Development and Validation of an Osteoporosis Risk Assessment Instrument (ORAI) to Select Women for Bone Densitometry

by

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ABSTRACT

Dual energy X-ray absorptiometry (DXA) is the standard for osteoporosis diagnosis. While mass screening for osteoporosis has not been recommended, there is no consensus regarding targeted screening. Baseline data from the Canadian Multicentre Osteoporosis Study were used to develop and validate an Osteoporosis Risk Assessment Instrument (ORAI) to select women for bone densitometry. ORAI uses a case-selective approach to screen for osteoporosis by summing a score based on current: age, weight and estrogen use, to identify women likely to have low bone mineral density who may be recommended for DXA testing. Appropriate therapy can then be offered to those at risk of debilitating osteoporotic fractures. The 3-item ORAI resulted in selection of over 90% of those with osteoporosis, and less than 43% of those with normal bone mineral density for DXA testing. This could mean 39% less DXA testing compared to a mass screening approach.

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A. INTRODUCTION and OVERVIEW

Osteoporosis is a major public health problem resulting in disability, deformity, pain, and fractures. Although established osteoporosis is difficult to reverse, early intervention can prevent osteoporotic fractures. Early intervention is based, in part, on the identification of decreased bone mineral density (BMD). Bone densitometry using dual-energy X-ray absorptiometry (DXA) is the standard in osteoporosis diagnosis based on BMD. Mass screening for osteoporosis, however, is not recommended. An alternate approach is to use DXA to screen high risk groups in order to facilitate the diagnosis of osteoporosis, and allow prophylactic treatment in the prevention of further bone degeneration and fracture. There are many published guidelines for identifying those at high risk of osteoporosis which provide indications for the diagnostic use of bone densitometry. However, these recommendations have not been evaluated, and are not always clear. For example, many of the guidelines include lists of "risk factors" for osteoporosis as indications for DXA testing, and often suggest that most postmenopausal women are candidates for testing. However, whether these risk factors are a relevant basis for selection of women to undergo densitometry remains undetermined.

This brings about the question as to whether or not it is possible to look at a person's clinical risk profile to pick out patients at higher or lower risk for low BMD. This might allow initial targeting of DXA testing to those at greater risk in a manner similar to that which has been done for hypercholesterolemia or hypertension. Accordingly, using DXA to screen high risk groups may facilitate osteoporosis diagnosis, allowing prophylactic treatment in the prevention of further bone loss/degeneration and fractures. This is important, as the burden of osteoporosis is increasing with the aging population. The annual cost for fracture treatment in Canada is estimated at one billion dollars. Case-finding may permit preventive therapy in those at risk of debilitating fractures, leading to a reduction in the impact of osteoporosis on individuals and the community.

Objective:

To develop and validate a clear and simple screening tool, from clinical risk factors, to select patients for bone densitometry. This instrument may be used by primary care practitioners to screen women most likely to have low BMD, avoid unnecessary testing, and contribute to the prevention of fragility fractures.

The thesis undertaking was approved by the Canadian Multicentre Osteoporosis Study (CaMos), as an add-on multi-centre project. CaMos data were made available from three sites (Hamilton, Kingston and Toronto) for this purpose. The thesis is an independent piece of work, separate from CaMos' objectives.

The first four chapters of the thesis are designed to cover all issues needed to ensure a full understanding of osteoporosis, the need for case-selective screening, and development of a prediction rule. Background for the thesis begins with **Chapter B** - Public Health Significance of Osteoporosis. Here, the rationale and importance of the thesis is emphasized as the severity of osteoporosis, and its associated disability, deformity and fractures are discussed. Fracture projections are provided, further signalling the importance of a case-selective approach for DXA testing to identify those in need of preventive therapy.

Chapter C - Pathophysiology of Osteoporosis outlines bone structure and integrity, the pathology of osteoporosis, and risk factors for the fragile bone condition. This information is imperative to understand what factors are associated with osteoporosis, and thus what may be important clinically, to predict low BMD as a case finding approach for DXA testing. Following, the clinical definition of osteoporosis is presented in **Chapter D** - Defining Osteoporosis, including discussion of diagnostic and intervention thresholds for osteoporosis. It is necessary not only to understand the techniques and issues surrounding BMD measurement, but to realize the importance of geographically defined reference values of BMD in order to diagnose osteoporosis. Background discussion ends with **Chapter E** - Clinical Practice Guidelines and Prediction Rules. In this chapter, current DXA practice guidelines, and suggested case-selective techniques for osteoporosis screening are reviewed. In addition, background information of CaMos and its usefulness for deriving a case finding instrument for DXA testing is described. Chapters B through E provide the necessary background to understand each dimension of the thesis, including methodology and results.

The remainder of the thesis describes the methods used to meet the objective, and presents the results, as well as an in-depth discussion of the thesis' findings, limitations, and recommendations. **Chapters F** - Methods, and **G** - Results are presented in a similar format, organized according to preliminary analyses, model development and model validation. Discussion and conclusions follow in **Chapter H**. Appendices include the CaMos data collection instrument used for analyses, and extra tables of data that may assist in understanding certain methods and results, but are not essential in the body of the thesis.

B. PUBLIC HEALTH SIGNIFICANCE OF OSTEOPOROSIS

B.1. Burden of Illness

Osteoporosis is a major public health problem resulting in disability, deformity, pain and fractures (Riggs & Melton III, 1995; Marshall *et al.*, 1996). In Canada, up to one in four women, and one in eight men over 50 years of age are affected by the disease (Hanley & Josse, 1996). The most common clinical consequences of osteoporosis are fractures leading to a decline in physical function, loss of independence, dissatisfaction with body image, and severe kyphosis with subsequent respiratory and/or gastrointestinal problems (Lydick *et al.*, 1997; Hawker, 1996a).

Osteoporosis predisposes individuals to minimal trauma fractures, usually occurring in the hip, vertebrae, wrist[1], humerus, pelvis, ankle and rib (Jaglal, 1998; Lindsay, 1995; Kreiger *et al.*, 1997; Kanis *et al.*, 1997). The most common osteoporotic fragility fractures are those of the vertebrae, wrist and hip (Gordon & Huang, 1995; Johnell, 1997; Kanis & McClowskey, 1992; Lindsay, 1995; Jaglal, 1998; Kanis *et al.*, 1997). Wrist fractures are the most common fractures occurring in women below 80 years of age (Jaglal, 1998). A steep rise in the incidence of wrist fractures occurs as early as 45 years of age in women (Singer *et al.*, 1998), with a stabilization of rates by around 60 years of age (Baron *et al.*, 1996). Women with wrist fractures have twice the expected risk of vertebral and hip fractures (Eastell, 1996). Distal forearm fractures before the age of 60 years are associated with an increased risk of vertebral fractures (Peel *et al.*, 1994; Peel *et al.*, 1996; Eastell, 1996), whereas those occurring after the age of 70 years are associated with an increased risk of hip fractures (Eastell, 1996). The incidence of hip fractures begins to increase at 60 years of age; it increases slowly to age 75, followed by a steep increase to 85, and exponential increase to 94 years of age (Singer *et al.*, 1998). Hip fracture is the most common osteoporotic fracture site in those over 80 years of age (Kreiger *et al.*, 1997).

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[1] For the purpose of this thesis, wrist fractures and Colles' fractures/distal forearm fractures are used synonymously.

Unlike hip and wrist fracture incidence, determining the incidence of vertebral fracture is much more difficult. Only about one third of all vertebral fractures come to clinical attention (Johnell, 1997; Ross, 1997). About one half of all those with radiographically identified fractures report no symptoms (Ross, 1997). Although the true incidence of vertebral fracture is unknown, evidence suggests that it increases exponentially with age in much the same way as for hip fracture (Kanis & McCloskey, 1992).

The annual cost of all fracture treatment in Canada is estimated at one billion dollars (Hanley & Josse, 1996). Given that underlying skeletal changes are asymptomatic, the economic costs are attributed to the treatment of fractures (Lindsay, 1995). Of the fractures linked with osteoporosis, hip fractures are most important in terms of functional dependence, mortality and social cost (Melton III, 1996; Cooper, 1997). Hip fractures related to osteoporosis result in death in up to 20% of cases (Cooper, 1997; Riggs & Melton III, 1995; Kanis *et al.*, 1997); contributing as a major cause of death in the elderly (Scientific Advisory Board of the Osteoporosis Society of Canada, 1996; Johnell, 1997; Council of the National Osteoporosis Foundation, 1996). In addition, more than 50% of hip fracture survivors will be incapacitated, many permanently (Anonymous, 1993). Cooper's review of the crippling consequences of osteoporotic fractures (1997), reports that one year after hip fracture, 40% of patients are still unable to walk independently, 60% have difficulty with at least one essential activity of daily living, and 80% are restricted in other activities, such as driving and grocery shopping. In addition, around 17-27% of hip fracture patients enter a nursing home for the first time as a direct result of the fracture (Cooper, 1997; Riggs & Melton III, 1995; Jaglal, 1998; Kanis *et al.*, 1997). This results in considerable costs to the health care system and the patient. The minimum yearly cost of caring for an individual in a nursing home in Ontario is $30,048; half of which the patient pays, and the other half is matched by the government (Jaglal, 1998).

Among those with vertebral fractures, physical function is impaired and changes in appearance (Dowager's hump) become obvious. These complications lead to social isolation and loss of self-esteem, impairing quality of life (Ross, 1997; Melton III, 1997). Furthermore, 5-year survival is significantly reduced in those with vertebral fractures (Cooper *et al.*, 1993a).

The burden of osteoporosis is increasing as the population ages. This is expected to increase as more live into the oldest age groups, since 75% of hip fractures occur in those aged at least 70 years (Jaglal, 1998). Canadian population projections depict an increase of 80 percent in Canadians aged 55 years and over from the year 1990 to 2013. Extrapolating projection figures to health care utilization, rates for hospital admissions and day rates associated with hip fractures will double by the second decade of the 21st century (Jaglal *et al.*, 1996; Millar & Hill, 1994). Further projections forecast the number of hip fractures in Canada to increase almost fourfold by 2041; from 23,375 in 1993/94, to an estimated 88,124 in the year 2041 (Papadimitropoulos *et al.*, 1997). Associated with this are an expected 7000 deaths (7.9%) from hip fractures. Likewise, other osteoporotic site fractures are increasing over time with the aging population, such as the number of minimal trauma rib fractures (Palvanen *et al.*, 1998), and osteoporotic pelvic fractures (Parkkari *et al.*, 1996). Effective preventive strategies must be implemented to control increasing numbers of age-related fractures. Even small reductions in fracture incidence may decrease the burden of the disease on individuals and the community (Millar & Hill, 1994).

B.2. Screening for Osteoporosis

Given that osteoporosis occurs gradually, and usually manifests itself asymptomatically until irreversible damage has occurred, relatively few people are diagnosed in time for effective therapy to be administered (Fitzsimmons *et al.*, 1995; Hawker *et al.*, 1996b). Once established, osteoporosis is difficult to reverse, but early intervention can prevent osteoporotic fractures (Hanley & Josse, 1996). Early intervention is based on the identification of decreased bone mineral density (BMD). This can be accomplished either through mass screening, or through more selective case finding. Dual-energy X-ray absorptiometry (DXA) has been identified as the standard in osteoporosis diagnosis (Hanley & Josse, 1996; Compston *et al.*, 1995). Many authors parallel the use of DXA BMD in predicting risk of fracture, to using blood pressure to predict stroke and serum cholesterol to predict cardiovascular disease (Marshall *et al.*,1996). It is recognized that the diagnosis and treatment of hypertension have contributed to the decline in cerebrovascular episodes and mortality since its inception. Lindholm and Ekbon's (1993) review of the literature on hypertension in the elderly reveals that drug treatment confers significant and clinically relevant reductions in cardiovascular (stroke especially) morbidity and mortality. Similarly, early identification of low bone mineral density, with subsequent treatment, may decrease the burden of osteoporosis on individuals and society.

Mass screening for osteoporosis has not been recommended by the OSC (Scientific Advisory Board of the Osteoporosis Society of Canada, 1996), the Canadian Task Force on the Periodic Health Examination (1994), or the US Preventive Services Task Force (1996). Although the harm (radiation exposure) and costs of DXA use are minimal compared with those associated with osteoporosis, BMD should only be measured to assist in making a clinical management choice (Sturtridge *et al.*, 1996). That is, even though DXA is crucial for a definitive diagnosis of osteoporosis for treatment purposes, there is no indication for DXA use in individuals at low risk of osteoporosis. Using DXA to screen high risk groups, however, is essential to facilitate osteoporosis diagnosis, allowing prophylactic treatment in the prevention of further bone degeneration and fracture. At present, there is no clear method for deciding who should be recommended to undergo DXA testing.

This brings about the question as to whether or not it is possible to look at a person's clinical risk profile to select patients at higher or lower risk for low BMD. This may allow initial targeting of DXA testing to those at greater risk in a manner similar to that which has been done for hypercholesterolemia or hypertension. Given limited resources, such a case finding approach would offer a rational way of selecting patients for DXA testing, an important avenue given that mass screening is not appropriate.

C. PATHOPHYSIOLOGY OF OSTEOPOROSIS

C.1. Bone

Bone is vital and dynamic connective tissue composed of an extracellular collagenous protein matrix upon which calcium salts are deposited (Vander *et al.*, 1990). The skeleton as a system is primarily a mechanically driven organ (Martin, 1993), providing the mechanical integrity for locomotion and protection of vital organs. In addition, bone plays an essential role in mineral homeostasis (Compston, 1993; Einhorn, 1996), mediating the direction and magnitude of minerals (such as calcium and phosphate; Compston, 1993), into and out of stored skeletal reserves (Glowacki, 1996; Jee, 1988).

C.1.1. Bone Remodeling

Bone remodels throughout life to the physiological and mechanical demands placed upon it (Eriksen, 1996; Einhorn, 1996). Bone remodeling is a continuous process whereby bone is renewed on bone surfaces through constant resorption and formation, i.e. replacement (Eriksen, 1996; Einhorn, 1996; Mundy, 1998). This process is governed by the activity of: i) **osteoblasts**, generally regarded as bone-forming cells, and ii) **osteoclasts**, the active agents in bone resorption (Christiansen, 1993; Einhorn, 1996; Eriksen, 1996; Jee, 1988; Mundy, 1998). Under normal physiologic circumstances, bone remodeling proceeds in highly regulated cycles (Jilka & Manolagas, 1994). Uncoupling of the remodeling cycle occurs when resorption exceeds formation, either because of enhanced recruitment of osteoclasts, or by impaired osteoblastic activity. Osteoclast-mediated bone resorption is relatively rapid (3-13 days) compared to formation (90-110 days), thus repetitive activation of the remodeling cycle potentiates an imbalance with osteoclastic activity exceeding osteoblastic function (Kessenich & Rosen, 1996). Any situation which interferes with the coupling process or causes imbalance between the bone-forming and bone-resorbing relationship can lead to significant loss of bone mass over time.

C.1.2. Bone Structure and Integrity

Structurally, two types of bone exist: trabecular and cortical. Trabecular bone, synonymous with spongy or cancellous bone, consists of bony trabeculae interconnected in a lattice designed to resist mechanical/compressive loads (Eriksen, 1996; Christiansen, 1993; Einhorn, 1996). Cortical bone is solid, arranged as cylinders ellipsoid in cross section (Einhorn, 1996). In addition to compressive

loads, cortical bone is subject to bending and torsional forces (Einhorn, 1996; Edelson & Kleerekoper, 1996). Cortical bone forms the outer casing of all bones, providing structural integrity to trabecular bone, and is the major constituent in the shafts of long bones (Gordon & Huang, 1995; Christiansen, 1993). Trabecular bone comprises about 20% of the skeleton, forming the inner meshwork of the vertebrae, pelvis, flat (cuboid) bones, and the ends of long bones (Gordon & Huang, 1995; Einhorn, 1996). Trabecular bone has a large surface area and is sensitive to metabolic changes (Kessenich & Rosen, 1996; Gordon & Huang, 1995; Einhorn, 1996). Rates of remodeling in trabecular bone are higher than cortical bone throughout life (Jilka & Manolagas, 1994; Einhorn, 1996). Approximately 26% of the trabecular bone is resorbed and replaced every year, compared to only 3% of cortical bone (Jilka & Manolagas, 1994). Given that trabecular bone is concentrated in the axial skeleton, changes in bone mass due to altered turnover may occur earlier and to a greater extent in the axial skeleton (Marcus, 1994; Mundy, 1998).

C.2. Osteoporosis Pathology

Osteoporosis is characterized by decreased bone mass, deterioration of bone tissue and subsequent increased bone fragility, resulting in reduced bone strength and increased risk of fracture (Anonymous, 1993). In the osteoporotic bone, the cortical shell and trabeculae become thinned. Eventually, the architecture of trabecular bone is destroyed, and trabeculae may become discontinuous or even disappear (Christiansen, 1993). Similarly elastic modules in cortical bone diminish with age (Martin, 1993). Accordingly, bone becomes increasingly brittle and fractures with less energy (Martin, 1993). The overall loss of bone that occurs with aging results in about a 35% reduction of cortical bone and a 50% reduction of trabecular bone in women. Men lose approximately 25% and 35% of cortical and trabecular bone respectively (Riggs & Melton III, 1986). Between the ages of 35 and 70 years, cortical bone bending strength is diminished by 15-20%, and trabecular compression strength is reduced by approximately 50% (Martin, 1993). Consequently, minimal trauma (e.g. sneezing, coughing, lifting a window against resistance, twisting, or slipping) in a person with very low bone mineral density (BMD) can result in debilitating fractures, such as compression fractures of the spine or hip fractures (Kessenich & Rosen, 1996).

Osteoporosis may be classified according to cause into **primary** osteoporosis (or natural progression), and **secondary** osteoporosis (increased bone loss subsequent to disease status and or medication use).

C.2.1. Primary (involutional) Osteoporosis

Two forms of aging-related primary osteoporosis are recognized; **Type I (high-turnover)**, or postmenopausal osteoporosis, is a specific consequence of menopausal estrogen deprivation and occurs in postmenopausal women between 50 and 65 years of age (Glowacki, 1996). Type I osteoporosis is characterized by vertebral and wrist fractures (Edelson & Kleerekoper, 1996) associated with accelerated trabecular bone loss (Glowacki, 1996) related to enhanced bone resorption (Aguado *et al.*, 1997; Kessenick & Rosen, 1996; Manolagas *et al.*, 1995).

Type II (low-turnover), or senile osteoporosis occurs in about one half of women and one in four men over 70 years of age (Gordan & Huang, 1995). Here, relative universal bone loss occurs resulting in osteoporosis from age-related decline in osteoblast function, i.e., the amount of bone resorbed by the osteoclast is not entirely replaced by osteoblasts (Mullender *et al.*, 1996; Cooper, 1993b; Wishart *et al.*, 1995; Glowacki, 1996; Martin, 1993; Manolagas *et al.*, 1995; Scane *et al.*, 1993), with normal or increased bone resorption (Kessenick & Rosen, 1996). Impaired calcium absorptive efficiency may play a role in Type II osteoporosis (Cooper, 1993b; Orwoll & Klein, 1995). Hip and vertebral wedge fractures characterize Type II osteoporosis (Gordan & Huang, 1995; Glowacki, 1996).

C.2.1.1. Risk Factors for Primary Osteoporosis

Regardless of the underlying type of osteoporosis, the two major determinants of osteoporosis are low peak bone mass (PBM) and the magnitude of subsequent bone loss (Marcus, 1994; Riis, 1996; Bachrach, 1994; Kelly, 1996; Cooper *et al.*, 1995). Major risk factors for primary osteoporosis are listed in **Table C.1.**

Table C.1 Major risk factors for primary osteoporosis

HEREDITY
-peak bone mass
-genetics
-ethnicity / race
-female sex
AGE
LIFETIME EXPOSURE TO GONADAL HORMONES
-estrogen in women
-puberty
-menopause
-testosterone in men
ENVIRONMENTAL INFLUENCE
-physical inactivity
-low weight
-diet
-low calcium
-low vitamin D
-tobacco use
-alcohol abuse

(compiled from: Gordon & Huang, 1995; Notelovitz, 1993; Lane *et al.*, 1996)

A description of the pathophysiology of each risk factor follows. It must be noted however, that many of the risk factors work in concert leading to BMD loss.

C.2.1.1.a. Heredity

Peak Bone Mass / Genetics

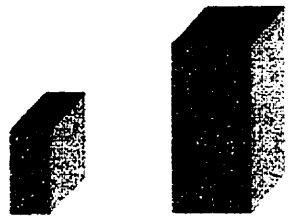
Peak bone mass (PBM) refers to the maximum amount of bone an individual acquires before bone loss begins. PBM is reported as areal bone mineral density (BMD), a function of bone mineral content (BMC) and projected area (Tsai *et al.*, 1997; Bachrach, 1994), and depends on rates of bone accretion. Rapid bone accretion occurs throughout childhood and peaks throughout adolescence (Wastney *et al.* 1996), as demonstrated by rapid growth spurts in these developmental periods. PBM is reached during the second or third decade of life. The actual age at which PBM is attained is not certain, specific sites may achieve PBM differentially (Teegarden *et al.*, 1995). Genetic factors account for a substantial amount of the variation in PBM, but the precise genes involved remain to be determined (Eastell *et al.*, 1998). No single gene has been found to dominate BMD, emphasizing the view that BMD is under polygenic control (Hobson & Ralston, 1997).

Achievement of PBM is analogous to attainment of final adult height; although the genetic potential for skeletal mass is predetermined, the actual PBM attained is influenced by environmental variables such as nutrition, mechanical factors (physical activity, muscle strength, body mass), and endocrine

function (Kahn *et al.*, 1994; Bachrach, 1994; Ziegler *et al.*, 1995; Marcus, 1994; Mundy, 1998). Bone formation commences *in utero* and continues during human development until skeletal maturity (Einhorn, 1996). Adequate nutrient supply and freedom from disease are the primary environmental factors influencing human growth and development. While growth is the primary determinant of the size of the skeletal envelope (Cooper *et al.*, 1995), activity modulates BMD within the skeletal envelope and may contribute to attainment of optimal PBM (Cooper *et al.*, 1995; Keen & Drinkwater, 1997; Madsen *et al.*, 1998; Nordstrom *et al.*, 1997). Effects of activity on bone is greatest just prior to puberty, a period when rapid natural bone mineral accumulation and rapid longitudinal growth occur. Before and after this time period, the loading effect is less clear (Haapasolo *et al.*, 1998). Too much physical activity however, may be detrimental to PBM attainment, as demonstrated in amennorheic athletes (Rencken *et al.*, 1996; Keen & Drinkwater, 1997).

Ethnicity / Race

In general, Blacks have higher BMD than Whites, who tend to have higher BMD than Asians (Bachrach, 1994; Mundy, 1995). Inherited similarities in bone size, body composition, and endocrine function likely explain much of the genetic similarities observed. However, several factors complicate the study of ethnic differences; ethnic identity may be determined as much by social and cultural factors as by inheritance. As such, diet, activity levels, and other life-style variables related to a common environment are likely to be similar within a given ethnic group (Bachrach, 1994). Therefore, a combination of genetic and environmental factors may contribute to ethnic differences in bone mass. In addition, comparisons of bone mass between ethnic groups are potentially confounded by differences in body size. BMD is an areal density rather than the true volumetric density (Tsai *et al.*, 1997; Meunier & Boivin, 1997). Therefore neither changes in BMC, or BMD accounts for change in bone thickness. As such BMD may overestimate the bone mass in larger bones and underestimate the bone mass in smaller bones (**Figure C.1**).



a = 1 x 2x 1 cm

b = 2 x 4x 2 cm

	a	b
volumetric bone density (g/cm^3)	1	1
projected area (cm^2)	2	8
volume (cm^3)	2	16
BMC (g)	2	16
BMD (g/cm^2)	1	2

Figure C.1 Effect of bone size on commonly measured bone mineral parameters*
Bone densitometry identifies the projected area, which is equal to the area on the front face of the bone. BMC is the total amount of bone mineral (g) in the sample. BMD is areal bone mineral density, calculated as BMC over the projected area. Both bone samples have identical volumetric densities, however, the BMD of the larger sample is twice that of the smaller sample.
*Carter *et al.*, 1992

Much of the difference in BMD between Asian and Caucasians may be related to body size. Ross *et al.* (1996) found that controlling for body size (weight, height, and muscle strength variables), Asian BMD was similar to BMD in Whites at the arm, pelvis, hip, spine and forearm. In fact, BMD of the wrist was significantly greater in Asians (4.64%, $p<0.05$). Lateral spine BMD was significantly higher among Whites (4.4%, $p<0.05$), although the reliability of lateral spine scans are questionable (Del Rio *et al.*, 1995). The reliability of lateral spine scans are discussed in **Chapter D** - Defining Osteoporosis, section D.1.2.. Other factors, such as muscle mass and muscular strength may also contribute to ethnic variations in BMD, and hip fracture rates. Cohn *et al.* (1977) suggest that muscle mass in Black women is in part a determinant of increased skeletal mass and resistance to osteoporosis and fracture.

C.2.1.1.b. Age and Sex

During adolescence, men and women have similar bone density (Rico *et al.*, 1992). By skeletal maturity, however, bone mineral content and area is more than 20% higher in males (Seeman, 1995). This observed difference is largely related to the size of males as compared to females (Seeman, 1995; Orwoll & Klein, 1995; Eastell *et al.*, 1998). After puberty, males have larger bones with greater cortical thickness than females. The main reason for this gender difference seems to

be the longer bone maturation period in males (Rizzoli & Bonjour, 1997; Eastell, 1998). Puberty affects bone size much more than volumetric mineral density. At the end of pubertal maturation, males and females differ very little in volumetric trabecular density (Rizzoli & Bonjour, 1997). In fact, men and women are likely to have the same cortical thickness if they have the same bone size (Seeman, 1998).

Following skeletal maturity, progressive bone loss occurs in all humans, beginning with an annual decline of 0.25-1% of PBM in both men and women (Edelson & Kleerekoper, 1996). This age-related bone loss may be a result of declining renal function, vitamin D deficiency, increased parathyroid hormone levels, low serum sex steroid (estrogen in women and testosterone levels in men), and / or low calcium intake and absorption (Eastell *et al.*, 1998; Arnaud, 1993). The physiological imbalance in bone resorption and formation potentiates type II osteoporosis and subsequent fracture, particularly in those with low PBM (Mundy, 1998).

Associated with falling levels of free androgens (Wishart *et al.*, 1995; Ongphiphadhanakul *et al.*, 1995), bone loss appears to accelerate in men from age 50 (Wishart *et al.*, 1995), but not to the extent of bone loss in women at menopause. The bone loss in men is low, reaching about 3-5% per decade (Christiansen, 1993). Postmenopausal women lose bone mass in two distinct phases. The first phase commences with irregularity of the menstrual cycle and attenuates within 5 years. Here, the lumbar spine loses BMD at a significantly higher rate for the first 2 years after menopause. Postmenopausal women lose a maximum of 3.1% BMD annually during this phase, with an overall bone loss of approximately 15.3%. The second phase of bone loss starts several years after the attenuation of the first phase and is evident in women who are menopausal for more than 10 years (Okano *et al.*, 1998). This may be viewed as a transitional process from estrogen-dependent to estrogen-independent bone loss (Okano *et al.*, 1998), which is consistent with the notion that two types of primary osteoporosis exist, i.e., postmenopausal and senile osteoporosis. After 65 years of age, BMD continues to decline at a similar rate in men and women (May *et al.*, 1994). Although the rate of BMD decline in the elderly is similar between the sexes, percentage declines from young adult means are higher in women, reflecting lower PBM, and rapid bone loss at the time of the menopause.

C.2.1.1.c. Lifetime Exposure to Gonadal Hormones

Sex steroids play an important role in the maintenance of bone mass. This is demonstrated by the development of osteopenia and osteoporosis in men and women with reduced levels of sex steroids (Kooh *et al.*, 1996; Holmes & Shalet, 1996; Anderson *et al.*, 1998), and by the preservation of bone mass by restoration of normal endogenous sex steroid level, or by treatment with exogenous sex steroids (Reid *et al.*, 1996; Hergenroeder, 1995; Nguyen *et al.*, 1995). A major etiologic component is estrogen deficiency, which in addition to increased osteoclastic resorbing capacity, both directly and indirectly decreases the efficiency of intestinal and renal calcium absorption and reabsorption respectively (Edelson & Kleerekoper, 1996). Hormone replacement therapy is recognized as a treatment of postmenopausal osteoporosis (Josse, 1996). Androgen deficiency is thought to play an important role in many cases of male osteoporosis (Anderson *et al.*, 1998).

C.2.1.1.d. Environmental Influences

Physical Activity

Physical activity confers protection from bone loss (Jaglal *et al.*, 1993; Jaglal *et al.*, 1995; Greendale *et al.*, 1995). Mechanical stress results in alterations of bone remodelling, having positive influences on bone mass (Rigotto *et al.*, 1984; Drinkwater *et al.*, 1995). The Osteoporosis Society of Canada (OSC) contends that physical activity improves balance, muscular strength, range of motion, endurance, posture, lessens pain and improves overall quality of life in osteoporotic individuals (Prior *et al.*, 1996). The response of bone to mechanical loads is immediate, specific to the bone under load, and involves both cellular and tissue reactions (Drinkwater *et al.*, 1995). It is the position of the American College of Sports Medicine, that weight-bearing physical activity is essential for the normal development and maintenance of a healthy skeleton (Drinkwater *et al.*, 1995). Changes in bone mass occur more rapidly with unloading than with increased loading. Habitual inactivity results in a downward spiral in all physiologic function (Drinkwater *et al.*, 1995). For example, inactivity and impaired weight-bearing result in demineralization of the bones of the lower extremity. This has been demonstrated in studies of bedridden subjects (del Puente *et al.*, 1996), and those impaired by fracture (Kannus *et al.*, 1994).

Body Weight

Low body weight is a major independent risk factor for low BMD (Ribot *et al.*, 1992; Carroll *et al.*, 1997; Elliot *et al.*, 1993; Slemenda *et al.*, 1990; Franceschi *et al.*, 1997; Kroger *et al.*, 1994; Ooms *et al.*, 1993; Lydick *et al.*, 1998 ; May *et al.*, 1994). The mechanism for the effect of weight on BMD is not well understood. Both mechanical forces, induced by greater body weight, and hormonal factors may be attributed to greater skeletal density in obese people (Fogelholm *et al.*, 1997). Bell *et al.* (1985) found alterations in the vitamin D-endocrine system in obese subjects with enhanced renal tubular reabsorption of calcium. In addition, obese women are at decreased risk of osteoporosis due to postmenopausal estrogen deprivation, because fat is a major site of the conversion of androstenedione to estrone, the principal estrogen in postmenopausal women (Gordon & Huang, 1995).

Nutrition

Nutrition may play a role in the development of osteoporosis. Here, adequate calcium and vitamin D are of primary concern. The adult skeleton contains 99% of total body calcium (Compston, 1993, Vander *et al.*, 1990; Whitney & Rolfes, 1993). The other 1% of body's calcium circulates under tight physiologic control in blood fluid. This extracellular calcium ion participates in regulation of muscle contraction, blood clotting, transmission of nerve impulses, secretion of hormones and activation of enzyme reactions (Whitney & Rolfes, 1993). In general, bone keeps blood calcium levels constant, releasing calcium from bone stores into extracellular fluid, and storing calcium into skeletal reserves as required. Two key systemic hormones of the calcium homeostatic system are parathyroid hormone (PTH) and 1,25-dihydroxy vitamin D_3 [$1,25(OH)_2D_3$], the active form of vitamin D. The OSC supports optimal calcium nutrition as an effective preventive measure against osteoporosis (Murray, 1996). It is recommended that adults (those aged at least 19 years) consume a minimum of 1000 mg of calcium per day. In addition, as adequate amounts of vitamin D are required for optimal calcium absorption, the OSC recommends that elderly people and those who use heavy sun screens should have a dietary intake of 400 to 800 IU of vitamin D per day (Murray, 1996). Vitamin D is normally obtained either in diet, or from sunlight, which induces the production of vitamin D in the skin.

Alcohol and Cigarette Smoking

Other lifestyle factors, such as excessive alcohol consumption and smoking are risk factors for the development of osteoporosis. Chronic abuse of alcohol is often associated with osteoporosis in men, as well as in younger premenopausal women (Christiansen, 1993). Alcohol's effect may be mediated through: i) its effects on vitamin D metabolism, or ii) a direct toxic action on bone cells, resulting in decreased bone formation and poor mineralization (Laitinen & Valimaki, 1991).

Cigarette smoking has deleterious effects on bone mass in men and women (Ortega-Centeno *et al.*, 1997; Christiansen, 1993; Egger *et al.*, 1996). Cigarette smoking may be a risk factor for at least four reasons: female smokers are thinner, have an earlier natural menopause, have higher catabolism of exogenous estrogen, and like alcohol consumption, cigarette smoking in itself may inhibit osteoblastic activity (Christiansen, 1993).

C.2.2. Secondary Osteoporosis

In addition to primary causes of osteoporosis, any disease or medication that interferes with mineral metabolism and results in the reduction of bone mass, predisposes the affected individual to osteoporosis and fractures. **Table C.2** lists various secondary causes of osteoporosis.

Table C.2 Secondary causes of osteoporosis

Predisposing Medical Condition	Medications
chronic renal failure	anticonvulsants
chronic liver disease	methotrexate
gastrectomy and intestinal bypass	warfarin
malabsorption syndromes	cyclosporine
primary biliary cirrhosis	glucocorticoids
scoliosis	aluminum-containing antacids
diabetes type I	diuretics (except thiazides)
hypogonadism	radiation treatment
hyperparathyroidism	heparin
hyperthyroidism	Isoniazid (INH)
growth hormone deficiency	
leukemia	
lymphoma	

(compiled from: Gordon & Huang, 1995; Notelovitz, 1993; Edelson & Kleerekoper, 1996)

C.3. Clinical Risk Factors to Screen for Osteoporosis

Risk factors for osteoporosis have historically been identified from case-control and cohort studies of osteoporotic fragility fractures. There is a large literature looking into risk factors for osteoporotic fractures. In addition to risk factors reported in the previous two sections (**C.2.1.1** and

C.2.2.), factors which contribute to falls, such as mobility (e.g. slower or abnormal gait speed), postural sway, poorer health status (Kreiger *et al.*, 1997), and cognizance (Jergas & Gluer, 1997), increase one's risk of fracture. Regardless, BMD is the best predictor of future fractures (Compston *et al.*, 1995). As such, identification of low BMD is used as an indication for prophylaxis from debilitating osteoporotic fractures (Joseph & Hughes, 1997; Jergas & Gluer, 1997; Council of the National Osteoporosis Foundation, 1996; Anonymous, 1997a; Scheiber II & Torregrosa, 1998; Christiansen, 1995). From this, it may be possible to select individuals for bone densitometry based on their clinical risk profile.

C.4. The Canadian Multicentre Osteoporosis Study (CaMos)

The Canadian Multicentre Osteoporosis Study (CaMos) is a cohort study (5 year follow-up) evaluating the multivariable relationship between osteoporotic fractures, measures of bone integrity, and risk factors for osteoporosis. CaMos catchment population included all non-institutionalized residents aged at least 25 years within 50 km of nine nation-wide study centres. These criteria cover 37% of the Canadian adult population. Random selection of residential telephone subscribers was used to enumerate eligible participants according to sex and age stratified criteria. Age strata were categorized by years as: 25-45, 46-50, 51-55, 56-60, 61-65, 66-70, 71-80, 81+. Sampling by sex and age strata were completed to permit an analysis of the relationship between various factors influencing osteoporosis and bone fractures through multivariate modelling (Canadian Multicentre Osteoporosis Study, 1995). For example, men over 60 years of age are at greater risk for osteoporosis, thus more men over 60 were sampled compared to those aged less than 60 years.

All CaMos participants were fluent in at least English or French, and in the case of Toronto and Vancouver sites, also Chinese. Through telephone contact, eligible individuals were invited to meet with a trained interviewer to complete a questionnaire and visit the clinic for bone densitometry using DXA (7 CaMos sites used Hologic DXA machines, and 2 sites used Lunar DXA machines). The CaMos questionnaire asks participants about all of the major risk factors for osteoporosis including: age, race/ethnicity, personal and family history of bone fragility, medical history (e.g. comorbid conditions, reproductive history, fractures), current medication and drug histories, physical characteristics (weight, height), and lifestyle factors (diet, alcohol consumption, smoking, physical activity, sunlight exposure). In addition to the CaMos questionnaire, the *Rand Short Form-36* and the *McMaster Health Utility Index* were included to collect information on health related

quality of life, and the *Mini Mental State Examination* (MMSE) was administered to those aged 65 years or more to identify those with cognitive impairment (Canadian Multicentre Osteoporosis Study, 1995).

Correction factors were applied to BMD values as applicable (Genant *et al.*, 1994). To permit pooling of BMD values across study sites, CaMos cross-calibrated BMD values to Hologic equivalents, using Genant *et al.*'s (1994) formula:

Femoral Neck: Neck Hologic = 0.836*(Neck Lunar) - 0.008
Lumbar Spine: L14 Hologic = 0.906*(L14 Lunar) - 0.025

CaMos used the corrected Hologic equivalent BMD values to determine Canadian young adult normals, **Table C.3**.

Table C.3 Canadian young adult normal bone mineral density[a]

	Females		Males	
Skeletal Site	**N**	**Mean BMD (SD)**	**N**	**Mean BMD (SD)**
Femoral Neck	354	0.836 (0.110)	291	0.898 (0.116)
Lumbar Spine (L1-L4)	352	1.037 (0.123)	292	1.056 (0.129)

[a] based on CaMos Hologic equivalent BMD values for individuals aged between 25 and 39 years (CaMos preliminary data)

Data collection (baseline) for CaMos began in January 1996, and ended in September 1997. All data were collected using the same protocol at each study site. Data were entered and cleaned in a central location to minimize error before being released to respective study sites.

CaMos data provide the opportunity to evaluate the influence of several clinical risk factors for osteoporosis using Canadian population-based data. More importantly, CaMos has derived Canadian young adult normal values for use with DXA measurements at both the femoral neck, and lumbar spine (L1-L4). These data may be ideal to develop a case-selective screening tool for bone densitometry for use in the Canadian population.

D. DEFINING OSTEOPOROSIS

D.1. Bone Mineral Density Measurement

The diagnosis of osteoporosis is based on the identification of decreased bone mineral density (BMD). Several measures exist to quantify BMD, including: conventional radiology, radiographic absorptiometry (RA), single photon absorptiometry (SPA), dual photon absorptiometry (DPA), single energy X-ray absorptiometry (SXA), dual energy X-ray absorptiometry (DXA), spinal and peripheral quantitative computed tomography (QCT, pQCT), quantitative ultrasound (QUS), neutron activation analysis, magnetic resonance imaging, and photon scattering. The performance of many of these techniques are included in **Table D.1**.

Up to 50% of bone must be lost before reduced bone density is apparent on spinal radiographs (Scane *et al.*, 1994). Therefore, conventional radiographs are not useful to identify and treat osteoporosis before fragility fractures occur. Conventional radiographs are often employed instead, to assess the severity of established osteoporosis (Scane *et al.*, 1994). In addition, they may be useful to characterize pre-existing abnormalities that falsely elevate DXA results, such as severe aortic calcification, degenerative osteoarthritis, and vertebral compression fractures (Sturtridge *et al.*, 1996; Scientific Advisory Board of the Osteoporosis Society of Canada, 1996).

Radiographic absorptiometry (RA) employs a calibration wedge with a standard imaging X-ray unit to quantify BMD. Similar to single energy absorptiometry (SPA/SXA), which measures BMD in peripheral sites (wrist/forearm, heel), RA is restricted to analysis of the hand. Although these techniques are portable and relatively inexpensive, neither RA nor SPA/SXA can be used to measure the clinically more important axial BMD of the spine or hip (Council of the National Osteoporosis Foundation, 1996; Kanis *et al.*, 1997; Melton III *et al.*, 1990). Dual-energy absorptiometry (DPA/DXA) machines are capable of measuring the hip and lumbar vertebrae (lateral and posteroanterior scans). DXA has largely replaced DPA, providing greater photon flux and thus shorter examination times, greater precision, improved resolution and longer source life (Blake & Fogelman, 1997b). Lateral spine DXA, however is not widely acceptable given the precision error (Council of the National Osteoporosis Foundation, 1996).

Table D.1 Performance summary of various techniques to assess bone mineral density

Technique	Precision Error (%)	Accuracy Error (%)	Effective dose equivalent (μSv)
Radiographic Absorptiometry (RA)[b,c]			
phalanx/metacarpal	1 - 2	5	~5
Single photon Absorptiometry (SPA)[d,g]			
radius/calcaneus	1 - 3	2.8	<1 - 10
Dual photon Absorptiometry (DPA)[d,g]			
femoral neck	2 - 4	3 - 4	4 - 50
lumbar spine	2 - 4	3 - 6	4 - 50
Single energy X-ray Absorptiometry (SXA)[b,c,g]			
radius/calcaneus	1 - 2	4 - 6	~1
Dual energy X-ray Absorptiometry (DXA)[b,c,e,g]			
proximal femur	1.5 - 3	6	~ 1 - 5
PA spine	1 - 1.5	4 - 8	~ 3 - 5
Lat spine	2 - 3	5 - 15	~ 1 - 5
forearm	~1	5	< 1
whole body	~1	3	~ 3
Quantitative Computed Tomography (QCT)[b-g]			
spine	2 - 6	5 - 15	50 - 1000
Peripheral Quantitative Computed Tomography (pQCT)[b,c,g]			
radius trabecular	1 - 2	?	~ 1 - 5
radius total	1 - 2	2 - 8	~ 1 - 5
Quantitative Ultrasound (QUS)[b,c]			
SOS calcaneus/tibia	0.15 - 1.2	?	0
BUA calcaneus	0.4 - 4.0	?	
Neutron Activiation Analysis (NAA)[c]			
whole body, or portions	1 - 5	3 - 5	2 - 11

[a] Table format adapted from Baran *et al.*, 1997; Genant *et al.*, 1996
[b] Baran *et al.*, 1997
[c] Genant *et al.*, 1996
[d] Melton III *et al.*, 1990
[e] Council of the National Osteoporosis Foundation, 1996
[f] Spadia *et al.*, 1996
[g] Anonymous, 1997b

Unlike energy absorptiometry, QCT can discriminate between the metabolically more active trabecular and cortical bone of the spine (Flynn & Cody, 1993; Council of the National Osteoporosis Foundation, 1996), increasing its applicability and accuracy in assessing early bone loss. However, QCT cannot assess BMD at the femoral neck (Council of the National Osteoporosis Foundation, 1996). In addition, due to the expense, low precision and comparatively high radiation dose (Kanis *et al.*, 1997), QCT is not suitable for patient follow-up (Council of the National Osteoporosis Foundation, 1996). Qualitative ultrasound measures both attenuation and velocity of sound,

providing information about the structural organization of bone, in addition to BMD. However, the accuracy of this portable radiation-free technique is unknown (Genant *et al.*, 1996; Baran *et al.*, 1997). Overall QUA's value as a diagnostic aid, or for monitoring treatment is not established (Kanis *et al.*, 1997; Pocock *et al.*, 1996; Njeh *et al.*, 1997).

Other experimental techniques for BMD measurement include neutron activation analysis, magnetic resonance imaging, and photon scattering (Baran *et al.*, 1997; Anonymous, 1997b). Neutron activation is an excellent method for measuring total, or regional body calcium, and thus may be the best method of measuring bone mass (Sturtridge *et al.*, 1996; Anonymous, 1997b). However equipment is not readily available (Sturtridge *et al.*, 1996), and may require access to a whole body device (Anonymous, 1997b).

Dual-energy X-ray absorptiometry (DXA) has been identified as the standard in osteoporosis diagnosis (Hanley & Josse, 1996; Compston *et al.*, 1995; Sturtridge *et al.*, 1996; Council of the National Osteoporosis Foundation, 1996; Jergas & Gluer, 1997; Hooper, 1997; Kroger & Reeve, 1998). Advantages of DXA include low radiation dose to patients, short scan times (3-10 minutes), high resolution images, accuracy, precision, and stability of calibration (Blake & Fogelman, 1997a). The Ontario Ministry of Health, and the Ontario Medical Association have recently revised physician services billing to include DXA, while deleting billing codes for "obsolete" technology including bone mineral content analysis, dual photon absorptiometry, and total body calcium measurement by neutron activation (Ontario Ministry of Health, 1998a; Ontario Ministry of Health, 1998b).

D.1.1. Factors Confounding BMD Measurement Accuracy

A number of factors impair the diagnostic accuracy of absorptiometric methods, **Table D.2**, such as the presence of extraskeletal calcification in posteroanterior scans of the spine, and the presence of osteoarthritis in the spine or hips. These problems are particularly apparent in the elderly, and are attributable to degenerative changes (Ryan, 1997; Rand *et al.*, 1997).

Table D.2 Factors which interfere with the interpretation of bone mineral measurement*

vascular calcification (esp spine)
osteoarthritis (esp spine)
osteomalacia
Paget's disease
osteophytosis
osteochondrosis
previous fracture (of relevant site)
overlying metal objects
contrast media (spine)
previous gold therapy
severe scoliosis
vertebral deformities due to osteoarthrosis, Scheuemann's disease

*Kanis *et al.*, 1997

Other factors such as prevalent fracture, and skeletal conditions, e.g., Paget's disease and osteomalacia, may confound BMD testing. Osteomalacia is characterized by a defect of mineralization of bone matrix which underestimates bone mass. Osteomalacia is most commonly due to impaired intake, production or metabolism of vitamin D (Kanis *et al.*, 1996). In addition, position errors (e.g. rotation of the hip) may cause large alterations in BMD measurements (Ryan, 1997). However, proper protocols should overcome errors due to positioning. In addition, heterogeneity of density due to osteoarthritis or previous fracture can often be detected on the scan and be excluded from the analysis. For example, a smaller region of interest can be selected to exclude the hip joint (Kanis *et al.*, 1996).

D.1.2. Which BMD Sites are Appropriate for Diagnosis of Osteoporosis

BMD varies between sites in the same individual due to differential rates of bone loss and varying ratios of cortical and trabecular bone throughout the body (Simmons *et al.*, 1997). Therefore, osteoporosis at one site may not be indicative of osteoporosis at other sites, and assessment of relevant biological sites is suggested. Posteroanterior spine and proximal femur DXA scans are the most widely used application because of their utility in treatment decisions and monitoring response to therapy (Blake & Fogelman, 1997a; Ryan, 1997). These are the best sites for axial fracture risk assessment and diagnosis of osteoporosis (Ryan, 1997). In fact, the Ontario Ministry of Health support DXA diagnostic testing in both the spine and hip. However peripheral DXA is considered investigative and is not covered for physician services billing (Ontario Ministry of Health, 1998b).

BMD in the hip can be measured in up to four regions: the femoral neck, trochanter, Ward's triangle, and total hip. The Ward's triangle area gives the best measure of trabecular bone in the proximal femur, and thus measures the earliest site of postmenopausal bone loss in the hip. In practice, however, use of the Ward's region is limited by poor precision, and femoral neck BMD has been the hip parameter most frequently used for making diagnosis of osteopenia and osteoporosis (Blake & Fogelman, 1997a). Although BMD may differ between right and left hips of the same individual, significant differences are restricted to the trochanter, thus a femoral neck DXA scan of one hip is sufficient (Bonnick *et al.*, 1996). Recently, however, the International Committee for Standards in Bone Measurement has recommended the use of the total femur region as the region of interest to evaluate hip BMD (Hanson, 1997; Formica, 1998), as evidence suggests that total femur evaluation is equally diagnostic, but more precise than femoral neck measurements.

In theory, lateral DXA scans of the spine may be more sensitive for detecting vertebral bone loss than posteroanterior (PA) spine, because lateral scans measure predominantly trabecular area excluding the posterior elements which are rich in cortical bone. That is, posteroanterior (PA) scan of the spine includes contributions from cortical bone and the spinous processes as well as the trabecular bone of the vertebral body. The pelvis and ribs, however, frequently obstruct BMD measurements of vertebrae L1, L4, and sometimes L3 in lateral spine scans. Therefore lateral scans usually capture the BMD for only one or two vertebrae (L2 and L3). Although lateral DXA measurements are more sensitive for detection of age-related bone loss, because of poorer precision (Rand *et al.*, 1997), the diagnostic sensitivity of PA scans are better (del Rio *et al.*, 1995). Averaging lumbar spine BMD values over L1-4 from PA scans gives greater diagnostic sensitivity for osteoporosis than individual vertebrae (Ryan *et al.*, 1994). Therefore at present, bone densitometry of the femoral neck, and PA lumbar spine (L1-L4), are regarded as the best sites for assessing fracture risk at the hip and spine respectively.

D.2. Bone Mineral Density and Fracture Risk

The distribution of BMD is approximately normal, irrespective of the technique used to evaluate BMD (Kanis *et al.*, 1997). From this, a person's BMD is usually represented in standard deviation (SD) units in relation to mean-normal ranges. These are expressed as a t-score, when used in reference to the young adult normal value (PBM), or z-score, when BMD is made in comparison to age-matched normals (Eastell *et al.*, 1998; Kanis *et al.*, 1997), **Figure D.1**.

$$t\text{-score} = \frac{\left(BMD_{\text{young adult mean}} - BMD_{\text{individual}}\right)}{SD_{\text{young adult mean}}}$$

$$z\text{-score} = \frac{\left(BMD_{\text{mean for age}} - BMD_{\text{individual}}\right)}{SD_{\text{mean for age}}}$$

Figure D.1 Equations to calculate a bone mineral density (BMD) t-score and z-score

BMD is the most important determinant of bone strength. As bone mass decreases, fracture risk increases exponentially (Miller *et al.*, 1996). Many prospective studies have identified an increased risk of fractures with decreasing BMD. A meta-analysis of these studies from 1985 to 1994 identifies a 2.3-2.6 fold increase of fracture risk for every 1 SD reduction in BMD at the spine and hips (Marshall *et al.*, 1996). Site specific predictive ability of a 1 SD decrease in BMD to identify future fracture at the spine or hip is comparable, if not better than, a 1 SD increase in blood pressure for stroke, and a 1 SD increase in serum cholesterol concentration for cardiovascular disease (Marshall *et al.*, 1996). Although the relationship between BMD and bone failure is strong, other factors contribute to bone failure, such as age and trauma/falls (Ott, 1993). Although BMD can predict risk of fracture, it cannot identify individual people who will have a fracture (Marshall *et al.*, 1996). Factors which may contribute to falls include mobility (e.g. slower or abnormal gait speed), postural sway, poorer health status, psychotropic medication (Kreiger *et al.*, 1997), and cognizance (Jergas & Gluer, 1997).

D.3. Clinical Definition of Osteoporosis

For diagnostic purposes two thresholds of BMD have been proposed by the World Health Organization (WHO) for Caucasian women, based on the t-score, **Table D.3**. WHO defines osteoporosis at a t-score ≤-2.5SD, which include the majority of individuals who will sustain a fracture in the future. Osteopenia, set at a higher threshold (t-score between -1.0 and -2.5SD) identifies those with low bone mass, and medium risk of fracture (Kanis *et al.*, 1994; Kanis *et al.*, 1997). Although low BMD at any site may indicate increased risk of fragility fracture in general, low BMD detected at a specific site is best for prediction of fracture at that site in the future (recall **section D.1.2.**). This is particularly true for low BMD at the hip.

Table D.3 WHO diagnostic categories based on BMD and recommendations within each category

diagnostic category	t-score (SD)[a]	risk of fracture
normal	≥ -1.0	low
osteopenia	between -1.0 and -2.5	medium
osteoporosis[b]	≤-2.5	high
established osteoporosis	≤-2.5 in the presence of fragility fracture	very high

[a] standard deviations from the young adult mean value in women

[b] the original WHO article reads osteoporosis as more than 2.5 standard deviations below the young adult mean value (Kanis *et al.*, 1994). Subsequent material including WHO collaboration classifies osteoporosis as a t-score ≤ -2.5 SD (Kanis *et al.*, 1996; Kanis *et al.*, 1997)

The Osteoporosis Society of Canada has adopted the WHO diagnostic criteria listed in Table D.3 for osteoporosis in women, using DXA (Sturtridge *et al.*, 1996). This classification of osteoporosis includes nearly all women who will sustain a fragility fracture and may be regarded as an indication for intervention (Compston *et al.*, 1995). Given that the criteria were derived from studies in women, controversy exists as to their usefulness in men (Sturtridge *et al.*, 1996). However, Orwoll & Klein's (1995) review of the literature regarding osteoporosis in men stipulates that the basic tenets should be applicable in men and there is no conceptual reason to deny WHO's diagnostic strategy in men. The WHO, in collaboration with the European Foundation for Osteoporosis and Bone Disease, suggest that the value for BMD used in women can be taken as a cut-off point for the diagnosis of osteoporosis in men, i.e. a value for BMD 2.5 SD below the young adult average for women (Kanis *et al.*, 1997).

Further to the diagnostic thresholds classified by the WHO, a t-score <-2.0 SD of the young healthy female normal is recognized as the "fracture threshold" (Council of the National Osteoporosis Foundation, 1996; Meema & Meema, 1987). This fracture threshold was derived from epidemiological studies showing that most patients with osteoporotic fractures have a BMD more than 2.0 SD below the normal mean for young adults (Joseph & Hughes, 1997; Jergas & Gluer, 1997). The term fracture threshold in its literal sense, however, may be misleading because of the substantial overlap between fracture and nonfracture patients (Jergas & Gluer, 1997). As previously mentioned, prediction based on BMD may be used as an estimate of the risk of future fractures, but not as an absolute prediction of fracture occurrence (Jergas & Gluer, 1997).

Depending on age, and associated risk factors for fracture, treatment thresholds in terms of t-scores vary (Lindsay, 1998; Kroger & Reeve, 1998). The WHO classification criteria are the accepted definition of osteopenia, and osteoporosis. However, suggested intervention thresholds for prevention of osteoporosis are not clear. WHO diagnostic thresholds do not identify treatment thresholds (Hodsman, 1998). In general, it is suggested that pharmacologic treatment be: considered in menopausal women, or those with high risk with BMD lower than 1.0 SD of the young normal (Joseph & Hughes, 1997; Jergas & Gluer, 1997; Council of the National Osteoporosis Foundation, 1996; Anonymous, 1996; Scheiber II & Torregrosa, 1998; Christiansen, 1995), and initiated in patients with fragility fractures (Joseph & Hughes, 1997; Council of the National Osteoporosis Foundation, 1996). The only clear consensus is that treatment is not indicated in individuals with BMD ≥ -1.0 SD of the young adult value (t-score ≥ -1.0 SD).

D.3.1. Variation in BMD Results Between Manufactured DXA Machines

Comparisons of BMD values at the same skeletal site in an individual obtained on two different DXA manufactured machines should be relatively consistent. However, due to calibration differences, BMD values (g/cm^2) cannot be directly compared across different DXA systems (Faulkner & McClung, 1996). In fact, BMD figures derived using equipment from different manufacturers may differ significantly if not expressed in standardized (cross-calibrated) BMD units (Faulkner *et al.*, 1996). Attempts to address the lack of agreement between DXA manufacturers are continually being developed. The most noteworthy standardization procedures, cross-calibrating BMD from different manufacturers, have been made by the International DXA Standardization Committee (IDSC) and the European Community's COMAC-BME programme (Dequecker *et al.*,

1993; Simmons *et al.*, 1997; Genant *et al.*, 1994; Steiger, 1995; Hanson, 1997; Formica, 1998). The IDSC provides equations to cross-calibrate BMD between Hologic, Lunar and Norland instruments, the three major DXA manufacturers (Genant *et al.*, 1994). These equations allow investigators to derive, for example, Hologic equivalent BMD results from Lunar and Norland machines, and vice versa. IDSC has also created equations to produce standardized BMD for use as a universal scanner calibration. With this, IDSC had introduced the term 'sBMD', expressed as mg/cm^2, to distinguish from manufacturer specific 'BMD' expressed in g/cm^2 (Genant *et al.*, 1994; Steiger, 1995; Hanson, 1997).

D.3.2. Defining Normal Population

Above and beyond the need to standardize BMD values between different DXA manufacturer's machines, different manufacturers' instruments have dissimilar reference databases for young adults. Hologic, for example uses cubic equations to define their reference curves, forcing a peak value to occur at the young normal age. In contrast, Lunar uses a tri-linear fit to the data, assuming BMD to be linear from age 20-45 years (Faulkner *et al.*, 1996). From this, the Hologic young normal value is relatively higher than the Lunar value (**Table D.4**), resulting in a larger observed prevalence of osteoporosis using Hologic machines. One approach is to use comparable reference populations in all instruments, as t-score results should be consistent (Blake & Fogelman, 1997b) when applied with manufacturer cross-calibrated BMD or sBMD units.

Table D.4 Reference data for young adult normals provided by the principal DXA manufacturers

Reference Data	Age (years)	Sample Size	BMD,g/cm^2 mean (SD)
Manufactured Reference Norms			
Hologic			
femoral neck [a,b]	22	-	0.895 (0.10)
lumbar spine, L1-L4[a]	30	-	1.047 (0.11)
lumbar spine, L2-L4[b]	-	-	1.079 (0.110)
Lunar			
femoral neck[b]	20-45	-	0.980 (0.120)
femoral neck[c]	20-29	479	0.994 (0.12)
lumbar spine, L1-L4[a]	20-45	-	1.200 (0.120)
lumbar spine, L2-L4[b]	-	-	1.20 (0.12)
lumbar spine, L2-L4[c]	20-29	467	1.188 (0.12)
Norland Europe			
femoral neck[b]	-	-	0.900 (0.120)
lumbar spine, L2-L4[b]	-	-	1.085 (0.115)
Norland US			
femoral neck[b]	-	-	0.928 (0.849)
lumbar spine, L2-L4[b]	-	-	1.164 (0.162)

[a] Faulkner *et al.*, 1997
[b] Simmons *et al.*, 1997
[c] as determined using Lunar DXA, Truscott *et al.*, 1997

The WHO criteria categorized individuals based on the normal BMD of young healthy adult females. What constitutes the young adult normal BMD, however, is controversial. Differences in risk of hip fracture between communities are not explicable solely on the basis of BMD, because young adult mean BMD varies by race and geographical region. Therefore, different cutoff values may be necessary to capture the same degree of fracture risk in different regions (Kanis *et al.*, 1994). The question arises whether risk assessment should be related to young normal values obtained in the local community, or to some composite normal value obtained by pooling results from many communities (Lunt *et al.*, 1997). Until a consistent normative database is developed, it is possible to overcome normative discrepancies using redefined young normal mean and SD in local communities/regions, **Table D.5**. Population specific reference values are essential to validly identify t-scores, and thus risk of fracture in the population of interest. IDSC recognizes that more effort must be directed toward the definition and establishment of reference data specific to geographic regions before the widespread application of standardized BMD (sBMD) can be suggested (Formica, 1998).

Table D.5 Study specific reference data for young adult normals

Reference Data	Age (years)	Sample Size	BMD,g/cm² mean (SD)		
Population Specific Reference Norms					
NHANES III, US					
femoral neck[a]			0.849	(0.109)	
sBMD[b] (mg/cm²)	20-29		956	(123)	(mg/cm²)
UK					
femoral neck[b]	20-29	141	1.009	(0.12)	
lumbar spine, L2-L4[b]	20-29	142	1.214	(0.13)	
southern England					
femoral neck[c]	20-29	91	1.03	(0.11)	
lumbar spine, L2-L4[c]	20-29	91	1.24	(0.11)	
American					
femoral neck[d]	30-34	19	0.801	(0.136)	
	35-39	39	0.796	(0.112)	
lumbar spine, L1-L4[d]	30-34	19	0.986	(0.119)	
	35-39	39	1.007	(0.133)	
Canada (CaMos)					
femoral neck[e]	25-39	354	0.836	(0.110)	
lumbar spine, L1-L4[e]	25-39	352	1.037	(0.123)	
Finnish					
femoral neck[f]	20-25	28	0.994	(0.120)	
	26-30	25	0.983	(0.147)	
lumbar spine, L2-L4[f]	20-25	28	1.153	(0.123)	
	26-30	25	1.186	(0.106)	
Greek					
femoral neck[g]	20-29	33	0.923	(0.11)	
lumbar spine, L2-L4[g]	20-29	33	1.033	(0.10)	

[a] as determined using Hologic QDR-1000 DXA, Looker *et al.*, 1995

[b] as determined by standardized BMD units cross-calibrated from various DXA machines, Hanson 1997

[c] as determined using Lunar DPA+, Petley *et al.*, 1996

[d] as determined using Lunar DXA, Truscott *et al.*, 1997

[e] as determined by Hologic equivalents, cross-calibrated from various DXA machines, CaMos preliminary data 1998

[f] as determined using Lunar DPA, Laitinen *et al.*, 1991

[g] as determined using Norland XR-26 MARK II DXA, Hadjidakis *et al.*, 1997

D.3.3. T-score Criticized

Recently the use of t-scores has been criticised (Hodsman, 1998; Webber, 1998) and the use of absolute BMD measurement cut-offs have been suggested as a more appropriate diagnostic strategy for osteoporosis (Hodsman, 1998; Webber, 1998; Truscott *et al.*, 1998; Murrills *et al.*, 1998). Criticisms have focused on uncertainties attributed to t-score development, such as uncertainty associated with a single BMD measurement, as well as uncertainties in the assumed values for BMD in young adults and the population standard deviation (Webber, 1998). Efforts are underway to reduce the uncertainties associated with young adult reference values by using representative samples of the general population, such as data from the National Health and Nutrition Examination Surveys III data (Looker *et al.*, 1995), and the Canadian Multicentre Osteoporosis Study (CaMos, 1995). Overall, t-scores are useful provided the proper reference data are applied. Evaluating BMD at more than one site, e.g. at the femoral neck and lumbar spine, should further reduce potential uncertainties associated with t-score diagnostic applications. Currently, the Ontario government requires that a minimum of 2 DXA measurements be taken at the spine and hip. Single site testing is paid only when 2 sites are technically infeasible (Ontario Ministry of Health, 1998b).

Bone densitometry is an established tool for the diagnosis of osteoporosis, since prospective data show that BMD is significantly associated with the risk of future fracture. This association is partly independent of age, and other significant predictors of fracture including falls, cognizance, and mobility (Jergas & Gluer, 1997). The predictive capability of BMD for fracture is comparable, if not better than that of blood pressure for stroke, and than that of serum cholesterol for cardiovascular disease (Marshall *et al.*, 1996). Nevertheless, a wide overlap exists between those patients who will develop a fracture and those who will not (Jergas & Gluer, 1997). Regardless, early identification of low BMD may be useful to identify those at risk for debilitating osteoporotic fractures, and thus prophylaxis / treatment can be applied to prevent further degenerative bone loss. Here, it is important that one does not rely on manufacturer's data to categorize individuals based on WHO criteria. There is a need for population specific reference ranges to ensure low BMD/osteoporosis is correctly diagnosed.

E. CLINICAL PRACTICE GUIDELINES / PREDICTION RULES

E.1. Clinical Practice Guidelines

Clinical practice guidelines, synonymous with terms such as practice protocols, practice parameters and clinical pathways (Citrome, 1998) are systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical problems (Woolf, 1990). These guidelines are usually the result of extensive literature reviews and reflect the best scientific evidence on effective and appropriate care. Science-based methodology is coupled with expert clinical judgment to develop specific statements and recommendations. The utility of the guidelines in clinical practice is subsequently evaluated by peer and field review to determine whether patient care is improved in terms of better outcomes, improved quality of care, and / or improved cost-effectiveness. Periodic review and revision are incorporated to reflect new research findings and experience with emerging technologies (Agency for Health Care Policy and Research, 1995; as cited in Citrome, 1998). Although practice guidelines have been criticized as representing a "cookbook" approach to medicine (Meeker, 1992), these guidelines do encourage sound medical practice and the implementation of evidence-based medicine (Harpwood, 1998). Clinical practice guidelines are one strategy to assist clinical decision making to improve the effectiveness and reduce variation in practice (Shine, 1997), as well as to reduce unnecessary costs of delivered health care services (Browman *et al.*, 1995; Citrome, 1998).

E.2. Prediction Rules

Clinical prediction rules (clinical decision rules) take practice guidelines a step further, intending to help physicians not only to interpret clinical information, but to reduce uncertainty inherent in medical practice by defining how to use clinical findings to make predictions. Methodological standards for clinical prediction rules were first developed in 1985 by Wasson *et al.*. These standards have recently been amended by Laupacis *et al.*, (1997), and are presented in **Table E.1**. The main changes made by Laupacis and colleagues (1997) were: increased emphasis on prospective validation, reliability of predictive variables and rules, the sensibility of derived rules, and to guide through a course of action rather than presenting a probability.

Table E.1 Laupacis *et al.*'s methodological standards for clinical prediction rules[a]

Outcome
Definition
Clinically Important*
Blind Assessment When Appropriate
Predictive Variables
Identification and Definition
Blind Assessment
Important Patient Characteristics Described
Study Site Described
Mathematical Techniques Described
Results of the Rule Described
Reproducibility
Of Predictive Variables*
Of the Rule*
Sensibility
Clinically Sensible*
Easy to Use*
Probability of Disease Described*
Course of Action Described*
Prospective Validation
Effects of Clinical Use Prospectively Measured

[a] Laupacis *et al.*, 1997

* included in the original methodological standards for prediction rules developed by Wasson *et al.*, 1985

Many of the recommended prediction rule methodological standards are common to the assessment of any scientific study. First and foremost, the outcome for which the prediction rule is created must be clinically important and clearly defined, in sufficient detail to allow replication in other settings (Laupacis *et al.*, 1997). Where possible, the predicted outcome should be biological rather than sociological or behavioral (Wasson *et al.*, 1985). Blind assessment of the outcome / predictor variables is required where appropriate. Not only should there be a clear, clinically sensible and reproducible definition of the variables in a prediction rule, but it is good practice to present information on variables that were not included in the rule, to assure other investigators that all potentially important predictive variables were evaluated (Laupacis *et al.*, 1997). In addition, predictors included in the rule should be simple to collect, and relevant (Wasson *et al.*, 1985), and a clear rationale provided where decisions are made to drop variables based on feasibility and relevance.

Performance of the rule should be described as sensitivity and specificity, including measure of variability such as 95% confidence intervals. Likelihood ratios are particularly useful for tests of prediction rules with more than two response categories. Receiver operating characteristic (ROC) analysis is useful for visual and statistical assessment between the characteristics of one or more

prediction rules. Prospective validation to assess the rule's effects in clinical use is critical. At present most articles presenting prediction rules have not incorporated this feature. To get a true sense of a prediction rule's validity and acceptance, it should be evaluated in a patient population other than the one in which it was developed and validated. As well, the effects of the prediction rule on process and outcome should be documented (Laupacis *et al.*, 1997).

One of the most important criteria of prediction rules is measures of sensibility. The likelihood that a prediction rule will be used is increased if it makes clinical sense, is easy to use and suggests a course of action. This portion of prediction rule development relies on judgement rather than statistical methods. Most clinicians should think that items in the rule are clinically sensible, that no obvious items are missing, that the method of aggregating component variables is reasonable, and that items seem appropriate for the rule's purpose. Ease of use includes factors such as time needed to apply the rule, and simplicity of use. Rules that require extensive calculations or use of a calculator are less likely to be used than rules with simple scoring schemes (Laupacis *et al.*, 1997).

Clinical prediction rules may be employed to help physicians identify patients who require diagnostic tests, treatment, or hospitalization. Examples of multifactorial risk scores, or prediction rules, include: selective radiographic assessment of extremity injuries (McConnochi *et al.*, 1990; Weber *et al.*, 1995; Stiell *et al.*, 1995), hospital admission for community acquired pneumonia (Fine *et al.*, 1997), ICU use for chest pain (Pozen et al., 1984), antibiotic prescribing (Centor *et al.*, 1981; McIsaac *et al.*, 1998), and length of ICU stay following cardiac surgery (Tu *et al.*, 1994; Tuman *et al.*, 1992). These instruments have been able to discriminate between groups at higher and lower risks for the condition of interest, and offer improved efficiencies in the utilization of technology, hospital admission, hospital bed use, medication prescribing, and optimizing resource planning, without adverse effects on patient outcomes. Stiell and colleagues, for instance, developed (1992), and refined (1993) the Ottawa ankle rules for use in emergency departments to assess the need for standard ankle and foot radiographic series. These decision rules have since proven to decrease use of ankle radiography, waiting times, and costs without patient dissatisfaction or missed fractures (Stiell *et al.*, 1994). Likewise, a randomized controlled trial in France found implementation of the Ottawa ankle rules to reduce the number of radiography requests (20% decrease in unnecessary radiographical evaluations) for patients with acute ankle or midfoot injuries (Auleley *et al.*, 1997).

E.3. Guidelines for the Diagnosis of Osteoporosis / Indications for Bone Densitometry

Mass screening for osteoporosis has not been recommended by the Osteoporosis Society of Canada (Scientific Advisory Board of the Osteoporosis Society of Canada, 1996), the Canadian Task Force on the Periodic Health Examination (1994), or the US Preventive Services Task Force (1996). Using DXA to screen high risk groups, however, is essential to facilitate osteoporosis diagnosis, allowing prophylactic treatment in the prevention of further bone degeneration and fracture. Although there are many published guidelines for identifying those at high risk of osteoporosis which provide lists of indications for the diagnostic use of bone densitometry, none have clear indications for who should be selected for DXA testing. The first of these guidelines was published in 1989 by the Scientific Advisory Board of the National Osteoporosis Foundation (NOF) in the United States. This article listed four indications for bone densitometry:

- in estrogen deficient women to diagnose significant low BMD in order to make decisions about hormone replacement therapy (HRT);
- in patients with vertebral abnormalities or roentgenographic osteopenia, to diagnose spinal osteoporosis in order to make decisions about further diagnostic evaluation and therapy;
- in patients receiving long-term glucocorticoid therapy, to monitor BMD and adjust therapy as required;
- in patients with asymptomatic primary hyperparathyroidism, to diagnose low BMD in order to identify those at risk of severe skeletal disease who may be candidates for surgical intervention

(National Osteoporosis Foundation, 1989).

In addition to these four indications, a list of other potential indications requiring further evaluation included factors such as: screening for fracture risk, monitoring therapy, and evaluating high risk patients (amenorrhea, steroid treatment, primary or secondary hyperparathyroidism, anticonvulsant therapy, thyroid replacement, anorexia nervosa, alcoholics, other diseases, multiple atraumatic fractures, disuse). Subsequent guidelines echo NOF guidelines, including indications for DXA use in estrogen-deficient women, long-term corticosteroid use, radiological osteopenia and/or vertebral fractures, other previous fragility fractures, and in primary hyperparathyroidism. In addition, all women with risk factors for osteoporosis around the age of menopause are indicated for DXA for diagnosis of osteoporosis and/or to aid in decisions about estrogen replacement therapy (Scheiber II & Torregrosa; Anonymous, 1997a; Kanis *et al.*, 1997; Scientific Advisory Board of the Osteoporosis Society of Canada, 1996; Society for Clinical Densitometry, 1995; Anonymous, 1997a; Kroger & Reeve, 1998; Scientific Advisory Board National Osteoporosis Foundation, 1989; Miller *et al.*, 1996; Baran *et al.*, 1997; Council for the National Osteoporosis Foundation, 1996;

Eastell *et al.*, 1998). **Table E.2** provides the list of indications endorsed by the European Foundation for Osteoporosis and Bone Disease (Kanis *et al.*, 1994; Kanis *et al.*, 1997), as an example.

Table E.2 European Foundation for Osteoporosis and Bone Disease clinical indications for the diagnostic use of bone densitometry

1 presence of strong risk factors
- estrogen deficiency
  - premature menopause (<45 years)
  - prolonged secondary amenorrhea (> 1 year)
  - primary hypogonadism
- corticosteroid therapy (>7.5 mg/d for 1 year or more)
- maternal family history of hip fracture
- low body mass index (<19 kg/m^2)
- other disorders associated with osteoporosis
  - anorexia nervosa
  - malabsorption
  - primary hyperparathoroidism
  - post-transplantation
  - chronic renal failure
  - hyperthyroidism
  - prolonged immobilization
  - Cushing's syndrome

2 radiographic evidence of osteopenia and/or vertebral deformity
3 previous fragility fracture, particularly of the hip, spine or wrist
4 loss of height, thoracic kyphosis
5 monitoring treatment

(taken from Kanis *et al.*, 1994; Kanis *et al.*, 1997)

On November 5, 1998, the National Osteoporosis Foundation in the United States released their new guidelines for selecting women for bone densitometry, as a physician's guide to prevention and treatment of osteoporosis (1998). These guidelines promote selecting the following women for BMD testing where the results could influence treatment decisions:

1. all postmenopausal women under age 65 who have a risk factor for osteoporosis (besides menopause),
2. all women aged 65 and older regardless of additional risk factors,
3. postmenopausal women who present with fractures,
4. women who are considering therapy for osteoporosis,
4. women who have been on hormone replacement therapy for prolonged periods.

Although these guidelines are more clear than those previously published, the first criterion for selection (postmenopausal women with a risk factor), continues the current uncertainty associated with determining which women should be selected for DXA testing. Therefore, though mass screening is not recommended, given current published guidelines for DXA indications, it is difficult not to use DXA as a screening tool in women over 50 years of age (Lindsay, 1998).

Overall, recommendations for DXA testing have not been evaluated, and are not always clear. For example, many of the guidelines include lists of "risk factors" as indications for DXA testing. However, what constitutes risk factors relevant for selection of densitometry remains unclear. At present, OSC promotes the "rational" use of DXA, yet forewarns poor understanding of clinical indications for DXA use (Sturtridge *et al.*, 1996). OSC acknowledges that further study is required to identify clear guides for DXA referral.

E.4. Screening and Case Finding for Osteoporosis - Current State of Knowledge

Few studies to date have attempted to develop predictive indices for osteoporosis to offer guides for DXA referral; performance has been poor in those completed. Reasons for poor performance in predictive models may include omission of important risk factors (unmeasured factors) in modelling equations (Ribot *et al.*, 1995), variation in outcome under study (e.g., osteopenia vs. vertebral fracture vs. bone mineral content), and variation in measures of outcome, including single photon absorptiometry, plain radiographs, DXA etc.

Regardless of the type of osteoporosis, basic principles are the same, i.e., osteoporosis is related to PBM and subsequent bone loss. Thus evaluating factors which influence PBM and bone loss may be used to screen for osteoporosis. Previous attempts at developing a case selective approach to identify those at high risk of osteoporosis are reported in the literature, usually focussing on postmenopausal women. A summary of various predictive models to identify BMD at the lumbar spine or femoral neck are provided in **Table E.3**. Similar studies evaluating independent factors for BMD at the lumbar spine or femoral neck are provided in **Table E.4**.

Besides age and weight, predictors varied between studies evaluated. Again, this may be due to a combination of variation in outcome under observation, different population mix, and predictors under consideration. Weight was a significant correlate in every article reviewed. Similarly, age was an independent determinant in most models evaluated. Here, years since menopause may be a surrogate for age, in addition to estrogen deprivation.

Table E.3 Summary of published articles suggesting predictive equations of low BMD at the femoral neck and/or lumbar spine in women

Authors	Population	Outcome	Statistical Methods	Predictors/ Correlates
Ribot *et al.*, 1992	1565 white women, 40-65 years of age - excluded if hypercortisolism, thyrotoxicosis, hyperparathyroidism, diabetes mellitus, malabsorpiton, or taking corticosteroids, or estrogens	low BMD L2-L4 < -2.0 SD, Lunar DPA (0.92g/cm^2 for their population and densitometer)	multiple stepwise logistic regression on all subjects (1565)	age weight (kg) height (cm) age at menarche menopause duration osteoarthritis
logit ($p_{low\ BMD}$)=	0.057(age)-0.072(weight)-0.023(height)+0.072(age at menarche)+0.0978(menopause)+0.081*(duration)-0.501(osteoarthritis)			
comments	- 21% had low BMD as defined -age, menopause and its duration most influential variables; height, age of menarche follow - subjects with osteoarthritis should have been excluded, finding the presence of osteoarthritis protective may be attributed to effects osteoarthritis has on BMD measurements, making BMD appear higher without added strength.			
Carroll *et al.*, 1997	117 postmenopausal (at least 6 months and high levels of FSH) women, normal and osteoporotic -excluded if any metabolic bone disease or any medication known to affect bone mass.	high-risk spine L1-L4, BMD value where 90% of population had a fracture (≥20% decrease in vertebral height no trauma) -used quantitative digital radiography	-stepwise forward linear regression to predict BMD as a function of current age, years since menopause (YSM), and weight, -log (YSM) since linear function	
lumbar spine BMD = 0.672624+log(YSM)–0.185511+(0.002045*weight)				
comments	- range 0-100 - to estimate proportion of remaining life at "high risk for fracture" - arbitrarily chose fixed age (82), only considered age, years since menopause and weight - no utility, did not look at predictors other than 3 set, nonstandard outcome			
Elliot *et al.*, 1993	320 females volunteers aged 20-76 years, 107 females sampled from electoral roll (20-83 years)	BMD at 2+ sites: L2-L4 femoral neck wards trochanteric -Lunar DPA	linear regression including variables significant by univariate analysis at 2+ sites	<u>women hip:</u> age, weight (kg), family history, inactivity, smoking <u>women spine:</u> age, weight (kg), smoking, delayed menarche
Femoral neck BMD =	0.962-0.0056(age)+0.0041(weight)-0.025(family history)-0.0211(inactivity)-0.035(smoker)-(mean BMD for age)			
Lumbar spine BMD =	1.2975-0.044(age)+0.0058(weight)-0.044(smoker)-0.014(menarche)-(mean BMD for age)			
comments	- assessed height, weight, age, daily calcium, inactivity, family history, smoking, age at menarche - models only explain 25% variance - poor performance may be due to errors in collection of risk factor data, and omission of key risk factors e.g. menopause, estrogen use, and dropping variables due to lack of significance at more than one site (we know predictors for BMD at spine may differ from those at hip).			

Table E.3 Summary of published articles suggesting predictive equations of low BMD at the femoral neck and/or lumbar spine in women [con't]

Authors	Population	Outcome	Statistical Methods	Predictors/ Correlates
Slemenda *et al.*, 1990	124 perimenopausal and postmenopausal white women, community volunteers.	value in the lowest tertile BMD for hip (<0.80 g/cm^2), and spine (<1.056g/cm^2) - DPA at lumbar spine, hip	-linear models, - kept variables p<0.1 in univariate for consideration -assigned scores based on regression coefficients	hip: weight (kg), calcium/ creatinine ratio, dietary calcium spine: height (cm), weight (kg), calcium/ creatinine ratio, cigarette smoking (pack-years), wrist breadth

regression equations:

femoral neck BMD = 0.79+0.001(height)+0.0041(weight)-0.00018(pack-years)-0.00023(calcium/creatinine)+0.00005(dietary calcium)

lumbar spine BMD = 0.69+0.00099(height)+0.0043(weight)-0.00044(pack-years)-0.00020(calcium/creatinine)+0.00002(dietary calcium)

scoring system:

	femoral neck	spine
height (cm)		
<165	n/a	1
165+	n/a	2
weight (kg)		
< 59	1	1
59-63	2	2
64-68	3	3
69-73	4	4
74+	5	5
calcium/creatinine ratio		
<0.367	3	3
0.367-0.177	2	2
0.478+	1	1
dietary calcium (g/d)		
< 1	1	n/a
1 +	2	n/a
cigarette smoking (pack years)		
<2	n/a	3
2-14	n/a	2
15+	n/a	1

comments
- assessed age, height, weight, BMI, personal and family fracture histories, anthropometric measurements (e.g. bicofemoral width and wrist breadth), circumference measurements, skinfold thickness, calcium, caffeine, alcohol, tobacco, urinary markers of bone turnover
- predictive equations for BMD and risk scoring system
- concluded that risk factors for osteoporosis are of limited use to identify women with low BMD around the time of menopause
- sensitivity less than 70%
- used method similar to increasing integer method of score assignment
-did not assess estrogen supplements, physical activity, menopausal status
- included variables which are not simple to identify e.g. calcium/creatinine ratio, dietary calcium

Table E.4 Summary of published articles evaluating independent predictors of low BMD at the femoral neck and/or lumbar spine in women

Authors	Population	Outcome	Statistical Methods	Predictors/ Correlates
Franceschi *et al.*, 1996	1373 women aged 40-64 years -excluded recent malignancy or other severe conditions requiring long-term immobilization	PA spine, L2-L4 -DPA (type not specified)	linear regression analysis -did not explain/detail well	age, menopausal status, weight, BMI
	-evaluated sociodemographic factors, current and past weight, height, smoking, alcohol, coffee, physical activity (both occupational and recreational at ages 12, 15-19, 30-39 and ≥ 50 yrs), menstrual and reproductive factors, menopausal status (at least 12 months) and lifelong history of potentially relevant medical conditions and drug intake. -did not quote significance or show confidence intervals (significance was calculated from provided β and SE(β) in tables), nothing significant except age, weight, bmi, height; however, only controlled for age at screening and menopausal status			
Kroger *et al.*, 1994	1600 perimenopausal women aged 48-59 years via postal enquiry -excluded women with history of a disease or medication known to affect bone metabolism	femoral neck, and lumbar spine (L2-L4) -Lunar DXA	multiple linear regression	hip: weight, menopause (6+ months), age, grip strength, physical activity spine: weight, menopause (6+ months), age, grip strength, alcohol
	- explained 18.7-25.4% of variability - included assessment of all important risk factors for osteoporosis via postal enquiry			
Ooms *et al.*, 1993	348 healthy women over 70 years of age residents in homes or apartments for elderly people -excluded hip fracture, total hip prosthesis, recent urolithiasis, hypercalcemia or sarcoidosis -all reasonably mobile	femoral neck BMD -Norland DXA	-stepwise multiple linear regression of anthropometric measures, weight, age and YSM -unadjusted analysis of other risk factors	weight, YSM unadjusted: impaired mobility loop diuretics oral corticosteroids
	-predict BMD by antropometric measures, age and years since menopause, impaired mobility, medication, smoking (current/past), alcohol use, fracture history, diuretic, corticosteroids, sunshine exposure, calcium - only independent significant predictors via stepwise linear regression were years since menopause and body weight -conclude that BMD cannot be adequately predicted in elderly women -YSM better than age in this age group (mean age 82.3 yrs)			

At present, no universally accepted policy for screening to identify patients with osteoporosis exists. In the absence of such policies, patients are identified as having osteoporosis largely because of a fragility fracture or sometimes by the presence of strong risk factors. BMD measurements can be used to enhance this case-finding approach (Kanis, *et al.*, 1997). Only two studies were identified which use a true case-selective approach for DXA testing which may be used in clinical practice. Michaëlsson *et al.*(1996) suggest body weight as a case selective approach for osteoporosis screening in postmenopausal women. They found that selecting any postmenopausal women who weighed less than 70 kg (about 155 lbs) resulted in a sensitivity of 94%, and specificity of 36% to diagnose osteoporosis (BMD < 2.5 SD below the young adult mean) at the hip, and a sensitivity of 89%, and specificity of 38%, to diagnose osteoporosis at the spine.

Recently, Lydick *et al.* (1998) created a screening tool from linear regression models to identify women likely to have low BMD (≤ -2.0 SD of the young adult normal), who may be selected for DXA. Sampling postmenopausal (amenorrheic for at least 6 months before study entry) women aged at least 45 years from specialty clinics (50% of sites sampled were from family medicine, geriatric, or general internal medicine; 20% from endocrinology specialists; 20% from rheumatology specialists; and 10% from gynaecology specialists), Lydick *et al.* (1998) developed and validated the Simple Calculated Osteoporosis Risk Estimation (SCORE), see **Figure E.1**. This instrument uses a case selective approach to screen for osteoporosis by summing a score based on: age, race, rheumatoid arthritis, history of nontraumatic fracture over 45 years of age, estrogen use, and weight. Authors developed SCORE with a target sensitivity of 90% which yielded at least 40% specificity depending on the subgroup of postmenopausal women under investigation.

SCORE has subsequently been validated using 398 postmenopausal women at least 45 years of age residing within 50 km of Toronto, Ontario, Canada (Cadarette *et al.*, 1998). At the recommended threshold of 6, SCORE had a sensitivity of 90%, specificity of 32%, and a positive predictive value of 64% to identify low BMD (t-score ≤ -2.0SD) at either the lumbar spine or femoral neck. This means that 90% of individuals with low BMD, and 68% (100% - specificity of 32%) of those with normal BMD would be selected for DXA. This high false positive rate would result in unnecessary referrals for DXA.

Variable	Score	if woman:
Race	5	is NOT black
Rheumatoid Arthritis	4	HAS rheumatoid arthritis
History of Fractures	4	for EACH TYPE (wrist, rib, hip) of nontraumatic fracture after age 45 (maximum score = 12)
Age	3	times first digit of age in years
Estrogen	1	if NEVER received estrogen therapy
Weight	-1	times weight divided by 10 and truncated to integer

SCORE: equals the sum of the above

THRESHOLD SCORE: a SCORE of 6 or greater

EXAMPLE: a 126-pound, 67 year old white woman with a history of rheumatoid arthritis, no history of fracture, and a history of estrogen therapy would have a SCORE of 15: 5 (for race) + 4 (for rheumatoid arthritis) + 18 (3x6 for age) + 0 (previous estrogen therapy) - 12 (-.1x12 for weight). This woman should be referred for bone densitometry (score above threshold of 6).

Figure E.1 The Lydick *et al.* (1998) Simple Calculated Osteoporosis Risk Estimation

Lydick and colleagues acknowledge that alternative thresholds should be considered when applying SCORE to different populations. However, no threshold SCORE was appropriate in the Toronto population-based sample: the area under the ROC curve was 0.71 (SE=0.025), a value of borderline utility (Swets, 1988). A number of methodological problems, such as sample selection, and choice of outcome may have contributed to SCORE's poor performance. First, Lydick *et al.*'s subjects were recruited from specialty clinics, and therefore SCORE may not be generalizable to all postmenopausal women. Rheumatoid arthritis, for instance, may be a surrogate for long term glucocorticoid use, a known cause of secondary osteoporosis (Scientific Advisory Board-Osteoporosis Society of Canada, 1996; Kanis *et al.*, 1997; Sambrook, 1996). Furthermore, more women in the Lydick cohorts were taking estrogens (27% in Toronto sample, vs. 45% in Lydick development cohort, and 54% in Lydick validation cohort, $p<0.01$). Estrogen therapy (ovarian hormone therapy) is recognized as a therapeutic intervention for the prevention of bone mineral loss in the menopausal years (Kanis et al., 1997; Scientific Advisory Board of the Osteoporosis Society of Canada, 1996; Council of the National Osteoporosis Foundation, 1996; Joseph & Hughes, 1997). As such, fewer women in the Lydick sample would be expected to have low BMD, as we observed (low BMD at both femoral neck and lumbar spine: 26% in Toronto sample, vs. 18% in Lydick development cohort, and 17% in Lydick validation cohort, $p<0.01$).

Beyond sampling issues, Lydick *et al.* combined BMD from different DXA manufacturers, and relied on respective manufactured reference populations to determine low BMD. BMD figures derived using equipment from different manufacturers, however, differ considerably if not expressed in standardized / cross-calibrated BMD units (Black & Fogelman, 1997a; Simmons *et al.*, 1997; Formica, 1998). In addition, reference populations differ between manufactured DXA machines, therefore low BMD by definition (≤ -2.0 SD of the young adult normal as determined by the manufacturer's reference population) is different between manufactured DXA machines (Blake & Fogelman, 1997a; Faulkner *et al.*, 1996). Pooling t-scores of BMD from 3 different manufactured DXA machines without cross-calibration may have affected development of SCORE from linear regression models of femoral neck BMD t-scores. In addition, focusing SCORE development on BMD of the femoral neck decreased SCORE's diagnostic ability to identify low BMD at either the femoral neck, or the lumbar spine. Above and beyond performance issues, based on methodological standards for prediction rules (Laupacis *et al.*, 1997), it is evident that the Lydick SCORE may not be a useful instrument in clinical practise. Lydick *et al.*'s SCORE is not only awkward to calculate, but it lacks content validity. Rheumatoid arthritis for instance may either be a surrogate for long-term glucocorticoid therapy, or possibly a risk factor in Lydick *et al.*'s highly selective population. However, applicability in the general population is questionable.

No clear effective guide exists to identify those at high risk of low BMD who should be screened using DXA. Overall, specificity of the SCORE is poor. At the recommended threshold of 6, 68% of those with normal BMD would be selected for bone densitometry (Cadarette *et al.*, 1998). Similarly, Michaëlsson's (1996) suggested screening approach is weak, selecting women who weigh less than 70 kg had a sensitivity of 72% to identify low BMD in Cadarette and colleagues' Toronto sample. There is a need to develop an effective simple screening approach to select patients for bone densitometry. This should be a priority to ensure not only that patients with low BMD are identified and treated/given prophylaxis as required to prevent debilitating osteoporotic fractures, but to protect against unnecessary DXA testing.

F. METHODS

F.1. Study Sample

CaMos Ontario baseline data were used for the purposes of this thesis. This included data from three CaMos sites: Hamilton, Kingston, and Toronto. BMD was measured using Hologic QDR 1000 DXA machines in both Kingston and Toronto, and a Lunar DPX Alpha in Hamilton.

All cognitively normal subjects (MMSE score > 20, Folstein *et al.*, 1975) with DXA data at both the femoral neck, and the lumbar spine (L1-L4) were eligible. All participants with a diagnosis of osteoporosis, or who were taking bone sparing prescription medication (calcitonin, didronel/etidronate or fluoride) at the baseline interview, were excluded.

F.2. Primary Outcome Variable

The main objective of the study was to identify which combination of clinical indicators best predicts low BMD, and thus who should be selected for confirmatory diagnosis using DXA. Creating an index to select those with WHO defined osteoporosis (a value 2.5 SD below the young adult value) is too conservative, as we aspire to prevent BMD reaching this low level, where fracture risk is highest. An outcome of -1.0 SD on the other hand may be too inclusive, resulting in unnecessary DXA referrals. From this, a BMD value ≤-2.0 SD of the young adult value was selected as the primary outcome of interest. Low BMD at either the femoral neck, or lumbar spine is clinically relevant for prophylactic treatment to prevent osteoporosis and possible fragility fractures (Scientific Advisory Board of the Osteoporosis Society of Canada, 1996; Council of the National Osteoporosis Foundation, 1996). Therefore a t score ≤ -2.0 SD of the Canadian female young adult mean (aged 29-39 years, 0.6157 g/cm^2 at the femoral neck, and 0.7904 g/cm^2 at the lumbar spine) was used to identify those with low BMD at either the femoral neck, or lumbar spine, our primary outcome of interest.

F.3. Predictor (independent) Variables

Information on risk factors was obtained through responses to the CaMos interview-based questionnaire. Attempts were made to group continuous variables consistent with other studies, and/or groupings recommended in the literature. Variables where at least 4% of the data were missing were dropped from the variable pool (e.g. family history of osteoporosis, greatest height). Categories were collapsed where proportions of low BMD were similar, as determined by Mantel-Haentzel chi-square. A description of the most important variables, follows:

F.3.1. Heredity

Race / ethnicity was assessed by the question: "how would you best describe your race or colour". All subjects documented as Chinese, Japanese, and/or Korean were grouped under "Asian" for demographic purposes.

F.3.2. Lifetime Exposure to Gonadal Hormones

Lifetime exposure to gonadal hormones in women was assessed by: age at menarche (before age 14, and 14 years of age or more), parity (yes/no), menopause (menstrual periods stopped for more than 1 year), tamoxifen use (see section F.3.5.), use of oral contraceptives, current/past/ever estrogen use, current estrogen use (yes/no), ovary and uterus removal, and breastfeeding.

F.3.3. Environmental Influence

Physical activity was assessed in a number of ways, including: current physical activity, and frequency, physical activity as a teen, and identification of previous immobilization. Influence of **weight** was explored based on groupings suggested by Michaëlsson *et al.* (1996), as at least 70 kg. Further exploration created categorization as: less than 60kg, at least 60kg but less than 70kg, and at least 70kg based on comparable risk within groups (i.e. homogeneous OR). In addition to weight, body mass index (BMI) was evaluated, first grouping as less than 20 kg/m^2, 20-24 kg/m^2, 25-26 kg/m^2, and at least 27 kg/m^2. In addition, Kanis' (1997) suggestion was evaluated comparing those with at least 19 kg/m^2, to those with less. The final BMI grouping based on proportions at risk were: less than 25 kg/m^2, between 25 and 27 kg/m^2, and at least 27 kg/m^2.

The OSC recommends that all individuals aged at least 19 years consume at least 1000 mg of **calcium** per day (Murray, 1996). Therefore a binary variable was created for calcium intake as less than 1000 mg/d, and at least 1000 mg/d. A second grouping was developed based on Canadian recommended nutrient intakes, i.e., at least 700 mg/d in women aged 25-49 years, and at least 800 mg/d in women aged at least 50 years. **Tobacco** use was assessed as cigarette smoking both as never/past/current, and never/ever. A variable to assess quantity of **alcohol** consumption as the number of drinks per week was derived from queries of the number of drinks consumed in the past year. This variable was then grouped by number of drinks per week, such as: none, less than seven, at least seven; none, less than 3, between 3 and 7, and at least seven drinks per week; and ever/never in the past year.

F.3.4. Predisposing Medical Conditions

The presence of various self-reported comorbid conditions were identified and assessed from the CaMos questionnaire, including: osteoarthritis, rheumatoid arthritis, diabetes (type I or type II), thyroid disease (hyperthyroidism or hypothyroidism), liver disease, scoliosis, eating disorders, breast cancer, uterine cancer, inflammatory bowel disease, kidney stones, hypertension, heart attack, stroke, neuromuscular disease, kidney disease, phlebitis / thrombophlebitis, Paget's disease of bone, and chronic obstructive pulmonary disease. In addition, history of various surgeries was assessed, including: parathyroid, thyroid, stomach, intestine, and gall bladder.

The CaMos questionnaire queried previous fracture including assessment of a trauma code (severe trauma, minimal trauma, and other disease), age at which the fracture occurred, and site of the fracture. Any minimal trauma fracture occurring at an osteoporotic site (back, ribs, pelvis, forearm/wrist, or hip), was categorized as a previous minimal trauma osteoporotic site fracture. Various combinations were explored based on age of minimal trauma fracture. The final grouping for analysis was: any osteoporotic site minimal fracture occurring at an age of at least 45 years, or no such fracture.

F.3.5. Medication

CaMos had specific questions to identify use (daily use for more than one month) of the most important drugs known to affect BMD, i.e. thyroid pills, dilantin/phenobarbiton, tamoxifen, calcitonin, didronet/etidronate, fluoride, diuretics, laxatives, cortisone/prednisone. The use of these

medications was quantified in terms of months taken. Use of thyroid pills, dilantin (anti-convulsive), tamoxifen, laxatives, and diuretics were assessed globally as yes (taken daily for more than one month), or no. In addition, cortisone/prednisone (corticosteroids) use was quantified into variables of at least 12 months of use; including at least 12 months of: oral corticosteroid use, inhaled glucocorticoid use, and oral or inhaled corticosteroid use.

In addition, the CaMos questionnaire queried current medications and self administered supplements. Unfortunately, these data were truncated to 11 characters, such that it was not feasible to identify specific medication names. As an example, although previous diuretic use was asked as a global question, type of diuretic was not identifiable through the current drug use question. Thus the distinction between type of diuretic used was not possible using CaMos baseline data. This was a limitation in the data because long duration thiazide diuretic use may be protective from fractures (Rejnmark *et al.*, 1998; Jones *et al.*, 1995), whereas loop diuretics are associated with decreased BMD and increased risk of fracture (Rejnmark *et al.*, 1998).

F.4. Statistical Analyses

F.4.1. Preliminary Data Analysis

Given the potential variation in osteoporosis pathogenesis between the sexes, all analyses were stratified by sex. Demographic data for a number of those who refused participation in the CaMos study were determined. These refusals were considered partial participants, as they provided basic demographic information such as age and race / ethnicity, over the telephone. These demographic data were compared to CaMos participants before exclusion criteria to assess generalizability of the study's sample. CaMos participants meeting inclusion criteria (cognitively normal subjects not taking bone sparing medication use, without a diagnosis of osteoporosis, and with DXA data at both the femoral neck, and lumbar spine) were randomly allocated into two groups. To increase the power in the model development, approximately 2/3 of the sample was allocated for model development, and 1/3 for model validation. Basic demographic data were tabulated for comparison of development and validation cohorts. Categorical variables were compared using Pearson chi-square tests for independent proportions, and *t*-tests were used to examine continuous variables.

The proportions of the study sample with low BMD and osteoporosis determined using: (i) the Canadian female young adult reference (CaMos unpublished data), and (ii) the manufacturer's results, were tabulated and compared using the Pearson chi-square statistic. From this preliminary analysis, it was determined that the prevalence of low BMD among men, regardless of age, was too low (less than 10%, see **Appendix A**) for developing a useful clinical index. Similarly, only one female aged less than 45 years (1 %) was identified with low BMD. Therefore creation of a risk scoring system to identify low BMD was restricted to women aged at least 45 years.

Pearson correlation coefficients of BMD at the femoral neck and lumbar spine, and Spearman correlation coefficients of low BMD (DXA bone mineral density $\leq$ -2.0 SD from the Canadian female adult normal) at the femoral neck, lumbar spine and at either site were computed to assess the relationship of BMD at the femoral neck, compared to that at the lumbar spine. Confidence limits for correlation coefficients were derived based on Fisher z transformation of the correlation coefficient (Rosner, 1995; Kleinbaum *et al.*, 1998).

F.4.2. Model Development

Given that factors which contribute to low BMD at the femoral neck may differ from correlates of low BMD at the lumbar spine (section D.1.2.), the first step was to develop logistic regression models of low BMD at the femoral neck and lumbar spine separately. The relationship between each risk factor, and the presence of low BMD at each of the femoral neck, and the lumbar spine (L1-L4) were determined. Chi-square analyses and unadjusted logistic regression (to estimate odds ratios), were used for all categorical variables, and *t*-tests for continuous variables. The odds ratio (OR) is a measure of the odds of an outcome occurring in one group relative to the odds of an outcome occurring in a reference group. An OR greater than 1 indicates a risk greater than that for the reference group, whereas an OR less than 1 indicates a risk less than that for the reference group. The reference group was selected to be protective compared to other categories for each variable under consideration, therefore producing OR estimates above one. This may facilitate the creation of a simple additive scoring system from OR/regression coefficient estimates.

All variables with a p-value of 0.2 or less, controlling for age grouped as: 45-54 years, 55-64 years, 65-74 years, at least 75 years, as well as all major known risk factors, were kept in the variable pool for consideration in multivariate logistic regression modeling. Spearman correlations were determined to identify collinearity between variables before multivariate modeling began. Biologically plausible interactions were also considered in model development. Backward selection and stepwise approaches were used in model building (Kleinbaum *et al.*, 1998).

A simplified predictive index for low BMD at either the femoral neck or lumbar spine was derived inclusive of femoral neck low BMD and lumbar spine low BMD equations. That is, variables in the best model to predict low BMD at the femoral neck, and variables in the best model to predict low BMD at the lumbar spine, were considered for inclusion into a model to predict low BMD at either of these two sites (femoral neck or lumbar spine). Effort was made to maximize predictive performance using variables that: can be easily determined in clinical practice, and can be reliably determined from self-report (given the nature of data collection).

Score assignment for each predictor was determined in three ways. First, scores were assigned by rounding the OR estimates for each risk factor in the final model to the nearest integer, assigning a score of zero to the reference group. This procedure has been used previously to develop length of ICU stay following cardiac surgery (Tu *et al.*, 1994; Tuman *et al.*, 1992). Similarly, the Charlson comorbidity index was created from simple addition of hazard ratios (Charlson *et al.*,1987). Second, the model was evaluated using a scoring system based on logistic regression coefficient estimates. Here, logistic regression coefficient estimates were multiplied by ten and then rounded to the nearest integer to develop an additive scoring system, a method suggested by Harrell (1996), who critiqued both the Charlson comorbidity index (1987), and Tu *et al.*'s (1994) methods of score creation. Third, considering the simplest possible additive system, a final scoring system was developed based on assigning values by increasing integer, starting with zero for the reference category. This method was used by McIsaac *et al.* (1998) in creation of a score to guide antibiotic prescription and throat culture use in patients presenting with sore throats.

F.4.3. Model Assessment

The ability of the multiple logistic regression models and the clinical risk scoring systems to predict low BMD at either the femoral neck or lumbar spine were evaluated non-parametrically. Receiver operating characteristic (ROC) analyses were used to evaluate the discriminatory performance of the clinical risk scoring system to identify low BMD at various cut points (thresholds). ROC is a graphic means for assessing the ability of a screening test to discriminate between healthy and diseased persons (Last, 1995). An ROC curve is constructed by plotting the sensitivity (true positive fraction) on the vertical axis against the false positive fraction (1-specificity) on the horizontal axis for each decision threshold (Metz, 1978; Hanley, 1989). ROC analysis is useful for comparing different techniques for it describes the inherent detection characteristics of tests, independent of disease prevalence and decision threshold effects (Metz, 1978; Metz, 1986; Hanley & McNeil, 1982). The area under the ROC curve provides this summary of diagnostic accuracy, interpreted as the average sensitivity over all decision thresholds (Begg, 1991; Swets, 1988; Hanley & McNeil, 1982). Values for area under the ROC curve range from 0.0 to 1.0, with 1.0 corresponding to perfect prediction, 0.5 to random performance (equivalent to chance alone; nondiscriminatory test), and 0.0 to completely incorrect prediction (Heffner *et al.*, 1995; Vida, 1993). Swets' paper (1988) depicts values for area under the ROC curve of 0.50 to 0.70 to represent low accuracy, where the true positive proportions are not much greater than the false positive proportions anywhere along the ROC curve. Values for area under the ROC curve between about 0.70 and 0.90 are reported useful for some purposes, and area under the ROC curve above 0.90 may be considered highly accurate. Areas under the ROC curves were produced using the trapezoidal rule, a method comparable to the Wilcoxon, or Mann-Whitney statistic when used with a large number of points, i.e., at least 5 or 6 cut points (Hanley & McNeil, 1982; Vida, 1993). Statistical properties of the area under ROC curves were determined using DeLong *et al.*'s (1988) theory based on the Mann-Whitney statistic (generalized U-statistic). This method is recommended to estimate the standard error nonparametrically for area under ROC curves, as it is comparable to the sampling variability obtained from parametric approaches (Hajian-Tilaki *et al.*, 1997).

Measures of criterion validity including sensitivity, specificity and positive predictive values (PPV) were evaluated at each threshold. Sensitivity (true positive fraction) identifies the probability of correctly diagnosing someone with low BMD, specificity (true negative fraction) is the probability of correctly identifying a person who should not be selected for DXA (normal BMD), and PPV

provides meaning to a positive result, identifying the probability of low BMD in those selected for DXA evaluation (Hanley, 1989; Vida, 1993; Lilienfeld & Stolley, 1994). The recommended threshold score to select patients for bone densitometry was chosen at a threshold with at least 90% sensitivity. This was to ensure that few subjects (less than 10%) with low BMD would be missed by the case-selective screen. Lydick and colleagues (1998) used the same criteria in an attempt to develop a case finding approach for bone densitometry. The best system for assigning scores was determined, not only by comparing performance, but considering the ease of using each scoring system. From this point, the potential screening tool was termed an Osteoporosis Risk Assessment Instrument (ORAI).

Final attempts to simplify the ORAI were made by eliminating least significant variables from the scoring system. As the model to identify low BMD at either the femoral neck or lumbar spine was developed from significant independent predictors of the best models to predict low BMD at each site individually, not all predictors were independent predictors to identify low BMD at either site. The predictive ability of each ORAI was further evaluated by eliminating significant predictors, including restriction to age and weight, and weight alone, the most important clinical predictors of low BMD (see section **E.4.**). Sensitivity analyses were performed by calculating and comparing each ORAI's predictive performance: i) in various subgroups, such as study site specific, postmenopausal only, premenopausal only; ii) to predict low BMD at the femoral neck, and lumbar spine separately; and iii) evaluating the discriminatory performance to identify BMD below -1.0 SD of the young adult normal, and to identify osteoporosis (≤-2.5SD of the young adult normal).

Final comparisons between developed ORAIs were made based on selection outcomes of each ORAI. Here, selection outcomes (i.e. proportion selected), for each ORAI were stratified in four categories of women based on BMD: normal BMD (t-score ≥ -1.0 SD), between -1.0 SD and -2.0 SD of the young normal, BMD≤-2.0 SD of the young normal, but not osteoporotic (t-score > -2.5 SD), and osteoporotic (t-score ≤-2.5 SD). The proportions in these four groups as selected by each ORAI, were used for comparisons to mass screening. This simulation was based on a sample of 1000 women aged at least 45 years of age. The proportion of the four categories in the development cohort were used with the proportion selected by each respective ORAI to identify the amount selected / not selected in each group, and determine the total amount selected/not selected by each

ORAI. The total percent not selected may be viewed as the percent DXA savings over a mass screen. Based on discriminatory performance, sensitivity analyses, and the simulation mass screen comparison, a final ORAI was selected.

F.4.4. Osteoporosis Risk Assessment Instrument Validation

The final ORAI was validated in a separate cohort of women, the validation cohort. Again, ROC analyses were conducted to assess the discriminatory performance of the instrument in the validation cohort. Similar sensitivity analyses were performed by calculating and comparing the risk score's predictive performance in various population subgroups, in addition to evaluating the scoring system's ability to predict BMD below -1.0 SD of the young adult normal, osteoporosis, and BMD $\leq$-2.0 SD of the young adult normal, at the femoral neck, and spine separately. Simulation comparisons to a population screening of 1000 women were repeated for each ORAI in the validation cohort.

G. RESULTS

G.1. Preliminary Analyses

G.1.1. Data Source Response Rates

CaMos' Ontario sample comprised 2090 women, and 952 men, reflecting a 42% (29% in Toronto, 49% in Hamilton and 50% in Kingston) response rate. About one half (44% in Toronto, 61% in Hamilton, 48% in Kingston), of all eligible individuals (at least 25 years of age) contacted answered a few background questions over the telephone. Demographic characteristics of CaMos participants, and non-responders (individuals who refused participation in CaMos, but did answer a few questions regarding demographics - partial participants) are tabulated in **Table G.1**. The following inferences regarding CaMos participants are based on comparisons to individuals contacted who refused participation in the study (non-responders, or partial-participants), but who agreed to answer a few questions over the telephone. Male participants were significantly different from non-responders in all areas evaluated. Although sampling groups (age groups) were significantly different between participating and non-responding women ($p<0.05$), the average age of a woman participating (62.9 years) was comparable to the average age of a non-respondent (63.5 years, $p=0.274$). Overall response rates among women by age group were similar (range from 71-77%, $p=0.563$), except in those aged at least 81 years, for which only 64% of those contacted participated in the study. The best response rates among men were seen between the ages of 56 and 80 years, with 72% participation. The response rate in men aged less than 56 years was 60%, and in those aged over 80 years was 67%.

G.1.2. Study Sample

Data from 1701 women with DXA data at both the femoral neck, and the lumbar spine were identified from CaMos' Ontario sites (Kingston, Hamilton and Toronto). Of these, 9 were excluded due to cognitive impairment. A further 170 were excluded for taking bone sparing prescription medication (calcitonin, didronel/etidronate or fluoride), or having a diagnosis of osteoporosis. This yielded a total sample size of 1522 women aged at least 25 years. Random allocation created a model development group with 1020 women, and a validation group of 502 women. Restricting

analyses to women aged at least 45 years of age resulted in a final sample size of 1376 women, or 926 allocated to the development phase, and 450 to validation. Demographic characteristics of these groups are tabulated in **Table G.2.** Development and validation groups were similar in all respects evaluated ($p>0.05$). All further analyses are restricted to women aged at least 45 years of age.

G.1.3. Prevalence of Low Bone Mineral Density and Osteoporosis

The prevalence of both low BMD (≤-2.0 SD of the young adult normal), and osteoporosis (≤-2.5 SD of the young adult normal) were significantly lower using the Canadian reference compared to results produced directly from DXA machines ($p<0.01$), regardless of BMD site under observation. The prevalence of osteoporosis just about doubled using DXA reference data, compared to the Canadian normal reference. Using Canadian reference data, 6.2% (SE=0.79) were identified with osteoporosis at the femoral neck, 7.0% (SE=0.84) at the lumbar spine, and 10.9% (SE=1.02) at either; compared to 18.5% (SE=1.28), 12.8% (SE=1.10) and 23.9% (SE=1.40) respectively relying on manufactured reference data. Similarly, 15.4% (SE=1.19) had low BMD at the femoral neck, 14.8% (SE=1.17) at the lumbar spine, and 22.7% (SE=1.38) at either site using the Canadian reference data; compared to 31.4% (SE=1.52), 21.7% (SE=1.35), and 38.4% (SE=1.60) respectively observed using manufactured reference data. These data are tabulated in **Appendix A.**

G.1.4. Correlations Between BMD at the Femoral Neck and Lumbar Spine

The Pearson correlation coefficient between BMD at the femoral neck, and BMD at the lumbar spine was 0.659 (95% CI = 0.621, 0.694). Spearman correlation between low BMD (≤-2.0 SD of the young normal) at the femoral neck, and low BMD at the lumbar spine was only 0.411 (95% CI = 0.356, 0.463). Correlations between these two sites, and the primary outcome of interest (low BMD at either site), were 0.789 (95% CI = 0.763, 0.811) for the femoral neck, and 0.769 (95% CI = 0.742, 0.794) at the lumbar spine.

G.2. Model Development

The unadjusted OR estimates for all major risk factors for osteoporosis, in addition to variables associated with low BMD at either the femoral neck, or the lumbar spine with a p-value of 0.2 or less (controlling for age), are tabulated in **Table G.3**. The highest correlations between predictor variables were as expected (variables correlated by nature, surrogates, or subsets of each other): body mass index (BMI) and body weight groups (r=0.810), breast cancer and tamoxifen use (r=0.612), hypertension and diuretic use (r=0.547), estrogen and progesterone use (r=0.529), and between age and menopausal status (r=0.486). No interactions explored (weight and: physical activity, alcohol consumption, diabetes type II, thyroid drug use, diuretic use, age, corticosteroid use, sunlight exposure, and estrogen use; calcium consumption and: kidney stones, alcohol consumption, race and physical activity; age and: menopausal status, gallbladder surgery; and alcohol consumption and: physical activity, falls in past month) were significant.

Tables G.4 and **G.5** present the results of logistic regression models to identify low BMD at the femoral neck and lumbar spine respectively. Although models to identify low BMD at the femoral neck are statistically different ($p<0.05$), based on the differences between -2 log likelihoods, the predictive performance of the variations are comparable (comparing area under ROC curves, $p > 0.05$). The same observation occurs for predictive models to identify low BMD at the lumbar spine since area under each model's ROC curve is comparable ($p > 0.05$). Age, weight, and current estrogen use were common independent determinants of low BMD at both the femoral neck, and lumbar spine. Other correlates of low BMD varied between the two bone sites, and thus may each independently be important in identifying low BMD at either the femoral neck, or lumbar spine (our primary outcome of interest). Inclusion of physical activity, and previous minimal trauma fracture from age 45 for instance, was restricted to the hip; whereas menopause and diuretic use was restricted to prediction of low BMD at the lumbar spine. Although diuretic use was an independent determinant of low BMD at the lumbar spine, recall from section F.3.5., that it was not possible to identify type of diuretic use from CaMos baseline data. Discriminatory performance of logistic regression models for low BMD at either site were similar when diuretic use was included (area under the ROC curve=0.818, SE=0.016), to when diuretic use was excluded (area under the ROC curve=0.812, SE=0.016). Therefore diuretic use was not included in the combined model to predict low BMD at either the femoral neck or lumbar spine. The clinical risk scoring systems for low BMD at either the femoral head or lumbar spine were created using a 6-item osteoporosis risk

assessment instrument (ORAI) including: age, weight, current estrogen use, menopausal status, current physical activity, and minimal trauma osteoporosis site fracture over 44 years of age. Parameter estimates for the adjusted 6 item logistic regression model are provided in **Table G.6**. Comparisons of the additive ORAIs developed from OR estimates, regression coefficients estimates, and increasing integers, are included in **Table G.7**. The threshold score to ensure at least 90% sensitivity was 12 using the OR estimate method, 38 using the regression coefficient estimates, and 4 using the increasing integer method (**Appendix B**). All three scoring systems promote the selection of all women aged at least 65 years (all postmenopausal), who are not currently taking estrogen for bone densitometry.

The increasing integer method of assigning scores was the simplest method of score derivation (range 0-9), followed by the OR estimate method (range 0-28), and finally the addition of regression coefficient estimates (0-74). The overall discriminatory performance of all three methods of score assignment was similar based on the area under ROC curves ($p>0.05$). However, specificity of the increasing integer method (38.8%) was significantly lower than the additive system using OR estimates (46.6%, $p<0.05$). Based on performance at the chosen cut point (to ensure at least 90% sensitivity), and on ease of use, the OR estimate method of assigning scores was selected over the regression coefficient estimates, or the increasing integer method for derivation of a final ORAI. Summary of score assignment and discriminatory performance of OR estimate based additive ORAIs, with one through six items, are presented in **Table G.8**.

The discriminatory performance of the one item ORAI (weight only) was significantly less than that observed for ORAIs with at least 3 items (at least age, weight and current estrogen use; based on area under ROC curves, $p<0.05$). It must be noted however, that area under the curve for the one item ORAI may be underestimated, given that it has less than 5 cut points. Regardless, no threshold score from the one item ORAI permitted close to 90% sensitivity, in fact, sensitivity permissible from the one item ORAI is significantly lower than all other ORAI examined ($p<0.05$). Weight alone is clearly insufficient as a case-selective approach for bone densitometry testing. Although the specificity of the one item approach is higher, it is not statistically different from that observed in the 5 and 6 item ORAIs. In addition, the specificity for all ORAIs with at least 2 items was selected based on a score with at least 90% sensitivity. A higher threshold score may be selected if one wishes to increase specificity at the expense of the sensitivity. Taking the 3-item ORAI, for

example, using a threshold score of 10 would result in a sensitivity of 87.1%, and specificity of 50.7%, which although not statistically different from weight alone (80.5% and 53.6% respectively, $p>0.05$), may be considered clinically superior. **Appendix C** tabulates criterion validity for various threshold scores for each of the OR estimate based additive scoring systems.

ORAIs with at least 4 items promote selection of all women at least 65 (all postmenopausal) years of age who are not currently taking estrogen. Both the ORAI with 3 items, and the ORAI with 2 items promote selection of all women at least 65 years of age, regardless of estrogen use. This suggests that ORAIs with at least 4 variables may be more case-selective. However, given that the criterion validity in terms of sensitivity and specificity of the 3 variable model is similar to more complex ORAIs (ORAIs with 4 to 6-items), simplicity of the 3 variable model is preferred. **Tables G.9** and **G.10** provide further information of each ORAI's discriminatory performance in various sub-samples of women, and for various outcomes. Specificity of the 2 variable model, although not statistically less, is clinically inferior, demonstrating consistent lower specificity of about 5% in all sensitivity analyses. **Table G.11** presents the proportion of women selected by BMD group for each ORAI evaluated. The proportions reported in **Table G.11** (percent each ORAI selects), are subsequently applied in a simulation of 1000 women aged at least 45 years of age with BMD distribution comparable to that observed in the development cohort. These data are tabulated in **Table G.12**. The total number "not selected" for DXA testing, as determined by each ORAI, estimates the proportion of DXA testing saved compared to a mass/population screening approach. Again, the ORAI with 3-item ORAI demonstrates comparable case-selective ability; this ORAI may save 38.5% of DXA testing from a "mass" screening approach, without compromising sensitivity to identify those with low BMD and osteoporosis as observed using weight alone (73.4%, and 88.1% respectively).

G.3. Osteoporosis Risk Assessment Instrument Validation

The 3-item ORAI was chosen as a clinical risk scoring system to select women for bone densitometry, **Figure G.1**. **Table G.13** provides summary statistics of its performance in various subgroups of the validation cohort, and for various outcomes. ROC curves of the 3-item ORAI to identify low BMD at the femoral neck, the lumbar spine and either site are provided in **Figures G.2** and **G.3** from the development and validation cohorts respectively. Discriminatory performance of the 3-item ORAI was similar in the development cohort (area under the ROC curve=0.789,

SE=0.017) and validation cohort (area under the ROC curve=0.770, SE=0.024). At the recommended threshold score of 9, the 3-item ORAI had a sensitivity of 90%, specificity of 45%, and PPV of 33% in the development cohort, and sensitivity of 93%, specificity of 46%, and PPV of 35% to identify low BMD in the validation set. In addition, sensitivity was 97% in the development cohort, and 94% in the validation cohort to select those with osteoporosis. When restricted to WHO defined osteopenia, specificity increased to 57% and 58% in the development and validation cohorts respectively. **Tables G.14** and **G.15** provide selection summaries of each ORAI, for comparative purposes to the recommended 3-item ORAI. In addition, using the 3-item ORAI may save at least 38% of unnecessary DXAs that would result from a mass screen of all women aged at least 45 years, a value comparable to ORAIs with more items, with the benefit of added simplicity.

Table G.1 Demographic characteristic of CaMos participants[a] and non-responders[b]

	Females					Males				
	Participants (N=2090)		Non-Responders (N=735)			Participants (N=952)		Non-Responders (N=475)		
	n	mean (SD)	n	mean (SD)		n	mean (SD)	n	mean (SD)	
Age in years	2090	62.9 (12.8)	735	63.5 (14.2)		952	60.1 (14.4)	475	57.0 (15.1)**	
	n	(%)	n	(%)	p[c]	n	(%)	n	(%)	p
Race[d]										
White	1974	94.5	684	91.9	0.004	853	89.6	410	85.1	0.001
Asian	62	3.0	22	3.0		52	5.5	19	3.9	
Other	54	2.6	38	5.1		47	4.9	53	11.0	
Age (years)[e]										
25-45	172	8.2	71	9.7	0.013	138	14.5	96	20.2	0.001
46-50	169	8.1	55	7.5		100	10.5	74	15.6	
51-55	211	10.1	81	11.0		104	10.9	58	12.2	
56-60	241	11.5	73	9.9		101	10.6	41	8.6	
61-65	316	15.1	98	13.3		119	12.5	60	12.6	
66-70	375	17.9	117	15.9		140	14.7	50	10.5	
71-80	463	22.2	159	21.6		192	20.2	67	14.1	
81+	143	6.8	81	11.0		58	6.1	29	6.1	
CaMos Study Site										
Hamilton	737	35.3	297	39.9	0.001	330	34.7	166	34.4	0.001
Kingston	748	35.8	191	25.7		327	34.4	94	19.5	
Toronto	605	29.0	256	34.4		295	31.0	222	46.1	

[a] all CaMos participants before exclusion in the study

[b] sex was missing for 4 contacts, these data are not included in the analysis

[c] probability based on Pearson's chi square statistic

[d] Asian indicates Chinese, Japanese or Korean

[e] age groups CaMos used for sampling purposes

** ($p<0.01$) based on t-test of independent samples

Table G.2 Demographic characteristic of development and validation cohorts, women aged at least 45 years

	Development Cohort (N=926)		Validation Cohort (N=450)		
	n	mean (SD)	n	mean (SD)	p-value
Age in years	926	62.8 (9.36)	450	63.5 (10.0)	0.175
femoral neck BMD	926	0.74 (0.13)	450	0.74 (0.13)	0.892
lumbar spine BMD	926	0.97 (0.17)	450	0.97 (0.18)	0.893
	n	(%)	n	(%)	p-value
Race[a]					
White	879	94.9	423	94.0	0.692
Asian	27	2.9	14	3.1	
Other	20	2.2	13	2.9	
Age (years)[b]					
45-50	120	12.1	50	11.1	0.231
51-55	120	13.0	62	13.8	
56-60	133	14.4	69	15.3	
61-65	168	18.1	72	16.0	
66-70	187	20.2	74	16.4	
71-80	181	19.6	103	22.9	
81+	25	2.7	20	4.4	
Education Level					
< grade 9	87	9.4	49	10.9	0.167
grades 9-13, non-grad	265	28.6	131	29.1	
high school graduate	160	17.3	83	18.4	
trades or professional grad	181	19.6	84	18.7	
some university, non-grad	60	6.5	42	9.3	
university certificate/diploma	40	4.3	15	3.3	
university degree	133	14.4	46	10.2	
Employment Status					
employed full time	179	19.3	84	18.7	0.441
homemaker (full time)	214	23.1	93	20.7	
employed part time	104	11.2	46	10.2	
unemployed	19	2.0	9	2.0	
disability	11	1.2	12	2.7	
retired	374	40.4	195	43.3	
other	25	2.7	11	2.4	
CaMos Study Site					
Hamilton	345	37.3	160	35.6	0.729
Kingston	313	33.8	151	33.6	
Toronto	268	28.9	139	30.9	

[a] Asian indicates Chinese, Japanese or Korean

[b] adapted from age groups CaMos used for sampling purposes

Table G.3 Unadjusted odds ratio estimates for low BMD[a] at the femoral neck and lumbar spine, women aged at least 45 years

Variable		Total n	Total (%)	low BMD at femoral neck (%)	low BMD at femoral neck OR (95% CI)	low BMD at lumbar spine (%)	low BMD at lumbar spine OR (95% CI)
HEREDITY & AGE							
RACE							
white		879	94.9	14.8	1.00	14.0	1.00
non-white		47	5.1	27.7	2.20 (1.13,4.29)*	29.8	2.61 (1.36,5.01)**
AGE (years)							
45-54		206	22.2	2.4	1.00	4.4	1.00
55-64		302	32.6	11.3	5.10 (1.96,13.27)**	12.6	3.15 (1.49,6.67)**
65-74		326	35.2	19.3	9.63 (3.80,24.38)**	19.9	5.45 (2.65,11.21)**
75+		92	9.9	44.6	32.32 (12.15,85.93)**	27.2	8.17 (3.63,18.37)**
LIFETIME EXPOSURE TO GONADAL HORMONES							
AGE AT MENARCHE							
early/norm (<14)		622	67.3	18.5	1.40 (0.97, 2.02)	13.0	1.52 (1.05,2.21)*
late (14+yrs)	2 missing	302	32.7	14.0	1.00	18.5	1.00
PAROUS							
yes		812	87.7	15.4	0.97 (0.57,1.66)	15.0	1.17 (0.66,2.08)
no		114	12.3	15.8	1.00	13.2	1.00
MENOPAUSE[b]							
yes		818	88.3	17.4	22.48 (3.11,162.37)**	16.5	10.48 (2.56,42.95)**
no		108	11.7	0.9	1.00	1.8	1.00
SURGICAL MENOPAUSE							
yes		153	16.6	16.3	1.10 (0.69,1.76)	11.8	0.74 (0.43,1.25)
no	3 missing	770	83.4	15.1	1.00	15.3	1.00
ENVIRONMENTAL INFLUENCES							
CURRENT PHYSICAL ACTIVITY (minimum 20 minutes once a wk)							
yes		448	48.4	17.2	1.00	14.7	1.00
no	1 missing	477	51.6	13.8	1.29 (0.90,1.85)	14.9	0.99 (0.69,1.42)
PHYSICAL ACTIVITY AS A TEEN							
less than peers		831	89.8	15.8	1.41 (0.73,2.72)	15.3	1.70 (0.84,3.47)
same or more than peers		94	10.2	11.7	1.00	9.6	1.00
	1 missing						
WEIGHT (kg)							
< 60		215	23.2	36.3	11.50 (6.78,19.50)**	30.2	5.90 (3.67,9.50)**
60-69.9		286	30.9	15.7	3.77 (2.18,6.54)**	15.0	2.41 (1.47,3.96)**
70+	1 missing	424	45.8	4.7	1.00	6.8	1.00
BMI (kg/m^2)							
< 25		299	32.2	27.8	4.87 (3.16,7.50)**	24.8	3.00 (2.00,4.48)**
25-26		162	17.5	16.0	2.42 (1.40,4.18)**	10.5	1.07 (0.59,1.92)
27+	1 missing	464	50.2	7.3	1.00	9.9	1.00
CALCIUM CONSUMPTION (mg/d)							
<1000		418	46.5	14.8	0.94 (0.65,1.36)	16.3	1.31 (0.90,1.90)
1000+	27 missing	481	53.5	15.6	1.00	12.9	1.00
SUNLIGHT IN PAST YEAR							
never		616	66.5	17.9	1.82 (1.20,2.76)*	15.6	1.21 (0.82,1.80)
seldom/regular/often		310	33.5	10.6	1.00	13.2	1.00

Table G.3 Unadjusted odds ratio estimates for low BMD[a] at the femoral neck and lumbar spine, women aged at least 45 years [con't]

Variable		Total n	Total (%)	low BMD at femoral neck (%)	low BMD at femoral neck OR (95% CI)	low BMD at lumbar spine (%)	low BMD at lumbar spine OR (95% CI)
ENVIRONMENTAL INFLUENCES [Con't]							
ALCOHOL CONSUMPTION (in last year)							
no		358	38.7	19.0	1.54 (1.07,2.21)*	16.2	1.20 (0.83,1.73)
yes		568	61.3	13.2	1.00	13.9	1.00
CIGARETTE SMOKING							
never		485	52.4	16.7	1.00	14.8	1.00
ever		441	47.6	14.1	0.82 (0.57,1.17)	14.7	0.99 (0.69,1.43)
COMORBID CONDITIONS							
MINIMAL TRAUMA OP SITE FRACTURE[c] (aged 45 years or more)							
ever		72	7.8	29.2	2.47 (1.44,4.25)**	26.4	2.24 (1.28,3.91)**
never		854	92.2	14.3	1.00	13.8	1.00
NON-INSULIN DEPENDENT DIABETES							
yes		43	4.6	7.0	1.00	2.3	1.00
no		883	95.4	15.9	2.51 (0.77,8.23)	15.4	7.65 (1.04,56.03)
SCOLIOSIS							
yes		45	4.9	24.4	1.85 (0.91,3.74)	8.9	0.55 (0.19,1.57)
no	9 missing	872	95.1	14.9	1.00	15.0	1.00
LIVER DISEASE							
yes		25	2.7	28.0	2.20 (0.90,5.37)	16.0	1.10 (0.37,3.25)
no	2 missing	899	97.3	15.0	1.00	14.8	1.00
KIDNEY STONES							
yes		57	6.2	10.5	1.00	10.5	1.00
no	6 missing	863	93.8	15.9	1.60 (0.68,3.81)	15.2	1.52 (0.64,3.62)
KIDNEY DISEASE							
yes		19	2.1	26.3	1.98 (0.70,5.60)	10.5	0.68 (0.16,2.96)
no	2 missing	905	97.9	15.2	1.00	14.8	1.00
BREAST CANCER							
yes		35	3.8	20.0	1.39 (0.59,3.24)	28.6	2.40 (1.13,5.12)
no	1 missing	890	96.2	15.3	1.00	14.3	1.00
UTERINE CANCER							
yes		22	2.4	18.2	1.22 (0.41,3.66)	4.6	0.27 (0.04,2.01)
no	2 missing	902	97.6	15.4	1.00	15.1	1.00
HIGH BLOOD PRESSURE							
yes		288	31.3	13.2	1.00	12.8	1.00
no	7 missing	631	68.7	16.6	1.31 (0.88,1.96)	15.8	1.28 (0.85,1.92)
GALL BLADDER SURGERY							
yes		165	17.8	15.8	1.03 (0.65,1.64)	10.3	0.61 (0.36,1.05)
no		761	82.2	15.4	1.00	15.8	1.00
THYROID SURGERY							
yes		288	3.0	25.0	1.87 (0.78,4.48)	10.7	0.68 (0.20,2.30)
no		98	97.0	15.1	1.00	14.9	1.00

Table G.3 Unadjusted odds ratio estimates for low BMD[a] at the femoral neck and lumbar spine, women aged at least 45 years [con't]

Variable	Total n	Total (%)	low BMD at femoral neck (%)	low BMD at femoral neck OR (95% CI)	low BMD at lumbar spine (%)	low BMD at lumbar spine OR (95% CI)
MEDICATION USE						
THYROID PILLS						
yes	161	17.4	16.2	1.00	11.2	1.00
no	765	82.6	15.3	0.94 (0.59,1.49)	15.6	1.46 (0.86,2.48)
TAMOXIFEN						
yes	159	1.6	6.7	0.39 (0.05,2.96)	33.3	2.95 (0.99,8.76)
no 1 missing	10	98.4	15.6	1.00	14.5	1.00
LAXATIVE USE						
yes	798	8.5	19.0	1.32 (0.73,2.38)	8.9	0.54 (0.24,1.19)
no	47	91.5	15.1	1.00	15.4	1.00
ORAL CORTICOSTEROIDS (at least one month)						
yes	468	5.0	19.6	1.35 (0.64,2.86)	8.7	0.53 (0.19,1.51)
no 3 missing	77	95.0	15.3	1.00	15.2	1.00
ORAL CORTICOSTEROIDS 1+yr						
yes	219	2.3	14.3	0.91 (0.27,3.14)	4.8	0.28 (0.04,2.13)
no 4 missing	01	97.7	15.4	1.00	15.0	1.00
DIURETICS						
yes	198	21.4	13.6	1.00	9.6	1.00
no	728	78.6	15.9	1.20 (0.76,1.87)	16.2	1.82 (1.09,3.04)*
CURRENT ESTROGEN USE						
yes	273	29.5	10.6	1.00	8.1	1.00
no	653	70.5	17.5	1.78 (1.15,2.75)**	17.6	2.44 (1.51,3.94)**
CURRENT PROGESTERONE USE						
yes	978	10.5	9.3	1.00	7.2	1.00
no	29	89.5	16.2	1.88 (0.93,3.84)	15.7	2.39 (1.08,5.28)*

[a] defined as ≤-2.0 SD of the Canadian young adult normal

[b] menstruation ceased at least 1 year, surgical or natural menopause

[c] minimal trauma fracture of the wrist/forearm, hip, back, pelvis or rib aged at lease 45 years

Table G.4 Logistic regression models to identify low BMD[a] at the femoral neck[b] (n=924)

	Variables in the model	-2 log likelihood	df	AUC	SE(AUC)
1	age, weight, minimal trauma fracture[c], physical activity[d], current estrogen use	592.654	9	0.843	0.017
2	age, weight,minimal trauma fracture, physical activity	602.060	8	0.839	0.016
3	age, weight, physical activity	606.260	7	0.834	0.016
4	age, weight	611.839	6	0.830	0.016

[a] defined as ≤ -2.0 SD of the Canadian young adult normal at the femoral neck
[b] all variables are statistically independent correlates of low BMD at the femoral neck
[c] minimal trauma fracture of the wrist/forearm, hip, back, pelvis or rib aged at least 45 years
[d] at least one 20 minute session once per week
df degrees of freedom
AUC area under the receiver operating characteristic curve

Table G.5 Logistic regression models to identify low BMD[a] at the lumbar spine[b] (n=925)

	Variables in the model	-2 log likelihood	df	AUC	SE(AUC)
1	age, weight, current estrogen use, menopause[c], diuretic use	651.399	9	0.786	0.02
2	age, weight, current estrogen use, menopause[c]	659.329	8	0.774	0.021
3	age, weight, current estrogen use	664.938	7	0.771	0.021
4	age, weight	679.503	6	0.750	0.022

[a] defined as ≤ -2.0 SD of the Canadian young adult normal at the lumbar spine (L1-L4)
[b] all variables are statistically independent correlates of low BMD at the lumbar spine
[c] menstruation ceased at least 1 year, surgical or natural menopause
df degrees of freedom
AUC area under the receiver operating characteristic curve

Table G.6 Adjusted logistic regression results to identify low BMD[a] at either the femoral neck, or lumbar spine

	Regression Coefficient Estimates	Odds Ratio Estimates	(95% CI)
AGE (years)			
45-54	-	1.00	
55-64	1.06	2.87	(1.34, 6.17)
65-74	1.54	4.69	(2.21, 9.95)
75+	2.04	7.80	(3.39, 17.98)
WEIGHT (kg)			
< 60	2.28	9.83	(6.17, 15.66)
60-69.9	1.24	3.45	(2.21, 5.38)
70+	-	1.00	
CURRENT ESTROGEN USE			
yes	-	1.00	
no	0.84	2.32	(1.52, 3.57)
MENOPAUSE[b]			
yes	1.53	4.60	(1.21, 17.44)
no	-	1.00	
CURRENT PHYSICAL ACTIVITY (minimum 20 minutes once per week)			
yes	-	1.00	
no	0.33	1.39	(0.97, 1.98)
MINIMAL TRAUMA FRACTURE[c] (aged 45 years or more)			
ever	0.47	1.60	(0.90, 2.86)
never	-	1.00	

[a] defined as ≤ -2.0 SD of the Canadian adult young normal at either the femoral neck or lumbar spine

[b] menstruation ceased at least 1 year, surgical or natural menopause

[c] minimal trauma fracture of the wrist/forearm, hip, back, pelvis or rib aged at least 45 years

Table G.7 Comparison of additive ORAIs developed from OR estimates, regression coefficient estimates, and increasing integers to identify low BMD[a] in women aged at least 45 years from the development cohort

	Odds Ratio Estimate Scores	Regression Coefficient Estimate Scores	Increasing Integer Scores
AGE (years)			
45-54	0	0	0
55-64	3	11	1
65-74	5	15	2
75+	8	20	3
WEIGHT (kg)			
< 60	10	23	2
60-69.9	3	12	1
70+	0	0	0
CURRENT ESTROGEN USE			
yes	0	0	0
no	2	8	1
MENOPAUSE[b]			
yes	5	15	1
no	0	0	0
CURRENT PHYSICAL ACTIVITY (minimum 20 minutes once per week)			
yes	0	0	0
no	1	3	1
MINIMAL TRAUMA FRACTURE[c] (aged 45 years or more)			
ever	2	5	1
never	0	0	0
range of possible scores	**0 - 28**	**0 - 74**	**0 - 9**
threshold score[d]	**12**	**38**	**4**
WOMEN 45+ (n=924)*			
area under the ROC curve (SE)	0.803 (0.017)	0.813 (0.016)	0.751 (0.017)
sensitivity % (95% CI)	91.9 (88.2,95.6)	91.4 (87.6,95.2)	93.3 (90.0,96.7)
specificity % (95% CI)	46.6 (43.0,50.3)	45.8 (42.1,49.5)	38.8 (35.2,42.4)
PPV % (95% CI)	33.6 (29.8,37.5)	33.2 (29.3,37.0)	31.0 (27.4,34.6)

[a] defined as ≤ -2.0 SD of the Canadian adult young normal at either the femoral neck or lumbar spine

[b] menstruation ceased at least 1 year, surgical or natural menopause

[c] minimal trauma fracture of the wrist/forearm, hip, back, pelvis or rib aged at least 45 years

[d] select all individuals for DXA with a score at or above the threshold score

* area under ROC curves are not statistically different (p>0.05)

ORAI osteoporosis risk assessment instrument

Table G.8 Odds ratio estimate based score assignment and discriminatory performance of various ORAIs, to identify low BMD[a] in women aged at least 45 years from the development cohort

Item Count:	6	5	4	3	2	1
AGE (years)						
45-54	0	0	0	0	0	
55-64	3	3	3	5	5	
65-74	5	5	5	9	9	
75+	8	8	8	15	16	
WEIGHT (kg)						
< 60	10	10	9	9	8	8
60-69.9	3	3	3	3	3	3
70+	0	0	0	0	0	0
CURRENT ESTROGEN USE						
yes	0	0	0	0		
no	2	2	2	2		
MENOPAUSE[b]						
yes	5	5	5			
no	0	0	0			
CURRENT PHYSICAL ACTIVITY (minimum 20 minutes once a week)						
yes	0	0				
no	1	1				
MINIMAL TRAUMA FRACTURE[c] (aged 45 years or more)						
ever	2					
never	0					
range of possible scores	0 - 28	0 - 26	0 - 24	0 - 26	0 - 24	0 - 8
threshold score[d]	12	12	11	9	8	3
Development Cohort (n=924)						
area under the ROC curve* (SE)	0.803 (0.017)	0.802 (0.017)	0.803 (0.017)	0.789 (0.017)	0.779 (0.017)	0.713 (0.019)
sensitivity (%) (95% CI)	91.9 (88.2,95.6)	91.4 (87.6,95.2)	91.9 (88.2,95.6)	90.0 (85.9,94.1)	93.8 (90.6,97.1)	80.5 (75.1,85.8)
specificity (%) (95% CI)	46.6 (43.0,50.3)	47.5 (43.8,51.1)	44.5 (40.9,48.2)	45.1 (41.4,48.7)	40.5 (36.9,44.1)	53.6 (50.0,57.3)
PPV (%) (95% CI)	33.6 (29.8,37.5)	33.9 (30.0,37.8)	32.8 (29.0,36.6)	32.5 (28.7,36.3)	31.7 (28.0,35.3)	33.8 (29.7,37.9)

[a] defined as ≤ -2.0 SD of the Canadian adult young normal at either the femoral neck or lumbar spine

[b] menstruation ceased at least 1 year, surgical or natural menopause

[c] minimal trauma fracture of the wrist/forearm, hip, back, pelvis or rib aged at least 45 years

[d] select all individuals for DXA with a score at or above the threshold score

* area under curve for the 1-item OSI is significantly less than that of OSI with at least 3 items, $p<0.05$

ORAI osteoporosis risk assessment instrument

Table G.9 Discriminatory performance of various ORAIs to identify low BMD[a] at either the femoral neck or lumbar spine, in various samples of women aged at least 45 years from the development cohort

	Area under ROC curve		Sensitivity		Specificity		PPV	
	area	SE	%	95% CI	%	95% CI	%	95% CI
All women aged 45+ yrs (N=924)								
6 item ORAI [b]	0.803	0.017	91.9	88.2,95.6	46.6	43.0,50.3	33.6	29.8,37.5
5 item ORAI	0.802	0.017	91.4	87.6,95.2	47.5	43.8.51.1	33.9	30.0,37.8
4 item ORAI	0.803	0.017	91.9	88.2,95.6	44.5	40.9,48.2	32.8	29.0,36.6
3 item ORAI	0.789	0.017	90.0	85.9,91.4	45.1	41.4,48.7	32.5	28.7,36.6
2 item ORAI	0.779	0.017	93.8	90.6,97.1	40.5	36.9,44.1	31.7	28.0,35.3
1 item ORAI [c]	0.713	0.019	80.5	75.1,85.8	53.6	50.0,57.3	33.8	29.7,37.9
Postmenopausal women (N=816)								
6 item ORAI	0.781	0.018	92.3	88.6,95.9	40.7	36.8,44.6	34.6	30.6,38.6
5 item ORAI	0.779	0.018	91.8	88.0,95.5	41.7	37.8,45.6	34.9	30.9,38.9
4 item ORAI	0.780	0.018	92.3	88.6,92.9	38.3	34.4,42.1	33.7	29.8,37.6
3 item ORAI	0.769	0.019	90.3	86.3,94.4	39.9	36.0,43.8	33.8	29.9,37.8
2 item ORAI	0.755	0.019	94.2	91.0,97.4	34.6	30.9,38.4	32.9	29.1,36.7
1 item ORAI	0.716	0.020	80.2	74.8,85.6	53.7	49.7,57.7	37.1	32.6,41.5
Premenopausal women (N=108)								
6 item ORAI	0.802	0.148	66.7	13.3,120.0	81.0	73.4,88.5	9.1	-2.9,21.1
5 item ORAI	0.805	0.144	66.7	13.3,120.0	81.0	73.4,88.5	9.1	-2.9,21.1
4 item ORAI	0.771	0.136	66.7	13.3,120.0	81.0	73.4,88.5	9.1	-2.9,21.1
3 item ORAI	0.768	0.139	66.7	13.3,120.0	75.2	67.0,83.5	7.1	-2.4,16.7
2 item ORAI	0.778	0.097	66.7	13.3,120.0	74.3	65.9,82.6	6.9	-2.3,16.1
1 item ORAI	0.808	0.081	100	100 ,100.0	53.3	43.8,62.9	5.8	-0.6,12.1
All women in Hamilton (N=343)								
6 item ORAI	0.792	0.028	87.1	80.3,93.9	48.0	41.8,54.2	38.4	31.8,45.0
5 item ORAI	0.795	0.028	87.1	80.3,93.9	48.8	42.6,55.0	38.8	32.2,45.4
4 item ORAI	0.793	0.028	88.2	81.6,94.7	46.4	40.2,52.6	38.0	31.5,44.4
3 item ORAI	0.774	0.029	86.0	79.0,93.1	45.6	39.4,51.8	37.0	30.6,43.5
2 item ORAI	0.764	0.029	91.4	85.7,97.1	40.8	34.7,46.9	36.5	30.3,42.7
1 item ORAI	0.724	0.029	78.5	70.1,86.8	58.0	51.9,64.1	33.8	33.8.48.2
All women in Kingston (N=313)								
6 item ORAI	0.802	0.027	97.0	92.9,101.1	45.5	39.3,51.8	32.7	26.1,39.2
5 item ORAI	0.797	0.028	95.5	90.6,100.5	46.3	40.1,52.6	32.7	26.1,39.2
4 item ORAI	0.800	0.027	95.5	90.6,100.5	41.5	35.3,47.6	30.8	24.5,37.0
3 item ORAI	0.792	0.028	92.5	86.2,98.8	42.7	36.5,48.9	30.5	24.2,36.9
2 item ORAI	0.776	0.029	97.0	92.9,101.1	37.0	31.0,43.0	29.5	23.5,35.6
1 item ORAI	0.697	0.034	80.6	71.1,90.1	50.8	44.6,57.1	30.9	24.0,37.7
All women in Toronto (N=268)								
6 item ORAI	0.826	0.031	94.0	87.4,100.6	46.3	39.7,52.9	28.7	21.7,35.6
5 item ORAI	0.823	0.031	94.0	87.4,100.6	47.2	40.6,53.9	29.0	22.0,36.0
4 item ORAI	0.828	0.030	94.0	87.4,100.6	45.9	39.3,52.5	28.5	21.6,35.4
3 item ORAI	0.812	0.032	94.0	87.4,100.6	47.2	40.6,53.9	29.0	22.0,36.0
2 item ORAI	0.806	0.032	94.0	87.4,100.6	44.0	37.4,50.6	27.8	21.1,34.6
1 item ORAI	0.730	0.037	84.0	73.8,94.2	51.8	45.2,58.5	28.6	21.3,35.9

[a] defined as ≤ -2.0 SD of the Canadian adult young normal

[b] selection based on a threshold score of 12 for 6 and 5 item ORAIs, a threshold score of 11 in the 4 item ORAI, threshold score of 9 in the 3 item ORAI, threshold of 8 in the 2 item ORAI, and threshold score of 3 in the 1-item ORAI (weight < 70kg).

[c] note that the 1-item ORAI has less than 5 cut points, thus AUC may be underestimated.

ORAI osteoporosis risk assessment instrument

Table G.10 Discriminatory performance of several ORAI's performance to predict various outcomes in women aged at least 45 years from the development cohort[a]

	Area under ROC curve		Sensitivity		Specificity		PPV	
	area	SE	%	95% CI	%	95% CI	%	95% CI
Performance to identify low BMD[b] at either the femoral neck or lumbar spine								
6 item ORAI[c]	0.803	0.017	91.9	88.2,95.6	46.6	43.0,50.3	33.6	29.8,37.5
5 item ORAI	0.802	0.017	91.4	87.6,95.2	47.5	43.8,51.1	33.9	30.0,37.8
4 item ORAI	0.803	0.017	91.9	88.2,95.6	44.5	40.9,48.2	32.8	29.0,36.6
3 item ORAI	0.789	0.017	90.0	85.9,91.4	45.1	41.4,48.7	32.5	28.7,36.6
2 item ORAI	0.779	0.017	93.8	90.6,97.1	40.5	36.9,44.1	31.7	28.0,35.3
1 item ORAI[d]	0.713	0.019	80.5	75.1,85.8	53.6	50.0,57.3	33.8	29.7,37.9
Performance to identify low BMD at the femoral neck								
6 item ORAI	0.839	0.016	95.1	91.6,98.6	43.9	40.4,47.4	23.7	20.2,27.2
5 item ORAI	0.836	0.016	95.1	91.6,98.6	44.8	41.3,48.3	24.0	20.5,27.5
4 item ORAI	0.836	0.016	95.8	92.5,99.1	42.1	38.7,45.6	23.3	19.8,26.7
3 item ORAI	0.824	0.017	94.4	90.6,98.2	42.9	39.4,46.4	23.2	19.8,26.7
2 item ORAI	0.818	0.017	97.9	95.6,100.3	38.3	34.9,41.7	22.5	19.2,25.8
1 item ORAI	0.745	0.026	86.0	80.3,91.7	51.7	48.2,55.2	24.6	20.8,28.4
Performance to identify low BMD at the lumbar spine								
6 item ORAI	0.766	0.021	91.2	86.5,96.0	42.9	39.5,46.4	21.8	18.4,25.2
5 item ORAI	0.762	0.021	90.5	85.6,95.4	43.7	40.2,47.2	21.9	18.5,25.3
4 item ORAI	0.766	0.021	90.5	85.6,95.4	40.9	37.5,44.4	21.1	17.8,24.3
3 item ORAI	0.747	0.022	89.1	83.8,94.3	41.7	38.2,45.1	21.0	17.1,24.3
2 item ORAI	0.731	0.022	91.2	86.5,96.0	36.8	33.5,40.2	20.1	16.9,23.2
1 item ORAI	0.688	0.023	78.8	72.0,85.7	50.2	46.7,53.7	21.6	18.0,25.2
Performance to identify BMD <-1.0 SD of Canadian adult young normal at either the femoral neck or lumbar spine								
6 item ORAI	0.756	0.016	78.2	74.7,81.7	60.2	55.3,65.1	73.2	69.5,76.8
5 item ORAI	0.753	0.016	77.5	73.9,81.0	61.0	56.1,65.8	73.4	69.7,77.0
4 item ORAI	0.749	0.016	79.0	75.5,82.4	57.4	52.4,62.3	72.0	68.4,75.6
3 item ORAI	0.741	0.016	77.1	73.5,80.6	56.8	51.9,61.8	71.3	67.6,74.9
2 item ORAI	0.730	0.016	81.6	78.3,84.8	52.5	47.5,57.4	70.4	66.8,74.0
1 item ORAI	0.655	0.017	65.4	61.3,69.4	61.5	56.7,66.3	70.2	66.2,74.2
Performance to identify osteoporosis[e] at either the femoral neck or lumbar spine								
6 item ORAI	0.849	0.019	97.0	93.7,100.3	42.2	38.8,45.5	17.1	14.0,20.2
5 item ORAI	0.846	0.019	97.0	93.7,100.3	43.0	39.6,46.4	17.3	14.2,20.4
4 item ORAI	0.849	0.019	97.0	93.7,100.3	40.3	37.0,43.7	16.6	13.6,19.6
3 item ORAI	0.831	0.020	97.0	93.7,100.3	41.3	37.9,44.7	16.9	13.8,19.9
2 item ORAI	0.814	0.021	97.0	93.7,100.3	36.3	33.0,39.6	15.8	12.9,18.6
1 item ORAI	0.759	0.023	88.1	81.8,94.4	50.1	46.6,53.5	17.8	14.4,21.2

[a] N = 924

[b] defined as ≤ -2.0 SD of the Canadian adult young normal

[c] selection based on a threshold score of 12 for 6 and 5 item ORAIs, a threshold score of 11 in the 4 item ORAI, threshold score of 9 in the 3 item ORAI, threshold of 8 in the 2 item ORAI, and threshold score of 3 to in the 1-item ORAI (weight < 70kg).

[d] note that the 1-item ORAI has less than 5 cut points, thus AUC may be underestimated.

[e] defined as ≤-2.5 SD of Canadian adult young normal (WHO definition, Kanis *et al.*, 1997)

ORAI osteoporosis risk assessment instrument

Table G.11 Proportion of development cohort selected by BMD t-score for bone densitometry using various ORAIs

	6 item ORAI[a] (% select)	5 item ORAI[a] (% select)	4 item ORAI[b] (% select)	3 item ORAI[c] (% select)	2 item ORAI[d] (% select)	1 item ORAI[e] (% select)
normal (t-score ≥-1.0)	39.8	39.0	42.6	43.2	47.5	38.5
-2.0 SD < t-score < -1.0	69.4	68.5	70.6	68.8	73.7	55.7
-2.5 < t-score ≤ - 2.0	87.2	86.2	87.2	83.5	90.8	73.4
osteoporosis (t-score≤ -2.5)	97.0	97.0	97.0	97.0	97.0	88.1

[a] threshold score of 12 to select for bone densitometry
[b] threshold score of 11 to select for bone densitometry
[c] threshold score of 9 to select for bone densitometry
[d] threshold score of 8 to select for bone densitometry
[e] threshold score of 3 (or simply weight less than 70kg) to select for bone densitometry
ORAI osteoporosis risk assessment instrument

Table G.12 Count of women selected by BMD t-score[a] for bone densitometry using various ORAIs, based on a sample size of 1000 women, and distribution in the development cohort

		Select (n)	No select (n)	Total (n)	% save*
6 item ORAI [b]					
normal (t-score ≥-1.0)		181	274	455	
-2.0 SD < t-score < -1.0		235	103	338	
-2.5 < t-score ≤-2.0		94	14	108	
osteoporosis (t-score≤-2.5)		96	3	99	
	Total	606	394	1000	39.4
5 item ORAI [b]					
normal (t-score ≥-1.0)		177	278	455	
-2.0 SD < t-score < -1.0		232	106	338	
-2.5 < t-score ≤-2.0		93	15	108	
osteoporosis (t-score≤-2.5)		96	3	99	
	Total	598	402	1000	40.2
4 item ORAI [c]					
normal (t-score ≥-1.0)		194	261	455	
-2.0 SD < t-score < -1.0		239	99	338	
-2.5 < t-score ≤-2.0		94	14	108	
osteoporosis (t-score≤-2.5)		96	3	99	
	Total	623	377	1000	37.7
3 item ORAI [d]					
normal (t-score ≥-1.0)		197	258	455	
-2.0 SD < t-score < -1.0		233	105	338	
-2.5 < t-score ≤-2.0		90	18	108	
osteoporosis (t-score≤-2.5)		96	3	99	
	Total	615	385	1000	38.5
2 item ORAI [e]					
normal (t-score ≥-1.0)		216	239	455	
-2.0 SD < t-score < -1.0		249	89	338	
-2.5 < t-score ≤-2.0		98	10	108	
osteoporosis (t-score≤-2.5)		96	3	99	
	Total	659	341	1000	34.1
1 item ORAI [f]					
normal (t-score ≥-1.0)		175	280	455	
-2.0 SD < t-score < -1.0		188	150	338	
-2.5 < t-score ≤-2.0		79	29	108	
osteoporosis (t-score≤-2.5)		87	12	99	
	Total	530	47.0	1000	47.0

[a] based on t-score distribution in the development cohort, 45.5% normal, 33.8% between -1.0 and -2.0, 10.8% between -2.0 and -2.5, and 9.9% ≤-2.5 SD.

[b] threshold score of 12 to select for bone densitometry

[c] threshold score of 11 to select for bone densitometry

[d] threshold score of 9 to select for bone densitometry

[e] threshold score of 8 to select for bone densitometry

[f] threshold score of 3 (or simply weight less than 70kg) to select for bone densitometry

* percent not recommended for DXA, thus percent DXA testing saved compared to a mass screen

ORAI osteoporosis risk assessment instrument

Table G.13 Validation of the 3- item ORAI[a] in women aged at least 45 years, using a threshold score of 9, in the validation cohort

	Area under ROC curve		Sensitivity		Specificity		PPV	
	area	SE	%	95% CI	%	95% CI	%	95% CI
Performance to identify low BMD[b] at either the femoral neck or lumbar spine								
All women aged 45+ yrs (N=450)	0.770	0.024	93.3	88.6,98.1	46.4	41.1,51.6	34.6	29.1,40.2
Postmenopausal women (N=394)	0.739	0.027	93.2	88.3,98.1	38.8	33.2,44.4	35.0	29.4,40.7
Premenopausal women (N=56)	0.912	0.046	100	100,100	87.0	78.1,96.0	22.2	-4.9,49.4
All women in Hamilton (N=160)	0.787	0.037	94.9	87.9,101.8	49.6	40.7,58.5	37.8	28.2,47.4
All women in Kingston (N=151)	0.756	0.045	91.7	82.6,100.7	41.7	32.7,50.8	33.0	23.8,42.2
All women in Toronto (N=139)	0.765	0.043	93.3	84.4,102.3	47.7	38.3,57.1	32.9	22.9,42.9
Performance to identify low BMD at the femoral neck								
All women (N=450)	0.782	0.025	95.1	90.3,99.8	44.2	39.1,49.2	27.2	22.0,32.4
Performance to identify low BMD at the lumbar spine								
All women (N=450)	0.708	0.029	93.7	87.6,99.7	42.1	37.2,47.0	20.8	16.1,25.6
Performance to identify BMD <-1.0 SD of Canadian adult young normal at either the femoral neck or lumbar spine								
All women (N=450)	0.741	0.023	77.2	72.2,82.3	58.2	51.1,65.4	73.1	68.0,78.3
Performance to identify osteoporosis[c] at either the femoral neck or lumbar spine								
All women (N=450)	0.768	0.030	94.4	88.3,100.6	41.4	36.6,46.3	18.0	13.5,22.5

[a] threshold score of 12 to select for bone densitometry

[b] defined as ≤ -2.0 SD of the Canadian adult young normal

[c] defined as ≤-2.5 SD of Canadian adult young normal (WHO definition, Kanis *et al.*, 1997)

ORAI osteoporosis risk assessment instrument

Table G.14 Proportion of validation cohort selected by BMD t-score for bone densitometry using various ORAIs

	6 item ORAI[a] (% select)	5 item ORAI[a] (% select)	4 item ORAI[b] (% select)	3 item ORAI[c] (% select)	2 item ORAI[d] (% select)	1 item ORAI[e] (% select)
normal (t-score ≥-1.0)	40.1	39.6	43.4	41.8	48.4	35.2
-2.0 SD < t-score < -1.0	63.8	63.2	65.0	66.9	68.7	55.8
-2.5 < t-score ≤ - 2.0	96.1	94.1	94.1	92.2	94.1	78.4
osteoporosis (t-score≤-2.5)	90.7	90.7	92.6	94.4	96.3	85.2

[a] threshold score of 12 to select for bone densitometry
[b] threshold score of 11 to select for bone densitometry
[c] threshold score of 9 to select for bone densitometry
[d] threshold score of 8 to select for bone densitometry
[e] threshold score of 3 (or simply weight less than 70kg) to select for bone densitometry

ORAI osteoporosis risk assessment instrument

Table G.15 Count of women selected by BMD t-score[a] for bone densitometry using various ORAIs, based on a sample size of 1000 women, and distribution in the validation cohort

		Select (n)	No select (n)	Total (n)	% save*
6 item ORAI [b]					
normal (t-score ≥-1.0)		179	267	446	
-2.0 SD < t-score < -1.0		218	124	342	
-2.5 < t-score ≤-2.0		100	4	104	
osteoporosis (t-score≤-2.5)		98	10	108	
	Total	595	405	1000	40.5
5 item ORAI [b]					
normal (t-score ≥-1.0)		177	269	446	
-2.0 SD < t-score < -1.0		216	126	342	
-2.5 < t-score ≤-2.0		98	6	104	
osteoporosis (t-score≤-2.5)		98	10	108	
	Total	589	411	1000	41.1
4 item ORAI [c]					
normal (t-score ≥-1.0)		194	252	446	
-2.0 SD < t-score < -1.0		222	120	342	
-2.5 < t-score ≤-2.0		98	6	104	
osteoporosis (t-score≤-2.5)		100	8	108	
	Total	614	386	1000	38.6
3 item ORAI [d]					
normal (t-score ≥-1.0)		186	260	446	
-2.0 SD < t-score < -1.0		229	113	342	
-2.5 < t-score ≤-2.0		96	8	104	
osteoporosis (t-score≤-2.5)		102	6	108	
	Total	613	387	1000	38.7
2 item ORAI [e]					
normal (t-score ≥-1.0)		216	230	446	
-2.0 SD < t-score < -1.0		235	107	342	
-2.5 < t-score ≤-2.0		98	6	104	
osteoporosis (t-score≤-2.5)		104	4	108	
	Total	653	347	1000	34.7
1 item ORAI [f]					
normal (t-score ≥-1.0)		157	289	446	
-2.0 SD < t-score < -1.0		191	151	342	
-2.5 < t-score ≤-2.0		82	22	104	
osteoporosis (t-score≤-2.5)		92	16	108	
	Total	521	479	1000	47.9

[a] based on t-score distribution in the validation cohort, 44.6% normal, 34.2% between -1.0 and -2.0, 10.4% between -2.0 and -2.5, and 10.8% ≤-2.5 SD.

[b] threshold score of 12 to select for bone densitometry

[c] threshold score of 11 to select for bone densitometry

[d] threshold score of 9 to select for bone densitometry

[e] threshold score of 8 to select for bone densitometry

[f] threshold score of 3 (or simply weight less than 70kg) to select for bone densitometry

* percent not recommended for DXA, thus percent DXA testing saved compared to a mass screen

ORAI osteoporosis risk assessment instrument

Osteoporosis Risk Assessment Instrument (ORAI)*		
AGE (years)		
45-54	0	
55-64	5	
65-74	9	
75+	15	
WEIGHT (kg)		
< 60	9	
60-69.9	3	
70+	0	+
CURRENT ESTROGEN USE		
yes	0	
no	2	+
	TOTAL:	

* select all women with a total score of **(9 or 10)** or higher for bone densitometry

Figure G.1 Osteoporosis Risk Assessment Instrument (ORAI) to select women for bone densitometry

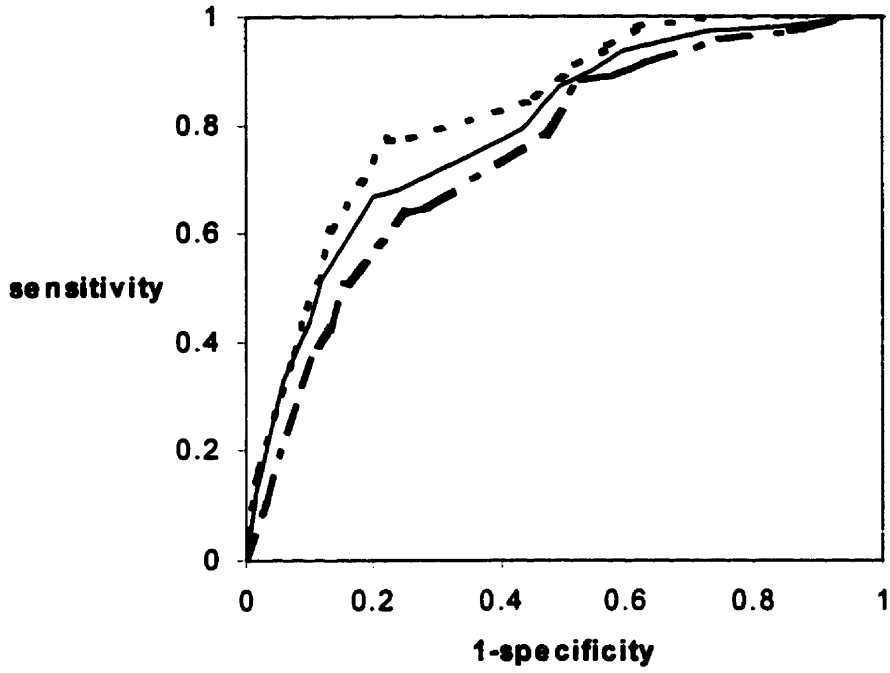


Figure G.2 Receiver operating characteristic curves of the 3-item ORAI's performance to identify low BMD at the femoral neck (dotted line), the lumbar spine L1-L4 (dashed line), and at either the femoral neck or lumbar spine (solid line), in the development cohort.

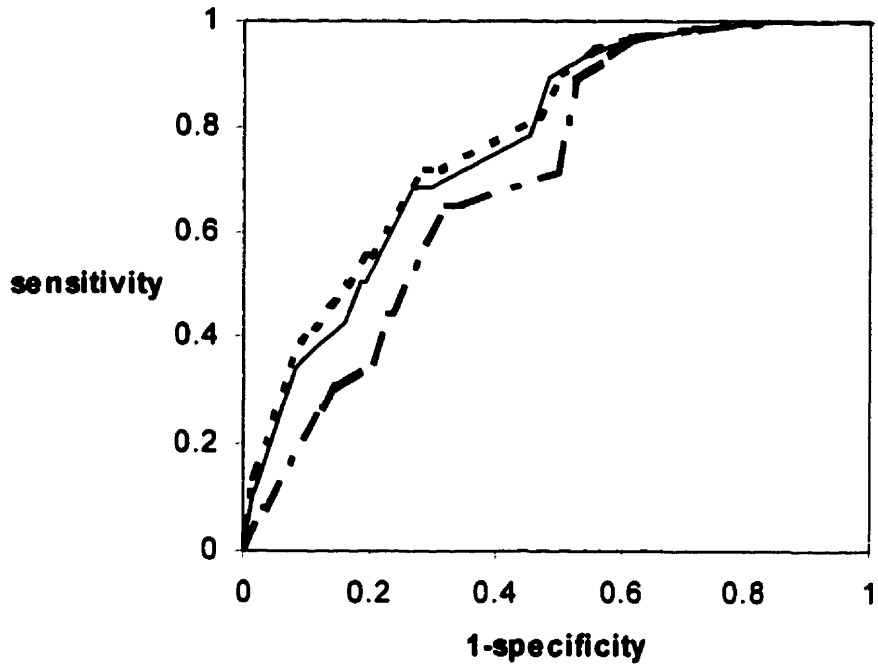


Figure G.3 Receiver operating characteristic curves of the 3-item ORAI's performance to identify low BMD at the femoral neck (dotted line), the lumbar spine L1-L4 (dashed line), and at either the femoral neck or lumbar spine (solid line), in the validation cohort.

H. DISCUSSION / CONCLUSIONS

Osteoporosis is a major public health problem which results in disability, deformity, pain and fractures. Fractures of the wrist, spine and hip are the most overt clinical sign of the degenerative bone disease, resulting in substantial costs to the individual and society. Osteoporotic fragility fracture rates increase exponentially with age and given the aging population, and increase in life expectancy, hip fractures are projected to double within 15 years. As strength of bone is the best predictor of future fracture (Compston *et al.*, 1995), recommendations for early identification of those at risk of osteoporotic fractures are based on bone densitometry measurements of BMD (Kanis *et al.*, 1997; Joseph & Hughes, 1997; Jergas & Gluer, 1997; Council of the National Osteoporosis Foundation, 1996; Anonymous, 1997a; Scheiber II & Torregrosa, 1998; Christiansen, 1995). DXA is the most accurate and commonly used technique for measuring BMD (Millard *et al.*, 1997), and thus making a diagnosis of osteoporosis. In fact the Ontario Ministry of Health, and the Ontario Medical Association have recently revised physician services billing to include DXA, while deleting billing codes for "obsolete" technology including bone mineral content analysis, dual photon absorptiometry, and neutron activation (Ontario Ministry of Health, 1998a; Ontario Ministry of Health, 1998b). While mass screening for osteoporosis is not recommended, using DXA to screen high risk groups is essential to facilitate early diagnosis of osteoporosis, allowing prophylactic treatment for the prevention of further bone loss and fracture. At present, there is no clear method for deciding who should undergo DXA testing. The identification of younger asymptomatic individuals who are at risk for osteoporotic fractures is imperative if the morbidity, mortality, and economic consequences of osteoporosis are to be reduced (Miller *et al.*, 1996).

Papa and Weber (1997) studied the use of bone densitometry in primary care practitioners (internists, geriatricians and family practitioners) in an urban community hospital in the United States cross-sectionally. Most physicians surveyed (75% response rate), simply did not use bone densitometry (72%). Physician-identified barriers to ordering BMD testing included potential cost to the patient (50%), unfamiliarity with guidelines (41%), uncertainty with clinical applicability of results (21%), minimal impact on treatment decisions (21%), availability of bone densitometer (21%), and other (7%). A definitive set of indications for bone densitometry could be useful given the uncertainty apparent in clinical practice, as indicated by the results of this study. In fact, Papa

and Weber's (1997) study found that significantly fewer patients with osteoporosis, or at risk of it were treated by physicians who did not use bone densitometry vs. users of bone densitometry ($p=0.005$).

WHO developed diagnostic thresholds for osteoporotic fracture risk based on BMD; however, the level at which to initiate treatment remains controversial (section D.3.). Many urge that clinical risk factors in addition to BMD t-score be taken into consideration (Joseph & Hughes, 1997; Council of the National Osteoporosis Foundation, 1996; Jergas & Gluer, 1997; Anonymous, 1997a; Scheiber II & Torregrosa, 1998; Christiansen, 1995). For this reason, a clinical risk scoring system to identify women with ≤-2.0 SD of the young normal value was created. This instrument may be used as a case finding approach to select women for bone densitometry. Evaluation of BMD via DXA is currently the best means for fracture prediction, and thus potential prophylactic intervention. Portable techniques such as ultrasound which evaluate bone structure beyond simple BMD (e.g., attenuation and velocity of sound through bone) may facilitate bone mineral testing in the future. At present however, ultrasound is still experimental in terms of identifying risk of fracture. That is, diagnostic criteria and intervention thresholds have yet to be established (Kanis *et al.*, 1997; Pocock *et al.*, 1996; Njeh *et al.*, 1997).

Six potential ORAIs were identified through the thesis based on an additive scoring system of OR estimates. Given that OR were produced through logistic regression, criticisms of the additive scoring scheme may arise as OR are in fact multiplicative. Tu *et al.* encountered this criticism (Harrell, 1996) in development (Tu *et al.*, 1994) and validation (Tu *et al.*, 1995) of an additive prediction index. Like Tu *et al.* (1997), use of an additive based scoring system in this study had comparable performance to simple use of the logistic model, or an additive scoring scheme based on regression coefficient estimates. Therefore, the simple nature of an additive scoring scheme based on OR estimates was preferred, and the ORAI was produced as an additive scoring system of OR estimates through logistic regression models.

The purpose of the ORAI is to screen for those likely to be at risk for the crippling consequences of osteoporosis. Selection of a final ORAI was based on the case finding potential inherent in the instruments. This evaluation included appraisal of performance in terms of sensitivity, specificity, and the ease/simplicity of use. Sensitivity and specificity are measures of criterion validity, with

opposing forces. That is, in attempts to maximize one component, the complement is sacrificed. For our purposes, identification of those at risk of osteoporosis, a minimum sensitivity of 90% was set to ensure that less than 10% of those at highest risk would be missed from our case finding scheme. Ensuring 90% sensitivity is an important factor given the debilitating costs associated with osteoporosis and fragility fractures (section B.1). As sensitivity and specificity act in concert, setting a higher sensitivity would compromise the specificity of the instrument, selecting more individuals unnecessarily. These criteria (sensitivity and specificity) were evaluated in specific subgroups of the population, such as by region (identified through CaMos study site), menopausal status (pre vs. post); and for various outcomes, such as to identify low BMD (≤-2.0 SD of the young adult normal) at either the femoral neck, or lumbar spine, and the performance to identify WHO define osteopenia (< -1.0 SD of the young adult normal), and osteoporosis (t-score ≤ -2.5SD).

In addition, proportions of those selected for DXA from each ORAI, based on different categories of BMD t-score: normal (t-score ≥ -1.0SD), between -1.0 SD and -2.0 SD, ≤ -2.0 SD to -2.5 SD, and osteoporosis (≤-2.5 SD) were assessed. Data derived from this final categorical assessment is important given the controversy inherent in treatment thresholds. Although treatment is not indicated in individuals with normal BMD (t-score ≥ -1.0 SD), recall from section D.3, osteoporosis guidelines generally suggest treatment in those with a BMD t-score less than -1.0 SD, in the presence of risk factors for bone loss (in fact initiate treatment in those with fragility fractures), and nearly always indicate treatment in those with WHO defined osteoporosis (t-score ≤ -2.5 SD).

Both the 2 and 3 item ORAIs support recommending that all women aged at least 65 years have DXA testing. ORAIs with more items enforce a more case-finding approach for recommending DXA testing, supporting women aged at least 65 years who are not currently taking estrogens (note all women aged at least 65 years in our population were postmenopausal). This suggests use of an ORAI with at least 4 items, preferentially over ORAIs with 2-3 items. However, the discriminatory performance in terms of sensitivity and specificity to identify low BMD (t-score ≤ -2.0 SD) of the 3-item ORAI were similar throughout sensitivity analyses to more complex ORAIs (with more items). The 2-item ORAI, however, was dropped from consideration due to compromized specificity. When comparing ORAIs with similar performance, the simplest instrument is considered superior, given potential benefits in clinical utility. Therefore, the 3-item instrument was selected as the definitive ORAI. Recall from section E.2 (clinical prediction rules), that the simpler

a prediction rule is (as long as it maintains sensibility), the more likely that it will be used in clinical practice, i.e., clinical utility (Laupacis *et al.*, 1997). Tu and Naylor (1997) suggest that an inverse relationship exists between the complexity of a clinical prediction rule and its utility to practicing clinicians. The prediction rule must be easy to use and offer face validity before it will be recognized and used widely in clinical practice.

Targeting high-risk populations is important for achieving cost-effective interventions (Jonsson, 1998). The 3-item ORAI supports selective case screening postmenopausal women at least 65 years of age and women who weight less than 60kg (or about 132 lbs). Selection of women aged 65+ years makes intuitive sense, as women at this age are entering the highest period of risk for hip fractures (Black, 1996), and supports Torgenson's (1998) view that screening should likely be aimed at women aged 65 years and older. This recommendation is also consistent with the recent National Osteoporosis Foundation (NOF) in the US's guidelines, indicating bone densitometry in all women aged at least 65 years, regardless of risk profile (National Osteoporosis Foundation, 1998). The 3-item ORAI may be considered superior to NOF recommendations, for NOF guidelines include the catch all indication: all postmenopausal women aged under 65 years of age who have one or more risk factors for osteoporosis (besides menopause), for BMD testing. Again, which risk factors are relevant for selection for bone densitometry is not clear, and any risk factor (besides menopause) is suggested as an indication by the NOF. The 3-item ORAI on the other hand gives specific recommendations for selection based on current weight and estrogen use.

Unlike Lydick *et al.* 's SCORE (1998), which required complex calculation and lacks content validity, the 3-item ORAI follows the methodological standards for clinical prediction rules (Wasson *et al.*, 1985; Laupacis *et al.*, 1997). This instrument is a simple additive scoring system to select women for bone densitometry using clinically sensible risk factors for osteoporosis. The course of action (select for bone densitometry), is clearly stipulated at a threshold of 9. All items included in the ORAI are known major risk factors for osteoporosis in women. However, although the instrument was validated in a sample of women separate from those used to develop the instrument, the validation cohort was drawn from the same underlying sampling initiative. Therefore, prospective validation is necessary to confirm the validity of the 3-item ORAI. That is, ORAI must be tested in a separate cohort of women to validate the sensitivity and specificity of selecting women with an ORAI score of 9 versus other thresholds.

Results in this study concur with Michaëlsson (1996), i.e., weight identified as less than 70kg, is the single best indicator of low BMD. However, weight alone is not sufficient to select women for bone densitometry, where 12-15% of osteoporotic individuals, and at least 20% of other individuals who may benefit from densitometry to assess risk of fracture, and initiate prophylaxis/treatment, would be missed. These proportions may be considered significant in light of the potential effects debilitating fractures may have not only on the individual, but to society as a whole. Use of the recommended 3-item ORAI, selecting all women with a score of at least 9, will ensure that at least 94% of all women with osteoporosis, and at least 90% of those with BMD $\leq$-2.0 SD of the young adult normal are selected for bone densitometry for confirmatory diagnosis. In addition, this criterion threshold of 9 has a specificity of around 57%, that is, only about 43% of those with normal BMD (BMD $\geq$-1.0 SD) would be selected for bone densitometry. Furthermore, the 3-item ORAI would recommend 39% less women for densitometry over a population based/mass screen. Population based/mass screening is not currently recommended by the Canadian Task Force on the Periodic Health Examination (1994), the OSC (Scientific Advisory Board of the Osteoporosis Society of Canada, 1996), or the US Preventive Services Task Force (1996), due to lack of evidence based outcome studies. However, if the current guidelines were followed, a population screen of all women aged at least 50 years may result (section E.3). Nevertheless, given the current under-utilization of BMD testing associated with unclear guidelines and asymptomatic nature of osteoporosis, use of the ORAI will in fact increase the use of DXA testing. Therefore, an initial increased cost to the health care system will result. Regardless, as DXA use may permit the early identification of low BMD/osteoporosis, and thus prophylaxis/treatment of osteoporosis and fragility fractures ensued, overall costs to the health care system may decrease due to decreased costs of treating fractures. Hip fractures in particular threaten the health care system, even a small reduction in fracture incidence may decrease the burden of osteoporosis on individuals and the community (Millar & Hill, 1994). Unfortunately, prospective data demonstrating that early identification of low BMD and subsequent therapy yields decreased fractures are still being collected. Nonetheless, BMD is the best single predictor of fragility fracture. Given that DXA testing would permit early identification of those at risk of debilitating fractures based on BMD status, use of ORAI to select women for DXA may result in decreased fragility fractures. Until data from prospective studies are available, one may assume from current data suggesting BMD's relationship to fracture (the higher the BMD, the less likely a fragility fracture will occur), that BMD testing and following prophylaxis/treatment may decrease fragility fractures.

H.1. Strengths / Limitations

H.1.1. Study Sample

Overall CaMos had difficulty recruiting subjects for participation. This was particularly true for sampling for the Toronto site, where less than 30% of those contacted participated fully in the CaMos study. However, demographic data were available in about one half of those who refused full participation. Using these data as a comparison to CaMos participants, participants and non-responders had comparable age distribution. Although race was statistically different among participants and non-participants, this may be related to measurement bias, due to differences in assessing information over the telephone compared to personal interview. Non-participants for instance may opt to answer "other" instead of specifying a race over the telephone. O'Neill *et al.* (1995) studied characteristics of responders and non-responders for participation in a multicentre population-based survey of vertebral osteoporosis. They found differences between responders and non-responders to be small and not consistent in either direction in terms of increased or decreased risk of osteoporosis. This finding persisted regardless of response rates between study centres. However, Beard and colleagues (1994) study found that response rates were lower in the oldest age groups (only 56% in those aged at least 70 years). This response difference was important, as more non-responders were found to have fractures (29.3% compared to 19.3% in participants; Beard *et al.*, 1994). Based on data comparing CaMos participants to non-responders (partial participants), CaMos participation in the oldest age groups were reasonable except for those aged over 80 years. Response rates were 74% in those aged between 71 and 80 years. However, response rates (participants vs. non-responders) dropped to 64% in those aged at least 81 years. This may indicate an under-representation of frail and sick individuals over 80 years of age (Melton III *et al.*, 1996). Regardless, age distribution of data from the three sites chosen are reasonable for our purposes. The goal of the thesis was to develop a clinical risk scoring system to identify those who should be selected for bone densitometry to diagnose and treat low BMD as required. As such, our scoring system attempts to identify individuals before becoming ill, as a preventive measure. If anything, given that the ORAI suggests selecting all women over 64 years of age, the specificity of the instrument may be underestimated.

Use of CaMos data to develop a case-selective strategy for bone densitometry was ideal; data were collected for the purpose of identifying osteoporosis related issues, and information on all of the major risk factors were collected. More importantly, all women had the reference standard test (i.e.,

DXA). Without DXA, we could not have proceeded. Regardless, generalizability of study findings must be discussed. Support for external validity lies in the fact that the 3-item ORAI demonstrated similar performance in each of the three sites evaluated. Sensitivity and specificity of the 3-item ORAI were: 86.0% and 45.6% in Hamilton, 92.5% and 42.7% in Kingston, and 94.0% and 47.2% in Toronto from the development cohort; compared to: 94.9% and 46.6% in Hamilton, 91.7% and 41.7% in Kingston, and 93.3% and 47.7% in Toronto. Not only was area under ROC curves statistically similar between the sites, but no trend existed between the development and validation cohorts. Therefore, there is similar discriminatory performance between the three sites. Nonetheless, criterion validity using Hamilton development cohort data may be considered clinically less. For this population, a threshold of 8 demonstrated better performance, with a sensitivity of 91.4%, and a specificity of 40.8%. Therefore, there is still a possibility that CaMos participants may not reflect the general population in Ontario. This potential difference is reflected in the overall response rate (42%). This enforces the need to validate the 3-item ORAI prospectively in a different sample of women aged at least 45 years of age. The instrument should be validated prospectively in a clinical setting, not only to assess validity, but to obtain clinical impressions of the instrument by those who we propose use it (Laupacis *et al.*, 1997).

Another important attribute which may affect the validity of the ORAI lies in the prevalence of low BMD in the population. As disease prevalence increases, so does the PPV. This is in fact why the PPV was fairly low in this study (about 34% to identify a t-score $\leq$ -2.0 SD). However, as our outcome (low BDM) under investigation is derived from a diagnostic test (DXA, and WHO defined diagnostic categories), the sensitivity and specificity of the instrument should remain constant (Choi, 1996; Brenner & Gefeller, 1997). This was observed through sensitivity analyses in the thesis.

H.1.2. Using the ORAI

ORAI is not to be an absolute indication for bone densitometry. Clinical judgement in case-selection is always important. The presented instrument was developed from population-based data exclusive of individuals with a diagnosis of osteoporosis, and those taking bone-sparing medications. Therefore, the 3-item ORAI may be viewed as a tool to select those at high risk of fracture due to primary osteoporosis. The prevalence of known secondary causes of osteoporosis were low in our sample, and thus there may not have been enough power to distinguish particular comorbidities and/or medication use related to secondary osteoporosis. Current guidelines for DXA

use clearly identify individuals at risk of secondary causes of osteoporosis, e.g., long-term corticosteroid use, and primary hyperparathyroidism (section E.3). It may be that this group of individuals were missed from our study sample, as they were already taking bone-sparing medications, or told they have osteoporosis. Exclusion of these individuals was imperative, however, to ensure that risk factors evaluated were not confounded by a change in behaviour, such as increasing calcium intake and physical activity, upon diagnosis of osteoporosis. Similarly, bone sparing drugs would reduce the impact of risk factors on bone loss. At the same time however, excluding individuals at risk who are currently on therapy to prevent further degeneration may have decreased the association of previous adult minimal trauma osteoporosis site fracture to yield significance as a predictor of low BMD in our ORAI.

In addition, as ORAI is primarily meant for initial selection for DXA testing, it does not address follow-up testing, either for future diagnostic evaluation, or to follow-up efficacy of treatment strategies. Physicians should refer to guidelines for the management of osteoporosis to determine whether a follow-up DXA may be indicated. A concensus statement from Australia (Anonymous, 1997a) recommends that if BMD t-score is >0 then no treatment is necessary, and DXA need not be repeated for five to ten years, whereas if BMD t-score is below 0, but still normal (≥-1.0 SD), then DXA may be repeated within two to five years, depending on risk factors, such as the individual's age, and menopausal status. Regardless, ORAI is aimed at helping physicians and women decide whether DXA would have impact on treatment. Torgerson *et al.* (1997) found that screening for low BMD significantly increased the use of treatment via hormone replacement therapy in a randomized trial of osteoporosis screening. This is an important finding given that Garton and colleagues (1997), suggest that screening women at risk for future fracture would have an impact on the numbers, and/or net costs of fractures prevented, provided screening influences treatment compliance.

Suggestion of the 3-item ORAI use in clinical practice does not mean that other items are not important in determining those with low BMD. However, in practice these 3 items are all that is necessary to base BMD testing. All items present in the 6-item ORAI (age, weight, current estrogen use, menopausal status, current physical activity, and adult minimal trauma osteoporosis site fracture), are important independent determinants of low BMD at the femoral neck, and/or lumbar spine. Therefore all these factors should be discussed with women in promoting bone health.

Similarly, physicians should promote adequate nutrition (calcium and vitamin D in particular), and avoidance of tobacco and excessive alcohol (Table C.1). Our study results are limited to the population under investigation. For example, ethnicity is purported to be an important factor affecting an individual's risk profile for low BMD and fragility fractures. Numbers in this study were not conducive, for instance, to evaluating the influence of a Black racial background.

H.1.3. Prevalence of Low Bone Mineral Density

Previous studies report clinical (historical) risk factors to be poor predictors of BMD (Ribot *et al.*, 1995). This finding may be, in part, attributed to misclassification of low BMD through the reliance on manufacturer norms. The need for local population reference ranges has been acknowledged by the IDSC (Hanson, 1997). Population-specific reference data are actively being produced for this purpose (Truscott *et al.*, 1997; Petley *et al.*, 1996; Laitinen *et al.*, 1991; Hadjidakis *et al.*, 1997). Population-specific data is useful to adjust for various confounding factors (e.g., ethnic mix and height) related to the population under investigation. As covered in section C.2.1.1.a, size is a major confounder associated with BMD testing. Since BMD is an areal measure of density, the size of bone artificially increases the value of BMD. Therefore in a population of taller individuals (generally larger bones), the mean and standard deviation of BMD would be higher than that of a population of smaller individuals. This is in fact why t-scores are used instead of absolute BMD values, as at least population references with associated t-scores are able to control for some factors of ethnicity and size by incorporating variance in the population under study. Until methods of measuring the structure of bone beyond simple BMD (e.g., qualitative ultrasound) are perfected, and diagnostic/treatment modalities are determined, DXA BMD is the best method available to access bone, osteoporosis, and fracture risk.

CaMos has derived a Canadian adult normal reference for use with cross-calibrated BMD values to identify low BMD and osteoporosis. Using the Canadian reference data resulted in significantly lower prevalence of osteoporosis. For example, 9.9% of women (25+ years) were classified has having osteoporosis (≤-2.5 SD at the femoral neck or lumbar spine) using the Canadian reference, compared to 22% obtained directly from DXA instruments. Similar results have been observed in a population from the United States. Ahmed and colleagues (1997) found that 7% of women aged 30-79 years were classified as osteoporotic (<-2.5 SD) at either the femoral neck, or lumbar spine using a study derived young normal reference, compared to 27% using manufactured normals.

Likewise, data available from the National Health and Nutrition Examination Surveys III data (NHANES III) indicate that in a sample of 1676 non-Hispanic white women, femoral neck BMD was 3-5% lower than the reference range recommended by the densitometer manufactured, and the SDs were 26-30% higher (Looker *et al.*, 1995). These findings highlight the importance of creating population specific reference data. Reliance on manufactured norms may result in misdiagnosis of low BMD/osteoporosis, resulting in unwarranted patient anxiety and potential mismanagement in patient care.

H.2. Recommendations / Conclusions

- It is important to develop population-specific references for DXA to ensure that appropriate diagnoses are made based on t-scores of BMD. Data presented suggest that reliance on manufactured reference data may result in misdiagnosis of low BMD, potentiating undue patient anxiety and mismanagement in patient care.

- All women aged at least 45 years could be screened for low BMD using the 3-item ORAI. It is recommended that all women with a score of **9** points undergo DXA for confirmatory diagnoses and prophylactic treatment of osteoporosis, as required.

- ORAI is meant as an initial case finding approach to screen for those who may benefit from treatment for osteoporosis/prophylaxis. It is not to replace clinical judgement by a physician who has knowledge of a given patient, for instance patients with major risk factors for secondary osteoporosis (e.g. long-term corticosteroid use), or patients with previous adult minimal trauma fracture.

- ORAI needs to be validated prospectively, not only to determine the validity of the instrument in an independent clinical setting, but to assess its acceptance and utility in clinical practice to physician and the women for which it is intended.

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Appendices

APPENDIX A Prevalence of low BMD and osteoporosis using Canadian reference population vs. DXA manufacturer reference data

Table Ap.A.1 Prevalence of low BMD and osteoporosis using Canadian reference population vs. manufactured data, in women

	prevalence using Canadian reference[a]		prevalence using manufacturer's reference[b]		
	n	% (SE)	n	% (SE)	p-value[c]
Females aged 25+ (N=1020)					
low BMD (≤ -2.0 SD)					
femoral neck	144	14.1 (1.09)	295	28.9 (1.42)	0.001
spine (L1-L4)	138	13.5 (1.07)	203	19.9 (1.25)	0.001
either	211	20.7 (1.27)	361	35.4 (1.50)	0.001
osteoporosis (≤ -2.5 SD)					
femoral neck	57	5.6 (0.72)	173	17.0 (1.18)	0.001
spine (L1-L4)	65	6.4 (0.77)	120	11.8 (1.01)	0.001
either	101	9.9 (0.94)	224	22.0 (1.30)	0.001
Females aged 45+ (N=926)					
low BMD (≤ -2.0 SD)					
femoral neck	143	15.4 (1.19)	291	31.4 (1.52)	0.001
spine (L1-L4)	137	14.8 (1.17)	201	21.7 (1.35)	0.001
either	210	22.7 (1.38)	356	38.4 (1.60)	0.001
osteoporosis (≤ -2.5 SD)					
femoral neck	57	6.2 (0.79)	171	18.5 (1.28)	0.001
spine (L1-L4)	65	7.0 (0.84)	119	12.8 (1.10)	0.001
either	101	10.9 (1.02)	221	23.9 (1.40)	0.001

Low BMD defined as 2.0 SD or more below the young female adult normal
Osteoporosis defined as 2.5 SD or more below the young female adult normal

[a] Hologic equivalent BMD values with Canadian normals as the reference (CaMos internal document)
[b] manufactured BMD with corresponding manufacturer normal reference
[c] based on chi-square test of significance

APPENDIX A Prevalence of low BMD and osteoporosis using Canadian reference population vs. DXA manufacturer reference data[con't]

Table Ap.A.2 Prevalence of low BMD and osteoporosis using Canadian reference population vs. manufactured data, in men

	prevalence using Canadian reference[a]			prevalence using manufacturer's reference[b]			
	n	% (SE)		n	% (SE)		p-value[c]
Males aged 25+ (N=535)							
low BMD (≤ -2.0 SD)							
femoral neck	15	2.8	(0.71)	113	21.1	(1.76)	0.001
spine (L1-L4)	23	4.3	(0.88)	58	10.8	(1.34)	0.001
either	32	6.0	(1.03)	132	24.7	(1.86)	0.001
osteoporosis (≤ -2.5 SD)							
femoral neck	3	0.6	(0.33)	52	9.7	(1.28)	0.001
spine (L1-L4)	4	0.7	(0.36)	32	6.0	(1.03)	0.001
either	7	1.3	(0.49)	68	12.7	(1.44)	0.001
Males aged 45+ (N=456)[d]							
low BMD (≤ -2.0 SD)							
femoral neck	15	3.3	(0.84)	109	23.9	(2.00)	0.001
spine (L1-L4)	23	5.0	(1.02)	54	11.8	(1.51)	0.001
either	32	7.0	(1.19)	126	27.6	(2.09)	0.001
osteoporosis (≤ -2.5 SD)							
femoral neck	3	0.7	(0.39)	52	11.4	(1.49)	0.001
spine (L1-L4)	4	0.9	(0.44)	31	6.8	(1.18)	0.001
either	7	1.5	(0.57)	67	14.7	(1.66)	0.001

Low BMD defined as 2.0 SD or more below the young female adult normal
Osteoporosis defined as 2.5 SD or more below the young female adult normal

[a] Hologic equivalent BMD values with Canadian normals as the reference (CaMos internal document)
[b] manufactured BMD with corresponding manufacturer normal reference
[c] based on chi-square test of significance
[d] prevalence of low BMD at either the femoral neck or lumbar spine (L1-L4) in males aged:
- at least 50 years: 29/406 = 7.1%
- at least 55 years: 24/340 = 7.1%
- at least 60 years: 20/275 = 7.3%
- at least 65 years: 17/207 = 8.2%
- at least 70 years: 12/128 = 9.4%
- at least 75 years: 7/63 = 11.1%

APPENDIX B Sensitivity, specificity and positive predictive value at each threshold score using various additive scoring systems

ROC analysis for low BMD at either the hip or spine
Odds Ratio Estimate Based Scoring System

Threshold SCORE	# true select	# false select	Sensitivity (%)	Specificity (%)	PPV (%)
28	1	1	0.5	99.9	50.0
27	5	1	2.4	99.9	83.3
26	16	6	7.6	99.2	72.7
25	26	11	12.4	98.5	70.3
24	29	12	13.8	98.3	70.7
23	48	20	22.9	97.2	70.6
22	61	33	29.0	95.4	64.9
21	72	40	34.3	94.4	64.3
20	89	53	42.4	92.6	62.7
19	98	62	46.7	91.3	61.3
18	106	89	50.5	87.5	54.4
17	110	104	52.4	85.4	51.4
16	129	139	61.4	80.5	48.1
15	150	179	71.4	74.9	45.6
14	160	208	76.2	70.9	43.5
13	177	309	84.3	56.7	36.4
12	**193**	**381**	**91.9**	**46.6**	**33.6**
11	201	475	95.7	33.5	29.7
10	204	530	97.1	25.8	27.8
9	205	558	97.6	21.8	26.9
8	208	604	99.0	15.4	25.6
7	209	612	99.5	14.3	25.5
6	209	629	99.5	11.9	24.9
5	209	660	99.5	7.6	24.1
4	210	661	100.0	7.4	24.1
3	210	692	100.0	3.1	23.3
2	210	709	100.0	0.7	22.9
1	210	712	100.0	0.3	22.8
0	210	714	100.0	0.0	22.7

APPENDIX B Sensitivity, specificity and positive predictive value at each threshold score using various additive scoring systems[con't]

ROC analysis for low BMD at either the hip or spine
Regression Coefficient Estimate Based Scoring System

Threshold SCORE	# true select	# false select	Sensitivity (%)	Specificity (%)	PPV (%)
74	1	1	0.5	99.9	50.0
71	5	1	2.4	99.9	83.3
69	17	6	8.1	99.2	73.9
66	28	12	13.3	98.3	70.0
64	46	19	21.9	97.3	70.8
63	46	20	21.9	97.2	69.7
61	59	33	28.1	95.4	64.1
60	69	35	32.9	95.1	66.3
58	77	44	36.7	93.8	63.6
57	85	54	40.5	92.4	61.2
56	87	58	41.4	91.9	60.0
55	95	68	45.2	90.5	58.3
54	98	69	46.7	90.3	58.7
53	115	86	54.8	88.0	57.2
52	117	91	55.7	87.3	56.3
51	120	92	57.1	87.1	56.6
50	135	115	64.3	83.9	54.0
49	144	146	68.6	79.6	49.7
47	146	148	69.5	79.3	49.7
46	160	200	76.2	72.0	44.4
45	161	209	76.7	70.7	43.5
43	165	219	78.6	69.3	43.0
42	167	238	79.5	66.7	41.2
41	180	302	85.7	57.7	37.3
39	181	303	86.2	57.6	37.4
38	**192**	**387**	**91.4**	**45.8**	**33.2**
37	197	440	93.8	38.4	30.9
35	197	449	93.8	37.1	30.5
34	200	496	95.2	30.5	28.7
33	202	504	96.2	29.4	28.6
31	202	516	96.2	27.7	28.1
30	204	535	97.1	25.1	27.6
29	205	554	97.6	22.4	27.0
28	205	555	97.6	22.3	27.0
27	205	563	97.6	21.1	26.7
26	208	602	99.0	15.7	25.7
23	209	619	99.5	13.3	25.2
20	209	633	99.5	11.3	24.8
19	209	636	99.5	10.9	24.7
18	209	646	99.5	9.5	24.4
16	209	647	99.5	9.4	24.4
15	210	661	100.0	7.4	24.1
12	210	662	100.0	7.3	24.1
11	210	692	100.0	3.1	23.3
8	210	709	100.0	0.7	22.9
3	210	712	100.0	0.3	22.8
0	210	714	100.0	0.0	22.7

APPENDIX B Sensitivity, specificity and positive predictive value at each threshold score using various additive scoring systems[con't]

ROC analysis for low BMD at either the hip or spine
Increasing Integer Based Scoring System

Threshold SCORE	# true select	# false select	Sensitivity (%)	Specificity (%)	PPV (%)
9	0	1	0.0	99.9	0.0
8	9	11	4.3	98.5	45.0
7	46	47	21.9	93.4	49.5
6	107	126	51.0	82.4	45.9
5	158	264	75.2	63.0	37.4
4	**196**	**437**	**93.3**	**38.8**	**31.0**
3	206	584	98.1	18.2	26.1
2	210	676	100.0	5.3	23.7
1	210	712	100.0	0.3	22.8
0	210	714	100.0	0.0	22.7

APPENDIX C Sensitivity, specificity and positive predictive value at threshold scores for each ORAI

ROC analysis for low BMD at either the hip or spine
6-item ORAI

Threshold SCORE	# true select	# false select	Sensitivity (%)	Specificity (%)	PPV (%)
28	1	1	0.5	99.9	50.0
27	5	1	2.4	99.9	83.3
26	16	6	7.6	99.2	72.7
25	26	11	12.4	98.5	70.3
24	29	12	13.8	98.3	70.7
23	48	20	22.9	97.2	70.6
22	61	33	29.0	95.4	64.9
21	72	40	34.3	94.4	64.3
20	89	53	42.4	92.6	62.7
19	98	62	46.7	91.3	61.3
18	106	89	50.5	87.5	54.4
17	110	104	52.4	85.4	51.4
16	129	139	61.4	80.5	48.1
15	150	179	71.4	74.9	45.6
14	160	208	76.2	70.9	43.5
13	177	309	84.3	56.7	36.4
12	193	381	91.9	46.6	33.6
11	201	475	95.7	33.5	29.7
10	204	530	97.1	25.8	27.8
9	205	558	97.6	21.8	26.9
8	208	604	99.0	15.4	25.6
7	209	612	99.5	14.3	25.5
6	209	629	99.5	11.9	24.9
5	209	660	99.5	7.6	24.1
4	210	661	100.0	7.4	24.1
3	210	692	100.0	3.1	23.3
2	210	709	100.0	0.7	22.9
1	210	712	100.0	0.3	22.8
0	210	714	100.0	0.0	22.7

APPENDIX C Sensitivity, specificity and positive predictive value at threshold scores for each ORAI[con't]

ROC analysis for low BMD at either the hip or spine
5-item ORAI

Threshold SCORE	# true select	# false select	Sensitivity (%)	Specificity (%)	PPV (%)
26	11	6	5.2	99.2	64.7
25	23	11	11.0	98.5	67.6
24	25	11	11.9	98.5	69.4
23	46	19	21.9	97.3	70.8
22	60	33	28.6	95.4	64.5
21	71	39	33.8	94.5	64.5
20	87	52	41.4	92.7	62.6
19	94	61	44.8	91.5	60.6
18	102	82	48.6	88.5	55.4
17	105	94	50.0	86.8	52.8
16	124	133	59.0	81.4	48.2
15	146	164	69.5	77.0	47.1
14	156	191	74.3	73.2	45.0
13	175	302	83.3	57.7	36.7
12	192	375	91.4	47.5	33.9
11	200	471	95.2	34.0	29.8
10	204	527	97.1	26.2	27.9
9	205	555	97.6	22.3	27.0
8	208	602	99.0	15.7	25.7
7	209	611	99.5	14.4	25.5
6	209	629	99.5	11.9	24.9
5	209	659	99.5	7.7	24.1
4	210	660	100.0	7.6	24.1
3	210	692	100.0	3.1	23.3
2	210	709	100.0	0.7	22.9
1	210	712	100.0	0.3	22.8
0	210	714	100.0	0.0	22.7

ROC analysis for low BMD at either the hip or spine
4-item ORAI

Threshold SCORE	# true select	# false select	Sensitivity (%)	Specificity (%)	PPV (%)
24	23	11	11.0	98.5	67.6
22	26	12	12.4	98.3	68.4
21	60	33	28.6	95.4	64.5
19	87	52	41.4	92.7	62.6
18	97	62	46.2	91.3	61.0
17	100	81	47.6	88.7	55.2
16	107	97	51.0	86.4	52.5
15	144	150	68.6	79.0	49.0
14	146	164	69.5	77.0	47.1
13	166	234	79.0	67.2	41.5
12	183	344	87.1	51.8	34.7
11	193	396	91.9	44.5	32.8
10	204	523	97.1	26.8	28.1
9	204	527	97.1	26.2	27.9
8	206	591	98.1	17.2	25.8
7	209	611	99.5	14.4	25.5
6	209	612	99.5	14.3	25.5
5	209	659	99.5	7.7	24.1
3	210	663	100.0	7.1	24.1
2	210	709	100.0	0.7	22.9
0	210	714	100.0	0.0	22.7

APPENDIX C Sensitivity, specificity and positive predictive value at threshold scores for each ORAI[con't]

ROC analysis for low BMD at either the hip or spine
3-item ORAI

Threshold SCORE	# true select	# false select	Sensitivity (%)	Specificity (%)	PPV (%)
26	23	11	11.0	98.5	67.6
24	26	12	12.4	98.3	68.4
20	70	43	33.3	94.0	61.9
18	83	58	39.5	91.9	58.9
17	91	71	43.3	90.1	56.2
16	108	83	51.4	88.4	56.5
15	108	85	51.4	88.1	56.0
14	140	144	66.7	79.8	49.3
12	143	172	68.1	75.9	45.4
11	166	310	79.0	56.6	34.9
10	183	352	87.1	50.7	34.2
9	189	392	90.0	45.1	32.5
8	197	425	93.8	40.5	31.7
7	204	517	97.1	27.6	28.3
5	206	602	98.1	15.7	25.5
3	207	619	98.6	13.3	25.1
2	210	685	100.0	4.1	23.5
0	210	714	100.0	0.0	22.7

ROC analysis for low BMD at either the hip or spine
2-item ORAI

Threshold SCORE	# true select	# false select	Sensitivity (%)	Specificity (%)	PPV (%)
24	26	12	12.4	98.3	68.4
19	39	30	18.6	95.8	56.5
17	83	58	39.5	91.9	58.9
16	91	73	43.3	89.8	55.5
13	111	104	52.9	85.4	51.6
12	143	172	68.1	75.9	45.4
9	164	304	78.1	57.4	35.0
8	197	425	93.8	40.5	31.7
5	206	566	98.1	20.7	26.7
3	207	619	98.6	13.3	25.1
0	210	714	100.0	0.0	22.7

ROC analysis for low BMD at either the hip or spine
1-item ORAI

Threshold SCORE	# true select	# false select	Sensitivity (%)	Specificity (%)	PPV (%)
8	98	117	46.7	83.6	45.6
3	169	331	80.5	53.6	33.8
0	210	714	100.0	0.0	22.7