PHYSICAL ACTIVITY AND OSTEOPOROSIS

THE EFFECT OF PHYSICAL ACTIVITY
ON
BONE MINERAL DENSITY AND FRACTURE RATE
IN
VERY OLD POST-MENOPAUSAL WOMEN

By:

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ABSTRACT

Physical activity is known to benefit many physiological processes, including bone turnover. There are; however, currently no clinical guidelines regarding the most appropriate type, intensity and duration of activity to prevent bone loss. To address this gap in the literature, we performed a retrospective analysis of data from the Canadian Multicentre Osteoporosis Study (CaMos), a prospective cohort of 10,000 adult patients. Female participants aged 75 and over provided information regarding their daily activity levels, including the amount of time spent each week performing moderate physical activity (e.g. housework, brisk walking). Outcome measures included bone mineral density and fracture rate. Multiple and linear regression analysis was used to determine the effect of increasing amounts of moderate physical activity on the outcome measures. The results indicate that a step increase in the amount of physical activity performed each day resulted in a positive effect on bone mineral density at the hip, Ward's triangle, trochanter and femoral neck ($B=0.006$ to 0.008, $p<0.05$). Regarding fracture rate, no statistically significant findings were noted in the Odds Ratio for each level of moderate physical activity. While 51% of participants reported a history of fracture, there was insufficient data to perform a fracture site-specific analysis. Secondary factors such as the use of anti-resorptive therapy, body mass index and age suggested that age had a negative effect on bone density while body mass index had a positive effect. Anti-resorptive therapy provided a protective effect against loss of bone density but not against fracture. The data indicate that a step increase in the amount of daily activity, using simple, daily performed tasks, can help prevent decreased in post-menopausal bone mineral density.

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LIST OF ABBREVIATIONS

BMU	bone multicellular unit
TNF	tumour necrosis factor
RANK	receptor activator of nuclear kappa B
RANKL	receptor activator of nuclear kappa B ligand
OPG	osteoprotegrin
NF-κB	nuclear kappa B
BMD	bone mineral density
DXA	dual x-ray absorptiometry
WHO	World Health Organization
SD	standard deviation
qCT	quantitative computed tomography
qUS	quantitative ultrasound
ONJ	osteonecrosis of the jaw
SERM	selective estrogen-receptor modulator
MORE	Multiple Outcomes of Raloxifene Evaluation trial
CORE	Conttinuing Outcomes Relevant to Evista trial
PEARL	Postmenopausal Evaluation and Risk-reduction with Lasofoxifene trial
PTH	parathyroid hormone

Sr	Strontium
SOTI	Spinal Osteoporosis Therapeutic Intervention trial
TROPOS	Treatment of Peripheral Osteoporosis
USD	United States dollars
FRAX	fracture assessment tool
CT	computed tomography
RCT	randomized controlled trial
SWB	static weight bearing
DWBLF	dynamic weight bearing exercise, low force
DWBHF	dynamic weight bearing exercise, high force
NWBLF	non-weight bearing exercise, low force
NWBHF	non-weight bearing exercise, high force
COMB	combined exercise program
CaMos	Canadian Multicentre Osteoporosis Study
MPA	moderate physical activity
OR	odds ratio
CONSORT	Consolidated Standards of Reporting Trials
BMI	body mass index
HRT	hormone replacement therapy

1.0 Introduction

1.1 Osteoporosis

1.1.1 Background

Osteoporosis is a common disease of bone metabolism characterized by the loss of bone density and an increased risk of fracture. While likely in existence throughout human history, osteoporosis has become a pressing concern in recent generations due in large part to the extension of the human lifespan (Raisz, 2005). Sir Astley Cooper, in the early 19th century, first described the "lightness and softness that (bones) acquire in the more advanced stages of life" and that this state of bone "favours much the production of fractures" (Cooper & Cooper, 1822). The term "osteoporosis" was coined by Johann Lobstein in the same era, although it is now thought that the condition to which he was referring was actually osteogenesis imperfecta (Schapira & Schapira, 1992) and not osteoporosis. It wasn't until 1941 when American endocrinologist Fuller Albright first described postmenopausal osteoporosis that impaired bone formation due to estrogen deficiency was proposed as a cause for osteoporosis (Albright et al., 1941).

Osteoporosis is a chronic progressive, multifactorial disease and the most common metabolic bone disease in the United States (Jacobs-Kosmin, 2012). Affecting

both male and females, it is more common in women, affecting post-menopausal women at a rate of 1 in 4 (National Osteoporosis Foundation, 2002). Osteoporosis is a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility (Ahmed & Elmantaser, 2009). With no outward signs or symptoms, osteoporosis has been referred to as the "silent thief", as it robs the patient of bone density without inflicting pain or disability, until a seemingly innocuous event causes a fracture.

1.1.2 Etiology

Osteoporosis has traditionally been grouped as either Type I (post-menopausal) or Type II (senile). More accurately, osteoporosis is classified as either localized or generalized (Jacobs-Kosmin, 2012). It is then further classified as either primary, where a secondary cause cannot be identified, or secondary, where decreased bone density is induced by a disease, deficiency or drug (AACE Guideline, 2003). It is estimated that up to one-third of osteoporotic patients have an underlying co-morbidity that is affecting bone density (AACE Guideline; Kelman & Lane, 2005).

Post-menopausal osteoporosis accounts for the majority of Type I diagnoses while Type II is generally found in aged patients with calcium deficiencies (AACE Guideline, 2003). A third variant of osteoporosis is that found in juvenile patients, which

is generally discovered secondary to traumatic fracture in patients between the ages of 8 and 14 years (Delalande et al., 2008).

Post-menopausal osteoporosis is discussed in detail in Section 1.3. Senile (Type II) osteoporosis is generally observed in patients over 70 years of age and is a result of calcium loss due to age. Fractures in this variant can occur in both the outer cortical bone and the inner trabecular bone, with the most common fracture sites being the proximal femur, vertebrae and wrist (Orcel and Funck-Brentano, 2011). Osteoporotic fractures are discussed in greater detail in Section 1.1.9.

Secondary osteoporosis encompasses diagnoses that are associated with a disease, deficiency or drug that induces the osteoporotic changes. Common secondary causes of osteoporosis include pharmacological causes such as glucocorticoid use or long-term heparin use, and co-morbidities such as hyperparathyroidism, or estrogen deficiency (AACE Guideline, 2003; Kelman & Lane, 2005; Mann et al., 2009; Holick, 2007; Migliaccio et al., 2009; van Staa et al., 2002). The disease process in secondary osteoporosis is identical to that of primary osteoporosis, the precipitating factor being the major difference between the two variants. Regardless of the causal event or condition, the key in osteoporosis is an alteration of the balance of bone remodeling that result in a progressive loss of bone density. The details of this alteration are discussed in detail in Section 1.1.4. Table I lists examples of secondary causes of osteoporosis.

1.1.3 Prevalence

Approximately 1 in 4 women and 1 in 8 men (National Osteoporosis Foundation, 2002) will be affected by osteoporosis over their lifetime. It is further estimated that 1 in 3 women and 1 in 5 men with osteoporosis will suffer a consequent fracture in their lifetime (osteoporosis.ca, 2012). Osteoporotic fractures are quite prevalent and in fact are more common than stroke, heart attack and breast cancer combined (osteoporosis.ca, 2012). By some estimates, osteoporosis affects 55% of Americans over the age of 50, a full 80% of whom are women (National Osteoporosis Foundation, 2002). By any measure, osteoporosis is a major condition, affecting a large portion of the population and resulting in important sequelae that have a potentially enormous impact on the healthcare system.

1.1.4 Pathophysiology

Bone is a dynamic structure, in a constant state of destruction and re-building. The processes of bone formation and resorption remain in balance in the healthy patient, resulting in a constant turnover of bone and maintenance of bone density. The decrease in bone density that is the hallmark of osteoporosis results from an imbalance in the formation-resorption processes, which result in either an increase in the bone's resorptive process or a decrease in the bone's formative process. Osteoblasts, derived from mesenchymal stem cells, are responsible for bone formation while osteoclasts,

derived from hematopoietic precursor cells, are responsible for bone resorption. These two types of cells are linked not only in function but in production, as the development of osteoclasts from hematopoietic precursors cannot be accomplished unless mesenchymal cells are present (Jacobs-Kosmin, 2012).

Bone remodeling continues throughout life due to the constant micro-trauma sustained by bone. The majority of this remodeling occurs in the trabecular or cancellous bone that comprises the mesh-like network of bone in the marrow cavity. The strength of bones comes from the hard, cortical bone that comprises the outer structure of bone and, while subject to the same remodeling processes, there is a distinct difference in the turnover rate between trabecular bone and cortical bone. In adults, approximately 25% of trabecular bone is resorbed and replaced each year, compared with only 3% of cortical bone (Jacobs-Kosmin, 2012).

Bone formation always follows resorption, a process known as coupling (Martin et al., 2009). The two processes are intimately linked both biochemically and functionally, with skeletal fragility developing from an interruption of the sometimes precarious balance between the two processes. Bone remodeling is an ongoing process and constitutes the majority of the activity of bone cells in the adult skeleton (Raisz, 2005). The major constituent of this process is the bone multicellular unit (BMU), first described by Frost and colleagues (Parfitt et al., 1995). These units occur on the surface of the trabecular bone in Howship lacunae or in cortical bone as relatively uniform

cylindrical haversian systems (Raisz, 2005). The components of the BMUs are tied together, with an interaction between osteoclastic prec ursors and osteoblastic cells required to propagate the system. The key pathophysiological process in the development of osteoporosis is the uncoupling of these processes. In addition, because the resorption phase of bone remodeling is relatively short and the formation phase is comparably long, any increase in the rate of bone remodeling will ultimately result in a loss of bone mass (Raisz, 2005). When uncoupled, a cascade effect follows, whereby the Howship lacunae and haversian canals, being emptied of the BMUs, weaken the mechanical structure of the bone (Raisz, 2005). Furthermore, the loss of trabecular bone decreases the amount of scaffolding or template to be used for bone formation, again slowing the process and weakening the bone (Raisz, 2005).

The concept of bone remodeling as a process of two opposing but ultimately intertwined systems was suspected for many years but the molecular mechanisms responsible for this system have been elucidated only in the last decade (Suda et al., 1999; Martin et al., 2009). Three members of the tumour necrosis factor (TNF) cytokine superfamily have been identified as integral to this system: the receptor activator of nuclear factor kappa B ligand (RANKL), its receptor, RANK (receptor activator of nuclear factor kappa B), and osteoprotegrin (OPG). Together, these components comprise the OPG/RANKL/RANK system.

1.1.4.1 OPG/RANKL/RANK System

The identification of the OPG/RANKL/RANK system established it as the predominant mediator of bone turnover. The system ultimately ties osteoclastogenesis to osteoblasts and provides the biochemical link between bone formation and bone resorption. The OPG/RANKL/RANK system comprises a trio of proteins that play a crucial role in bone metabolism and dynamics (see Figure 1). RANK is expressed on the surface of osteoclasts and is involved in their activation on the binding ligand (RANKL), which in turn is found on the surface of stromal cells, osteoblasts and T-cells (Suda et al., 1999; Wong et al., 1999; Theill et al., 2002). The binding of RANKL to RANK activates nuclear kappa B (NF-κB), a protein complex that controls the transcription of DNA. NF-κB plays a key role in the regulation of the immune response, inflammation and cell survival and differentiation, important in its role in bone metabolism (Krakauer, 2008). OPG manipulates this system by acting as a decoy receptor for RANKL (Krakauer, 2008). By binding RANKL, OPG inhibits NF-κB. This ultimately can lead to the reduced production of osteoclasts by inhibiting the differentiation of osteoclast precursors (Bergh et al., 2004). The RANKL/RANK interaction is critical for both differentiation and maintenance of osteoclast activity (Raisz, 2005). As such, it represents a final common pathway for any pathogenic factor that acts by increasing bone resorption (Raisz, 2005).

1.1.5 Risk Factors

Although all populations can be affected by osteoporosis, there are risk factors and demographics that are at greater risk for the development of osteoporosis and consequent fractures. General osteoporosis risk factors include: family history, being of thin or slight build, low dietary calcium and a low level of activity, in addition to pharmacological causes including prolonged use of the anti-coagulant heparin, glucocorticosteroids, anticonvulsants and thyroid supplements (AACE Guideline, 2003; Kelman & Lane, 2005; Mann et al., 2009; Holick, 2007; Migliaccio et al., 2009; van Staa et al., 2002).

General risk factors predisposing patients to osteoporotic fractures include advanced age, family history and low bone density (osteoporossis.ca, 2012). Because of the innocuous nature of the onset of osteoporosis and the lack of outward symptoms proceeding fracture, bone mineral density is used as the most appropriate surrogate outcome measure. As such, there are many risk factors that may lead to a dangerous decrease in bone density and therefore to an increased risk of fracture. Table II summarizes several categories of risk factors for decreased bone density.

Cummings et al. (1999) examined the role of various risk factors in fracture prediction by following a cohort of over 9500 women, aged 65 years or older, for a period of approximately 4 years. They noted that risk for fracture was higher in women with a maternal history of hip fracture (resulting in a doubling of the relative risk of hip

fracture); in women who had previous fractures of any type after age 50; were tall at age 25; rated their health as fair or poor; had a history of hyperthyroidism, anticonvulsant medication, excessive caffeine ingestion or spent less than 4 hours per day on their feet. Conversely, women who had gained weight since the age of 25 were found to have a decreased risk of fracture. Other findings associated with fracture risk included inability to rise from a chair without using one's arms, poor depth perception, poor contrast sensitivity and tachycardia at rest. Cummings concluded that women with multiple risk factors and a low bone density had an especially high risk of hip fracture (Cummings et al., 1999). Factors deemed not to contribute to increased risk based on this study included hair colour, number of children breast fed, prior smoking history or use of short-acting benzodiazepines.

1.1.6 Diagnosis

The Consensus Meeting on Osteoporosis of 1993 established a definition of osteoporosis as: “a systemic skeletal disease characterized by low bone mass and micro-architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture” (Conference Report, 1993). This definition does not require that a patient have suffered a fracture to be diagnosed with osteoporosis. Although it could be argued that, basing a diagnosis on a risk factor (bone mineral density) instead of a disease state is incorrect, the logic behind this approach rests on

the fact that fractures often occur late in the disease process and it is more desirable to identify those at risk of fracture, in order to maximize preventative treatment (Blake & Fogelman, 2002).

Today, measurement of bone mineral density (BMD) is agreed to be the most appropriate method to identify osteoporotic patients and those at risk of fracture (Blake and Fogelman, 2002). Based on the widespread availability and use of bone densitometry measurement, primarily dual energy x-ray absorptiometry (DXA), the World Health Organization (WHO) has developed definitions of osteoporosis based largely on BMD measurements. In 1994, a WHO working group recommended a clinical definition of osteoporosis based on BMD measurement of the spine, hip or forearm, expressed in standard deviation (SD) units termed T-scores (WHO Scientific Group, 2000). The T-score is a statistical grouping of raw bone density scores that are used to classify results from bone density scans. The T-score represents a comparison of the patient's bone density to that of a healthy 30-year-old subject of the same ethnicity. This value is used in the diagnosis of osteoporosis in men and women over the age of 50 because it has been shown to better predict the risk of future fracture (Richmond, 2007). The T-score is calculated as follows:

$$\text{T-score} = \frac{\text{Measured BMD} - \text{Young adult mean BMD}}{\text{Young adult standard deviation}}$$

The T-score indicates the difference between the patient's measured BMD and the ideal peak bone mass achieved by a young adult (Heaney et al., 1978). A negative T-score suggests that the patient has either failed to achieve optimum BMD or has lost bone mass due to the effects of aging or disease (Blake & Fogelman, 2002). The World Health Organization has determined the following criteria for T-scores in relation to osteoporosis: a T-score between 0 and -1 indicates normal bone density, a T-score between -1 and -2.5 indicates osteopenia and a T-score less than -2.5 indicates osteoporosis (see Table III).

These WHO groupings of normal, osteopenic and osteoporotic are intended to reflect patients with low, intermediate and high risk of fracture (Blake & Fogelman, 2002). These classifications, though, only apply when considering bone density as measured at the spine, hip or forearm and cannot be applied to other DXA measurement sites or to other methods of measurement including quantitative computed tomography (qCT) (Guglielmi, 2002) or quantitative ultrasound (qUS) (Stewart & Reid, 2002).

A second method for expressing BMD measurements is by using Z-scores which, like T-scores, is expressed in units of population SD. The Z-score compares the patient's BMD not with a young adult mean but instead compares it to the expected BMD of a healthy peer for each particular patient (matched for age, gender and ethnicity). The Z-score is calculated as outlined below:

$$\text{Z-score} = \frac{\text{Measured BMD} - \text{age matched mean BMD}}{\text{Age matched standard deviation}}$$

Although not used to diagnose osteoporosis, the Z-score is a useful measure as it approximates the patient's risk of sustaining a fracture relative to their peer group (Blake & Fogelman, 2002). Each 1 SD decrease in BMD equates to a two-fold increase in the likelihood of fracture (Marshall et al., 1996). Therefore, patient's with a Z-score of less than -1 are at a substantially increased risk of fracture, as compared to their peers.

BMD has been established as the preferred method of assessing osteoporosis status and the risk for future fracture, with DXA measurements considered the "gold standard" (Genant et al., 1996; Baran et al., 1997; Kanis et al., 1997) for BMD evaluation. Measurements of BMD using DXA have been shown to be the most reliable predictors of the risk of future fracture in the hip (Cummings et al., 1993; Black et al., 2000) and spine (Eastell, 1998). In addition, DXA has the added practical advantages of high precision, short scan times, stable calibration and low radiation dose (Njeh et al., 1999), which is comparable to the average daily dose from natural background radiation. More information on the DXA process is summarized in greater detail in Section 1.2.

1.1.7 Treatment

Decreases in bone density, both osteopenic and osteoporotic, are each generally addressed in a clinical setting, with the specific treatment approach dependent largely upon the nature of the decrease in bone density and the clinical importance of the bone loss. Treatment for osteopenic patients, i.e. those with a T-score between -1 and -2.5, generally focuses on prevention of further bone loss. Osteopenic patients are generally not prescribed medication, instead being counseled regarding diet, exercise and supplementation. The goal of this approach is to prevent further losses in bone density while attempting to re-build lost bone.

Patients with diagnosed osteoporosis (i.e. T-score less than -2.5) have several treatment options, the goal of which is to slow or stop the bone loss, with the secondary goal of rebuilding of lost bone. Therapeutic agents include supplementation with calcium and vitamin D or hormone replacement therapy, although the primary pharmacological intervention are the anti-resorptive bisphosphonates, a group of drugs commonly prescribed to prevent bone loss. General management of osteoporosis involves avoidance or modification of risk factors, of which smoking and excessive alcohol intake are important lifestyle factors to be taken into account (Body, 2011; Body et al., 2011). Maintenance of mobility is another important factor, as lack of mobility is known to negatively affect bone density (Body, 2011; Body et al., 2011). In elderly patients, assessment of the risk of falls and preventative measures to address these risks

is an important factor in limiting fractures. Finally, maintaining adequate intake of calcium and vitamin D through diet or dietary supplementation is strongly recommended as part of the plan of management for osteoporotic patients.

1.1.7.1 Calcium and Vitamin D

Combined calcium and vitamin D intake is a basic recommendation for patients with or at risk of osteoporosis, regardless of secondary factors (Rizzoli et al., 2008), as these supplements are known to have a protective effect on bone density (Body, 2011). In addition, a minimum of 800 IU/day of vitamin D has been shown to significantly improve body sway and lower extremity strength, thus decreasing the likelihood of falls (Rizzoli et al., 2008).

Vitamin D is actually a group of fat-soluble compounds known as secosteroids. In humans, vitamin D is unique because, although it is obtained through dietary sources, it is not an essential dietary vitamin. Vitamin D can be ingested as either cholecalciferol (vitamin D3) or ergocalciferol (vitamin D2) but can also be synthesized from cholesterol when the skin is exposed to sufficient sunlight. In the skeleton, vitamin D acts to maintain calcium balance by promoting the absorption of calcium in the intestines, promoting bone resorption by increasing osteoclast number, maintaining calcium and phosphate levels for bone formation and allowing proper functioning of parathyroid hormone to maintain serum calcium levels (Bell et al., 2010).

Both calcium and vitamin D have non-skeletal roles as part of their physiological effects. These include clinically important aspects such as muscle function, cardiovascular disease, autoimmune diseases and important roles in several common cancers (Body, 2011). Much of the evidence for these roles comes not from clinical studies but from laboratory investigations and observational studies (Body, 2011). However, regarding the effect of vitamin D and calcium on fracture rate, a recent meta-analysis (Boonen et al., 2007) suggested that there is an 18% decrease in the relative risk of non-vertebral fracture associated with calcium and vitamin D supplementation.

1.1.7.2 Bisphosphonates

The development of bisphosphonate medications revolutionized the treatment of osteoporosis. First discussed by Fleisch in the late 1960's (Fleisch et al., 1969a,b), bisphosphonates were initially known over 100 years ago and used extensively as industrial water softeners (Reid, 2011). Their initial medicinal use was in the management of Paget's disease (Altman et al., 1973; Smith et al., 1973). By the late 1970's, Bijvoet (Frijlink et al., 1979) had demonstrated the efficacy of bisphosphonates in the management of the hypercalcemia and osteolytic bone disease of malignancy (van Breukelen et al., 1979) and the 1980's saw the extrapolation of the antiresorptive properties of bisphosphonates in the management of osteoporosis (Valkema et al., 1989). The first randomized, controlled trial of a bisphosphonate was published in 1988

(Reid et al., 1988a,b), which began in earnest their application as the primary antiresorptive agent used in the management of osteoporosis. Additionally, bisphosphonates continue to be used extensively for Paget's disease and their role in oncology has extended to include a major role in the prevention of skeletal-related events in a number of malignancies, specifically multiple myeloma and breast and prostate tumours (Reid, 2011).

i. Pharmacology

Sructurally, bisphosphonates are comprised of a nucleus of two phosphate groups joined through a linking carbon atom, to which two other side groups are linked (Reid, 2011). The side groups commonly are composed of hydroxyl groups, giving the entire structure a strong negative charge that is attracted to the positively charged surface of bone (see Figure 2). This affinity results in avid and prolonged binding of these drugs to the bone mineral (Reid, 2011). A second side group on the bisphosphonate is often a ring or carbon chain structure that reflects the relative antiresorptive potency of the drug. Potent bisphosphonates often contain a nitrogen atom in their side chain; this facilitates binding to the enzyme farnesyl pyrophosphate synthase, the molecular target of the bisphosphonate (Reid, 2011). Farnesyl pyrophosphate synthase is integral to the cholesterol synthesis pathway. Its inhibition compromises cytoskeletal function and ultimately cell viability (Reid, 2011). Bisphosphonates target these characteristics, with the only way to mobilize the action through osteoclastic bone resorption. The only cells

that therefore accumulate bisphosphonates are osteoclasts, providing the bisphosphonates with remarkable cell-specificity (Reid, 2011).

ii. Efficacy

The use of bisphosphonates results in a rapid protective effect on bone density. The effect is noted within the first few days of drug administration and, based on studies examining biochemical markers of bone turnover, results in a reduction of markers of bone resorption by as much as 90%, depending on drug of choice, dose and route of administration (Christiansen et al., 2003; Watts et al., 2008). Over the first 3 months of use, bone formation indices are observed to decrease (Christiansen et al., 2003), although this effect is often transient. Bone balance remains positive over long-term bisphosphonate use, with some studies observing positive results as much as 10 years following introduction of therapy (Mellstrom et al., 2004; Black et al., 2006), although the long-term efficacy of bisphosphonates is still contested.

In osteoporosis, the most critical outcome measure is fracture rate. Bisphosphonates, by targeting bone resorption, aim to limit the loss of bone mass and strength and therefore limit the possibility of fracture. Studies have shown this to be the case with all of the currently registered bisphosphonates, with variations only in potency and success variable. Typically, fracture risk decreases by approximately 50% with bisphosphonate administration, although zolendronate has been shown to decrease vertebral fracture risk by up to 70% (Black et al., 2007). The majority of

osteoporotic fractures are non-vertebral in nature, and bisphosphonates have been shown to be less effective at their prevention. Bisphosphonate use, while associated with a 20-30% decrease in overall fracture risk (Black et al., 2007; Marcus et al., 2002), are associated with only a 40-50% success rate in preventing hip fracture. This is an important factor, as a large proportion of the economic burden associated with osteoporosis relates directly to the costs, morbidity and mortality associated with hip fractures (Reid, 2011). Risedronate (McClung et al., 2001), alendronate (Black et al., 1996) and zoledronate (Black et al., 2007) have all been shown to decrease the likelihood of hip fracture.

The long-term protective effect of bisphosphonates appears to be beneficial but continues to be debated. Several studies have attempted to determine the long-term protection against loss of bone density, however, none have been properly powered to assess fracture incidence of long periods of time (i.e. 6-10 years) (Reid, 2011). There have been suggestions that the protective effect of bisphosphonates remains for up to 5 years following cessation of treatment, although this is as of yet unproven (Reid, 2011).

iii. Adverse Effects

Bisphosphonates are generally administered either orally or intravenously. Of patients receiving bisphosphonates orally, gastrointestinal intolerance is a relatively common adverse effect and is thought to result in the discontinuation of the drug in up to 20% of patients (Reid, 2011). Regarding intravenous administration, a flu-like illness occurs in

approximately 30% of subjects (Reid et al., 2010). These symptoms are generally trivial, but the persistence of symptoms commonly extends up to 2 weeks, which is often disconcerting to patients.

Oncology patients receiving bisphosphonates prophylactically are often at increased risk of osteonecrosis of the jaw (ONJ) (Reid, 2009). ONJ presents as exposed bone in the mouth and is often precipitated by invasive dental procedures, such as extractions (Reid, 2011). The incidence of ONJ associated with bisphosphonates is approximately 1 in 100,000, though, which is comparable to the incidence in the oncology population (Reid, 2011). This, combined with the observation that another powerful anti-resorptive agent, denosumab, is also associated with ONJ, suggest that ONJ may not be specific to bisphosphonates (Stopeck et., 2010) but may be more closely associated with an oncology diagnosis.

A worrisome adverse effect of long-term bisphosphonate use is the potential for femoral fracture. Case reports (Kwek et al., 2008; Lenart et al., 2008; Feldman, 2011) have described a syndrome in bisphosphonate users of transverse fractures of the upper femoral shaft, with some evidence of preceding stress fractures. The incidence of sub-trochanteric fracture has been estimated at 5% of femoral fractures (Reid, 2011), although there is a lack of evidence from randomized trials demonstrating this as a common adverse effect. Meta-analyses of clinical trials (Black et al., 2010) and large national databases (Nieves et al., 2010) have failed to demonstrate this effect, and only

one (Park-Wylie et al., 2011) of several large cohort studies has demonstrated an increase in sub-trochanteric fractures.

1.1.7.3 Selective Estrogen-receptor Modulators

Selective estrogen-receptor modulators (SERMs) are a class of drugs that act on estrogen receptors. SERMs have a variable effect on different tissues in the body, in that they can act as either agonists (bind to receptor and triggers a response by cell in question) or antagonists (bind to receptor and block cellular response) on estrogen receptors. This characteristic provides the possibility of selectively inhibiting or stimulating estrogen-like action in various tissues. Several SERMs are commercially available and have a variety of clinical uses, which are summarized in Table IV.

Several trials and meta-analyses have investigated the effect of various SERMs on bone. One meta-analysis (Seeman et al., 2006) demonstrated that in prospective studies, raloxifene resulted in a reduction of the risk for vertebral fracture by 40% (RR 0.60; 95% CI, 0.49 to 0.74). The Multiple Outcomes of Raloxifene Evaluation (MORE) trial studied 7705 post-menopausal women with osteoporosis. This placebo-controlled trial found that raloxifene significantly reduced the risk of vertebral fractures without increasing the risk of endometrial hyperplasia or cancer (Ettinger et al., 1999). They found, though, that there was no change in the risk of hip fracture. Raloxifene, like tamoxifen in other studies (Cummings et al., 1999), significantly reduced the risk of

invasive breast cancer but increased the risk of venous thromboembolism (Ettinger et al., 1999; Cummings et al., 1999). The MORE trial was followed by the Continuing Outcomes Relevant to Evista (CORE) trial (Seeman et al., 2006), which followed MORE participants for an additional 4 years. MORE participants who had received placebo continued to receive placebo throughout the CORE trial (n=1286) while those that had received raloxifene (at doses of 60 or 120 mg/d) continued to receive raloxifene, but at a set dose of 60 mg/d (n=2725). After a total of 8 years, raloxifene therapy did not significantly decrease the incidence of non-vertebral fractures between groups, but did reduce the frequency of invasive breast cancer by 66% (RR 0.34; 95% CI 0.22-0.50) (Seeman et al., 2006). The authors recognized that their study had some limitations with respect to fracture risk assessment, but also noted that BMD increases were maintained after 7 years of raloxifene use (Siris et al., 2005).

One complicating factor regarding the use of raloxifene for bone density preservation is its effect on cardiovascular disease. Raloxifene has been shown to impart no preventative effect on cardiovascular disease (Body, 2011). Indeed, raloxifene was noted to lead to a small but significant increase in the risk of fatal stroke as well as venous thromboembolism (Body, 2011). The development of newer SERMs, including lasofoxifene and bazedoxifene, may confer an improved risk/benefit ration, as they have been shown to significant reduce non-vertebral fractures in high risk women (Body, 2011). The Postmenopausal Evaluation and Risk-reduction with Lasofoxifene (PEARL) study (Cummings et al., 2010), a placebo-controlled trial of 8566 osteoporotic

women treated over a 3-year period, found that the risk of new vertebral fractures (RR 0.58; 95% CI 0.45-0.73) and of non-vertebral fractures (RR 0.78; 95% CI 0.64-0.96) were both reduced, as compared to placebo. Lasofoxifene was also shown to reduce the risk of estrogen-receptor positive breast cancer (RR 0.24; 95% CI 0.09-0.65), coronary heart disease and stroke, although the incidence of venous thromboembolism was increased (RR 2.40; 95% CI 1.21-4.74). It has been suggested that a combination of bazedoxifene and estrogens could have a beneficial effect on non-vertebral fractures and control menopausal symptoms (Body, 2011).

1.1.7.4 Parathyroid hormone peptides

Parathyroid hormone (PTH) is a hormone secreted by the parathyroid glands and has effects on several tissues, generally acting to affect calcium levels in tissues. In bone, it enhances the release of calcium from the large reservoirs contained within bones (Poole & Reeve, 2005). PTH ultimately enhances bone resorption, doing so paradoxically by binding to osteoblasts and inducing a cascade of events that leads to the formation of new osteoclasts and a resultant increase in bone resorption (Poole & Reeve, 2005). Peptides from the parathyroid hormone family can be used pharmacologically as anabolic agents stimulating bone formation. Teriparatide (recombinant human 1-34 PTH peptide) has been the most studied peptide and is often administered via subcutaneous injection in daily dose of 20 μg (Body, 2011). These alternatives to anti-

resorptive therapies are of clinical interest due to their greater potential for restoration of bone mass and possibly also bone structure in osteoporotic patients through an increase in number and activity of osteoblasts (Body, 2011). Teriparatide was evaluated in an important randomized, clinical trial that involved 1637 postmenopausal women with a history of vertebral fracture (Neer et al., 2001). Following treatment with teriparatide for a median time of 21 months, the relative risk of vertebral fracture was reduced to 0.35 (95% CI, 0.22-0.55), as was the occurrence of non-vertebral fractures (RR 0.47; 95% CI 0.25-0.88). Side effects were noted following this study, including mild hypercalcaemia in up to 11% of participants (Neer et al., 2001). Other side-effects included nausea, dizziness and headache (Body, 2011). While the potential preventative effect on BMD was observed, the permanence of this improvement was called into question, as it was also noted that a rapid decrease of BMD accompanied cessation of teriparatide therapy.

1.1.7.5 Strontium Ranelate

Strontium ranelate is a medication for osteoporosis that is based on the element Strontium (Sr), an element belonging to group II of the periodic table. Due to its similarity to calcium, strontium is easily taken up by the body and incorporated into structures in place of calcium. This phenomenon has been exploited in attempts to regulate bone loss associated with osteoporosis, with strontium ranelate the result.

Strontium ranelate has been dubbed a “dual action bone agent”, as it has been shown to both increase the activity of bone-producing osteoblasts and decrease the activity of bone-resorbing osteoclasts. Strontium ranelate promotes bone formation by stimulating calcium-sensing receptors and ultimately leading to differentiation of pre-osteoblast cells to mature osteoblasts, which in turn increases bone formation. Conversely, strontium ranelate also stimulates osteoblasts to secrete osteoprotegerin, a protein that inhibits osteoclasts, thus decreasing bone resorption (Body, 2011).

Clinically, strontium ranelate use has been shown to increase bone density, although part of this increase is due to the direct incorporation of strontium into bone, which ultimately affects the accuracy of DXA measurements (Body, 2011). Several clinical trials have investigated strontium ranelate as it relates to bone density preservation. The SOTI (Spinal Osteoporosis Therapeutic intervention) trial (Meunier et al., 2004) aimed to assess the effect of strontium ranelate on the risk of vertebral fractures. This study was a double-blind, placebo-controlled trial, with a duration of 5 years and statistical analysis performed following an additional 3 years of follow-up. The study found that the risk of new vertebral fractures following strontium ranelate use was reduced by 41% (RR 0.59; 95% CI 0.48-0.73). A separate trial, the TROPOS (Treatment Of Peripheral Osteoporosis) trial (Reginster, 2005) evaluated the effect of strontium ranelate on peripheral fractures (i.e. non-spinal). Over a period of 3 years, strontium ranelate use was associated with a 16% reduction in non-vertebral fractures (RR 0.84; 95% CI 0.702-0.995). Post-hoc analysis revealed that, in a high-risk fracture

sub-group, treatment was associated with a 36% decrease in the risk of hip fracture (RR 0.64; 95% CI 0.412-0.997) (Reginster, 2005).

Strontium ranelate was associated with a small increase in the reported risk of venous thromboembolic disease (RR 1.42; 95% CI 1.02-1.98) (Reginster, 2005) and was also associated with rare instances of hypersensitivity reactions (Body, 2011).

1.1.7.6 Denosumab

Denosumab is a monoclonal antibody to RANKL that prevents the interaction of RANKL with its receptor RANK by binding RANKL. This leads to a rapid and profound inhibition of bone resorption (Body, 2011). For cancer patients with bone metastases, denosumab is administered as subcutaneous injections of 120 mg monthly; for osteoporotic patients, it is administered at a dose of 60 mg every 6 months (Body, 2012). The FREEDOM trial (Cummings et al., 2009) evaluated the efficacy of denosumab in close to 7900 post-menopausal women over a 3 year period. The results indicate a 68% reduction in the incidence of new vertebral fractures (RR 0.32; 95% CI, 0.26-0.41). The incidence of non-vertebral fractures was decreased by 20% (RR 0,80 95% CI, 0.67-0.95) while the risk of hip fractures was decreased by 40% (RR 0.60; 95% Ci, 0.37-.97) (Cummings et al., 2009). Denosumab was tolerated well, with the incidence of adverse effects similar in the placebo and treatment groups (Cummings et al., 2009). Overall

safety has been confirmed in phase II clinical trials (Body, 2011) and there was a continued accrual over a 6 year follow-up period (Body, 2011).

1.1.8 Socioeconomic Burden of Osteoporosis

Osteoporosis affects an estimated 10 million patients in the United States (Becker et al., 2010) and is estimated to be responsible for between 1.5 to 2 million fractures each year (Burge et al., 2007). It is similarly prevalent in other developed nations, with prevalence and incidence in Scandinavian (Borgstrom et al., 2007) and European (Konnopka et al., 2009) nations similar to that of North America.

A large economic burden is associated with osteoporosis, including both the monetary costs associated with caregiving and the non-monetary costs of poor health (Becker et al., 2011). Projections for costs and future needs are impacted significantly by the pending demographic shift associated with the aging of the baby-boom generation (Becker et al., 2011). Indeed, the proportion of patients expected to access Medicare in the United States is expected to double between 2005 and 2030 (Kaiser Foundation, 2005).

The combined aging of the “baby boom” cohort and the continuing gains in life expectancy will sharply impact the societal burden of osteoporosis in the coming decades. The growth of this older population is expected to result in increases in the

prevalence of osteoporosis, among other chronic diseases associated with aging (Sambrook & Cooper, 2006). The additional difficulty with regards to osteoporosis is that it is associated with an increased risk of severe acute events such as fracture, that can be costly to treat and potentially debilitating for patients (Becker et al., 2011). Health care expenditures relating to this demographic shift are predicted to triple by 2030 (Thorpe & Howard, 2006). As such, efforts to address these expected increases in spending are being focused on reducing the prevalence of chronic disease (Becker et al., 2011). In the case of osteoporosis, this includes reducing the incidence of fragility fractures (Becker et al., 2011).

The annual medical costs associated with osteoporosis currently range from USD $14 to 20 billion (Burge et al., 2007; Ray et al., 1997; Hoerger et al., 1999; Chrischilles et al., 1994; Phillips et al, 1986). Concretely determining such costs is difficult; however, as the cost estimate will ultimately depend on the approach used to obtain said estimate. Two broad approaches are generally utilized. The first is termed a "top-down" approach, and compares the annual expenditures of individuals with osteoporosis to observationally similar patients without osteoporosis (Sasser et al., 2005). This approach, although used extensively in the estimation of costs in chronic disease, assumes that patients with and without osteoporosis differ only in their diagnosis and not in any unobservable dimension that may affect health expenditures (Thorpe et al., 2010; Dawson et al., 2002; Hogan et al., 2003). Alternatively, a "bottom-up" approach, using the costs of osteoporosis-related fractures to derive estimates of the total cost

burden of osteoporosis, are more often used in cost studies of osteoporosis (Becker et al., 2011). Such studies are associated with the problem of defining osteoporosis-related fractures and determining which costs are directly attributable to fracture (Becker et al., 2011).

Burge et al. (2007), in an attempt to provide an estimate of the total cost burden associated with osteoporotic fractures, estimated the annual costs for each of hip, vertebral, wrist, pelvic and "other" fractures. They estimate that, in 2005, the total cost associated with osteoporotic fractures was USD $16.9 billion, of which 57% was related to inpatient care, 13% to outpatient care and 30% in long-term care (Burge et al., 2007). These estimates are likely conservative, though, as they are limited to the first-year costs and do not take into account the lifetime costs, including transition to long-term nursing care facilities (Braithwaite et al., 2003). Of their estimate, 72% are accounted for by hip fractures, despite representing only 14% of all incident fractures (Becker et al., 2011). Based on their analysis, Burge et al. (2007) predict that the total cost of osteoporotic fractures in the United States could reach USD $25.3 billion by 2025. They anticipate that 87% of these costs would be associated with the "baby boom" cohort, highlighting the growing burden of osteoporosis on the health care system in the coming years.

1.1.9 Osteoporosis-related fracture

Fractures associated with osteoporosis are referred to as "fragility fractures". They are characterized by spontaneous onset or onset following a low-energy trauma and are a complication of the changes in bone mass and ultrastructure that accompany osteoporosis (Orcel & Funck-Brentano, 2011). The most common fracture sites are the proximal femur, wrist and vertebrae (Orcel & Funck-Brentano, 2011). It is estimated that one in two women will have a fracture between menopause and the end of her life (Orcel & Funck-Brentano, 2011). After the age of 80, the likelihood of osteoporosis sequelae increase dramatically, as up to 70% of women over the age of 80 have osteoporosis and 60% have had at least one fracture (Bass et al., 2007).

A low-energy trauma is defined as a fall from standing or from a height of less than 50 cm, either during walking or after having come to a stop (Orcel & Funck-Brentano, 2011). Almost any bone, save for the skull, cervical and upper thoracic spine and the extremities, can be the site of a fragility fracture. Osteoporosis can, though, increase the chance of fracture during a high-energy trauma. Incomplete fractures without cortical breach can also be considered fragility fractures, although a portion of these fractures are likely associated with excessive mechanical stress that ultimately leads to bone failure (Ferrari et al., 2006; Fiorano-Charlier et al., 2002).

The most clinical serious osteoporotic fracture is the proximal femoral fracture. These fractures are associated with significant morbidity and mortality (Ioannidis et al.,

2009; Bljuc et al., 2009). Elderly patients often suffer a loss of independence or autonomy following such a fracture, and have a two to four times greater chance of dying within the first year following such a fracture, when compared with the general population (Ioannidis et al., 2009; Bljuc et al., 2009).

Unlike femoral fractures, vertebral fractures are difficult to diagnose and identify, largely because they can present as asymptomatic or very mildly symptomatic. By some estimates, only one-third of vertebral fractures are properly diagnosed (Orcel & Funck-Brentano, 2011), as the symptoms often present as simple low or mid back pain. The incidence of vertebral fractures is variable, increasing with age. In women age 55-59, 5.5 per 1000 people/year are diagnosed with a vertebral fracture. This number increases to 29.3 per 1000 people/year in women aged 75-79 years (Lindsay et al., 2001). In addition, women who have had a vertebral fracture are five times more likely to have another fracture within one year (Lindsay et al., 2001). As with non-vertebral fractures, the risk of fracture is greatest in the two years following menopause (Orcel & Funck-Brentano, 2011).

Fractures of the wrist, including the distal radius, are relatively common in osteoporotic populations, and can result in major disruption of functional ability and are also associated with secondary sequelae such as complex regional pain syndrome (Orcel & Funck-Brentano, 2011). These fractures are often referred to as "sentinel fractures"

(Orcel & Funck-Brentano, 2011) and should be taken as a warning by clinicians and patients that other fragility fractures may be possible.

Assessing the individual patient risk of future fracture has become an important aspect of osteoporosis management, in that prevention is a more cost-effective method of managing long-term disease such as osteoporosis. The WHO commissioned the creation of such a prediction tool, using the data from multiple international databases to calculate the individual fracture risk as a function of risk factors and clinical data. This fracture assessment tool (FRAX), estimates risk by determining individual probability of fracture at 10 years, either for major osteoporotic fractures (e.g. femoral neck, vertebrae, wrist, proximal humerus) or specifically for the femoral neck (Orcel & Funck-Brentano, 2011). FRAX is accessed via its website (www.shef.ac.uk/frax) and requires the simple input of clinical risk factors including age, weight, sex, personal fracture history and family history among others. Femoral neck BMD data can also be entered (but is not required). The result is a 10-year estimate of major osteoporosis related fracture (hip, spine, humerus and forearm) and the hip independently (McCloskey et al., 2011).

While a valuable tool in predicting future fracture risk, FRAX is not without its limitations. The use of femoral neck BMD measurements alone has been a cause for concern. It has been argued that there is often a conflict between the femoral neck values and the typically lower spine values, especially in younger post-menopausal

women (Orcel & Funck-Brentano, 2011). Also, the femoral neck measurement is less reproducible (Orcel & Funck-Brentano, 2011). Secondly, the fracture history used in FRAX does not take into account the location of the fracture nor does it consider the number of previous fractures. These factors are important when considering that vertebral and hip fractures are known to have a greater effect on future risk of new fractures (Orcel & Funck-Brentano, 2011). Likewise, while FRAX factors in medications such as glucocorticosteriod use, it does not consider the cumulative use of these drugs. This ultimately limits the applicability of FRAX predictions in patients with long-term inflammatory conditions. Finally, FRAX raises concerns regarding the interpretation of results and their effect on subsequent clinical decision making (Orcel & Funck-Brentano, 2011). For this reason, FRAX is used most often in pharmacoeconomic studies to help establish cost-efficacy thresholds for age ranges (Orcel & Funck-Brentano, 2011).

1.2 Bone Mineral Density

There are several methods commonly used to measure bone mineral density. Some methods utilize computed tomography (CT) or ultrasound technology, although the most common method for measuring bone mineral density is dual x-ray absorptiometry. DXA was first developed by Cameron and his colleagues at the University of Wisconsin, Madison (Cameron et al., 1968) in the 1960's, although was not in widespread use until the mid-1990's. By 1959, had Cameron realized that there was no effective method of early detection of osteoporosis, even though fractures of the hip were a relatively common clinical finding. In 1960, he developed the first DXA machine, but it was not adopted as a diagnostic tool because there were still very few successful treatments for osteoporosis.

DXA uses a relatively simple process whereby two low-dose x-ray beams are projected towards the patient. These two beams have distinct peak energy values, the lower of which is absorbed by the soft-tissues in the body such as muscle and fat and the higher of which is absorbed by both the bones and soft-tissues. The signal from the low intensity beam is then subtracted from that of the high intensity beam. The resulting difference represents the amount of radiation absorbed by the bone. The more dense the bone, the more energy is absorbed (Eck & Sheil, 2012). DXA measurements require no additional injectibles, nor do they require any special

preparation. There are no known adverse effects associated with DXA measurement, although typical radiological contraindicators such as pregnancy remain.

1.3 The Effect of Menopause on Bone Density

A connection between menopause and bone loss was first proposed by Albright in 1941 (Albright et al., 1941). Subsequent studies documented cortical bone loss in the metacarpals (Meema, 1963; Young and Nordin, 1969), radius (Garn, 1970), mid-femoral shaft (Nordin et al., 1966) and humerus (Bloom & Laws, 1970), with thinning of the cortex due primarily due to endosteal resorption (Garn, 1970). Rates of bone loss are site-dependent and the effect of menopause on consequent bone loss is equally variable. Spinal bone density generally shows only small age-related decreases prior to menopause but is associated with a large change following the onset of menopause (Hedlund & Gallagher, 1989). Comparably, age-related decreases in hip bone density begin as much as 20 years prior to menopause (Hedlund & Gallagher, 1989).

With the advent of quantitative computed tomography (qCT) technology in the 1980s, more accurate and detailed measurement of changes in bone density was possible. An added benefit of the use of qCT is that it allows the separate measurement of the cortical and trabecular bone, and thus demonstrates the differing affects of estrogen withdrawal on these two bone compartments (Gallagher, 2007). It was subsequently demonstrated that bone loss from trabecular sites is six to seven times greater than that from cortical sites (Gallagher, 2007). This is thought to be due to the greater surface area available for the resorptive process in trabecular bone (Gallagher,

2007). Similarly, the trabecular bone responds more vigorously to anti-resorptive therapy (Gallagher, 2007).

Post-menopausal bone loss tends to occur most rapidly in the few years following the onset of menopause and progressively slowing in subsequent years. The initial "acute loss" phase generally lasts 4 to 5 years, followed by a period of slowing bone loss (Pouilles et al., 1993; Hashimoto et al., 1995; Guthrie et al., 1998; Okano et al., 1998; Ito et al., 1999; Tsurusaki et al., 2000; Lindsay et al., 2002; Prior et al., 1997). Bone loss does not; however, continue without limit but instead plateaus at a new, lower level, even though the estrogen deficiency continues (Riggs et al., 1998; Riggs et al., 1995). Based on DXA measurements, the average annual rate of spinal bone loss following menopause onset is 2.5% for the first 2 years, decreasing to 1.8% between years 2 and 4 and finally to 1 to 1.3% for subsequent years. The rate of loss from the spine is approximately double that of the hip (Pouilles et al., 1993; Lindsay et al., 2002). Using qCT to estimate the rate of bone loss results in estimates of greater loss in the initial stages: qCT measurements have estimated the annual loss in the first 4 to 5 years following menopause as averaging 4 to 5% (Gudmundsdottir et al., 1993; Seifert-Klauss et al., 2006). This difference is likely due to the differing rates of turnover of the cortical versus trabecular bone and the superior ability of qCT to determine these specific changes, as qCT is able to measure only the trabecular bone while DXA measurements represent the combined cortical and trabecular bone results. Some studies have estimated the rate of trabecular bone loss in post-menopausal women as up to 10 times

the pre-menopausal loss rate (Block et al., 1989; Gudmundsdottir et al., 1993; Seifert-Klauss et al., 2006).

While osteoblasts and osteoclasts are responsible for bone formation and resorption, respectively, they do not act independently, and in fact act in a synergistic manner. Each cell type relies upon and requires the other to perform their respective functions (Frost, 1999). The combined functional components of bone turnover (basic multicellular units (BMUs)) were proposed by Frost (1999) and outlined earlier in this thesis. Osteocytes are the third important component of the BMU. Osteocytes are derived from osteoblasts and are proposed to be mechanosensor cells that control the activity of osteoblasts and osteoclasts within a BMU (ran Bezooijen et al.., 2005). Osteocytes generate an inhibitory signal that is passed through their cell processes to osteoblasts to assist with recruitment and enable bone formation, thus playing an important role as a regulator of bone mass (Marotti et al., 1992). Frost (1999), in proposing this mechanism, suggested that BMUs function in one of two modes: the "conservative mode", which turns over bone without an appreciable change in overall bone density, and the "disuse mode", where BMUs produce less bone than they resorb, resulting in a loss of bone density. The loss of density is proposed to occur largely within the trabeculae, with expansions in bone marrow cavity and a reduction in the spongiosa in that cavity concurrent with a reduction of cortical thickness (Frost, 1969). No changes in exterior bone diameter would be associated with such change, though.

Estrogen exerts its effects on bone turnover by acting through high-affinity estrogen receptors (ERs) in both osteoblasts (Eriksen et al., 1988; Komm et al., 1988) and osteoclasts (Oursler et al., 1991) to restrain bone turnover. When this restraint is lost at menopause, bone turnover increases (Riggs et al., 1998). In addition, estrogen deficiency also increases the sensitivity of bone to parathyroid hormone (PTH) (Cosman et al., 1993), a bone resorption-inducing hormone, which further enhances resorptive effect. Additionally, however, estrogen withdrawal has an important effect on bone formation. At menopause, the rate of bone resorption is known to increase more than the rate of bone formation (Garnero et al., 1996; Heaney et al., 1978). Ivey and Baylink (1981) used calcium kinetic data analysis to demonstrate that inadequate compensatory increases in bone formation, required to offset the increased in bone resorption, was an important cause of bone loss in the early stages of menopause. Lips and Meunier (1978) used histomorphometric analysis of bone biopsy samples to demonstrate decreased wall thickness of trabecular packets, which indicates the decreased bone formation rate at a cellular level.

1.4 Exercise and Bone Density

The prevailing opinion regarding exercise and bone mineral density is that unloading of the skeleton induces bone loss (Zerwekh et al., 1998) while loading promotes increased bone mass (Howe et al., 2011). The bone protective effects of loading the skeleton have been demonstrated variously in athletes (Taaffe et al., 1997) and in animal models (Robling et al., 2002). In general, mechanical loading through exercise has the potential to be a safe and effective method for averting or delaying the onset of post-menopausal osteoporosis (Howe et al., 2011). A recent Cochrane review (Bonaiuti et al., 2002) of the effect of exercise on bone density found that exercise has beneficial effects on bone density in the hip and spine, but long-term data regarding any subsequent effect on fracture rate was rare. In addition to mechanical effects, it is also known that strength and balance exercises contribute to reduced fracture risk by reducing the likelihood of falls (Gillespie et al., 2009).

Howe et al. (2011), in their recent Cochrane Review of the effect of exercise on bone density, completed a comprehensive review of all types of exercise programs, both land and water-based, to determine the overall effect of exercise on bone density. Their findings indicate that, in general, a small, statistically significant protective effect of exercise on bone density was noted in post-menopausal women as compared with control groups. Howe et al. separated exercise into several different categories, summarized in Table V.

Howe et al. compiled data from 43 randomized controlled trials (RCTs), comparing exercise with "usual activity" or exercise plus a pharmacological intervention with pharmacological products alone. They found that the overall risk of fracture in intervention groups versus control groups was not significantly different (OR 0.61; 95% CI 0.23 to 1.64) (Howe et al., 2011). They did note; however, that exercise resulted in significant increases in BMD at three skeletal sites: spine (MD 0.85; 95% CI 0,62 to 1.07), total hip (MD 0,41; 95% CI -0,64 to 1.45) and trochanter (MD 1.03; 95% CI 0,56 to 1.49). Improvements in bone mineral density were exercise- and site-specific and were associated with differing exercise programmes.

Dynamic exercise programmes were noted to have protective effects on BMD, with the varying levels of activity resulting in differing effects on skeletal regions. High force exercise (jogging, jumping, vibration platforms) resulted in an increase in BMD at the total hip and trochanter, as compared to control groups (Howe et al., 2011). Howe et al. compiled data from eleven studies (Cheng et al., 2002; Going et al., 2003; Grove & Londeree, 1992; Iwamoto et al. 2005; Karinkanta et al., 2007; Maddalozzo et al., 2007; Newstead et al., 2004; Rubin et al., 2004; Russo et al., 2003; Uusi-rasi et al., 2003; Verschueren et al., 2004,) totaling 568 participants. The results of their meta-analysis showed that there was a statistically significant effect on percentage change in BMD of the hip (MD 1.55; 95% CI 1.41 to 1.69) and trochanter (MD 1.23; 95% CI -0.01 to 2.47) (Howe et al., 2011). No statistically significant difference was noted in the femoral neck, spine or lower leg bones. Conversely, lower force dynamic exercise (walking or Tai chi)

had a significant effect on BMD at the spine and wrist (Bravo et al., 1996; Chan et al., 2004; Chow et al., 1987; Ebrahim et al., 1997; Grove & Londeree, 1992; Hatori et al., 1993; Lau et al., 1992; Lord et al., 1996; Martin & Notelovitz, 1993; Preisinger et al., 1995; Prince et al., 1991; Prince et al., 1995).

Non-weight bearing exercise at high force (progressive resistance training) had a significant effect on BMD at the spine and wrist. Howe et al. performed a meta-analysis of nine studies (Bemben et al., 2000; Bocalini et al., 2009; Brentano Cadore et al., 2008; Chilibeck et al., 2002; Chuin et al., 2009; Kerr et al., 2001; Nelson et al., 1994; Pruitt et al., 1996; Smidt et al., 1992) evaluating the effect of progressive strengthening exercise programmes, involving 292 participants. The results indicated that there was a statistically significant protective effect on BMD at the spine (MD 0,86; 05% CI 0,58 to 1.13) and the femoral neck (MD 1.03; 95% CI 0.24 to 1.82). Lower force non-weight bearing programmes (low load, high repetition) (Bemben et al., 2000; Brentano Cadore et al., 2008; Kerr et al., 2001; Pruitt et al., 1996; Revel et al., 1993; , Sinaki et al., 1989) had no significant effect on bone density at any site. Finally, static exercise, in a study of 31 participants, had a positive effect on BMD in the hip (MD 2.42; 95% CI 0.73 to 4.10) (Sakai et al., 2010).

Combined (COMB) exercise programmes showed a significant improvement in BMD at three sites: femoral neck, spine and trochanter. Howe et al. combined the results from eleven studies (Bergstrom et al., 2008; Chow et al., 1987; Chubak et al.,

2006; Englund et al., 2005; Iwamoto et al., 2001; Karinkanta et al., 2007; Keinanen-Kiukaanniemi et al., 2006; Metcalfe et al., 2001; Papaioannou et al., 2003; Tolomio et al., 2009; Von Stengel et al., 2009) that included more than one of the above described interventions. The meta-analysis reported on 823 participants and showed that the risk of fractures in the exercise groups was significantly lower than that in controls (OR 0.33; 95% CI 0.13 to 0.85) (Howe et al., 2011). They also demonstrated that there was a significant improvement in the percent change in BMD in the spine (MD 3.22; 95% CI 1.80 to 4.64), trochanter (MD 1.31; 95% CI 0.69 to 1.92) and femoral neck (MD 0.45; 95% CI 0.08 to 0.82). Paradoxically, though, they noted a statistically significant difference in BMD in the total hip, favouring control groups (MD -1.07; 95% CI -1.58 to -0.56) (Howe et al., 2011).

1.5 The Canadian Multicentre Osteoporosis Study

In the late 1990's, little was known about the factors in Canada that led to osteoporosis and its associated fractures. The Canadian Multicentre Osteoporosis Study (CaMos) was conceived as a method to answer these questions and provide insight into the incidence and prevalence of declining bone mass and fractures in Canada. CaMos is a prospective cohort study drawing a random sample of non-institutionalized men and women 25 years of age and older living within 50 kilometres of the nine cities in Canada that constitute the CaMos centres (Kreiger et al., 1999).

From an organizational perspective, CaMos is a nationwide network of researchers investigating the clinical and economic effects of osteoporosis on the Canadian population. CaMos is comprised of researchers from nine different universities across Canada, including McMaster University in Hamilton. As listed on the organization's website (www.camos.org), the mission of CaMos is to be the premier study:

- That assesses the burden of osteoporosis and fracture in Canadian women and men;
- That identifies factors associated with osteoporosis and fracture which lead to improved diagnosis and prevention; and
- That measures the health and economic consequences of osteoporosis and fracture.

CaMos is based upon a long-range survey study conducted over a period of 10 years. This study gathered data from close to 10,000 participants, using both long- and short-form questionnaires (see Appendix A) to collect data regarding patients'

experiences and clinical status. Recruitment occurred between 1995 and 1997; an additional cohort of younger participants, both male and female and aged 16-24, was recruited between 2004 and 2006.

Data was collected at serial time-points over the 10 year duration of the study. Baseline, year 3, year 5 and year 10 questionnaires were administered, with a follow-up questionnaire completed annually (CaMos website). Any self-reported fractures were confirmed by medical report or hospital discharge (CaMos website). Bone density was measured using dual-energy X-ray absorptiometry at the lumbar spine and hip, while ultrasound was used at the shin and wrist (CaMos website).

Table VI provides a comprehensive list of the nine CaMos sites throughout Canada.

1.6 Objectives

Physical activity is clinically accepted as a beneficial activity for osteoporotic patients, although little information exists regarding the best and most appropriate type, duration and intensity of exercise to provide the maximum protective effect against bone loss. As such, no clinical guidelines exist that can be utilized by clinicians in prescribing exercise for osteoporotic patients. The overall objective of this study is to contribute to the formation of such clinical guidelines, such that clinicians will be able to strategically prescribe exercise to patients, based on the specific demographics and clinical requirements of each patient. In order to meet this broad objective, the work undertaken examined the CaMos database to determine the relationship, if any, between activity level and bone density and fracture rate in post-menopausal women aged 75 years and older. The study had several specific objectives:

1.6.1 Specific Objectives

i. To determine the relationship between the amount of daily moderate physical activity and bone mineral density in post-menopausal women aged 75 and over.

ii. To determine the relationship between the amount of daily moderate physical activity and fracture rate in post-menopausal women aged 75 and over.

1.6.2 Research Questions

In order to address the specific objectives of this study, the following research questions were proposed:

i. In post-menopausal women aged 75 and over, does an increase in the amount of daily moderate physical activity performed, as compared to inactive controls, have a positive effect on bone density?

ii. In post-menopausal women aged 75 and over, does an increase in the amount of daily moderate physical activity performed, as compared to inactive controls, decrease fracture rate?

1.7 Scope

The work undertaken has a broad scope when considering the impact of the findings on the development of clinical guidelines for prescription of exercise to post-menopausal women at risk of osteoporotic fracture. The results will contribute to the current knowledge and to the development of such guidelines, but will not facilitate their complete construction. The specific scope of this work is to examine the effect of different levels of physical activity on bone mineral density and fracture rate in Canadian women, aged 75 and over. This sample is generally thought to be representative of the Canadian population at large, with respect to post-menopausal women over age 75 (CaMos.org, 2012).

2.0 Methods

2.1 Canadian Multicentre Osteoporosis Study (CaMos)

The Canadian Multicentre Osteoporosis Study is a prospective cohort study investigating the incidence and prevalence of osteoporosis in Canada. It seeks to determine the factors that contribute to the disease in Canada and provide information to assist clinicians and researchers with diagnosis, treatment and prevention. The study is an ongoing population-based cohort study involving an age-, sex- and region-specific sample of the Canadian population (Ioannidis et al., 2009). The population includes 9423 participants (2884 male, 6539 female), aged 25 years and older, living in the community within 50 kilometres of one of the nine CaMos centres (see Table VI). It is estimated that the catchment area encompassed by these centres, which includes both urban and rural settings, represents approximately 40% of the Canadian population.

Sampling of participants began with a database of residential telephone subscribers. Each of the provincial telephone companies created random samples in lots of 10,000 of all of their subscribers within specified postal codes (Ioannidis et al., 2009). Participants provided informed consent to participate in the study, which was given approval by all institutional review boards prior to commencing.

2.2 The Effect of Physical Activity on Bone Mineral Density and Fracture Rate in Very Old Post-menopausal Women

2.2.1 Study Design, Population and Inclusion/Exclusion Criteria

The study population for this investigation is a sub-group of the CaMos cohort. Beginning with the initial CaMos cohort, participants were stratified by age. All participants aged 74 years and younger were ineligible for this study. The initial CaMos cohort included both male and female participants. As the current study was concerned with only post-menopausal women, all male participants were also deemed ineligible.

2.2.2 Data Collection at Study Entry

Data collected at study entry comprised information gained from questionnaires and from physical examinations. Categories for which information was collected included basic demographic information, physical activity level and participation, fracture status, bone mineral density, health habits and medications. Physical activity was quantified based on the level of activity and the reported frequency and duration of said activity over the course of the previous 12 months. Anthropometric and demographic details were gathered, including age, sex, study centre, height and weight. Medications identified for analysis included bisphosphonates, hormone replacement therapy and corticosteroids. Health-related habits including caffeine intake, calcium intake from supplements/drugs, alcohol intake and smoking status were also gathered.

2.2.3 Assessment of Physical Activity Level

Physical activity was assessed through self-reporting on the CaMos questionnaire (see Appendix A). Section 11 addresses the participants' physical activity level. Two aspects of physical activity were of interest in this study. Firstly, the current level of activity for each participant was assessed in Section 11. Participants were asked to report on their current level of regular physical activity, based on the amount of time spent performing each activity in a typical day or week. Participants were asked if they participated in a regular activity program and, if so, how many times per week and the duration of that activity. Participants were then asked to indicate how many hours per week, over the previous 12 months, that they had spent performing specific activities. Activities were stratified into "strenuous" (e.g. jogging, bicycling up hills, tennis, racquetball, swimming laps), "vigorous" (e.g. moving heavy furniture, loading or unloading trucks, shoveling, weight lifting) or "moderate" (housework, brisk walking, golfing, bowling, bicycling on level ground). For each activity, participants were asked to indicate how many hours per week they spent performing those specific activities. Response options included: never, 0.5-1.0 hours, 2-3 hours, 4-6 hours, 7-10 hours, 11-20 hours, 21-30 hours and 31+ hours.

2.2.4 Assessment of Bone Density

Bone density was assessed using DXA measurements. All nine CaMos centres employed dual x-ray absorptiometry to determine bone mineral density. Bone density was measured at five sites: lumbar spine (L1-4), femoral neck, total hip, Ward's triangle and trochanter. Of the nine CaMos centres, seven used Hologic densitometers (Hologic Inc., Waltham, MA) while the remaining two used lunar densitometers (GE Lunar, Madison, WI). Machines were calibrated daily, as per the manufacturer's recommendations. Daily monitoring was also used to assess and correct longitudinal drift. Measurements derived from the Lunar instruments were converted to equivalent Hologic values using standard reference formulas (Genant, 1995; Lu et al., 2001). Cross-calibration of machines was achieved using an anthropomorphic phantom that was circulated and scanned at each centre.

2.2.5 Assessment of Fracture

Appendix A is a sample of the CaMos questionnaire; Section 4 pertains to fractures. Participants self-reported fractures and verification was obtained through communication with the attending or family physician. Up to six incident fractures were catalogued per participant. Fractures were categorized into one of seven categories: "back", "ribs", "pelvis", "forearm/wrist", "hip" and "other"; a seventh category was used for participants who had not suffered a fracture. Fractures included in the "other"

category included any fracture except for a location specified above and those involving the toes, fingers or face.

2.2.6 Statistical Analysis

To determine the relationship between the amount of moderate physical activity performed and bone mineral density and fracture rate, two approaches were used.

Initial demographic analysis determined the general features of the cohort, including average age, height, weight, body mass index and similar descriptive statistics. Moderate physical activity (MPA) was analyzed and the cohort examined for frequency patterns. Because fracture rate is an important outcome for this study, demographic and descriptive statistics was also evaluated using the presence or absence of fracture as a comparison.

To determine the effect of MPA on bone density, regression analysis was used. Bone density measurements were taken from 5 specific sites: lumbar spine, femoral neck, total hip, Ward's triangle and trochanter. Linear regression analysis was used to evaluate the effect of varying levels of MPA at each of these individual sites. Multiple regression analysis was used to determine the relative effect of increased amounts of MPA bone density, taking into account possible confounding factors such as the use of anti-resorptive therapy, body mass index and participant age.

The effect of MPA on fracture rate was also evaluated. Univariate and multivariable logistic regression analyses were used to calculate an odds ratio (OR) for each level/amount of MPA as well as anti-resorptive medication, body mass index and age with incident fracture as a dependent variable. All analyses were performed using SPSS 19 (Chicago, IL).

3.0 Results

3.1 Canadian Multicentre Osteoporosis Study (CaMos)

A total of 9423 participants were included in the CaMos cohort, 2884 men and 6539 women. Data was gathered through personal interviews with each participant. Interviews were conducted with CaMos personnel available to provide assistance to each participant. A copy of the questionnaire administered as part of this study is included as Appendix A. Participants were gathered from all nine of the CaMos study sites, the populations of which comprise approximately 40% of the Canadian population. The major demographic not represented in this study is the native (Inuit, Indian) population, who generally reside in the northerly regions of Canada. Their exclusion from the study population is a product of logistical and financial barriers only. Statistically, the population gathered for this study is an accurate representation of the target population of persons with or at risk of osteoporosis.

3.2 The Effect of Physical Activity on Bone Mineral Density and Fracture Rate in Very Old Post-menopausal Women

3.2.1 Study Design, Population and Inclusion/Exclusion Criteria

For the purposes of this study, we selected CaMos participants who were: a) aged 75 and over and, b) female. Figure 3 is a CONSORT diagram summarizing the eligibility

criteria for the sub-group in question. Following exclusion of ineligible participants, a total of 1169 participants were selected for inclusion in the study.

Demographic and anthropometric data for eligible participants was collected. This data is summarized in Table VII. The average age of participants was 79.8 $\pm$ 4.4 years (median: 79.0), with the majority of participants (983/1169, 84.1%) falling in the decade between 75 and 84 years of age. Of 1103 respondents, 45.9% indicated that they had been diagnosed with osteoporosis (506/1103) and 68.7% (388/565) of respondents reported that they were currently receiving treatment for osteoporosis. Data regarding physical characteristics indicated an average height of 156.6 $\pm$ 6.5 cm (median height: 156.0), an average weight of 64.2 $\pm$ 12.1 kg (median weight: 63.0) and an average body mass index (BMI) of 26.2 $\pm$ 6.5 (median BMI: 26.0). This BMI measurement equates to a classification of "overweight", according to the World Health Organization classification (apps.who.int).

Participants were asked several questions relating to their level of activity (see Appendix A). When asked if they participated in a regular activity program, 47.6% (557/1169) of participants indicated that they did participate in some type of activity program. Levels of activity were classified as moderate, strenuous or vigorous. Moderate physical activity was defined as activities such as housework, brisk walking, golfing, bowling, bicycling on level ground or gardening. Strenuous sports were defined as jogging, bicycling on hills, tennis, racquetball, swimming laps or aerobics while

vigorous activity was categorized as activities such as moving heavy furniture, loading or unloading trucks, shovelling, weight lifting, or equivalent manual labour. Participants were asked to indicate how many hours per week they devoted to activities representative of each level of activity, ranging from no time to greater than 30 hours (a total of 8 categories). Table VIII summarizes the distribution of each level of activity throughout the participants. Distribution of participants among the varying levels of MPA reflected a normal distribution. Vigorous and strenuous activity; however, were much less represented. The majority of respondents indicated that they had little participation in strenuous or vigorous activity. Indeed, only 36 participants (3.2%) indicated that they took part in any amount of regular strenuous activity. Likewise, only 41 participants (3.6%) responded that they were regularly involved in vigorous activity. The small number of participants that reported taking part in regular activity at a level considered strenuous or vigorous was insufficient to perform statistical analysis. As such, only the effect of varying frequency of MPA on bone mineral density and fracture rate was analyzed.

3.2.2 Effects of Secondary Factors

To address the possible confounding effects on bone density and fracture rate of secondary factors such as age, BMI, race and concurrent medication, data was collected regarding these variables. Data regarding age and BMI is summarized previously. Demographic information regarding race and ethnic background indicate that the vast

majority of participants were Caucasian, with fully 97.9% of participants (1144/1169) identifying themselves as "white" (see Table IX). Fourteen participants identified themselves as Chinese, while the remaining twelve participants were represented as south Asian (1), black (4), native/aboriginal (2), Filipino (1), southeast Asian (1), Latin American (1) and Japanese (2). One participant identified herself as both white and native/aboriginal.

Participants were asked to provide information regarding prescribed medications as part of this study. This data included information regarding medications that may or are known to affect bone metabolism, including hormone replacement therapy, corticosteroids and anti-resorptive therapies. For the purposes of this study, the data gathered regarding those participants who were currently taking either anti-resorptive therapy (e.g. bisphosphonates, SERMs) was most important. The results of this are summarized in Table X. Of the 1169 participants, 150 indicated that they were currently using some type of anti-resorptive medication. One-third (50) of that group indicated that they were using bisphosphonates (although the specific bisphosphonate used was not recorded); very few (5) indicated that they were currently taking SERMs.

3.2.3 Effects on Bone Mineral Density

3.2.3.1 The Effect of Moderate Physical Activity on Bone Mineral Density

Bone density was measured at five locations: the lumbar spine (L1-L4), the femoral neck, trochanter, Ward's triangle and total hip. Each participant was asked to indicate how many hours per week, on average, they spent participating in activities that would be considered of moderate intensity. To determine the effect of different levels of MPA on BMD, linear regression analysis was used. Table XI summaries the results from this analysis. Linear regression revealed positive coefficients for all BMD sites with the exception of the lumbar spine, which was associated with a negative coefficient. All positive coefficients represented statistically significant findings. The results indicate that, for all measured locations, save for the lumbar spine, a step increase in the amount of daily MPA (e.g. increasing activity from 2-3 hours per week to 4-6 hours per week) resulted in a statistically significant increase in BMD. The greatest effect was noted at the total hip (B=0.008 [0.002, 0.013], p=0.004) with the femoral neck (B=0.006 [0.002, 0.010], p=0.006), trochanter (B=0.006 [0.002, 0.011], p=0.004) and Ward's triangle (B=0.006 [0.001, 0.011], p=0.024) all noting a similar effect. At the lumbar spine, a negative coefficient was produced (-0.006), suggesting that there is a negative relationship between MPA and bone density, although this finding was not statistically significant (B=-0.006 [-0.013, 0.00], p=0.066).

3.2.3.2 The Effect of Secondary Factors on Bone Mineral Density

To evaluate the effect of secondary factors on bone mineral density, multiple regression analysis was utilized. The results from this analysis are summarized in Table XII. Bone mineral density was evaluated at each of five body sites: lumbar spine (L1-4), femoral neck, total hip, Ward's triangle and the greater trochanter. As noted following linear regression analysis, increasing MPA had a statistically significant positive effect on bone mineral density in the femoral neck (B=0.004 [0.000, 0.008], p=0.042), trochanter (B=0.005 [0.001, 0.009], p=0.018) and total hip (B=0.006 [0.001, 0.011], p=0.019), although not in the lumbar spine (B=-0.006 [-0.013, 0.000], p=0.067) or Ward's triangle (0.004 [-0.001, 0.009], p=0.132). MPA was associated a negative coefficient in the lumbar spine, a finding that, while not statistically significant, suggests that increasing MPA, when combined with other secondary factors, resulted in a decrease in the likelihood of a protective effect against BMD in the lumbar spine.

Information was gathered regarding current medications being used by participants. Of importance to this study was the use of anti-resorptive medications such as hormone replacement therapy (HRT), bisphosphonates and selective estrogen receptor modulators. The data regarding use of specific medications indicated that there was insufficient use of the various anti-resorptive medications to allow individual analysis (see Table X). As such, all anti-resorptive medications were pooled and those data were utilized in the analysis. Multiple regression analysis indicated that, for all five

BMD sites, the use of anti-resorptive therapy produced a positive regression coefficient, although only in the lumbar spine and femoral neck were these findings statistically significant. In the lumbar spine (B=0.040 [0.006, 0.074], p=0.021) and femoral neck (0.022 [0.001, 0.043], p=0.038), increases in MPA were associated with a protective effect on BMD. In the remainder of BMD sites, regression analysis indicated that there were positive effects on BMD, although not statistically significant (total hip: B=0.017 [-0.008, 0.042], p=0.175; Ward's triangle: 0.016 [-0.009, 0.041], p=0.213; trochanter: 0.004 [-0.017, 0.025], p=0.731).

The average (± SD) age for participants was 79.8 (± 4.4) years, with the majority of participants (84.1%) falling within the decade from 75 to 84 years of age. Multiple regression analysis including the participants' age as a variable produced uniformly negative coefficients, indicating a negative relationship between increasing age and BMD (see Table XII). In all hip-related BMD sites, increasing age was associated with statistically significant negative regression coefficients (femoral neck: B=-0.005 [-0.007, -0.003], p=0.001; total hip: B=-0.006 [-0.009, -0.004], p=0.001; Ward's triangle: B=-0.005 [-0.008, -0.003], p=0.001; trochanter: B=-0.004 [-0.006, -0.002], p=0.001). In the lumbar spine, increasing age was also associated with a negative coefficient, although this finding was not statistically significant (B=-0.002 [-0.005, 0.002], p=0.293).

Body mass index is a widely accepted method of evaluating body fat and body composition. Height, weight and BMI data were collected for each participant in this

study. The effect of BMI on BMD was included as part of the multiple regression analysis for this study. The results demonstrate that, for all BMD sites, BMI was associated with a positive and statistically significant coefficient (see Table XII). In the lumbar spine (B=0.011 [0.008, 0.014], p=0.001), the femoral neck (B=0.008 [0.006, 0.010], p=0.001), the total hip (B=0.011 [0.009, 0.013], p=0.001), Ward's triangle (B=0.007 [0.006, 0.009], p=0.001) and the trochanter (B=0.008, [0.007, 0.010], p=0.001), the regression coefficient suggested a positive associated between BMI and BMD, with the greatest effect noted in the total hip and lumbar spine.

3.2.4 Effects on Fracture Rate

Of the 1169 participants in this study, 575 reported a history of at least one fracture. While details of these fracture incidents were collected, there was insufficient data to allow for analysis of specific fracture sites. As such, all fracture data was pooled. Table IX summarizes the demographic data collected from the participants. The age, age breakdown, height, weight, BMI and racial/ethnic distribution in the fracture and non-fracture groups are very similar, and very closely mirror the overall demographics of the group as a whole.

3.2.4.1 The Effect of Frequency of Moderate Physical Activity on Fracture Rate

A total of 575 participants reported a prior fracture. Fractures were classified as back (vertebral), rib, pelvic, forearm, hip or other. Although data were provided for any fracture, for the purposes of this study, we limited our analysis to the first reported fracture. The presence or absence of fracture was the key outcome for this analysis. Also, because there was insufficient data to allow for analysis of specific fracture sites, this type of analysis was not performed. Instead, the presence of a fracture was sufficient for that participant to be included in the "fracture" group. To determine the effect of the frequency of MPA on fracture rate, univariate analysis using logistic regression was used to determine the odds ratio (OR) associated with fracture with increasing frequency of MPA, as compared to the lowest recorded level of activity ("never"), which represented inactive participants. Logistic regression analysis demonstrated that increasing frequency of MPA had no statistically significant impact on the OR for fracture (see Table XIII). OR ranged from 0.67 ([0.37, 1.24], p=0.20) for 2-3 hours per week to 1.28 ([0.67, 2.42], p=0.46) for 0-0.5 hours per week. All ORs for MPA, save for that associated with 4-6 hours of activity, were below 1, suggesting a trend towards decreased risk of fracture with greater activity.

3.2.4.2 The Effect of Secondary Factors on Fracture Rate

The effect of secondary factors on fracture rate was evaluated using both univariate and multivariable analysis. In each case, an OR was calculated for each variable reflecting that variable's effect on the likelihood of spontaneous fracture. Secondary variables included participant's age, BMI and the use of anti-resorptive medication. Univariate analysis demonstrated that neither age nor BMI had a significant effect on fracture rate. Age was associated with an OR of 1.01 ([0.98, 1.03], p=0.59), which would indicate essentially no change to the likelihood of fracture. BMI was associated with an OR of 0.99 ([0.97, 1.01], p=0.43), likewise indicating essentially no change in the odds of fracture. Neither of these findings, though, was statistically significant.

Anti-resorptive therapy was also evaluated using univariate analysis. The analysis produced an OR of 1.41 ([0.99, 1.99], p=0.05), indicating an increased risk of fracture associated with the use of anti-resorptive medication. This finding was the only statistically significant finding in the univariate analysis of secondary factors on fracture rate.

Multivariable analysis of the primary and secondary factors produced results similar to those from the univariate analysis. Multivariable analysis included all possible levels of MPA (as compared to inactive participants), age, BMI and use of anti-resorptive medication. As evident in the accompanying table (Table XIII), the OR calculated for each level of MPA in the multivariable analysis were very similar to those calculated in

the univariate analysis. Also, like the univariate analysis, none of these findings were statistically significant. Similarly, the ORs calculated from the multivariable analysis for age and BMI were unchanged from that of the univariate analysis. In each case, the upper limit of the 95% confidence interval extended very slightly further, although the actual OR value was unchanged. These findings were also not statistically significant.

Analysis of the effect of anti-resorptive medication on fracture rate in the multivariable analysis was also similar to the results of the univariate analysis. The OR calculated from the multivariable analysis was 1.46 ([1.02, 2.08], p=0.04), slightly greater than the 1.41 calculated in the univariate analysis and also statistically significant, suggesting an increased risk of fracture associated with the use of anti-resorptive therapy.

4.0 Discussion

Physical activity is known to be beneficial for a myriad of physiological reasons, including cardiovascular health and overall well-being. It is also known to provide protection against decreases in bone density and, as such, physical activity is routinely prescribed by clinicians for patients at risk for osteoporosis. Unfortunately, while widely recommended, there are no specific guidelines for clinicians regarding the type, duration or intensity of physical activity that is most appropriate for at-risk patients. As such, recommendations are often general and based largely on anecdotal evidence gathered from each practitioner's experience.

To address the lack of information regarding the prescription of exercise for at-risk patients, data from the Canadian Multicentre Osteoporosis Study was analyzed, with the objective of determining the most appropriate type, duration and intensity of physical for the prevention of bone loss and fracture. With the average female lifespan in Canada currently at 83 years (Fang & Millar, 2009), clinicians must be concerned not only with the bone health of their female patients in the first few years following menopause but in the decades following menopause. This study, by focusing on women 75 years of age and older, provides important data regarding bone health 25 years or more following the onset of menopause.

4.1 Physical Activity in Women Aged 75 and Over

From the initial cohort of 9423 participants, a total of 1169 female participants aged 75 and over were identified. Anthropometric analysis indicated that the height, weight and body mass index for these participants represented a normal distribution, suggesting that the study cohort could be considered to statistically represent that population as a whole.

The results of this study provide an important perspective regarding the activity level of Canadian women. The results show that the vast majority of participants reported some level of involvement in moderate physical activity, i.e. that which could be considered activity over and above the general activity of day-to-day life, such as brisk walking, golfing, housecleaning, etc. Statistics from both Canada and the United States suggest that over half of the elderly population is inactive, with women more likely to be inactive than men. In Canada, up to 64% of female seniors were inactive (www.phac-aspc.gc.ca) while in the United States, the Centers for Disease Control reported that over 60% of senior women were not meeting the minimum recommendations for regular physical activity (approximately 15-20 minutes daily) (cdc.gov). In this study, a large proportion (71.7%) of participants reported that they take part in these types of activity for at least 4 hours each week; this equates to approximately 35 minutes per day. This suggests that the women in this study are active at a level above the average for Canadian women. A total of 28.3% of

respondents were active for less than the national average, with 14.4% reporting that they are moderately active for less than 1 hour each week. Bone health notwithstanding, the fact that close to 15% of women over age 75 are moderately active for less than an average of 10 minutes each day is an alarming statistic when other health concerns such as cardiovascular health and mental health and acuity are considered. Physical activity is essential for the maintenance of cardiovascular health but is also important in the maintenance of mental health and acuity (www.phac-aspc.gc.ca, cdc.gov) and therefore should be an important part of every senior citizen's life in order to improve and maintain quality of life.

From a clinical standpoint, though, an encouraging finding from this study is that close to three-quarters of participants (71.7%) reported that they are moderately active for at least 4 hours per week. Whether these women are active on the advice of their physician or doing so by their own volition, the fact that they are active to this degree should be viewed as a positive sign.

4.2 Effects on Bone Mineral Density

The findings of this study indicate that MPA can help to improve bone density in post-menopausal women, although these improvements were limited largely to the hip region. These findings echoes that of similar studies that have shown that the benefits from exercise or physical activity are generally noted in the hip but not in the lumbar spine. Bolton et al. (2012) demonstrated this effect in a recent randomized, controlled trial of post-menopausal women. Over the course of one year, participants either took part in a general exercise program that included 60-minute exercise training three times each week, while control participants continued in their normal daily routine. The exercise training group performed tasks including resistance training, moderately intense exercise and training. The authors found that there was a positive (although not statistically significant) effect on bone density in the hip region but a negative (although also not statistically significant) decrease in bone density in the lumbar spine. The measured change in BMD measurement in this study closely approximately that of the Bolton study. These findings are likely not unexpected, as the benefit gained from resistance or impact exercise relates largely to the effect of loading on the skeleton (Kelley et al., 1998; Kerr et al., 1996; Bravo et al., 1996). The hip joint will absorb the majority of the forces applied during land-based exercise, while the lumbar spine will absorb very little physical force. As such, the majority of exercises are designed to address the hip, an important fact due to the simple fact that the hip, being the

structure that absorbs more force during these type of tasks, is also the structure more likely to be damaged (i.e. to suffer a fracture).

The results from this study indicate that there was a statistically significant improvement in bone density associated with a step increase in the amount of MPA performed on a daily basis. The essential question, then, is: is this improvement clinically important? The most common treatment for osteoporosis are the bisphosphonates. These medications have been shown to induce an average increase of approximately 0.019 g/cm^2 following a one-year course of treatment. The findings from this study indicate that the improvements in bone density range from 0.006 g/cm^2 (for femoral neck, Ward's triangle and the trochanter) to 0.008 g/cm^2 (for the total hip). These improvements represent between 30-50% of the improvement expected from bisphosphonate treatment. Warming et al., (2002) performed a prospective study to evaluate the normal changes in BMD in the forearm, hip, spine and total body, in otherwise healthy men and women. They used DXA measurements at 2 year intervals in over 500 participants and found that, in women, the only pre-menopausal bone loss was noted at the hip (<0.003 g/cm^2/year). In women after menopause, though, bone loss ranging from 0.002 g/cm^2/year to 0.006 g/cm^2/year was noted in all sites. The greatest post-menopausal bone loss was found in forearm, where 1.2% (0.006 g/cm^2/year) was lost following menopause, a change that remained constant throughout life. While the changes noted in this study do not meet the level of bisphosphonate treatment, it appears that an increase in the amount of MPA on a daily basis may be enough to offset

the normal bone loss that occurs following menopause. If this is indeed the case, the importance of encouraging elderly patients to remain active on a daily basis is underscored.

When considering the effect of secondary factors on BMD, the results indicate that, perhaps expectedly, the use of anti-resorptive therapy reversed the negative effect on BMD in the lumbar spine and increased the protective effect in each of the other BMD sites, although only the improvements in the lumbar spine and femoral neck were statistically significant. It is not surprising that anti-resorptive therapy counteracted the observed decrease in BMD noted in the lumbar spine and result instead in a positive regression coefficient and a relative increase in BMD. In all other sites, increases in BMD ranged from a relatively unaltered change of 0.004 g/cm^2 in the trochanter to a significant improvements of 0.022 g/cm^2 (femoral neck) and 0.040 g/cm^2 (lumbar spine).

Other secondary effects that were considered in this study included body mass index (BMI) and participant age. Because race and/or ethnicity are known to impact on bone loss and the incidence of osteoporosis, race was also initially intended to be considered as a secondary factor. Analysis of the database; however, indicated that the large majority of participants (97.9%) identified themselves as "white", which essentially made an examination of the effect of race on bone loss impossible. This observation is addressed in greater detail in Section 4.4 (Limitations). The relationship between BMI and BMD indicated that increased BMI resulted in a relative protective effect on bone

density. The regression coefficients for this analysis were all positive, ranging between 0.007 g/cm^2 (Ward's triangle) to 0.011 g/cm^2 (lumbar spine and total hip). These findings support those of several authors (Heaney & Rafferty, 2008; One, 2008; Reid, 2008), who have also observed that increased BMI is associated with a lower risk of osteoporosis. Arab et al., (2012), in a survey of post-menopausal women, found that lower BMI was a statistically significant risk factor for osteoporosis while increased BMI was a significant protective factor. They noted that bone density is generally lower in patients with a BMI between 22 and 24, as compared to a patient with a BMI of between 26 and 28. They also confirmed a prior finding that a 4-8% greater lumbar spine BMD and 8-9% greater hip BMD can be expected in patients with a BMI of 30 or more (Wardlaw, 1996; Arab et al., 2012).

An important finding from this study was to observation that, with increased age, there is a negative correlation with bone mineral density. Multiple regression coefficients for all BMD sites were negative, with all, save for lumbar spine, being statistically significant. While this finding may merely be interpreted as an expected decrease in bone density with age, the fact that the participants were all over age 75 when beginning the study provides an important perspective. With the increase in lifespan, the average Canadian women can expect to live close to a decade following her 75th birthday. If bone density continues to fall with each successive year, as suggested by this analysis, then the risk of fracture is also expected to increase with increasing age. This would be expected to increase the already significant stress placed on the health

care system and should serve to underscore the importance of promoting continued activity for females well into their ninth decade.

4.3 Effects on Fracture Rate

Bone mineral density, in studies such as this, acts as a surrogate outcome, as the more pressing clinical problem is that of fracture. The difficulty with using fracture as the primary outcome measure, though, is that the power required to elicit meaningful statistical findings is generally prohibitive. The CaMos dataset contains information on fracture history, which allows analysis of the incidence of fracture, which can then be correlated to variables such as MPA, BMI, age and anti-resorptive medication.

Analysis of the demographics of those who reported fracture versus those who did not revealed two essentially identical cohorts (see Table IX). As such, there does not appear to be any specific characteristic that pre-disposes participants to fracture. Indeed, fracture rate among the age groups, which could be expected to result in greater fracture rate, was also essentially identical. As discussed previously, the racial make-up of the cohort was too homogenous to allow for sub-group analysis based on racial or ethic classification. This would have been a helpful analysis, as there is much evidence to indicate that certain racial/ethnic groups are more susceptible to osteoporosis and therefore fracture (osteoporosis.ca).

Univariate and multivariable analysis of the fracture rate did not elicit any statistically significant findings, save for the effect of anti-resorptive medication on fracture rate. The level of MPA was used as a predictor for fracture in both analyses, with each level of MPA being compared against the lowest level (inactive controls). The

resulting odds ratios were generally below 1, suggesting that increased MPA decreases the fracture risk, but these findings were not statistically significant. The OR values for univariate and multivariable analysis were very similar, though, with each value including 0 in its 95% confidence interval. The most interesting finding may be that the OR for fracture in the univariate analysis of the lowest level of activity (less than 0.5 hours per week) was 1.28, suggesting an increased risk of fracture (findings not significant). Increasing MPA to 2-3 hours per week resulted in an OR below 1. This suggests that even a small amount of physical activity, perhaps as little as 10-15 minutes each day, could be sufficient to protect against fracture.

In this analysis, secondary factors such as age and BMI had no effect on the odds of fracture. In each case, the calculated OR was equal in both univariate and multivariable analysis. Also, with each value being essentially 1 (BMI: 0.99, age: 1.01), there is no demonstrable impact of age or BMI regarding the rate of fracture in this study.

Calculation of the odds ratio associated with the use of anti-resorptive therapy revealed an increased risk of fracture. This, of course, is counter to the expected results from the use of anti-resorptive therapy. Anti-resorptive medications such as bisphosphonates are a cornerstone of pharmacological treatment for osteoporosis because of their ability to slow bone resorption and decrease the rate of loss of bone density. As such, they are integral in the prevention of fracture. Recently, there have

been concerns that long-term bisphosphonate use can lead to an increase in atypical subtrochanteric femoral fracture risk (Yoon et al.., 2011), due to increased fragility. The evidence surrounding a link between these atypical fractures and bisphosphonate use is certainly not definitive and, to date, there is no protocol in place to manage these fractures. It is conceivable that the observed increase in OR for fracture associated with anti-resorptive use is due to this increased fragility of bone. Unfortunately, no data were available from the study information to indicate the amount of time that each particular participant had been taking these medications. As a result, it is not possible to determine if this is the cause of the increased odds of fracture associated with anti-resorptive therapy.

Because the reporting of fracture was retrospective in nature, it is possible that the apparent increase in fracture risk associated with anti-resorptive use is a result of participants having been prescribed anti-resorptive medication following a fracture. If the majority of participants using anti-resorptive therapy had also suffered a prior fracture, it would be expected that the majority of these patients would currently be using anti-resorptive therapy in an attempt to limit the possibility of future fracture. As a result, there would be a strong association between the use of anti-resorptive therapy and a reported fracture.

4.4 Limitations

This study has several limitations which prevent the direct application of its findings to clinical settings.

The homogeneity of the cohort with respect to racial and/or ethnicity make-up makes application of the results difficult. With 97.9% of participants identifying themselves as "white", the ability to determine racial differences is impossible. The CaMos cohort, while sampling from a large proportion of the Canadian population as a whole, does not fully reflect Canadian society as a whole. Indeed, taking the entire CaMos cohort into account, 94.9% of the 9423 participants identified themselves as white. While this may a valuable factor when considering that Caucasian women are at a higher risk of osteoporosis as compared to other racial groups such as blacks or hispanics, the ability to apply the findings to an increasingly racially diverse Canada is limited by these demographics.

The initial plan for this study was to compare physical activity considered part of normal day-to-day activity with more strenuous activity, to determine the relative effects on bone density and fracture rate. The observation that over 96% of the study cohort took part in no vigorous or strenuous activity whatsoever made that analysis impossible. It is unfortunate that more participants were not active to these greater degrees, as it would have better reflected the potential role of exercise in the protection against fracture. However, this finding is mitigated by the fact that beneficial effects

were noted simply by increasing the amount of MPA performed each day, which is likely easier in it implementation than incorporating a vigorous exercise program into the routines of elderly patients.

An important factor in this study was the use of anti-resorptive medication by some participants. These medications certainly have a positive effect on bone density; however, their use, in combination with exercise and activity, is an important clinical consideration, especially when clinicians are faced with the choice of prescribing medication for their patients. Of the 1169 participants in this study, only 150 reported currently using anti-resorptive medication. Of those, only 50 were using bisphosphonates, the most common anti-resorptive medication, and a mere 5 were using SERMs. This represents less than 0.5% of the entire study cohort. The lack of statistically significant findings with respect to the use of anti-resorptive medication is likely due to the low usage. There was simply not enough data to elicit meaningful results and conclusions.

Fracture, or the prevention of fracture, is the ultimate goal of therapy or interventions regarding osteoporosis. As such, the most valuable information is that which provides direct evidence that an intervention prevents fracture. The essential limitation with this approach; however, is that the statistical power required to elicit this type of result is prohibitive. Therefore, investigators are left using surrogate outcomes such as bone density or are forced to look retrospectively at reported fractures to

determine if an effect exists. This is an important methodological limitation in this study. While approximately half of the participants of this study reported a fracture, the self-reporting nature of fractures did not have a timeline; therefore fractures that occurred years prior could have been included. Attempts at analysis of data for fracture sites common in osteoporosis (vertebrae, hip, wrist) were inconclusive, due to low number of reported fractures. As such, presence or absence of fracture was determined to be the course of action for this study. To provide more comprehensive results, prospective studies should be attempted whenever possible. Alternatively, further study could use the subsequent questionnaires administered to each participant and track whether any fractures had occurred in the time between questionnaire administration.

One final limitation identified in this study relates to the potential limitations associated with patient self-reporting. While commonly used surveys are generally validated and therefore provide useful and accurate information (Hagiwara et al., 2008; Ngai et al., 2012; Svege et al., 2012), there is a concern that, when asked to quantify an activity, respondents may over or under-estimate their participation, thereby affecting the results. Prince et al. (2008) demonstrated this in their systematic review of direct versus self-report measures for assessing physical activity in adults. They found that correlations between self-report and direct report measures were generally low-to-moderate, ranging between -0.71 and 0.96. They further noted that no clear pattern emerged for the mean differences between self-report and direct measures of physical

activity. As a result, they concluded that the method of measurement may have a significant impact on the observed levels of physical activity, having noted that self-report measures of physical activity were both higher and lower than directly measured levels. As such, the findings in the current study, based on the self-reported nature, may be subject to errors associated with the manner in which the data was collected.

5.0 Conclusions

The results of this study indicate that the amount of moderate physical activity in which patients take part each day can have a significant impact on the maintenance of bone density. Increasing the amount of time spent daily on generally "normal" tasks can have a potentially important protective effect on bone density in regions susceptible to fracture. While exercise is certainly valuable in promoting improved bone density, the findings of this study indicate that a specific exercise program may not be absolutely necessary to impart some level of protection against decreased bone density. Compliance with exercise regimens in the elderly is potentially problematic; this study indicates that, by increasing the amount of normal activity, participants may be able to improve their bone density without having to begin a specific exercise regimen.

5.1 Future Direction

Future studies should address areas of deficiency noted in this study and expand upon the findings of this study. To determine the effect of increasing physical activity on fracture rate, future studies should attempt compare fracture incidence in each participant by tracking those fractures that are reported in the time between administration of each questionnaire. This may provide more direct evidence of a link between fracture rate and activity level.

Possible confounding factors considered in this study included age, BMI and anti-resorptive medication. Based on the impact that dietary intake of calcium can have on bone density and overall bone health, subsequent studies should attempt to take into account these factors. Perhaps by stratifying participants based on their dietary intake of minerals such as calcium, patterns would emerge reflecting the value of dietary supplementation in addition to physical activity.

Finally, this study evaluated the effect of physical activity on women 25-30 years after menopause. An interesting question raised is whether or not increased activity in the first 5-10 years following the onset of menopause has any type of effect on bone health two decades later. The CaMos database contains information regarding the activity level of participants in various decades of their life, including in their 50's. Analysis of this data would provide information regarding the effect of physical activity in the first few years following menopause has any lasting effect on bone density or long-term protective effect against fracture.

FIGURES

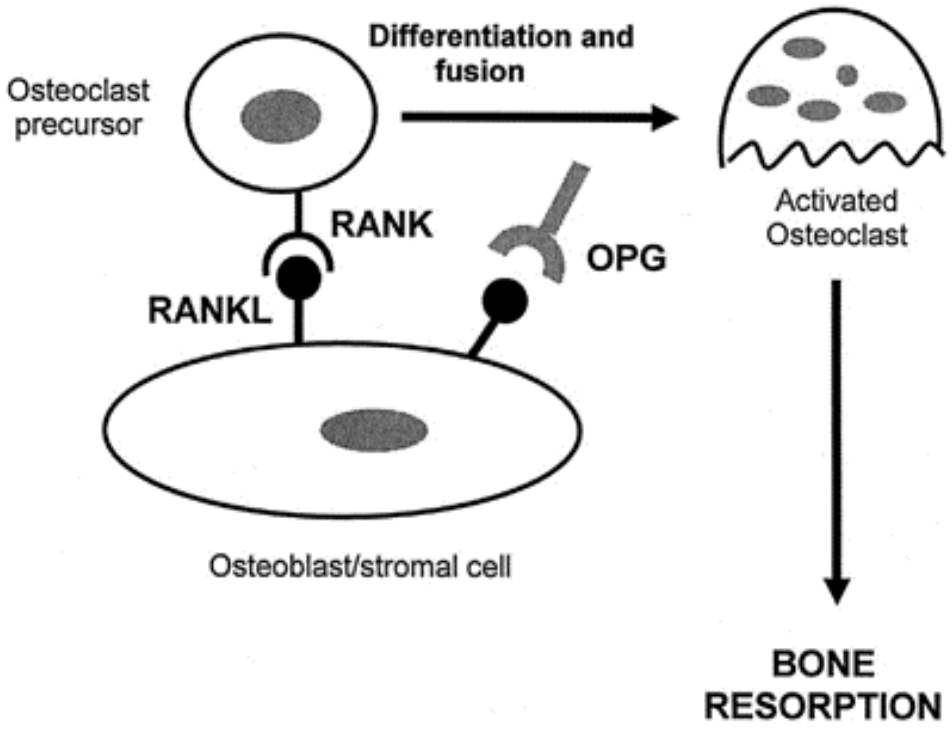

Figure 1. Schematic representation of the OPG-RANK-RANKL system. OPG: osteoprotegrin, RANK: receptor activator of nuclear factor kappa B, RANKL: receptor activator of nuclear factor kappa B ligand.

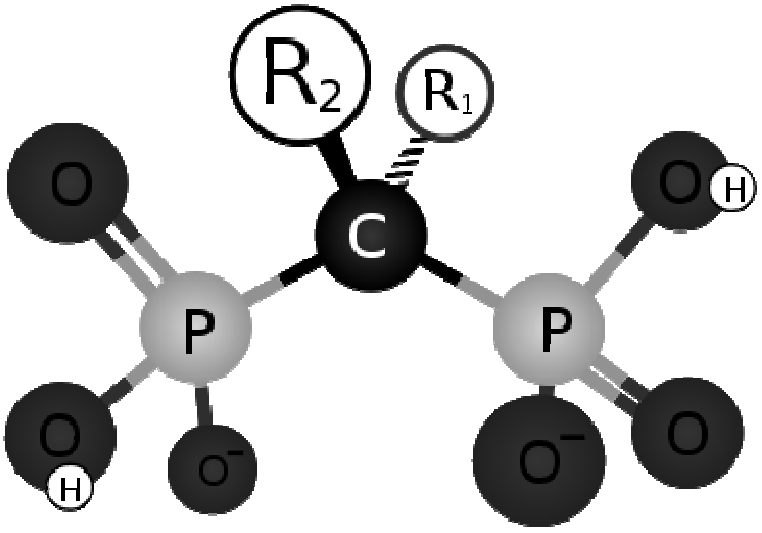

Figure 2. Schematic representation of the chemical structure of the bisphosphonate class of medications. R_1 and R_2 represent variable side chains. Each different bisphosphonate medication is distinctive in its side chains. O: oxygen, P: phosphorus, H: hydrogen, C: carbon.

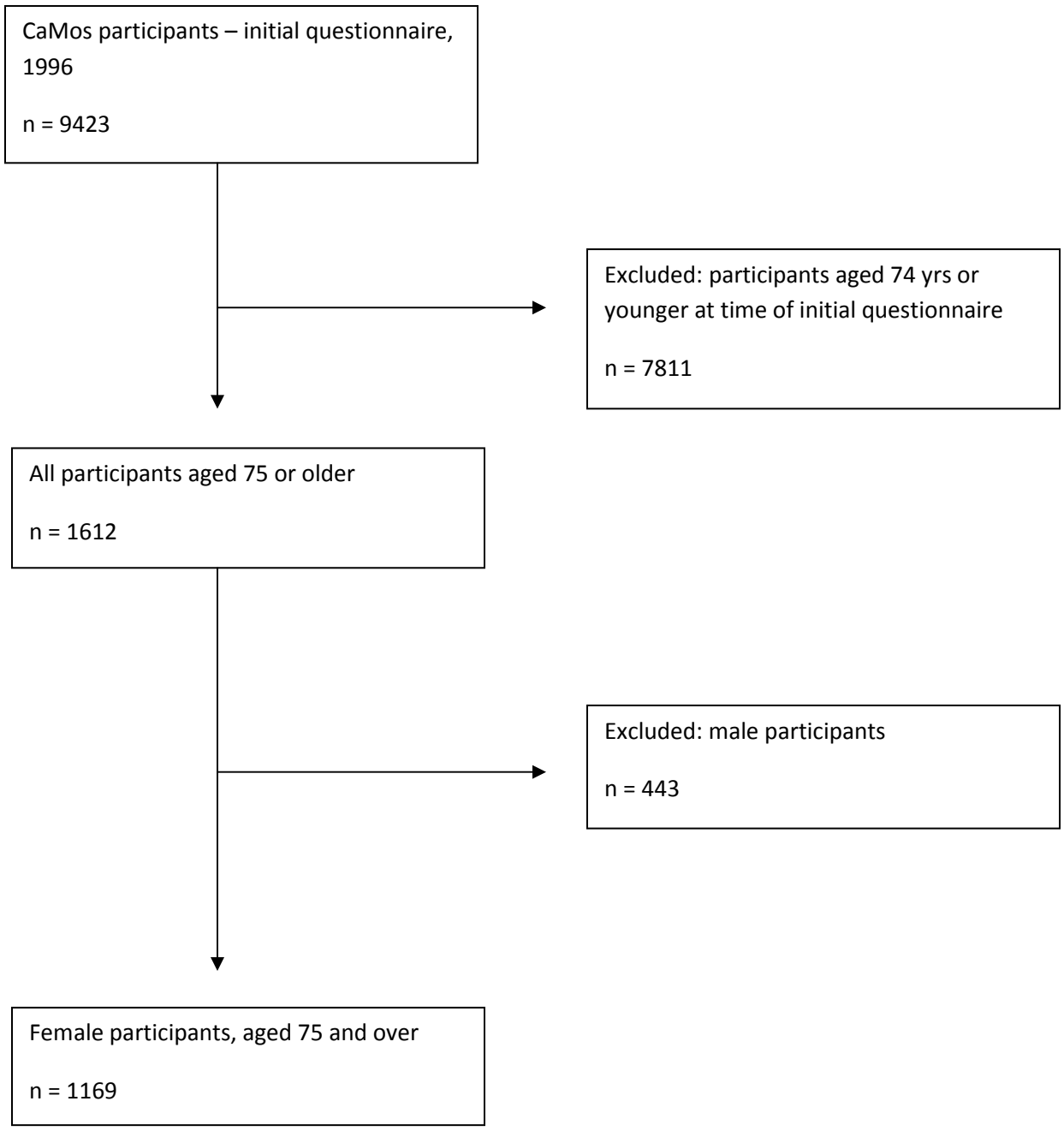

Figure 3. CONSORT flow chart summarizing participant eligibility criteria and resulting number of participants.

TABLES

Table I. Examples of conditions associated with a diagnosis of secondary osteoporosis (AACE Guideline, 2003; Kelman & Lane, 2005; Mann et al., 2009; Holick, 2007; Migliaccio et al., 2009; van Staa et al., 2002).

Category	Condition	
Genetic	Cystic fibrosis Ehlers-Danlos syndrome Glycogen storage disease Gaucher disease Hemochromatosis Homycystinuria Hypophosphatasia	Idiopathic hypercalciuria Marfan syndrome Menkes steely hair syndrome Osteogenesis imperfecta Porphyria Riley-Day syndrome
Hypogonadal states	Androgen insensitivity Anorexia nervosa/bulimia nervosa Female athlete triad Hyperprolactinemia	Panhypopituitarism Premature menopause Turner syndrome Klinefelter syndrome
Endocrine disorders	Acromegaly Adrenal insufficiency Cushing syndrome Estrogen deficiency Diabetes mellitus	Hyperparathyroidism Hyperthyroidism Hypogonadism Pregnancy Prolactinoma
Deficiency states	Calcium deficiency Magnesium deficiency Protein deficiency Vitamin D deficiency Bariatric surgery Celiac disease	Gastrectomy Malabsorption Malnutrition Parenternal malnutrition Primary biliary cirrhosis
Inflammatory diseases	Inflammatory bowel disease Anklyosing spondylitis	Rheumatoid arthritis Systemic lupus erythematosus
Medications	Anticonvulsants Antipsychotics Antiretrovirals Aromatase inhibitors Chemotherapeutic or transplant agents Furosemide Glucocorticosteroids	Heparin Hormonal/endocrine therapies Lithium Methotrexate Selective serotonin reuptake inhibitors Thyroxine
Miscellaneous	Alcoholism Amyloidosis Chronic metabolic acidosis Congestive heart failure Depression Emphysema Chronic or end-stage renal disease Chronic liver disease HIV/AIDS	Idiopathic calciuria Idiopathic scoliosis Immobility Multiple sclerosis Ochronosis Organ transplantation Pregnancy/lactation Sarcoidosis Weightlessness

Table II. Summary of risk factors for decreased bone density.

Category	Risk Factors
Demographic	Advanced age (> 50 years) Female gender Ethnicity (Caucasian or Asian) Thin or small body stature (body weight < 55-60 kg) Family history
Endocrine	Amenorrhea Late menarche Early menopause Post-menopause Androgen/estrogen deficiency
Lifestyle	Physical inactivity, immobilization Alcohol use Tobacco use Calcium deficiency
Pharmacological	Anticonvulsants Glucocorticosteroids Thyroid supplements Heparin Chemotherapeutic agents Insulin

Table III. Summary of T-score relationship to osteoporosis diagnosis.

Diagnosis	T-score
Normal bone density	Greater than -1
Osteopenia	Between -1 and -2.5
Osteoporosis	Less than -2.5 and/or 1 confirmed osteoporotic fracture

Table IV. Summary of selection of SERMs and their respective effect on various tissues.

Generic Name	**Use(s)**	**Effect/location**
Clomifene	Anovulation	Antagonist at hypothalamus
Femarelle	Menopausal symptoms, osteoporosis	Agonist at brain and bone
Ormeloxifene	Contraception	Agonist at bone; antagonist at breast and uterus
Raloxifene	Osteoporosis, breast cancer	Agonist at bone; antagonist at breast and uterus
Tamoxifen	Breast cancer	Agonist at bone and uterus; antagonist at breast
Toremifene	Breast cancer	Agonist at bone and uterus; antagonist at breast
Lasofaoxifene	Osteoporosis, breast cancer, vaginal atrophy	Agonist at bone; antagonist at breast and uterus

Table V. Summary of categories of exercise used by Howe et al. (2011) in their Cochrane Review of the effect of exercise on bone density in post-menopausal women.

Category	**Examples**
Static weight bearing (SWB)	Standing on one leg for up to three minutes per day
Dynamic weight bearing exercise, low force (DWBLF)	Walking, Tai-chi
Dynamic weight bearing exercise, high force (DWBHF)	Jogging, running, jumping, dancing and vibration platform
Non-weight bearing exercise, low force (NWBLF)	Low load, high repetition strength training
Non-weight beaing exercise, high force (NWBHF)	Progressive resisted strengthening exercise
Combination (COMB)	More than one of the above exercises

Table VI. Canadian Multicentre Osteoporosis Study site list.

Site	**Affiliated post-secondary institution**
Vancouver	University of British Columbia
Calgary	University of Calgary
Saskatoon	University of Saskatchewan
Toronto	University of Toronto
Hamilton	McMaster University
Kingston	Queen's University
Quebec	Laval University
Halifax	Dalhousie University
St. John's	Memorial University

Table VII. Summary of selected demographic and anthropometric characteristics of the study participants.

Characteristic	**Result (n=1169)**
Age *(mean ± SD) years*	79.84 ± 4.43
Age breakdown (number) years	
75-79	646 (55.3%)
80-84	337 (28.8%)
85-89	143 (12.2%)
90-94	39 (3.3%)
95+	4 (0.3%)
Height in cm *(mean ± SD)*	156.57 ± 6.48
Weight in kg *(mean ± SD)*	64.20 ± 12.14
Body Mass Index (BMI) *(mean ± SD)*	26.19 ± 6.48
Osteoporosis diagnosis? *(number)*	
Yes	506
No	597
Osteoporosis treatment? *(number)*	
Yes	388
No	177

SD: standard deviation
BMI: body mass index

Table VIII. Summary of level of participation in each category of activity for female participants aged 75 years and older.

	Level of participation							
	Never	**0.5-1 hr**	**2-3 hrs**	**4-6 hrs**	**7-10 hrs**	**11-20 hrs**	**21-30 hrs**	**31+ hrs**
	Count (%)	*Count (%)*	*Count (%)*	*Count (%)*	*Count (%)*	*Count (%)*	*Count (%)*	*Count (%)*
Moderate	75 (6.4)	94 (8.0)	163 (13.9)	189 (16.2)	222 (19.0)	219 (18.7)	130 (11.1)	76 (6.5)
Strenuous	1132 (96.8)	15 (1.3)	17 (1.5)	2 (0.2)	1 (0.1)	1 (0.1)	n/r[1]	n/r
Vigorous	1127 (96.4)	31 (2.7)	8 (0.7)	2 (0.2)	n/r	n/r	n/r	n/r

1. no respondents for this category

Table IX. Summary of selected demographic and anthropometric characteristics of the study participants, sub-grouped according to presence or absence of previous fracture.

Characteristic	**Fracture (n=575)**	**No fracture (n=594)**
Age *(mean ± SD) years*	79.92 ± 4.54	79.77 ± 4.33
Age breakdown (number, %) years		
75-79	318 (55%)	328 (55%)
80-84	158 (27%)	179 (30%)
85-89	76 (13%)	67 (11%)
90-94	20 (3%)	19 (3%)
95+	3 (0.5%)	1 (0.1%)
Height in cm *(mean ± SD)*	157.01 ± 6.59	156.15 ± 6.37
Weight in kg *(mean ± SD)*	64.27 ± 12.29	64.13 ± 12.01
Body Mass Index (BMI) *(mean ± SD)*	26.08 ± 4.79	26.30 ± 4.74
Race		
White	567[1]	577
Chinese	6	8
South Asian *(e.g. East Indian, Pakistani)*	0	1
Black *(e.g. African, Haitian, Jamaican)*	1	3
Native/Aboriginal	1[1]	1
Arab/West Asian	0	0
Filipino	0	1
South East Asian *(e.g. Cambodian, Indonesian)*	0	1
Latin American	1	0
Japanese	0	2
Korean	0	0
Medication		
Currently taking antiresorptive medication *(number, %)*	85 (15%)	65 (11%)

SD: standard deviation
BMI: body mass index
1. one respondent identified herself as both “white” and “native/aboriginal”

Table X. Distribution of selected pharmacological interventions used by study participants.

Medication	Status – currently taking?			
	Yes	%	No	%
Hormone replacement therapy (HRT)	102	8.7	1067	91.3
Bisphosphonates	50	4.3	1119	95.7
Selective Estrogen Receptor modulators (SERMs)	5	0.4	1164	99.6
Antiresorptive therapy	150	12.8	1019	87.2
Corticosteroids	38	3.3	1131	96.7

HRT: hormone replacement therapy
SERM: selective estrogen receptor modulator

Table XI. Effect of increasing amounts of daily moderate physical activity on bone density at various body sites in study participants.

Site	Estimated Coefficient (B)	95% Confidence Interval	p-value
Lumbar spine	-0.006	[-0.013, 0.00]	0.066
Femoral neck	0.006	[0.002, 0.010]	0.006*
Total hip	0.008	[0.002, 0.013]	0.004*
Ward's triangle	0.006	[0.001, 0.011]	0.024*
Trochanter	0.006	[0.002, 0.011]	0.004*

* statistically significant

Table XII. Results from multiple regression analysis of the relative effects of moderate activity and secondary factors on bone mineral density at various body sites.

Variable	BMD site	Coefficient (B), 95% CI	p-value
Moderate activity	Lumbar spine (L1-4)	-0.006 [-0.013, 0.000]	0.067
	Femoral neck	0.004 [0.000, 0.008]	0.042*
	Total hip	0.006 [0.001, 0.011]	0.019*
	Ward's triangle	0.004 [-0.001, 0.009]	0.132
	Trochanter	0.005 [0.001, 0.009]	0.018*
Anti-resorptive therapy	Lumbar spine (L1-4)	0.040 [0.006, 0.074]	0.021*
	Femoral neck	0.022 [0.001, 0.043]	0.038*
	Total hip	0.017 [-0.008, 0.042]	0.175
	Ward's triangle	0.016 [-0.009, 0.041]	0.213
	Trochanter	0.004 [-0.017, 0.025]	0.731
Body mass index	Lumbar spine (L1-4)	0.011 [0.008, 0.014]	0.001*
	Femoral neck	0.008 [0.006, 0.010]	0.001*
	Total hip	0.011 [0.009, 0.013]	0.001*
	Ward's triangle	0.007 [0.006, 0.009]	0.001*
	Trochanter	0.008 [0.007, 0.010]	0.001*
Age (years)	Lumbar spine (L1-4)	-0.002 [-0.005, 0.002]	0.293
	Femoral neck	-0.005 [-0.007, -0.003]	0.001*
	Total hip	-0.006 [-0.009, -0.004]	0.001*
	Ward's triangle	-0.005 [-0.008, -0.003]	0.001*
	Trochanter	-0.004 [-0.006, -0.002]	0.001*

* statistically significant

Table XIII. Results of univariate and multivariable regression analysis of moderate activity level and secondary factors to determine odds ratio for fracture (as compared to lowest level of activity reported (inactive)).

	Univariate Analysis		**Multivariable Analysis**	
Predictor	**OR [95% CI]**	**p-value**	**OR [95% CI]**	**p-value**
Activity level [1] (hr/wk)				
0-0.5	1.28 [0.67, 2.42]	0.46	1.05 [0.52, 2.13]	0.88
2-3	0.67 [0.37, 1.24]	0.20	0.66 [0.35, 1.26]	0.21
4-6	1.09 [0.63, 1.87]	0.77	1.06 [0.60, 1.86]	0.85
7-10	0.90 [0.53, 1.53]	0.70	0.85 [0.49, 1.48]	0.57
11-20	0.93 [0.55, 1.57]	0.79	0.94 [0.55, 1.60]	0.82
21-30	0.77 [0.46, 1.30]	0.32	0.77 [0.45, 1.32]	0.34
>31	0.98 [0.56, 1.72]	0.94	0.98 [0.54, 1.76]	0.94
Anti-resorptive medication	1.41 [0.99, 1.99]	0.05*	1.46 [1.02, 2.08]	0.04*
BMI	0.99 [0.97, 1.01]	0.43	0.99 [0.97, 1.02]	0.52
Age (years)†	1.01 [0.98, 1.03]	0.59	1.01 [0.98, 1.04]	0.57

* statistically significant

† expected change in 1 year

1. as compared to the minimum level of reported activity

BMI: body mass index

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APPENDIX A

Canadian Multicentre Osteoporosis Study (CaMos)

Initial Questionnaire, 1996

Respondent I.D. # _____

Canadian Multicentre Osteoporosis Study
Étude canadienne multicentrique sur l'ostéoporose

QUESTIONNAIRE

Respondent I.D. # _____

CaM*os*
Canadian Multicentre Osteoporosis Study

RESPONDENT

*PROVINCIAL HEALTH # _____

NAME _____ _____
Last (Maiden in Quebec) First

_____
* ETHNIC NAME (Last) (First)

ADDRESS _____ _____ _____
No. Street Apt. #

_____ _____ | | | | | | | |
City Province Postal Code

TELEPHONE # ( ) _____
Area Code

DO YOU PLAN TO MOVE IN THE NEXT YEAR? ☐ YES ☐ NO

└→ When? _____

CONTACT PERSON *

NAME _____ _____
Last (Maiden in Quebec) First

ADDRESS _____ _____ _____

_____ _____

TELEPHONE # ( ) _____ ( ) _____
Home Work

RELATION TO RESPONDENT: _____

Respondent I.D. # _____

*See notes in manual

CaM*os*
Canadian Multicentre Osteoporosis Study

CENTRE NUMBER ⌊⊥⌋

INTERVIEWER ID # _____ NAME _____

LOCATION OF INTERVIEW ☐ HOSPITAL ☐ HOME ☐ OTHER _____

DATE OF INTERVIEW _____ / _____ / _____
Day Month Year

TIME BEGAN ⌊⊥⌋ HRS ⌊⊥⌋ MIN.

TIME ENDED ⌊⊥⌋ HRS ⌊⊥⌋ MIN.

RESPONDENT

NUMBER OF RESIDENTIAL TELEPHONE # IN HOME ⌊⊥⌋

IF RESPONDENT ASSISTED, BY WHOM? _____

LANGUAGE OF INTERVIEW ☐ FRENCH ☐ ENGLISH ☐ OTHER _____

HEARING IMPAIRMENT ☐ YES ☐ NO VISUAL IMPAIRMENT ☐ YES ☐ NO

FIRST INTERVIEW (PHASE I) SCHEDULED _____ D/M/Y ☐ INCOMPLETE ☐ COMPLETED _____ D/M/Y

CLINICAL ASSESSMENT	DEXA	ULTRASOUND	BLOOD	URINE	X-RAY
	☐ Yes	☐ Yes	☐ Yes	☐ Yes	☐ Yes
	☐ No	☐ No	☐ No	☐ No	☐ No
			☐ N/A	☐ N/A	☐ N/A

RESULTS TO BE SENT TO PHYSICIAN ☐ YES ☐ NO FOLLOW UP ☐ YES ☐ NO

CAMOS DATA ENTRY DATE _____ / _____ / _____
Day Month Year

COMMENTS _____

* See note manual

To begin the questionnaire I would like to ask you general questions about yourself.

1. SOCIO-DEMOGRAPHIC INFORMATION

1.1 Sex: ☐ Male ☐ Female

1.2 Date of Birth: _____ / _____ / _____ (Present age ____)
Day Month Year

1.3 In what country were you born? _____

1.4 a) * How many years have you lived in Canada? ____ years

b) If less than 5 years, Country where respondant has lived for the most number of years _____

1.5 * To which ethnic or cultural group(s) did your ancestors belong?
(*For example: French, British, Chinese, etc.*)

(*Do not read list. Mark all that apply*)

- ☐ Black
- ☐ Canadian
- ☐ Chinese
- ☐ Dutch (Netherlands)
- ☐ English
- ☐ French
- ☐ German
- ☐ Inuit/Eskimo
- ☐ Irish
- ☐ Italian
- ☐ Jewish
- ☐ Métis
- ☐ North American Indian
- ☐ Polish
- ☐ Portuguese
- ☐ Scottish
- ☐ South Asian
- ☐ Ukrainian
- ☐ Other ethnic or cultural group(s) (Specify _____)

1.6 * What is the language that you first learned at home in childhood and can still understand?

(*If can no longer understand the first language learned, choose the second language learned*).

(*Do not read list. Mark all that apply*)

- ☐ English
- ☐ French
- ☐ Arabic
- ☐ Chinese
- ☐ Cree
- ☐ German
- ☐ Greek
- ☐ Hungarian
- ☐ Italian
- ☐ Korean
- ☐ Persian (Farsi)
- ☐ Polish
- ☐ Portuguese
- ☐ Punjabi
- ☐ Spanish
- ☐ Tagalog (Filipino)
- ☐ Ukrainian
- ☐ Vietnamese
- ☐ Other (Specify _____)

* See notes in manual

1.7 * How would you best describe your race or colour?
(*Do not read list. Mark all that apply*)

- ☐ White
- ☐ Chinese
- ☐ South Asian (e.g. East Indian, Pakistani, Punjabi, Sri Lankan)
- ☐ Black (e.g. African, Haitian, Jamaican, Somali)
- ☐ Native/Aboriginal Peoples of North America (North American Indian, Métis, Inuit/Eskimo)
- ☐ Arab/West Asian (e.g. Armenian, Egyptian, Iranian, Lebanese, Moroccan)
- ☐ Filipino
- ☐ South East Asian (e.g. Cambodian, Indonesian, Laotian, Vietnamese)
- ☐ Latin American
- ☐ Japanese
- ☐ Korean
- ☐ Other (Specify _____)

1.8 How many years of school have you finished? (*Mark the highest grade completed*)

- ☐ less than grade 9
- ☐ grades 9-13, without certificate or diploma
- ☐ high school certificate or diploma
- ☐ trades or professional certificate or diploma (CEGEP in Quebec)
- ☐ some university without certificate or diploma
- ☐ university certificate or diploma
- ☐ university degree

1.9 * What is your current employment status?

- ☐ employed full time
- ☐ homemaker (full time)
- ☐ employed part time
- ☐ unemployed
- ☐ disability
- ☐ retired → How old were you? ___ years
- ☐ other (specify _____)

1.10 Do you live alone ? ☐ Yes ☐ No

→ Do you live with another adult?

☐ Yes ☐ No

1.11 Do you have a particular doctor or clinic that you would call your regular doctor or clinic? ☐ Yes ☐ No

* See notes in manual

Now we'll review your past health.

2. MEDICAL HISTORY

2.1 * Has a doctor ever told you that you have any of the following conditions?

	DIAGNOSIS			TREATMENT			
	Yes	No	DK	Yes	No	DK	N/A
Osteoporosis							
Rheumatoid arthritis							
Osteoarthritis							
Thyroid disease: 1 = Hyperthyroidism 2 = Hypothyroidism							
Liver disease							
Scoliosis							
Eating disorder							
Breast cancer * (*for all*)							
Uterine cancer (*for females*)							
Inflammatory bowel disease							
Kidney stones							
Hypertension							
Heart attack							
Stroke TIA (*Transient Ischemic attack*)							
Neuromuscular disease: 1 = Parkinson's 2 = Multiple Sclerosis 3 = Other							
Diabetes: Age 1 = Insulin Dependent 2 = Non Insulin Dependent							
Kidney disease							
Phlebitis, thrombophlebitis							
Prostate cancer (*for males*)							
Paget's Disease of Bone							

* See notes in manual

2.2 * Have you ever been confined to a bed, a wheelchair or by a cast for more than one month at a time?

☐ Yes ☐ No
↓

How many episodes? ____

(1st episode) At what age? ____ years

For how long? ____ months

(most recent episode) At what age? _____ years

For how long? ____ months

2.3 * Which of the following surgeries have you had in the past? How old were you?

	YES	NO	AGE
Parathyroid			
Thyroid			
Stomach			
Intestine			
Gall Bladder			

2.4 * Have you fallen in the past week? ☐ Yes ☐ No
↓

How many times? ____

2.5 * Have you fallen in the past month? ☐ Yes ☐ No
↓

How many times? ____

* See notes in manual

Now I will ask you about any medicines you may have taken.

3. DRUGS AND MEDICATIONS

3.1 * Have you ever taken any of the following medications daily for more than one month?

If YES: For approximately how many months total have you taken it?

	YES	NO	TOTAL # OF MONTHS TAKEN
Thyroid pills (Synthroid[R])			
Dilantin (Seizure Pills) / Phenobarbital			
Tamoxifen (Nolvadex)			
Calcitonin (Calcimar)			
Didronel[R] / Etidronate			
Fluoride (Fluatic)			
Diuretics - Thiazide / Other			
Laxatives			
Cortisone / Prednisone			
1 = Oral			
2 = Inhaled *			
			FREQUENCY OF INJECTION
3 = Injection a) Intravenous			
b) Intramuscular, Subcutaneous			

* See notes in manual

3.2 * Current medications and or self administered supplements taken on a regular basis.

Medications: From contents of medicine cabinet		
NAME	DOSE	FREQUENCY

* See notes in manual

Now I would like to know about any broken bone you may have had.

4. FRACTURES

4.1 * Have you ever fractured any bones? ☐ Yes ☐ No → Go to 5.1 If female
→ Go to 6.1 If male

Complete the table below

(*Refer to picture of body skeleton if necessary*)

Use the following trauma codes to indicate how it happened.

1 = severe trauma
2 = minimal trauma
3 = other disease

(See manual for definitions)

INCIDENT(S)	TRAUMA CODE	AGE (years)	BONE SITE										OTHER					
			BACK		RIBS		PELVIS		FOREARM /WRIST		HIP		BONE SITE		BONE SITE		BONE SITE	
			#	X	#	X	#	X	#	X	#	X	#	X	#	X	#	X
1																		
2																		
3																		
4																		
5																		
6																		

# = fracture
x = x-ray

* See notes in manual

In this section I would like to ask you questions that will help us understand how women's hormones relate to bone structure. We ask everyone these questions.

5. REPRODUCTION HISTORY (FEMALES)

5.1 * Before menopause, have you ever gone 3 months or more without a menstrual period? (*not including pregnancy or during breastfeeding*)

☐ Yes ☐ No
↳ Go to 5.2

What was the longest single period of time without a menstrual flow? _____ months

If you count all the periods you have missed throughout your menstruating years, how many months would that be? _____ months
(*this question asks for the cumulative time)*

5.2 * Have your menstrual periods stopped for more than one year?
(*No period one year or more after last menstruation)*

☐ Yes ☐ No
↳ At what age? _____ years

5.3 Have you had your uterus removed (*hysterectomy*)?

☐ Yes ☐ No
↳ At what age? ____ years

5.4* Have you ever had one or both ovaries removed?

☐ Yes, one ovary removed at what age? ____
☐ Yes, both ovaries removed at what age? ____
(if ovaries were removed on separate occasions, write the age at which the second ovary was removed)
☐ Yes, do not know how many at what age? ____
☐ No

* See notes in manual

5.5* Do you or did you ever take **estrogen** for menopause or for any other reason ?

☐ Yes, currently ☐ No

☐ Yes, but not now ↳ Go to 5.6

↓

What type(s)?

(*Interviewers to show Ogen[R], Premarin[R] pills, colors and doses and Estraderm[R], Estracomb[R,] patches, sizes and doses)*

☐ Pill

Pill Nº	Number of days/month	Age started	Age stopped	Total number of months taken

☐ Patch

Patch Nº	Number of days/month	Age started	Age stopped	Total number of months taken

☐ Injection How many times/year? _____
How many years? _____

☐ Vaginal cream How frequently? _____

* See notes in manual

5.6 * Do you or did you ever take Provera[R], for menopause or for any other reason?

☐ Yes, currently
☐ Yes, but not now
↓

☐ No
↳ Go to 5.7

What type(s)? (*Interviewers to show Provera[R] pills, colors and doses*)

☐ Pill

Pill N°	Number of days/month	Age started	Age stopped	Total number of months taken

☐ Injection How many times/year? _____
How many years? _____

5.7 * Have you ever used birth control pills or oral contraceptives?

☐ Yes
↓

☐ No → Go to 5.8
→ Go to 5.9 (*if periods have stopped permanently through natural/surgical menopause)*

At what age did you start? ____ years (*approximately*)

* For approximately how long did you use birth control pills? ____ years ____ months

Are you still using birth control pills?

☐ Yes
↓
Go to 5.9

☐ No
↳ At what age did you stop using birth control pills?
____ years

* See notes in manual

5.8 * (*If not using birth control pills, not menopausal, have not had both ovaries removed)*

Can you tell by the way you feel that your period is coming?

☐ Yes, every month
☐ Yes, most months
☐ Yes, less than half the time
☐ Yes, one or twice a year
☐ Never

If YES, to any of the above:

What signs or symptoms indicate to you that your period is coming?

☐ menstrual cramps or aching back or legs
☐ bloating, fluid retention
☐ increased appetite (*in general or for sweet, salty or spicy foods*)
☐ moodiness (*frustration, irritability, sadness*)
☐ breast tenderness in the front or the nipple
☐ breast tenderness up under the arm or on the outer sides of the breast
☐ breast swelling
☐ headaches (*migraine or tension*)
☐ acne / pimples / blemishes
☐ other _____

5.9 * How many times have you been pregnant? ____ → If 0 : Go to 5.12
(*Pregnancy confirmed by a physician or pregnancy test)*

5.10 * How many of these pregnancies resulted in at least one live birth? ____ → If 0 : Go to 5.12
(Count twins and triplets as 1)
↓
Age at 1st birth? ____ years

5.11 Did you breast feed any of your children? ☐ Yes ☐ No
↳ For how many months total ___ months
(*i.e. adding up the months with each child*)

5.11a)* Have you given birth in the last 12 months? ☐ Yes ☐ No
(Ask if aged 25 to 50, uterus and ovaries intact and not menopausal)
(In in third trimester of pregnancy answer yes).

5.12 How old were you when you had your first menstrual period? _____ years

* See notes in manual

5.13* a) Did you have regular periods once they began?

☐ Yes ☐ No
↳ Go to 5.14

b) If you had irregular periods, did they become regular?

☐ Yes ☐ No → Go to 5.14
↳ At what age ____ years

c) Have your periods been made regular by medication?

☐ Yes ☐ No
↳ At what age ____ years

5.14 On average, how often did you have menstrual periods when you were in your 20's and 30's?

☐ 20 days or less
☐ 21-25 days
☐ 26-30 days
☐ 31-36 days
☐ 37 or more days
☐ do not know

In this section, I would like to ask you questions that will help us understand how men's hormones relate to bone structure. We ask everyone these questions.

6. REPRODUCTION HISTORY (MALES)

6.1 Have you fathered any children?

☐ Yes ☐ No
↓ ↳ Have you ever been diagnosed with a fertility problem?
☐ Yes ☐ No ☐ Don't know

How many ? ____

6.2* Which of the following is your usual experience regarding spontaneous erections not related to sex?

☐ one or more times a day (*for example, first thing when I wake up*)
☐ most days
☐ some days
☐ occasionally
☐ rarely
☐ never

* See notes in manual

Now I will ask about your family history.

7. FAMILY HISTORY

7.1 * How many brothers and/or sisters do/did you have? (*not adopted*)

____ siblings ☐ do not know

7.2 * I would like to ask about the following family members and their medical history.

DIAGNOSIS	PARENTS			SIBLINGS				CHILDREN			
	Yes	No	DK	Yes	No	DK	NA	Yes	No	DK	NA
Fracture											
Osteoporosis											
Osteoarthritis											
Scoliosis											
CVD, stroke, aneurysm, hypertension											
Breast cancer											
Ovarian cancer											
Uterine cancer											
Prostatecancer											

* See notes in manual

In this section I will ask you about diet, exercise programs and eating

8. PHYSICAL CHARACTERISTICS

8.1 What was your **greatest** adult height? ___ feet ___ inches - or - ___ cm ☐ do not know

Go to 8.3 if subject to undergo DEXA measurement

8.2 * *If not scheduled for DEXA, measure height with carpenter's ruler)*

What is your current height? ___ feet ___ inches - or - ___ cm (*to be measured in the home)*

8.3 What was your **greatest** adult weight? ___ lbs - or - ___ kg ☐ do not know
(*when over 25 yrs old and not pregnant*)

8.4 What was your **lowest** adult weight? ___ lbs - or - ___ kg ☐ do not know
(*over age 25*)

Go to 8.6 if subject to undergo DEXA measurement

8.5 * *If not scheduled for DEXA, weigh with portable scale*

What is your current weight? ___ lbs - or - ___ kg (*to be measured in the home)*

8.6 * Have you ever lost more than 10 pounds: (*other than after childbirth, re: one year post-partum)*

☐ Yes ☐ No → Go to 8.7

↳ Did you regain the lost weight?

☐ Yes ☐ No

↳ How much did you lose? ____ lbs -or- _____ kg

(*In lifetime)*

How many times have you lost and regained 10-20 pounds (6-10 kg)? _____

How many times have you lost and regained over 20 pounds (over 10 kg)? _____

* See notes in manual

I'm going to ask you a few questions on your eating

8.7 a) I am going to read two sentences for you. Please answer True (T) or False (F) for each statement as it pertains to you.

I enjoy eating too much to spoil it by counting calories or watching my weight. T ☐ F ☐

I consciously hold back at meals in order not to gain weight. T ☐ F ☐

b) Which of these best describes you?

On a scale of 0 to 5, where 0 means no restraint in eating (*eating whatever you want, whenever you want it*) and 5 means total restraint (*constantly limiting food intake and never "giving in"*), what number would you give yourself?

0 Eat whatever you want, whenever you want it
1 Usually eat whatever you want, whenever you want it
2 Often eat whatever you want, whenever you want it
3 Often limit food intake, but often "give in"
4 Usually limit food intake, rarely "give in"
5 Constantly limiting food intake, never "giving in"

Now the questions I will ask will relate to the use of tobacco.

9. TOBACCO

9.1 Have you ever used any of the following tobacco products daily for at least 6 months?

Cigarettes	☐ Yes	☐ No	
Pipes	☐ Yes	☐ No	
Cigars	☐ Yes	☐ No	
Chewing tobacco	☐ Yes	☐ No	→ If NO to all: go to 9.3

9.2 Complete the following table for each product used.

→ At what age did you begin to ..... daily? (*for at least 6 months*)
→ Are you currently smoking?
→ At what age did you stop?
→ Approximately how many every day? (*number of cigarettes, bowls of pipe tobacco, number of cigars, number of chews*)
→ Have you temporarely stopped ..... and started again? (*total up all periods and covert to years*)

	AGE STARTED	CURRENTLY SMOKING		AGE STOPPED	AMOUNT PER DAY	TEMPORARELY STOPPED (YEARS)
		YES	NO			
Cigarettes						
Pipe						
Cigar						
Chewing tobacco						

9.3 a) On average, over the last month, have you been exposed to the tobacco smoke of others (*i.e. environmental tobacco smoke (ETS)*)?

☐ Not at all
☐ < 3 hours/day
☐ 3-8 hours/day
☐ 9 or more hours per day

b) Have you ever been exposed to ETS for more than 6 months?

☐ Yes ☐ No

↳ ☐ < 3 hours/day
☐ 3-8 hours/day
☐ 9 or more hours per day

Number of years ____

* See notes in manual

Now I will ask you in detail about the foods you eat

10. FOOD INTAKE

10.1 * How often (on the average) have you eaten the following items?

	During the last 12 months?					In your 30's (If subject 40 years or over)				In your teens?				As a child?			
Food	Never	servings per month	servings per week	servings per day	Serving Size	Never	Less	Same	More	Never	Less	Same	More	Never	Less	Same	More
Milk to drink incl. choc. milk & hot cocoa w/milk					☐ 125 ml (0.5 cup) ☐ 250 ml (1.0 cup) ☐ 375 ml (1.5 cup)												
Milk on cereal					☐ 60 ml (.25 cup) ☐ 125 ml (0.5 cup) ☐ 250 ml (1.0 cup)												
Milk/cream in tea/coffee					☐ 15 ml (1 tbsp) ☐ 30 ml (2 tbsp) ☐ 60 ml (4 tbsp)												
Milk desserts (tapioca, rice pudding)					☐ 125 ml (0.5 cup) ☐ 250 ml (1.0 cup)												
Hard cheese (to eat, in sandwich or mixed dish)					☐ 15 g (0.5 oz) ☐ 30 g (1 oz) ☐ 60 g (2 oz)												
Yogurt					☐ 125 ml (0.5 cup) ☐ 175 ml (single) ☐ 250 ml (1 cup)												
Ice-cream, ice milk or frozen yogurt					☐ 125 ml (0.5 cup) ☐ 250 ml (1.0 cup) ☐ 375 ml (1.5 cup)												
Cream soups made with milk					☐ 125 ml (0.5 cup) ☐ 160 ml (.67 cup) ☐ 250 ml (1.0 cup)												

* See notes in manual

	During the last 12 months?					In your 30's (If subject 40 years or over)				In your teens?				As a child?			
Food	**Never**	**servings per**			**Serving Size**	**Never**	**Less**	**Same**	**More**	**Never**	**Less**	**Same**	**More**	**Never**	**Less**	**Same**	**More**
		month	**week**	**day**													
Canned salmon or sardines with bones					☐ 30 g (1 oz) ☐ 60 g (2 oz) ☐ 90 g (3 oz)												
Broccoli					☐ 60 ml (.25 cup) ☐ 125 ml (0.5 cup) ☐ 250 ml (1 cup)												
Dark leafy greens (bok choy, kale, gailan (Chinese broccoli), collards, dandelion greens)					☐ 60 ml (.25 cup) ☐ 125 ml (0.5 cup) ☐ 250 ml (1 cup)												
Dried peas or beans (navy, pinto, kidney)					☐ 60 ml (.25 cup) ☐ 125 ml (0.5 cup) ☐ 250 ml (1 cup)												
Whole wheat buns, bread, rolls, bagels					☐ 1 serving = 1 slice ½ bagel ½ pita												
White bread, buns, rolls, bagels, etc.					☐ 1 serving = 1 slice ½ bagel ½ pita												
Tofu					☐ 60 ml (.25 cup) ☐ 125 ml (0.5 cup) ☐ 250 ml (1 cup)												
Multivitamin, Vit. D or cod liver oil					☐ 1 supplement												
Calcium suppl. or "TUMS"					☐ 200 mg ☐ 300 mg ☐ 500 mg												

Now some questions about the liquids/fluids you might choose to drink.

BEVERAGES *

10.2 How many of the following drinks did you consume?

In these questions, one serving of alcoholic beverage is:
- 1 bottle or can of beer or a glass of draft (12 oz):
- 1 glass of wine or a wine cooler (4-5 oz)
- 1 straight or mixed drink with (1-1½ oz) hard liquor
- 1 serving of tea or coffee is 6 oz
- 1 serving of cola is 12 oz - 1 can (355 ml)

Beverages		During the past 12 months?				In your 30's (If subject is 40 years or over)				When in your teens?			
		None	Serving /month	Serving /week	Serving /day	None	Less	Same	More	None	Less	Same	More
Coffee	caffeinated												
	decaffeinated												
Tea	caffeinated												
	decaffeinated												
Colas	caffeinated												
	decaffeinated												
Alcoholic beverages													

* See notes in manual

In this section I will ask you about your physical activities and exercise.

11. PHYSICAL ACTIVITY

11.1 During a typical week in the past 6 months, how much time did you usually spend walking to work or school or while doing errands?

☐ None
☐ Less than 1 hour
☐ Between 1-5 hour
☐ Between 6-10 hours
☐ Between 11-20 hours
☐ More than 20 hours

11.2 Which of the following describes the paid work you usually do or what you consider your job?

Or if retired or unemployed, which best describes your (*past or longest*) job?

☐ I am usually sitting during the day and do not walk around very much
☐ I stand or walk quite a lot during the day but I do not have to lift or carry heavy things
☐ I usually lift or carry light loads or I often have to climb stairs or hills
☐ I do heavy work or have to carry loads

11.3 Do you currently participate in any regular activity or programme (*either on your own or in a formal class*)?

☐ Yes ☐ No

→ How many times a week? _____

→ How long per session ? _____ minutes

* See notes in manual

11.4* On the average, during the last year, how many hours <u>in a week</u> did you spend in the following activities?

	Never	1/2-1 hr	2-3 hrs	4-6 hrs	7-10 hrs	11-20 hrs	21-30 hrs	31 hrs +
STRENUOUS SPORTS (such as jogging, bicycling on hills, tennis, racquetball, swimming laps, aerobics)								
VIGOROUS WORK (such as moving heavy furniture, loading or unloading trucks, shovelling, weight lifting, or equivalent manual labour)								
MODERATE ACTIVITY (such as housework, brisk walking, golfing, bowling, bicycling on level ground, gardening)								

11.5 * On the average, during the last year, how many hours <u>in a day</u> did you spend in the following sitting activities?

	Never	Less than 1 hr	1 to 2 hrs	3 to 4 hrs	5 to 6 hrs	7 to 10 hrs	11 hrs or more
Sitting in car or bus							
Sitting at work							
Watching TV							
Sitting at meals							
Other sitting activities (such as reading, playing cards, sewing)							

11.6 On the average, during the last year, how many hours <u>in a day</u> did you sleep (*include naps*)?

☐ 5 hours or less ☐ 7 hours ☐ 9 hours
☐ 6 hours ☐ 8 hours ☐ 10 hours or more

* See notes in manual

11.7 * Rate your overall level of physical activity compared to your peers during certain times in your past life.

	When you were about 50 ~~if subject 60 y. and over~~	When you were about 30 ~~if subject 40 y. and over~~	Teenager	Child
A lot less active				
Somewhat less active				
About the same				
Somewhat more active				
A lot more active				

Now I want to ask you questions about being in the sunlight

12. SUNLIGHT EXPOSURE

12.1 * Did you ever expose a considerable part of your body to direct sunlight?

A. During the past 12 months?
- ☐ never
- ☐ seldom
- ☐ regularly
- ☐ often

If 60 years old or more.

B. When you were about 50 years old?
- ☐ never
- ☐ seldom
- ☐ regularly
- ☐ often

If 40 years old or more.

C. When you were about 30 years old?
- ☐ never
- ☐ seldom
- ☐ regularly
- ☐ often

For all.

D. When you were a child or teenager?
- ☐ never
- ☐ seldom
- ☐ regularly
- ☐ often

* See notes in manual

PLEASE ADMINISTER THE MMSE

HERE IF RESPONDENT

MEETS CRITERIA

Now I would like to ask you how your health has been on the average, over the past week. I will ask you about different areas of general health. For some of the questions, I want you to tell me which statement most closely describes how you felt.

13. HEALTH STATUS QUESTIONNAIRE : * TORRANCE QUESTIONNAIRE

INTERVIEWER ADMINISTERED VERSION

NOTE to interviewer: For each question that lists a number of choices, circle the letter for the one choice that the respondent feels best describes the usual level of ability over the past week.

1.1 Are you able to see well enough without glasses or contact lenses to read ordinary newsprint?

☐ Yes → Go to 2.1
☐ No

1.2 If not, which of the following describes your *usual* ability to see well enough to read ordinary newsprint? Are you:

a. Able to see well enough but with glasses or contact lenses.
b. Unable to see well enough even with glasses or contact lenses.
c. Unable to see at all.

2.1 Are you able to see well enough without glasses or contact lenses to recognize a friend on the other side of street?

☐ Yes → Go to 3.1
☐ No

2.2 If not, which one of the following best describes your *usual* ability to see well enough to recognize a friend on the other side of the street? Are you:

a. Able to see well enough but with glasses or contact lenses.
b. Unable to see well enough even with glasses or contact lenses.
c. Unable to see at all.

* GW Torrance and DH Feeny, McMaster University
Questionnaire development supported through research grants funded by the Ontario Ministry of Health and US Agency for Health Care Policy and Research.

3.1 Are you able to hear what is said in a group conversation with at least three other people *without* a hearing aid?

☐ Yes → Go to 4.1
☐ No

3.2 If not, which statement describes your *usual* ability to hear in a group conversation with at least three other people? Are you:

a. Able to hear what is said with a hearing aid.
b. Unable to hear what is said even with a hearing aid.
c. Unable to hear what is said, but don't wear a hearing aid.
d. Unable to hear.

4.1 Are you able to hear what is said in a conversation with one other person in a quiet room without a hearing aid?

☐ Yes → Go to 5.1
☐ No

4.2 If not, which one of the following best describes your usual ability to hear what is said in a conversation with one other person in a quiet room? Are you:

a. Able to hear what is said with a hearing aid.
b. Unable to hear what is said even with a hearing aid.
c. Unable to hear what is said, but don't wear a hearing aid.
d. Unable to hear.

5.1 Are you able to be understood when speaking the same language with strangers?

☐ Yes → Go to 6.1
☐ No

5.2 If not, which of the following best describes your *usual* ability to be understood when speaking the same language with strangers? Are you:

a. Able to be understood partially.
b. Unable to be understood.
c. Unable to speak at all.

6.1 Are you able to be understood when speaking the same language with people who know you well?

☐ Yes → Go to 7.1
☐ No

6.2 If not, which of the following best describes your *usual* ability to be understood when speaking the same language with people who know you well? Are you:

a. Able to be understood partially.
b. Unable to be understood.
c. Unable to speak at all.

7.1 Which one of the following best describes how you usually feel? Are you:

a. Happy and interested in life.
b. Somewhat happy.
c. Somewhat unhappy.
d. Very unhappy.
e. So unhappy that life is not worthwhile?

8.1 Are you free of pain and discomfort?

☐ Yes → Go to 9.1
☐ No

8.2 If not, which one of the following best describes your level of pain? Do you have:

a. Mild to moderate pain that prevents no activities.
b. Moderate pain that prevents a few activities.
c. Moderate to severe pain that prevents some activities.
d. Severe pain that prevents most activities.

9.1 Are you able to walk around the neighbourhood **without** difficulty and **without** walking equipment, and have no health limitation in vigourous activities such as running and strenuous sports?

NOTE: Walking equipment refers to mechanical supports such as braces, a cane, crutches or a walker.

☐ Yes → Go to 10.1
☐ No

9.2 If not, which of the following best describes your *usual* ability to walk. Are you:

a. Able to walk around the neighbourhood without difficulty and without walking equipment, and have some health limitation in vigourous activities such as running and strenuous sports.

b. Able to walk around the neighbourhood with difficulty, but without walking equipment or a helper.

c. Able to walk around the neighbourhood with walking equipment, but without a helper.

d. Able to walk only short distances with walking equipment. Able to walk short distances with a helper, and require a wheelchair to get around the neighbourhood.

e. Unable to walk alone, even with walking equipment. Able to walk short distances with a helper, and require a wheelchair to get around the neighbourhood.

f. Cannot walk at all.

10.1 Do you have full use of two hands and ten fingers?

☐ Yes → Go to 11.1
☐ No

10.2 If not, which of the following best describes your usual ability to use your hands and fingers? Do you have:

a. Limited use of hands or fingers, but do not require special tools or help from others.
b. Limited use of hands or fingers, require special tools but do not require help from others.
c. Limited use of hands or fingers, require the help of another person for some tasks.
d. Limited use of hands or fingers, require the help of another person for most tasks.
e. Limited use of hands or fingers, require the help of another person for all tasks.

11.1 Are you able to remember most things?

☐ Yes → Go to 12.1
☐ No

11.2 If not, which of the following best describes your *usual* ability to remember things?

a. Somewhat forgetful.
b. Very forgetful.
c. Unable to remember anything at all.

12.1 Are you able to think clearly and solve day to day problems?

☐ Yes → Go to 13.1
☐ No

12.2 If not, which of the following best describes your usual ability to think and solve day to day problems?

Do you:

a. Have a little difficulty when trying to think and solve day to day problems.
b. Have some difficulty when trying to think and solve day to day problems.
c. Have great difficulty when trying to think and solve day to day problems.

or are you:

d. Unable to think or solve day to day problems.

JUST A FEW MORE QUESTIONS:

13.1 Do you eat, bathe, dress and use the toilet normally?

☐ Yes → Go to 14.1
☐ No

13.2 If not, which of the following best describes your usual ability to perform these basic activities?

a. Eat, bathe, dress and use the toilet **independently, with difficulty.**
b. Requires mechanical equipment to eat, bathe, dress or use the toilet independently.
c. Requires the help of another person to eat, bathe, dress or use the toilet.

14.1 Are you generally happy and free from worry?

☐ Yes → Go to 15.1
☐ No

14.2 If not, which of the following best describes how you usually feel?

a. Occasionally fretful, angry, irritable, anxious or depressed.
b. Often fretful, angry, irritable, anxious or depressed.
c. Almost always fretful, angry, irritable, anxious or depressed.
d. Extremely fretful, angry, irritable, anxious or depressed, usually requiring hospitalization or psychiatric institutional care.

This is the last question. It is a different question about pain. Just to remind me:

15.1 Are you free of pain and discomfort?

☐ Yes → *That ends the questionnaire. Thank you for your help.*
☐ No

15.2 If not, which one of the following best describes your usual level of pain?

a. Occasional pain. Discomfort relieved by non-prescription drugs or self-control activity without disruption of normal activities.

b. Frequent pain. Discomfort relieved by oral medicines with occasion disruption of normal activities.

c. Frequent pain. Frequent disruption of normal activities. Discomfort requires prescription narcotics for relief.

d. Severe pain. Pain not relieved by drugs and constantly disrupts normal activities.

In this section, I will give you a small questionnaire for you to complete by yourself. For each question, you are asked to read the question, and then circle the number you choose as closest to your experience.

14. RAND HEALTH SCIENCE PROGRAM (SF-36)

1. In general, would you say your health is:

(*Circle One Number*)

Excellent 1
Very good 2
Good 3
Fair 4
Poor 5

2. Compared to one year ago, how would you rate your health in general now?

(*Circle One Number*)

Much better than one year ago 1
Somewhat better now than one year ago 2
About the same 3
Somewhat worse now than one year ago 4
Much worse now than one year ago 5

3. The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

(*Circle One Number on Each Line*)

ACTIVITIES	Yes, limited a lot	Yes, limited a little	No, not limited at all
a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports...	1	2	3
b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling or playing golf...	1	2	3
c. Lifting or carrying groceries...	1	2	3
d. Climbing several flights of stairs...	1	2	3
e. Climbing one flight of stairs...	1	2	3
f. Bending, kneeling or stooping...	1	2	3
g. Walking more than one mile...	1	2	3
h. Walking several blocks...	1	2	3
i. Walking one block...	1	2	3
j. Bathing or dressing yourself...	1	2	3

4. During the past 4 weeks, have you had any of the following problems with your work or regular daily activities as a result of your physical health?

(*Circle One Number on Each Line*)

	Yes	No
a. Cut down the amount of time you spent on work or other activities...	1	2
b. Accomplished less than you would like...	1	2
c. Were limited in the kind of work or other activities...	1	2
d. Had difficulty performing the work or other activities (for example, it took extra effort)...	1	2

5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

(*Circle One Number on Each Line*)

	Yes	**No**
a. Cut down the amount of time you spent on work or other activities...	1	2
b. Accomplished less than you would liked...	1	2
c. Didn't do work or other activities as carefully as usual...	1	2

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?

(*Circle One Number*)

Not at all 1
Slightly 2
Moderately 3
Quite a bit 4
Extremely 5

7. How much bodily pain have you had during the past 4 weeks?

(*Circle One Number*)

None 1
Very mild 2
Mild 3
Moderate 4
Severe 5
Very severe 6

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

(*Circle One Number*)

Not a bit 1

A little bit 2

Moderately 3

Quite a bit 4

Extremely 5

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks.....

(Circle One Number on Each Line)

	All of the time	**Most of the time**	**A good bit of the Time**	**Some of the time**	**A little of the time**	**None of the time**
a. Did you feel full of pep?	1	2	3	4	5	6
b. Have you been a very nervous person?	1	2	3	4	5	6
c. Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
d. Have you felt calm and peaceful?	1	2	3	4	5	6
e. Do you have a lot of energy?	1	2	3	4	5	6
f. Have you felt downhearted and blue?	1	2	3	4	5	6
g. Did you feel worn out?	1	2	3	4	5	6
h. Have you been a happy person?	1	2	3	4	5	6
i. Did you feel tired?	1	2	3	4	5	6

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

(*Circle One Number*)

All of the time 1
Most of the time 2
Some of the time 3
A little of the time 4
None of the time 5

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

(*Circle One Number on Each Line*)

	Definitely True	**Mostly True**	**Don't Know**	**Mostly False**	**Definitely False**
a. I seem to get sick a little easier than other people...	1	2	3	4	5
b. I am as healthy as anybody I know...	1	2	3	4	5
c. I expect my health to get worse...	1	2	3	4	5
d. My health is excellent...	1	2	3	4	5

THAT ENDS THE QUESTIONNAIRE. THANK YOU VERY MUCH FOR YOUR HELP.

Respondent I.D. # _____

INTERVIEWER'S ASSESSMENT

As an interviewer my assessment of the process and the respondent was:

(*Circle One Number on Each Line*)

	Not at all	**Not much**	**Moderate**	**Somewhat**	**A great deal**
a. The respondent appeared or seemed interested in the research	1	2	3	4	5
b. The respondent seemed to cooperate with me	1	2	3	4	5
c. I believe that the respondent understood the questions	1	2	3	4	5
d. I believe that the respondent listened well	1	2	3	4	5
e. I perceived that the respondent was restless or wanted to hurry the process	1	2	3	4	5
f. The respondent expressed feelings of tiredness during the interview	1	2	3	4	5

The respondent required assistance with the Rand SF-36 ☐ Yes ☐ No

Comments :

Time finished _____ hrs _____min.