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Risk-equivalent T-score Adjustment For Using Lumbar Spine Trabecular Bone Score (TBS): The Manitoba BMD Registry

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Abstract

Purpose—To develop an approach for using TBS in clinical practice based upon a "risk-equivalent" adjustment to the BMD T-score.

Methods—We identified 45,185 women age 40 years and older with baseline spine and hip DXA, TBS and FRAX probabilities including femoral neck BMD. Incident major osteoporotic fractures (MOF, n=3925) were identified from population-based health services data (mean follow-up 7.4 years comprising 335,910 person-years). Cox proportional hazards models adjusted for age- and BMI were first used to estimate the risk for MOF from BMD T-score alone, then after

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Roles:

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including TBS and a multiplicative age interaction term. From the parameter estimates we developed a TBS offset to the BMD T-score based upon change in TBS that would give the same risk as a unit change in BMD T-score for the femoral neck, total hip and lumbar spine.

Results—All BMD measurements, TBS and the age interaction term independently predicted MOF ($p<0.001$). Measures of risk stratification and model fit were improved for the TBS-adjusted BMD T-score versus the unadjusted BMD T-score ($p<0.001$). There was a high level of agreement between MOF probability estimated from TBS-adjusted MOF FRAX probability and FRAX probability using the "risk-equivalent" femoral BMD T-score: MOF probability $r^2 = 0.98$, slope = 1.02, intercept = -0.3; hip probability $r^2 = 0.95$, slope = 1.07, intercept = 0.0.

Conclusions—The BMD-independent effect of lumbar spine TBS on fracture risk can be estimated as a simple offset to the BMD T-score.

Keywords

Osteoporosis; Fracture prediction; Bone densitometry; DXA; Trabecular bone score

Introduction

The World Health Organization (WHO) defines osteoporosis conceptually as a systemic skeletal disease characterized by low bone mass (decreased quantity) and microarchitectural deterioration of bone tissue (decreased quality) with a consequent increase in bone fragility and susceptibility to fracture (1). In the absence of a typical fragility fracture, the operational definition of osteoporosis is based on the quantity of bone, defining osteoporosis as a T-score -2.5 standard deviations (SDs) or lower, where the T-score is the number of SDs by which the mineral density (BMD) differs from the mean for young individuals (2, 3). The reference standard for osteoporosis diagnosis is femoral neck BMD assessed by dual-energy X-ray absorptiometry (DXA) using the Third National Health and Nutrition Examination Survey (NHANES III) reference database from women aged 20-29 years (4).

Despite the proven ability of BMD to stratify fracture risk, it has low sensitivity (5). In fact, most fractures occur in individuals who do not have an osteoporotic BMD, implying that factors other than BMD influence bone strength and fracture risk (6, 7). This fact has stimulated the development of risk algorithms that integrate multiple risk factors for fracture and interest in new techniques for bone quality assessment. The most widely used tool for fracture risk assessment is FRAX, developed by the Collaborating Centre for Metabolic Bone Diseases at Sheffield, UK, as a computer-based algorithm that computes the 10-year probability of major osteoporotic fracture (MOF) (hip, clinical spine, forearm and humerus fracture) and hip fracture. Fracture risk is computed from easily assessed clinical risk factors (CRFs) for fracture and (optionally) femoral neck BMD (8). FRAX is country specific and is currently calibrated for over 60 countries (9).

Among the techniques recently developed for bone quality assessment, trabecular bone score (TBS) has been most extensively studied (10, 11). TBS is derived from a previously acquired lumbar spine DXA scan and is a texture parameter that predicts fracture risk independently from standard BMD measurements and from FRAX. TBS has been used to

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modify the output from FRAX to enhance fracture prediction, and includes a multiplicative age interaction term (12, 13). TBS can help enhance fracture prediction when used in conjunction with FRAX probability estimated with BMD (14). This approach facilitates clinical integration of TBS in guidelines where FRAX is used to determine treatment eligibility. However, many guidelines continue to emphasize a diagnosis of osteoporosis based on the BMD T-score as an indication for treatment (15, 16). Therefore, we explored an alternative approach for combining the information on bone quality assessed by TBS and bone quantity assessed by the BMD T-score. We hypothesized that using TBS to generate a "risk-equivalent" offset adjustment to the BMD T- score would improve fracture prediction versus the unadjusted BMD T-score alone.

Materials and Methods

Study population

In the Canadian province of Manitoba, health services are provided to nearly all residents through a single public health care system (17). For each health system contact, information is recorded to document the patient's demographics, date and type of service, and diagnostic code(s). DXA testing through the Manitoba Density Program has been managed as an integrated program since 1997 (18). This clinical program is based upon targeted case finding for women prior to age 65 years and endorses screening for women after age 65 years. The Manitoba Density Program maintains a database of all DXA results that can be linked with other population-based databases through an anonymous personal identifier. The associated database exceeds 99% in terms of completeness and accuracy (19). In this study we included women 40 years of age or older who had undergone baseline BMD measurement of the spine (L1-L4) and hip with a single fan-beam DXA configuration (Prodigy, GE Healthcare, Madison, WI, USA). The study was approved by the Research Ethics Board of the University of Manitoba and the Health Information Privacy Committee of Manitoba Health.

Measurement of Bone Mineral Density

All spine and hip DXA scans were performed using Prodigy scanners (GE-Healthcare, Madison, WI, USA) and analyzed in accordance with manufacturer recommendations (enCore Software 12.4, GE-Healthcare, Madison, WI, USA). BMD measurements were recorded for the lumbar spine (L1-L4 with exclusion of levels affected by artifact), total hip and femoral neck. Vertebral exclusions were determined by International Society for Clinical Densitometry (ISCD) certified physicians using a standardized clinical procedure: visual inspection of the scan for localized artifact, T-scores discordances between adjacent vertebral levels exceeding 1 SD, and correlation with additional imaging where available. Hip BMD T-scores were calculated using the NHANES III white female reference values (20). For the lumbar spine, manufacturer reference data for white US women were used. Instruments were cross-calibrated using anthropomorphic phantoms. All three instruments used for this study exhibited stable long-term performance (coefficient of variation (CV) <0.5%).

Measurement of Trabecular Bone Score

All TBS measurements were performed in the Bone Disease Unit at the University of Lausanne, Switzerland (TBS iNsight Software, Version 2.1, Med-Imaps, Merignac, France), using anonymized spine DXA files to ensure blinding of the Swiss investigators to all clinical parameters and outcomes. We excluded women with body mass index (BMI) outside the range 15-37 kg/m^2 as recommended by the TBS manufacturer (11). For each region used in the lumbar spine BMD measurement, TBS was evaluated based on gray-level analysis of the DXA images as the slope at the origin of the log-log representation of the experimental variogram (21). In the current analysis, we used a research version of the TBS iNsight software that allows for large-batched analyses from a workstation and provides outputs identical to the commercially available software. No significant calibration differences in mean TBS levels were seen for the three DXA scanners used. Short-term reproducibility (CV) for TBS calculated from all three instruments used for this study and from multiple technicians was 2.1% in 92 individuals with repeat spine DXA scans performed within 28 days (51 same day, 41 different day) (22).

FRAX assessment and fracture clinical risk factors

Ten-year probability of MOF and hip fracture was calculated using the World Health Organization FRAX tool, Canadian version (FRAX Desktop Multi-Patient Entry, version 3.7). The Canadian FRAX tool was calibrated using nationwide hip fracture data, and its predictions agree closely with observed fracture risk (23, 24). Weight and height were measured at the time of DXA, and BMI was calculated as weight (in kilograms) divided by height (in meters) squared. Parental hip fracture was by self-report (only available 2005 onwards). Prior fracture and other FRAX input variables/proxies were assessed using linkage to the population-based research registry that includes hospital discharge abstracts and physician billing claims as previously described (23). We defined prior fragility fracture as any non-traumatic MOF that occurred before the baseline DXA test using records back to 1987. Prolonged oral corticosteroid use (>90 days dispensed in the 1 year prior to DXA) was obtained from the provincial pharmacy system (25).

Assessment of incident fractures

Longitudinal health service records were assessed between April 1, 1987 and March 31, 2011 for the presence of fracture not associated with codes indicative of severe trauma (i.e., external injury) using validated definitions (26). Non-traumatic MOF that occurred after BMD testing were evaluated as the primary outcome. Secondary outcomes were hip fracture alone or any fracture (excluding head/neck, hand/foot and ankle). Fractures were ascertained through a combination of hospital discharge abstracts and physician billing claims because this method allows complete capture of any fractures that require treatment irrespective of hospital admission. To minimize potential misclassification of prior incident fractures, we required that there be no hospitalization or physician visit(s) with the same fracture type in the 6 months preceding an incident fracture diagnosis.

Statistical analyses

Statistical analyses were performed with Statistica (Version 13.0, StatSoft Inc, Tulsa, OK). Descriptive statistics for demographic and baseline characteristics are presented as mean ± SD for continuous variables or number (%) for categorical variables. Age- and BMI-adjusted Cox proportional hazards models were first used to study time to first MOF from BMD T-score alone. TBS (mean-centered and age-normalized) was then added to the model to estimate the BMD-independent effect of TBS on MOF risk. We included a multiplicative interaction term with age (mean-centered) to account for the larger effect of TBS on fracture risk in younger individuals, which parallels the approach used for developing the TBS-adjustment to FRAX (13). From the parameter estimates we developed a TBS adjustment to the BMD T-score based upon the change in TBS that would give the same predicted risk as a unit change in the BMD T-score (see Appendix). Analyses were performed separately for femoral neck, total hip and lumbar spine BMD T-scores. Risk gradients are presented as hazard ratio (HR) per SD decrease with 95% confidence intervals (CI).

As internal validation, we compared TBS-adjusted FRAX probabilities based upon McCloskey et al (13) with the output from the FRAX algorithm when TBS-adjusted femoral neck BMD T-score was used as the BMD input to FRAX. We then compared measures of fracture risk stratification and model fit for the unadjusted BMD T-score and for TBS-adjusted BMD T-score in Cox proportional hazards models adjusted for FRAX CRFs. The Wald Chi^2 statistics for the BMD T-scores (unadjusted and TBS-adjusted) are presented as a measure of effect size, and the model likelihood ratio is presented as a measure of global model fit. Improvement in model fit was assessed using the likelihood ratio test for nested models (unadjusted and TBS-adjusted T-score together versus either alone) adjusted for other FRAX CRFs. To illustrate the potential clinical impact of the TBS-adjusted BMD T-score, we examined four hypothetical cases, two women 55 years of age and two women 75 years of age, with femoral neck BMD T-scores of -1.7 (osteopenic) and -2.7 (osteoporotic).

Results

Study population

A total of 45,185 women with mean age of 63.5 (± 10.8) years were included in this analysis. The other baseline characteristics of the participants are shown in Table 1. Over a mean follow-up period of 7.4 (± 3.4) years (335,910 person-years), 3,925 (8.7%) of these women had one or more incident MOF, among which 1,040 (2.3%) had one or more incident hip fractures.

Derivation of TBS-adjusted BMD T-scores

The risk estimates derived from the Cox proportional hazards models are shown in Table 2. TBS and all BMD measurements were independent predictors of MOF ($p<0.001$), and the age interaction term was significant in all BMD models ($p<0.001$). Each SD reduction in TBS was significantly associated with 25% (HR=1.25, 95% CI=1.21-1.30), 22% (HR=1.22, 95% CI=1.18-1.26) and 26% (HR=1.26, 95% CI=1.22-1.31) greater risk of MOF in the femoral neck, total hip and lumbar spine BMD models, respectively. As expected, each SD decrease in BMD for the femoral neck, total hip and lumbar spine was significantly

associated with 70% (HR=1.70, 95% CI=1.63- 1.77), 82% (HR=1.82, 95% CI=1.75-1.90) and 47% (HR=1.47, 95% CI=1.41-1.52) increased risk of MOF, respectively. Results were minimally attenuated when adjusted for TBS and the age interaction term. From the parameter estimates we developed a TBS adjustment to the BMD T-score based upon change in TBS that would give the same risk as a unit change in BMD T-score for the femoral neck, total hip and lumbar spine (see Appendix).

Performance of TBS-adjusted BMD T-scores

As shown in Figure 1, there was a high level of agreement between MOF probability estimated from TBS-adjusted MOF FRAX probability (13) and MOF probability calculated using the TBS-adjusted femoral neck BMD T-score as the BMD input to FRAX: r^2=0.98, slope=1.02, intercept=-0.3. A similarly high level of agreement was also seen between hip fracture probability estimated from TBS-adjusted FRAX (13) and probability calculated using the TBS-adjusted femoral neck BMD T-score as the BMD input to FRAX: r^2=0.95, slope=1.07, intercept=0.0.

In models adjusted for all FRAX CRFs, TBS-adjusted BMD T-scores outperformed the unadjusted BMD T-scores for MOF and hip fracture prediction based upon an increase in the gradient of risk (HR per SD), Wald Chi^2 for the TBS-adjusted BMD T-scores, and global model fit estimated from the likelihood ratio (Table 3). The likelihood ratio test confirmed a significant improvement in model fit when the TBS-adjusted T-score was added to a model including unadjusted T-score and other FRAX CRFs ($p<0.001$), but not when the unadjusted T-score was added to a model including TBS-adjusted T-score.

Illustrative examples

Figure 2 illustrates the potential impact of applying the TBS adjustment to femoral neck BMD T-scores in four hypothetical women (ages 55 and 75 years, BMD T-score -1.7 and -2.7). The steeper slope in younger women is consistent with the expected age interaction. For an osteopenic femoral BMD T-score of -1.7, risk would be equivalent to an osteoporotic T-score of -2.5 when TBS falls below 1.2 in a woman age 55 years but would not reach the threshold in a woman aged 75 years for a TBS value within the age-specific 95% CI range. Conversely, for an osteoporotic femoral BMD T-score of -2.7, risk would be equivalent to an osteopenic T-score of -2.4 when TBS exceeds 1.4 at both ages.

Discussion

There is no international consensus on the management of osteoporosis, as seen in the diversity of guidelines and intervention strategies (9, 16). Moreover, an osteoporosis diagnosis based upon BMD T-score is still a relevant intervention and reimbursement threshold in many countries. In the present study, we confirmed the ability of TBS to enhance fracture prediction independently of BMD and propose a new approach for using TBS in clinical practice, the TBS-adjusted BMD T-score, derived as a risk-equivalent offset adjustment to the BMD T-score. As hypothesized, the TBS-adjusted BMD T-scores outperformed unadjusted BMD T-scores in fracture risk assessment for all three BMD measurement regions. We also confirmed high agreement between FRAX probabilities

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estimated from TBS-adjusted FRAX tool using the method of McCloskey et al (13) and probabilities estimated using the TBS-adjusted femoral neck BMD T-score as the BMD input to FRAX, further supporting their equivalence.

We propose a single metric that takes into account both the density and the quality of bone. McCloskey et al. (13) introduced a similar approach by generating an adjustment algorithm to take into account the independent contribution of TBS to fracture risk assessed by CRFs and BMD. In our hypothetical cases we found that TBS will probably be most helpful in those close to a BMD T-score intervention threshold, but will probably not be contributory in those with very low BMD (or very high BMD) for whom treatment is already indicated (or not indicated). This is consistent with recent data from Martineau et al. (14) showing that the information provided by TBS adjustment was unlikely to reclassify someone with a very low fracture risk to a treatment threshold.

An obvious strength of this study is the large population size, but several limitations should be acknowledged. Firstly, the population studied was derived from a clinical registry rather than a random sample of the population. However, our population is likely representative of patients typically encountered in clinical practice. Secondly, our study population was limited to women and was largely Caucasian, which may limit its applicability to men and other ethnicities. The meta-analysis from McCloskey et al (12) showed that the relationship of TBS with fracture was robust across sexes and ethnicities. Thus, the BMD T-score adjustments derived in our cohort may have broader applicability, but further validation is needed. Finally, the fracture definitions used are based upon administrative data rather than direct x-ray review (26). We excluded fractures associated with codes indicative of external injury, but the mechanism of fracture is otherwise unknown and could include some with traumatic or pathologic etiologies. However, the expected effect would be to bias towards the null (i.e., produce conservative estimates).

In conclusion, this study confirms that lumbar spine TBS is an independent predictor of fracture, and the BMD-independent effect of TBS on fracture risk can be estimated as a simple offset to the BMD T-score for all three regions commonly used in clinical practice: femoral neck, total hip and lumbar spine. Pending independent confirmation, this approach may be helpful in regions where intervention guidelines and/or reimbursement are primarily based on BMD T-score.

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Appendix

Mean-centered age (Age_C) is calculated as Age – 63.5; mean-centered age-normalized TBS (TBS_{CAN}) is calculated as TBS_{CAN} = (TBS – 1.32) + Age_C*0.00413, where 1.32 is the mean TBS of the study population, 63.5 is the mean age, and 0.00413 is the β-coefficient of age in the linear regression with TBS.

Relative gradients were calculated as the ratios of the Cox model parameter estimates of BMD T-score alone versus the parameter estimate of TBS_{CAN}, or versus the parameter estimate of Age_C*TBS_{CAN} interaction term. From Table 2, the relative gradients for TBS_{CAN} for the femoral neck (FN), total hip (TH) and lumbar spine (LS) regions were 0.28, 0.29 and 0.13, respectively, and for the Age_N*TBS_{CAN} interaction term were -7.63, -6.89 and -3.26, respectively. The calculation of TBS-adjusted BMD T-scores for the three regions follows:

TBS-adjusted FN BMD T-score = FN BMD T-score + TBS_{CAN}/0.28 – Age_C*TBS_{CAN}/7.63

TBS-adjusted hip BMD T-score = hip BMD T-score + TBS_{CAN}/0.29 – Age_C*TBS_{CAN}/6.89

TBS-adjusted LS BMD T-score = LS BMD T-score + TBS_{CAN}/0.13 – Age_C*TBS_{CAN}/3.26

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Mini-Abstract

Lumbar spine trabecular bone score (TBS) can be used to modify the output from the fracture risk assessment tool, FRAX, to enhance fracture prediction. An alternative approach for using TBS in clinical practice, based upon an adjustment to the bone mineral density (BMD) T-score, may be helpful in regions where intervention guidelines and/or reimbursement are primarily based on BMD T-score.

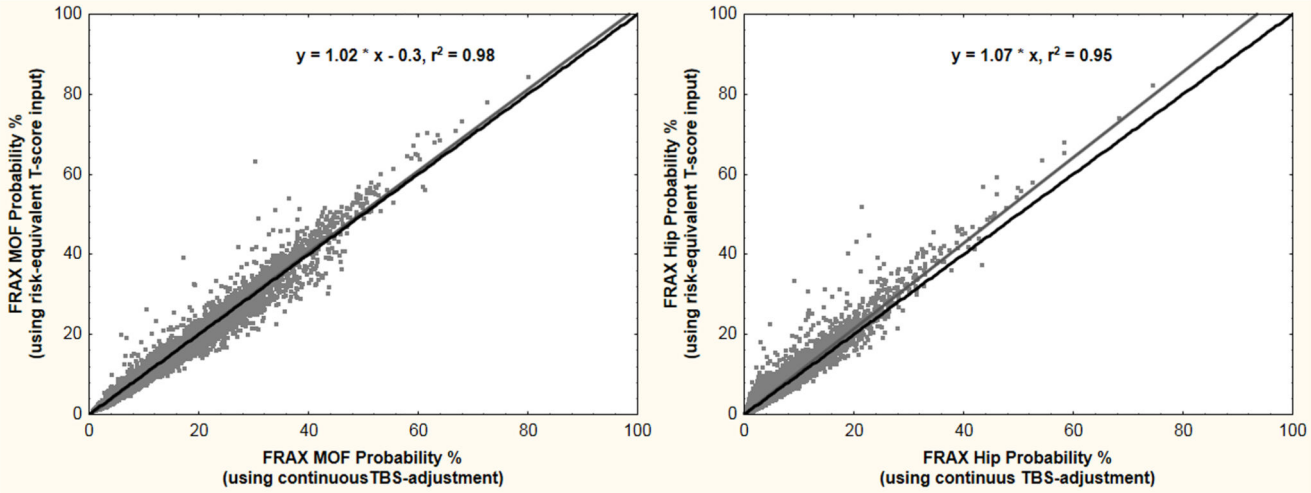

Figure 1.

Concordance between fracture probability computed using the TBS-adjustment to FRAX and a TBS-adjusted BMD T-score input to FRAX. Black = line of identity. Gray = regression line.

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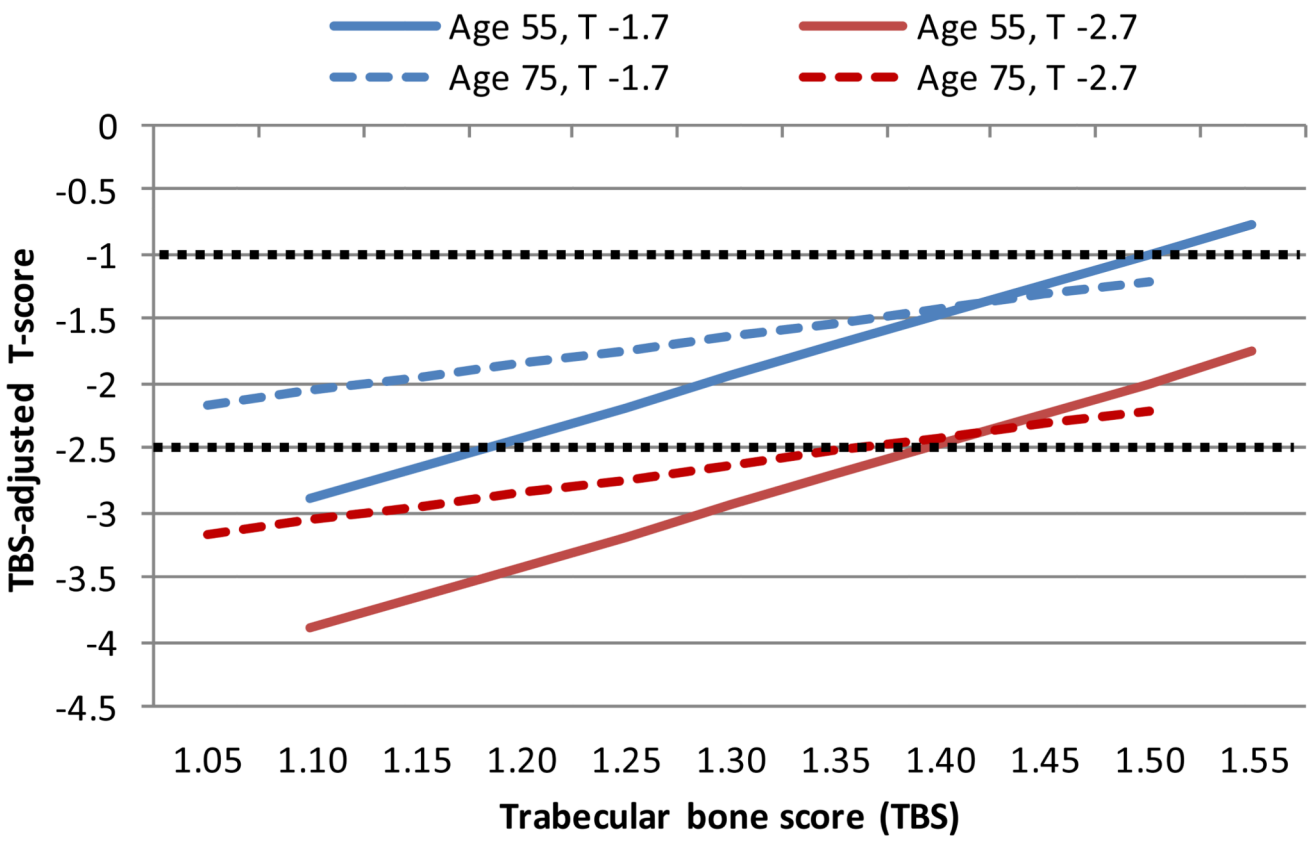

Figure 2.

Effect of applying the TBS adjustment to femoral neck T-score in four hypothetical women. Results are plotted for the age-specific 95% range in TBS measurements.

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Table 1

Baseline characteristics of the study population.

Characteristic	*N* = 45,185
Age (years)	63.5 ± 10.8
BMI (kg/m^2)	26.1 ± 4.4
Femur Neck BMD T-score (SD)	-1.4 ± 1.0
Total Hip BMD T-score (SD)	-1.0 ± 1.2
Lumbar Spine BMD T-score (SD)	-1.3 ± 1.5
Lumbar Spine TBS (SD)	1.317 ± 0.121
FRAX 10-year MOF probability with BMD (%)	7.9 (5.2-12.9)
FRAX 10-year hip fracture probability with BMD (%)	0.9 (0.3-2.7)
Prolonged glucocorticoid use	1,834 (4.1)
Chronic obstructive lung disease (smoking proxy)	3,501 (7.7)
Previous osteoporotic fracture	6,338 (14.0)
Parental hip fracture	2,756 (6.1)
Rheumatoid arthritis	1,433 (3.2)
High alcohol use	1,208 (2.7)

BMI body mass index; BMD bone mineral density; TBS trabecular bone score; MOF major osteoporotic fracture. Data expressed as mean ± SD, *N* (%) or median (interquartile range).

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Table 2

Hazard ratios (HR) for incident major osteoporotic fracture with 95% confidence intervals (CI) per standard deviation reduction. All models are adjusted for age and body mass index (BMI).

Region	Model	Parameter	Beta	TBS risk = 1 SD BMD	HR (95% CI)
Femoral Neck	Model 1	BMD T-score	-0.555		1.70 (1.63-1.77)
	Model 2	BMD T-score	-0.487		1.59 (1.53-1.66)
		TBS[a]	-2.011	0.276	1.25 (1.21-1.30)
		Age*TBS[a]	0.073	-7.633	0.92 (0.89-0.95)
Total Hip	Model 1	BMD T-score	-0.508		1.82 (1.75-1.90)
	Model 2	BMD T-score	-0.457		1.72 (1.65-1.79)
		TBS[a]	-1.756	0.289	1.22 (1.18-1.26)
		Age*TBS[a]	0.074	-6.885	0.92 (0.89-0.94)
Lumbar Spine	Model 1	BMD T-score	-0.258		1.47 (1.41-1.52)
	Model 2	BMD T-score	-0.203		1.35 (1.30-1.41)
		TBS[a]	-2.055	0.126	1.26 (1.22-1.31)
		Age*TBS[a]	0.079	-3.263	0.91 (0.88-0.94)

BMD bone mineral density; TBS trabecular bone score.

[a]TBS mean-centered and age- normalized; Age mean-centered.

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Table 3

Hazard ratios (HR) for incident fracture with 95% confidence intervals (CI) per standard deviation reduction. All models are adjusted for FRAX clinical risk factors.

	Major osteoporotic fracture			Hip fracture			Any fracture		
Region	**HR (95% CI)**	**Wald Chi^2**	**Model LR**	**HR (95% CI)**	**Wald Chi^2**	**Model LR**	**HR (95% CI)**	**Wald Chi^2**	**Model LR**
Femoral Neck (FN)									
Unadjusted FN BMD T-score	1.61 (1.68-1.55)	514.0	2244.0	1.98 (2.16-1.82)	247.2	1767.0	1.56 (1.61-1.50)	582.8	2412.2
TBS-adjusted FN BMD T-score	1.66 (1.73-1.60)	641.4	2361.3	2.10 (2.29-1.93)	292.2	1808.0	1.60 (1.66-1.55)	730.2	2548.8
Total Hip (TH)									
Unadjusted TH BMD T-score	1.72 (1.79-1.65)	679.6	2398.6	2.12 (2.30-1.95)	326.9	1835.9	1.67 (1.73-1.61)	779.6	2599.1
TBS-adjusted TH BMD T-score	1.76 (1.83-1.69)	781.5	2491.2	2.22 (2.41-2.05)	361.6	1869.1	1.70 (1.76-1.64)	897.8	2706.8
Lumbar Spine (LS)									
Unadjusted LS BMD T-score	1.41 (1.46-1.36)	318.5	2034.2	1.17 (1.25-1.09)	17.7	1519.3	1.37 (1.42-1.33)	350.9	2164.5
TBS-adjusted LS BMD T-score	1.48 (1.53-1.42)	437.7	2144.9	1.33 (1.44-1.23)	53.0	1555.2	1.43 (1.48-1.39)	489.9	2294.5

LR likelihood ratio; BMD bone mineral density; TBS trabecular bone score.