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Premenopausal and Early Postmenopausal Trabecular Bone Score (TBS) and Fracture Risk: Study of Women's Health Across the Nation (SWAN)

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Abstract

Background.—Evidence that trabecular bone score (TBS), an index of bone microstructure, is a risk factor for future fracture comes mainly from studies of late postmenopausal women.

Objective.—To discern whether premenopausal TBS or early postmenopausal TBS predict fracture.

Design.—A 22-year, prospective analysis from the Study of Women's Health Across Nation.

Setting.—Community-based cohort.

Participants.—272 Black, 174 Japanese, and 364 White women

Main Outcome Measures.—Incident fractures: 292 in premenopausal sample and 141 in early postmenopausal sample.

Results.—Separate Cox proportional hazard regressions modeled time to incident fracture as a function of TBS measured during premenopause or early postmenopause. Models were initially adjusted for age, race/ethnicity, SWAN clinical site, body mass index, use of calcium, vitamin D, bone beneficial or bone adverse medication. Next, we added lumbar spine (LS) or femoral neck (FN) bone mineral density (BMD) and, finally, history of prior fracture, to the models. For each standard deviation decrement in premenopausal TBS, fracture hazard was elevated by 17% (relative hazard [RH] 1.17 [95% CI, 1.02-1.35]); after adjusting for LS or FNBMD, the relation between premenopausal TBS and fracture was no longer statistically significant. There was a similar-magnitude, marginally statistically significant, association between early postmenopausal TBS and fracture, unadjusted for BMD (RH 1.15 [0.95- 1.39]).

Conclusions.—Variation in premenopausal TBS is related to fracture risk, but this association is not independent of BMD.

Keywords

menopause; trabecular bone score; epidemiology; cohort; longitudinal

1. INTRODUCTION

Trabecular bone score (TBS) is a recently developed index of bone microstructure, which is estimated from lumbar spine (LS) bone mineral density (BMD) scans. Although TBS is not equivalent to trabecular microarchitecture, it quantifies grey-scale variation in the LS scan, capturing a domain of bone strength that is distinct from areal BMD. In several longitudinal cohorts of postmenopausal women, lower TBS was related to greater fracture risk, independent of BMD [1, 2, 3, 4, 5, 6]. Whether TBS, assessed when women are younger and

premenopausal (and at, or close to, peak bone mass), predicts fracture remains unexplored. Additionally, evidence for fracture risk stratification by TBS in postmenopause predominantly comes from studies of late postmenopausal women, with average ages in the mid 60's to mid 70's at the time of TBS assessment [1, 2, 3, 4, 5, 6]. The potential contribution of TBS in early postmenopause to fracture prognostication in younger, early postmenopausal women is an open question. It is likely that deterioration of bone structure (the construct captured by TBS) is more advanced when women are one or two decades post-menopause. In contrast, in the early postmenopause, bone structure may not have declined sufficiently to contain fracture prognostic information independent of that contained in BMD.

We used longitudinal data from the Study of Women's Health Trabecular Bone Study (SWAN TBS) to address the following primary questions. Does TBS, assessed during premenopause, predict incident fracture, and if so, is the risk conferred by TBS independent of BMD? Does TBS, measured during early postmenopause, predict fracture, and, if so, is this risk independent of BMD?

2. MATERIALS AND METHODS

2.1 Study Sample

The Study of Women's Health Across the Nation (SWAN) is 7-site, US-based, cohort study of the menopause transition (MT) and mid-life, previously described [7]. Five SWAN sites conducted BMD studies. Because TBS can only be measured using BMD scans acquired on a 4500A (or newer) instrument, women from the 3 sites that used appropriate machines at SWAN's inception make up the SWAN TBS cohort (N=1436). The current analysis sample required that, at SWAN TBS baseline, women were premenopausal (defined as no change in menstrual cycle predictability compared to their usual) or early perimenopausal (defined as less predictable cycles than their usual, but no overt gaps in cycles). To be in the analysis, the participant must have had at least one subsequent visit to permit outcome observation. Exclusions were use of any bone beneficial medication (systemic hormone therapy, bisphosphonates, raloxifene, calcitonin, parathyroid hormone, or calcitriol) at the initial TBS visit, resulting in an analysis sample size of 1362 [Figure 1]. No participants were taking bone active medicines, other than HT, at the time of their first premenopausal or first early perimenopausal TBS assessment. For the remainder of this manuscript, we refer to the pre- and early perimenopausal group as the premenopausal sample (**sample 1**); they represented 95% of the entire SWAN TBS sample.

To address the question or whether TBS measured in early postmenopause was related to fracture prediction, we constructed a subset of sample 1, consisting of women who had TBS assessed at their first study visit after becoming postmenopausal and attended at least one subsequent visit (**sample 2**, Figure 2). We applied the same exclusions as those used to generate the premenopausal sample, yielding an early postmenopausal sample size of 891.

Sites obtained institutional review board approval and participants gave written, informed consent.

2.2 Outcome

The primary outcomes were: 1) time to first fracture that occurred after TBS baseline measurement, when women were premenopausal (sample 1) and 2) time to first fracture that occurred after the first early postmenopausal TBS measurement (sample 2). Standardized questionnaires inquired about number of fractures, bone site, and degree of trauma. Fractures were classified as minimal-trauma if they did not occur due to fall from a height > 6 inches, a motor vehicle accident, moving fast (e.g., skating), playing sports, or from impact with heavy or fast-moving projectiles. SWAN began recording fracture dates and conducting medical record confirmation at follow-up visit 7. Prior to this, we imputed fracture date using the midpoint between the fracture-report visit and the prior visit; the imputation window was relatively small, as time between follow-up visits averaged ~18 months. In sample 1, 103 (35.3%) fractures were recorded prior to V7; in sample 2, 9 (6.4%) fractures were recorded prior to visit 7. We succeeded in obtaining medical records for 75% of self-reported fractures; the false positive rate was 1.9%. We did not count fractures of the face, skull, fingers, and toes as study outcomes. Analyses include traumatic and minimal trauma fractures, because risk of both types increases with lower BMD, rates of subsequent low trauma fractures are increased similarly in individuals with prior low or high trauma fracture, and osteoporosis pharmacotherapy results in a similar (~25%) reduction in risk for incident fractures considered low trauma or high trauma [8,9,10]. Fracture follow-up extended through SWAN follow-up visit 16, which concluded in 2017.

2.3 Primary Predictor

We assessed TBS using retrieved LS BMD scans from SWAN baseline through follow-up visit 13. Acquisition, quality control, and cross-calibration protocols for SWAN BMD and TBS measures are published [11, 12,]. Despite BMI correction, TBS acquired using Hologic densitometers demonstrate a negative correlation between TBS and BMI [12, 13]. We therefore computed TBS with a *beta* version of tissue thickness corrected TBS (TBSTH), which corrects for DXA-measured soft tissue thickness rather than for BMI (shortened to TBS in the remainder of this report) [12, 14]. Although others report no correlation between Hologic-acquired TBS TH and BMI, we found a 3-segment, cross-sectional association between TBS TH and BMI: positive until a BMI of ~24 kg/m², no relation when BMI was between 24 and 31 kg/m², and negative when BMI was greater than 31 [12, 14]. Data analyses, therefore, use 3-segment linear spline to model the association of BMI with TBS (see section 2.5).

2.4 Covariates

Standardized interviews ascertained age (years), self-defined race/ethnicity (Black, Japanese, White), menstrual bleeding patterns, calcium supplement (yes/no), vitamin D supplement (yes/no), medication use, history of an adult fracture prior to SWAN baseline, and occurrence of fractures during SWAN. SWAN defined premenopause as no change in predictability of menses. Decreased predictability, but reporting no gaps of 3 months, defined early perimenopause. No menses for 3-11 months characterized late perimenopause. Absent menses for 12 months marked natural postmenopause; surgical postmenopause occurred at the time of bilateral oophorectomy with or without hysterectomy. We censored

data from women who underwent hysterectomy without bilateral oophorectomy prior to their final menstrual period, because MT stage becomes undefinable. Indicator variables captured use of bone beneficial drugs (systemic hormone therapy, bisphosphonates, raloxifene, calcitonin, parathyroid hormone, or calcitriol) and bone adverse drugs (corticosteroids, GnRH agonists, aromatase inhibitors, chemotherapy, or anti-seizure medications), collected at each study visit. We measured weight (kilograms) and height (meters) at each visit, using calibrated scales and stadiometers and calculated BMI [weight in kg/(height in m)²]. Age, MT stage (premenopausal sample only), weight, height and BMI values were those measured at the visit corresponding to the primary TBS predictor (i.e., the first TBS visit for sample 1 and the early postmenopausal visit for sample 2).

2.5 Statistical analysis

Characteristics of the SWAN bone cohort, TBS cohort and each of the analysis samples were summarized as means (SD) for continuous variables and number (%) for categorical variables. Correlations between TBS and BMD were estimated using Pearson product moment and Spearman rank order correlation coefficients. We performed separate Cox proportional hazard regressions to model time to first fracture as a function of TBS or BMD (LS or FN) measured during pre- or early perimenopause (referred to as “premenopausal TBS or BMD”) or in early postmenopause (“early postmenopausal TBS or BMD”). To evaluate the fracture prediction capacity of TBS, independent of premenopausal BMD (LS or FN), we constructed staged models with the following primary predictors: 1) premenopausal TBS; 2) premenopausal BMD (LS or FN); 3) premenopausal TBS plus contemporaneous LS BMD; 3) premenopausal TBS plus contemporaneous FN BMD. Finally, we added history of an adult fracture prior to SWAN to the models containing TBS and BMD. To quantify incident fracture prediction capability of TBS independent of early postmenopausal BMD, we ran the same set of models, using postmenopausal TBS and contemporaneous LS or FN BMD values (sample 2). For the early postmenopausal analysis, final models included adult fracture prior to SWAN as well as fractures that occurred between SWAN TBS baseline and the first visit early postmenopausal visit. All models were adjusted for age, race/ethnicity, SWAN-TBS clinical site, BMI as a 3-segment linear spline (< 24, 24 to 31, >31), prior fracture history, and percent of visits at which use of calcium, vitamin D, bone beneficial or bone adverse medication were used. Additionally, we adjusted premenopausal TBS models for MT stage (pre- or early perimenopausal). We present the hazard ratio for fracture per standard deviation decrement in TBS or BMD. Analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA).

3 RESULTS

On average, women in the premenopausal analysis sample were aged 46.4 years at study baseline and those in the early postmenopausal sample were 54.1 years of age at that sample's baseline, which was the first visit at which the participant was postmenopausal [Table 1]. Racial/ethnic composition of the pre- and postmenopausal samples were alike, approximately 20% Japanese, 34% Black and the remainder White. Average LS BMD at the time of the premenopausal assessment was 1.080 g/cm² (standard deviation [SD], 0.141) and at the early postmenopausal measurement 1.023 g/cm² (SD, 0.157). Mean FN BMD was

0.857 (SD, 0.141) in premenopause and 0.811 (SD, 0.137) in early postmenopause. TBS averaged 1.440 (SD, 0.090) in premenopause and 1.411 (SD, 0.085) in early postmenopause. Dispersion of LS BMD values (SD/mean) was 13% and 15% at the pre- and early postmenopausal measures, respectively. TBS dispersion was 6% at each of these measurement times. Other relevant characteristics of each analysis sample, along with those of the parent SWAN BMD sample, are also summarized in Table 1

The Pearson correlation between TBS and LS BMD was 0.29 in the premenopausal analysis sample and 0.53 in the early postmenopausal sample [Table 2]. In the premenopausal sample, TBS was not correlated with FN BMD, but TBS was correlated with FN BMD at 0.30 in the early postmenopausal sample. The magnitudes of race/ethnicity-specific correlations between TBS and BMD were similar to those of the overall samples, with the exception of the Japanese women, in whom TBS and BMD were more highly correlated [Table 2]. Results of Spearman correlations were similar to those of Pearson correlations (data not shown).

In the premenopausal sample, median follow-up time to first fracture (or end of observation period, if no fracture) was 15.3 years, ranging from 0.3 to 21.8 years. The total number of person-years (PY) under observation for the premenopausal sample was 20899. In total, 292 incident fractures occurred after study baseline. Of these, 111 (38.0%) were minimal trauma fractures. The most commonly occurring fractures were foot (23%), ankle (16%), wrist (15%), arm (11%), and leg (9%). The remaining 26% of fractures were constituted by ribs, patella, hand, spine, shoulder, hip, pelvis, coccyx, and sternum, in descending order of frequency. Median follow-up time in the postmenopausal sample was 10.1 years (range 0.2 to 20.0 years). Total PY under observation for the early postmenopausal sample was 8999.8. After the first postmenopausal visit (analysis baseline for the early postmenopausal sample), there were 141 incident fractures, of which 60 (42.6%) were minimal trauma. In the sample whose follow up started at the first postmenopausal visit, the proportion of fractures at each skeletal site were paralleled those of the premenopausal sample.

Adjusted for age, race/ethnicity, BMI, and use of bone active medications, calcium or vitamin D supplements over time, premenopausal TBS was statistically significantly associated with incident fracture [Table 3]. For each standard deviation decrement in premenopausal TBS, fracture hazard was elevated by 17%. Multiply adjusted, premenopausal LS and FN BMD levels were significantly related to incident fracture, with relative hazards of 1.36 and 1.50 per SD decrement, at each respective site. When TBS was additionally adjusted for LS or FN BMD, the relation between premenopausal TBS and fracture was no longer statistically significant, with point estimates approaching or at unity. Adjustment for fracture prior to SWAN did not alter the results. To assess whether the relation between premenopausal TBS and fracture depended on the level of either LS or FN BMD, we tested interaction terms between TBS and BMD, but there was no evidence for effect modification ($p>0.4$ for LS interaction and $p>0.6$ for FN interaction, data not shown).

Early postmenopausal TBS, adjusted for age, race/ethnicity, BMI, use of bone active medications, and calcium or vitamin D supplements, was not statistically significantly associated with incident fracture risk, although the estimated effect size, a 15% reduction in

risk per SD decrement, was similar to that for premenopausal TBS [Table 3]. In multiply adjusted models, incident fracture hazard increased by 25% for each SD decrement in early postmenopausal LS BMD, with marginal statistical significance. Each SD decrement in multiply adjusted, early postmenopausal FN BMD was statistically significantly associated with incident fracture hazard (RH 1.58 [1.22, 2.14]). Further adjustment of postmenopausal TBS for LS or FN BMD reduced the estimated TBS effect size to approximately one; additional adjustment for fracture that occurred prior the first postmenopausal visit had not effect on the results. The relation between early postmenopausal TBS and fracture was not modified by either LS or FN BMD level (p- value for each interaction >0.8, data not shown).

4 DISCUSSION

This study investigated the capacity of TBS, measured in either premenopause or early postmenopause, to predict fracture. In multiply adjusted models that did not include BMD, for each SD decrement in premenopausally acquired TBS, there was a 17% greater hazard of incident fracture. However, with the addition of either LS or FN BMD to the multivariable models, premenopausal TBS was no longer a statistically significant predictor of fracture. The first postmenopausal measurement of TBS was not statistically significantly related to fracture risk, either before or after BMD adjustment, although the magnitude of risk associated with TBS was similar to that observed for the premenopausal sample. In this study, the association between TBS and fracture did not depend upon BMD level, evidenced by non-significant tests of interaction between TBS and BMD.

Our premenopausal TBS assessment provides insight into the role of peak TBS in fracture prediction. SWAN's premenopausal TBS is a credible approximation of peak TBS for two reasons. First, while there are differences in absolute values of TBS among studies owing to hardware and software variations, the average thickness-adjusted TBS value in the SWAN premenopausal sample is 1.44, towards the high end of the range, and similar to mean TBS levels in a population based sample the 20-40 year-olds in the Japanese Population-based Osteoporosis Study (JPOS) [3]. Second, until 1.5 years prior to the final menstrual period, when women are, on average, in their mid to late 40's, SWAN TBS values are stable: the annual rate of change is 0.12% (not distinguishable from zero) [12]. JPOS reported similar stability of young to midlife TBS values: the rate of change in TBS among women aged 20-40 years was 0.13% [3].

Although it is widely held that peak bone strength (principally operationalized as BMD) is a determinant of fracture risk, until recently, this assumption relied on linking individual findings: 1) the amount and quality of the skeleton is a function of multiple endogenous and exogenous influences from conception to young adulthood; 2) in older adult life, bone loss predominates; 3) bone mass dispersion does not widen with increasing age; and 4) bone mass tracks through life (a person's relative position in the bone disturbing remains the same over time) [15]. Formal testing of this deduction was accomplished in SWAN, in which premenopausal BMD measures and sufficient follow up were available [16, 17]. Ishii and colleagues reported that for each SD decrement in premenopausal FN BMD (an estimate of peak by the same reasoning as outlined above for TBS), the risk of fracture increased by 60% [11, 17]. Cauley *et.al.* found a similar gradient of fracture risk in relation to peak LS

BMD, a 50% increase per SD decrement [16]. The present study has a smaller analysis sample and somewhat different design compared to those of Ishii and Cauley, which precludes direct comparison. Nonetheless, it agrees with the prior results, finding a 36% increase in risk and a 50% increase in fracture risk for each SD decrement of premenopausally measured LS or FN BMD, respectively.

Bone strength is a function of several elements besides BMD, including macro- and microarchitecture and material properties [15, 18]. Thus, obtaining a premenopausal (approximate peak) TBS allowed us to test whether the structural characteristics captured by this measure predicted fracture apart from the information provided by peak BMD. We did observe a modest risk increase of 17% per SD decrement, which suggests that even at high TBS values there is sufficient grey-scale variation to stratify risk. However, among SWAN's premenopausal women, when both TBS and BMD are at peak or near peak, the structural information in TBS did not contribute additional information to risk estimation beyond that contained in areal BMD.

Plausibly, the contribution of TBS to fracture prediction could become stronger when the structural characteristics captured by TBS start to deteriorate, as in early menopause; thus, we investigated whether early postmenopausal TBS was related to fracture [12]. Although the magnitude of the relation between fracture and early postmenopausal TBS, a 15% increase per SD decrement, was similar to that observed for premenopausal TBS, the early postmenopausal TBS association with fracture was not statistically significant. Also like the premenopausal TBS findings, adjustment of early postmenopausal TBS for BMD brought the effect estimate down to one. While this correspondence in the pattern of pre- and postmenopausal results suggests that the associations are similar, the latter results are constrained by the substantially smaller early postmenopausal sample size, shorter follow up period, and fewer fracture outcomes. In the premenopausal sample, with 292 fractures, we had 80% power to detect a fully adjusted (all covariates, including FN BMD) fracture hazard of 1.25 or greater per SD decrement in TBS. In the early postmenopausal sample, 141 fractures provided 80% power to detect a fully adjusted fracture hazard of 1.28 or greater per SD decrement in TBS.

The central focus of this analysis is whether TBS adds fracture prediction information independent of that already provided by either pre- or early postmenopausal BMD. Because both TBS and BMD are derived from DXA scans, it is appropriate to consider their correspondence, especially at the LS. If the BMD and TBS shared variance were too high, then one could not test their independence in a multivariable model. In our overall premenopausal sample, the correlation between TBS and LS BMD of 0.29 yields a shared variance of 0.08%; in premenopause, TBS and FN BMD were uncorrelated. Although the TBS-LS and TBS-FN correlations were greater in early postmenopause, they only result in shared variances of 27% and 9% respectively. The TBS-BMD correlations reported by other studies that found a BMD-independent association between TBS and fracture in older postmenopausal women (using Hologic instruments) are of similar magnitude to those in our overall early postmenopausal sample, ranging between ~0.5 at the LS and ~0.3 at the FN [1, 5]. A slightly higher magnitude correlation of ~0.6 between TBS and LS BMD in Japanese postmenopausal women has been described [3].

Strengths of this study include its well-characterized, community-based cohort sample and long duration of follow-up. We also used thickness-adjusted TBS (which limits, but does not eliminate, confounding by BMI) and gave scrupulous attention to the analytic treatment of BMI, to further mitigate against depression of TBS values by obesity [12]. Because SWAN participants are middle-aged, fractures are mainly appendicular; this may be construed as a limitation of conducting fracture research in middle aged women. However, appendicular fractures are associated with an increased risk of hip fractures in later life [19]. Additional evidence for the importance of prior, mainly appendicular, fracture comes from recent work by Leslie and colleagues, who found that history of prior high or low trauma fracture at younger ages was a statistically significant predictor of later life major osteoporotic fractures (hip, clinical spinal, forearm, or humerus) [10]. Thus, early and midlife fractures, which may seem minor when they occur, are harbingers of later life fractures. Finally, a substantial limitation of this analysis is the early postmenopausal sample size of 891 women, in whom there were 141 fracture events, which limits our ability to detect associations in this group.

In summary, the SWAN TBS study finds that variation in premenopausal TBS, a plausible estimate of peak TBS, is related to fracture risk, but this association is not independent of BMD. Based on these results, we conclude that BMD predicts fracture in the premenopausal sample and that TBS does not add additional information you know the BMD value. The same inference may apply to early postmenopausal women (i.e., that TBS does not add independent fracture prediction information beyond that contained in BMD), however, our power to detect associations in early postmenopause is insufficient to warrant a conclusion.

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Figure 1. Derivation of the Premenopausal Trabecular Bone Score Analysis Sample

Derivation of the **Premenopausal TBS Analysis Sample**, consisting of premenopausal (no change in menstrual cycles) and early perimenopausal (no menstrual cycle gaps of 3 months) women from the SWAN TBS study.

Figure 2. Derivation of the Early Postmenopausal TBS Study Sample

Derivation of the **Early Postmenopausal TBS Sample**, which begins its observation period at the first postmenopausal trabecular bone score measurement.

Table 1.

Characteristics of participants in the Study of Women's Health Across the Nation (SWAN) Bone Cohort and the SWAN Trabecular Bone Score Study (SWAN TBS) Analytic Samples

Participant Characteristics ^a	SWAN Bone Cohort ^b (N=2344-2352)	Premenopausal TBS Analytic Sample ^c (N=1361-1362)	Early Postmenopausal TBS Analytic Sample ^d (N=858-891)
SWAN Clinical Site			
Boston, MA	435 (18)	401 (29)	275 (31)
Detroit, MI	530 (23)	495 (36)	321 (36)
Los Angeles, CA	476 (20)	466 (34)	295 (33)
Davis, CA	455 (19)	NA	NA
Pittsburgh, PA	456 (19)	NA	NA
Race/Ethnicity			
Black	659 (28)	466 (34)	303 (34)
Japanese	270 (11)	264 (19)	183 (21)
White	1173 (50)	632 (46)	405 (45)
Chinese	250 (11)	NA	NA
Age (years)	46.4 (2.7)	46.4 (2.7)	54.1 (3.0)
Menopause Transition Stage			
Premenopausal	1274 (54)	728 (53)	NA
Early Perimenopausal	1064 (46)	634 (47)	NA
Postmenopausal	N/A	N/A	891 (100)
Body Mass Index (kg/m ²)	27.5 (6.9)	28.2 (7.3)	29.3 (7.3)
Lumbar Spine BMD(g/cm ²)	1.077 (0.140)	1.080 (0.141)	1.023 (0.157)
Femoral Neck BMD (g/cm ²)	0.846 (0.135)	0.857 (0.141)	0.811 (0.137)
Lumbar Spine TBS	NA	1.440 (0.090)	1.411 (0.085)
Percent Visits Reporting Use ^e			
Calcium Supplements		53.7 (32.8)	55.4 (36.8)
Vitamin D Supplements		47.3 (31.6)	55.8 (36.1)
Bone Detrimental Medications		7.2 (16.0)	8.7 (20.1)
Bone Beneficial Medications		13.3 (20.2)	6.3 (14.4)

^aValues in table are means (standard deviation) for continuous variables and numbers (percentages) for categorical variables. Sample sizes shown vary slightly due to missing data for some variables.

^bWomen were recruited into the SWAN bone cohort at 5 SWAN sites. Most women joined the SWAN bone cohort at SWAN baseline, but women could enroll in the bone study through the third SWAN follow-up visit.

^cSWAN TBS was conducted using data from the Boston, Detroit and Los Angeles SWAN sites because, from the outset of SWAN, these centers used Hologic 4500 (or later model) instruments, which are required to ascertain TBS. The premenopausal analytic sample was limited to participants from the SWAN TBS cohort who were premenopausal or early perimenopausal at the time of first TBS measurement (referred to as the premenopausal sample). For detailed exclusion criteria, see Methods and Figure 1.

^dThe early postmenopausal analytic sample was a subset of the premenopausal sample. To create this sample, we used data from women who had a TBS assessment at their first study visit after becoming postmenopausal and who attended at least one subsequent visit (see Methods and Figure 2).

^eSupplements and medications ascertained at each study visit by standardized questionnaires. The percent of visits at which calcium supplements (yes/no), vitamin D supplements (yes/no), bone detrimental (any, yes/no) or bone beneficial medications (any, yes/no) were computed. Bone

beneficial drugs included hormone therapy, bisphosphonates, raloxifene, calcitonin, parathyroid hormone, or calcitriol. Corticosteroids, GnRH agonists, aromatase inhibitors, chemotherapy, or anti-seizure medications were coded as bone detrimental drugs.

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Table 2.

Pearson Correlations Between Trabecular Bone Score (TBS) and Lumbar Spine or Femoral Neck Bone Mineral Density in Premenopausal or Early Postmenopausal Analysis Samples, Study of Women's Health

Across the Nation TBS Study^{a, b}

	Premenopausal Sample		Early Postmenopausal Sample	
	Lumbar Spine	Femoral Neck	Lumbar Spine	Femoral Neck
Overall	0.29 (p<0.0001)	0.02 (p=0.41)	0.53 (p<0.0001)	0.30 (p<0.0001)
Racial/Ethnic Sub-Groups				
Black	0.34 (p<0.0001)	0.09 (p=0.04)	0.53 (p<0.0001)	0.27 (p<0.0001)
White	0.37 (p<0.0001)	0.18 (p<0.0001)	0.55 (p<0.0001)	0.45 (p<0.0001)
Japanese	0.74 (p<0.0001)	0.49 (p<0.0001)	0.73 (p<0.0001)	0.53 (p<0.0001)

^aPremenopausal analysis sample includes women who were premenopausal, defined as no change in predictability of menses, or early perimenopausal, defined as decreased cycle predictability, but no menstrual gaps of 3 months at the time of their first TBS measurement.

^bThe early postmenopausal sample is a subset of the premenopausal sample. It consists of women who had TBS assessed at their first study visit after becoming postmenopausal and attended at least one subsequent visit.

Table 3.

Hazard of Incident Fracture per Standard Deviation Decrement in Premenopausal or Early Postmenopausal Trabecular Bone Score (TBS), Lumbar Spine (LS) BMD, and Femoral Neck (FN) BMD, Before and After Mutual Adjustment, Study of Women's Health Across the Nation TBS Study^{a, b}

Menopause Transition Stage	Predictor	Model with TBS Only ^c	Model with LS BMD Only ^c	Model with FN BMD Only ^c	Model with TBS and LS BMD ^c	Model with TBS and FN BMD ^c	Model with TBS, LS BMD and Prior Fracture ^c	Model with TBS, FN BMD and Prior Fracture ^c
Premenopausal	TBS	1.17 (1.02, 1.35)	-	-	0.95 (0.79, 1.14)	1.02 (0.87, 1.19)	0.94 (0.79, 1.12)	1.00 (0.86, 1.17)
	LS BMD	-	1.36 (1.19, 1.57)	-	1.41 (1.18, 1.67)	-	1.39 (1.16, 1.65)	-
	FN BMD	-	-	1.50 (1.27, 1.78)	-	1.49 (1.24, 1.79)	-	1.48 (1.23, 1.78)
Early Postmenopausal	TBS	1.15 (0.95, 1.39)	-	-	1.03 (0.79, 1.33)	0.96 (0.77, 1.21)	0.99 (0.76, 1.30)	0.94 (0.74, 1.18)
	LS BMD	-	1.25 (0.99, 1.57)	-	1.22 (0.89, 1.66)	-	1.21 (0.88, 1.65)	-
	FN BMD	-	-	1.58 (1.20, 2.08)	-	1.63 (1.18, 2.24)	-	1.55 (1.13, 2.12)

^aPremenopausal analysis sample includes women who were premenopausal, defined as no change in predictability of menses, or early perimenopausal, defined as decreased cycle predictability, but no menstrual gaps of 3 months at the time of their first TBS measurement.

^bThe early postmenopausal sample is a subset of the premenopausal sample. It consists of women who had TBS assessed at their first study visit after becoming postmenopausal and attended at least one subsequent visit.

^cAll models were adjusted for age, menopause transition stage (premenopausal sample only [pre or early perimenopausal]), race/ethnicity, SWAN-TBS clinical site, BMI linear spline (< 24, 24 to 31, >31), and percent of visits at which use of calcium, vitamin D, bone beneficial or bone adverse medications were reported (see methods for list of bone medications). Age, MT stage (premenopausal sample only), weight, height and BMI values were those measured at the visit corresponding to the primary TBS (and/or BMD) predictor.