# Hip Axis Length is a FRAX and Bone Density Independent Risk Factor for Hip Fracture in Women

William D. Leslie [1]; Lisa M. Lix [1]; Suzanne N. Morin [2]; Helena Johansson [3]; Anders Odén [3]; Eugene V. McCloskey [3]; John. A. Kanis [3]

(1) University of Manitoba, Winnipeg, Canada;

(2) McGill University, Montreal, Canada;

(3) Centre for Metabolic Bone Diseases, Sheffield, UK.

**Corresponding Author and Person to Whom Reprint Requests Should Be Addressed:**

William D. Leslie, MD MSc

Department of Medicine (C5121)

409 Tache Avenue

Winnipeg, Manitoba, Canada R2H 2A6

Phone: 204-237-2311

Fax: 204-237-2007

Email: bleslie@sbgh.mb.ca

**ABSTRACT**

*Context:* Bone mineral density (BMD) measurement from dual-energy X-ray absorptiometry (DXA) is widely used to assess skeletal strength in clinical practice, but DXA instruments can also measure biomechanical parameters related to skeletal shape.

*Objective*: To determine whether DXA-derived hip geometry measures provide information on fracture prediction that is independent of hip fracture probability determined from the FRAX® algorithm.

*Design and Setting:* Retrospective registry study using BMD results for Manitoba, Canada.

*Patients:* Women age 40 years and older with baseline hip DXA, derived hip geometry measures and FRAX scores (N=50,420).

*Main Outcome Measures:* Hospitalized hip fracture (N=1,020) diagnosed during 319,137 person-years of follow-up (median 6.4 years).

*Results:* Among the hip geometry measures, hip axis length (HAL) showed a consistent association with hip fracture risk when adjusted for age (hazard ratio [HR] 1.30 per standard deviation [SD] increase, 95% confidence interval [CI] 1.22-1.38) and this was unaffected by further adjustment for BMD or FRAX score. Adjusted for FRAX score with BMD, there was a significant effect of increasing HAL quintile on hip fracture risk (linear trend P<0.001); relative to quintile 1 (referent), the HR (95% CI) increased from 1.43 (1.12-1.82) for quintile 2, 1.61 (1.27-2.04) for quintile 3, 1.85 (1.47-2.32) for quintile 4, and 2.45 (1.96-3.05) for quintile 5. There was a modest but significant improvement in net reclassification improvement (1.5%) and integrated discrimination improvement (0.7%) indices. The effect of HAL was particularly strong among younger, non-osteoporotic women (FRAX-adjusted HR 1.70 per SD increase, 95% CI 1.48-1.94).

*Conclusions*: DXA-derived hip geometry measurements are associated with incident hip fracture risk, but many do not confer significant independent predictive information. HAL was found to predict hip fractures when adjusted for BMD or FRAX score, and may be of clinical value in refining hip fracture risk.

**INTRODUCTION**

Approximately 9 million new osteoporotic fractures occur worldwide, each year (1) with a global burden of osteoporosis projected to increase markedly over the next decades as the number of elderly individuals increases (2). Hip fractures are particularly devastating, leading to significant long-term disability, decreased quality of life (3;4) and a case-fatality rate that exceeds 20% (5;6). Compromised skeletal strength is fundamental to the increased fracture risk seen in osteoporosis (7). Bone mineral density (BMD) measured from dual-energy X-ray absorptiometry (DXA) is the most readily quantified measure of skeletal strength and meta-analyses have confirmed that BMD predicts low-trauma fractures (8;9). Bone densitometry of the proximal femur measured by dual energy x-ray absorptiometry (DXA) has been designated as the reference methodology for the densitometric diagnosis of osteoporosis based upon a T-score of -2.5 or lower when compared with a standardized reference population (Caucasian female NHANES III) (10). Although areal bone mineral density (BMD) from DXA is widely used for fracture prediction, its accuracy is limited. Paradoxically, most hip fractures occur in individuals with BMD is above the osteoporotic threshold (i.e., T-score 2.5 standard deviations below the young adult mean), highlighting the need for better prediction tools (9;11-13).

In 2008 the WHO Collaborating Centre released the fracture risk assessment tool (FRAX®) for estimation of individualized ten year probability of hip and major osteoporotic fracture (composite of hip, clinical spine, distal forearm, and proximal humerus) (14). The input variables were selected following a series of meta-analyses using data from 9 prospective international population-based cohorts (15). In addition to

age, sex, and body mass index (BMI), additional clinical risk factors (CRFs) for fractures include prior fragility fracture, parental history of hip fracture, prolonged use of glucocorticoids, rheumatoid arthritis, current cigarette smoking, alcohol intake of 3 or more units/day and secondary osteoporosis and (optionally) femoral neck BMD. The use of these CRFs has been shown to enhance prediction of hip fractures and other major osteoporotic fractures over the use of BMD alone (16).

DXA instruments are also capable of measuring some biomechanical parameters related to skeletal shape, strength and adaptation to loading (17;18). The two-dimensional curved-beam model was the basis for Hip Structural Analysis (HSA) and related implementations of this method (17;19). Studies indicate that some of these geometric measures are associated with fracture risk but it is uncertain whether they provide clinically useful information that is independent of hip fracture probability as currently assessed with the FRAX algorithm (20-23). A large clinical cohort with linkage to fracture outcomes was studied to address this question.

**METHODS**

*Study population*

We identified all women age 40 years and older registered for health coverage in the province of Manitoba, Canada who underwent baseline bone density measurement of the proximal femur with a single fan-beam scanner configuration (Prodigy, GE Healthcare). For women with more than one eligible set of measurements, only the first record was included. In Manitoba, health services are provided to virtually all residents and recorded through a single public healthcare system. Bone density testing with DXA has been

managed as an integrated program since 1997 and uses targeted case-finding rather than population screening (24).  Criteria and testing rates for this program have been published (25).  The program maintains a database of all DXA results which can be linked with other population-based computerized health databases through an anonymous personal identifier (26).  The DXA database has been previously described with completeness and accuracy in excess of 99%.  The study was approved by the University Research Ethics Board.

*Bone Density Measurements*

DXA scans were performed and analyzed in accordance with manufacturer recommendations.  Hip T-scores were calculated using NHANES III White female reference values (10;27).  All hip scans were then reprocessed using a single unmodified commercial version of software to evaluate additional parameters of hip geometry (enCore version 14.x, GE Healthcare).  The software includes Advanced Hip Assessment (AHA) and includes the following structural parameters: hip axis length (HAL, mm): distance from base of greater trochanter to inner pelvic rim; cross-sectional moment of inertia (CSMI, cm$^4$): distribution of material around the neck axis for calculating resistance to bending; cross sectional area (CSA, mm$^2$): surface area of bone in the cross-section excluding soft tissue voids; femoral strength index (SI, unitless): ratio of estimated compressive yield strength of femoral neck to expected compressive stress of a fall on the greater trochanter adjusted for the patient's age, height and weight; neck shaft angle (degrees): the obtuse angle created by the lines of intersection from the femoral shaft and femoral neck; section modulus, a measure of bending strength derived from CSMI and femoral neck width; and buckling ratio: an index of structural stability derived

from femoral neck width and estimated cortical thickness using an annulus model (20;28). The commercial software derives hip geometry and strength parameters from the standard DXA-defined femoral neck region, and does not consider the intertrochanter or femoral shaft regions (20;28).

The three DXA instruments used in the province were cross-calibrated using anthropomorphic phantoms and no clinically significant differences were identified (T-score differences < 0.1). Therefore all analyses are based upon the unadjusted numerical results provided by the instrument. No magnification effects have been reported with the densitometer used in this study (20;29). Densitometers showed stable long-term performance (coefficient of variation [CV] < 0.5%) and satisfactory in vivo precision (CV 2.3% for the femoral neck).

*Fracture Probability Calculations*

Ten-year probability of a hip fracture was calculated using the Canadian FRAX tool (FRAX® Desktop Multi-Patient Entry, version 3.7). Briefly, prior fracture and other conditions required for calculating fracture probability with FRAX were assessed through a combination of hospital discharge abstracts (diagnoses and procedures coded using the ICD-9-CM prior to 2004 and ICD-10-CA thereafter) and physician billing claims (coded using ICD-9-CM) as previously described (30). Proxies were used for smoking (chronic obstructive pulmonary disease diagnosis) and high alcohol intake (alcohol or substance abuse diagnosis) over the same time frame; prevalences and weights of these surrogate variables have been shown to be similar to population-based data (30;31). Prolonged corticosteroid use (over 90 days dispensed in the year prior to DXA testing) was obtained from the provincial pharmacy system (32). We adjusted for the effect of incomplete

parental hip fracture information on FRAX probability estimates prior to 2005 using age- and sex-specific adjustment factors derived from 2005-2008 parental hip fracture responses (30). Predictions with the Canadian FRAX tool have been shown to agree closely with observed fracture rates in our cohort and in the general Canadian population (30;31).

*Fracture Outcomes*

An individual's longitudinal health service records were assessed for the presence of hip fracture codes not associated with trauma codes after the index BMD testing (33). The incidence of hip fracture was ascertained by the presence of a primary diagnosis of hip fracture in the hospital discharge abstracts (coded in the primary position of all hospitalization diagnoses, using the ICD-9-CM prior to 2004 and ICD-10-CA thereafter) (34). To minimize potential misclassification with a prior fracture, we required that there be no hospitalization for hip fracture in the six months preceding an incident fracture diagnosis.

*Statistics*

Group comparisons for continuous data were conducted with Student's independent sample *t*-test and for categorical data using a $\chi^2$ test of independence. Bivariate Pearson correlation coefficients between geometric and non-geometric measurements were estimated. Independent sample *t*-tests were used to compare baseline measures in women with hip fractures versus women without hip fractures. Cox proportional hazards regression models were constructed for time to hip fracture. Hazard ratios (HRs), expressed as a gradient of risk per SD with 95% confidence intervals (95% CIs), were obtained for each hip geometry parameter. HRs were sequentially adjusted for age; age

and femoral neck BMD; FRAX 10-year hip fracture risk without BMD, and finally

FRAX 10-year hip fracture risk with BMD. FRAX scores, which are skewed, were log-transformed to produce a normal distribution. For sensitivity analyses, models were re-run including subject height as a covariate, since this showed a significant correlation with many of the hip geometry measurements. No violations of the proportional hazards assumption were identified. Models were assessed for evidence of multicollinearity and none was observed (all variance inflation factors <4). HAL was also studied in relation to quintile category using the unadjusted Kaplan-Meier estimator and Cox proportional hazards model adjusted for relevant covariates. The net reclassification improvement (NRI) and integrated discrimination improvement (IDI) indices associated with combining HAL and FRAX with BMD were derived as described by Pencina et al (35). The NRI was derived from the reclassification table constructed separately for participants with and without events, and quantifies the correct movement in categories—upwards for events and downwards for non-events—relative to an intervention threshold of 3% 10-year hip fracture risk as per the National Osteoporosis Foundation (NOF) (36). The IDI, which does not depend on the particular risk categorization, is based upon the difference in model-based discrimination slopes, and represents the integrated difference in sensitivities and the integrated difference in 'one minus specificities' between the new and old models over all possible cut-offs. Statistical analyses were performed with Statistica (Version 10.0, StatSoft Inc, Tulsa, OK).

**RESULTS**

*Population*

The baseline characteristics of the 50,420 women in the study population are summarized in **Table 1**. The mean age was 64.3 ± 11.1 years and the femoral neck mean T-score was -1.4 ± 1.0 consistent with low bone mass (osteopenia). Mean FRAX 10-year hip fracture risk was 3.2% computed without BMD and 2.5% computed with BMD. Women who sustained a hip fracture were significantly older, had lower femoral neck T-scores and greater FRAX scores (calculated without and with BMD). All hip geometry measurements were also significantly different between those with and without hip fractures; HAL, neck shaft angle and buckling ratio were significantly greater in women with hip fractures, whereas CSMI, CSA, strength index and section modulus were significantly lower.

*Correlations*

Statistically significant correlations were estimated between the majority of the covariates studied (**Table 2**), though most of these were relatively small. As expected, HAL was most strongly correlated with height (r=0.51) whereas CSMI, CSA and section modulus were most strongly correlated with femoral neck T-score (r=0.47 to 0.89). Strength index, neck shaft angle and buckling ratio showed only weak correlations with height or femoral neck T-score. FRAX scores without BMD showed weak correlations with hip geometry measurements (strongest for CSA, r=-0.32) and slightly stronger correlations when the FRAX score was computed with BMD (CSA r=-0.52). Correlation between hip geometry measurements was highest for CSMI and section modulus (r=0.93). HAL,

strength index, neck shaft angle and buckling ratio showed relatively weak correlations with all other geometry measures.

*Fractures*

During 319,137 person-years of follow-up (median 6.4 years, interquartile range 3.2-9.4), 1020 hip fractures were recorded. Adjusted HRs for hip fracture prediction are summarized in **Table 3**. When adjusted for age alone, CSA showed the strongest association with incident hip fractures (HR 1.86 per SD decrease, 95% CI 1.72-2.01) and was similar when adjusted for FRAX score without BMD (HR 1.79, 95% CI 1.66-1.94). There was high collinearity between CSA and BMD; when adjusted for FRAX score with BMD the effect of CSA was greatly attenuated (HR 1.11, 95% CI 1.01-1.22). CSMI, strength index, section modulus and buckling ratio showed significant but weaker associations with hip fracture prediction in age adjusted models, but again these effects were attenuated when adjusted for BMD. HAL showed a significant association with hip fracture risk when adjusted for age alone (HR 1.30 per SD increase, 95% CI 1.22-1.38) and this was unaffected by adjustment for BMD. Neck shaft angle was also associated with hip fracture prediction in age adjusted models (HR 1.23 per SD increase, 95% CI 1.17-1.30), with little change when adjusted for FRAX score with BMD. Buckling ratio showed a similar modest association with hip fracture prediction that was identical in models adjusted for age alone or FRAX score with BMD (HR 1.21 per SD increase). Additional adjustment for height did not appreciably affect these results, and in particular did not attenuate the relationship between HAL and hip fractures.

A final model was constructed that included FRAX score with BMD, HAL, neck shaft angle and buckling ratio since these showed minimal interdependence (all

redundancy $r^2<0.1$).  In this model, the effect of HAL was unchanged (HR 1.30 per SD increase, 95% CI 1.22-1.38, $\chi^2 = 71.5$) with relatively weaker effects from neck shaft angle (HR 1.10, 95% CI 1.04-1.16, $\chi^2 = 10.5$) and buckling ratio (HR 1.07, 95% CI 1.01-1.14, $\chi^2 = 5.8$).

*Additional HAL analyses*

When HAL was categorized into quintiles, there was a stepwise increase in the number of hip fractures from the shortest HAL (quintile 1<99.5 mm) 106/10,080 (1.05%) to the longest HAL (quintile 5>109.9 mm) 316/10,093 (3.13%) with a significant linear trend (P<0.001) (**Table 4**).  The fracture-free survival curves (Kaplan-Meier estimator) to 10 years show a stepwise decrease in time to hip fracture from quintile 1 to quintile 5 (log-rank P<0.001) (**Figure 1**).  For quintile 1, cumulative hip fracture incidence was 0.6% (95% CI 0.5-0.8) at 5 years and 1.8% (1.4-2.2) at 10 years compared with quintile 5 2.0% (1.7-2.3) at 5 years and 4.9% (4.3-5.5) at 10 years.  Adjusted for FRAX score with BMD, there was again a significant effect of increasing HAL quintile on hip fracture risk (linear trend P<0.001); relative to quintile 1 (referent), the HR (95% CI) increased from 1.43 (1.12-1.82) for quintile 2, 1.61 (1.27-2.04) for quintile 3, 1.85 (1.47-2.32) for quintile 4, and 2.45 (1.96-3.05) for quintile 5.

The incremental clinical utility of including HAL with FRAX score calculated with BMD on clinical management was assessed with the NRI assuming a 3% cutoff for intervention.  This showed an increase of 2.0% for hip fracture case identification with a 0.4% decrease in non-fracture subjects, for an overall NRI index of 1.5% (*p*-value=0.024).  Among those with a hip fracture event, predicted fracture risk was increased from 8.0% to 8.8%, whereas for those without a hip fracture the predicted

fracture risk was unchanged (2.4% vs 2.5%). The overall IDI index value was 0.7% (*p*-value<0.001).

Finally, we tested for effect modification (interactions) between HAL and femoral neck T-score, age, FRAX score and height. Significant interactions were detected for femoral neck T-score (non-osteoporotic versus osteoporotic, *p*-value=0.005). When analyses were stratified by femoral neck T-score, there was a larger FRAX-adjusted effect for HAL among non-osteoporotic women (HR 1.49 per SD increase, 95% CI 1.38-1.62) than among osteoporotic women (HR 1.18, 95% CI 1.08-1.29). Significant interactions were also detected for age (<70 versus ≥70 years, *p*-value=0.046). Age and T-score stratified analyses showed the largest FRAX-adjusted effect for HAL among non-osteoporotic women age <70 years (HR 1.70 per SD increase, 95% CI 1.48-1.94), intermediate results for osteoporotic women age <70 years (HR 1.37, 95% CI 1.08-1.73) and non-osteoporotic women age ≥70 years (HR 1.39, 95% CI 1.25-1.53), with the weakest effect among osteoporotic women age ≥70 years (HR 1.13, 95% CI 1.02-1.25).

**DISCUSSION**

This large registry-based study found that several hip geometry measures predict hip fracture risk independent of age or FRAX score calculated without BMD. Adjustment for BMD directly or as part of the FRAX score attenuated this relationship for some of the geometry measures. HAL remained a robust predictor of hip fractures in all models including those that used BMD, height and other geometry measures. There was a greater than two-fold difference in the numbers of fractures, cumulative incidence (5 years and 10 years) and FRAX-adjusted HR for the highest quintile (HAL>109.9 mm)

versus the lowest quintile (HAL<99.5 mm). To the best of our knowledge, this is the first study to examine the utility of HAL and other hip geometry measures in relation to hip fracture probability derived from the FRAX algorithm.

This study complements previous reports showing the ability of hip geometry to assess hip fracture risk (17;19-23;37), and that some of these parameters are partially independent of bone mass (20;22;23;37). No study has specifically addressed the additional contribution of hip geometry to hip fracture prediction from the FRAX risk algorithm, however. Our study suggests that HAL may be a clinically useful modifier of hip fracture risk independent of BMD and FRAX. This was confirmed in the finding of a modest but significant improvement in the overall NRI and IDI. The effect of HAL was particularly strong among younger, non-osteoporotic women. The explanation for this age-interaction is uncertain, but it is worth noting that femoral neck BMD also shows a larger gradient of risk for hip fracture in younger than older individuals and it has been postulated that age may adversely affect the structural or material properties of the femur (8). Although HAL was not a strong risk factor for hip fracture among osteoporotic women age ≥70 years, these women would already be designated at high fracture risk and appropriate for treatment (36).

Findings related to HAL, defined as the distance from the base of greater trochanter to the inner pelvic rim, may not apply to other measures of femoral neck length. In a prospective study 7474 women from the Study of Osteoporotic Fractures (SOF) with 635 incident hip fractures recorded over 13 years, Kaptoge et al. (22) found that femur neck length, defined as the distance from the center of the femoral head to the intersection of the femoral neck and shaft axes, was the only hip geometry variable that

showed no significant association with hip fractures. Negative results have also been

observed for femoral neck axis length defined as the linear distance from the base of the

greater trochanter to the apex of the femoral head (38). Therefore, the segment of the

HAL that is critical in determining hip fracture susceptibility remains unclear. The exact

mechanism for the relationship between HAL and fracture risk is not known (39), though

the presumption is that this is related to a longer "lever arm" which would increase

loading stresses on the femoral neck. Experimental studies are needed to define the

biomechanical mechanisms through which HAL affects hip fracture risk.

Limitations to this analysis are acknowledged. There are obvious technical

difficulties and simplifications when describing three-dimensional hip geometry from

two-dimensional DXA (18), though the ability to assess hip geometry from DXA has

been validated against phantoms and *in vivo* computed tomography (40;41). Only a

single scanner configuration and software implementation was studied. Whether similar

results would be seen with other manufacturers or scanners is unclear. As HAL is a

simple length measurement it would likely show higher levels of agreement than other

parameters. The nature of our population (99% white) precludes an assessment of

whether ethnic variation HAL and other indices of geometry lead to ethnic differences

(interactions) in fracture prediction (42;43). Previous studies show shorter HAL in Asian

and Black women and men, even after adjustment for height and weight differences, and

this may contribute to their lower hip fracture rates (43). Our analysis also did not

address men. HAL may be useful for initial fracture risk assessment, but as this

parameter is not amenable to fracture prevention treatment it is unlikely to be useful for

serial assessment. It may also be affected by osteoarthritis of the hip which limits the

ability of the subject to achieve optimal internal rotation of the hip for profiling of the proximal femur, and this may explain the small positive association between age and HAL noted here and elsewhere (44;45). Our analysis did not differentiate site of hip fracture, though previous work suggests that prognostic measures based upon femoral neck geometry operate similarly for intracapsular versus extracapsular proximal femoral fractures (22;37;46). Despite these limitations, our findings still showed that HAL was a robust predictor of hip fracture risk. HAL and hip geometry measurements appear to be useful for assessment of hip fracture risk. Whether more sophisticated tools for hip strength assessment based upon finite element modelling (FEM) from two-dimensional DXA images will become clinically useful is an important, evolving area of research (19;47;48). One such FEM has demonstrated a significant ability to provide BMD-independent and FRAX-independent information on hip fracture risk in several population-based studies (46).

In conclusion, we found that DXA-derived hip geometry measurements are associated with incident hip fracture risk. Many of these geometric parameters are strongly associated with BMD, and do not confer significant BMD- or FRAX-independent predictive information. On the other hand, HAL was found to robustly predict hip fractures when adjusted for a wide range of covariates including FRAX score with BMD, with a significant improvement in overall risk reclassification. This suggests that HAL may be of clinical value in refining hip fracture risk and better identifying those in whom osteoporosis treatment should be considered.

**DETAILS OF CONTRIBUTORS AND GUARANTOR:**

Authors substantially contributed to: conception, design and analysis (WDL), interpretation of data (All Authors); drafting the article (WDL); critically revising the article for important intellectual content (All Authors); and final approval of the version to be published (All Authors).  WDL accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

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1 **Table 1. Study population baseline characteristics.**
2

| | Overall | No Hip Fracture | Hip Fracture | *p*-value |
|---|---|---|---|---|
| N= | 50,420 | 49,400 | 1020 | |
| Age (years) | 64.3 ± 11.1 | 64.3 ± 11 | 75.3 ± 9.4 | <0.001 |
| Height (cm) | 160.2 ± 6.5 | 160.2 ± 6.5 | 158.8 ± 7.0 | <0.001 |
| Femoral neck T-score | -1.4 ± 1.0 | -1.4 ± 1.0 | -2.3 ± 0.8 | <0.001 |
| FRAX 10 year hip fracture risk without BMD | 3.2 ± 4.9 | 3.2 ± 4.8 | 8.8 ± 7.1 | <0.001 |
| FRAX 10 year hip fracture risk with BMD | 2.5 ± 4.3 | 2.5 ± 4.2 | 8.0 ± 6.9 | <0.001 |
| HAL (mm) | 104.7 ± 6.2 | 104.7 ± 6.2 | 106.9 ± 6.2 | <0.001 |
| CSMI ($mm^4$) | 8,873 ± 2438 | 8873 ± 2430 | 8224 ± 2737 | <0.001 |
| CSA ($mm^2$) | 127.1 ± 22.1 | 127.1 ± 22.0 | 109.3 ± 19.1 | <0.001 |
| Strength index | 1.38 ± 0.4 | 1.38 ± 0.40 | 1.30 ± 0.38 | <0.001 |
| Neck shaft angle (degrees) | 126.3 ± 4.3 | 126.3 ± 4.3 | 127.1 ± 4.3 | <0.001 |
| Section modulus | 529.7 ± 116.6 | 529.7 ± 116.3 | 467.7 ± 112.6 | <0.001 |
| Buckling ratio | 3.92 ± 1.88 | 3.92 ± 1.89 | 4.38 ± 1.75 | <0.001 |

3

4 Continuous variables expressed as mean ± SD. HAL: hip axis length; CSMI: cross sectional moment of inertia; CSA: cross sectional area.

5

6    **Table 2. Bivariate Pearson correlation coefficients.**

7

|  | HAL | CSMI | CSA | Strength index | Neck shaft angle | Section modulus | Buckling ratio |
|---|---|---|---|---|---|---|---|
| Age | **0.11** | **-0.08** | **-0.32** | **-0.07** | **-0.07** | **-0.21** | **0.13** |
| Height | **0.51** | **0.45** | **0.42** | **-0.04** | **0.05** | **0.44** | **-0.01** |
| Femoral Neck T-score | **0.02** | **0.47** | **0.89** | **0.21** | **-0.08** | **0.66** | **-0.28** |
| FRAX 10 year hip fracture risk without BMD | **0.09** | **-0.10** | **-0.32** | 0.00 | **-0.03** | **-0.20** | **0.13** |
| FRAX 10 year hip fracture risk with BMD | **0.05** | **-0.23** | **-0.52** | **-0.11** | **0.01** | **-0.36** | **0.19** |
| HAL | -- | **0.40** | **0.20** | **-0.24** | **0.13** | **0.32** | **0.11** |
| CSMI | **0.40** | -- | **0.76** | **0.34** | **-0.09** | **0.93** | **0.02** |
| CSA | **0.20** | **0.76** | -- | **0.33** | **-0.12** | **0.87** | **-0.21** |
| Strength index | **-0.24** | **0.34** | **0.33** | -- | **-0.37** | **0.38** | **-0.11** |
| Neck shaft angle | **0.13** | **-0.09** | **-0.12** | **-0.37** | -- | **-0.14** | **0.16** |
| Section modulus | **0.32** | **0.93** | **0.87** | **0.38** | **-0.14** | -- | **-0.09** |
| Buckling ratio | **0.11** | **0.02** | **-0.21** | **-0.11** | **0.16** | **-0.09** | -- |

8

9    HAL: hip axis length; CSMI: cross sectional moment of inertia; CSA: cross sectional area; SI: strength index.  Boldface indicates $p$-value<0.01.

10

**Table 3. Hazard ratios (HRs) and 95% confidence intervals (95% CI) for hip fracture prediction, per standard deviation (SD) change.**

| Adjusted for: | Age | Age with BMD | FRAX without BMD | FRAX with BMD |
| --- | --- | --- | --- | --- |
| | HR (95% CI) | HR (95% CI) | HR (95% CI) | HR (95% CI) |
| HAL | **1.30 (1.22-1.38)** | **1.32 (1.25-1.41)** | **1.30 (1.22-1.38)** | **1.30 (1.22-1.38)** |
| CSMI* | **1.21 (1.13-1.30)** | **0.90 (0.85-0.95)** | **1.19 (1.11-1.28)** | **1.08 (1.01-1.15)** |
| CSA* | **1.86 (1.72-2.01)** | **0.86 (0.74-1.00)** | **1.79 (1.66-1.94)** | **1.11 (1.01-1.22)** |
| Strength index* | **1.28 (1.19-1.38)** | **1.10 (1.02-1.19)** | **1.27 (1.18-1.37)** | **1.08 (1.00-1.16)** |
| Neck shaft angle | **1.23 (1.17-1.30)** | **1.15 (1.09-1.22)** | **1.23 (1.17-1.30)** | **1.23 (1.17-1.30)** |
| Section modulus* | **1.50 (1.40-1.61)** | 0.97 (0.89-1.05) | **1.47 (1.36-1.58)** | 1.04 (0.97-1.12) |
| Buckling ratio | **1.21 (1.15-1.26)** | **1.09 (1.03-1.15)** | **1.21 (1.15-1.26)** | **1.21 (1.14-1.28)** |
| Adjusted for: | Age + Height | Age with BMD + Height | FRAX without BMD + Height | FRAX with BMD + Height |
| | HR (95% CI) | HR (95% CI) | HR (95% CI) | HR (95% CI) |
| HAL | **1.30 (1.21-1.40)** | **1.26 (1.17-1.35)** | **1.30 (1.21-1.39)** | **1.30 (1.21-1.39)** |
| CSMI* | **1.33 (1.23-1.44)** | 0.95 (0.88-1.02) | **1.25 (1.16-1.35)** | 1.05 (0.98-1.12) |
| CSA* | **2.09 (1.93-2.27)** | 1.04 (0.89-1.23) | **1.98 (1.82-2.15)** | **1.19 (1.08-1.32)** |
| Strength index* | **1.27 (1.18-1.36)** | 1.06 (0.99-1.15) | **1.27 (1.18-1.37)** | 1.06 (0.99-1.15) |
| Neck shaft angle | **1.23 (1.17-1.30)** | **1.14 (1.08-1.21)** | **1.23 (1.17-1.30)** | **1.23 (1.17-1.30)** |
| Section modulus* | **1.66 (1.54-1.79)** | 1.07 (0.98-1.17) | **1.58 (1.46-1.70)** | **1.10 (1.01-1.19)** |
| Buckling ratio | **1.21 (1.15-1.26)** | **1.07 (1.01-1.14)** | **1.21 (1.15-1.26)** | **1.21 (1.14-1.28)** |

* per SD decrease, others are per SD increase. HAL: hip axis length; CSMI: cross sectional moment of inertia; CSA: cross sectional area.  Boldface indicates *p*-value <0.05.
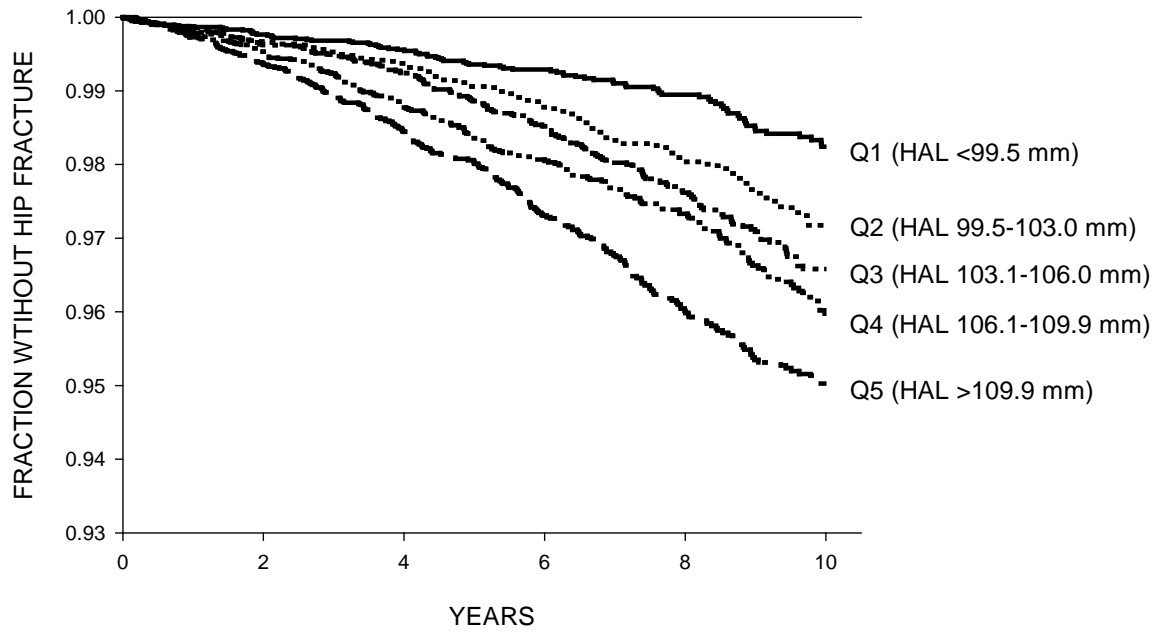
**Table 4. Numbers of hip fractures, cumulative incidence and FRAX with BMD-adjusted hazard ratios (HRs) according to hip axis length (HAL) quintile.**

| | Number of fractures / number at risk (%) | Cumulative % fracture incidence at 5 years (95% CI) | Cumulative % fracture incidence at 10 years (95% CI) | FRAX-adjusted HR (95% CI) |
|---|---|---|---|---|
| Quintile 1 (HAL <99.5 mm) | 106 / 10,080 (1.05%) | 0.6 (0.8-0.5) | 1.8 (2.2-1.4) | 1 (referent) |
| Quintile 2 (HAL 99.5-103.0 mm) | 165 / 10,074 (1.64%) | 0.9 (1.2-0.7) | 2.8 (3.3-2.3) | 1.43 (1.12-1.82) |
| Quintile 3 (HAL 103.1-106.0 mm) | 197 / 10,114 (1.95%) | 1.1 (1.4-0.9) | 3.4 (4.0-2.9) | 1.61 (1.27-2.04) |
| Quintile 4 (HAL 106.1-109.9 mm) | 236 / 10,059 (2.35%) | 1.6 (1.9-1.4) | 4.0 (4.6-3.4) | 1.85 (1.47-2.32) |
| Quintile 5 (HAL >109.9 mm) | 316 / 10.093 (3.13%) | 2.0 (2.3-1.7) | 4.9 (5.5-4.3) | 2.45 (1.96-3.05) |

21    **Figure 1.  Hip fracture-free survival (Kaplan-Meier estimator) according to hip axis length**

22    **(HAL) quintile.**



23