A comparison of physical and behavioural characteristics between postmenopausal women with low bone mass on or off bone medication

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Submitted in fulfilment of the requirements of the degree for the
Master of Medical Research

August 2020

Abstract

BACKGROUND: Identifying the relationships between physical and behavioural characteristics with the presence or absence of pharmacotherapy (on or off bone medication) for postmenopausal women with low bone mass could assist healthcare professionals to individualise bone health management plans and provide better patient-centred care. Linking patient characteristics with attitudes and motivations behind their decisions would be helpful for healthcare professionals in identifying what gaps in knowledge and types of therapy patients would most likely be open to initiating, adhering to and persisting. A cross-sectional study such as this has not previously been undertaken.

METHODS: A convenience sample of 349 postmenopausal women with low bone mass were recruited from participants of the Medication and Exercise for Osteoporosis (MEDEX-OP) trial, women who were excluded from the MEDEX-OP trial and clients of The Bone Clinic in Brisbane, Australia. The baseline data from participants of the MEDEX-OP trial and the data from a routine assessment from clients of The Bone Clinic were obtained for analysis. A questionnaire requesting demographic information as well as attitudes toward medication and motivations to be on or off bone medication was emailed or sent via mail to women who had been excluded from the MEDEX-OP trial. Data was analysed via univariable and multivariable logistic regression to identify physical or behavioural characteristics related to being on or off bone medication.

RESULTS: The majority of participants were aged in their early sixties, with 256 (73.4%) off bone medication and 93 (26.6%) currently taking antiresorptive bone medication. Age in years (OR 1.05, 95% CI 1.01-1.09), two or more fragility fractures (OR 5.08, 95% CI 2.60-9.94), previously took bone medication (OR 2.48, 95% CI 1.44-4.26), fracture risk calculated as a percentage using the Garvan Institute Fracture Risk Calculator (OR 1.03, 95% CI 1.01-1.06), back extensor strength measured in kilograms (OR 0.96, 95% CI 0.93-0.98), five times sit to stand measured in seconds (OR 1.16, 95% CI 1.04-1.30), and having a pro-medication attitude (OR 5.95, 95% CI 2.92-12.12) or ambivalent attitude toward medication in general (OR 1.51, 95% CI 0.73-3.09) were statistically significant variables that were found to be related to being on or off bone medication following the univariable logistic regression analyses. People with ambivalent attitudes were found to be just as

likely as those with anti-medication attitudes to be on bone medication. At the adjusted multivariable level, having two or more fractures (OR 3.87, 95% CI 1.53-9.79), previous bone medication (OR 2.81, 95% CI 1.36-5.78), having poor back extension strength (OR 0.95, 95% CI 0.92-0.98), and having a pro-medication attitude (OR 6.41, 95% CI 2.73-15.07) were associated with being on bone medication.

CONCLUSION: Fragility fracture history, previous use of bone medications, back extensor strength and attitudes toward medication in general were strongly related to being on or off bone medication among postmenopausal women with low bone mass. Healthcare professionals should consider these four characteristics when involving patients in the decision-making process of making a bone health management plan.

Signed 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.

(Digitally signed)

Jedidah Yong

19/08/2020

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Statement of acknowledgement

This is to acknowledge the MEDEX-OP investigators and supervisors for this study, Belinda Beck, Benjamin Weeks, and Melanie Kistler-Fischbacher for their support and assistance with providing the MEDEX-OP baseline dataset, as well as Belinda Beck and Lisa Weiss, directors of The Bone Clinic, for their permission to use data from The Bone Clinic for the purposes of this study. Acknowledgement is also given to Ricardo Maldonado from Power Stats Pty Limited for his assistance with the statistical data analyses.

A comparison of physical and behavioural characteristics between postmenopausal women with low bone mass on or off bone medication

Lay title: Are there characteristic differences between postmenopausal women with low bone mass who are on or off bone medication?

1.0 Introduction

Poor bone health is a problem that is more prevalent with advancing age, particularly for postmenopausal women (1-4). Reduced bone mass increases the risk of fracture from low force trauma, commonly referred to as fragility fracture, such as occurs during slips or falls (5-8). Such fractures may lead to disability, reduced independence and poorer quality of life (9-11). Antiresorptive bone medication can be taken by people with low bone mass in order to reduce the risk of fracture (12-16), but not all choose to do so. It is not known whether there are any physical or behavioural differences between women who choose to take bone medications compared with those who do not.

The Medication and Exercise for Osteoporosis (MEDEX-OP) trial (17) is a randomised controlled trial designed to examine whether taking bone medications influences the effectiveness of a bone-targeted exercise program in postmenopausal women with low bone mass. At the same time, women regularly attend The Bone Clinic, a bone research clinic, for management of their bone health via resistance training. For this reason, women both on and off stable doses of bone medication have been recruited to participate. Taking advantage of this convenience sample, the main aim of the current cross-sectional study was to determine if there are physical or behavioural differences between postmenopausal women who are taking bone medications compared with those who are not. Findings may assist doctors to identify women reluctant to accept a bone medication prescription.

2.0 Aims and Objectives

Primary aim: To compare physical and behavioural characteristics of postmenopausal women either on or off bone medication

Secondary aim: To examine relationships between physical or behavioural factors with motivations for therapy choices in the management of low bone density among postmenopausal women.

Objectives:

1. To identify differences in musculoskeletal traits or function between postmenopausal women either on or off bone medication.

2. To identify relationships between the physical and behavioural factors between postmenopausal women either on or off bone medication.

3. To identify whether there is a relationship between the physical and behavioural factors with motivations for therapy in the management of low bone density.

A study comparing groups of postmenopausal women in this way has not previously been undertaken. Discovering and understanding what factors are most related or predictive of a person to be on or off bone medication would help healthcare professionals to seek to better understand their patient's position and plan individualised bone health management strategies together with their patients. In this way their patients with low bone mass will be more likely to adhere and persist with their treatment plans. It would guide clinicians to better predict the patterns of their patients' behaviour and recommend the types of bone health management strategies (whether lifestyle changes, medication, physical activity or a combination) that their patients are most open to while also being the most suitable for them.

3.0 Background

3.1 The biology of bone

3.1.1 Bone tissue

Bone is a living, active tissue of the body that provides structural support, protects the softer internal organs, and acts as a storage bank for minerals such as calcium. It is comprised of trabecular (or cancellous) bone and cortical (or compact) bone tissue. The distribution of the two bone tissues varies according to skeletal site. Trabecular bone is arranged in a latticework of struts and plates that form the internal scaffolding of bones and is commonly found in the centres of short and irregular bones (e.g. vertebrae) and at the ends of long bones. Cortical, or compact, bone is much denser that trabecular bone. It is predominantly found in the shafts of long bones and forms the outer shell of all other bones (18-21).

3.1.2 Bone cells

There are three main bone cell types, namely osteoclasts, osteoblasts and osteocytes. Osteoclasts resorb old or damaged bone tissue. Osteoblasts synthesise new bone by secreting a substance known as osteoid, which then is mineralised to become rigid bone (22). Osteocytes are the most common cells in bone and are former osteoblasts that have become trapped within the bone matrix by the secretion of osteoid. They have long dendritic extensions that run through narrow tubules or canaliculi within the bone matrix and form a network for intercellular communication. Osteocytes are the main sensors of mechanical stimuli, with the ability to direct bone resorption and/or formation (19, 23, 24).

3.1.3 Bone remodelling and modelling

Bone remodelling is the coupled process of bone resorption and formation that occurs continuously without affecting the external shape of the bone (25). It is upregulated in response to hormonal or other chemical changes, mechanical loading and/or microdamage (5, 26, 27). Broadly speaking, bone remodelling involves osteoclasts resorbing bone, and then osteoblasts laying down new bone to refill the cavity (28). Bone remodelling has four phases: activation of osteoclasts (activation phase), resorption of bone by osteoclasts (resorption phase), recruitment of osteoblasts and osteoclast apoptosis (reversal phase), followed by laying down of new organic bone matrix and mineralisation

by osteoblasts (formation phase) (20). When there is insufficient loading of the bones over time or micro-damage inducing levels of mechanical strain in bone tissue, there is increased apoptosis of osteocytes. This is thought to induce greater activity of osteoclasts and so increasing bone resorption (19).

Bone modelling on the other hand, relates to the process of uncoupled resorption or formation to the extent that the shape and mass of a bone changes (25, 26). It is primarily a response to changes in mechanical loading, but is likely to be modulated by genetics and hormones (20).

3.1.4 Mechanical forces in bone

The mechanism by which mechanical forces are converted to biochemical signals to bring about modelling and remodelling is known as mechanotransduction (29). Mechanical forces are thought to be received via the osteocyte network within the bone matrix, although the exact mechanism by which this occurs is as yet uncertain (19). It is thought that mechanical loading causes deformation of the bone, which in turn causes a flow of fluid through canaliculi that osteocytes detect through the shear stress on their dendritic membranes. The osteocytes then produce molecular signals that regulate the activity of osteoclasts and osteoblasts thereby affecting the rate of bone resorption and formation (23, 30-32). The concept of mechanical strain stimulating bone to adapt and remodel, altering both the internal and external architecture of bone has been attributed to Julius Wolff in 1892 (24). Due to some disagreement with certain aspects of what is known as Wolff's law, 'bone functional adaptation' has also been used to provide a more general description of this law (33). With the adaptability of bone to mechanical forces and its ability to improve bone formation (21), physical activity is seen as an important aspect of maintaining good bone health.

3.1.5 Hormones affecting bone

Calcitonin, parathyroid hormone (PTH), cholecalciferol (vitamin D_3) and oestrogen are the four main hormones affecting bone remodelling (22). Calcitonin directly inhibits osteoclast activity (34). PTH stimulates bone formation, as well as increased reabsorption of calcium in the kidneys and indirectly stimulates bone resorption to assist with maintaining serum calcium levels. PTH also activates vitamin D_3, which in turn facilitates

absorption of calcium from the gut and kidneys, and also helps regulate bone resorption (22). Oestrogen plays a large role in the remodelling cycle by inhibiting osteoclasts to reduce bone resorption. It is thought to also play a role in bone formation, although the mechanisms of action for the latter are not well understood (22, 35).

3.1.6 Changes in bone through life

Bone mass is gained and modelled throughout early life until adulthood. In the majority of people, peak bone mass is achieved by the end of the second decade or during the third decade of life, declining from there with increasing age (3). For women, the five to ten years around menopause is known to be an unstable period due to the fluctuations in oestrogen production (1, 2). Oestrogen deficiency results in increased osteoclast activity and resorption with resultant net loss of bone (18, 20, 28). The net deficit in bone following menopause results in a thinning of cortical and trabecular bone, together with the loss of trabecular structure, which may lead to osteoporosis (20).

3.2 Osteopenia and osteoporosis

Osteoporosis is a silent, chronic, systemic skeletal condition resulting from the deterioration of bone mass and microstructure that leads to greatly increased fracture risk, and osteopenia is the less severe form of osteoporosis (5, 36, 37). Both osteoporosis and osteopenia are sometimes called low bone mass or low bone mineral density conditions. The WHO (37) definition to diagnose osteoporosis utilises bone mineral density (BMD) of the femoral neck in grams per centimetre squared, measured by dual-energy x-ray absorptiometry (DXA). The BMD result is expressed as a T-score, reflecting the number of standard deviations from a young adult reference mean.

Osteoporosis is identified by a BMD T-score less than -2.5 either with or without fragility fracture. Osteopenia is defined as a BMD T-score of between -1 to -2.5 (18, 37). Collectively, osteoporosis and osteopenia are of clinical concern since fragility fractures do not only occur within the osteoporotic range (38). Nevertheless, fractures are more prevalent in women with osteopenia due to osteopenia having greater prevalence than osteoporosis (11, 39). Consequences of fracture may include deterioration in posture, chronic pain, disability, reduced independence and quality of life, as well as death (3, 9, 40).

3.3 Prevalence and burden of osteoporosis

In 2017-2018, approximately 3.8% of Australians had osteoporosis (9). At least 55% men and 49% women between 50-69 years of age had osteopenia, with a similar prevalence of osteopenia for those over 70 years old (41). The prevalence of osteoporosis, particularly among women, greatly increases from 45 years of age (9). By the time women are over 75 years old, they are three times more likely than men of the same age group to have osteoporosis (9).

Fragility fracture is the main clinical consequence of osteoporosis. Osteoporosis therapy is largely focussed upon fracture prevention, where successful treatment will result in an absence of fracture during therapy (42). At least one in five fragility fractures in people ≥ 50 years old are likely to have osteoporosis (43) and 61% of those who experience fragility fractures are women (10). Those who have had a fragility fracture in the past are almost twice as likely to have a subsequent fragility fracture in the future (44, 45), and the risk of subsequent fracture is greatest within the first year after the initial fragility fracture (46). Besides increased pain, fragility fracture can result in physical, emotional and psychological disabilities, resulting in reduced quality of life (47). Other consequences of fracture include impaired physical function, reduced independence, higher morbidity, increased likelihood of institutionalisation and mortality (48-50). Of the deaths attributed to fragility fracture, 49% were due to hip fractures and 16% were due to vertebral fractures, with 70% of these deaths occurring in women ≥70 years old (41).

Due to the many subsequent problems associated with post fragility fracture management, there is a high burden of disease associated with osteoporosis. In 2017, the total direct cost of low BMD related fractures in Australia was an estimated $3.44 billion. When compared with $2.75 billion in 2012, the costs related to fragility fractures has increased with the ageing of the population and associated high prevalence of osteoporosis among Australians 50 years old and above. By 2022, total costs relating to low bone mass are predicted to increase to $3.84 billion (11, 41).

3.4 Osteoporosis management

While the WHO (37) definition of osteoporosis is useful for determining prevalence, it is not as useful as a guide for treatment, since bone quality and risk of fractures are

affected by a variety of factors other than low BMD (51, 52). Non-modifiable factors include age, gender, genetics, family history, previous fracture, other comorbidities and white ethnic background. Modifiable factors include nutrition, physical activity, falls risk, weight loss, smoking, alcohol consumption, medications and stress (53).

Various clinical guidelines and literature reviews (5, 15, 18, 52, 54-56) have recommended that the management of low bone density should involve lifestyle changes to reduce modifiable risk factors for fracture such as:

- smoking cessation;
- dietary and nutrition advice including adequate calcium and vitamin D intake, and avoidance of excessive alcohol intake;
- physical activity to include weight bearing, strength training and balance exercises;
- pharmacotherapy; and
- other falls prevention management strategies.

For those at greater risk of fracture who are receiving pharmacotherapy, consideration should also be given to length of prescription, drug holidays, and frequency as well as type of monitoring (15, 56). Like pharmacotherapy, there are many studies that have addressed the efficacy of lifestyle changes due to the complicated interactions between the various lifestyle factors, such as different types of nutrition, or nutrition and exercise. Notwithstanding, there is good evidence for certain types of physical exercise (57).

Adherence is an important area of osteoporosis management, as low adherence to a therapy makes it difficult to measure the actual effects of a therapy and naturally leads to poorer outcomes. Adherence to medication is seen to have three components:

- initiation – when a patient first takes their prescribed medication;
- implementation – how closely a patient follows the directions given or regimen of therapy; and
- discontinuation – the end of therapy or when the next dose is not taken and no more doses are taken again (58, 59).

Persistence is defined as the time from which therapy was initiated to its discontinuation (58). Reasons for non-adherence are complex due to the large variety of factors involved

and for this reason, influencing patient choices to improve adherence is difficult. One large factor on patient choices and adherence are the patient's values and beliefs. Patient beliefs and preferences are known to affect the acceptance of therapy recommendations according to clinical guidelines, thereby affecting behaviours and outcomes of therapy (60).

3.4.1 Diet and Nutrition

Nutrition plays a large role within the environmental factors affecting osteoporosis (57), however the relationship between nutrition and BMD is not well characterised due to the variety of age groups and assessment methods examined (61). As such, most nutritional advice provided to patients tends to be general and focuses upon calcium and vitamin D intake as an adjunct to other osteoporosis management strategies (18, 62, 63). According to a recent study (64), both women with osteoporosis as well as women with a high fragility fracture risk moderately used supplements such as digestive aids, herbs, vitamins and minerals. The use of supplements appeared to increase over time. This shows that most women with higher risk of fragility fracture are more likely to use nutritional supplements in order to manage their health as opposed to women with lower risks of fragility fracture.

Calcium is critical to the function of many body systems and so when calcium in the blood is insufficient, bone is resorbed in order to restore calcium homeostasis. Calcium absorption from the gut is reduced with age, particularly after 75 years of age (65). A reduced ability to absorb calcium requires increased resorption of bone to maintain calcium homeostasis in postmenopausal women, thereby increasing the risk of developing osteoporosis. Therefore, adequate calcium intake is an important aspect of managing osteoporosis. The Australian recommended dietary calcium intake for women older than 50 years is 1300 mg or at least three serves of dairy food per day (63). There is some concern regarding the relationship between calcium supplements and increased risk of cardiovascular events, and so calcium via diet is the preferred source of calcium intake (62, 66).

Vitamin D (cholecalciferol) promotes the absorption of calcium, and is also associated with muscle function and falls. As many osteoporotic fractures are a direct result of a fall, maintaining adequate vitamin D levels are vital for not only assisting with calcium absorption, but for also reducing the risk of falls and subsequent fractures. Vitamin D may

be produced by the body via exposure of skin to the sun. The amount of adequate and safe sun exposure required for the skin to produce sufficient vitamin D differs between season, skin colour and location (63). As sun exposure is contraindicated for some (67), and an ineffective strategy for others (68), supplementation is sometimes necessary. While supplementation of high doses of daily vitamin D does not reduce the risk of falls or fracture, daily moderate doses may help reduce falls in people who are vitamin D deficient (66). General recommendations for daily Vitamin D intake are 400 IU of cholecalciferol for all adults and 800 IU for postmenopausal women over 50 years old who are at greater risk of fracture (62).

Other general dietary advice may be provided to patients. Excessive salt (sodium) intake increases urinary calcium excretion (69). At least four cups of coffee containing caffeine (330 mg/day caffeine) may be associated with increased fragility fractures (70), but this risk may be reduced by increasing milk consumption (71). High calorie diets and excessive alcohol consumption have been related to low BMD and higher fracture risk (53). Excessive alcohol consumption predisposes to falls, calcium deficiency and chronic liver disease, which leads to Vitamin D deficiency (3, 63). The recommended alcohol intake for people with low BMD or at risk of fracture is less than seven drinks per week (3).

3.4.2 Exercise for bone health

Physical activity is important for the maintenance of bone health and the prevention of falls. Depending on the type of physical activity, it can reduce the risk of fracture by improving or maintaining BMD, as well as reduce the risk of falls by improving muscle strength and balance (57). Animal studies suggest that high magnitude strains are required to stimulate positive bone adaptation, and thus, high impact combined with progressive resistance training is likely to be most efficacious (72, 73). Traditional guidelines for the management of osteoporosis recommend general low to moderate intensity exercise for reasons of safety, but human studies have typically found limited efficacy (74, 75). It has been shown that high impact combined with progressive resistance exercise is effective for improving low bone mass (76, 77), and that muscle strengthening and balance exercises are effective for falls prevention (57, 78-80).

Current guidelines on osteoporosis management recommend older adults with osteoporosis be prescribed regular exercise sessions at least two to three days per week with high impact, high intensity progressive resistance and balance components to reduce fall and fracture risks (52, 63). The Lifting Intervention for Training Muscle and Osteoporosis Rehabilitation (LIFTMOR) trial (81) and Erlangen Fitness Osteoporosis Prevention Study (EFOPS) (82) trial have shown that high impact and progressive resistance training for postmenopausal women with low bone density is safe when supervised and effective in improving BMD, strength and balance. Despite this, adherence to exercise for osteoporosis management is poor with at least 50% of women who commence an exercise program dropping out within the first six months largely due to insufficient time or transport (83).

A qualitative study (84) found three main barriers for the participation of older adults in higher impact exercises for bone health. The first barrier was that participants found bones difficult to relate to due to not being able to see or feel the bones. The second barrier was the concern that higher impact exercises would damage their joints and for one participant with knee replacements, their doctor had recommended against it. The third barrier was the fear of falling, concerns about safety and other social-psychological concerns. This was of greater concern to those who lived alone. It was also found that participants who were given clear explanation as to the benefits of higher impact exercise, and participants who were able to incorporate the exercise into activities of daily living or existing exercise routines were more likely to start and adhere to high impact exercises.

3.4.3 Pharmacotherapy

Medications for the management of osteoporosis (bone medications) are generally categorised as either antiresorptive or anabolic therapies (18, 53). Calcium and vitamin D are generally recommended as adjunct therapies to prescribed medications (15), however unless deficient, the evidence of benefit to community-dwelling people is low (63).

Antiresorptive medications include bisphosphonates, denosumab, selective estrogen receptor modulators (SERMs) and hormone therapy (15, 18, 53). Such medications inhibit osteoclast activity, reducing the rate of bone resorption. Bisphosphonates and denosumab are among the more commonly prescribed medications for the management of osteoporosis in Australia. Bisphosphonate therapy is recommended primarily for the prevention of

vertebral fractures in women at least ten years post menopause with osteopenia, but may also be used to reduce the risk of other fractures in postmenopausal women over 50 years old. Where postmenopausal women have an increased risk of fragility fracture, denosumab is recommended (63).

Anabolic therapies stimulate bone formation. One such anabolic therapy is PTH known as teriparatide (15, 18, 53, 54, 85). Teriparatide is recommended for more severe cases of osteoporosis when other treatment has failed and should only be used for 18 months, due to the uncertain risk of side effects. For longer term management, bisphosphonates are recommended (15, 62, 63). Newer therapies, including abaloparatide (86) and romosozumab (87), are emerging (88) but not yet available on the Australian Pharmaceutical Benefits Scheme.

While antiresorptive medications have been proven to be effective in the management of osteoporosis (62, 63, 89), there is a complexity of attitudes, barriers and other reasons affecting the decision of a patient to adhere to therapy (59, 89, 90). Of the patients who have been prescribed pharmacotherapy for osteoporosis management, at least a third to a half do not take their medication (91) and patients who have not adhered to therapy may often refill prescriptions only after long periods of nonadherence (92). Adherence and persistence to oral bisphosphonate medication in particular is poor (93). Because the efficacy of antiresorptive medication when used in such an interrupted way is not fully known, it is important for patients who have been prescribed medication to persist with their therapy (59). Poor adherence to osteoporosis pharmacotherapy has been linked with increased risk of fragility fracture when compared to adherence to pharmacotherapy as recommended (94).

Osteoporotic patients were found to be willing to pay more or to prefer medications that avoided the things they disliked about particular drugs such as side effects but this varied (95). While patients considered side effects and medication efficacy as important factors, the drugs requiring less frequent dosages were preferred (96). It has been found that there is a similar pattern in the use of bone medication between those with advanced age and high risk of fracture, as well as those with osteoporosis and high fragility fracture risk (64). The better pharmacotherapy interventions for osteoporosis management with

increased adherence and/or persistence are believed to be interventions which actively involve patients in the decision making and involve multiple components (97). Therefore clinical decision making should be performed together with patients, taking their preferences into account in order to improve adherence to pharmacotherapy (96).

3.4.4 Patient attitudes and choices

According to two studies, patient beliefs and attitudes toward medication may be a powerful predictor of medication adherence (98, 99). Patient perceptions and preferences for pharmacotherapies in the management of osteoporosis have been shown to affect both adherence (100) and persistence (101). It could then be inferred that patient beliefs and attitudes toward medication may then also influence their choices to initiate drug therapy for osteoporosis. Patient beliefs may be at odds with current scientific research and so unearthing these beliefs in order for them to be carefully addressed is an integral part of patient-centred care (102). Most patient choices are not permanent decisions and so patient decisions can be monitored over time in order for healthcare providers to individualise recommendations as situations change (103).

One qualitative study found that postmenopausal women with osteoporosis did not seem to relate fragility fractures with bone fragility, but instead, the women saw the condition as a normal part of ageing (104). In the same study, some physicians did not always relate fractures with osteoporosis and saw the condition as a normal part of ageing. The asymptomatic and silent nature of the disease seemed to reduce the perceived need for therapy (104, 105). This study (104) showed that not all doctors were familiar with osteoporosis and osteoporosis management, which fed the uncertainties of patients and affected both the treatment recommendations and subsequently the patients' decisions. This shows that to improve adherence to recommended therapies, education regarding osteoporosis management should not just be targeted at patients, but also at the clinicians who provide recommendations to their patients.

In addition, a qualitative systematic review of patient experiences of osteoporosis (106) showed that uncertainty regarding what osteoporosis was and involved played a large role in how the condition and the subsequent effect it had on patients' self-image were perceived. The uncertainty was often based upon the relationship the patient had with their

healthcare provider as well as the education provided. Patients had a lack of understanding about the potential effects of the condition and the importance of adhering with pharmacotherapy and/or lifestyle changes. A longitudinal observation study (105) found that awareness of the disease was associated with higher education levels but worsening health conditions as well as the fear of adverse events, specifically osteonecrosis of the jaw, were some of the main reasons for ceasing pharmacotherapy.

A discrete choice experimental study of Dutch patients who had or were at risk of developing osteoporosis, looked into understanding patient characteristics and preferences for osteoporosis treatment (107). This study found that while subgroups were found in their analysis, patterns could not be related to socio-demographics or characteristics such as previous fracture, gastrointestinal problems, body mass index and whether patients were taking anti-osteoporosis medication. This study involved questionnaires that focussed more upon preferred modes of drug delivery, such as intravenous as opposed to subcutaneous injections or oral medications. While this Dutch study is the closest in relevance found so far, its aims were only somewhat related to the cross-sectional study performed as part of this Thesis.

Another similar study to this current one is a study that looked at predictors of treatment with osteoporosis medication after a recent fragility fracture (108), but that study did not include outcome measures of posture, strength, balance or function, nor consider attitudes and reasons behind choice of therapy. Other similar studies to this were two trials on hormone therapy (109, 110) that looked at patient characteristics and choices of therapy however due to their focus being on hormone therapy, these two studies were mostly irrelevant to the aims of this study. Hormone therapy works through completely different pathways from bisphosphonates and denosumab. One study (111) that sought to find health belief models for womens' choices in antiresorptive therapies as opposed to hormone therapy found that while their health belief models were more related to antiresorptive therapies, it was likely that hormone therapies were largely initiated for reasons other than low bone mass. This was somewhat corroborated by one of the two trials on hormone therapy (110) that found that women were more likely to take hormone therapy for the management of menopausal symptoms. In addition, the study by Cline et al (111) when comparing choices in antiresorptive therapies with hormone therapy found that women who

had received a test or been diagnosed with low BMD were much more likely to start taking a different antiresorptive bone medication as opposed to non-prescribed drug therapy.

There are many reasons for a patient to not commence therapy, and their choices may not always line up with doctor's recommendations (112). The most common reasons not to initiate therapy included existing use of supplements as an alternative, fear of medication side effects, preference for lifestyle changes and practitioner discouragement (113). Some beliefs involved unresolved doubts and concerns about therapy or their doctors' care for them as an individual, and the risk-benefit ratio, i.e. whether their bone density warrants the potential adverse effects. Other common concerns include drug dependence, cost, alternative therapies, efficacy of medication, complexity of dosage regimens, lack of information, lack of communication with healthcare providers as well as long term safety of medication, and convenience of therapy (59, 98, 99, 113).

4.0 Methods

4.1 Study Design

The study was a cross-sectional analysis and performed in two parts. Part I involved baseline measures of participants included in the MEDEX-OP trial and clients of The Bone Clinic. Part II involved a questionnaire.

The MEDEX-OP trial was an eight-month randomised controlled trial involving postmenopausal women who either had or had not been taking antiresorptive bone treatment medication for the previous 12 months. Participants were randomly allocated into a low intensity or a high intensity exercise group. The Bone Clinic is an Australian osteoporosis clinic specialising in assisting clients make lifestyle changes via diet and bone-specific exercise with a goal of preventing osteoporotic fracture. Clients attending The Bone Clinic for their usual assessments were also included in the sample as they undergo the same baseline measures as participants of the MEDEX-OP trial.

4.2 Ethical approval

The MEDEX-OP trial is registered on the Australian and New Zealand Clinical Trials Registry (ANZCTR) (Registration ID: ACTRN12617001511325). Ethical approval for the MEDEX-OP trial was obtained from the Griffith University Human Research Ethics

Committee (HREC) (Protocol number: 2017/739) (Appendix A). Two variations to the ethics approval were obtained to include an additional questionnaire relating to motivations and attitudes toward medication within the MEDEX-OP trial (Appendix B), and to permit contact with people who had been screened out from the MEDEX-OP trial (Appendix C). People who had been screened out from the MEDEX-OP trial were emailed the questionnaire relating to motivations and attitudes toward medication along with a few basic questions regarding demographics and behaviours. Consent was assumed if they returned the completed questionnaire.

Clients from The Bone Clinic have previously consented to allow their de-identified data to be used for research purposes. Those clients were asked at one of their regular clinic assessments if they would be willing to complete the questionnaire regarding their motivations and attitudes toward medication.

4.3 Participants

The inclusion and exclusion criteria of the MEDEX-OP trial (17) were applied to participants of Part I of this study. Included participants were women who were at least one-year post menopause, had good general health and had low bone mass, defined as T-score $\leq$ -1 at the femoral neck or lumbar spine measured by dual-energy x-ray absorptiometry. Participants may or may not have been taking antiresorptive bone medication to manage their low bone mineral density (BMD). Individuals were excluded if they had conditions or problems that contraindicated participation in heavy exercises, such as uncontrolled cardiovascular disease, recent surgery, recent fracture, or acute pain. Other exclusion criteria included taking medications known to influence bone mass (e.g. teriparatide, hormone therapy, corticosteroids, thyroxine, thiazides, antiretrovirals, chemotherapy or radiation therapy), or having any conditions that are known to affect bone health (e.g. diabetes, hyperparathyroidism, renal disease, cancer, secondary osteoporosis).

Participants included in Part II of the study were postmenopausal women with suspected or known osteopenia or osteoporosis who may or may not have been taking any type of pharmacotherapy for the primary management of low bone mass. They were recruited from the MEDEX-OP trial, The Bone Clinic, and from women who expressed interest in the MEDEX-OP trial but did not meet the inclusion criteria.

4.4 Recruitment

4.4.1 Part I

MEDEX-OP participants were recruited from the community via advertisements on social media (e.g. Facebook), the Road Ahead magazine, television, radio, official website (www.medexop.org) and the spread of brochures in GP clinics. Various participants were also recruited via word of mouth and talks at local community groups. Those who were interested in the study were given a screening interview over the phone and an appointment for an assessment was booked when inclusion criteria were met. For those who did not know what their bone density was like, the final criterion of having bone mineral density within the osteopenic or osteoporotic range was assessed when they had their bone density scans during the initial assessment (see Appendix D for the case report form used).

In order to obtain data from a wider sample range, during the period of two months, data of The Bone Clinic clients were collected from the results of a routine annual assessment or initial assessment for new clients.

4.4.2 Part II

Some of the participants from the MEDEX-OP trial had already concluded their exercise programs by the time Part II was implemented. They, along with the people who had been screened out from the MEDEX-OP trial were emailed the questionnaire (see Appendix E). The questionnaire could be completed within the email and sent back via reply email. For those who found it difficult to complete the questionnaire via the email were able to request to complete the questionnaire over the phone or receive it in the mail with a reply-paid envelope. Participants already undergoing the MEDEX-OP trial were provided the questionnaire at the end of one of their exercise sessions, while other participants completed it at their baseline or post-intervention assessment.

The Bone Clinic clients received the questionnaire during one of their routine assessments.

4.5 Outcome measures

The majority of outcomes were measured using established and validated instruments, such as questionnaires and physical measures. Participant choices and attitudes toward medication were determined from a questionnaire.

PART I

4.5.1 Physical factors

Medical histories were self- reported by participants and conditions considered chronic were included for data analysis. Chronic conditions were medical conditions that had persisted beyond three months. These included food or contact allergies or intolerances that may have not been formally diagnosed but were reported as problems by the participant.

4.5.1.1 Anthropometrics and vital signs

Anthropometric data included weight, height, body mass index (BMI) (114) and waist circumference (114). Weight was measured without shoes on a Charder model MS 4202L (Adult) electronic weighing scale. Height was measured with a Seca model 216 wall-mounted stadiometer, ensuring the heels were against the wall. BMI was measured in kg/m^2 via the equation: $BMI = \frac{Weight}{Height^2}$

4.5.1.2 Body composition and fracture risk

BMD was obtained via dual X-ray absorptiometry (DXA) scans at the dominant hip and spine using a Medix DR (Medilink, France) or an XR-800 (Norland, Fort Atkinson) densitometer. Hip DXA scans were performed with participants lying supine and using a hip sling and foot block to aid in obtaining the appropriate amount of hip rotation for the hip scan. Where participants had a hip replacement in the dominant hip, the non-dominant hip was used. The BMD and T-scores of the total hip were used for data analysis. Lumbar spine DXA scans were performed with participants lying supine with a leg block underneath the lower limbs to approximate 90° angles at the hips and knees. The BMD scores of the lumbar vertebrae L1-L4 were used for analysis.

Fracture risk was calculated using the Garvan Institute Fracture Risk Calculator (115) where DXA hip scan data was available. The Garvan Institute Fracture Risk

Calculator provides the five and ten year risk of any osteoporotic fracture and hip fracture by including the following factors into its equation: sex, age, number of fractures since the age of 50 years, number of falls over the past 12 months and T-score of the femoral neck . The Garvan Institute Fracture Risk Calculator can be found at the following website: https://www.garvan.org.au/promotions/bone-fracture-risk/calculator/index.php.

Whole body bone mineral content was not measured for participants who had a joint replacement. For participants who had prosthetic breasts, the fat mass, lean mass and percentage of body fat were not measured. In the case of bilateral hip replacement, fracture risk was not calculated as the Garvan Calculator relies upon T-scores of the neck of femur.

4.5.1.3 Posture

Tragus to wall

The forward head posture required a measurement in centimetres of the distance between the tragus of the ear and the wall with a stainless steel CraftRight ruler when the participant stood in their normal standing posture with their back against the wall (116, 117). The average of three repeated measures was used for analysis.

4.5.1.4 Strength, balance and function

Clinical measures of strength, balance and function included back extensor strength (118), the functional reach (119) and five times sit-to-stand (120, 121) tests. A standard chair (height: 46cm, width: 43cm, depth: 42.5cm) was used for the five times sit-to-stand.

Functional reach test

For the functional reach test, participants stood next to a wall where a horizontal ruler had been mounted on the wall roughly at shoulder height. From a normal relaxed, standing position perpendicular to the wall with feet lined up behind a marked position on the floor, participants were asked to make a fist. The fist was held out in front of the participant at shoulder height and the original starting position of the fist from the end of the third metacarpal along the wall mounted ruler was noted using a metal ruler. Participants were then asked to reach as far forward as they could without taking a step or losing their balance, and the point at which the end of the third metacarpal of the fist reached on the

wall mounted ruler was recorded. The distance between the end position and the original position was recorded as the functional reach score in centimetres. Participants were not allowed to touch the wall at any point during this test. The test was repeated thrice and the best or furthest reach of three attempts was included in the analysis.

Back extensor strength

The back extensor strength test required participants to stand with their back and heels against a wall between two vertically anchored rails, while an inelastic strap is firmly secured to the rails and the participants, sitting approximately one centimetre below the anterior superior iliac spine. This prevented movement away from the wall during the test. The dynamometer (Lafayette Model 01165 Manual Muscle Tester, Indiana, USA) (118) was placed between the wall and the participant's back at the spinous process of T7. The participant pushed the dynamometer back into the wall with their arms crossed over their chest. The strength of the isometric contraction was measured in kilograms. The participant was given a trial attempt to get the feel of the movement and then the best of three attempts was used in analysis.

Five times sit-to-stand

The five times sit to stand is a test of functional lower limb strength. The participant was instructed to start sitting in a standard chair with their feet flat on the floor, arms folded across their chest and back against the back rest. The participant was then instructed to stand up and sit down as fast as possible, ensuring their back returns to an upright position after each stand. Standing was defined as full extension at the hips and knees. The timer was started from the moment the back left the backrest and stopped the moment the vertical back touched the backrest after five sit-to-stands. The fastest time taken of three attempts to perform five consecutive sit-to-stands was included in the analysis.

4.5.2 Behavioural factors

To quantify historical participation in bone-relevant physical activity, scores from the Bone-specific Physical Activity Questionnaire (BPAQ) (122) were recorded. The Australian Calcium-Specific Diet Questionnaire (AusCal) (123) was used to estimate daily dietary calcium intake.

Current smoking and alcohol intake were recorded during the assessment. All of these were administered during the MEDEX-OP baseline assessment or a routine assessment of The Bone Clinic where an assessor was present, so that questions for clarification could be asked and the investigator could ensure all assessments were properly completed.

PART II

4.5.3 Attitudes and motivations

Participant motivations to take antiresorptive bone medication were obtained using a short two-item questionnaire developed specifically for the study (see page six of Appendix D). Participants were asked to rank a list of relevant reasons to take or not take antiresorptive bone medication and note their attitudes toward medication in general. Other information such as age, diagnosis of osteoporosis or osteopenia, family history of osteoporosis, history of falls, history of fractures, current smoking status, frequency of alcohol intake, prescribed medication or nutritional supplements, and previous anti-osteoporosis medication use was also obtained from participants who had been screened out of the MEDEX-OP trial (see Appendix E), or derived from client records at TBC.

If participants did not have or were unsure if they had low BMD, their answers were included if they answered the questions as if they had been diagnosed with low BMD. In some cases, a participant may have previously been on bone medication and then ceased it, and so were not currently taking any medication for the primary management of their bone health. If these participants completed both sections of the questionnaire as to why they had initially commenced bone medication, as well as their reasons why they were not currently taking bone medications – their answers for both sections of the questionnaire were included in the analysis.

Participants who were on pharmacotherapy could select and rank their answers from a total of seven motivations as to why they chose to commence or continue taking their prescribed antiresorptive bone medication. Number one was considered to be the main reason or motivation. The available motivations were as follows:

- My doctor recommended it

- I have seen the experience of an acquaintance
- I have heard good things about it – where did you hear about it?
- I have read good things about it – where did you read about it?
- I was worried about my bone health
- I thought it was worth a try
- Other (please specify)

Participants not taking any bone medication were asked whether they had considered going on medication when they first discovered they had low BMD (yes/no). They then had a total of nine motivations they could select from and rank in order of which were the closest reasons to why they had chosen not to undertake pharmacotherapy, as follows:

- I don't like taking medication/ I take as few drugs as possible
- I don't want to become reliant upon medication
- I would rather make lifestyle changes to improve my health than take drugs
- I was concerned about an interaction with other medications or a medical condition I already take/have (This reason included any participant concerns about side effects)
- I have seen the experience of an acquaintance
- I have heard bad things about side effects of bone drugs – where did you hear this?
- I have read bad things about the side effects of bone drugs – where did you read this?
- I don't feel I know enough about bone medication to make a decision
- Other (please specify)

Finally, both groups were asked to identify with one of three options: pro-medication, anti-medication and ambivalent toward medication. Participants would take medication when needed but otherwise prefer to avoid taking medication were advised to select 'ambivalent toward medication'.

4.4 Statistical analysis

Data analyses were performed using Stata V16.2 (StataCorp. 2019. *Stata Statistical Software: Release 16*. College Station, TX: Stata Corp LLC). Normality was tested using skewness and kurtosis, the Kolmogorov-Smirnov test and Shapiro-Wilk test. For continuous data, frequencies were presented as means and standard deviations for normally distributed data, whereas medians with the interquartile ranges were used for data that was not normally distributed. Categorical data frequencies were presented as numbers and percentages.

The Purposeful Selection Method (124) was used to build the statistical models used in this study. The aim of the Purposeful Selection Method is to reduce the number of variables using forwards elimination until the model that is parsimonious or is as concise as possible, but still describes the data has been found. Purposeful selection requires a univariable analysis of each of the variables. Any variable that is considered significant becomes a candidate for inclusion in the multivariable analysis. Non-significant variables that are not confounders are removed from the model.

Significance during the building of the statistical model was initially evaluated at an alpha level of 0.1, since the use of 0.05 p-values may not identify important variables (124, 125). Confounding variables were defined as a change in any remaining parameter estimates that were greater than 20 percent in the univariable models as compared to the full multivariable model (125). In the final multivariable model, only significant covariates and confounders with a p-value less than 0.05 were included.

Continuous variables were included in a univariable logistic regression to explore the association between bone medication status and the other participant variables. The Wald test (124) was used to test the null hypothesis. A p-value less than 0.1 was considered significant at this stage. Significant or borderline significant continuous variables from the univariable logistic regression were included in a correlation matrix using the Pearson correlation coefficient (r). Categorical variables were assessed by setting them up as the response variable in a logistic regression model in order to discover whether any other independent variables were associated with it until all variables had been tested against each other.

Using the Pearson correlation matrix and repeated univariable logistic regression analyses, variables that were correlated with each other and may not be necessary for inclusion in the same model as a set or were confounders were identified.

Following this, a multivariable logistic regression model involving the variables showing significant relationships from the univariable analysis was used to determine the characteristics that most strongly predicted BMD measures or therapy choices in each group. P-values less than 0.05 were considered significant.

5.0 Results

5.1 Recruitment

A total of 349 women were recruited. Participants were recruited from three groups: MEDEX-OP participants, people excluded from the MEDEX-OP trial and The Bone Clinic clients. The recruitment of participants can be seen graphically in Figure 1.

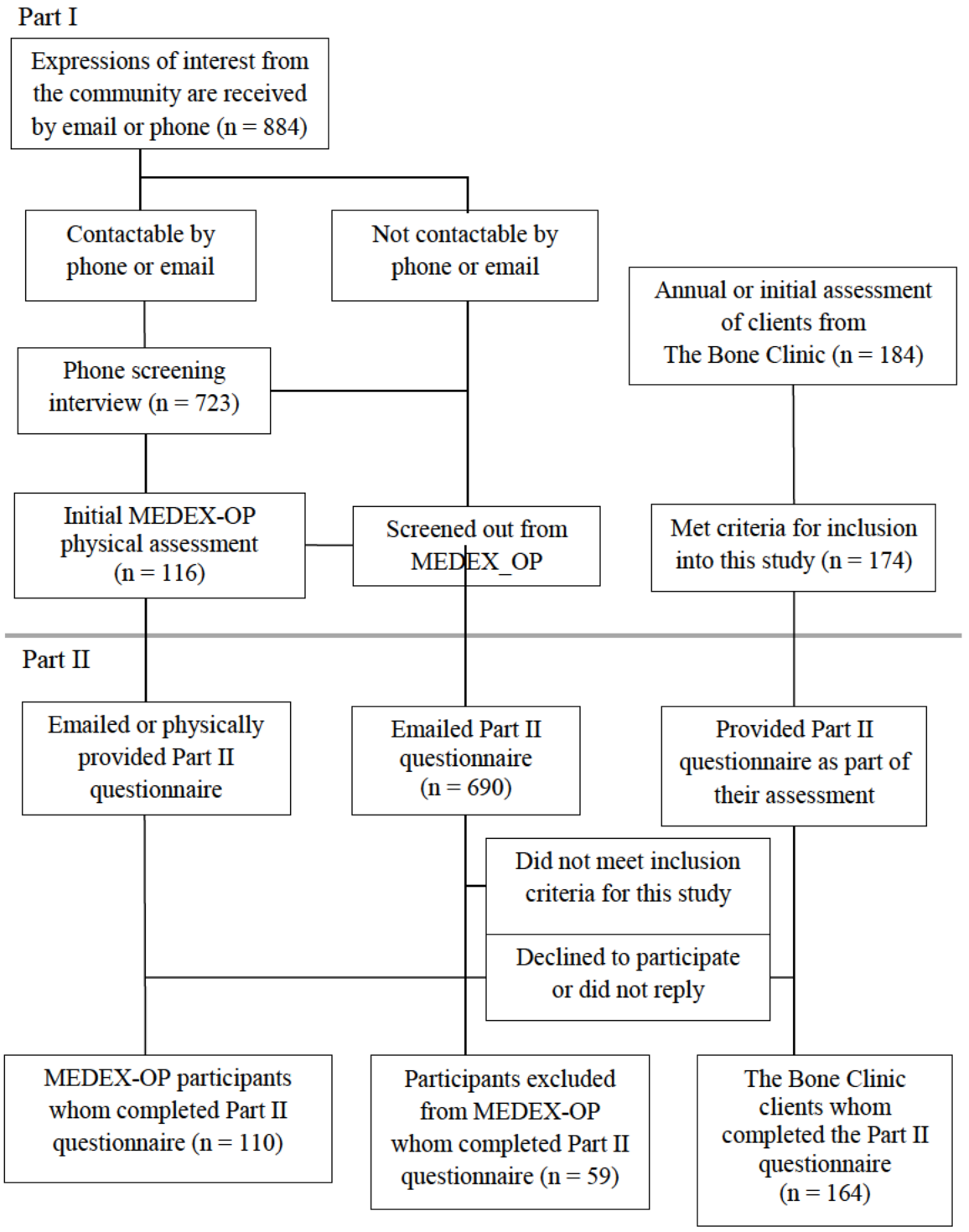
There were 116 (33.2%) MEDEX-OP participants and two participants decline to participate in the Part II questionnaire regarding choices in osteoporosis management, and four did not reply to the survey but did complete all other assessments.

People who were excluded from the MEDEX-OP study were contacted via email with a questionnaire to obtain their demographic data and the Part II questionnaire regarding choices in osteoporosis management. There were 680 emails sent out. Only 72 people replied despite follow up emails and phone calls. Of the respondents, 13 were excluded as they did not meet the inclusion criteria for this study. Therefore 59 of these women (16.9%) were included into this study. It should be noted that these women did not undergo a physical assessment.

Of the total participants in this study, 174 (49.9%) were women who were currently attending The Bone Clinic for their routine assessments and met the inclusion criteria. Due to the convenience sampling, not all participants completed all assessments, questionnaires and surveys. This resulted in a large amount of missing data. Thus, the descriptive results tables (Tables 1, 3, 4, 5 and 7) have identified the percentage of participant data included in

analysis for that variable. Where the population sample percentages were not provided in the tables, there was no missing data for that variable.

Figure 1. Recruitment of participants



5.2 Demographics

The sample consisted of a total of 349 women who were at least one year post menopause of which 256 (73.4%) women were off bone medication and 93 (26.6%) were on bone medication. All the participants on bone medication were taking antiresorptive drugs, with 35 (39.3%) taking a bisphosphonate, 52 (58.4%) taking denosumab, and two (2.2%) taking a SERM.

Table 1 details the descriptive statistics and association with bone medication using a univariable logistic regression analysis for the demographics, medical history, number of prescribed medications (other than bone medication) as well as the number of daily supplements and/or over the counter medications variables. The Wald test p-value is shown in the table. Only the number of chronic comorbidities was normally distributed. All other variables were not normally distributed. Due to some missing data, the number and percentage of included data are also shown for the relevant variables within the table.

Table 1. Descriptive statistics and Wald test p-values from a univariable logistic regression of participant demographics, medical history, prescribed medication and daily supplements and/or over the counter medications

	Off Bone Meds N = 256	On Bone Meds N = 93	*p*-value
Age *median (IQR)*	63.00 (8.00)	65.00 (10.00)	**0.008**
Age of menopause *median (IQR)*	*n = 216 (84.4%)* 50.00 (5.00)	*n = 64 (68.8%)* 50.00 (8.00)	0.748
Postcode *n (%)*	*n = 252 (98.4%)*	*n = 93 (100.0%)*	0.237
Low socio-econ lvl	11 (4.4)	3 (3.2)	
Moderate s/e lvl	49 (19.4)	26 (28.0)	
High s/e lvl	192 (76.2)	64 (68.8)	
BMI *median (IQR)*	*n = 224 (87.5%)* 23.51 (5.46)	*n = 66 (71.0%)* 23.29 (6.33)	0.311
Fragility fractures *median (IQR)*	*n = 256 (100.0%)* 0.00 (1.00)	*n = 92 (98.9%)* 0.00 (1.00)	**<0.001**
Number of chronic comorbidities *mean (SD)*	*n = 244 (95.3%)* 3.14 (2.23)	*n = 75 (80.6%)* 3.29 (2.19)	0.590
Number of prescription medications *median (IQR)*	*n = 256 (100.0%)* 1.00 (2.00)	*n = 93 (100.0%)* 1.00 (3.00)	**0.036**
Previously took bone medication *n (%)*			**0.001**
Yes	43 (16.8)	31 (33.3)	
No	213 (83.2)	62 (66.7)	
Number of daily supplements/ over the counter medications *median (IQR)*	*n = 255 (99.6%)* 2.00 (3.00)	*n = 92 (98.9%)* 2.00 (2.00)	0.380

Being on bone medication was not associated with age of menopause, socio-economic level based upon postcode, BMI, number of chronic comorbidities, and the number of daily supplements and/or over the counter medications. There were statistically significant positive associations between being on bone medication and age, fragility fracture, number of prescribed medication and whether participants had previously been on bone medications. The odds ratios and 95% confidence intervals for these statistically significant variables are shown in Table 2 as an alternate way to present these results.

Table 2. Odds ratios and 95% confidence intervals from the univariable logistic regression of statistically significant demographic variables with bone medication univariable

Predictor variables	OR (95% CI)
Age (years)	1.05 (1.01-1.09)
Fragility fractures (base = nil fractures)	
1 fracture	1.14 (0.61-2.15)
2+ fractures	5.08 (2.60-9.94)
Number of prescription medications (base = nil meds)	
1 prescription medication	0.84 (0.44-1.61)
2 prescription medications	1.31 (0.65-2.63)
3+ prescription medications	2.24 (1.19-4.22)
Previously took bone medication	2.48 (1.44-4.26)

Results showed that when the odds of being on bone medication were compared between women on prescribed medication as opposed to three or more prescribed medications, the odds of being on bone medication were 2.66 times as large as the odds of only being on one prescribed medication (Wald test $p < 0.008$). The odds comparing women on three or more medications with women on two prescribed medications were not statistically significant.

Women who had previously been on bone medication had roughly 2.5 times the odds of currently being on bone medication compared to the odds of a woman who had never taken bone medication before (Wald test $p = 0.001$).

Table 3. Categories of chronic comorbidities

Categories of chronic comorbidities	Off bone medication n = 256 *n (%)*	On bone medication n = 93 *n (%)*
Musculoskeletal	179 (69.9)	56 (60.2)
Cardiovascular	86 (33.6)	27 (29.0)
Digestive	57 (22.3)	17 (18.3)
Cancers/ tumours	46 (18.0)	23 (24.7)
Respiratory	32 (12.5)	12 (12.9)
Autoimmune	32 (12.5)	7 (7.5)
Neurological	30 (11.7)	7 (7.5)
Mental health	23 (9.0)	16 (17.2)
Endocrine	21 (8.2)	8 (8.6)
Eyes/ ears	11 (4.3)	4 (4.3)
Allergy	10 (3.9)	5 (5.4)
Blood disorders	7 (2.7)	3 (3.2)
Diabetes	6 (2.3)	0 (0.0)
Skin	4 (1.6)	1 (1.1)
Urinary	3 (1.2)	0 (0.0)

The number of chronic comorbidities that participants had at the time of assessment or survey was not associated with being on bone medication, nevertheless chronic musculoskeletal conditions were the most common type of medical condition. This was followed by cardiovascular disorders and digestive disorders. The frequencies for the chronic comorbidities can be found in Table 3.

5.3 Physical characteristics

Table 4 shows the results of bone density as measured by DXA scanning at the lumbar spine and total hip of the dominant leg, as well as the 10-year risk of hip fragility fracture. DXA scan results at the lumbar spine and dominant total hip were normally distributed and did not show a statistically significant association between BMD and being on bone medication. However, the 10-year risk of a hip fragility fracture as measured using the Garvan Institute fracture risk calculator were not normally distributed but showed a statistical significance between fracture risk with being on bone medication.

Of the four included physical measures, only the tragus to wall was normally distributed, whereas back extensor strength, the functional reach and five times sit to stand were not normally distributed. Back extensor strength and the five time sit to stand measures were negatively associated with being on bone medication, whereas posture, as measured via the tragus to wall, and the functional reach test were not associated with currently being on bone medication. Table 5 shows the odds ratios and 95% confidence intervals of the statistically significant physical variables found in the univariable logistic regression analyses

Beside the univariable logistic regression, the Mann-Whitney U test was also applied to observe if there were differences between musculoskeletal traits or function between women who were on or off bone medication. The results reflected those that were found in the univariable logistic regression shown in Table 4. It was found that the Garvan 10-year risk of hip fracture ($U = 5304.50$, $p = 0.003$), back extensor strength (kg) ($U = 5360.50$, $p = 0.001$), and five times sit to stand ($U = 5892.00$, $p = 0.012$) were statistically significant between groups. All other physical factors did not show a statistical significance between groups. This suggests the possibility that risk of future fragility fracture, back extensor strength and lower limb function may be physical traits indicative of whether women are on or off bone medication.

Table 4. Descriptive statistics and Wald test p-values from a univariable logistic regression of participant bone density scans, fragility fracture risk, posture, strength, function and balance

Measures	Off bone medication N = 256	On bone medication N = 93	*p*-value
DXA scan			
L1-L4 BMD (g/cm^2) *mean (SD)*	*n = 223 (87.1%)* 0.85 (0.14)	*n = 65 (69.9%)* 0.85 (0.12)	0.916
Dominant total hip BMD (g/cm^2) *mean (SD)*	*n = 223 (87.1%)* 0.78 (0.10)	*n = 64 (68.8%)* 0.76 (0.09)	0.094
T-score *mean (SD)*	-1.53 (0.68)	-1.66 (0.67)	0.185
Garvan Institute fracture risk calculator			
10-year risk of hip fracture (%) *median (IQR)*	*n = 223 (87.1%)* 4.00 (5.30)	*n = 63 (67.7%)* 6.00 (9.00)	**0.019**
Posture, strength, function and balance			
Posture Tragus to wall (mm) *mean (SD)*	*n = 224 (87.5%)* 131.53 (23.86)	*n = 66 (71.0%)* 131.45 (24.32)	0.979
Strength Back extensor strength (kg) *median (IQR)*	*n = 224 (87.5%)* 30.80 (14.50)	*n = 66 (71.0%)* 27.10 (13.10)	**0.001**
Function and balance Functional reach (cm) *median (IQR)*	*n = 223 (87.1%)* 39.00 (5.10)	*n = 66 (71.0%)* 37.00 (5.00)	0.065
Five times sit to stand (s) *median (min-max)*	*n = 224 (87.5%)* 9.94 (2.71)	*n = 66 (71.0%)* 10.54 (3.04)	**0.006**

Table 5. Odds ratios and 95% confidence intervals from the univariable logistic regression for significantly related physical variables with bone medication

Predictor variables	OR (95% CI)
Garvan 10-year risk of hip fracture	1.03 (1.01-1.06)
Back extensor strength (kg)	0.96 (0.93-0.98)
Five times sit to stand (s)	1.16 (1.04-1.30)

5.4 Behavioural characteristics

The descriptive data regarding the behavioural characteristics such as total calcium intake, total bone-specific physical activity score, current smoking status and alcohol intake can be seen in Table 6. The Wald test p-values from the univariable logistic regression have also been included. Neither the total calcium intake nor the total bone-specific physical activity score were normally distributed. Due to too much missing data, data for other behavioural factors could not be included in the logistical regression analysis. Neither the average number of glasses of alcohol taken per week nor current smoking status showed a statistically significant association with being on bone medication. There were only 10 current smokers compared to 335 non-smokers and so the results regarding the relationship between currently smoking and being on bone medication is likely to be unreliable.

Table 6. Descriptive statistics, Wald test p-values, odds ratios and 95% confidence intervals from a univariable logistic regression of total calcium intake, total bone-specific activity score, smoking status and alcohol intake

Behavioural factors	Off bone medication N = 256	On bone medication N = 93	*p*-value	OR (95% CI)
Total calcium intake (mg/day) *median (IQR)*	**n = 222 (86.7%)* 1122.00 (712.30)	*n = 66 (71.0%)* 1203.89 (558.82)	0.534	1.00 (0.9996-1.0008)
Total BPAQ *median (IQR)*	*n =185 (72.3%)* 11.2 (19.08)	*n = 51 (54.8%)* 18.35 (24.24)	0.084	1.02 (0.9982-1.0337)
Current smoker *n (%)*	*n = 252 (98.4%)*	*n = 93 (100.0%)*	0.364	1.84 (0.5082-6.6819)
Yes	6 (2.4)	4 (4.3)		
No	246 (97.6)	89 (95.7)		
Alcohol intake *n (%)*				
Never	50 (20.7)	19 (20.4)		
Rarely	50 (20.7)	24 (25.8)		
Regular alcohol intake	142 (58.7)	50 (53.8)		
Average number of glasses/week *median (IQR)*	*n = 234 (91.4%)* 2.0 (5.00)	*n = 92 (98.9%)* 1.0 (6.00)	0.924	1.00 (0.9497-1.0586)

5.5 Attitudes and choices in therapy

5.5.1 Attitudes toward medication in general

Of the 349 participants, 328 (94.0%) completed the questionnaire on choices and attitudes toward pharmacotherapy in management of osteoporosis. Table 7 shows the frequencies of attitudes toward any medication in general. Univariable logistic regression showed a statistically significant association between being on bone medication and attitudes toward medications in general, particularly for people who were pro-medication or anti-medication. The results suggested that the odds of women who are pro-medication had odds almost six times as great as the odds women who are anti-medication of being on bone medication. Women who were ambivalent about medication in general were just as likely as those who were anti-medication to be on bone medication. Alternatively, when the model base was changed to ambivalent toward medication, women who were pro-medication had odds almost five times as great as the odds of women who were ambivalent toward medication (Wald test $p < 0.001$) to be on bone medication.

Table 7. Descriptive statistics, Wald test p-values, odds ratios and 95% confidence intervals from a univariable logistic regression of attitudes toward medication in general

Attitudes toward medication	Off bone medication (n = 240) *n (%)*	On bone medication (n = 88) *n (%)*	*p*-value	OR (95% CI)
Attitudes toward medication			<0.001	
Pro-medication	48 (20.0)	47 (53.4)		5.95 (2.92-12.12)
Anti-medication	79 (32.9)	13 (14.8)		(used as base)
Ambivalent toward medications	113 (47.1)	28 (31.8)		1.51 (0.73-3.09)

5.5.2 Reasons to be off bone medication

There were 241 participants who completed the questionnaire on reasons not to take bone medications. The questionnaire provided nine choices and the frequencies from the results of the questionnaire can be found in Tables 8 to 11. Most women (n = 152, 61.4%) had not considered taking bone medication when they discovered they had low BMD, with 'I would rather make lifestyle changes to improve my health than take drugs' being the most common main reason as well as being a frequent second reason to not take bone medications. 'I don't like taking medication/ I take as few drugs as possible' was the most common second reason, but was also a frequent first motivator to not take bone meds. 'I don't want to become reliant upon medication was the most common third reason that participants chose.

Table 8. Reasons to not take bone medication

Motivations	Not on bone medications (n = 241) *n (%)*	Common reasons *n (%)*
Considered taking bone medication when discovered low BMD	*n = 237 (98.3%)*	
Yes	85 (35.9)	
No	152 (64.1)	
I don't like taking medication/ I take as few drugs as possible	148 (61.4)	**Most common second reason 52 (21.6)** First reason 40 (16.6) Third reason 17 (7.1)
I don't want to become reliant upon medication	99 (41.1)	Second reason 24 (10.0) **Most common third reason 26 (10.8)** Fourth reason 14 (5.4)
I would rather make lifestyle changes to improve my health than take drugs	185 (76.8)	**Most common first reason 86 (35.7)** Second reason 36 (14.9) Third reason 16 (6.6)
I was concerned about an interaction with drugs or a medical condition I already take/have	39 (16.2)	
I have seen the experience of an acquaintance	40 (16.6)	Third reason 11 (4.6)
I have heard bad things about side effects of bone drugs	70 (29.0)	Second reason 12 (5.0) **Most common fourth reason 15 (6.2)**
I have read bad things about side effects of bone drugs	65 (27.0)	Second reason 11 (4.6)
I don't feel I know enough about bone medication to make a decision	81 (33.6)	First reason 11 (4.6) Third reason 17 (7.1)
Other	53 (22.0)	First reason 31 (12.9)

There were three open text sections where participants could provide their own responses if they felt that the reasons provided did not match their main motivations for not taking bone medication (see Tables 9 to 11). These responses were then categorised into common themes. From the results, women were most likely to hear bad things about bone medication from a health professional, such as a doctor (see Table 9); read bad things about bone medication on the internet (see Table 10); or have another reason not to be on bone

medication (see Table 11). The most common 'other' reason participants provided was that their doctor did not mention or offer bone medication as a choice of osteoporosis management.

Table 9. Where participants have heard bad things about bone medication

Motivations	Not on bone medications (n = 241) *n (%)*
I have heard bad things about side effects of bone drugs	70 (29.0)
Where:	
Internet	9 (12.9)
Google	3 (1.4)
Record of people's experiences	1 (4.3)
Save Our Bones program	2 (2.9)
Health professional	22 (31.4)
Dentist	7 (10.0)
Dental technician	1 (1.4)
Physiotherapist	1 (1.4)
Doctor	10 (14.3)
Specialist doctor	1 (2.4)
Pharmacist	2 (2.9)
Complementary health therapist	1 (1.4)
Homeopath	1 (1.4)
Friends/ acquaintances	19 (27.1)
Other clients at The Bone Clinic	1 (1.4)
Social media groups	1 (1.4)
Family	8 (11.4)
Parent	5 (7.1)
Sister-in-law	2 (2.9)
Media	2 (2.9)
TV	2 (2.9)
The Bone Clinic seminar	2 (2.9)
Hearsay/ word of mouth	3 (4.3)
Self-research	3 (4.3)
Don't remember	1 (1.4)

Table 10. Where participants have read bad things about bone medication

Motivations	Not on bone medications (n = 241) *n (%)*
I have read bad things about side effects of bone drugs	65 (27.0)
Where	
Internet	42 (64.6)
Google	3 (4.6)
Save Our Bones program	3 (4.6)
Forums	1 (1.5)
Medical website	1 (1.5)
YouTube	1 (1.5)
Articles/reports	5 (7.7)
Patient reviews	1 (1.5)
Medical journal articles	2 (3.1)
Medical reference guide	1 (1.5)
Medical research	2 (3.1)
Medical information/ factsheets/ brochures/ flyers	3 (4.6)
Medication brochure/ drug product information	1 (1.5)
Family/friends/acquaintances	3 (4.6)
Parent	1 (1.5)
Social media groups	1 (1.5)
Media	6 (9.2)
Social media	1 (1.5)
Print media (magazine/newspaper)	4 (6.2)
The Bone Clinic reviews	1 (1.5)
Health books/articles	3 (4.6)
Hearsay/word of mouth	1 (1.5)
Self-research	13 (20.0)
Don’t remember	1 (1.5)

Table 11. Other motivations not to take bone medication

Motivations	Not on bone medications (n = 241) *n (%)*
Other	53 (22.0)
Doctor did not give any suggestions/ recommendations	5 (9.4)
Doctor recommended against taking bone medications	2 (3.8)
Doctor did not mention/ offer bone medications	10 (18.9)
Doctor said bone medications not necessary	2 (3.8)
Doctor recommended lifestyle changes instead	1 (1.9)
Doctor recommended supplements instead	4 (7.5)
Taking supplements didn't help	1 (1.9)
Taking supplements instead	2 (3.8)
Previously on bone medications	8 (15.1)
Stopped due to side effects	4 (7.5)
Stopped when bone density was within the normal range	1 (1.9)
Stopped upon GP recommendation regarding long term use	1 (1.9)
Worried about side effects	4 (7.5)
Did not feel bone density was bad enough to need bone meds	6 (11.3)
Family/friend's advice	2 (3.8)
Dental issues	1 (1.9)
Thought bone meds were elderly person's last resort to manage osteoporosis	1 (1.9)
Lack of information on osteoporosis	2 (3.8)
Discovered low BMD as part of the MEDEX-OP study	1 (1.9)
Doctor recommended exercise instead	1 (1.9)
Trialling exercises first	1 (1.9)
Had improved BMD with exercise	1 (1.9)
Awaiting doctor's review/advice	1 (1.9)
Self-research	3 (5.7)
Due to lack of symptoms, hard to get motivated to take bone meds	1 (1.9)
BMD has improved with supplements and better nutrition	1 (1.9)
Does not feel medications solve the root of the problem	1 (1.9)
Previous fragility fractures	1 (1.9)
Avoiding starting bone meds for now	1 (1.9)

5.5.3 Reasons to be on bone medication

There were 90 participants (96.8%) who completed the questionnaire on reasons to be on bone medication. The questionnaire provided seven choices and the frequencies from the results of the questionnaire can be found in Table 12 to 15. The most common main reason for being on bone medications was 'my doctor recommended it', followed by 'I was worried about my bone health' being the most common second reason, and 'I thought it was worth a try' being the most common third reason.

Table 12. Reasons for being on bone medication

Motivations	On bone medications (n = 90) *n (%)*	Common reasons *n (%)*
My doctor recommended it	83 (92.2)	**Most common first reason 56 (62.2)** Second reason 13 (14.4) Third reason 5 (5.6)
I have seen the experience of an acquaintance	8 (8.8)	
I have heard good things about it	12 (13.5)	
I have read good things about it	11 (12.1)	
I was worried about my bone health	54 (60.0)	**Most common second reason 25 (27.8)** First reason 13 (14.4) Third reason 5 (5.6)
I thought it was worth a try	29 (32.2)	**Most common third reason 14 (14.4)**
Other	22 (23.6)	First reason 8 (9.0) Second reason 6 (6.7)

There were three free text sections where participants could provide more detail or add their own responses if they felt that the reasons provided did not match their main motivations for being on bone medication (see Tables 13 to 15). These responses were then categorised into common themes or categories where possible. Women were most likely to hear good things about bone medication from acquaintances or friends (see Table 13), and read good things about bone medication on the internet (see Table 14). The most common

'other' reason participants provided was that they had previously suffered from a fragility fracture (see Table 15).

Table 13. Where participants have heard good things about bone medication

Motivations	On bone medications (n = 90) *n (%)*
I have heard good things about it	12 (13.5)
Where:	
Health professional	2 (16.7)
Dentist	1 (8.3)
Doctor	1 (8.3)
Complementary health therapist	1 (8.3)
Naturopath	1 (8.3)
Acquaintances/ friends	3 (25.0)
Family	2 (16.7)
Parent	1 (8.3)
Daughter	1 (8.3)
Media	2 (16.7)
Radio	1 (8.3)
Hearsay/ word of mouth	1 (8.3)

Table 14. Where participants have read good things about bone medications

Motivations	On bone medications (n = 90) *n (%)*
I have read good things about it	11 (12.1)
Where:	
Internet	6 (54.5)
Google	1 (9.1)
Articles/reports	1 (9.1)
Medical journal articles and guidelines	2 (18.2)
Medical research	1 (9.1)
Medical information fact sheet/ brochures/ flyers	1 (9.1)
Medication brochure/ drug product information	1 (9.1)
Friends/acquaintances	1 (9.1)
Social media groups	1 (9.1)
Media	4 (36.4)
Print media (magazines/ newspapers)	3 (27.3)
Social media	1 (9.1)

Table 155. Other motivations to be on bone medication

Motivations	On bone medications (n = 90) *n (%)*
Other	22 (23.6)
Was not aware of other options	1 (4.5)
Felt bone meds were the only option	1 (4.5)
Previous fragility fracture	9 (40.9)
Want to avoid fracture	1 (4.5)
Secondary OP	3 (13.6)
Family history of OP	2 (9.1)
Wanted to do something about bone density after	1 (4.5)
dropped out of the MEDEX-OP study	1 (4.5)
Doctor suggested a bone scan	1 (4.5)
Did not feel had much choice	1 (4.5)
Unsure of the efficacy of other OP management options	1 (4.5)
Previous HRT	1 (4.5)
Bone cyst	1 (4.5)
Lack of information on alternate OP management options	1 (4.5)
Didn't have time to research	1 (4.5)
Changed between bone meds due to side effects	1 (4.5)

5.6 Multivariable analysis

The independent variables for this model consisted of both continuous and categorical variables. Variables with a univariable p-value greater than 0.1 were extremely unlikely to become significant in a multivariable model and therefore excluded. The significant and borderline significant continuous variables (where $p < 0.1$ or approximated 0.1) at the univariable level were entered into a Pearson correlation matrix (see Table 16). These included:

- Age
- Total BPAQ (t-BPAQ)
- Dominant hip BMD (dh BMD)
- Garvan 10-year risk of hip fracture (Garvan)
- Back extensor strength (BE)
- Functional reach (FR)
- Five times sit to stand (5xSTS)

From the correlation matrix, it was observed that there were mostly low to moderate relationships between these variables.

Table 16. Pearson correlation matrix of significant and borderline significance univariables

Variables	Age	t-BPAQ	dh BMD	Garvan	BE	FR	5xSTS
Age	1.00						
t-BPAQ	-0.08	1.00					
dh BMD	-0.10	0.07	1.00				
Garvan	0.22	-0.08	-0.30	1.00			
BE	-0.22	0.05	-0.01	-0.05	1.00		
FR	-0.16	-0.06	0.05	0.02	**0.35**	1.00	
5xSTS	0.14	0.05	0.12	-0.08	**-0.41**	-0.15	1.00

This correlation matrix suggests that back extension, functional reach and the five times sit to stand may not necessarily be part of the same model at a set. It is possible that only one of these variables needs to be included in the model.

To assess categorical variables, different categories were used as the response variables in a logistic regression to discover whether any other variables (whether categorical or continuous) were associated with it. Model reduction was thus conducted by removing variables that became insignificant once adjusted by other variables in the model one at a time. In this way, it was found that age and dominant hip BMD were related with previous bone medication. This suggests that only one of these three variables is needed in the model. Age, fragility fractures and Garvan 10-year risk of hip fractures were also found to be related, and only one of these variables needs to be included in the final model.

Some of the variables that were significant at the univariable level may have become non-significant due to several reasons. The loss of degrees of freedom leads to an increased number of parameters that need to be estimated, leading to lower precision. Some variables being related to each other, may have measured similar things and ended up competing with each other in significance in the correlation of regressors. The model may have been misspecified in that the univariable level models may have suffered from omitted

variable bias. That is, relevant variables may have been missed when they should have been included. The number of variables that were able to be included in this study were limited due to unacceptably large type I errors when more variables were included. As such, there may be other important variables that may not have been accounted for in this study. Due to some missing data, some variables may have also lost power and been missed.

As a result the following variables were associated to participants being on or off bone medication on a univariable level:

- Age
- Number of fragility fractures
- Number of prescribed medications
- Previously taken bone medication
- Garvan10-year risk of a hip fragility fracture
- Back extensor strength
- Five times sit to stand
- Attitudes toward medication

Using the Purposeful Selection Method (124) to reduce the models, two potential multivariable logistic regression models were obtained. Model One included ‘Fragility fractures’, ‘Previous bone medication’, ‘Back extensor strength’ and ‘Attitudes toward medication in general’ (see Table 17). Model Two considered the association between ‘Fragility fractures’ and ‘Garvan 10-year risk of hip fracture’ by replacing ‘Fragility fractures’ with Garvan hip fracture risk. This allowed ‘Total BPAQ’ to also be included into Model Two (see Table 18).

Table 17. Model One - Associations between bone medication and statistically significant predictor values using odds ratios and 95% confidence intervals from the multivariable logistic regression analysis

Predictor variables	OR (95% CI)
Fragility fractures (base = nil fractures)	
1	1.20 (0.56-2.57)
2+	**3.87 (1.53-9.79)**
Previous bone medication (base = no)	**2.81 (1.36-5.78)**
Back extensor strength (kg)	**0.95 (0.92-0.98)**
Attitudes toward medication (base = anti-medication)	
Pro-medication	**6.41 (2.73-15.07)**
Ambivalent	1.39 (0.61-3.20)

Table 18. Model Two - Associations between bone medication and statistically significant predictor values using odds ratios and 95% confidence intervals from the multivariable logistic regression analysis

Predictor variables	OR (95% CI)
Previous bone medication (base = no)	
Yes	**3.76 (1.67-8.46)**
Total BPAQ score	**1.02 (1.00-1.05)**
Garvan 10-year risk of hip fracture	**1.04 (1.01-1.08)**
Back extensor strength (kg)	**0.95 (0.92-0.99)**
Attitudes toward medication (base = anti-medication)	
Pro-medication	**8.01 (2.81-22.83)**
Ambivalent	2.11 (0.77-5.77)

Back extensor strength on a univariable level had a statistically significant Wald test p-value, indicating that the null hypothesis was likely to be false. Although its resultant odds ratio and 95% confidence intervals were small at both univariable and multivariable levels, the small Wald test p-values in both cases indicated that the variable was meaningful in relation with being on bone medication. As such, it was important for back extensor

strength to be included in both models, as it was likely to be true that it had a strong negative association with being on bone medication.

Both models were considerably strong and had similar characteristics. Model One may be more robust as it used more data, and both models addressed the objective to discover relationships of physical or behavioural factors with bone medication. As a result, Model One was decided upon as the final model, although Model Two could be used as well.

For the number of fragility fractures, the results in Table 17 shows that the odds for women with more than two fragility fractures to be on bone medication was 3.9 times higher than women with no previous fractures. A further analysis regarding fragility fractures in Table 17 compared one fracture with more than two fractures. This suggested that the odds for women with more than two fractures to be on bone medication are 3.22 times higher than women with one previous fracture ($p = 0.029$). However, this is borderline significant due to there being three multiple comparisons, otherwise the alpha level should be adjusted to approximately 0.017.

The results for women who are pro-medication in Model One suggest that the odds of being on bone medication are 6.4 times as great as the odds of women who are anti-medication ($p < 0.001$), whereas women who are ambivalent about medication are just as likely as those who are anti-medication to be on bone medication ($p = 0.435$). When an alternate model was run where the base reference was women who were pro-medication, the odds of being on bone medication were 4.6 times as large as the odds of those who were ambivalent toward medication ($p < 0.001$). Therefore, being ambivalent toward medication was not a significant predictor of being on bone medication whereas being pro or anti-medication were significant predictors.

6.0 Discussion

6.1 Overview of outcomes

The purpose of the current study was to compare physical and behavioural characteristics of postmenopausal women either on or off bone medication for the

management of low BMD. Participants on bone medication were more likely to have two or more fragility fractures, have previously been on bone medication, have poor back extensor strength and have a pro-medication attitude. Conversely, women not on medication were more likely to have had none or one fragility fracture, have not previously been on bone medication, have greater back extensor strength and have an anti-medication attitude. More physical than behavioural characteristics were found to be related to bone medication status.

Other studies that have looked at the associations between initiating or persisting with bone medication and patient characteristics found the following characteristics to be likely predictors: the discovery of low BMD via radiological investigation and/or the diagnosis of osteoporosis (102, 108, 126-131), older age for initiating bone medication (126, 132), younger age for persisting with bone medication (133), low BMI (132, 134), previous fractures (102, 131, 133, 134) in certain locations (femur, hip, pelvis, spine) (108, 126), supplement use (calcium and/or vitamin D) (108, 126) and health beliefs (102, 111, 128, 135).

Our study had a comparable proportion of 73.4% participants off bone medication and 26.6% on bone medication to a study that looked at predictors for bone medication use after a recent fragility fracture (108), where 78.9% of their participants were currently off bone medication and 21.1% currently on bone medication. Another similarity was that in our study, age was not related to being on or off bone medication once adjusted by other variables in the final model of the multivariable logistic regression. An Australian study (64) found that the odds of women using bone medication increased over time but still remained relatively low, which correlated with the findings of this study. On one hand, older ages are related to initiating bone medication (126, 132), but on the other hand, younger women are more likely to persist with bone medication (133). Older ages prior to 80 years and above were also found to be positively related to persisting and adhering to oral bisphosphonates in a systematic review (93).

Studies regarding the relationship between the age of menopause with bone medication use could not be found. A Turkish study (136) did not find the age of menopause to be related to osteoporosis. A systematic review (137) concluded that women

who entered menopause before 45 years of age had an increased risk for fractures compared to women who had menopause after 45 years of age, but it did not include any data on follow-up treatment and whether or not they were prescribed bone medication. However, other studies regarding the treatment of low bone density stated that a large majority of postmenopausal women with low bone density are not on bone medication (18, 55, 108, 134, 138).

The results did not show that the postcode related socio-economic status of participants was related to whether women were on bone medication for management of low BMD. There have been conflicting reports regarding the relationship between socio-economic status and low BMD. It has been reported that a lower socio-economic status is related to low BMD (139-141) or that socio-economic status may not be related to fragility fractures (142). Unlike our study, most studies involving bone medication did find the socio-economic status to be related, albeit specifically to the adherence and persistence with pharmacotherapy (93, 143). While our study used the residential postcodes of participants to estimate the socio-economic status of participants using the Index of Relative Socio-economic Advantage and Disadvantage (IRSAD), other studies calculated the socio-economic situation by using household income, monthly income or occupation (141). These differences, as well as the relatively low numbers of women in the group on bone medication compared to the group off bone medication may be among the reasons in why the results of this study did not show a relationship between socio-economic status and being on or off bone medication.

In contrast to our observation that BMI was not associated with being on bone medication, two other studies found that a low BMI was predictive of initiating or being on bone medication (132, 134). Increasing BMI has been found to have a strong positive association with BMD (144, 145), and is thought to increase the effects of antiresorptive bone medication in the elderly (146), while a low BMI is thought to be related to increased fracture risk (147). A study looking at physical and biochemical characteristics in healthy perimenopausal and early postmenopausal women with osteoporosis (148) found significantly lower body weight and BMI in women with osteoporosis compared to a control group of healthy women. In comparison, our study found there was no significant

difference between the two groups. The average BMI across both groups of women on or off bone medication were more similar to that of the control group of that study (148) rather than their osteoporosis group. Consequently it could be concluded that postmenopausal women with osteoporosis may not necessarily have a lower BMI when compared with healthy women of the same age range, however a lower BMI coupled with osteoporosis may be related to an increased risk of fragility fractures (147, 149).

Our study found an average of at least three chronic comorbidities in both the groups on and off bone medication. There was no relationship found between bone medication status and number of chronic comorbidities. This was in line with one study that looked at predictors of initiating bisphosphonate therapy (132) and another study looking at correlations with anti-fracture therapy use (127) however comorbidities may be linked with adherence and persistence with bone medications (150). Nevertheless, the presence of chronic comorbidities could increase the risk of falls (151) and consequently increase the risk of fractures (5, 152). A study on perimenopausal women found the presence of even one comorbidity to increase the risk of fracture by predisposing women to osteoporosis and increasing the risk of falls (153). The presence of comorbidities could also be a major risk factor leading to the non-treatment of osteoporosis (154), and be linked with persistence and adherence to oral bisphosphonates (93). Some specific comorbidities could be associated with osteoporosis treatment failure (155), or the increased risk of another fragility fracture following a previous fragility fracture (156, 157).

Chronic musculoskeletal conditions like osteoarthritis or degenerative joint diseases were one of the most common chronic comorbidities followed by respiratory conditions like asthma and chronic bronchitis or emphysema in another study. That study grouped postmenopausal women on bone medication by their number of fragility fractures in order to find predictors of osteoporosis treatment failure (155). They found women who had suffered two or more fractures also had two or more chronic comorbidities, as opposed to the other groups of women who had one or no previous fractures. Our study also found women on bone medication to have chronic musculoskeletal disorders as the most common chronic comorbidity, but this was followed by chronic cardiovascular conditions, and this pattern was the same in the group off bone medication, whereas an association between the

number of fragility fractures and chronic comorbidities was not found. Chronic digestive system issues such as gastrointestinal disorders was our third most commonly identified chronic comorbidity in the group off bone medication, and a systematic review identified upper gastrointestinal problems as potentially being related to persistence and adherence with oral bisphosphonates (93). The same systematic review also identified rheumatoid arthritis, mental disorders and diabetes as other comorbidities that were potentially related to persistence and adherence.

Our study found having a history of two or more fragility fractures to be positively related to being on bone medication, and the previously mentioned study looking at predictors of osteoporosis treatment failure found having previous fractures to be predictive of osteoporosis treatment failure since one fragility fracture greatly increases the risk of another fragility fracture (155). They considered that some patients on bone medication may be at such an advanced stage of osteoporosis such that the deterioration and fragility of the bones can only be partially treated by pharmacotherapy (155). A history of fractures was identified as a possible determinant of persisting and adhering to oral bisphosphonates in a systematic review (93), but there were conflicting reports. Some studies found fragility fractures at common sites for fragility fractures (such as the hip, spine, femur, pelvis or wrist), multiple fractures, or any fragility fracture (102, 108, 126, 131, 133, 134) to be related with being on or off bone medication, however one study did not find an association between prior fractures and the use of bone medications (127). On another note, our study observed that the majority of people with previous fracture were unlikely to receive pharmacotherapy for management of low BMD, which is consistent with other literature (108, 126, 127, 134). A study looking at the low prevalence of pharmacotherapy in patients with osteoporosis found that at least two thirds of patients with previous fragility fracture and who presented with a new fracture still did not commence pharmacotherapy, and suggested that this was thought to be due to an incorrect assessment of fracture risk while the fracture was being managed in an acute setting (154).

The number of prescription medications other than bone medication was only positively related to being on bone medications at the univariable level but not at the multivariable level after the model had been adjusted in our study. To complement this, the

study on correlations with initiating anti-fracture therapy (127) found that being on more medications was not related to being off bone medication. Instead, the number of prescription medications could be associated with persistence and adherence to bone medication, where higher numbers of prescription medication may increase the likelihood of discontinuing bone medication (93, 150) and be related to an increased fragility fracture risk (158).

Women who had previously been on bone medications before were much more likely to be on bone medication than women who had never taken bone medication before in our study. The further information that some of these women volunteered at the time of their assessment usually by writing them onto the questionnaire form on attitudes and motivations to be on or off bone medication was interesting to note in adjunct with their questionnaire answers. Two women stated they had taken a drug holiday prior to commencing their current bone medication, of which one of them was hoping to wean off bone medication and cease pharmacotherapy for her bone medication due to fear of adverse effects. At least four women stated they had changed bone medications due to adverse reactions. In comparison, a study on long term persistence and switching patterns in bone medications found that women who experienced moderate or strong adverse reactions were less likely to persist with bone medication (159). Because reasons for stopping and recommencing bone medication was not a question asked of the participants in our study, nor was it a focus of this study, no conclusions regarding this can be made.

Our study did not find total calcium intake or the use of daily supplements of any kind and/or over the counter medications to be related to being on or off bone medications, which was in contrast to a study that found women who were taking calcium but not vitamin D were more likely to be on bone medication (108). A recent study on bone medication use in Australian women over the last two decades showed an increase in anti-fracture medication and supplement use over time (64) despite the fact that the use of calcium and vitamin D supplementation (whether on its own or as an adjunct to bone medication) is both controversial and inconsistent in the literature (18, 66). The American National Osteoporosis Foundation's systematic review found good evidence for the effects of calcium intake on bone, particularly in children (160), while a study on peri and

postmenopausal women suggested that calcium metabolism disorders may be undiagnosed and underestimated in older women (148) despite their supplement intake. A few participants in our study volunteered the information that they did not take their supplements regularly, but this was not fully documented and while any irregular supplementation was excluded in this study, further research in the area of inconsistent supplement usage may be worthwhile, particularly when combined with bone medication or exercise. The fact that any type of regular supplement or over the counter medication was included in the data may have had a somewhat confounding effect in the multivariable analysis for this variable.

6.2 Interpretation of physical characteristics results with previous literature

The mean BMD in our study at both the total hip and lumbar spine for both groups on and off bone medication fell within the osteopenic range. This is congruent with research which states that osteopenia is more prevalent than osteoporosis (39, 161-163), as opposed to a study of participants on bone medication that found a higher prevalence of osteoporosis (37%) than osteopenia (32%), with 43% not having a DXA diagnosis (164). The Australian clinical guidelines for management of osteoporosis in postmenopausal women (63) does not recommend bone medication for people with BMD within the osteopenic range at the spine or proximal femur unless there has been a fragility fracture, or the presence of other risk factors, including the 10-year fracture risk calculated using the Garvan Institute Fracture Risk Calculator or FRAX being greater than three percent at the hip or greater than 20% for any fracture. This seems to be somewhat reflected in our data where (n = 74) 28.9% of the group off bone medications had one or more fragility fractures, as opposed to (n = 43) 46.7% in the group on bone medication. The 10 year risk of hip fracture had a median greater than the three percent mentioned in the clinical guidelines, being four percent in the group off bone medications and six percent in the group on bone medications, but with a large and similar range from 0.3% to 57% across both groups. This indicates that there appear to be some women in the group off bone medications who could benefit from pharmacotherapy according to the Australian guidelines.

While fracture risk in our study showed a positive relationship with bone medication at the univariable level, it no longer showed a relationship in the adjusted

multivariable model. This was similar to the findings of a study that attempted to predict osteoporosis treatment after a fragility fracture in postmenopausal women (108), indicating that fracture risk is more multifactorial and should not be used as an independent predictor of being on or off bone medication.

It was difficult to find studies with participants on medication using the same physical outcome measures in order to compare results. A systematic review and meta-analysis on exercise and functional outcomes in people with osteoporosis found over 40 different types of outcome measures that were reported in the studies included in the review (75). As a result, the findings from our study were mostly compared with other studies from the same population group, namely postmenopausal women with osteoporosis or osteopenia or healthy postmenopausal women but who may not have been on bone medication. It is also possible that some confounding factors or other variables affecting physical ability may have been missed in this study.

Thoracic hyperkyphosis, and increased forward posture as a consequence, is a possible indicator of vertebral fragility fracture and a risk factor for future fractures regardless of the presence of low BMD or previous fracture (165), therefore outcome measures such as kyphotic angles and the tragus to wall test are used to assess severity of the hyperkyphosis or forward head posture. Improved back extensor strength is important for maintaining good functional posture (166) however existing literature reports a high degree of variation in measures of both posture and back extensor strength that are not similar enough to this study to be compared (75).

The occiput to wall and tragus to wall tests are used to measure forward flexed or forward head posture and indirectly measure thoracic kyphosis in the literature. The occiput to wall test has been shown to be negatively related to the five times sit to stand measure (167) and as the occiput to wall test is very similar to the tragus to wall test, it could be assumed that the tragus to wall test may also be related to the five times sit to stand measure in a similar way. Our study found that while the tragus to wall measure was not related to being on or off bone medication, the mean tragus to wall measure was 13.15 cm with a standard deviation of approximately 2.40 cm across both groups, which is a little greater than the findings of other studies involving older women in relatively healthy

populations (means ranged from 9.9 cm - 12.9 cm, with standard deviations 0.8 cm - 1.4 cm) (117).

We found back extensor strength had a strong inverse relationship with being on bone medication. When considered in light of the importance of back extensor strength in maintaining good thoracic kyphosis posture and its relationship with lumbar spine BMD (118), it makes sense that the stronger the back extensor muscles are the less likely women are to be on bone medication. While back extensor strength was comparable to a study performed in a similar population of women in the LIFTMOR trial (81), another study using the same method of measuring back extensor strength within the same population group, particularly for women on bone medication, could not be found.

The functional reach test of balance was not related to being on or off bone medication in our study. Although an article involving the association of the functional reach in postmenopausal women with bone medication was not found, a literature review has found that the functional reach tends to be significantly lower in people with vertebral fractures (168). When comparing the results of our participants with women of similar ages, our medians of the off and on medication groups, seemed to close to the normal values of healthy women of the 40-59 age range in the off bone medication group and 50-69 age range in the on bone medication group (169), and indeed, the off bone medication group did have a slightly younger median age (63 years) than the on bone medication group (65 years). This showed that women in the off bone medication group generally had better balance than women in the on bone medication group, however the difference is not significant. Our results showed that our participants had slightly lower functional reach with 39.0 cm (14.0 cm - 50.9 cm) and 37.0 cm (18.0 cm - 47.0 cm) in the off and on bone medication group respectively. This is in contrast to the postmenopausal women from the LIFTMOR trial who had a mean age of 65 years, functional reach mean 40 cm, standard deviation 4.7 cm in their control group, and mean 41.1 cm, standard deviation 4.9 cm in their high intensity resistance training group (81). Our results were higher than the participants from a study on women with osteoporosis who had a mean age of 71years, functional reach median 28.8 cm and min-max 7.3-39.6 cm (170), likely because our participants were younger and were mostly osteopenic rather than osteoporotic.

In our study, the five times sit to stand measure was only significant at the univariable but not the multivariable level. Again, it was difficult to find any studies that looked at the relationship between this functional measure and being on or off bone medication. In one study with a similar population, participants who took longer than 15 seconds to perform five repeated sit to stands were more likely to have recurrent falls (120), and in another study, a time longer than 12 seconds indicated an increased risk of falls (121). When comparing our study with these two aforementioned studies, our participants were not likely to have an increased risk of recurrent falls (120), or have a higher risk of falls (121), and our off bone medication group had similar times when compared to the participants from the LIFTMOR trial but our on bone medication group was slightly slower (81).

6.3 Interpretation of behavioural characteristics results with previous literature

Physical activity over the lifetime is known to be positively related to bone health (171) and while there are many studies regarding this (52, 74, 160, 171), only two studies were found to find a possible relationship between current physical activity with being on or off bone medication, albeit in relation to persistence and/or adherence to bone medication. Both studies found the lack of regular current physical activity to be a predictor of discontinuing bone medication (159, 172). A study that considered both past and current physical activity and bone medication was not found. Although the results of this study have not shown an association between being on or off bone medication with past and current physical activity via the BPAQ, our study had a large amount of missing BPAQ data, particularly among the participants on bone medication. As such, further research in this area would be beneficial in order to confirm or deny a possible relationship between physical activities over the lifetime with the use of bone medication.

Our study found very few current smokers amongst the participants. Possibly because many of the participants were attending The Bone Clinic for resistance training exercise for the management of their bone health and may have previously received education regarding smoking, or when including all the participants regarding the MEDEX-OP study, whether they were included or excluded, may have a greater interest in maintaining a healthy lifestyle and so were not smokers. Due to the low numbers of

smokers in the study, the results in our study regarding the non-association between smoking and being on or off bone medication is unreliable. Despite this, a systematic review has found that smoking was related to lower adherence with bone medication (173) and another study found the current smokers had lower BMD than those who had never smoked before (174).

In corroboration with the previously mentioned systematic review (173), our study did not find alcohol intake to be associated with being on or off bone medication, although it was found to have a positive relationship with BMD at the ultradistal radius in another study (174). Alcohol did not seem to be related to being willing to be assessed or treated for osteoporosis in a Korean study (139) but people who drank at least two glasses of alcohol a day were more likely to have very low adherence or persistence to their prescribed bone medication (175) which seemed to match with our group that were off bone medication. Another study identified regular alcohol drinkers to also be related to poor adherence with taking a regime of calcium and vitamin D supplements. Similar to our study, regular alcohol intake or alcoholism as it was called in another study (153), did not find a relationship between lumbar spine or femoral neck BMD, while another study did (176), but this is possibly due to the fact that the latter study was related to women with alcohol dependence or alcohol abuse, whereas the Korean study and our study may not have included participants that were so highly dependent on alcohol.

Attitudes toward any medication were strongly related to being on or off bone medication in our study, which agreed with the results of several other studies (173, 177). Similar to the results of our study, many patients found the role of doctors to be influential in motivations to go on or not take bone medication (178, 179). Our study however, found that more women weighed the preference to make lifestyle changes and preferring not to take medications higher than the number of women who were off bone medication due to the advice of doctors. There was not an included reason with a doctor's advice in the questionnaire regarding motivations to be off bone medications, which could have affected our results. Women who found a doctor's advice to be one of their main reasons not to be on bone medication wrote it into the free text section of the 'other' option that was provided.

It has been found in a different study that decisions that have been made are not permanent and can be persuaded to change (178). Decisions can be unpredictable, very personal, often changing over time because medications are complex social phenomena (112, 180). Knowledge and beliefs regarding osteoporosis are thought to be related with bone protecting actions, particularly in dietary and lifestyle changes (181), but most decisions around bone medication are based around the perceived risk versus benefits of the medication (182). Based on the results of a few systematic reviews (8, 179, 182-184), perceived needs seemed to be based around a need for knowledge and information regarding the disease and management options such as pharmacotherapy and lifestyle changes, with doctors often being an initial source of information and ongoing monitoring of bone health with the relationship between doctor and patient also being a need important to patients.

6.4 Implications

Two characteristics relating to medical history, one physical characteristic and one behavioural characteristic were identified to be associated with being on or off bone medication. This shows that obtaining a good medical history, particularly in relation to fracture history and previous use of bone medication, assessing back extensor strength, and obtaining patient views toward medication and management are highly important for individualising a bone health management plan that the patient is highly likely to adhere to and persist with.

Patient decisions should be monitored regularly together with their bone health reviews in order maintain bone health management plans that patients are likely to continue. Both pharmacotherapy and lifestyle options should be provided to patients together with education and information on osteoporosis or osteopenia and ongoing management options.

6.5 Limitations

This study may involve some selection bias inherent in convenience samples. Postmenopausal women who have chosen to take part in an exercise program for bone health may not be representative of the general demographic of postmenopausal women

with low bone mass. Furthermore, data was not available for all participants derived from The Bone Clinic, and people who had been excluded from the MEDEX-OP trial. The data could have been improved if obtaining data from The Bone Clinic clients and MEDEX-OP exclusions had been included in the initial planning. Being a cross-sectional study design, this study was only able to assess relationships but not confirm causality behind any of the findings. The analyses used in this study were simple statistical analyses and future studies with deeper, more complex analyses would be beneficial in deepening the understanding of how physical and behavioural characteristics may be related to commencing or persisting with treatment.

There were some limitations within the statistical analysis which may have affected the results as well. Some important variables may have been inadvertently missed when choosing which variables to include in the statistical analyses due to the limited number of variables which could be included while keeping the type I error at a manageable level. Some limitations lie in the Purposeful Selection Method itself. Some variables that could be significant when put together with covariates may have been missed, multicollinearity between significant variables might be retained during the selection process due to their significant effects, and some confounders might be retained since it is assumed and that all covariates are as important as each other (125).

6.6 Future directions

Further research regarding associations or causal links between postmenopausal women with low BMD on and off bone medication with physical and behavioural characteristics would be beneficial in expanding knowledge in this area. Future studies could conduct more complex analyses involving mediating or moderating variables, and consider other variables that were not included in this study, particularly those relating to behaviour. Subgroup analyses involving characteristics, attitudes and motivations would help health care practitioners to know what types of interventions their patients would be most open to initiating, adhering to and persisting with.

7.0 Conclusions

Fragility fracture history, previous use of bone medications, poor back extensor strength and a pro-medication attitude were strongly and positively related to being on bone medication among postmenopausal women with low bone mass. The findings of this study suggest that medical history, back extensor strength, and the attitudes and motivations for therapy are important factors in the decision-making process for postmenopausal women in the management of their low bone mass. Fracture history, medication history, physical strength and patient views should all be taken into consideration when healthcare professionals attempt to individualise a bone health management plan to provide better patient-centred care.

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9.0 Appendices

Appendix A – MEDEX-OP ethical approval

Subject: Full Research Ethics Clearance 2017/739
From: rims@griffith.edu.au <rims@griffith.edu.au>

Mon, Sep 25, 2017 at 10:05 AM

To: m.fischbacher@griffith.edu.au, B.Weeks@griffith.edu.au, b.beck@griffith.edu.au
Cc: researchethics@griffith.edu.au, k.madison@griffith.edu.au

GRIFFITH UNIVERSITY HUMAN RESEARCH ETHICS REVIEW

Dear Prof Belinda Beck

I write further to the additional information provided in relation to the provisional approval granted to your application for ethical clearance for your project "Bone-targeted exercise and medication to reduce risk of fracture in postmenopausal women with low bone mass: The MEDEXOP trial" (GU Ref No: 2017/739).

This is to confirm that this response has addressed the comments and concerns of the HREC. The ethics reviewers resolved to grant your application a clearance status of "Fully Approved". Consequently, you are authorised to immediately commence this research on this basis.

Regards

Kim Madison | Human Research Ethics

Office for Research
Griffith University | Nathan | QLD 4111 | Level 0, Bray Centre (N54)
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Appendix B – Ethics approval – variation 1

Subject: 2017/739 - Variation Approved
From: rims@griffith.edu.au

Mon 5/08/2019 10:56 AM

To: Melanie Fischbacher <melanie.fischbacher@griffithuni.edu.au>; B.Weeks@griffith.edu.au <B.Weeks@griffith.edu.au>; b.beck@griffith.edu.au <b.beck@griffith.edu.au>; Jedidah Yong <jedidah.yong@griffithuni.edu.au>
Cc: research-ethics@griffith.edu.au <research-ethics@griffith.edu.au>; k.madison@griffith.edu.au k.madison@griffith.edu.au

GRIFFITH UNIVERSITY HUMAN RESEARCH ETHICS COMMITTEE

Dear Prof Belinda Beck

I write further to your application for a variation to your approved protocol "Bone-targeted exercise and medication to reduce risk of fracture in postmenopausal women with low bone mass: The MEDEX-OP trial" (2017/739). This request has been considered by the Office for Research.

The Office for Research resolved to approve the requested variation:

1) To remove Lisa Weis from the research team and to add Jedidah Yong, physiotherapist and Master of Medical Research student, to the team.

2) For student researcher, Jedidah Yong, to conduct an analysis of the baseline data collected for the MEDEX trial to investigate whether there are physical or behavioural characteristic differences between postmenopausal women with low bone density who choose to take or not take bone medication.

3) To expand the questionnaire to include additional questions relating to the decision to take (or not take) bone medication. Recruitment for the MEDEX-OP trial is ongoing and for any participants newly recruited into the study, these questions will be part of the baseline assessment. For those currently in the study, the questions will be administered at the post-intervention assessment. For those who have completed their involvement in the study. They will be sent the questions by email or letter. If the latter, a reply-paid envelope will be provided. A copy of the email/letter to be sent to participants who have completed the trial, and the revised participant information and consent materials, has been submitted with this variation request.

This variation request is approved on the condition that Chief Investigator, Professor Belinda Beck's name is also included in the email/letter to the former participants. This should assure these participants that the request for their further participation pertains to the same research project and that CI Professor Beck is supportive of this additional data collection.

This variation is approved on the condition that the new team members have been provided with a copy of the ethics application for the project, and are aware of the scope of the ethics approval for the protocol. All team members covered under this protocol are expected to conduct the approved research in accordance with the National Statement on Ethical Conduct in Human Research (2007): https://nhmrc.gov.au/about-us/publications/national-statement-ethical-conduct-human-research-2007-updated-2018

This decision is subject to ratification at the next meeting of the HREC. However, you are authorised to immediately commence the revised project on this basis. I will only contact you again about this matter if the HREC raises any additional questions or comments about this variation.

Regards
Kim Madison | Human Research Ethics

Office for Research
Griffith University | Nathan | QLD 4111 | Level 0, Bray Centre (N54)
T +61 7 373 58043 | email k.madison@griffith.edu.au

Appendix C – Ethics approval – variation 2

Subject: 2017/739 - Variation Approved
From: rims@griffith.edu.au

Tue 29/10/2019 3:12 PM

To: Melanie Fischbacher <melanie.fischbacher@griffithuni.edu.au>; B.Weeks@griffith.edu.au <B.Weeks@griffith.edu.au>;
b.beck@griffith.edu.au <b.beck@griffith.edu.au>; Jedidah Yong <jedidah.yong@griffithuni.edu.au>
Cc: research-ethics@griffith.edu.au <research-ethics@griffith.edu.au>; k.madison@griffith.edu.au k.madison@griffith.edu.au

GRIFFITH UNIVERSITY HUMAN RESEARCH ETHICS COMMITTEE

Dear Prof Belinda Beck

I write further to your application for a variation to your approved protocol "Bone-targeted exercise and medication to reduce risk of fracture in postmenopausal women with low bone mass: The MEDEX-OP trial" (2017/739). This request has been considered by the Office for Research. The Office for Research resolved to approve the requested variation:

To send an email to people who volunteered but were screened out from the MEDEX-OP trial in order to examine reasons for choosing to take or not take bone medication. The information will be included in Jedidah Yong's analysis of baseline data collected from the MEDEX-OP trial to investigate whether there are physical or behavioural characteristic differences between postmenopausal women with low bone density who choose to take or not to take bone medication.

The questionnaire will take roughly 5-10 minutes to complete. Participants can alternatively request for the questionnaire to be conducted over the phone or by letter. If the latter, a reply-paid envelope will be provided. A copy of the invitation email and revised questionnaire has been submitted with this variation request.

This decision is subject to ratification at the next meeting of the HREC. However, you are authorized to immediately commence the revised project on this basis. I will only contact you again about this matter if the HREC raises any additional questions or comments about this variation.

Regards

Kim Madison | Human Research Ethics
Office for Research
Griffith University | Nathan | QLD 4111 | Level 0, Bray Centre (N54)
T +61 7 373 58043 | email k.madison@griffith.edu.au

Appendix D – MEDEX-OP baseline case report form

Case Report Form – Baseline Visit

PARTICIPANT DETAILS

Participant ID: _____ **Date testing:** _____

Randomisation: _____

Name: _____

Address: _____

DOB: _____

Home phone: _____ Mobile: _____

Email: _____

SCREENING

☐ Written informed consent obtained

☐ Lumbar spine and/or femoral neck T-score < -1.0

☐ Not meeting inclusion/exclusion criteria or declined to participate

Reason: _____

BASELINE VISIT

Race ☐ Caucasian ☐ Asian ☐ African
☐ Middle Eastern ☐ Hispanic
☐ Other, specify:

Alcohol intake

☐ Average number of _____ glasses/day OR glasses/week
☐ Very rarely drink alcohol
☐ Never drink alcohol

Smoking status

☐ Current smoker Average number of cigarettes/day _____ for _____ years
☐ Ex-smoker Average number of cigarettes/day _____ for _____ years
☐ Never smoked

Functional limb dominance

Handedness: ☐ Right ☐ Left ☐ Ambidextrous
Footedness: ☐ Right ☐ Left ☐ Ambidextrous

MEDICAL HISTORY

Last period: __ years ago Age: __ years

Corticosteroids for > 3 months previously?
☐ Yes ☐ No

Secondary osteoporosis?
☐ Yes ☐ No

Did either of your parents fracture a hip?
☐ Yes ☐ No

Do you have a family history of osteoporosis?

- ☐ No
- ☐ Not sure
- ☐ Yes
  - ☐ mother
  - ☐ grandmother
  - ☐ grandfather
  - ☐ father
  - ☐ grandmother
  - ☐ grandfather
  - ☐ Siblings

Are you currently taking bone medications?

- ☐ No
- ☐ Yes

Brand name: _____

Started intake: _____ (mm/yy)

Side effects from bone meds? Tick if applicable

- ☐ Gastrointestinal
- ☐ Skin conditions
- ☐ Muscle pain
- ☐ Joint pain
- ☐ Flu like symptoms
- ☐ Dizziness
- ☐ Osteonecrosis of the jaw
- ☐ Atypical femoral fracture
- ☐ other: _____

If you are on Prolia or Aclasta, when was your last injection/infusion and when will the next one be?

Last: _____ Next: _____

Have you previously taken bone medication?

- ☐ No
- ☐ Yes

Dates from _____ to _____ Brand: _____

Dates from _____ to _____ Brand: _____

Please list current and past medical conditions:

_____

_____

_____

Please list any prescribed medications you are currently taking:

_____

_____

_____

Please list any over-the counter medications such as vitamins, minerals and supplements:

_____

_____

Please list surgical procedures – type of operation, approximate age and length of stay:

_____

_____

_____

Do you have any metal implants, piercings or joint replacements?
☐ Yes ☐ No Details: _____

In the past 12 months, have you had exposure to radiation, occupational or medical (e.g. x-rays)?
☐ Yes ☐ No Details: _____

PELVIC FLOOR HEALTH

Pregnancies:

Number of pregnancies: _____
Number of vaginal deliveries: _____
Number of caesarean sections: _____

Have you had a hernia?
☐ Yes ☐ No Details: _____

Have you had a pelvic organ prolapse?
☐ Yes ☐ No Details: _____

Have you had a hysterectomy or other surgery to correct prolapse/incontinence?
☐ Yes ☐ No Details: _____

FALL AND FRACTURE HISTORY

Have you had any falls in the last 12 months? ☐ No ☐ Yes, _____(#)

___ (#) low-trauma falls. Please specify.

_____

___ (#) high-trauma falls. Please specify.

_____

Have you had any low-trauma falls prior to the last 12 months?
☐ No ☐ Yes, _____(#)

Have you had any fx in the last 12 months? ☐ No ☐ Yes, _____(#)

___ (#) low-trauma fx. Please specify.

_____

___ (#) high-trauma fx. Please specify.

_____

Have you ever had any fractures in your life? ☐ No ☐ Yes, _____(#)

Affected Bone: _____ Age: _____ y Details: _____
Affected Bone: _____ Age: _____ y Details: _____
Affected Bone: _____ Age: _____ y Details: _____

OSTEOARTHRITIS

☐ Yes, affected joints: _____

☐ No

WILLINGNESS TO PAY

How much would you be willing to pay per month for an exercise program that has been shown to build bone and reduces your risk to fracture?

$ _ _ _/month

QUESTIONNAIRES

☐ BPAQ ☐ PACES ☐ WOMAC ☐ PAR-Q & YOU ☐ PFDI-20 ☐ PFIQ-7

☐ AusCal Total mg daily: _ _ _ _mg Supplement daily: _ _ _ _mg

☐ SF-36 Physical health score: _____ Mental health score: _____

Specify if one questionnaire was not completed: _____

ANTHROPOMETRICS

Height [cm]: _____ _____ Average [cm] _____

Weight [kg]: _____ BMI [kg/m²]: _____

Waist [cm]: _____ _____ Average [cm] _____

VITAL SIGNS – LEFT ARM

Measurement 1: SBP _____ DBP _____ HR _____

Measurement 2: SBP _____ DBP _____ HR _____

Measurement 3: SBP _____ DBP _____ HR _____

Average measurement 2 & 3:

Resting sitting SBP/DBP [mmHg]: ___/___ Resting sitting Heart rate [bpm]: _____

VITAL SIGNS – RIGHT ARM

Measurement 1: SBP _____ DBP _____ HR _____

Measurement 2: SBP _____ DBP _____ HR _____

Measurement 3: SBP _____ DBP _____ HR _____

Average measurement 2 & 3:

Resting sitting SBP/DBP [mmHg]: ___/___ Resting sitting Heart rate [bpm]: _____

PHYSICAL PERFORMANCE

Functional Reach:					Best [cm]
Tragus to wall:					Average [mm]
Back extension:					Best [kg]
Timed Up and Go:					Best [s]
Sit to Stand:					Best [s]
Grip strength R:					Best [kg]
Grip strength L:					Best [kg]
	Setting: 1: ☐	2: ☐	3: ☐	4: ☐ 5: ☐	
Kyphosis relaxed:					Average [°]
Kyphosis erect:					Average [°]
Tandem Walk:					Best [s]
					No. mistakes
6m gait speed:				Average [s]	Gait speed
6m gait speed fast:				Average [s]	Gait speed
LES 115° [kg]:					Peak [N*sec]

No of links LES: _____

DXA

Lumbar spine: ☐ Yes ☐ No, Comments: _____

Dual Hip: ☐ Yes ☐ No, Comments: _____

Lateral spine: ☐ Yes ☐ No, Comments: _____

Whole Body: ☐ Yes ☐ No, Comments: _____

Forearm: ☐ Right ☐ Left ☐ No, Comments: _____

Additional questions for people **on bone medications**:

1. What was your motivation to go on bone medication?

   (Please rank the options below, with the number 1 being the reason closest to yours. Leave blank any reasons that do not apply to you.)

   [__] My doctor recommended it

   [__] I have seen the experience of an acquaintance

   [__] I have heard good things about it – where?_____

   [__] I have read good things about it – where?_____

   [__] I was worried about my bone health

   [__] I thought it was worth a try

   [__] Other _____

Additional question for people **not on** bone medications:

2. Did you consider going on medication when you discovered you had low bone density?
   - ☐ Yes
   - ☐ No

   Why did you decide not to go on medication?

   (Please rank the options below, with the number 1 being the reason closest to yours. Leave blank any reasons that do not apply to you.)

   [__] I don't like taking medication/ I take as few drugs as possible

   [__] I don't want to become reliant upon medication

   [__] I would rather make lifestyle changes to improve my health than take drugs

   [__] I was concerned about an interaction with other medications or a medical condition I already take/have

   [__] I have seen the experience of an acquaintance

   [__] I have heard bad things about side effects of bone drugs – where did you hear this?_____

   [__] I have read bad things about the side effects of bone drugs – where did you read this?_____

   [__] I don't feel I know enough about bone medication to make a decision

   [__] Other_____

3. What is your attitude toward **medication in general**? (Mark one box only)
   - ☐ Pro-medication
   - ☐ Anti-medication
   - ☐ Ambivalent toward medication

Appendix E – Email to women excluded from MEDEX-OP

Dear <participant name>,

Recently you expressed interest in participating in the MEDEX-OP trial, a study investigating exercise therapy for osteoporosis in postmenopausal women. While we were unable to enrol you in the trial at the time due to screening criteria, another opportunity has arisen for you to contribute to our important project.

We are interested in the reasons why people decide to take or not take bone medication after a diagnosis of osteoporosis. We have developed a brief questionnaire to help us understand this issue better and would very much appreciate your opinion. It will take around 5-10 minutes to complete. Most are yes/no answers.

Completing and returning the questionnaire to us will be taken as consent for us to use your answers in our research project. If you would prefer, we would be happy to conduct the questionnaire over the phone, or even send a paper copy through the post with a reply paid envelope.

Your information will be kept private and confidential. It will not be disclosed to a third party without your consent, except to meet government, legal or other regulatory authority requirements. A de-identified (meaning you cannot be identified from it) copy of your data may be used in other research analyses. You will not be referred to by name during research reporting. All information will be stored on a computer restricted by password for a minimum of 5 years. For further information regarding privacy and confidentiality, you may consult the Griffith University Privacy Plan at http://www.griffith.edu.au/privacy-plan or phone (07) 3735 4375.

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, Phone: 3735 4375 or research-ethics@griffith.edu.au .

For further information, please call 0468 527 219 or to email jedidah.yong@griffithuni.edu.au .

Thank you very much for your time and participation.

Kind regards,

Jedidah Yong, BPhty
Master of Medical Research Candidate
School of Allied Health Sciences
Griffith University, Gold Coast campus

Professor Belinda Beck, PhD
School of Allied Health Sciences
Menzies Health Institute Queensland
Griffith University, Gold Coast campus

Ms Melanie Fischbacher, MSc
PhD Candidate
School of Allied Health Sciences
Griffith University, Gold Coast

Dr Benjamin Weeks, BPhty(Hons), BExSc, PhD
School of Allied Health Sciences
Griffith University, Gold Coast

QUESTIONNAIRE

Please click Reply then complete the questionnaire below (it will appear in the body of this original email), e.g. type your name, age, postcode in the boxes, and delete options that do not apply as relevant, e.g. ~~yes~~ / no. If you have any difficulty understanding what to do, please call Jedidah on 0468 527 219 or email jedidah.yong@griffithuni.edu.au .

PARTICIPANT INFORMATION

1.	**Name:**					
2.	**Age:**					
3.	**Postcode:**					
4.	**Highest level of education** *Please delete all the incorrect responses*					
	Never been to school					
	Primary education					
	Secondary education (high school)					
	Tertiary education					
5.	**Do you live alone?** *Please delete the incorrect response*					
	Yes	No				
6.	**Do you have a diagnosis of osteopenia/osteoporosis?** *Please delete the incorrect response*					
	Yes	No				
	When were you diagnosed?	*Month*		*Year*		
7.	**Have you had any falls in the past 12months?** *Please delete the incorrect response and then enter a number, if relevant*					
	Yes	No	**How many?**			
8.	**Have you had any low trauma fractures since the age of 40 years?** (Low trauma fractures are bones broken through an event that would not normally break a bone, such as a slip, trip, bump, sneeze or lift) *Please delete the incorrect response and enter a number if relevant*					
	Yes	No	**How many?**			
9.	**Do you have a family history of osteoporosis?**					
Only choose one	Yes	No	Don't know			

10.	**Have your parents ever fractured a hip?** *Please delete the incorrect responses*					
	Yes	No				
11.	**Do you drink alcohol?**	*Please delete the incorrect response. If yes, please provide a number.*				
Only choose one	Yes	No	Rarely	**Number of glasses per week**		
12.	**Are you a current smoker?**	*Please delete the incorrect response*				
	Yes	No				
13.	**Do you have arthritis?**	*Please delete the incorrect responses*				
	new	Yes, osteoarthritis	Yes, rheumatoid arthritis	No	Other	
14.	**Do you regularly use steroid medications in tablet or inhaler form?** *Please delete the incorrect response*					
	Yes	No				
	If yes, how many weeks per year do you use steroid medications?					
15.	**Have you taken cancer medication before (tablet or infusion)?** *Please delete the incorrect response*					
	Yes	No				
16.	**What is your total number of daily prescribed medications of any kind?**					
17.	**What is your total number of daily supplements?**					
18.	**Have you ever taken medication for osteoporosis (past and present)?** *Please delete the incorrect response and fill in sections as relevant. Add additional rows if necessary by pressing Return (or Enter) at the end of a row*					
	Yes	No				
If yes, please indicate:	**What?**	1. 2. 3.		**When?**	1. 2. 3.	
19.	**What is your attitude toward medication in general?** *Please delete all the irrelevant responses*					
	Pro-medication		Anti-medication		Ambivalent toward medication	

IF YOU ARE CURRENTLY TAKING BONE MEDICATION:

What was your motivation to go on bone medication? *Please rank the options below, with the number 1 being the reason closest to yours. Leave blank any reasons that do not apply to you. Please add details for any options where indicated in red, as relevant.*	
Rank (#)	**Reasons**
	My doctor (GP or specialist) recommended it
	I have seen the experience of an acquaintance
	I have heard good things about it – where did you hear this? *(please provide details below)*
	Enter text here
	I have read good things about it – where did you read this? *(please provide details below)*
	Enter text here
	I was worried about my bone health
	I thought it was worth a try
	Other *(please provide details below)*
	Enter text here

IF YOU ARE NOT CURRENTLY TAKING BONE MEDICATION:

PART 1	Did you consider going on bone medication when you discovered you had low bone density? *(Please delete the incorrect response)*		
	Yes	No	

PART 2	Why did you decide not to take bone medication? *Please rank the options below, with the number 1 being the reason closest to yours. Leave blank any reasons that do not apply to you. Please add details for any options where indicated in red, as relevant.*
Rank (#)	**Reasons**
	I don't like taking medication/ I take as few drugs as possible
	I don't want to become reliant upon medication
	I would rather make lifestyle changes to improve my health than take drugs
	I was concerned about an interaction with other medication or a medical condition I already take/have
	I am aware of a negative experience of an acquaintance
	I have heard bad things about side effects of bone drugs. Where did you hear these things? *(Please provide details below)*
	Enter text here
	I have read bad things about the side effects of bone drugs. Where did you read these things? *(Please provide details below)*
	Enter text here
	I don't feel I know enough about bone medications to make a decision
	Other *(please provide details below)*
	Enter text here