, how many admissions and the approximate duration for each? What were they for?

---

---

**Questionnaires:**

- BPAQ
- AusCal
- WHOQOL
- PACES

Participant ID: _____
Date: _____

**Anthropometrics**

Height: \_\_\_\_\_

Weight: \_\_\_\_\_

BP: \_\_\_\_\_ / \_\_\_\_\_

Waist Circumference \_\_\_\_\_

**Physical Performance**

LL Strength: 1: \_\_\_\_\_ 2: \_\_\_\_\_ Average: \_\_\_\_\_

BES Test 1: \_\_\_\_\_ 2: \_\_\_\_\_ Average: \_\_\_\_\_

TUG: 1: \_\_\_\_\_ 2: \_\_\_\_\_ 3: \_\_\_\_\_ Average: \_\_\_\_\_

5x STS: 1: \_\_\_\_\_ 2: \_\_\_\_\_ 3: \_\_\_\_\_ Average: \_\_\_\_\_

FRT: 1: \_\_\_\_\_ 2: \_\_\_\_\_ 3: \_\_\_\_\_ Average: \_\_\_\_\_

**Vertical**

Jump: 1: <input type="checkbox"/> _____	2: <input type="checkbox"/> _____
3: <input type="checkbox"/> _____	4: <input type="checkbox"/> _____
5: <input type="checkbox"/> _____	6: <input type="checkbox"/> _____
7: <input type="checkbox"/> _____	8: <input type="checkbox"/> _____

**Body Composition**

**DXA**

Whole Body:  Comments: \_\_\_\_\_

Lumbar Spine:  Comments: \_\_\_\_\_

**Proximal Femur: Right**

R  Comments: \_\_\_\_\_

L  Comments: \_\_\_\_\_

**QUS**

Left:  Comments: \_\_\_\_\_

Right:  Comments: \_\_\_\_\_



## Appendix H: Follow-up case report form

# Case Report Form – Follow up



## LIFTMOR – Lifting Intervention For Training Muscle and Osteoporosis Rehabilitation

Participant Ref Number: Date:
-------------------------------------

### Participant Details:

Name: \_\_\_\_\_ DOB: \_\_\_\_\_

### Medical History:

Please list current medical conditions (if applicable):

---

---

---

Please list any medications you're currently taking (if applicable):

---

---

---

Did you have any falls over the past 8 months?

Yes/No      If yes, how many \_\_\_\_\_, when was your last? \_\_\_\_\_ (approximate date)

Did you have any fractures over the past 8 months?

Yes/No      If yes,  
details: \_\_\_\_\_

Do you have any comments regarding the exercise program (if applicable):

---

---

---

---

**Questionnaires:**

- BPAQ
- AusCal
- WHOQOL
- PACES

Participant ID: \_\_\_\_\_

Date: \_\_\_\_\_

**Anthropometrics**

Height: \_\_\_\_\_

Weight: \_\_\_\_\_

BP: \_\_\_\_\_ / \_\_\_\_\_

Waist Circumference \_\_\_\_\_

**Physical Performance**

LL Strength: 1: \_\_\_\_\_ 2: \_\_\_\_\_ Average: \_\_\_\_\_

BES Test 1: \_\_\_\_\_ 2: \_\_\_\_\_ Average: \_\_\_\_\_

TUG: 1: \_\_\_\_\_ 2: \_\_\_\_\_ 3: \_\_\_\_\_ Average: \_\_\_\_\_

5x STS: 1: \_\_\_\_\_ 2: \_\_\_\_\_ 3: \_\_\_\_\_ Average: \_\_\_\_\_

FRT: 1: \_\_\_\_\_ 2: \_\_\_\_\_ 3: \_\_\_\_\_ Average: \_\_\_\_\_

**Vertical**

Jump: 1:  \_\_\_\_\_ 2:  \_\_\_\_\_

3:  \_\_\_\_\_ 4:  \_\_\_\_\_

5:  \_\_\_\_\_ 6:  \_\_\_\_\_

7:  \_\_\_\_\_ 8:  \_\_\_\_\_

**Body Composition**

**DXA**

Whole Body:  Comments: \_\_\_\_\_

Lumbar Spine:  Comments: \_\_\_\_\_

**Proximal Femur: Right**

R  Comments: \_\_\_\_\_

L  Comments: \_\_\_\_\_

**QUS**

Left:  Comments: \_\_\_\_\_

Right:  Comments: \_\_\_\_\_



## Appendix I: BPAQ







## **Appendix J: AusCal**

## AusCal DIET QUESTIONNAIRE

NAME: *(Leave blank if you are completing this questionnaire anonymously. Consult the study investigators if unsure.)*

SUBJECT ID: \_\_\_\_\_ DATE: \_\_\_\_\_ STUDY ID: \_\_\_\_\_

INSTRUCTIONS: Over the last year, on average, how frequently did you eat the following foods?  
*Circle options where available and specify detail where appropriate (e.g. fat content, type, brand, etc.)*

Food item	Serve size	Times/ day	Times/ week	Times/ month	Rarely or never <i>(tick)</i>
<b>Example:</b>					
Milk plain	1 cup = 250 ml		5		
Cheese on pizza	1 x 10 cm wide slice			3	
Milk <input type="checkbox"/> plain/flavoured/in soup	1 cup = 250 ml				
<input type="checkbox"/> in tea or coffee	1 tablespoon = 20 ml				
<input type="checkbox"/> with cereal	½ cup = 125 ml				
Cheese <input type="checkbox"/> hard (cheddar, etc.)	1 slice				
<input type="checkbox"/> processed	1 slice				
<input type="checkbox"/> brie, camembert, blue	1 wedge = 30 g				
<input type="checkbox"/> cottage cheese	1 tablespoon				
<input type="checkbox"/> cream cheese	1 tablespoon				
<input type="checkbox"/> ricotta	1 tablespoon				
<input type="checkbox"/> feta	1 cm cube				
<input type="checkbox"/> parmesan	1 tablespoon				
<input type="checkbox"/> cheese spread <i>(Brand?)</i>	1 tablespoon				
<input type="checkbox"/> cheese sauce (homemade)	1 tablespoon				
<input type="checkbox"/> on pizza <i>(specify usual)</i>	1 x 10 cm wide slice				
Yoghurt <input type="checkbox"/> without fruit <i>(Fat/NF)</i>	1 tub = 200 ml				
<input type="checkbox"/> with fruit <i>(Fat/NF)</i>	1 tub = 200 ml				
Desserts <input type="checkbox"/> ice cream <i>(Fat/NF)</i>	3 level scoops				
<input type="checkbox"/> custard <i>(Fat/NF)</i>	½ cup				
<input type="checkbox"/> cream	1 tablespoon				
<input type="checkbox"/> sour cream	1 tablespoon				
<input type="checkbox"/> other dairy dessert	<i>specify type and size</i>				
Bread <i>(circle usual type)</i>	white wholemeal multigrain 1 slices or ½ roll				
Muesli bar <i>(specify usual type)</i>	1				
Cereal					
<input type="checkbox"/> Cheerios					
<input type="checkbox"/> Special K					
<input type="checkbox"/> Nutrigrain					
<input type="checkbox"/> other cereal <i>(specify)</i>	1 cup				
Pasta – any type	1 cup cooked				
Orange <input type="checkbox"/> whole	1				
<input type="checkbox"/> juice	1 cup = 250 ml				

Food item	Serve size	Times/ day	Times/ week	Times/ month	Rarely or never ( <i>tick</i> )
Spinach (cooked)	½ cup				
Broccoli (cooked)	3 flowerets				
Baked beans in tomato sauce	1 sm can = 220 g				
Peas - green	½ cup				
Beans - green	½ cup				
Carrot	½ medium				
Cabbage ( <i>raw or cooked - circle</i> )	½ cup				
Potato <input type="checkbox"/> Mashed <input type="checkbox"/> Chips/fries	1 cup 20				
Tomato <input type="checkbox"/> fresh <input type="checkbox"/> canned or puree	½ medium ½ cup = 125 ml				
Hamburger ( <i>specify usual type</i> )	1				
Cheeseburger ( <i>specify usual type</i> )	1				
Pork or Ham ( <i>circle one or both</i> )	85 g or 2 slices				
Chicken ( <i>circle usual</i> )	½ breast, 1 thigh, 6 nuggets, drumstick				
Red meat ( <i>beef, lamb, mince, etc.</i> )	Small Med Large <100 g 200 g 400 g ( <i>circle which</i> )				
Salmon, tinned with bones	½ cup = 125 g				
Fish – white (incl. fish fingers)	1 fillet = 100 g				
Egg (including quiche, etc.)	1 med large ( <i>circle which</i> )				
Tofu (bean curd)	1 thick slice = 125 g				
Milk Chocolate	Sm solid bar = 30g				
Coffee ( <i>instant or grounds - circle</i> )	1 cup = 220 ml				
Beer ( <i>specify usual type</i> )	1 glass = 375 ml				
Wine ( <i>red or white - circle</i> )	1 glass = 150 ml				
Calcium supplement <i>Insert brand and tablet content</i>					
<b>Office Use Only</b>	Total calcium from above sources				
	Additional calcium from second table				
	Total daily calcium (mg)				

1. Do you have any food allergies or intolerances? Please list.

---



---

2. How much milk in total do you usually have each day? (include all milk, i.e. in drinks, cooking..)

- |   |   |
|---|---|
| <input type="checkbox"/> More than 1 litre      | <input type="checkbox"/> 150 ml (half small carton) |
| <input type="checkbox"/> 1 litre                | <input type="checkbox"/> less than 150 ml           |
| <input type="checkbox"/> 600 ml (medium carton) | <input type="checkbox"/> none                       |
| <input type="checkbox"/> 300 ml (small carton)  | <input type="checkbox"/> other (please specify)     |

3. Which milk do you normally drink? Tick one from the following list. (NF = no fat; LF = low fat)

- |   |   |                                     |   |                                     |
|---|---|-------------------------------------|---|-------------------------------------|
| <input type="checkbox"/> Whole              | <input type="checkbox"/> Anlene (LF)    | <input type="checkbox"/> A2         | <input type="checkbox"/> So Good Essential  | <input type="checkbox"/> Goats milk |
| <input type="checkbox"/> Junior (whole)     | <input type="checkbox"/> PhysiCAL LF    | <input type="checkbox"/> A2 Light   | (with Calcium)                              | <input type="checkbox"/> Buttermilk |
| <input type="checkbox"/> Lite Milk (LF)     | <input type="checkbox"/> PhysiCAL NF    | <input type="checkbox"/> Parmalat   | <input type="checkbox"/> So Good (other)    | <input type="checkbox"/> Evaporated |
| <input type="checkbox"/> Trim (LF)          | <input type="checkbox"/> Shape (NF)     | (whole organic)                     | <input type="checkbox"/> Soy Life Hical     | <input type="checkbox"/> Condensed  |
| <input type="checkbox"/> Lite White (LF)    | <input type="checkbox"/> Puratone (NF)  | <input type="checkbox"/> Parmalat   | <input type="checkbox"/> Soy Life (other)   | <input type="checkbox"/> Rice       |
| <input type="checkbox"/> Light Start (LF)   | <input type="checkbox"/> Skim (NF)      | (lactose free)                      | <input type="checkbox"/> Vitasoy Calci-Plus | <input type="checkbox"/> Other      |
| <input type="checkbox"/> Smarter white (LF) | <input type="checkbox"/> Slim Milk (NF) | <input type="checkbox"/> Simply Soy | <input type="checkbox"/> Vitasoy (other)    | _____                               |

4. From the diagrams on the next page, select the size of **hard cheese** (e.g. cheddar, colby, edam etc.) that is closest to the size you would normally cut for yourself and tick the appropriate box.

- |                                  |                                  |
|----------------------------------|----------------------------------|
| <input type="checkbox"/> Slice A | <input type="checkbox"/> Slice E |
| <input type="checkbox"/> Slice B | <input type="checkbox"/> Slice F |
| <input type="checkbox"/> Slice C | <input type="checkbox"/> Slice G |
| <input type="checkbox"/> Slice D |                                  |

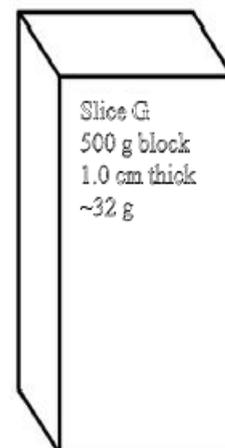
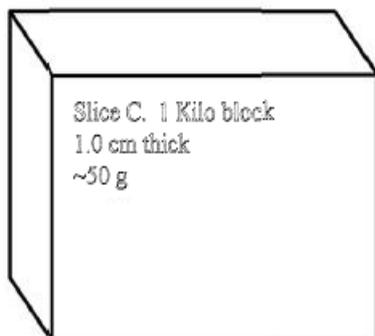
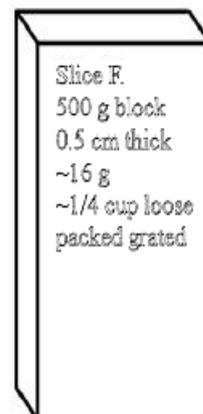
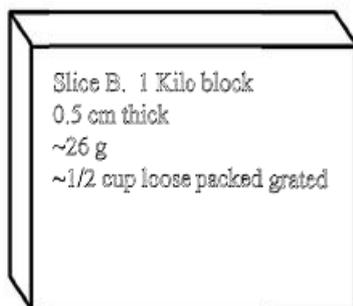
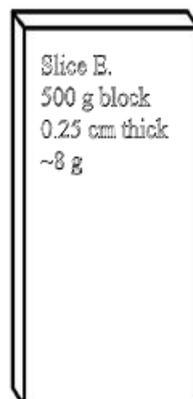
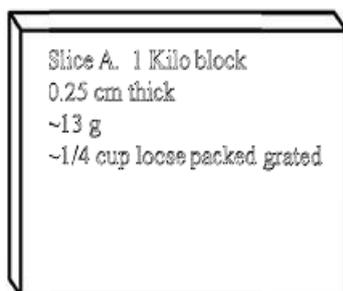
5. Tick any of the following that you regularly eat more than twice per week, year round.

- |   |                                       |                                      |  |   |
|---|---------------------------------------|--------------------------------------|--|---|
| <input type="checkbox"/> Chick peas       | <input type="checkbox"/> Almonds      | <input type="checkbox"/> Canned tuna | <input type="checkbox"/> Celery          | <input type="checkbox"/> Banana         |
| <input type="checkbox"/> Split peas       | <input type="checkbox"/> Brazil nuts  | <input type="checkbox"/> Prawns      | <input type="checkbox"/> Asparagus       | <input type="checkbox"/> Pear           |
| <input type="checkbox"/> Cous Cous        | <input type="checkbox"/> Hazelnuts    | <input type="checkbox"/> Scallops    | <input type="checkbox"/> Cauliflower     | <input type="checkbox"/> Grapefruit     |
| <input type="checkbox"/> Lentils          | <input type="checkbox"/> Walnuts      | <input type="checkbox"/> Oysters     | <input type="checkbox"/> Pumpkin         | <input type="checkbox"/> Peach          |
| <input type="checkbox"/> Oat bran muffins | <input type="checkbox"/> Macadamias   | <input type="checkbox"/> Mustard     | <input type="checkbox"/> Olives          | <input type="checkbox"/> Dried apricots |
| <input type="checkbox"/> White cake       | <input type="checkbox"/> Cashews      | <input type="checkbox"/> Parsley     | <input type="checkbox"/> Chili           | <input type="checkbox"/> Pineapple      |
| <input type="checkbox"/> Cocoa or other   | <input type="checkbox"/> Peanuts      | <input type="checkbox"/> Soy sauce   | <input type="checkbox"/> Vegetable juice | <input type="checkbox"/> Watermelon     |
| chocolate drink powder                    | <input type="checkbox"/> Mixed nuts   | <input type="checkbox"/> Tomato      | <input type="checkbox"/> Rhubarb         | <input type="checkbox"/> Rockmelon      |
| <input type="checkbox"/> White chocolate  | <input type="checkbox"/> Peanut paste | sauce                                | <input type="checkbox"/> Grapes          | <input type="checkbox"/> Paw Paw        |

6. Please complete the following table for any of the foods you have ticked in item 5.

Food item	Serve size	Times/ day	Times/ week	Times/ month	Rarely or never <i>(tick)</i>
Total additional calcium (mg)				Office use only	

Slices from various blocks of cheese for use in Item 4 on previous page.





## Appendix K: WHOQOL

## WHOQOL-BREF

The following questions ask how you feel about your quality of life, health, or other areas of your life. I will read out each question to you, along with the response options. **Please choose the answer that appears most appropriate.** If you are unsure about which response to give to a question, the first response you think of is often the best one.

Please keep in mind your standards, hopes, pleasures and concerns. We ask that you think about your life **in the last four weeks.**

		Very poor	Poor	Neither poor nor good	Good	Very good
1.	How would you rate your quality of life?	1	2	3	4	5

		Very dissatisfied	Dissatisfied	Neither satisfied nor dissatisfied	Satisfied	Very satisfied
2.	How satisfied are you with your health?	1	2	3	4	5

The following questions ask about **how much** you have experienced certain things in the last four weeks.

		Not at all	A little	A moderate amount	Very much	An extreme amount
3.	To what extent do you feel that physical pain prevents you from doing what you need to do?	5	4	3	2	1
4.	How much do you need any medical treatment to function in your daily life?	5	4	3	2	1
5.	How much do you enjoy life?	1	2	3	4	5
6.	To what extent do you feel your life to be meaningful?	1	2	3	4	5

		Not at all	A little	A moderate amount	Very much	Extremely
7.	How well are you able to concentrate?	1	2	3	4	5
8.	How safe do you feel in your daily life?	1	2	3	4	5
9.	How healthy is your physical environment?	1	2	3	4	5

The following questions ask about how completely you experience or were able to do certain things in the last four weeks.

		Not at all	A little	Moderately	Mostly	Completely
10.	Do you have enough energy for everyday life?	1	2	3	4	5
11.	Are you able to accept your bodily appearance?	1	2	3	4	5
12.	Have you enough money to meet your needs?	1	2	3	4	5
13.	How available to you is the information that you need in your day-to-day life?	1	2	3	4	5
14.	To what extent do you have the opportunity for leisure activities?	1	2	3	4	5

		Very poor	Poor	Neither poor nor good	Good	Very good
15.	How well are you able to get around?	1	2	3	4	5

		Very dissatisfied	Dissatisfied	Neither satisfied nor dissatisfied	Satisfied	Very satisfied
16.	How satisfied are you with your sleep?	1	2	3	4	5
17.	How satisfied are you with your ability to perform your daily living activities?	1	2	3	4	5
18.	How satisfied are you with your capacity for work?	1	2	3	4	5
19.	How satisfied are you with yourself?	1	2	3	4	5

20.	How satisfied are you with your personal relationships?	1	2	3	4	5
21.	How satisfied are you with your sex life?	1	2	3	4	5
22.	How satisfied are you with the support you get from your friends?	1	2	3	4	5
23.	How satisfied are you with the conditions of your living place?	1	2	3	4	5
24.	How satisfied are you with your access to health services?	1	2	3	4	5
25.	How satisfied are you with your transport?	1	2	3	4	5

The following question refers to how often you have felt or experienced certain things in the last four weeks.

		Never	Seldom	Quite often	Very often	Always
26.	How often do you have negative feelings such as blue mood, despair, anxiety, depression?	5	4	3	2	1

**Do you have any comments about the assessment?**

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*[The following table should be completed after the interview is finished]*

		Equations for computing domain scores	Raw score	Transformed scores*	
				4-20	0-100
27.	<b>Domain 1</b>	$(6-Q3) + (6-Q4) + Q10 + Q15 + Q16 + Q17 + Q18$ $\square + \square + \square + \square + \square + \square + \square$	a. =	b:	c:
28.	<b>Domain 2</b>	$Q5 + Q6 + Q7 + Q11 + Q19 + (6-Q26)$ $\square + \square + \square + \square + \square + \square$	a. =	b:	c:
29.	<b>Domain 3</b>	$Q20 + Q21 + Q22$ $\square + \square + \square$	a. =	b:	c:
30.	<b>Domain 4</b>	$Q8 + Q9 + Q12 + Q13 + Q14 + Q23 + Q24 + Q25$ $\square + \square + \square + \square + \square + \square + \square + \square$	a. =	b:	c:

\* See Procedures Manual, pages 13-15



# Appendix L: PACES

# PACES: Physical Activity Enjoyment Scale

## LIFTMOR – Lifting Intervention For Training Muscle and Osteoporosis Rehabilitation

For each of the scales below, please circle the most appropriate number relating to your thoughts of physical activity participation. *Note: the higher the number the greater your enjoyment of physical activity*

<b>I find it unpleasurable</b>	1		2		3		4		5		6		7	<b>I find it pleasurable</b>
<b>It's no fun at all</b>	1		2		3		4		5		6		7	<b>It's a lot of fun</b>
<b>It's very unpleasant</b>	1		2		3		4		5		6		7	<b>It's very pleasant</b>
<b>It's not at all invigorating</b>	1		2		3		4		5		6		7	<b>It's very invigorating</b>
<b>It's not at all gratifying</b>	1		2		3		4		5		6		7	<b>It's very gratifying</b>
<b>It's not at all exhilarating</b>	1		2		3		4		5		6		7	<b>It's very exhilarating</b>
<b>It's not at all stimulating</b>	1		2		3		4		5		6		7	<b>It's very stimulating</b>
<b>It's not at all refreshing</b>	1		2		3		4		5		6		7	<b>It's very refreshing</b>

Adapted from Mullen et al (2011) Measuring enjoyment of physical activity in older adults: invariance of the physical activity enjoyment scale (paces) across groups and time



## **Appendix M: Exit Survey**



Participant Ref Number:
Date:

# Exit Survey

## LIFTMOR – Lifting Intervention For Training Muscle and Osteoporosis Rehabilitation

Please read the following statements about your participation in the LIFTMOR study and circle your agreement for each. Please ensure answers are whole numbers.

Statement	Strongly disagree	Disagree	Neutral	Agree	Strongly Agree
I was enthusiastic to commence the exercise program in the LIFTMOR study	1	2	3	4	5
I was familiar with resistance training exercises before I joined the study	1	2	3	4	5
I was happy with my allocation to the home/supervised exercise program (please circle)	1	2	3	4	5
I was enthusiastic to do each exercise session during the LIFTMOR study	1	2	3	4	5
I found it easy to learn and perform the LIFTMOR study exercises	1	2	3	4	5
I found the LIFTMOR exercises physically challenging throughout the study	1	2	3	4	5
I did not feel any physical discomfort (some level of pain) as a result of the LIFTMOR study	1	2	3	4	5
I did not feel that muscle soreness as a result of the LIFTMOR affected my daily life	1	2	3	4	5
I felt safe from injury while undertaking my exercise program	1	2	3	4	5
I noticed changes to my bodily appearance as a result of the LIFTMOR program	1	2	3	4	5
I noticed changes to my physical ability as a result of the LIFTMOR program	1	2	3	4	5
I plan to continue/take up resistance training at the end of my involvement in the LIFTMOR study	1	2	3	4	5
I would participate in the LIFTMOR study again if I had the chance	1	2	3	4	5