RESEARCH ARTICLE

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Increased Bone Material Strength Index Is Positively Associated With the Risk of Incident Osteoporotic Fractures in Older Swedish Women

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ABSTRACT

No previous studies have investigated the association between the bone material strength index (BMSi; an indicator of bone material properties obtained by microindentation) and the risk of incident fracture. The primary purpose of this prospective cohort study was to evaluate if BMSi is associated with incident osteoporotic fracture in older women and, secondarily, with prevalent fractures, anthropometric traits, or measurements of bone mineral density (BMD) by dual-energy X-ray absorptiometry (DXA). In a population-based cohort, 647 women aged 75 to 80 years underwent bone microindentation using the OsteoProbe device. Data on clinical risk factors (CRFs), prevalent fractures, and incident fractures were collected using questionnaires, medical records, and a regional X-ray archive. BMD and vertebral fracture assessment (VFA) were assessed by DXA (Hologic, Discovery A). Associations between BMSi, anthropometrics, BMD, and prevalent fractures were investigated using correlation and linear and logistic regression. Cox proportional hazards and competing risks analysis by Fine and Gray were used to study the association between BMSi and the risk of fracture and mortality. BMSi was weakly associated with age ($r = -0.13$, $p < 0.001$) and BMI ($r = -0.21$, $p < 0.001$) and with BMD of lumbar spine ($\beta = 0.09$, $p = 0.02$) and total hip ($\beta = 0.08$, $p = 0.05$), but only after adjustments. No significant associations were found between BMSi and prevalent fractures (self-reported and/or VFA identified, $n = 332$). During a median follow-up time of 6.0 years, 121 major osteoporotic fractures (MOF), 151 any fractures, and 50 deaths occurred. Increasing BMSi (per SD) was associated with increased risk of MOF (hazard ratio [HR] = 1.29, 95% confidence interval [CI] 1.07–1.56), any fracture (HR = 1.29, 95% CI 1.09–1.53), and mortality (HR = 1.44, 95% CI 1.07–1.93). The risk of fracture did not materially change with adjustment for confounders, CRFs, femoral neck BMD, or when considering the competing risk of death. In conclusion, unexpectedly increasing BMSi was associated with greater fracture risk. The clinical relevance and potential mechanisms of this finding require further study. © 2023 The Authors. *Journal of Bone and Mineral Research* published by Wiley Periodicals LLC on behalf of American Society for Bone and Mineral Research (ASBMR).

KEY WORDS: OSTEOPOROSIS; BONE MICROINDENTATION; DXA; FRACTURE RISK ASSESSMENT

Introduction

Fragility fractures are an important cause of morbidity, mortality, and disability, resulting in personal suffering for those affected and increasing costs for society.[1] It is estimated that in western societies, at the age of 50 years, one in three women and one in five men in their remaining lifetime will sustain an osteoporotic fracture.[2] After sustaining a hip fracture, only 80% survive the first year and as few as 30% regain their normal level of activity.[3] The absolute number of fractures is projected

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to increase, and to address this growing public health problem, a multifaceted approach is needed, including improvements in primary prevention, fracture risk assessment, diagnosis, secondary prevention, and rehabilitation.[2] The current gold standard for diagnosing osteoporosis is based on the assessment of bone mineral density (BMD) by dual-energy X-ray absorptiometry (DXA).[4] This method is widely used in clinical practice to predict, monitor, and aid treatment decisions, and it is well documented that increased fracture incidence is highly associated with low BMD.[5,6] However, the majority of fragility fractures occur in individuals who do not have osteoporosis as defined by a DXA-derived BMD *T*-score ≤ -2.5.[7,8] Furthermore, there are several well-established characteristics, commonly referred to as bone quality, that determine bone strength other than BMD.[9-11] In addition, there are numerous fracture risk factors partially independent of BMD, such as heredity for fracture, glucocorticoid therapy, bone turnover, falls, and previous fractures.[5,12] Fracture risk assessment algorithms such as FRAX that incorporate some of these risk factors are widely used and improve the ability to predict and prevent fractures.[13]

Impact microindentation (IMI) by the OsteoProbe device (ActiveLife, Santa Barbara, CA, USA) is a novel technique based on the reference-point indentation (RPI) principle and allows for in vivo analysis of bone in a clinical setting. The OsteoProbe device was developed to evaluate the material properties of bone in addition to the mineralized component already assessable by DXA.[14] A portable handheld microindenter with a replaceable probe is used to penetrate the outer tissues and challenge the cortical bone matrix with an impact force. The average indentation depth on cortical bone is compared to a reference material and the bone material strength index (BMSi) is calculated.[15] Previous studies investigating the association between BMSi and prevalent fracture have yielded discordant results.[16-18] Importantly, no studies are yet available investigating the association between BMSi and incident fractures. The primary purpose of this prospective cohort study was to evaluate if BMSi is associated with incident osteoporotic fracture in older women and, secondarily, with prevalent fractures, anthropometric traits, or measurements of BMD by DXA in a large cohort of older Swedish women.

Materials and Methods

Study subjects

The participants included in this study were originally part of the Sahlgrenska University Hospital Prospective Evaluation of Risk of Bone Fractures (SUPERB) study, a population-based cohort study performed in the greater Gothenburg area, Sweden, with the overall aim to determine predictors of fragility fractures. The cohort included a total of 3028 women aged 75 to 80 years, randomly recruited via the Swedish national population register from March 2013 to May 2016. Detailed characteristics of the cohort have previously been published.[19]

In total, 6832 women received a formal invitation to partake in the study, via letter and followed by telephone contact. Of those, 436 women (6.4%) met the study exclusion criteria, which were bilateral hip replacement, not being ambulant (aided or unaided), and lack of ability to communicate in Swedish. Another 3368 (52.6%) declined to participate, and as a result, 3028 women were included in the SUPERB study (inclusion rate 47.4%). The study protocol was approved by the Regional Ethical Review Board in Gothenburg, and all subjects signed an informed consent form before participation. All examinations took place at the Department of Geriatrics, Sahlgrenska University Hospital in Mölndal, Sweden. The participants completed validated questionnaires and underwent examinations of anthropometrics, physical function, and bone measurements using DXA.

Upon completion of the initial examinations, the participants were invited to undergo microindentation by the OsteoProbe device. The device was not available at the commencement of the SUPERB study; therefore, only the latter 1613 women were asked to participate in the present study with the first woman included in September 2014. The additional exclusion criteria for the present study were ongoing immunosuppression, local or systemic infection, local edema, or allergy to the local anesthetic. A total of 647 women accepted, signed a separate informed consent form, underwent bone microindentation, and were included in this study. The inclusion rate for the microindentation procedure was 40%.

Anthropometrics

Standardized equipment was used to measure body height and weight. Two height measurements were performed, and the mean values were used in the analyses. In cases of ≥5 mm difference between measured heights, an additional third measurement was obtained and the average of the two most similar measurements was used. Weight to the nearest 0.1 kg was measured by the same scale for the entire study population.

Questionnaires

A standardized questionnaire, completed by all participants, was used to assess information regarding medical history, medication, and FRAX clinical risk factors (CRFs). The FRAX CRFs included previous fracture, parental hip fracture, current smoking, oral glucocorticoid use, rheumatoid arthritis, secondary osteoporosis (diabetes mellitus type 1 or 2, hyperthyroidism, chronic liver disease, inflammatory bowel disease, or premature menopause), and excessive alcohol intake (3 or more units per day). The Physical Activity Scale for the Elderly (PASE) was used to estimate the physical activity level within the last week before the baseline visit.[20] A higher PASE score indicates a higher level of physical activity. The questionnaire was also used to assess dietary calcium intake.[21]

Physical function

Physical function was evaluated with the timed up-and-go (TUG) and 10-meter walking speed tests. The TUG test assesses mobility, balance, and functional ability.[22,23] The TUG test measures the time it takes to rise from a chair, walk 3 meters, turn around, walk back, and sit down. The 10-meter walking speed test measures the self-chosen walking speed. The average speed (m/s) across the middle 6 meters from two trials was used in the analysis.

DXA and vertebral fracture assessment (VFA)

DXA was used for the assessment of areal BMD (aBMD), body composition (total body lean mass and total body fat mass), and vertebral fracture assessment (VFA) as previously described.[19,24,25] The same device was used for all subjects (Hologic Discovery A; Hologic, Waltham, MA, USA). Areal BMD measurements were performed at the following sites: the

femoral neck, total hip, lumbar spine (L_1 to L_4), and the middle third of the nondominant radius. The coefficients of variation (CV) were 1.3% at the femoral neck, 0.8% at the total hip, 0.7% at the lumbar spine, and 3.1% at the radius. The CVs were obtained by two repeated measurements on 30 women, 75 to 80 years old, for the femoral neck, the total hip, and the lumbar spine and by three repeated measurements on one woman for the radius site, all with full repositioning. Identification of vertebral fractures was performed using lateral scans by DXA and graded using the semiquantitative classification of Genant.[26] One physician (LJ) evaluated all scans and graded the fractures as mild, moderate, or severe according to the height reduction of the vertebrae. The reproducibility was tested, and as previously reported, the intra-observer agreement was 98.9% (kappa score 0.72) for all fractures and 100% (kappa score 1.0) for moderate and severe vertebral fractures.[27]

Bone microindentation

The IMI procedure using the OsteoProbe device has previously been described for a subset of the current cohort;[17] the same procedure was applied to the entire cohort. After the application of local anesthesia, indentations were performed at the midshaft of the tibia defined as the midpoint of the distance between the distal apex of the patella and the medial malleolus. At least 11 indentations were performed in a circular manner and separated by a minimum of 2 mm. The first indentation was discarded because the probe was potentially not fully established on the cortical surface. All indentations were validated and those that deviated due to technical or methodical reasons were deleted. The mean of all valid indentations, at least 10 per participant, was used in the subsequent analyses. After the indentations, the OsteoProbe software graded the indentation stability as unstable, stable, or very stable based on the variation of the indentation results. Five different operators conducted the procedure. To ascertain all operators conducted the procedure consistently, at least two operators were present during the first 100 measurements. As previously described,[17] the intra-observer CV was 3.2% (same operator at a different site) and the inter-observer CV was 5.2% (different operators).

Incident fractures and mortality

The regional radiology archives for the Västra Götaland region were used to retrieve data on incident fractures. The archives were assessed from baseline (March 2013 to April 2016) to the end of July 2021. All radiology reports were reviewed and, in the case of a missing report, an experienced orthopedic surgeon was consulted to determine the existence of fracture. Incident fractures were categorized as a major osteoporotic fracture (MOF; hip, clinical spine, wrist, or humerus) or any type of fracture (any fracture). Data regarding mortality were obtained from the regional population registry (Västfolket).

Statistical analysis

Associations between BMSi and cohort characteristics were investigated using Pearson and Spearman correlations for continuous variables and independent *t* tests and Mann–Whitney *U* tests for dichotomous variables. Associations between BMSi quartiles and continuous cohort characteristic variables were investigated by one-way ANOVA and Kruskal–Wallis tests with Bonferroni post hoc analysis; associations to dichotomous variables were analyzed by chi-square tests and Fisher exact tests. Multiple linear regression models were used to identify age, BMI, and indentation stability as the independent predictors of BMSi and were used to adjust all further regression models. Independent *t* tests and adjusted logistic regression models were used to investigate the association between BMSi and prevalent fractures. Survival analysis using adjusted Cox proportional hazards models was used to study if BMSi predicted incident fractures and mortality. Competing risks analysis by Fine and Gray[28] was used to analyze the association between BMSi and incident fractures with death as a competing event. Statistical imputation was performed for missing CRF variables using the MICE package (multivariate imputation by chained equations) in R-Studio, using 20 iterations with Nelson–Aalen estimates for all the outcomes. In addition to the FRAX fracture outcomes, all the other CRFs were included in the imputation. Imputation was conducted to some extent for 33 (5%) of the women encompassing missing information on 35 data points, including 8 regarding parental hip fracture, 2 for rheumatoid arthritis, and 25 for secondary osteoporosis (24 for premature menopause and 1 for inflammatory bowel disease). Statistical computation was performed using IBM SPSS (version 28, IBM Corp., Armonk, NY, USA) and STATA (version 17, StataCorp, College Station, TX, USA) for competing risk analysis. The applied level of significance was $p < 0.05$.

Results

Cohort characteristics and associations with BMSi

The cohort characteristics, including associations with BMSi, of the 647 women included in the present study are presented in Table 1. BMSi was inversely correlated with age ($r = -0.13$, $p < 0.001$), weight ($r = -0.17$, $p < 0.001$), BMI ($r = -0.21$, $p < 0.001$), total body lean mass ($r = -0.10$, $p = 0.02$), total body fat mass ($r = -0.20$, $p < 0.001$), and TUG ($r = -0.10$, $p = 0.02$; Table 1). A weak and positive correlation was found between daily dietary calcium intake and BMSi ($r = 0.13$, $p = 0.001$; Table 1). Women with rheumatoid arthritis had a higher BMSi (median BMSi 81.5 ± 10.5 versus 78.6 ± 10.2, $p = 0.02$; Table 1). Similarly, significant differences were observed between quartiles of BMSi with regard to age, body weight, BMI, total body fat mass, and calcium intake (Supplemental Table S1). No significant correlations between BMSi and 10-meter walking speed test, PASE, other CRFs, or FRAX probabilities were found (Table 1).

BMSi, aBMD, and osteoporosis treatment

No significant correlations between BMSi and DXA-derived aBMD parameters were found (Table 2). In adjusted linear regression models (adjusted for age, BMI, and indentation stability), BMSi was significantly associated with lumbar spine aBMD ($\beta = 0.09$, $p = 0.02$) and total hip aBMD ($\beta = 0.08$, $p = 0.05$; Table 2). A significant difference in BMSi (80.0 ± 8.1 versus 77.9 ± 7.3, $p = 0.04$) was observed between women previously treated with osteoporosis medication (bisphosphonates, Prolia, strontium ranelate, parathyroid hormone analogs) and untreated women (Supplemental Table S2). However, no significant difference was found in BMSi between women with current bisphosphonate medication and women without (78.2 ± 6.7 versus 78.0 ± 7.4, $p = 0.91$; Supplemental Table S2).

Table 1. Cohort Characteristics and Associations to BMSi

Characteristic	All	BMSi *r*	Cases (BMSi)	Controls (BMSi)	*p*
BMSi	78.0 ± 7.4	-			-
Age (years)	77.2 ± 1.4	**−0.13**			**<0.001**
Weight (kg)	68.4 ± 11.4	**−0.17**			**<0.001**
Height (cm)	162.1 ± 5.8	0.05			0.19
BMI (kg/m^2)	26.0 ± 4.1	**−0.21**			**<0.001**
Total body lean mass (kg)[a]	42.5 ± 5.4	**−0.10**			**0.02**
Total body fat mass (kg)[a]	26.1 ± 7.0	**−0.20**			**<0.001**
Timed up-and-go (TUG) (s)[b,c]	7.8 ± 2.3	**−0.10**			**0.02**
10-meter walking speed (m/s)[b]	1.3 ± 0.2	0.07			0.06
PASE score[a,c]	100.0 ± 61.0	0.06			0.10
Calcium dietary intake (mg/d)[c]	447.5 ± 641.5	**0.14**			**<0.001**
Previous fracture	249 (38.5%)		77.9 ± 7.3	78.1 ± 7.4	0.70
Family history of fracture	103 (15.9%)		77.8 ± 6.6	78.1 ± 7.5	0.71
Current smoking[d]	25 (3.9%)		79.7 ± 8.9	78.7 ± 10.1	0.49
Oral glucocorticoid exposure[d]	19 (2.9%)		80.1 ± 7.9	78.7 ± 10.3	0.39
Rheumatoid arthritis[d]	24 (3.7%)		81.5 ± 10.5	78.6 ± 10.2	**0.02**
Secondary osteoporosis	158 (24.4%)		77.8 ± 7.8	78.1 ± 7.2	0.66
Alcohol (3 or more units/d)[d]	3 (0.5%)		78.4	78.7 ± 10.1	0.92
Diabetes (type 1 or 2)	58 (9.0%)		77.7 ± 8.4	78.1 ± 7.3	0.74
FRAX 10-year MOF probability, without FN BMD[c]	27.0 ± 14.5	0.03			0.40
FRAX 10-year MOF probability, with FN BMD[c]	19.2 ± 12.2	−0.05			0.24
FRAX 10-year hip fracture probability, without FN BMD[c]	13.0 ± 10.3	0.07			0.09
FRAX 10-year hip fracture probability, with FN BMD[c]	6.8 ± 7.7	−0.04			0.35

Abbreviation: BMI = body mass index; BMSi = bone material strength index; FN BMD = femoral neck bone mineral density; MOF = major osteoporotic fracture; PASE = Physical Activity Scale for the Elderly.

Note: Cohort characteristics are presented as mean ± standard deviation (SD) for continuous variables and *n* (%) for dichotomous variables. Associations to BMSi are presented as Pearson correlation coefficients for continuous variables and independent *t* tests for dichotomous variables. Significant values are shown in bold.

[a]*N* = 645.

[b]*N* = 644.

[c]Median ± IQR and Spearman correlation.

[d]Median ± IQR and Mann–Whitney *U* test.

Prevalent fractures

No association was found between BMSi and self-reported prevalent fractures (Table 3). Similarly, there was no significant difference in BMSi between those with prevalent fracture, including both self-reported fractures and/or VFA-identified vertebral fractures, and those without (Table 3). To further analyze the association of BMSi and fracture prevalence, BMSi was compared for groups with prevalent fractures (VFA identified and/or self-reported) limited to those with femoral neck *T*-score ≤ −2.5 and women without a previous fracture and −1 < femoral neck *T*-score < +2. In this analysis, women with prevalent fracture and osteoporosis had significantly lower BMSi compared with women without prevalent fracture and normal aBMD (76.4 ± 6.5 versus 79.5 ± 6.5, $p < 0.01$; Table 3).

Incident fractures

During a median follow-up time of 6.0 years (interquartile range [IQR] 5.5–6.4), 151 women sustained any fracture with a median time to fracture of 3.1 years. Of those, 121 fractures were classified as MOF with a median time to fracture of 3.5 years (Table 4*A*).

Table 2. Associations Between DXA-Derived BMD and BMSi

aBMD site	BMSi r	*p*	Adjusted standardized β (95% CI)	*p*
Lumbar spine (g/cm^2)	0.04	.32	**0.09 (0.02 to 0.17)**	**0.02**
Femoral neck (g/cm^2)	0.04	.26	0.08 (−0.00 to 0.16)	0.05
Total hip (g/cm^2)	0.03	.45	**0.08 (0.00 to 0.15)**	**<0.05**
Radius (g/cm^2)[a]	0.00	.91	0.04 (−0.04 to 0.12)	0.36
Whole body (g/cm^2)[a]	0.05	.21	0.08 (−0.00 to 0.16)	0.06

Abbreviation: aBMD = areal bone mineral density; BMSi = bone material strength index; CI = confidence interval.

Note: Associations between DXA variables and BMSi are presented. Crude associations are Pearson correlation coefficients. Adjusted associations, presented as standardized beta, are derived from adjusted linear regression models (adjusted for age, body mass index, and indentation stability) with aBMD sites as dependent variables. Significant values are shown in bold.

[a]*N* = 645.

Table 3. Association Between BMSi and Prevalent Fracture

	BMSi previous fracture (*n*)	BMSi no previous fracture (*n*)	*p*1	*p*2
Self-reported previous fracture	77.9 ± 7.3 (249)	78.1 ± 7.4 (398)	0.70	0.63
Self-reported and/or VFA-identified vertebral fracture	77.9 ± 7.3 (332)	78.1 ± 7.4 (301)	0.73	0.49
Self-reported and/or VFA-identified vertebral fracture and BMD criteria	76.4 ± 6.5 (85)[a]	79.5 ± 6.5 (85)[b]	**0.02**	**0.04**

Abbreviation: BMD = bone mineral density; BMSi = bone material strength index; VFA = vertebral fracture assessment.

Note: The differences in BMSi between previous fracture and no previous fracture groups were evaluated using independent samples *t* test and adjusted logistic regression models (adjusted for age, body mass index, and indentation stability). Means ± standard deviations and *p* values are presented. *p*1 = *p* value for independent *t* test; *p*2 = *p* value for adjusted logistic regression. Significant values are shown in bold.

[a]Previous fracture (VFA or self-reported) and femoral neck (FN) or spine bone mineral density (BMD) *T*-score ≤2.5.

[b]No previous fracture (VFA or self-reported) and −1 < FN BMD *T*-score < +2.

In unadjusted Cox regression models, increasing BMSi (per SD) was associated with an increased risk of MOF (hazard ratio [HR] = 1.29, 95% confidence interval [CI] 1.07–1.56) and any fracture (HR = 1.29, 95% CI 1.09–1.53; Table 4*B*). Adjustments for age, BMI, indentation stability, CRFs (previous fracture, parent fracture history, current smoking, oral glucocorticoid use, rheumatoid arthritis, secondary osteoporosis, and a high alcohol consumption) and FN BMD did not materially change the association between BMSi and risk of MOF or any fracture (Table 4*B*). Similarly, further adjustments for current bisphosphonate treatment did not substantially alter the association with BMSi and MOF (HR = 1.31, 95% CI 1.07–1.60) or any fracture (HR = 1.29, 95% CI 1.08–1.54). Highly similar associations were found when considering the competing risk of death using Fine and Gray models (Table 4*B*). Fracture incidence was also analyzed according to quartiles of BMSi. Both the proportion of fractures and cumulative hazard for MOF and any fracture were greatest in the fourth quartile of BMSi, although group-to-group differences in HRs were not significant (Fig. 1; Supplemental Table S3).

BMSi and incident fracture risk according to osteoporosis status

In the osteoporotic subgroup (FN BMD *T*-score < −2.5 SD), consisting of 79 women with a FN BMD *T*-score of −2.84 ± 0.31 (mean ± SD), increasing BMSi (per SD) was associated with an increased risk of MOF (HR = 2.26, 95% CI 1.12–4.59) and any fracture (HR = 1.83, 95% CI 1.03–3.28) in models adjusted for age,

Table 4. Association Between BMSi, Incident Fracture, and Mortality

(*A*) Incident fracture and mortality	MOF	Any fracture	Mortality
Event, *n* (%)	121 (18.7)	151 (23.3)	50 (7.7)
Incidence per 1000-person years	34.7	44.6	13.1
Time (years) at risk, median (IQR)	5.78 (1.03)	5.74 (1.08)	6.04 (0.85)

(*B*) BMSi and incident fracture	MOF	*p*	Any fracture	*p*
BMSi HR per SD (95% CI)				
Crude	**1.29 (1.07 to 1.56)**	**<0.01**	**1.29 (1.09 to 1.53)**	**<0.01**
Adjusted	**1.30 (1.06 to 1.58)**	**0.01**	**1.27 (1.06 to 1.51)**	**<0.01**
+CRFs	**1.26 (1.04 to 1.54)**	**0.02**	**1.24 (1.04 to 1.48)**	**0.02**
+FN BMD	**1.31 (1.07 to 1.60)**	**<0.01**	**1.29 (1.08 to 1.54)**	**<0.01**
SHR per SD	**1.29 (1.06 to 1.58)**	**0.01**	**1.28 (1.07 to 1.52)**	**<0.01**

(*C*) BMSi and mortality	Mortality	*p*
BMSi HR per SD (95% CI)		
Crude	**1.44 (1.07 to 1.93)**	**0.02**
Adjusted	**1.50 (1.11 to 2.04)**	**<0.01**
+Medical history	**1.50 (1.11 to 2.03)**	**<0.01**

Abbreviation: BMSi = bone mineral strength index; CI = confidence interval; CRF = clinical risk factor; FN BMD = femoral neck bone mineral density; HR = hazard ratio; IQR = interquartile range; MOF = major osteoporotic fracture (hip, clinical spine, wrist, or humerus); SHR = subdistribution hazard ratio (analysis according to Fine and Gray with competing risk of death).

Note: (*A*) The number of events: fracture, no fracture, and death are presented according to fracture group (MOF and any fracture) and mortality. Incidence of fracture and mortality is shown as the incidence of fracture per 1000-person years. Both the median time at risk and the median time to event are presented in years.(*B*) The associations between BMSi and incident fractures (MOF and any fracture) are presented as results from Cox proportional hazards models and competing risks analysis by Fine and Gray. The competing event in the Fine and Gray model was death. Adjusted: adjusted for age, BMI, and indentation stability. +CRFs: additional adjustments for previous fracture, parent fractured hip, current smoking, glucocorticoids, rheumatoid arthritis, secondary osteoporosis, and alcohol 3 or more units per day. +FN BMD: additional adjustment for FN BMD. The Fine and Gray model (SHR) is fully adjusted.(*C*) Cox proportional hazards models are used to evaluate the association between BMSi and death. Adjusted: adjusted for age, body mass index, and indentation stability. +Medical history (current smoking and diabetes).

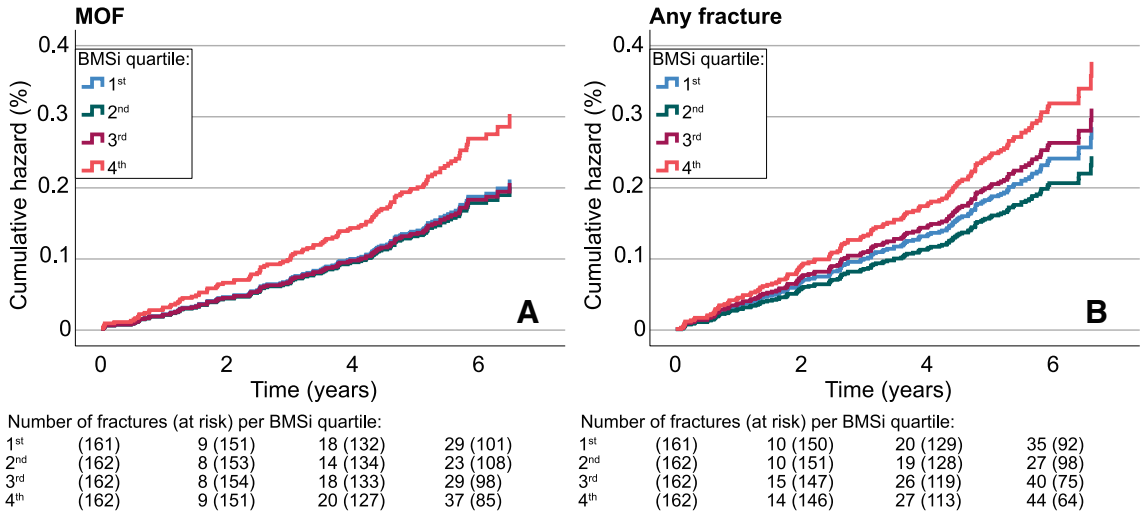

Fig. 1. The cumulative hazard functions are presented according to quartiles of BMSi for major osteoporotic fracture (MOF) (*A*) and any fracture (*B*). The hazard functions are adjusted for age, body mass index, indentation stability, clinical risk factors, and femoral neck bone mineral density. The number of fractures (and individuals at risk) per BMSi quartile at 2-year intervals are displayed below each graph.

BMI, and indentation stability. In the non-osteoporotic subgroup, consisting of 568 women with a FN BMD *T*-score −1.41 ± 0.74 (mean ± SD), increasing BMSi (per SD) was associated with an increased risk of MOF (HR = 1.24, 95% CI 1.00–1.53) and any fracture (HR = 1.23, 95% CI 1.02–1.48) in models adjusted for the same confounders. In contrast to the osteoporotic group, BMSi was not associated with fracture risk in the non-osteoporotic women in fully adjusted models (Supplemental Table S4).

Mortality

During follow-up, 50 deaths occurred with a median time to event of 4.5 years (Table 4*A*). Increasing BMSi (per SD) was associated with an increased risk of death (HR = 1.50, 95% CI 1.11–2.03) in a model adjusted for age, BMI, and indentation stability (Table 4*C*). Additional adjustments for current smoking and diabetes did not change the magnitude or statistical significance of the association (Table 4*C*).

Discussion

In this population-based study of older women, we found a significant association between a higher BMSi and an increasing risk of incident fracture and mortality. This association, particularly apparent in women with osteoporosis, was very robust and did not materially change with adjustments for a wide range of confounders.

To the best of our knowledge, this is the largest study on IMI and the first to investigate the association between BMSi and incident fracture risk. Studying the association with incident fracture is of overt importance to evaluate the clinical utility of the OsteoProbe device as a tool for fracture risk assessment. The unexpected finding that the risk of future fracture, both for MOF and any fracture, increased with a greater bone material strength, as indicated by BMSi, is surprising given that some previous studies have found that a high BMSi is associated with fewer prevalent fractures.[16,18] Even when adjusting for multiple confounders, including clinical risk factors used in FRAX, the associations remained mainly unaltered and significant. Additionally, the association was independent of BMD, which seems logical given the very weak or nonexisting associations between BMSi and BMD, a finding supported by numerous previous studies, including our own, demonstrating no or little correlation between BMD and BMSi.[17] Comparable results were obtained when adjusting for the risk of death in models by Fine and Gray, suggesting that the competing risk of death did not affect the associations between BMSi and fracture risk. Although there was no statistically significant difference in fracture incidence between the quartiles of BMSi, the highest cumulative incidence rate was clearly observed in the fourth quartile for both MOF and any fracture. However, low statistical power in this analysis due to the low number of fractures in each quartile likely influenced these results. The pronounced fracture risk in the fourth quartile could not be explained by any unadjusted differences when analyzing cohort characteristics across BMSi quartiles. A post hoc exploratory analysis of BMSi and incident fracture risk according to osteoporosis status indicated a higher fracture risk with increasing BMSi in the osteoporotic subgroup relative to the non-osteoporotic group. In the non-osteoporotic subgroup, the association was no longer significant when adjusting for CRFs and FN BMD, which indicates that BMSi has greater clinical utility in older women with osteoporosis than in those without.

Finding an explanation for the association between BMSi and incident fractures proves challenging as most of the previous cross-sectional studies on the determinants of BMSi points toward a lower fracture risk with increasing BMSi.[16,18]

It is particularly interesting that, for the same individuals, our results show a lack of association with prevalent fractures. This is in line with our previous conclusions drawn upon results obtained using a smaller sample of the herein investigated cohort.[17] However, numerous previous publications found associations between prevalent fractures and low BMSi,[14,18,29-32] although this discrepancy may be attributable to publication bias, in that studies with positive findings are

more often published. In an attempt to reproduce the association with prevalent fractures in combination with having osteoporosis, reported in a previous study,[31] we created subgroups based on the same criteria of both BMD and prevalent fractures. The group with an osteoporotic BMD and prevalent fracture had significantly lower BMSi than the group with no previous fracture and a non-osteoporotic/osteopenic BMD. However, we believe this difference in BMSi is not due to fracture status but instead the additional BMD criteria, with pronounced reductions in BMD in the osteoporotic group, which was not adjusted for in this particular analysis.[31] This is supported by the lack of association in the entire cohort without the additional BMD criteria. The lack of agreement with previously published results may also be attributable to factors such as differences in study type, inclusion criteria, indentation methodology, fracture classification, the timing of fractures, and geographical differences. In our study, all prevalent fractures were included irrespective of trauma mechanism, possibly inflating BMSi in our fracture group.[33] Additionally, Sweden has one of the highest fracture rates globally, and a previous study has shown geographical variations of BMSi.[34] The participants in our study were ambulatory, community-dwelling, and had not previously received bilateral hip replacement, thus contributing to a potential selection bias of healthier and perhaps fitter individuals with lower fracture risk and higher BMSi.

The dissenting results impel us to question which properties of bone are assessed by IMI and to speculate the underlying cause of the increased risk of fracture and mortality. Since the introduction of the OsteoProbe, published research on the determinants of BMSi has been limited. In a previous study, BMSi was closely correlated to hardness, measured by traditional instrumental methods on polymers.[35] Similarly, a finite element study simulating IMI on a human cortical bone model found BMSi to be positively correlated to Young's modulus, an indicator of material stiffness, and to compressive yield strength.[36] Although the latter study is only a computational simulation, it is appealing to speculate that the increased fracture risk with increasing BMSi may be due to flexibility-related issues. If women with a higher BMSi have more brittle bones, they would be more prone to fracture due to trauma, compared with women with lower BMSi and more flexible bones. Future studies are needed to investigate if IMI is associated with material stiffness and fracture load and whether IMI improves fracture prediction over and above these measures. Interestingly, our results also indicate that there may be a threshold level of BMSi, above which the fracture risk is more pronounced, as our results indicated that the incidence of fracture was highest in the fourth quartile of BMSi. However, the increased fracture risk was independent of BMD, with the bone mineral providing the hardness properties of bone, and there were only weak and adjustment-dependent associations between BMSi and BMD parameters. Bone brittleness is, however, not only determined by the mineral content of bone but also constituents such as collagen and collagen cross-linking, contributing tensile properties of bone, and thereby allowing elastic and plastic deformation.[37] The importance of functioning collagen is evident in patients with osteogenesis imperfecta, a heritable disease also known as brittle bone disease, resulting in more fragile bones and an increased risk of fracture.[38] However, a review of the current literature on the determinants of BMSi reveals no support for our speculation. Previous studies have found a reduced BMSi in subjects with type 2 diabetes mellitus (T2DM), a disease thought to be associated with an increased fracture risk.[39-41] BMSi has also been inversely correlated to levels of advanced glycation end products (AGEs), the duration of T2DM, and 10-year mean glycated hemoglobin (HbA1c) levels before indentation.[39,42] A study concurrently analyzing transiliac bone biopsies using Raman microspectroscopy and IMI at the tibia observed that BMSi was inversely correlated to cortical nanoporosity and positively correlated to the pyridinoline content, an enzymatic collagen cross-link.[43] Adding to the complexity is the observed increased BMSi in the women previously treated with antiresorptive medications, well known to reduce fracture risk. Also, a previous study on treatment-naïve patients with low bone mass showed that BMSi increased after treatment with bisphosphonates or denosumab during a mean of 2 years.[44]

The association between the risk of death and BMSi has not previously been reported. Although the association was robust and largely unaffected by adjustment for multiple confounders, the significantly increased risk of death with increasing BMSi was based solely on 50 deaths. Adjustment for age, BMI, indentation stability, diabetes, and smoking strengthened the association between BMSi and mortality, providing no insight regarding any potential mechanism for this association. Future studies are needed to confirm this finding and to identify possible mechanism explaining the association.

Similar to previous studies, we found that BMSi was inversely associated with age, BMI, and whole body fat mass.[14,18,32,45,46] After adjustments, BMSi was weakly associated with lumbar spine BMD and total hip BMD, which agrees with earlier findings of no or weak associations.[17,18,32,43] Interestingly, there was no association between BMSi and radius BMD, indicating a discrepancy between load-bearing and non-load-bearing skeletal sites. However, this discrepancy could be because the indentations were performed at a load-bearing site (tibia). In comparison to a previously published subset of the present cohort,[17] we found similar associations between BMSi and areal BMD variables with the exception for the lack of association with radius areal BMD in the present study. The current cohort contains more than three times as many participants and therefore provides much more robust statistical power for the investigation between BMSi and BMD. When looking at the correlations, we report highly similar associations as in the previous study, except for the radius aBMD site. We speculate that this discrepancy could be attributable to different confounders used in adjusted models and lower statistical power in the previous study.[17]

There are several limitations to this study that should be acknowledged. The cohort only included older women with a narrow age span (75–80 years), which may limit the generalizability of these results to other populations. Although we were able to adjust for many confounders, other factors beyond our control may have influenced the association between BMSi and incident fracture. The strengths of this study include the large cohort size, the considerable length of follow-up, and the substantial number of incident fracture, providing sufficient statistical power, and enabling the investigation of the association between BMSi and risk of incident fracture for the first time. In addition, all incident fractures were X-ray verified. Lastly, the cohort is population based, making the results more applicable on a general basis.

In conclusion, increasing BMSi was associated with higher fracture risk in older women, independently of BMD and clinical risk factors, suggesting that this skeletal trait can be used to improve fracture prediction. The mechanism behind this finding needs further study.

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Author Contributions

Raju Jaiswal: Writing – review and editing; formal analysis; visualization; data curation; writing – original draft; investigation; methodology; software; validation. **Michail Zoulakis:** Conceptualization; formal analysis; visualization; investigation; data curation; writing – review and editing; methodology; software; validation. **Kristian F Axelsson:** Writing – review and editing; investigation; software; data curation; formal analysis; visualization. **Anna Darelid:** Investigation; methodology; writing – review and editing; data curation. **Robert Rudäng:** Methodology; writing – review and editing; investigation; data curation. **Daniel Sundh:** Data curation; investigation; methodology; writing – review and editing. **Henrik Litsne:** Data curation; formal analysis; writing – review and editing; software. **Lisa Johansson:** Investigation; data curation; writing – review and editing; methodology; formal analysis. **Mattias Lorentzon:** Conceptualization; data curation; formal analysis; visualization; methodology; investigation; supervision; project administration; writing – review and editing; software; validation; funding acquisition; resources.

Disclosures

KFA has received lecture fees from Lilly, Meda/Mylan, and Amgen, all outside the submitted work. LJ has received lecture fees from UCB Pharma, all outside the submitted work. ML has received lecture fees from Astellas, Amgen, Lilly, UCB Pharma, and Meda/Mylan, all outside the submitted work. All other authors have no conflicts of interest.

Peer Review

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Data Availability Statement

Data cannot be made publicly available for ethical and legal reasons. Such information is subject to legal restrictions according to national legislation. Specifically, in Sweden, confidentiality regarding personal information in studies is regulated in the Public Access to Information and Secrecy Act (SFS 2009:400). The data underlying the results of this study might be made available upon request, after an assessment of confidentiality. There is thus a possibility to apply to get access to certain public documents that an authority holds. In this case, the University of Gothenburg is the specific authority that is responsible for the integrity of the documents with research data. Questions regarding such issues can be directed to the head of the Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden. Contact information can be obtained from medicin@gu.se.

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