Development of an algorithm to predict appendicular lean mass (ALM) from regional spine and hip DXA scans

by

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Abstract

Background: Sarcopenia is characterized by progressive muscle loss with reduced physical function and/or reduced muscle strength. Sarcopenia is common in older individuals and negatively impacts quality of life. It is associated with several adverse health outcomes, including but not limited to falls, reduced mobility, and increased mortality. All current operational definitions of sarcopenia include a measurement of muscle mass, most often Dual-energy X-ray Absorptiometry (DXA)-derived appendicular lean mass (ALM). ALM can only be derived from whole-body DXA scans. However, whole-body DXA scans are performed less commonly than hip and spine DXA scans as part of clinical care. The primary objective of our study was to develop an algorithm to predict ALM from regional spine and hip DXA scan. The exploratory objective of this study was to determine if self-reported history of falls is associated with sarcopenia, as determined using predicted ALM.

Methods: We performed a retrospective cross-sectional study using a subset of patients from the Manitoba BMD clinical database who had whole-body DXA scans and hip and spine DXA scans at the same visit. We developed the algorithm using backward stepwise multiple linear regression and report the proportion of variation explained (i.e., R^2), adjusted for the covariates age, sex, height, weight, spine and hip fat fraction, spine and hip tissue thickness. We internally validated the algorithm using the bootstrap method. Mean bootstrap parameter estimates were used as the final equation. We evaluated the relationship between sarcopenia, defined as low predicted-ALM/height^2, and self-reported falls using logistic regression; odds ratios (OR), area under the curve (AUC) and 95% confidence intervals (CI) are reported.

Results: There were 678 patients with both whole-body and hip and spine DXA scans included in our dataset. Mean age was 52.6 (standard deviation [SD] 21.0) and 77.0% identified as female. Mean ALM was 18.0 kg (SD 5.0 kg). The final predictive model included sex, age, log of weight, spine average fat fraction and hip average fat fraction; it had an adjusted R^2 of 0.891 (95% CI 0.876 – 0.906). Sarcopenia, defined as low predicted-ALM/ht^2, was not associated with increased odds of falls (OR 0.92, 95% CI 0.31 – 2.74, p=0.88).

Conclusion: Our evidence supports that hip and spine DXA scans can be used to predict ALM, but that low ALM index is not associated with increased odds of falls.

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Table of Abbreviations

Abbreviation	English Name
ALM	Appendicular Lean Mass
ASM	Appendicular Skeletal Mass
AWGS	Asian Working Group on Sarcopenia
BIA	Bioelectric Impedance Analysis
BMD	Bone Mineral Density
BMI	Body Mass Index
CI	Confidence Interval
CT	Computed Tomography
DXA	Dual-Energy X-ray Absorptiometry
ESPEN	European Society for Clinical Nutrition and Metabolism
EWGSOP	European Working Group on Sarcopenia in Older People
EWGSOP2	European Working Group on Sarcopenia in Older People updated 2019
FNIH	Foundation for the National Institute of Health
FRAX	Fracture Risk Assessment Tool
HGS	Hand Grip Strength
IQR	Interquartile Range
IWGS	International Working Group on Sarcopenia
MRI	Magnetic Resonance Imaging
SPPB	Short Physical Performance Battery

Chapter 1: Introduction

Sarcopenia is a condition associated with aging and is characterized by progressive muscle loss with reduced physical function and/or reduced muscle strength.[1–4] Sarcopenia is common, negatively impacts quality of life, and is associated with reduced mobility, reduced independence, increased mortality, and increased surgical complications and length of hospital-stay post-surgery.[3,5] Sarcopenia is common in the older population. In community dwelling older adults, the prevalence of sarcopenia is dependent on the definition used and ranges from 9.9% to 40.4%.[6] Many different operational definitions for sarcopenia have been developed and revised, yet no universal definition is currently available.[7] Despite the lack of consensus on an operational definition, appendicular lean mass (ALM) is a common variable among definitions of sarcopenia.[4,7–10] Lean mass is fat-free mass and includes muscle, organs, and connective tissue. ALM includes lean mass in both arms and both legs and acts as a surrogate measurement for muscle mass in the diagnosis and identification of sarcopenia. ALM is used preferentially as a surrogate measurement for this purpose over whole-body lean mass because muscle mass constitutes a larger proportion of appendicular lean mass compared to whole body lean mass.

Dual-energy X-ray Absorptiometry (DXA) derived ALM is approved as part of the International Classification of Diseases (ICD) diagnosis for sarcopenia and is supported by the expert committees who have developed the current definitions for this condition.[11] DXA scans are fast, relatively inexpensive, non-invasive and expose the patient to minimal radiation.[12,13] Computed tomography (CT) and magnetic resonance imaging (MRI) are the gold standard for measuring low body mass but have drawbacks, such as increased wait times, costs, radiation exposure and the need for highly trained technicians, that make DXA the ideal measurement tool for lean mass in research and some clinical settings.[11] DXA is the gold standard for measuring bone mineral density (BMD) and is the most common reason for referral for DXA scans. Regional hip and spine scans are performed for BMD testing whereas whole-body DXA scans are typically used for assessment of body composition.[14] Due to their common use for diagnosing osteoporosis in clinical care, the availability of regional hip and spine DXA scans is much higher in administrative healthcare databases than whole body scans. If data from regional spine and hip scans can be used to accurately predict ALM, studies examining the prevalence and health

services impact of sarcopenia can be conducted on a population level using this data. From a clinical standpoint, the development of an algorithm that accurately estimates ALM from DXA scans performed for osteoporosis assessment could help clinicians identify patients at risk for adverse outcomes associated with sarcopenia who may benefit from interventions to mitigate or prevent sarcopenia. The purpose of this project is to develop an algorithm to predict appendicular lean mass from regional spine and hip DXA scans in the MB Bone Mineral Density Database a provincial repository of DXA scans which is well described, population based, and linked to other administrative health data.[15]

Chapter 2: Literature Review

2.1 Defining Sarcopenia

Rosenberg devised the term sarcopenia, which is derived from the Greek work "*sarx*" meaning flesh and "*penia*" meaning loss, in 1989.[16,17] The general definition of sarcopenia is age-related muscle loss and function.[1–4,18] Conditions that potentially lead to sarcopenia are age-related (decreased sex hormones, apoptosis, mitochondrial dysfunction), neurodegenerative diseases (motoneuron loss), muscle disuse (immobility, physical inactivity, zero gravity), cachexia, starvation, malabsorption, decreased vascular supply, small birth weight, polypharmacy, and endocrine causes (glucocorticoids, decreased growth hormone, decreased IGF-1, thyroid, insulin resistance).[19–21] Acute sarcopenia, lasting less than 6 months, is more likely to be the result of an acute illness or injury whereas chronic sarcopenia, lasting 6 months or longer is more likely due to a chronic process or illness.[4] Chronic sarcopenia is related to increased mortality whereas there is less research on the effects of acute sarcopenia on long-term outcomes.[4,22] Sarcopenia can also occur in the context of increased fat mass and the combination of low lean mass and excess adipose tissue is termed sarcopenic obesity.[4]

The first operational definition of sarcopenia was developed by Baumgartner *et al.* and was defined as height standardized appendicular muscle mass ≥ 2 standard deviations (SD) below the mean muscle mass of healthy young adults measured using DXA.[23] Since the development of this definition, further research has been conducted to establish better conceptual and operational definitions that identify individuals with sarcopenia with improved prediction of

negative health outcomes. (citation) Prior to the 2010 European Working Group Sarcopenia (EWGSOP) guidelines, sarcopenia was primarily discussed in the field of geriatrics and the new guidelines brought sarcopenia to a wider scope of clinicians.[24] Most definitions now contain measures of physical function and/or performance in addition to measures of muscle quantity. Research demonstrates physical function and/or performance are better predictors of negative health outcomes in sarcopenia compared to ALM.[5,25] However, sarcopenia is by name loss of muscle mass and ALM is still included in the definitions. This is further explored in the sections *Association of Sarcopenia with Adverse Health Outcomes* and *Appendicular Lean Mass in Sarcopenia.* Cut-off points used in definitions for muscle quantity are often 2 standard deviations (SD) below a young adult reference standard group in the relevant population.[4,8] If a more conservative cut-off point is required in a specific circumstances, ≥2.5 SD below the young reference group can be used.[4] However, the International Working Group on Sarcopenia(IWGS) set its cut-off points for lean mass as <20th percentile of a young adult reference standard.[9] Most definitions determined cut-off points for physical strength and performance based on research conducted in the population in which the definition is designed or using 2 SD below a young adult reference standard group values. Table 1 outlines consensus and operational definitions often referenced and used for defining and identifying sarcopenia in research and clinical practice. The European Working group on Sarcopenia in Older People 2018 (EWGSOP2) definition and Asian Working Group for Sarcopenia (AWGS) 2019 definition use hand grip strength, DXA-derived ALM/ht^2 and Gait speed as criterion.[4,8] The International Working Group on Sarcopenia, the Foundation for the National Institute of Health Sarcopenia project and European Society for Clinical Nutrition and Metabolism (ESPEN) Special Interest Group all use a measure of ALM and gait speed as their variables to define sarcopenia.[9,10,19]

2.2 Epidemiology of Sarcopenia

2.2.1 Why Does Muscle Mass Decrease with Age?

There is both muscle fibre atrophy and muscle fibre loss with age.[26] Age-related factors that contribute to muscle fibre atrophy and loss include disuse, oxidative stress and inflammation, fat infiltration of muscle and bone, endocrine imbalance, neuroprogressive disorders, and poor nutrition.[27] The Copenhagen Sarcopenia Study found a weak association between higher hsCRP

levels and lower muscle mass ($p<0.001$) however there was no association with other inflammatory markers researched in this study.[28] The authors suggest that low-grade inflammatory in otherwise health elderly males may not play a significant role as previously believed in muscle mass decline however still contribute to physical function? decline.[28] Smoking has been shown to be related to reduced muscle and bone mass.[27] Genetic factors and epigenetic changes also contribute to the loss of muscle mass with aging.[27]

2.2.2 Impact of Sarcopenia Definitions and Population Characteristics

The prevalence of sarcopenia varies by up to 40% in the same population depending on the definition used to identify this condition.[6] According to a 2018 systematic review by Mayhew *et al.*[6], the prevalence of sarcopenia using the EWGSOP/AWGS, IWGS and FNIH definitions were 12.9%, 9.9% and 18.6% respectively.[6] In this review, which included studies with participants >55 years of age, the highest prevalence of sarcopenia was seen in studies that defined sarcopenia using standardized ALM and did not include physical performance or muscle strength components.[6] Prevalence ranged from 24.2% to 40.4% for studies that defined sarcopenia by ALM/BMI or ALM/weight, respectively.[6] In addition, prevalence of sarcopenia was higher when sarcopenia was measured by bioimpedance analysis (BIA) as compared to DXA.[6]

Considering older adults may require long-term care, some studies focused on the prevalence in nursing homes and long-term care institutions. In older community dwelling adults sarcopenia prevalence using the EWGSOP definition (1-29%) was similar to that of older adults in long-term care institutions (14-33%).[29,30] A more recent study conducted in nursing homes in Belgium, found the prevalence of severe and moderate sarcopenia to be 17% and 45%, respectively, which is higher than other similar literature despite excluding patients with conditions that affect the immune system.[31] Prevalence of sarcopenia in nursing home residents was 41% (95% CI 32-51) using the EWGSOP definition and 59% (95% CI 24-93) using skeletal muscle index (SMI) in a meta-analysis by Shen et al.[32] Prevalence of sarcopenia was not significantly different by gender in this meta-analysis of 15 studies.[32] It may be difficult to analyse comparisons in long-term care institution statistics due to the differences in admittance criteria for nursing homes, and personal care homes amongst countries.[31]

Age, sex, and lifestyle factors are significant factors contributing to the prevalence of sarcopenia. In a study using data from the Fourth and Fifth Korea National Health and Nutrition Examination Survey (KNHANES) in participants who were not pregnant and without malignancy, prevalence of sarcopenia increased with age from 19.2% to 31.0% to 35.2% for the 20-39 years, 40-64 years and ≥65 years age groups respectively.[33] In this study, sarcopenia was defined as ASM/weight (%) <1 SD below the mean of a sample of healthy adults 20-39 years old.[33] Prevalence of sarcopenia by sex was different for each age group. In the 20–39 year age group sarcopenia was more prevalent in men compared to women; in the 40-64 year age group sarcopenia was more prevalent in women, and in the ≥ 65 age group there was no significant difference in prevalence between men and women.[33] The prevalence of sarcopenia was higher in participants with lower socioeconomic status (SES) in patients who were ≤ 64 years but not in those ≥ 65.[33] Prevalence of sarcopenia was also higher in those who smoked, frequently drank alcohol and had a lower physical activity, as assessed by the international physical activity questionnaire, in all age groups.[33] When the study evaluated metabolic markers, abdominal obesity, increased blood pressure, high fasting blood glucose and high triglycerides were associated with increased prevalence of sarcopenia in all age groups.[33] The study also looked at influencing factors for sarcopenia. In the 20-39 age group, the statistically significant influencing factors were low physical activity, high blood pressure, abdominal obesity, high triglycerides, low energy intake, and low serum vitamin D.[33] In the 40-64 age group, risk of sarcopenia was higher in men than women.[33] The influencing factors in this age group were medium and low physical activity, high blood pressure, abdominal obesity, diabetes, dyslipidemia, suicidal ideation, fall experience , perceived poor health status, osteoarthritis, mobility problems, low energy intake, low protein intake and low serum vitamin D level.[33] In the ≥65 year age group, risk of sarcopenia is higher in men and city dwellers.[33]

Comorbid conditions contribute to increased prevalence of sarcopenia. According to a systematic review by Pacifico et al., sarcopenia is highly prevalent in cardiovascular disease (CVD), dementia, diabetes mellitus (DM) and respiratory disease.[34] In studies that had non-diseased control groups, there was a 3.14 (95% CI 1.51-6.55) increased odds of sarcopenia in individuals with dementia, 2.07 (95% CI 1.62-2.65) increased odds of sarcopenia in individuals with DM and 2.71(95% CI 2.03-3.62) increased odds of sarcopenia in individuals with respiratory disease

compared to non-disease controls.[34] The prevalence of sarcopenia in the above studies were 26.4% (95% CI 13.6 -44.8), 31.1% (95% CI 19.8-45.2) and 26.8% (95% CI 17.8-38.1) respectively.[34] In studies that did not include controls, prevalence of sarcopenia was 31.4% (95% CI 22.4-42.1) in individuals with CVD, 27.4% (95% CI 14.4-45.8) in individuals with dementia, 20.7% (95% CI 14.5- 28.7) in individuals with DM, and 25..4% (95% CI 16.8-36.5) in individuals with respiratory disease.[34] Regardless of definition used or continent of the study, prevalence of sarcopenia was higher in individuals who were known to have the above diseases.[34] However, it is important to note that there was significant heterogeneity in the above meta-analysis results.[34] High between-study heterogeneity can cause included studies to be more equally weighted, despite different sample sizes, therefore smaller studies may have a greater impact on the overall mean. The prevalence of stroke-related sarcopenia was 42% (95% CI 32-66), with a prevalence of 50.4% (95% CI 41.0-58.9) less 1 month post stroke (4 studies) and 33.6% (95% CI 16.5-56.4) greater than 6 months post stroke (3 studies) in a meta-analysis of 7 studies.[35] In a study of 12 healthy older adults, 10 days of bed rest led to a 6.3% (3.1-9.5) reduction in lower extremity lean mass and 3.2% (1.4-5.0) reduction in whole body lean mass as measured using DXA.[36]

Race and ethnicity are additional factors that affect prevalence of sarcopenia. The National Health and Nutritional Examination Survey (NHANES 1999-2022 and 2011-2014), is a "program of studies designed to assess the health and nutritional status of adults and children in the United States"[37]. From these surveys, overall non-Hispanic Blacks had the lowest prevalence of sarcopenia (4.4% to 27.7%) and Hispanics had the highest prevalence (21.1% to 36.0%).[38] Non-Hispanic Blacks had lower odds of developing sarcopenia (Odds ratio (OR) 0.26 $p<0.001$) compared to non-Hispanic Whites by ALM/BMI definitions.[38] Whereas Hispanics (OR = 2.79, $p<0.001$) and Asians/Others (OR=3.02, $p<0.001$) had a significantly higher odds of developing sarcopenia compared to non-Hispanic whites by ALM/BMI definitions.[38] Alternatively, when sarcopenia was defined by only gait speed, those who identified as non-Hispanic Black had the highest prevalence of sarcopenia (27.7%).[38] None of the studies evaluated during the literature review provided information on the prevalence of sarcopenia and ethnicity/race of Canadians.

Aging is often accompanied by decreased muscle mass, increased fat mass and decreased height.[39] By the third decade of life, there is already a decrease in muscle mass; however strength is not significantly affected until the fifth decade.[40] Studies have demonstrated an annual decrease in lean mass between 0.11% to 0.68% from the third decade of life .[39,41] The worldwide population is aging and by 2050, the World Health Organization estimates there will be 2 billion people over the age of 60.[42] Since sarcopenia is associated with ageing, it is anticipated that there will also be increased prevalence and incidence of musculoskeletal disorders in the overall population.[39]

2.3 Association of Sarcopenia with Adverse Health Outcomes

Reduced muscle mass, strength and physical function have implications for older adults. Sarcopenia was associated with an 3.60 increased odds (95% CI 2.96-4.37, n= 14,035) of mortality compared to no sarcopenia in a meta-analysis of prospective studies using the EWGSOP definition in community dwelling older adults with follow-up times ranging from 3 months to 10 years.[43] The association between sarcopenia and mortality was significantly higher in individuals ≥ 79 years old compared to individuals <79 years old.[43] Sarcopenic older adults also had greater odds of functional decline (OR 3.03; 95% CI 1.80 – 5.12) assessed using the Katz Activities of Daily Living scale, Lawton Instrumental Activities of Daily Living scale, Barthel Index and self-reported functional limitations in a meta-analysis of six trials.[43] In both community dwelling older adults and those living in nursing homes, sarcopenia was associated with increased risk of falls (OR 1.60; 95% CI 1.31-1.97; n=12,261) as determined from participants' medical records, or by self-report.[44] Sarcopenia was also found to be a risk factor for reduced mobility, and reduced ability to perform activities of daily and instrumental activities of daily living in community dwelling older adults in Japan and China.[45,46]

Chronic conditions leading to secondary sarcopenia, loss of muscle mass in relation to causes other than or in addition to aging, may increase falls risk in individuals with low ALM/muscle mass.[4,20,47] This usually occurs alongside age-related loss of muscle mass and is due to chronic illness, in particular those that involve an inflammatory process, and multiple diseases that occur in the elderly. [4,20,47] Chronic health conditions can lead to reduction in sensation (ex. vision, hearing, touch) and syncope which contribute to increased falls.[48,49] Medication use and

polypharmacy are common among patients with chronic disease and the elderly. Medication use and polypharmacy, in particular medications that lead to syncope, confusion, sedation, sleep disturbances, orthostatic hypotension, dizziness and other central nervous side effects, increase falls risk.[48]

Considering the negative outcomes associated with sarcopenia, it is not surprising that individuals with sarcopenia have a lower quality of life compared to their non-sarcopenic counterparts.[50] Sarcopenia is associated with fragility fractures (risk ratio (RR) 1.35; 95% CI 1.11 – 1.63; n=1,258), disability (OR 3.04; 95% CI 1.80-5.12; n=8,569), increased length of hospital stay (OR 1.58; 95% CI 1.13-2.20; n=4,000) in the community setting and an increased rate of hospitalization and hospital readmission (RR 1.40; 95% CI 1.31-1.89; n= 1,357) in community, nursing home and acute care wards settings.[44]

In a study by Pasco et al. using the Geelong Osteoporosis Study data from Australia, Fracture Risk Assessment Tool (FRAX without BMD predicted 10-year risk of sarcopenia in women with high sensitivity and moderate specificity.[51] The addition of BMD to FRAX did not significantly improve 10-yr prediction of sarcopenia.[51] FRAX is a tool developed to predict 10-year risk of fractures in patients with osteoporosis. FRAX includes age, weight, height, hx of previous fracture, parental hip fracture, current smoking status, use of glucocorticoids, rheumatoid arthritis, history of secondary osteoporosis, alcohol consumption >3 or more units per day and femoral neck BMD.[52] HF-FRAX (hip fracture- FRAX) predicted sarcopenia with a sensitivity of 90.9% and specificity of 62.4%.[51] MOF-FRAX (major osteoporotic fracture-FRAX) predicted sarcopenia with a sensitivity of 81.8% and specificity of 71.7%.[51] This suggests that the risks for future fractures and risk for developing sarcopenia are similar. In hospitalized patients with gastric cancer, sarcopenia is associated with post-operative complications, including operative ileus.[44] In a systematic review by Wong *et al*., sarcopenia was more prevalent in participants with hip fractures compared to participants with vertebral and distal radius fractures.[53] In addition, prevalence of sarcopenia increased significantly after hip fracture compared to pre-surgery (EWSOP criteria: 12.4–18.3%; AWGS criteria: 44.3-68.2%) and post-surgery (EWSOP criteria: 34.9% - 58%; AWGS criteria: 67.7 – 73.6%).[53] An increased odds of restrictive lung disease was seen in patients with sarcopenia and sarcopenic obesity (OR 2.00, 95% CI 1.38-2.89

and OR 2.81, 95% CI 1.72-4.59 respectively) in a cross-sectional survey of 3044 adults aged > 60 from Korea.[54] Sarcopenic obesity was associated with a greater increased odds of restrictive lung disease in men (OR 4.32; 95% CI 2.21–8.45) than in women (OR 1.96, 95% CI 1.00–3.84).[54]

Sarcopenia also has major public health implications.[55] Although its association with functional decline, disability and loss of productivity and autonomy can ultimately lead to increased healthcare costs, few studies have extensively and adequately evaluated the economic burden of sarcopenia on health care systems.[55,56] A 2004 study estimated that the direct US healthcare costs attributable to sarcopenia was $18.5 billion dollars, which accounted for 1.5% of total healthcare expenditure.[57] This estimate did not take into account the comorbidities associated with sarcopenia that may inflate sarcopenia associated costs.[55] $1.1 billion US dollars per year could be saved in United States healthcare costs if the prevalence of sarcopenia was reduced by 10%.[33,57] A systematic review of studies comparing healthcare costs of treating sarcopenic and non-sarcopenic patients conducted by Bruyère *et al.* observed a trend of sarcopenic individuals having higher healthcare costs than non-sarcopenic individuals.[56] However, in view of the heterogenous populations and lack of adjustment for relevant confounding variables in most of the studies included in the review, they identified the need for more research to confirm this finding.[56]

Recent developments will help facilitate sarcopenia research to address knowledge gaps. These include increased recognition regarding the importance of sarcopenia, progress in the development of a clear sarcopenia definition and the recognition that muscle mass and function play a role in other disease conditions.[5] Additionally, in September 2016, a unique ICD-10-CM code (M62.84) was developed for sarcopenia allowing physicians to bill for sarcopenia-related care.[58,59] This ICD code facilitates clinical diagnosis of sarcopenia, leading to increased capacity for research using administrative databases in this area.[5]

2.4 Appendicular Lean Mass in Sarcopenia

Appendicular lean mass is measured as the total lean mass in the arms and legs. ALM has been central to the definition of sarcopenia since the first official definition by Baumgartner *et al.*.[23]

This initial paper reported that sarcopenia defined as ALM/height^2 was associated with increased disability, falls and abnormalities in balance and gait.[25] Using a large Manitoba bone mineral density health database, annualized loss of total body lean mass measured using DXA was associated with a statistically significant increased risk of major osteoporotic fracture and incident hip fracture even after adjusting for individual FRAX risk factors and BMD (HR 1.07; 95% CI 1.02-1.11 and HR 1.31; 95% CI 1.16-1.47 respectively).[60] In the Osteoporotic Fractures in Men Study cohort of 10,411 men aged 65 and greater, which included participants from China, USA and Sweden, increased ALM/height^2 measured using DXA reduced the risk of incident fracture (HR 0.89; 95% CI, 0.84 to 0.93) before adjusting for BMD.[61] Low DXA-derived ALM/height^2 was protective of 2 year major osteoporotic fracture risk (OR 0.68; 95% CI 0.51-0.91) and falls risk (OR 0. 0.85 (0.75, 0.97) in women and was associated with a higher 2 year major osteoporotic fracture risk (OR 1.72; 95% CI 1.01 – 2.93) in men participating in a Chinese study of 4000 individuals aged 65 and greater.[62] Converse**l**y, the Health ABC study (USA) found that decreased DXA-derived ALM/height^2 was a risk factor for hip fracture in women (HR 1.56; 95% CI 1.19 - 2.03**)** but not men.[63] In a large Australian prospective study, decreasing ALM/BMI was associated with increased mortality (RR 1.52; 95% CI 1.13-2.06) but not increased 10-year risk of fracture or falls.[64] In frail and prefrail older adults (≥65 years) from the United States who participated in the National Health and Nutrition Examination Survey (NHANES III), reduced ALM measured using BIA was independently associated with increased mortality and the addition of ALM improved age and sex mortality predictions.[65] Increased mortality risk was also observed in DXA derived ALM/height^2 evaluated using DXA of Chilean older adults whose lean mass was in the lowest quartile.[66] When evaluating gait speed, AUC ROC analysis demonstrated that appendicular lean mass did not convey additional accuracy at discriminating slowness (Men AUC= 0.70; Women AUC= 0.62) as measured using the 6 m walk speed test over age alone (Men AUC= 0.68; Women AUC= 0.61) in a pooled data analysis of 8 cohort studies of community dwelling adults.[67] Finding from the Women's Health Initiative study by Harvey et al. demonstrated that lower DXA-derived ALM/height^2 was not associated with falls (Hazard Ratio per SD 0.98, p=0.15) however greater ALM/height^2 was associated with decreased risk of incidental fracture (HR 0.91, p<0.01).[68] This relationship was not significantly different when falls was added to the analyses but the relationship was attenuated when FRAX

risk calculated with femoral BMD was added to the analyses.[68] In the same study, increase by an SD ALM/height^2 was associated with increased risk of death (HR 1.1, $p<0.001$).[68]

Currently, presumed sarcopenia is identified using physical strength parameters but a valid measurement of low ALM, often using DXA, is required to confirm diagnosis and consider an individual sarcopenic. Considering the potential limitations of ALM in predicting sarcopenia-related outcomes, the role of ALM in definitions of sarcopenia is contested among experts in the field with proponents both strongly for and against its inclusion.[25,69] The association between fracture and sarcopenia definitions that use ALM become weakened when the models are adjusted for femoral BMD but strengthened with the addition of measures of physical function.[68,70] However at this time, ALM plays an integral role in clinical diagnosis and research related to sarcopenia where cut offs are important for developing participant cohorts and eligibility criteria.

2.5 Predictors of ALM

As previously mentioned, age and sex are predictors of ALM. Lean mass decreases with age starting after the third decade of life with men having a higher annualised loss of mass than women despite having higher overall lean mass.[39–41,71] Age alone explained 26.4% of the variance in ALM in men and 15.5% of ALM in women in the Geelong Osteoporosis Study.[27,72] The difference in the annualized decrease in ALM by sex and total loss of ALM also varies by ethnicity.[73] In the Health ABC study, a cohort of participants aged 70-79 at baseline from the United States who were followed for 10 years, an annual decrease of 0.7% of ALM was observed (95% CI 0.1 – 1.4).[74] In the same population, decline in fat mass, BMD and measures of physical function accelerated with age whereas ALM declined linearly.[74] Height and weight are significantly associated with lean mass in both men ($r= 0.48$; $r=0.69$, respectively) and women ($r=0.53$; $r= 0.65$, respectively).[40] Using data from NHANES (1999-2004), ALM was significantly different according to BMI-derived categories with ALM increasing with increased BMI.[75] BMI was a predictor of muscle mass depletion as defined by reduced ALM/height^2 in a Korean population.[76] Height, weight and BMI are commonly used to create adjusted indices of ALM (ex. ALM/height^2, ALM/BMI) for predicting outcomes such as mortality and disability related to reduced ALM.[76,77]

2.6 DXA and Its Role in Estimating ALM

2.6.1 DXA for Estimating Muscle Mass

DXA was developed in 1987 to measure bone mineral density (BMD)[78] but has been increasingly used to estimate muscle mass. DXA scans determine the mass of a material based on the attenuation of polychromatic Xray spectra for each image.[79] The elemental content of tissue determines the high to low energy ratio of attenuation.[80,81] The DXA system separates body mass into three components (bone mineral, fat tissue and fat-free soft tissue) known as the three-compartment model.[80] Muscle mass makes up the largest proportion of fat-free soft tissue which also includes organs and connective tissue. Muscle mass estimation from DXA has been shown to be strongly correlated with muscle mass estimation from CT and MRI scans at a single time point. [82–85] Additionally, DXA lean mass and fat mass estimates have been shown to be reproducible[12,86], and relatively fast, accessible and cost-effective compared to CT and MRI.

2.6.2 Advantages and Disadvantages of DXA For Estimating ALM

There are many methods available to estimate muscle mass including DXA, CT, MRI, D_3-creatine dilution, ultrasound, anthropometry, and BIA. Anthropometry and BIA are more convenient and cost-effective compared to the other methods, making them a good choice for use in the primary care setting.[12] However, they are less accurate and less precise than the other methods available and tend to overestimate muscle mass.[13] CT and MRI are the most accurate and precise methods for estimating muscle mass but are expensive, have limited availability in the healthcare system, and are time-consuming. As well, CT scans expose the patient to higher levels of radiation than other methods.[12,13] The cost of a CT or MRI scan can range from $600 to well over $1000[87] whereas a DXA scan costs approximately $40-200.[88,89] Radiation exposure from DXA is minimal. A single whole body DXA scans exposure patients to less than 0.01mSv.[90] In comparison, we are exposed to an average effective dose of 2.4 mSv per year from the natural environment; a whole-body CT scan exposes the patient to an effective dose of 8 mSv.[91] Therefore, CT and MRI are generally limited to research settings for use in estimating muscle mass. Another method used to estimate muscle mass is the D_3-creatine dilution method. D_3-creatine dilution is a measure of muscle mass as opposed to a lean mass measurement in DXA.[92,93] In brief, D_3-creatine dilution method involves ingestion of a 30-mg dose of stable

isotope labeled creatine (D_3-creatine) and a 72-144 fasting, morning urine sample which is assessed for D_3-creatine, unlabeled creatine, and creatine.[92–94] Dilution of creatine is used to estimate the total body creatine pool size and therefore the skeletal muscle mass.[92–94] It is believed to be a more accurate measure of muscle mass than DXA and provides muscle mass measures closer to those derived from MRI.[92,94] Some research conducted in older men from the United States suggests that the D_3-creatine dilution method of assessing muscle mass is superior to DXA-derived ALM in predicting negative outcomes associated with low muscle mass.[93,95,96] However, DXA has an advantage in also providing fat mass and BMD data. DXA scans are accurate, precise, relatively cost-effective and expose patients to a minimal amount of radiation.[13] A review by Buckinx et al. suggests that DXA can be considered as the reference standard, but not gold standard, for measuring lean body mass.[97] DXA has become the most commonly used method to estimate muscle mass for sarcopenia and is included in most operational and consensus definitions of sarcopenia.[98] However, DXA has its limitations, some of which have already been noted above. Hydration status of the patient influences the lean mass measurements derived from DXA. Acute ingestion of water prior to DXA scan and edema secondary to underlying diseases (kidney, heart, liver) increase the DXA-derived lean mass and bias the measurement.[99,100] Another major limitation of DXA is the inability to quantify the distribution of intermuscular adipose tissue (IMAT) and intramuscular adipose tissue which have been shown to have an impact on muscle density and function.[101] DXA-derived ALM is not an estimate of total body muscle mass because it uses a three-compartment model, which means that lean mass consists of muscle mass, connective tissue and organs.[80] Lean mass of arms and legs, with exclusion of trunk lean mass, is used as an estimate of muscle mass because legs and arms contain fewer organs and provide a better estimate of muscle mass compared to the trunk or whole body.

2.7 Lean Mass and DXA

DXA scans are performed as part of routine clinical care for a variety of reasons. Figure 1 outlines the Manitoba BMD program guidelines for requesting a DXA scan. DXA is most commonly used for osteoporosis assessment, fracture risk and monitoring corticosteroid use. Regional hip, lumbar spine, and forearm DXA scans are usually performed as part of clinical care for bone mineral testing. Whole-body scans are required to measure ALM and are

predominantly performed less frequently; predominately for body composition analysis evaluating fat mass and/or lean mass.[14] Consequently, administrative databases contain predominantly hip, and spine DXA scans with fewer whole-body scans. At least three equations have been developed estimating whole-body lean mass or ALM from regional DXA scans.[102–104] Leslie *et al* estimated whole-body lean mass from hip and spine DXA scans in the Manitoba BMD database.[102] The equation included age, sex, height, weight, spine fat fraction and hip fat fraction as the independent variables.[102] Salamat, M *et al*. developed an equation in the Iranian population that predicts whole body lean mass from hip and spine regional DXA scans using gender, height, weight, waist circumference, spine fat fraction and hip fat fraction as independent variables.[103] Rosenthall, L *et al.* incorporated proximal femur fat fraction, lumbar spine fat fraction and weight in their estimation of whole body lean mass from regional hip and spine DXA scans in stable, actively treated HIV-positive males.[104]. Thackeray et al. (2022) developed an equation to predict both whole body lean mass and appendicular lean mass from spine and hip DXA scan in 2427 participants from the Geelong Osteoporosis study (Australia).[105] The final model to predict ALM included age, sex, weight, height spine fat percentage and hip fat percentage and was created using linear regression with forward stepwise selection.[105] The equation was as follows: ALM(kg) = -8.150 – 0.014*age + 4.641*sex + 0.207*weight + 0.101*height -7.667*spine%fat – 12.516*hip%fat. The adjusted R-squared for this equation was 0.912 and a root mean square error of 1.594.[105]. The current project differs from Thackeray et al. in the population being used and the methods of data collection.[105] The Geelong Osteoporosis study identified participants via Australian electoral roll and participants were invited to participate by mailing out invitations.[106] Thackeray et al. included participants from the Geelong Osteoporosis Study who had whole-body DXA scans of women for their 10 year follow-up visit and baseline visit for men.[105] The population used in our project reflects patients who received DXA scans as part of their clinical care in Manitoba. DXA scans in Manitoba are typically only conducted if there is a clinical indication therefore our study population more accurately reflects the population that would have DXA scans completed. This is important as future research would likely be applying this algorithm to DXA scans performed as part of routine clinical care.

2.8 Summary of Literature Review

Sarcopenia is the age related loss of muscle mass and reduced physical function. Sarcopenia has been increasingly recognized as associated with several negative health outcomes. Currently, definitions of sarcopenia include a measure of muscle mass, most commonly ALM. Whole-body DXA scans are used to measure ALM.

Development of an algorithm that predicts ALM from regional hip and spine DXA scans from a provincial repository from the Manitoban population would be useful in both clinical practice and research. An accurate prediction of ALM using regional DXA scans would minimize the number of whole-body DXA scans required for diagnosing sarcopenia and would allow for estimation of ALM in individuals who received DXA scans for osteoporosis. Manitoba has a provincial repository of DXA scans (Manitoba BMD Database) which is well described, population based, and linked to large administrative health databases.[15] There are also BMD datasets from the United States, Taiwan, Switzerland, South Korea, Sweden and Norway. The algorithm to predict ALM from regional hip and spine scans would allow studies examining the prevalence and health services impact of sarcopenia to be conducted at a population level.

Chapter 3: Materials and Methods

3.1 Research Objectives

Our primary objective was to develop and validate an algorithm to predict ALM using regional spine and hip DXA scans.

Our exploratory objective was to determine if height-adjusted ALM predicted using the algorithm and considered low according to the EWGSOP2 definition (< 7.0 kg/m^2 for men and < 5.5 kg/m^2 for women)[4] is associated with an increase in falls in the 12 months preceding the whole body DXA scan.

3.2 Study Design and Population

This retrospective cross-sectional study uses a subset of patients included in the Manitoba BMD clinical database to develop an algorithm predicting ALM from regional hip and spine DXA scans.

The study population includes adult patients (≥ 18 years) who underwent DXA evaluation of the lumbar spine, hip, and whole body at the same visit as part of clinical care in Manitoba from January 2000 until March 2018. All participants had scans performed with single-manufacturer fan-beam DXA systems (Prodigy; GE Lunar, Madison, WI) or iDXA (GE Lunar).

3.3 Data Source

For this study, we used the Manitoba BMD database. A de-identified subset of this database was provided for analysis. Ethics approval was obtained from the University of Manitoba research ethics board and data access approval was approved by the Manitoba Bone Density Program Committee and Shared Health Manitoba.

The Manitoba BMD database was developed to monitor the Manitoba Bone Density Program and provide a dataset for future research.[15] The program started in 1997 to provide BMD testing guidelines for physicians.[15] Figure 1 outlines the criteria for bone mineral testing and the general reasons participants have DXA scans performed. There are currently BMD testing sites in Winnipeg and Brandon. The program ensures that there is uniformity in testing criteria, requisition process and collection of data. Each site within the program has a charge technologist responsible for accreditation and technician performance oversight at their respective site.[15] Technician performance and reproducibility are evaluated annually.[15] Densitometers undergo daily evaluation of stability using an anthropomorphic spine phantom.[102] In 2005, validation of the Manitoba BMD database found that the dataset was >99% complete.[107]

All clinical bone densitometry in Manitoba is performed within this program.[102] The database contains all DXA scan data from the Manitoba clinical bone density testing sites since 1990 (database backfilled after initiation of database in 1998) however we did not use scans obtained on pencil-beam DPX scanners.[15] Height and weight are measured at the time of the patient's

visit.[102] Height is measured using a wall-mounted stadiometer and weight is measured using a standard floor scale without patients' shoes.[102] The Manitoba BMD database can be linked to other administrative databases in Manitoba, which are housed at the Manitoba Centre for Health Policy (MCHP) using an anonymized personal health identification number. However this was not done in this study.[15]

Every patient who has a BMD appointment in Manitoba receives a questionnaire to complete 2-4 weeks before their appointment.[108] Fall history has been collected with this questionnaire since September 1, 2012 with the following question: "Have you fallen in the last year? (Do NOT include minor slips or from sports.) If Yes, how many times?, No, Don't know."[108]

3.4 Variables

Dependent variable for primary objective: The outcome of interest in this study is appendicular lean mass (ALM). ALM was calculated as the sum of arms tissue lean mass (g) and legs tissue lean mass (g). Dependent variable for exploratory objective: The outcome of interest is self-reported falls in 12 months preceding whole-body DXA scan.

Candidate Independent Variables: Candidate variables were selected based on their availability in the Manitoba BMD database, their relevance to ALM and their inclusion in previous algorithm derivations.[102] The following variables were selected for this study and tested in different models:

- Age (age in years)
- Sex (Male, Female)
- Weight (kg)
- Height (cm)
- BMI (derived from height and weight)
- Spine and Hip Average Fat Fraction measured using DXA
- Spine and Hip Average Tissue Thickness (cm) measured using DXA

Descriptive variables: In addition to the above variables, we used the following variables to describe the patients and examine the relationship of ALM to self-reported falls:

- Total Body Average Fat Fraction measured using DXA
- Total Body Lean Mass measured using DXA
- Total Body Fat Mass measured using DXA
- Falls in the 12 months preceding the whole-body DXA scan (count)

DXA scans prior to 2010 were performed with a Prodigy fan-beam DXA system (GE Lunar, Madison, WI). Since 2010, DXA scans have been performed on the GE Lunar iDXA (GE Healthcare Lunar, Madison, WI). We excluded earlier scans performed on the pencil-beam DPX scanners.

3.5 Statistical Analysis

There were 678 individuals included in the dataset. Participants with >0.1 kg difference between the "spine weight" variable and "hip weight" variable were removed from the dataset. These observations were removed prior to receiving the dataset as we were unable to confirm the accurate weight or height.

Descriptive statistics are reported for the cohort. Categorical variables were analyzed using percentages and frequencies. Continuous data was analyzed using means and standard deviations for normally distributed data and medians and interquartile ranges for non-normally distributed data. Descriptive statistics for the sub-group of patients with FRAX and falls data was analyzed separately. Non-normally distributed variables were transformed using either square root or log. Histograms of transformed variable were assessed to confirm distribution. When evaluating the skew and histograms of the candidate variables, weight was moderately right skewed with a skewness of 0.812. The variable was logarithmically transformed, and skew improved. Height and both spine and hip tissue thickness were also skewed and benefitted from logarithmic transformation. Age was uniformly distributed with a minimum age of 18 and a maximum age of 95.

The algorithm to predict ALM was developed using multiple linear regression with the aforementioned candidate predictor variables. A series of models of differing complexity were developed using backward stepwise multiple linear regression. Variables included in the model

met statistical significance at the univariate level ($p<0.05$). Additional models with two-way interaction terms and models that were stratified by BMI, sex and age were developed. We chose to stratify by BMI ≤ 25 and BMI <25 because BMI of 25 is the cut-off for overweight. The performance of the models was compared using R^2, adjusted R^2, mean square error (MSE) and Mallow's Cp. R^2 measures how much of the total variability is explained by the model.[109] We used adjusted R^2 as our primary model performance statistic because it accounts for the number of predictors included which penalizes the R^2 in models that include nonsignificant predictors.[110,111] Mallow's Cp was used to compare the model with all explanatory variables to the smaller models.[111] The assumptions of multiple linear regression were evaluated including linearity, independence of errors, homoscedasticity, and normality of residuals. Scatterplots and Pearson correlation were assessed to evaluate for multicollinearity. Pearson correlation of the candidate variables demonstrated strong correlation between average spine tissue thickness and average spine fat fraction. We used Pearson correlation because scatterplots demonstrated possible linear relationship between candidate variables. Table 2 depicts the Pearson correlation coefficients of candidate variables and measured ALM to assess for multicollinearity. Residual plots for each variable were visually inspected to assess distribution of residuals and identify any outliers. Calibration of the algorithm was assessed using a calibration slope of observed vs predicted ALM.

After deriving the algorithm, we internally validated the algorithm using the bootstrap method.[112] We chose to use this method as we were able to use the parameter estimates from the bootstrap for our final model and allowed for utilization of the entire dataset for derivation of the algorithm. We conducted 500 replication analyses and performed sampling with replacement.[113] Each bootstrap sample with replacement was drawn from the original dataset. The sample drawn was the same size as the original dataset. Multiple linear regression using the same variables from the model derived in the original sample was performed in each bootstrap sample. The mean, median, 95% confidence interval and histograms of each bootstrap parameter estimate were evaluated. The mean bootstrap parameter estimates for each variable were used to determine the final equation. The Bland-Altman plot was assessed for bias and precision of the bootstrap model in the original dataset sample. Bland-Altman plots are used to assess the agreement of two methods, in our case, measuring ALM using DXA or our algorithm.[114] The

plot contains the line of the estimated mean difference of the two methods and the Bland-Altman limits of agreement in which "approximately 95% of all population differences would lie".[114] We also validated the Thackeray et al. equation in our dataset. We performed Pearson correlation of the measured ALM and Thackeray-derived predicted ALM. We also performed Pearson correlation of our algorithm predicted ALM and the Thackeray-derived predicted ALM.

We performed logistic regression model to test the relationship between predicted ALM and falls (i.e., exploratory objective). There were 131 patients within the dataset for whom self-reported falls information was provided. Falls were categorized into fall or no fall in the 12 months preceding DXA scan. Data are presented as odds ratios, ninety-five percent confidence interval and p value. A p value <0.05 was considered statistically significant.

Goodness of fit of the multivariable logistic regression model was assessed using the pseudo R^2 statistic, produced using the natural logarithm of the likelihood function, and the chi-square goodness of fit tests and deviance. We calculated the area under the receiver operating characteristic curve to measure discrimination of the model. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc, Cary, North Carolina).

3.6 Sample Size Considerations

Using the multiple linear regression rule of thumb for sample size $N \geq 50 + 8m$, where N is sample size and m represents number of independent variables in the model[115], and considering ALM is measured for all participants in the study, at least 146 participants are required. There are 678 eligible participants in the Manitoba BMD database, providing a sufficient sample size to achieve at least 80% power with alpha 0.05. If we assume 10% of patients without sarcopenia have had at least one fall and 15% of patients with sarcopenia fall, to provide a sufficient sample size to achieve at least 80% power with alpha of 0.05 we would require at least 503 patients therefore we do not have sufficient sample size to achieve power.

Chapter 4: Results

4.1 Primary Objective: Derivation of ALM Algorithm

4.1.1 Baseline Characteristics

Descriptive characteristics of the cohort are presented in Table 3. There were 678 patients with whole body scans in the dataset, which had complete data for hip DXA scans, spine DXA scans, arm and leg lean mass measurements and descriptive statistics as outlined in the methods section. The mean age of patients was 52.6 years of age (SD 21.0) and 522 (77.0%) identified as female. A total of 667 (98.4%) of the patients identified as white. Mean ALM was 18.0 kg (SD 5.0 kg) for the cohort. Median weight was 69.5 kg (IQR 66.7 - 79.8 kg) and median height was 162.4 cm (IQR 156.2 - 168.9 cm). The median BMI was 25.5 kg/m^2 (IQR 21.7 to 28.6 kg/m^2).

4.1.2 Development of the Algorithm in the Original Dataset

Using backward stepwise regression and resulting performance statistics from univariate analysis, the final algorithm model for ALM was developed in the original dataset using male as the reference for sex.

In univariate analysis, log of hip tissue thickness, log of spine tissue thickness and log of height were not statistically significant and were excluded from the final model. Subsequently in backward stepwise regression, log average hip tissue thickness was removed in the first step (p =0.776), then log average spine tissue thickness (p=0.216) was removed in step 2 and log mean of height (p=0.202) was removed in step 3.

The final fitted model was (Table 4).

ALM = -56.5 + (-2.13*sex[female=1, male=0]) + (0.00808*age [years]) + (45.0*log of weight [kg]) + (-9.47*average spine fat fraction + (-13.1*average hip fat fraction)

R^2 for final model was 0.889 (95% CI 0.873 – 0.905) and adjusted R^2 for final model was 0.889 (95% CI 0.873 – 0.905). Mean squared error of the model was 2.80 kg. Plot of the studentized residuals versus predicted ALM (Figure 2) revealed that some residual values were larger at the extremes of predicted ALM, however no obvious pattern is observed. Additionally, analysis of

the plot of measured ALM vs predicted ALM suggests that there is generally good correlation between the two values despite some deviation from the line of fit at the extremes of measured ALM (Figure 3). The residuals were normally distributed for this model. Residuals for the individual covariates in the final model demonstrated no pattern (Figure 4).

4.1.3 Sensitivity Analyses

Pearson correlation coefficient for weight and height was estimated as 0.420 ($p<0.001$) suggesting a weak to moderate relationship between the two variables therefore we considered it acceptable to include the two covariates in the model building. The final model with height and weight separately predicted ALM better than the model with BMI as a composite variable. (R^2 of 0.738 and adjusted R^2 of 0.736). Models without any transformation, without log of weight and with age^2 were evaluated. The model without any transformations included age, sex, height, weight and spine and hip fat fraction. Adjusted R^2 for the model was 0.889. Residual plots had subjectively less deviation at the extremes compared to the residual plots from the model with transformations. In the model where weight was not transformed (height and tissue thickness still transformed), age, sex, log of height, log of spine tissue thickness and hip and spine fat fraction were included. Adjusted R^2 of this model was 0.889. In the model with age^2, age, sex, log of weight, and spine and hip fat fraction were included. The adjusted R^2 of this model was 0.888. Results for these models are presented in Tables 5-8.

We also stratified by BMI categories and sex categories. The model was not improved when stratifying by sex based on adjusted R^2. Adjusted R^2 for female cohort was 0.886 and R^2 for the male cohort was 0.856. Stratifying by BMI $\geq$25 kg/m^2 or <25 kg/m^2 did not improve the fit, rather the adjusted R^2 were 0.663 and 0.748 respectively. Results for these models are presented in Tables 9 and 10.

We also evaluated the following interaction terms: BMI*hip fat fraction, BMI* spine fat fraction, sex*age, log of weight*sex and weight*sex. Interaction of BMI*Hip fat fraction was significant ($p<0.001$) when added to our model. In the model with sex*age interaction term included the interaction term was not significant ($p=0.146$). Log of weight*sex and weight*sex interaction

terms were significant ($p<0.001$) in their respective models. Results for these models are presented in Tables 11-13.

We performed ANOVA to assess if there were interaction between the covariates and sex. Age ($p<0.001$), log of spine height ($p<0.001$), spine weight ($p<0.001$), hip average fat fraction ($p<0.001$) and log of spine average tissue thickness ($p<0.001$) were significantly different by sex. Log of hip average tissue thickness ($p=0.883$) and spine average fat fraction ($p=0.260$) were not significantly different between male and female patients.

We also looked at the model using ALM/ht^2 as the outcome. The final model predicting ALM/ht^2 was:

$$\text{ALM/ht}^2 = 35.9 + (-0.518*\text{sex [Female =1, Male =0]}) + (0.00290*\text{age[years]}) + (-25.6*\text{log of height[cm]}) + (16.4*\text{log of weight[kg]}) + (-3.29*\text{average spine fat fraction}) + (-4.47*\text{average hip fat fraction})$$

The R^2 of this model was 0.852 and the adjusted R^2 was 0.850. Plot of the residuals versus predicted ALM/ht^2 did not reveal an obvious pattern, however there were a few points at the higher end of the predicted values that were associated with larger residuals. The residual plots for individual variables did not demonstrate a pattern.

We also looked at the model using ALM with removing an outlier which had a height approximately 40 cm less than the next lowest height. The final model predicting ALM was:

$$\text{ALM} = -70.3 + (-2.02*\text{sex [Female =1, Male =0]}) + (0.0083*\text{age[years]}) + (7.00*\text{log of height[cm]}) + (43.9*\text{log of weight[kg]}) + (-8.82*\text{average spine fat fraction}) + (-12.8*\text{average hip fat fraction})$$

The R^2 of this model was 0.890 and the adjusted R^2 was 0.889. Plot of the residuals versus predicted ALM values did not demonstrate an obvious pattern however there were a few points

at the higher end of the predicted values that were associated with larger residuals. The residual plots for individual variables did not demonstrate a pattern.

4.1.4 Validation of the Algorithm

Table 14 presents the mean and standard deviation of the parameter estimates and performance statistics for the bootstrap analysis. Table 14 also compares the bootstrap estimates to the model from the original dataset. The equation using the values from the bootstrap analysis, considered the final model, is as follows:

ALM = -56.5 + (-2.13*sex [Female =1, Male =0]) + (0.00824*age[years]) + (45.0*log of weight [kg]) + (-9.41* average spine fat fraction) + (-13.1*average hip fat fraction)

Mean of the intercept was -56.5 (SD 1.96) compared to -56.5 in the original cohort. Mean of the parameter estimate age was 0.00824 (SD 0.00322) compared to 0.00808 in the original cohort. Mean of the parameter estimate sex was -2.13 (SD 0.234) compared to -2.14 in the original cohort. Mean of the parameter estimate log of weight was 45.0 (SD 1.14) compared to in the 45.0 original cohort. Data as shown in the histogram of the log weight parameter estimate in the 500 bootstrap cohorts were normally distributed. Mean of the parameter estimate average spine fat fraction was -9.41 (SD 1.02) compared to -9.47 in the original cohort. Data as shown in the histogram of the average spine fat fraction parameter estimate in the 500 bootstrap cohorts were normally distributed. Mean of the parameter estimate average hip fat fraction was -13.1 (SD 1.26) compared to in the -13.1 cohort. Data as shown in the histograms of the intercept and all variables in the 500 bootstrap cohorts were normally distributed. Figure 5 presents Bland-Altman plot using the bootstrap model. Most values on the Bland-Altman plot lie between +/- 2 SD of the difference of predicted and measured ALM, and only 9 values extend past +/- 3 SD. Calibration plot of final bootstrap model predicted ALM including sex, age, log of weight, average spine fat fraction, and average hip fat fraction and measured ALM is shown in figure 6.

Next, we validated the Thackeray et al. algorithm in our dataset and compared it to our algorithm predicted-ALM. Pearson correlation coefficient of Thackeray-derived predicted ALM and calculated ALM in our dataset was 0.898 ($p<0.001$). Pearson correlation coefficient of

Thackeray-derived predicted ALM and ALM predicted from our algorithm was 0.946 ($p<0.001$). Figure 7 demonstrates the scatter plots of Thackeray-derived predicted ALM and measured ALM. Figure 8 demonstrates the scatter plot of Thackeray-derived predicted ALM and ALM predicted from our algorithm.

4.2 Exploratory Objective: Relationship between Predicted Sarcopenia and Falls

4.2.1 Baseline Characteristics

A subset of 131 patients with self-reported falls information was identified in the original dataset cohort (Table 15). In patients that have at least one response for FRAX data, Table 16 demonstrates descriptive characteristics of those with and without falls data. One hundred eight patients (82.4%) had no falls in the year preceding the whole-body DXA scan and 23 patients had at least 1 fall (17.6%). 13 patients (9.92%) had 1 fall, and 10 patients (7.7%) had 2 falls or more. The mean age of patients was 50.7 years of age (SD 20.7) and 100 patients (76.3%) identified as female. Mean ALM was 18.3 (SD 4.93) for the cohort and mean predicted ALM was 18.7 (SD 4.65). The median BMI was 25.9 kg/m^2 (IQR 21.3 to 29.4 kg/m^2), median weight was 68.9 kg (IQR 59.0 to 82.6 kg) and median height was 164.3 cm (IQR 157.7 to 170.7 cm).

4.2.2 Sarcopenia and Falls

Sarcopenia was defined as ALM/ht^2 <7.0 kg/m^2 for men and <5.5 kg/m^2 for women. Thirty patients (22.9%) were classified as having sarcopenia. Sarcopenia, as defined by the algorithm developed to predict ALM, was not associated with falls (OR 0.92, 95% CI 0.31 – 2.74, $p=0.884$). Area under the curve of the ROC curve for the model was 0.507 (CI 0.412 – 0.602). Wald chi-square was 0.0213.

Chapter 5 Discussion

5.1 Summary of Findings

In a retrospective cross-sectional study of 678 Manitobans who received DXA scans as part of routine clinical care, we suggest that hip and spine DXA scans can be used to predict appendicular lean mass (ALM). Our study found that an algorithm including sex, age, weight,

average spine fat fraction and average hip fat fraction was capable of accurately predicting ALM. For the most part, the variables included in the final algorithm correlated clinically. Male sex is associated with increased ALM[77] and, in our algorithm, female sex decreases the predicted ALM by 2.13 kg. Increased spine and hip fat fraction was associated with lower predicted ALM. Considering weight was included in the final algorithm, this indicates that as fat fraction increases, a larger portion of the weight is fat compared to muscle mass and therefore predicted ALM decreases. The only variable that was surprising was that predicted ALM increased with age considering muscle mass decreases with age in the general population.

In a subset of patients with data on number of self-reported falls in past year, sarcopenia as determined by algorithm derived ALM was not associated with falls however the sample size was not large enough for adequate power to make any conclusions about the relationship.

5.2 Comparison with Previous Studies

This is the second known algorithm to predict ALM from hip and DXA scans and the first using data collected as part of clinical care. The first study was by Thackeray et al (2022) in Australia. The 2427 participants included in this study were participating in the Geelong Osteoporosis study.[105,106] Their final equation, developed using forward stepwise linear regression, included age, sex, weight , spine fat percentage and hip fat percentage.[105] Our final model had similar covariates except height was not found to be statistically significant in our model. Adjusted R^2 of their final model was 0.912 compared to 0.889 in our final bootstrap equation however confidence intervals were not reported. Our study differed from the Thackeray et al. study in multiple respects. As noted, all data collected from their study was for participants who chose to participate via mailed-out invitations whereas the Manitoba BMD dataset, used for our study, collects all DXA scans performed in the province. As such, there is less risk of selection bias. Our study is more likely to be representative of the population who receives DXA scans but not necessarily of the general population. Our study had 77% females compared to only 42.3% in the Thackeray study. Another major difference between the studies was our decision to use bootstrapping to internally validate the equation and ultimately use the bootstrap model as the final model. Thackeray et al. used five-fold cross validation to compare R^2 and mean square errors. Five-fold cross validation and bootstrapping are both validation methods that use

resampling. Benefit of five-fold cross validation is that each datapoint is only used once compared to sampling with replacement in bootstrapping which can introduce more bias.[116] However, simple bootstrap validation was beneficial for our study because we were able to use the bootstrap parameter estimates as our final algorithm. The use of bootstrapping allowed us to create a robust model despite a small sample size compared to the Tackeray study.

Other studies have used similar models to develop algorithms to predict whole-body lean mass, rather than appendicular lean mass, from hip and spine DXA scans. One of the first models was created by Leslie (2009).[102] In this study, whole-body lean mass, trunk fat mass and whole body fat mass were predicted from hip and spine DXA scans from an earlier iteration of the dataset used in our study.[102] This original equation to estimate whole-body lean mass included spine and hip fat fraction, age, sex, height and weight.[102] This study similarly used backward stepwise linear regression however they chose to split the cohort to have a derivation cohort and a validation cohort.[102] Additionally, this study did not include spine or hip thickness as candidate variables.[102] Leslie's study was successful with their final model of predicting whole-body ALM from hip and spine DXA scans having an adjusted-R^2 of 0.87.[102] Salamat et al. (2014) subsequently developed an equation from 143 Iranian men and women who were referred for both hip and spine, and whole-body scans as part of clinical care.[103] Distribution of gender/sex in this study was more comparable (F=62.83%) to our study (F= 79%) than the Thackeray et al. study (42.3%). Their equation included waist circumference in addition to spine fat fraction, hip fat fraction, gender, and weight. [103] Waist circumference was a variable not available in the Manitoba BMD dataset. Salamat et al. also used a split sample to derive the equation in 100 of the participants and validate the equation in the other 43 participants.[103] Their final model estimating whole body mass from hip and spine DXA scans had an R^2 of 0.950.[103] Rosenthall et al. (2010) developed a similar equation in HIV positive males who were on highly active antiretroviral therapy.[104] They also used a backward stepwise linear regression model and a split sample validation that included derivation and validation cohorts.[104] The final model for estimating total-body lean mass included hip fat percentage, lumbar spine fat percentage and weight.[104] R^2 for this model was 0.92. The population in this study differed significantly from the population used in our study and in both the Leslie, WD and Salamat et al. studies.

In the subset of participants with self-reported falls data, we did not find a relationship between low ALM/ht^2 and falls however sample size was not large enough to achieve power. Balogun et al. (2017) similarly found that low ALM was not associated with increased falls.[64] In this study, ALM was presented as four different measures (ALM/ht^2, ALM/BMI, ALM/weight times 100 and residuals of linear regression of ALM on height and DXA derived total body fat) and 10 years fall risk was assessed using the short form Physiological Profile Assessment.[64] Lower muscle mass, as defined by the four measures, were not associated with increased 10 years falls risk (ALM/BMI falls risk z score 0.08, 95% CI -0.15 to 0.32) using Poisson regression.[64] The Women's Health Initiative study also did not observe a relationship between ALM and falls.[68] In this large study of 161,808 women aged 50-79 at baseline, DXA-derived ALM/ht^2 was associated was not significantly associated with incident falls (β= 0.98, 95% CI 0.96 -1.01, p=0.18).[68] Hassan, E et al. (2022) evaluated the role of lean muscle mass on balance.[117] They also did not observe a significant associated between ALM and falls. There was not a significantly change in incidence of falls based on ALM/ht^2 (Incidence Ratio (IR) = 1.05, 95% C?I 0.98 -1.12, p=0.17) or ALM/BMI (IR=0.96, 95% CI 0.91- 1.02, p=0.227).[117] Participants for these studies were recruited and falls and DXA data was not collected as part of clinical care. Additionally, these studies did not define low ALM and used ALM as a continuous variable in their regression models. Malmstrom et al (2013) found that African-American participants with low ALM/ht^2 had a marginally significant increased number of falls in past year at 6 year follow-up compared to the cohort without low ALM/ht^2 .[118] At the 6 year follow-up, 40.4% participants with low ALM/ht^2 had a fall in the past year compared to only 28.3% is the population without low ALM/ht^2 (p=0.095).[118] However, in the cross sectional analyses, there was not a significant difference between the two ALM groups (p=0.311).[118] ALM/ht^2 was considered low if it was <7.96 kg/m^2 in men and <7.06 kg/m^2 in women, compared to <7.0 kg/m^2 for men and <5.5 kg/m^2 for women in our study.[118] Therefore more women would be classified as low-ALM in comparison to our study. An umbrella review of meta-analyses of observational studies by Xia et al. (2020) found an 1.75 increase in risk of falls (95% CI 1.55 – 1.97) in community dwelling older adults with sarcopenia compared to those without sarcopenia.[119] Another umbrella review of observational studies by Veronese et. al (2019) also found an increased risk of falls (OR 1.60, 95% CI 1.31-1.97) in a sample of 12 261 participants.[44] However, these two studies included

systematic reviews that primarily used sarcopenia definitions that included both muscle quantity and functional status parameters.[44,119]

5.3 Implications

The successful derivation and validation of such an algorithm has both clinical and research implications. Whole-body DXA scans only make up a small portion of these records and the development of an algorithm would allow for larger scale administrative data studies to be conducted on sarcopenia and other investigations related to muscle quantity. The algorithm could have clinical relevance by reducing the number of whole-body DXA scans required when diagnosing sarcopenia and following change in sarcopenia status with attempted treatment interventions. Another potential clinical use for this algorithm is a system where family physicians are alerted of patients who received DXA scans as part of clinical care and were found to have ALM >2SD below average. This would allow family physicians to further evaluate sarcopenia in patients and suggest interventions such a diet and exercise to help increase ALM. This algorithm could be of particular significance in areas with limited resources and access to DXA instruments and technicians.

5.4 Strengths and Limitations

This study has its strengths as well as limitations. Strengths of our study include the use of the Manitoba BMD database. The database is well monitored, the DXA scanners are assessed daily. There is appropriate technologist oversight and evaluation of DXA scanners. Additionally, the database contains all DXA scans in Manitoba taken as part of clinical care since 1990 providing a large sample size. Another strength of our study was the use of bootstrapping to validate our algorithm. Using the bootstrap technique allowed us to use the entire 678 patients as our cohort for developing the algorithm and subsequently using the parameter estimates from the bootstrap models for the final mode. This enabled us to produce a more robust model than if we had split the dataset into a derivation cohort and a validation cohort. However, bootstrapping also has its limitations compared to other validation methods. The resampling we used in our simple bootstrap validation can cause our samples to be more biased compared to split validation and k-fold cross validation. Compared to validating the algorithm in a different dataset (ex: from a

different population), with simple bootstrapping there is more risk for bias and we are limited in our discussion on generalizability of our algorithm.

A limitation of our study is that our study population was not representative of the Manitoba population. As well, 98.4% of patients identified as white, and only 1.6% identified as another ethnicity. However, 98.4% white may not truly represent the diversity of the population as "White" may encompass other ethnicities, such as Indigenous, that were not options when entering the data. Data within the Manitoba BMD database is collected as part of clinical care with reasons for referral outlined in Figure 1. Therefore, patients within the database are not representative of the Manitoban population, rather they are representative of individuals with an indication for BMD testing. It is possible that there is a difference between patients who required whole body DXA scans and those that only required regional hip and spine DXA scans however we were unable to assess as part of this study. Data on chronic disease are not available in the Manitoba BMD database therefore we are missing potentially important covariates in our ALM prediction model. Comorbid conditions such as cardiovascular disease, dementia, diabetes and respiratory disease are associated with increased prevalence of sarcopenia.[34] Either stratifying by presence of comorbid condition or adding as a covariate may contribute to a more accurate algorithm. My assumption would be that adding the comorbid conditions to the algorithm would contribute to patients with comorbid conditions having a lower predicted ALM than their non-comorbid condition counterparts. Additionally, we are not accounting for chronic disease, a confounder, in the model evaluating the relationship between ALM and falls. There is also the potential for unknown and residual confounding. Falls within the past year is self-reported therefore data collected on falls history are subject to self-reporting bias. However, previous research has shown that self-reported falls data is predictive of fracture outcomes and therefore an appropriate method for obtaining falls data.[108] Additionally, the subset of patients with falls data was not large enough confer statistical significance or adjust for variables collected as part of FRAX.

5.5 Future Directions

The next step for this project is to use the algorithm to calculate ALM in the larger Manitoba BMD database. In 2018 there were approximately 88,000 individual patients in the Manitoba

BMD database, and approximately 140,000 total records. This dataset has >40,000 sets of falls data. This would allow for a sample size large enough to have power to assess the relationship between sarcopenia, as determined by ALM/ht^2, and falls. This dataset also has FRAX data that would provide additional covariates that could impact the relationship between falls and sarcopenia. We are also considering linking the Manitoba BMD database to large databases, like those at Manitoba Centre for Health Policy, for further research into the relationship between low ALM and chronic disease.

5.6 Conclusion

To summarize, our study demonstrates that hip and spine DXA scans can be used to predict ALM with an adjusted R^2 of 0.889 in the Manitoba population. Age, sex, weight, and spine and hip average percent fat derived from DXA scans are relevant to predicting ALM. Additionally, sarcopenia as defined by low ALM/ht^2 was not associated with increased odds of falls.

Tables and Figures

Table 1: Definitions of Sarcopenia

European Working Group on Sarcopenia in Older People (EWGSOP)[1] **– *2010****	Criterion 1: Low muscle mass (ASM/height^2: Men <7.26 kg/m^2, Women <5.5 kg/m^2 [2 SD below mean of young adults]) Criterion 2: Low muscle strength (HGS: Men < 30kg, Women <20 kg) Criterion 3: Low physical performance (Gait Speed: ≤ 1 m/s for 6 m)
Revised European Working group on Sarcopenia in Older People (EWGSOP2)[4] **– *2018****	Criterion 1: Low muscle strength (HGS: Men < 27kg, Women <20 kg) Criterion 2: Low muscle quantity or quality (ASM/height^2: Men <7.0 kg/m^2, Women <5.5 kg/m^2) Criterion 3: Low physical performance (Gait Speed: ≤0.8 m/s for 6 m)
International Working Group on Sarcopenia[9] **- *2009***	a. Reduced appendicular lean mass (<20th percentile of healthy young adults; ALM/ht^2: Men ≤7.23 kg/m^2, Women ≤ 5.67 kg/m^2); b. Poor physical function, identified by a low gait speed (<1.0 m/s for 4 m course), with or without increased fat mass.
Asian Working Group for Sarcopenia[120] **(AWGS) - *2014***	a. Low muscle mass (DXA ALM/ht^2 : Men <7.0 kg/m^2, Women <5.4 kg/m^2) b. Low muscle strength (HGS: Men <26 kg, Women <18 kg c. Low physical performance (usual gait speed: <0.8 m/s for 6 m course)
Revised Asian Working Group for Sarcopenia[8] **(AWGS) - *2019***	a. Low muscle mass (DXA ALM/ht^2 : Men <7.0 kg/m^2, Women <5.4 kg/m^2) b. Low muscle strength (HGS: Men <28 kg, Women <18 kg) c. Low physical performance (usual gait speed: <1.0 m/s for 6 m course) Cut off for screening: Age greater than 60 or 65 years of age
Foundation for the National Institute of Health (FNIH) Sarcopenia Project [10]**- *2012***	Definition 1: Low BMI-adjusted ALM (ALM/BMI: Men < 0.789; Women <0.512) and low muscle strength (HGS: Men <26 kg, Women <16 kg). Definition 2: Definition 1 plus low physical performance measured as a gait speed ≤0.8 m/s.[53]
European Society for Clinical Nutrition and Metabolism (ESPEN) Special Interest Group[19] **- *2010***	a. Low muscle mass (≥ 2 SD below mean measured in young adults) b. Low gait speed (<0.8m/s for 4 m course).

* For definition 1 and 2: a. *Pre-/probable sarcopenia* if criterion 1 present; b. *Sarcopenia* if criteria 1 plus criteria 2 (or 3 for 2010 guidelines); c. *Severe sarcopenia* if all 3 criteria met
ASM/ht^2 = appendicular skeletal mass divided by height squared; ALM/BMI = ALM/body mass index; HGS = hand grip strength

Table 2: Pearson Correlation of Candidate Variables for Development of Algorithm

	ALM (kg)	Sex	Age (years)	Height (cm)	Weight (kg)	Spine Avg Fat Fraction	Hip Avg Fat Fraction	Spine Avg Tissue Thickness (cm)	Hip Avg Tissue Thickness (cm)
ALM (kg)	1.00	-0.512 (<.0001)	-0.0876 (0.0226)	0.646 (<.0001)	0.818 (<.0001)	0.261 (<.0001)	-0.149 (<.0001)	0.606 (<.0001)	0.583 (<.0001)
Sex	-0.512 (<.0001)	1.00	0.182 (<.0001)	-0.478 (<.0001)	-0.241 (<.0001)	0.0435 (0.258)	0.318 (<.0001)	-0.193 (<.0001)	0.00145 (<.0001)
Age (years)	-0.088 (0.0226)	0.182 (<.0001)	1.00	-0.181 (<.0001)	0.0443 (<.0001)	0.268 (<.0001)	0.319 (<.0001)	0.201 (<.0001)	0.119 (0.0019)
Height (cm)	0.646 (<.0001)	-0.478 (<.0001)	-0.181 (<.0001)	1.00	0.420 (<.0001)	-0.0822 (0.0323)	-0.308 (<.0001)	0.106 (0.0055)	0.0886 (0.021)
Weight (kg)	0.818 (<.0001)	-0.241 (<.0001)	0.0443 (0.250)	0.420 (<.0001)	1.00	0.644 (<.0001)	0.302 (<.0001)	0.872 (<.0001)	0.874 (<.0001)
Spine Avg Fat Fraction	0.261 (<.0001)	0.0435 (0.260)	0.268 (<.0001)	-0.0822 (0.0323)	0.644 (<.0001)	1.00	0.637 (<.0001)	0.797 (<.0001)	0.691 (<.0001)
Hip Avg Fat Fraction	-0.149 (<.0001)	0.318 (<.0001)	0.319 (<.0001)	-0.308 (<.0001)	0.302 (<.0001)	0.637 (<.0001)	1.00	0.457 (<.0001)	0.464 (<.0001)
Spine Avg Tissue Thickness (cm)	0.606 (<.0001)	-0.193 (<.0001)	0.201 (<.0001)	0.106 (0.0055)	0.872 (<.0001)	0.797 (<.0001)	0.457 (<.0001)	1.00	0.868 (<.0001)
Hip Avg Tissue Thickness (cm)	0.583 (<.0001)	0.00145 (0.970)	0.119 (0.0019)	0.0886 (0.021)	0.874 (<.0001)	0.691 (<.0001)	0.464 (<.0001)	0.868 (<.0001)	1.00

Presented as Pearson's coefficient (p-value)

Table 3: Descriptive Characteristics of Dataset

Characteristic	Value
Total	n=678
Age (years)	52.6 ± 21.0
Sex (% Female)	522 (77.0%)
Weight (kg)	66.7 (56.7 – 79.8)
Height (cm)	162.4 ± 10.7
BMI (kg/m^2)	25.5 (21.7 - 28.6)
Ethnicity	
White	667 (98.4%)
Non-White	11 (1.6%)
Scan Location	
Winnipeg	641 (95.4%)
Brandon	37 (5.6%)
Scanner	
Prodigy	548 (80.8%)
iDXA	130 (19.2%)
Average Fat Fraction	
Spine	0.292 ± 0.131
Hip	0.296 ± 0.0942
Total Body	0.421 (0.363 – 0.471)
Average Tissue Thickness (cm)	
Spine	17.8 (15.4 – 20.7)
Hip	14.6 (13.3 – 16.1)
Total Body	9.92 (8.85 – 11.10)
Lean Mass (kg)	
ALM	17.3 (14.6 – 2.05)
Total Body	39.4 (34.7 – 45.9)
Fat Mass (kg)	
Total	25.6 (17.9– 33.6)

iDXA= GE Lunar iDXA™

Normally distributed continuous data presented as mean ± SD. Non-normally distributed data presented as median (IQR). Categorical data presented as n (%).

Table 4. Algorithm Model Developed in Original Dataset

	Final Model	Step 2	Step 1	Step 0
Variable	**Parameter estimate (p-value)**			
Intercept	-56.5	-64.0 (<.0001)	-69.4 (<.0001)	-70.4 (<.0001)
Sex (ref =Male)	-2.13	-2.08 (<.0001)	-1.99 (<.0001)	-2.00 (<.0001)
Age (per year)	0.00808	0.00807 (0.014)	0.00708 (0.036)	0.00711 (0.035)
Log Weight (per kg)	45.0	44.3 (<.0001)	42.6 (<.0001)	42.2 (<.0001)
Log Height (per cm)	-	3.93 (0.202)	6.14 (0.085)	6.62 (0.093)
Spine Average Fat Fraction	-9.47	-9.08 (<.0001)	-9.60 (<.0001)	-9.57 (<.0001)
Hip Average Fat Fraction	-13.1	-12.8 (<.0001)	-12.8 (<.0001)	-12.9 (<.0001)
Log of Spine Tissue Thickness (per cm)	-	-	2.92 (0.21)	2.83 (0.24)
Log of Hip Tissue Thickness (per cm)	-	-	-	0.794 (0.77)
Performance Statistics				
R^2	0.889 (0.873-0.905)	0.890 (0.874-0.905)	0.890 (0.874-0.905)	0.890 (0.874-0.905)
Cp	6.24	6.62	7.08	9.00
Adjusted R^2	0.889	0.889	0.889	0.889
MSE	2.80	2.80	2.80	2.80

Note: MSE = mean squared error; Cp= Mallow's Cp
Steps= steps of backward stepwise regression

Table 5: Sensitivity Analysis: Predictive Model using BMI Rather than Height and Weight

	Step 2	Step 1	Step 0
Variable	**Parameter Estimate (p-value)**		
Intercept	-50.9 (<.0001)	-50. 1 (<.0001)	-50.1 (<.0001)
Sex (ref =Male)	-3.78 (<.0001)	-3.87 (<.0001)	-3.84 (<.0001)
Age (per year)	-	-	-0.00328 (0.52)
Log of BMI (kg/m^2)	-	5.78 (0.0)	5.57 (0.062)
Spine Average Fat Fraction	-8.69 (<.0001)	-8.98 (<.0001)	-8.96 (<.0001)
Hip Average Fat Fraction	-18.26 (<.0001)	-18.4 (<.0001)	-18.3 (<.0001)
Spine Tissue Thickness (cm)	21.3 (<.0001)	18.3 (<.0001)	18.8 (<.0001)
Hip Tissue Thickness (cm)	45.4 (<.0001)	41.1 (<.0001)	40.9 (<.0001)
Performance Statistics			
R^2	0.738	0.740	0.740
Cp	8.21	6.41	8.00
Adj R^2	0.736	-	-
MSE	6.62	6.59	6.60

Note: MSE = mean squared error; Cp = Mallow's Cp; BMI = $height/weight^2$
Steps = steps of backward stepwise regression

Table 6: Sensitivity Analysis: Predictive Model without Transformation of Candidate Variables

	Step 2	Step 1	Step 0
Variable	**Parameter Estimate (p-value)**		
Intercept	-0.0470 (0.972)	-0.666 (0.705)	-0.225 (0.908)
Sex (ref =Male)	-1.96 (<.0001)	-1.92 (<.0001)	-1.89 (<.0001)
Age (per year)	0.0107 (0.0011)	-0.0103 (0.0022)	-0.0102 (0.0026)
Weight (per kg)	0.252 (<.0001)	0.247 (<.0001)	0.251 (<.0001)
Height (per cm)	0.0450 (<.0001)	0.0476 (<.0001)	0.0458 (<.0001)
Spine Average Fat Fraction	-6.45 (<.0001)	-6.68 (<.0001)	-6.75 (<.0001)
Hip Average Fat Fraction	-13.4(<.0001)	-13.4 (<.0001)	-13.4 (<.0001)
Spine Tissue Thickness (per cm)	-	0.247 (<.0001)	0.0389 (0.508)
Hip Tissue Thickness (per cm)	-	-	-0.0393 (0.601)
Performance Statistics			
R^2	0.890	0.890	0.890
Cp	5.58	7.27	9.00
Adjusted R^2	0.889	-	-
MSE	2.80	2.80	2.81

Note: MSE = mean squared error; Cp = Mallow's Cp
Steps = steps of backward stepwise regression

Table 7: Sensitivity Analysis: Predictive Model without Transformation of Weight

	Step 1	Step 0
Variable	**Parameter Estimate (p-value)**	
Intercept	-39.4 (<.0001)	-46.6 (<.0001)
Sex (ref=Male)	-1.83 (<.0001)	-1.93 (<.0001)
Age (per year)	0.0084 (0.0131)	0.00862 (0.0109)
Weight (per kg)	0.235 (<.0001)	0.222 (<.0001)
Log Height (per cm)	18.5 (<.0001)	20.3 (<.0001)
Spine Average Fat Fraction	-7.85 (<.0001)	-7.77 (<.0001)
Hip Average Fat Fraction	-13.4 (<.0001)	-13.5 (<.0001)
Log of Spine Tissue Thickness (cm)	5.80 (0.0107)	4.91 (0.0347)
Log of Hip Tissue Thickness (cm)	-	4.59 (0.0782)
Performance Statistics		
R^2	0.890	0.891
Cp	10.11	9.00
Adj R^2	0.889	-
MSE	2.79	2.78

Note: MSE = mean squared error; Cp = Mallow's Cp
Steps = steps of backward stepwise regression

Table 8: Sensitivity Analysis: Predictive Model with Age Squared

	Step 3	Step 2	Step 1	Step 0
Variable	**Parameter estimate (p-value)**			
Intercept	-56.5 (<.0001)	-63.9 (<.0001)	-69.8 (<.0001)	-79.7 (<.0001)
Sex (ref =Male)	-2.12 (<.0001)	-2.07 (<.0001)	-1.97 (<.0001)	-1.98 (0.0825)
Age^2 (per year)	0.0000649 (0.0377)	0.0000649 (0.0375)	0.0000552 (0.0843)	0.0000554 (0.0835)
Log Weight (per kg)	45.1 (<.0001)	44.3 (<.0001)	42.5 (<.0001)	42.1 (<.0001)
Log Height (per cm)	-	3.96 (0.199)	6.37 (0.0738)	6.79 (0.0846)
Spine Average Fat Fraction	-9.39 (<.0001)	-9.00 (<.0001)	-9.58 (<.0001)	-9.55 (<.0001)
Hip Average Fat Fraction	-13.0 (<.0001)	-12.8 (<.0001)	-13.8 (<.0001)	-12.8 (<.0001)
Log of Spine Tissue Thickness (per cm)	-	-	3.19 (0.177)	3.11 (0.192)
Log of Hip Tissue Thickness (per cm)	-	-	-	0.700 (0.800)
Performance Statistics				
R^2	0.889	0.889	0.890	0.890
Cp	6.54	6.89	7.06	9.00
Adjusted R^2	0.888	-	-	-
MSE	2.81	2.81	2.80	2.81

Note: MSE = mean squared error; Cp = Mallow's Cp
Steps = steps of backward stepwise regression

Table 9: Sensitivity Analysis: Predictive Model Stratified by BMI

	BMI ≥25	BMI <25
Variable	**Parameter Estimates (p-value)**	
Intercept	-55.2 (<0.001)	-51.6 (<0.001)
Sex (ref=M)	-3.31 (<0.001)	-3.77 (<0.001)
Age (per year)	-	-0.0119 (0.0229)
BMI	-	12.1 (0.0012)
Spine Average Fat Fraction	-14.1 (<0.001)	-8.79 (<0.001)
Hip Average Fat Fraction	-23.2 (<0.001)	-11.3 (<0.001)
Log of Spine Tissue Thickness (cm)	34.5 (<0.001)	9.69 (0.0070)
Log of Hip Tissue Thickness (cm)	37.5 (<0.001)	43.0 -8.79 (<0.001)
Performance Statistics		
R^2	0.668	0.753
Cp	4.01	8.00
Adj R^2	0.663	0.748
MSE	8.31	3.68

Note: MSE = mean squared error; Cp = Mallow's Cp; BMI = height/weight^2

Table 10: Sensitivity Analysis: Predictive Model Stratified by Sex

	Female (n=522)	**Male** (n=156)
Variable	**Parameter Estimate (p-value)**	
Intercept	-51.1 (<0.001)	-80.8 (<0.0001)
Age (per year)	-	-
Log Weight (per kg)	40.3 (<0.0001)	58.9 (<0.0001)
Log Height (per cm)	-	-
Spine Average Fat Fraction	-8.24 (<0.0001)	-12.9 (<0.0001)
Hip Average Fat Fraction	-9.74 (<0.0001)	-14.5 (<0.0001)
Log of Spine Tissue Thickness (cm)	-	-
Log of Hip Tissue Thickness (cm)	-	-
Performance Statistics		
R^2	0.886	0.854
Cp	5.09	2.00
Adj R^2	0.886	0.851
MSE	1.63	4.903

Note: MSE = mean squared error; Cp = Mallow's Cp

Table 11: Sensitivity Analysis: Predictive Model using BMI and Fat Fraction Interaction Terms

	Step 2	Step 1	Step 0
Variable	**Parameter Estimate (p-value)**		
Intercept	-86.1 (<.0001)	-85.3 (<.0001)	-86.3 (<.0001)
Sex (ref =M)	-3.62 (<.0001)	-3.62 (<.0001)	-3.52 (<.0001)
Age (per year)	-	-	-0.00774 (0.122)
Log of BMI	27.0 (<.0001)	26.7 (<.0001)	26.8 (<.0001)
Spine Average Fat Fraction	-11.2 (<.0001)	-37.3 (0.0080)	-35.6 (0.011)
Hip Average Fat Fraction	81.8 (<.0001)	105.2 (<.0001)	106.9 (<.0001)
Log of Spine Tissue Thickness (cm)	19.3 (<.0001)	18.9 (<.0001)	20.2 (<.0001)
Log of Hip Tissue Thickness (cm)	46.1 (<.0001)	46.0 (<.0001)	45.61 (<.0001)
BMI*Spine Fat Fraction	-	18.8 (0.061)	17.5 (0.081)
BMI*Hip Fat Fraction	-71.4 (<.0001)	-88.2 (<.0001)	-89.1 (<.0001)
Performance Statistics			
R^2	0.760	0.761	0.762
Cp	11.9	10.4	10.0
Adj R^2	0.757	-	-
MSE	6.10	6.07	6.06

Note: MSE = mean squared error; Cp = Mallow's Cp; BMI = height/weight^2
Steps = steps of backward stepwise regression
Interaction terms: BMI*Spine fat fraction and BMI*Hip fat fraction; BMI and average percent fat were highly correlated.

Table 12: Sensitivity Analysis: Predictive Model using Age and Sex Interaction Term

	Step 4	Step 3	Step 2	Step 1	Step 0
Variable	**Parameter Estimate (p-value)**				
Intercept	-56489 (<.0001)	-56816 (<.0001)	-64001 (<.0001)	-69380 (<.0001)	-70673 (<.0001)
Sex (ref =M)	-2135 (<.0001)	-1631 (<.0001)	-1595 (<.0001)	-1504 (0.0002)	-1518 (0.0001)
Age (per year)	8.08 (0.0139)	16.4 (0.0129)	16.1 (0.0144)	15.1 (0.0230)	15.2 (0.0221)
Log Weight (kg)	45038 (<.0001)	45010 (<.0001)	44271 (<.0001)	42636 (<.0001)	42078 (<.0001)
Log Height (cm)	-	-	3772 (0.221)	5972 (0.0937)	6565 (0.0952)
Spine Average Fat Fraction	-9471 (<.0001)	-9589 (<.0001)	-9208 (<.0001)	-9728 (<.0001)	-9690 (<.0001)
Hip Average Fat Fraction	-13058 (<.0001)	-12913 (<.0001)	-12705 (<.0001)	-12698 (<.0001)	-12726 (<.0001)
Log of Spine Tissue Thickness (cm)	-	-	-	2904 (0.219)	2790 (0.242)
Log of Hip Tissue Thickness (cm)	-	-	-	-	983 (0.721)
Age*Sex	-	-10.8 (0.146)	-10.4 (0.159)	-10.4 (0.161)	-10.5 (0.157)
Performance Statistics					
R^2	0.889	0.890	0.890	0.890	0.890
Cp	7.26	7.14	7.64	8.13	10.0
Adj R^2	0.889	-	-	-	-
MSE	2.8E6	2.8E6	2.8E6	2.8E6	2.8E6

Note: MSE = mean squared error; Cp = Mallow's Cp
Steps = steps of backward stepwise regression

Table 13: Sensitivity Analysis: Predictive Model using Log of Weight and Sex Interaction Term

	Step 4	Step 3	Step 2	Step 1	Step 0
Variable	**Parameter Estimate (p-value)**				
Intercept	-76559 (<.0001)	-78017 (<.0001)	-89023 (<.0001)	-88095 (<.0001)	-86140 (<.0001)
Sex (ref =M)	23032 (<.0001)	23333 (<.0001)	23227 (<.0001)	22866 (<.0001)	23058 (<.0001)
Age (per year)	-	-	-	2.81 (0.381)	2.71 (0.399)
Log Weight (kg)	55761 (<.0001)	54679 (<.0001)	52809 (<.0001)	52994 (<.0001)	52955 (<.0001)
Log Height (cm)	-	-	5469 (0.101)	5127 (<.0001)	4166 (0.262)
Spine Average Fat Fraction	-9679 (<.0001)	-10465 (<.0001)	-10379 (<.0001)	-10386 (<.0001)	-10454 (<.0001)
Hip Average Fat Fraction	-11599 (<.0001)	-11745 (<.0001)	-11540 (<.0001)	-11664 (<.0001)	-11609 (<.0001)
Log of Spine Tissue Thickness (cm)	-	2920 (0.122)	4655 (0.0315)	4181 (0.0609)	4370 (0.0525)
Log of Hip Tissue Thickness (cm)	-	-	-	-	-1578 (0.5450)
Log of Weight*Sex	-13511 (<.0001)	-13640 (<.0001)	-13524 (<.0001)	-13344 (<.0001)	-13429 (<.0001)
Performance Statistics					
R^2	0.902	0.902	0.902	0.902	0.903
Cp	8.23	7.83	7.13	8.37	10.0
Adj R^2	0.901	-	-	-	-
MSE	2.49E6	2.48E6	2.48E6	2.48E6	2.48E6

Note: MSE = mean squared error; Cp = Mallow's Cp
Steps = steps of backward stepwise regression

Table 14: Bootstrap Model Parameter Estimates Compared to Parameter Estimates from Derivation of Algorithm

Variable	**Parameter Estimate** (Mean ± SD)	**Parameter Estimate from Derivation of Algorithm**
Intercept	-56.5 ± 2.08	-56.5
Age (per year)	0.00808 ± 0.00337	0.00808
Sex (Female)	-2.13 ± 0.220	-2.13
Log weight (per kg)	45.05 ± 1.21	45.0
Spine Fat Fraction	-9.50 ± 0.98	-9.47
Hip Fat Fraction	-13.1 ± 1.29	-13.058
Adjusted R^2	0.890 ± 0.00898	0.885

Table 15: Descriptive Statistics for Patients with At Least One Self-Reported Fall

Characteristic	Value
Total	n=131
Age (years)	50.7 ± 20.7
Sex (% Female)	100 (76.3%)
Measured ALM (kg)	18.3 ± 4.93
Predicted ALM (kg)	18.7 ± 4.65
Weight (kg)	68.9 (59.0 – 82.6)
Height (cm)	164.3 (157.7 – 170.7)
BMI (kg/m^2)	25.9 (21.3 – 29.4)
Sarcopenia	
Yes	30 (22.9%)
No	101 (77.1%)
Self-Reported Fall	
0	108 (82.4%)
≥1	23 (17.6%)

Normally distributed continuous data presented as mean ± SD. Non-normally distributed data presented as median (IQR). Categorical data presented as n (%).

Table 16: Descriptive Statistics for Patients With and Without Falls Data (In Patients With At Least One FRAX Variable)

Characteristic	Falls Data	No Falls Data
Total	n=131	n=165
Age (years)	50.7 ± 20.7	47.2 ± 19.1
Sex (% Female)	100 (76.3%)	110 (66.7%)
Weight (kg)	68.9 (59.0 – 82.6)	73.7 ± 21.1
Height (cm)	164.3 (157.7 – 170.7)	164.6 ± 10.2
BMI (kg/m^2)	25.9 (21.3 – 29.4)	27.1 ± 6.92

Normally distributed continuous data presented as mean ± SD. Non-normally distributed data presented as median (IQR). Categorical data presented as n (%).

Figure 1: Bone Density Testing Guidelines Used by the Manitoba Bone Density Program[121]

Specific criteria have been identified which allow targeted testing to be performed. These are as follows:

- Vertebral low-trauma (fragility) fracture proven by x-ray (Note: Bone density testing is not required for diagnosis of osteoporosis as active treatment is usually indicated. Attach copy of x-ray report as this will help in test interpretation.)
- Non-vertebral fragility fracture proven by x-ray
- Osteopenia or osteoporosis identified on x-ray
- Systemic corticosteroid therapy for more than 3 months in the last year
- Aromatase inhibitor therapy for breast cancer
- Prolonged amenorrhea, surgical menopause or premature menopause prior to age 45
- Woman age 65 or older (screening in men, and in women younger than age 65, are not approved indications unless additional risk factors are provided below)
- Follow up of a previous bone density measurement (recommended initial interval 3 years for most patients, at least 5 years if previously reported as low risk, 1 year in patients on systemic corticosteroid therapy or aromatase inhibitors)

Other indications may be considered if appropriate clinical justification is provided.

Figure 2: Plot of Studentized Residuals vs Predicted ALM Values

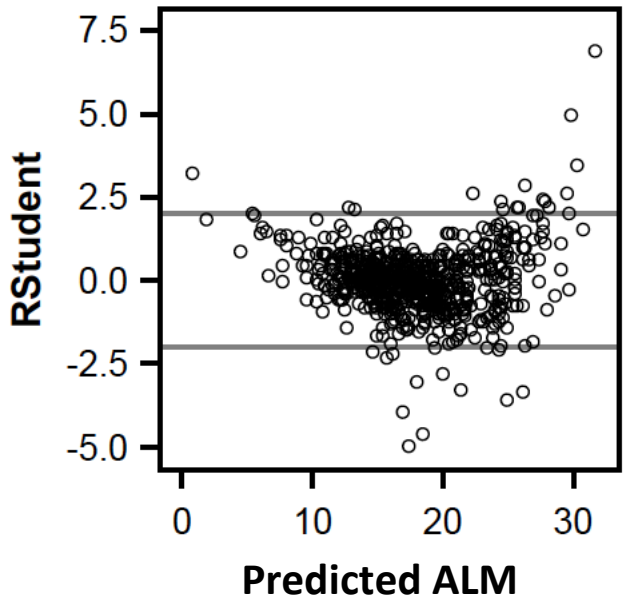


Figure 3: Plot of Measured ALM vs Predicted ALM

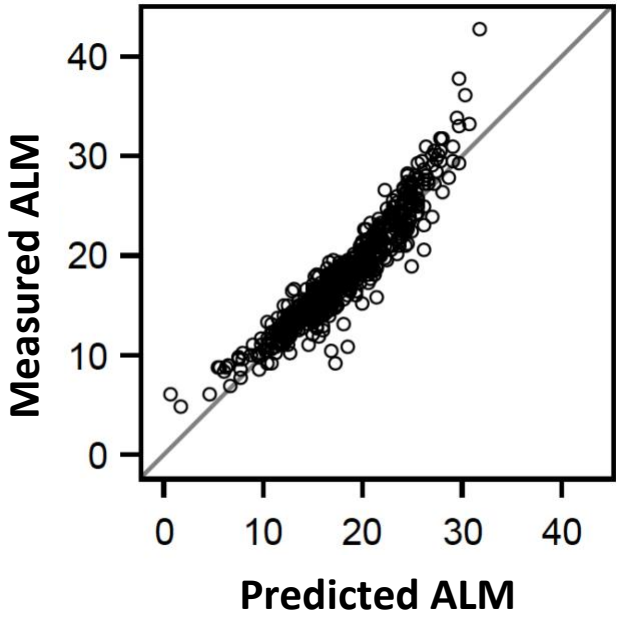


Figure 4: Plot of Residuals by Regressors for Measured ALM

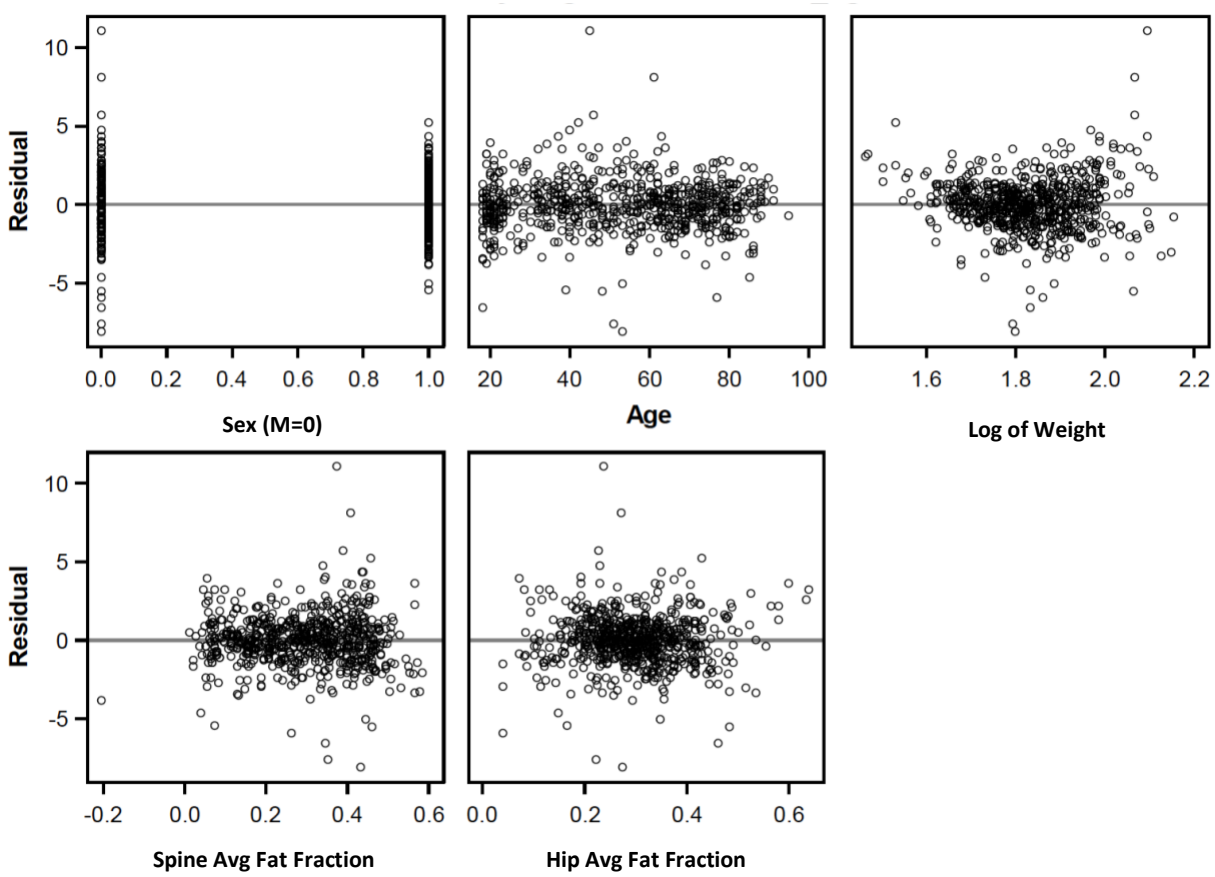
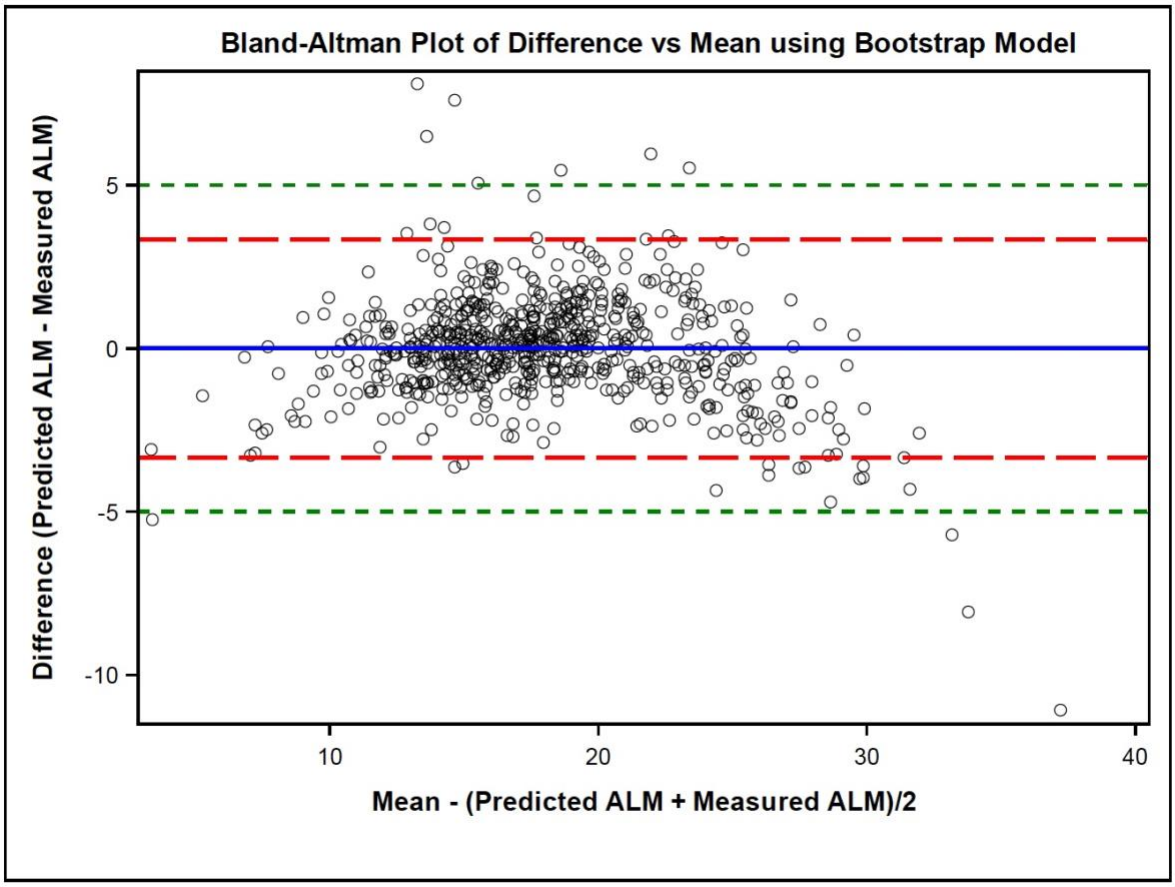
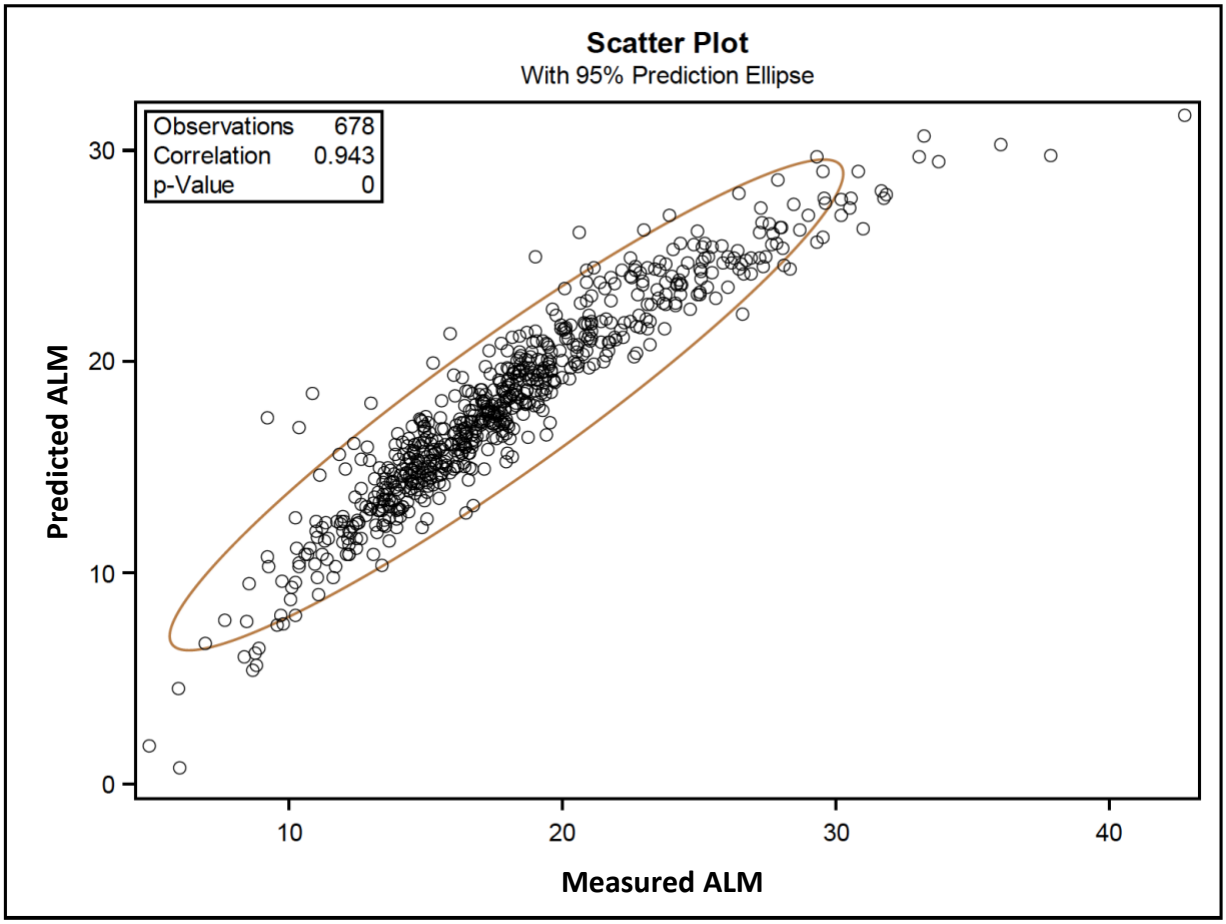


Figure 5: Bland-Altman Plot



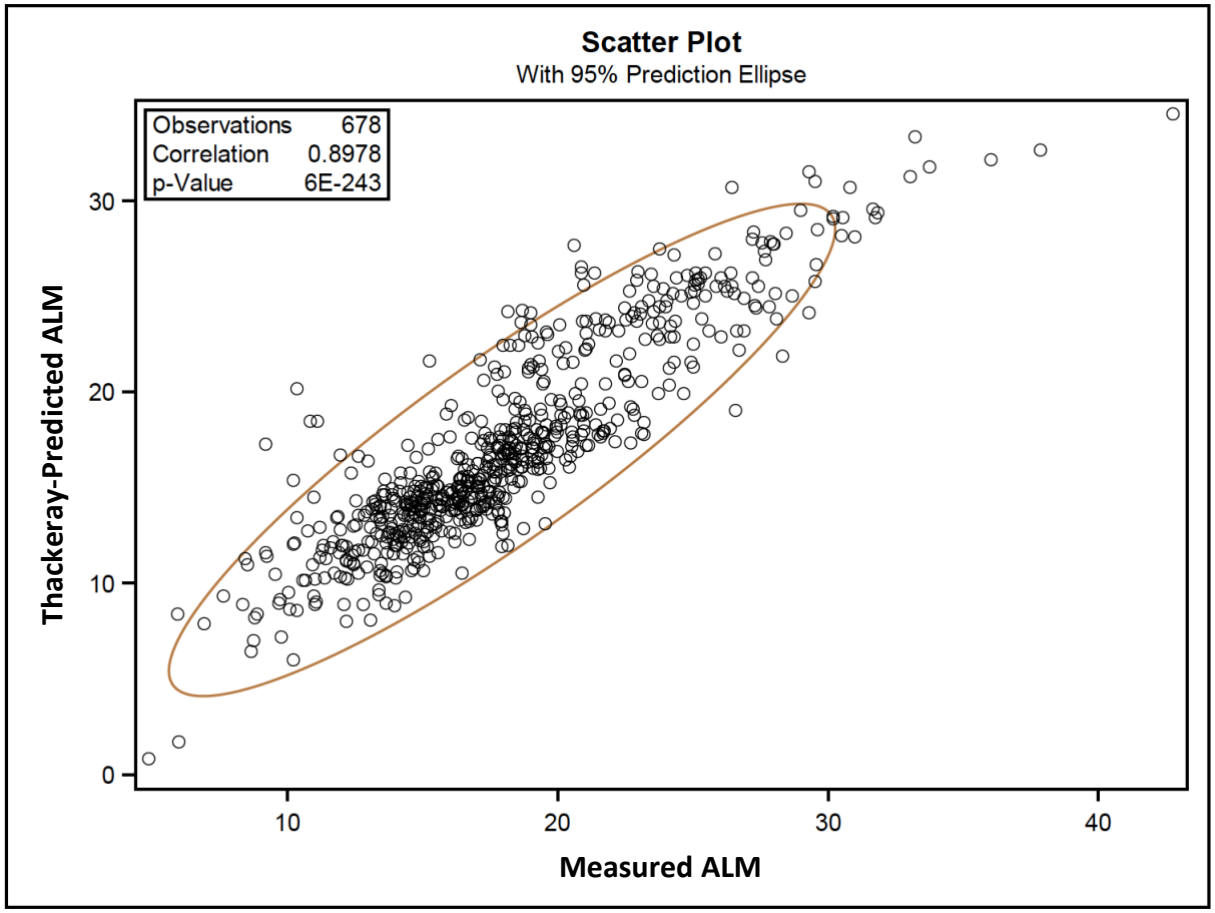
Red lines refer to ±1 SD and green lines refer to ±2 SD

Figure 6: Plot of Bootstrap-Derived Predicted ALM and Measured ALM



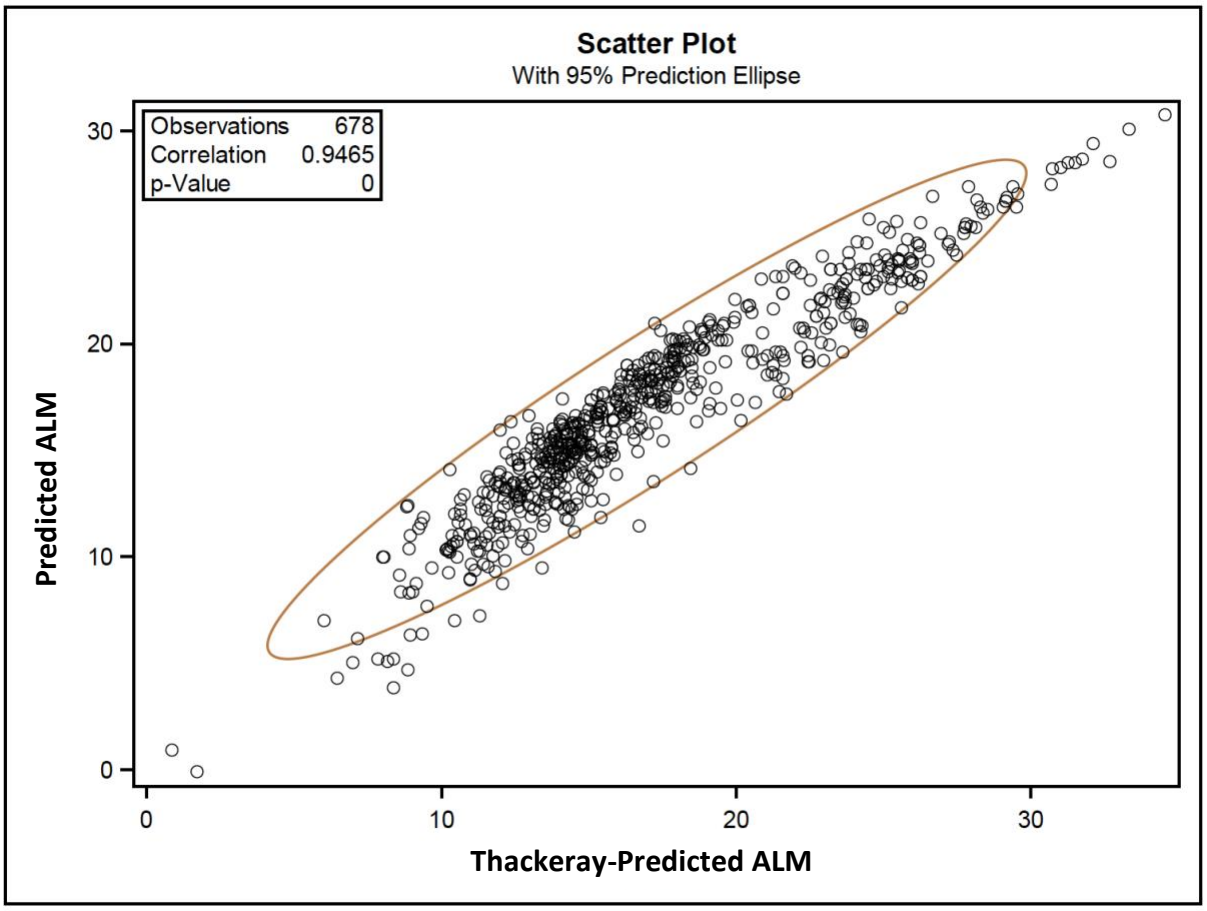
Note: Predicted ALM = ALM predicted using bootstrap-derived algorithm; Measured ALM = ALM measured using DXA scanner; Orange ellipse is the smallest ellipse containing 95% of values

Figure 7: Plot of Thackeray et al. -Derived Predicted ALM and Measured ALM



Note: Thackeray-Predicted ALM = ALM predicted using Thackeray et al. algorithm; Measured ALM = ALM measured using DXA scanner; Orange ellipse is the smallest ellipse containing 95% of values

Figure 8: Plot of Thackeray et al. -Derived Predicted ALM and ALM Predicted Using Bootstrap Algorithm



Note: Predicted ALM = ALM predicted using our bootstrap-derived algorithm; Thackeray-Predicted ALM = ALM predicted using Thackeray et al. algorithm; Orange ellipse is the smallest ellipse containing 95% of values

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