Original Article

Multisite Quantitative Ultrasound for the Prediction of Fractures Over Five Years of Follow-up: The Canadian Multicentre Osteoporosis Study[†]

W.P. Olszynski MD, PhD[1], J.P. Brown MD[2], J.D. Adachi MD[3], D.A. Hanley MD[4], G. Ioannidis PhD[3], K.S. Davison PhD[5] and the CaMos Research Group

[1]Department of Medicine, University of Saskatchewan, Saskatoon, SK, Canada
[2]Department of Medicine, Laval University, Quebec City, QC, Canada
[3]Department of Medicine, McMaster University, Hamilton, ON, Canada
[4]DAH: Department of Medicine, University of Calgary, Calgary, AB, Canada
[5]University of Victoria, Victoria, BC, Canada

Corresponding Author and Reprint Requests:
Wojciech P. Olszynski
Address: 103-39 23rd St E, Saskatoon, SK S7K 0H6,
Telephone: 306-244-2277
Fax: 306-244-6755
Email: wpolszynski@sasktel.net

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Abstract:

This study assessed the ability of multisite quantitative ultrasound (mQUS) to predict fracture over a five-year follow-up. Participants were a subset of the Canadian Multicentre Osteoporosis Study. mQUS-assessed speed of sound (SOS in m/s) at three sites (distal radius, tibia and phalanx) and extensive questionnaires were completed, after which participants were followed for five years and incident fractures recorded. Two survival analyses were completed for each site – a univariate analysis and an adjusted multivariate analysis controlling for age, anti-resorptive use, femoral neck bone mineral density, number of diseases, previous fractures, BMI, parental history of hip fracture, current smoking, current alcoholic drinks >3 per day, current using glucocorticoids, and rheumatoid arthritis diagnosis (variables from the FRAX 10-year fracture risk assessment tool). The unit of change for regression analyses was one standard deviation for all measurement sites, specific to site and sex. Separate analyses were completed for all clinical fractures, non-vertebral fractures and hip fractures by sex. There were 2633 women and 1108 men included and they experienced 204 incident fractures over five years (5.5% fractured). Univariate models revealed statistically significant ($p<0.05$) predictive ability of mQUS for all three measurement sites for women alone for all three fracture types (one standard deviation decrease in SOS was associated with a 52-130% increase in the risk of fracture), but not for the men's group. The adjusted model found that measures at the distal radius and tibia in the women's group could significantly ($p<0.05$) predict all clinical fractures and non-vertebral fractures within the next five years (one standard deviation decrease in SOS was associated with a 25-31% increase in the risk of fracture). mQUS provided significant five-year clinical fracture prediction in women, independent of bone mineral density and other significant risk factors for fracture, when measured at the distal radius and tibia sites.

Keywords: bone, fracture, prospective, multisite, quantitative ultrasound.

Introduction:

According to World Health Organization classification, osteoporosis is defined by a bone mineral density (BMD) measurement, as assessed by dual-energy x-ray absorptiometry (DXA), lower than two-and-a-half standard deviations below the young adult mean BMD (T-score ≤-2.5) (1). It has been well-established that fragility fracture risk varies inversely with DXA BMD (2-4); however, the majority of women who suffer a fragility fracture possess BMD levels above that which would be considered osteoporotic (2;5). Recently, tools have been developed to better identify men and women at a high risk for fragility fracture who may not possess an osteoporotic BMD by combining information provided from numerous clinical risk factors for fracture with DXA BMD (i.e. FRAX or Canadian Association of Radiologists and Osteoporosis Canada 10-year fracture risk assessment tools) (6;7). While the identification of patients at high risk is generally improved with these new tools, particularly for osteopenic individuals (T-score between -1 and -2.5), there is room for improvement.

Bones that have insufficient strength to withstand normal loading strains are predisposed to fragility fractures. Bone strength is determined by numerous factors including bone micro and macro-structure, organic and inorganic material characteristics and the activity of bone-regulating cells (8). While DXA BMD accounts for some of the variation of these bone strength characteristics (bone mass, bone size, areal density), it does not assess all of them, leaving a significant component of fracture risk unaccounted for when using DXA BMD alone as a risk factor for fracture. Accordingly, there is need to identify additional variables other than BMD and the variables already integrated into the popular fracture risk models that are easily measured in the clinic that can provide additional information to better stratify individual fracture risk.

Quantitative ultrasound (QUS) has been used to assess bones with the hopes of being able to identify those individuals who are at an increased risk for fracture. QUS devices are attractive as they are portable, comparatively inexpensive, require little training for their use, and emit no ionizing radiation during their use. Among manufacturers, there are a number of assessments that can be made of bone using a QUS: broadband ultrasound attenuation (BUA), quantitative ultrasound index stiffness and speed of sound (SOS).

A number of prospective investigations have demonstrated that QUS can predict fracture as well as, or better than, DXA BMD (9-12) and that this predictive ability is somewhat independent of BMD. The majority of QUS devices assess bone at the calcaneus, but there are QUS devices that can assess bone at the kneecap, tibia, radius, and/or phalanx. One QUS device is capable of providing SOS measurements from a number of different sites including the tibia, distal radius and phalanx.

This investigation assessed the capability of a multisite QUS device (mQUS; BeamMed Omnisense MultiSite Quantitative Ultrasound) to prospectively assess fracture risk over five years in a large cohort of randomly selected men and women from the Canadian Multicentre Osteoporosis Study (CaMos).

Materials and Methods:

This investigation utilized a subset of participants from the CaMos cohort. The methods and objectives of the CaMos study have been previously published (13). Briefly, CaMos is an ongoing, prospective cohort study involving 9423 randomly selected community-dwelling women (n = 6539) and men (n = 2884) aged 25 years and older at baseline and who lived within 50 km of nine major Canadian cities (St. John's, Newfoundland and Labrador; Halifax, Nova Scotia; Quebec City, Quebec; Toronto, Hamilton and Kingston, Ontario; Saskatoon, Saskatchewan; Calgary, Alberta; and Vancouver, British Columbia). Households were randomly selected from a list of residential phone numbers, and participants were randomly selected from eligible household members using standard protocol. Of those selected, 42% agreed to participate and had a baseline interview. All research carried out in the CaMos has been approved by local University ethics boards in each of the cities the study had centres in and have satisfied the criteria of the World Medical Association Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects.

Data collection at baseline and each follow-up visit included an extensive, standardized interviewer-administered questionnaire and a clinical assessment. The questionnaire covered socio -demographic information, general health, medical and fracture history, family history, dietary intake, physical activity, tobacco smoking and quality of life. The questionnaire was designed to capture detailed information about risk factors for fractures including information about prior fractures and, as such, assessed all previous fractures

(fracture site, date, and circumstances), family history of osteoporosis/fracture, and falls in the past month. Clinical assessment measures included height, weight and DXA BMD of the spine (lumbar vertebrae L1–L4), femoral neck and total hip. Lateral lumbar and thoracic spine X-rays were performed in all subjects who were ≥50 years of age. Vertebral deformities were assessed from X-rays by a trained technologist using digital vertebral morphometry.

Full assessments (clinical measures and questionnaires) occurred at baseline, after three years (only for participants aged 40–60 years at baseline), after five years, and after 10 years. In years that participants did not come to a study center, a self-administered fracture questionnaire was mailed out to identify incident fractures. Confirmation and further information concerning the fracture was gathered using a structured interview that included items on date, fracture site, circumstances leading to fracture, X-ray report (if obtainable), and medical treatment.

At the five-year follow-up investigation, a number of the clinical sites expanded their protocol by assessing participants with a mQUS (at the five-year follow-up Sunlight Omnisense MultiSite Quantitative Ultrasound 7000S and now BeamMed Omnisense MultiSite Quantitative Ultrasound 7000S, Israel), in addition to the normal CaMos assessments (Calgary, Saskatoon, Hamilton, Quebec City, Halifax, St. John's). mQUS measurements were obtained at three anatomical sites (distal third of radius, midshaft tibia and proximal phalanx) on the non-dominant side of the participant and were recorded as SOS in meters per second (m/s). The mQUS was equipped with two handheld probes specifically designed for measurements of axial SOS along the surfaces of bone: one probe was suitable for measurements at the radius and tibia while the other was used to measure the phalanx. Details regarding the standard manufacturer-suggested techniques involved with bone measurement with the mQUS have been detailed previously and these standards were employed in this investigation (14-18). Briefly, the mQUS emits and detects acoustic waves at a frequency of 1.25 MHz. The SOS measure acquired is the time taken for the sound wave to travel from the emission to the detection. Quality control measurements were performed daily following procedures recommended by the manufacturer. Intra-observer in-vivo short-term precision has been reported as 0.76% for the radius, 0.47% for the tibia, and 1.54% for the phalanges and inter-observer precision from 0.77% to 2.39% (19).

After mQUS assessment, all participants were prospectively followed for a five-year period (year five of CaMos until year 10 of CaMos) during which time all information with regards to incident fractures were recorded in detail. Only low-trauma fractures (occurred without major trauma or from a fall of standing height or less or atraumatic) were included in the analyses. Further, fractures of the skull, face, hands, and feet were excluded. To insure that there were no duplicate events in the database, all repeat fractures of the same skeletal site and all multiple fractures were assessed for possible replication using X-ray and/or medical reports.

There were three separate survival analyses (Cox proportional hazards regression) done for each skeletal site grouping (all clinical fractures, all non-vertebral fractures and all hip fractures) – an uncontrolled univariate analysis, a multivariate analysis controlling for a large number of clinical risk factors for fracture and a backward elimination regression with all variables initially entered into the model (not detailed here, but similar results to full multivariate analyses). Analyses were completed modeling a one standard deviation (SD) loss in SOS, with different SDs used for each skeletal site assessed and for each sex. Adjustments were made for age, anti-resorptive use, femoral neck BMD, number of diseases, previous fractures, body mass index, sex (in model with both men and women), parental history of hip fracture, current smoking, current alcoholic drinks more than three per day, current use of glucocorticoids, and diagnosis of rheumatoid arthritis (self-reported). Many of these variables were selected for control because they are used in the FRAX 10-year fracture risk assessment tool now used world-wide (7). Further, all analyses were completed for men and women separately. For each participant, the follow-up time corresponded to the number of days between the randomization date and the earliest date for one of the following events: the date of fracture (event of interest), date of death (censored), the date of the ten year follow-up interview (censored), or the date of last correspondence (censored).

Basic descriptive (demographic information) and frequency (controlled variables) analyses were completed, with significant differences between sexes assessed via independent, two-tailed t-tests and chi-squared tests, respectively. All analyses were completed on a Windows-based workstation with SAS 9.3. Statistical significance was considered to have occurred at an alpha of 0.05.

Results:

A total of 4126 patients had an mQUS performed during their year-five evaluation. However, 385 participants had no follow-up after the mQUS measurement and were therefore excluded from the analyses, leaving a total of 2633 (70.4%) women and 1108 (29.6%) men (total sample of 3741). Those excluded were significantly older (mean age = 69.6y), and had significantly lower SOS measures at all sites.

A total of 204 incident fractures occurred over five years of observation (5.5% of cohort suffered a fracture). When stratified by sex, incident fractures occurred in 177 women (4.8%) and in 27 men (0.7%) over the five-year follow-up. Hip fractures occurred in 42 individuals (34 or 1.23% in women and 8 or 0.20% in men) and non-vertebral fracture events occurred in 187 individuals (161 or 4.28% in women and 26 or 0.69% in men).

Table 1. provides the general characteristics of the participants assessed. The mean age of the men was significantly younger than the women (63 vs 66 years old, respectively). The men possessed significantly higher SOS values at all three investigated sites as compared to the women and had a significantly higher FN BMD. While men were significantly taller than women on average, they also were significantly heavier, resulting in similar body mass indices between the sexes.

Table 2. details the prevalence of the different variables selected for control in the multivariate models. Use of anti-resorptive therapy was low in women, but almost non-existent in men. Women were also administered more glucocorticoids than men, but not significantly so. Prior fracture, incidence of parental hip fracture and diagnosis of rheumatoid arthritis were significantly higher in women. In terms of lifestyle variables, on average women smoked tobacco and drank three or more alcoholic drinks a day significantly less often as compared to men.

The uncontrolled results of the univariate Cox proportional hazard models for all three fracture groupings are provided in Table 3. For the women, a one SD decrease in the SOS measurement was associated with a significant increase in the risk of any clinical fracture (52-83% increased risk), hip fracture (100-130% increased

risk) or non-vertebral fracture (54-85% increased risk). However, while the point estimates were in the same direction as the women, none of the mQUS measures significantly predicted fracture risk in any of the three skeletal groupings for men.

The adjusted Cox proportional hazard models for all three fracture groupings are provided in Table 4. After adjustment for other known variables that predict fracture risk (which are incorporated into the FRAX 10-yr fracture risk assessment (7)), there was a general attenuation of the predictive ability of the mQUS measures, as expected. In women, a one SD decrease in SOS did not add any significant predictive power for hip fracture above the incorporated FRAX variables, but did provide significant predictive ability in addition to the FRAX variables for any clinical fracture and non-vertebral fracture when assessed at either the distal radius or tibia sites (25-31% increased risk). As in the unadjusted models, the mQUS measures did not significantly stratify fracture risk in men.

Discussion:

In this large, prospective, population-based investigation, mQUS measurements at the tibia, distal radius and phalanx predicted increased risk for all clinical fractures, hip fractures and non-vertebral fractures in women over a five-year follow-up, but did not do so in men. On average, a one SD decrease in SOS was associated with an approximate 52-130% higher fragility fracture risk over five years in women. This finding was important as it demonstrated that mQUS was able to independently assess the risk of clinical fragility fracture in women, without consideration of BMD or other clinical risk factors.

The women in this cohort had characteristics that would suggest that they had a higher baseline risk for fracture than the men: they were older, had a greater incidence of prior fracture, lower FN BMD and more frequent history of a parental hip fracture as compared to the men. Thus, the men in this study in all likelihood had a lower general risk of fracture, which was borne out by the fracture incidence: after five years of follow-up, the rate of fracture was 4.8% for the women and 0.7% for the men, almost a seven-fold greater incidence in the women. The incidence of fractures was so low in men in this population-based sample that the power to find a significant effect was likely insufficient. It is important to note that the CaMos dataset describes the experience of a general Canadian population and not that of a Canadian patient population; thus, the expected rates of events of interest (i.e. fracture) will be lower as the CaMos population is healthier than a patient population selected on the basis of compromised bone strength.

In this trial, adjustment for BMD and other pertinent clinical risk factors decreased the independent predictive ability of the mQUS, as was expected as there is undoubtedly shared variance among BMD, the clinical risk factors and SOS in their ability to predict fragility fracture. Adjustment for FN BMD and the clinical risk factors included in the FRAX 10-year fracture risk assessment tool (20) was completed to investigate whether the information provided by the mQUS measures would be additive to these BMD and the clinical risk factor measures, which they largely were (excepting the phalanx measurement site and the prediction of hip fracture). These findings suggest that the inclusion of mQUS variables to the FRAX 10-year fracture assessment tool

would provide statistically significantly greater prognostic ability to FRAX. However, whether these improvements reflect increased clinical significance is unknown at this time. Other trials have found a similar trend in that the models with the greatest predictive ability for hip fracture included both QUS measures and other clinical risk factors (21;22).

A number of studies have reported mean population values for the BeamMed mQUS used in this study. The women in the present cohort had similar mean mQUS SOS measures as those reported previously by Drake et al. (23), who published North American normative information for Caucasian women, with the exception of the phalanx site, which was notably lower in the population-based sample presented here as compared to their sample (means of 4092 vs 3791 m/s). Similarly, Njeh et al. (15) assessed North American women by mQUS and Hayman et al. (24) reported mean mQUS SOS values for North American women and men, respectively, that were similar to those found in this study. Thus, although this investigation included significantly more participants than the other investigations, the results of this study are generally comparable to other North American studies with respect to mean SOS values as assessed by BeamMed mQUS.

While this was the first investigation to assess the prospective ability of mQUS to predict fracture, other investigations have assessed this device retrospectively (14-19;23-39). Multiple investigations have compared the mQUS-assessed SOS between fractured and unfractured cohorts to determine whether the mQUS could differentiate those who had suffered a fracture from those who had not. Weiss et al. (37) utilized the mQUS (distal radius) in a group with and without hip fracture and found that for each decrease of one standard deviation in SOS there was a significant increase in hip fracture risk (odds ratio =1.92; 95% CI: 1.22, 3.02; $p = 0.005$). Damilakis et al. (19) compared a group of healthy postmenopausal women to a group of postmenopausal women who had suffered a fragility fracture with both DXA (BMD) and the mQUS. Both BMD and SOS values in the fractured cohort were significantly ($p<0.01$) lower than in the non-fractured cohort. When the odds ratios for fracture prediction were assessed, the QUS had impressive diagnostic abilities for prediction of fracture with odds ratios of 1.47 for the tibia (p=NS), 1.69 for the radius (p=0.04), and 2.69 for the phalanx (p=0.004; BMD OR ranged from 2.08-3.26, all $p<0.01$). This study demonstrated that both QUS and BMD could significantly discriminate between those who had and had not fractured, but perhaps just as

importantly, that these abilities were relatively independent from one another. Damilakis et al. (27) assessed women who had suffered a hip fracture (n=51) to those who had not suffered a hip fracture (n=51) with mQUS and DXA. While the odds ratios associated with the prediction of hip fracture were significant with mQUS phalangeal measurement (2.63; $p<0.001$), FN BMD was superior (OR=3.61; $p<0.001$), but not significantly so when assessed with receiver operator curves of each technique against hip fracture prevalence. In a similar investigation by Hans et al. (30), women with (n=45) and without (n=40) hip fracture were assessed by three QUS devices (Hologic Sahara, GE-Lunar Achilles+, and Sunlight Omnisense mQUS). For a one standard deviation in SOS, the adjusted odds ratio for hip fracture was 2.83 for the Omnisense SOS mQUS, 2.42 with the Sahara BUA and 3.29 for the Achilles BUA. Lastly, Nguyen et al. (35) also found that mQUS was able to discriminate between fractured and unfractured women and that this discriminatory ability was independent from both BMD and age.

Numerous previous studies have confirmed the utility of single-site QUS for prospectively stratifying fragility fracture risk, and most of these have been reviewed by the International Society for Clinical Densitometry (ISCD) in a 2008 publication by Krieg et al. (40). The majority of the trials reviewed were followed for three or fewer years, with studies assessing the ability of QUS to predict hip, non-vertebral and/or all fragility fracture. The relative risk (RR) or HR estimates provided for these single-site QUS devices ranged from an insignificant 1.1 (0.7, 1.7) to a significant 2.8 (1.5, 5.0) for a one SD decrease in the measure. While some of the significant point estimates were higher than those reported in this investigation, none of the reviewed investigations corrected for all of the variables included in the FRAX 10-year fracture assessment tool as was done in the current analyses, or for as many variables as in this investigation. The univariate analyses performed here had some point estimates similar to the highest point estimates found in the review. However, since the analyses all included different control variables to this study, direct comparison is not possible. The most compelling statement that the current research can make is that mQUS measures performed at either the radius or tibia can add statistically significant prognostic ability to the variables included in the FRAX 10-year fracture assessment tool – and is currently the only QUS instrument to show this prospectively.

Since the review by Krieg et al. (40) for the ISCD, there have been a number of other prospective investigations assessing the ability of QUS to assess fracture risk. In a meta-analysis of trials that assessed the use of single-site QUS for the prediction of fracture, Moayyeri et al. (41) found that when after adjusting for hip BMD, QUS was a significant predictor of fracture risk (RR = 1.34). Chan et al. (42) followed a cohort of men and women over a mean 13 years and concluded that the combination of QUS and FN BMD predicted fracture better than FN BMD or QUS alone for the women, but for the men the addition of QUS to FN BMD did not improve the predictive power for fracture. Increased predictive power by combining clinical risk factors with QUS measures were found by Moaryyari et al. (21) and Hans et al. (22), similar to what was found in this study.

mQUS may hold some advantages over single-site, typically calcaneal QUS assessment. One advantage is that the mQUS is able estimate bone strength at the radius, a site of frequent fracture in osteoporosis whereas QUS typically assesses at the calcaneus, a site where fracture is rare in osteoporosis. Further, the mQUS is able to assess weight-bearing (tibia) and non-weight-bearing (radius, phalanx) sites, whereas the QUS is only able to assess one weight-bearing site. Also, by having three assessments, the mQUS may hold utility in that the lowest of the three sites may offer a greater prognostic utility than one site alone.

While some trials have attempted to justify the use of QUS for screening for DXA, perhaps its greatest asset may be that it predicts fracture risk somewhat independently from that of BMD. In other words, the strength of QUS is not in its ability to assess BMD but to predict fracture risk. QUS measures may be impacted by mechanical and structural properties of the bone whereas BMD is largely a factor of overall bone surface area and bone mass. Cook et al. (26) investigated the concordance between DXA-assessed axial BMD and two QUS devices, the CUBA Clinical and the Sunlight Omnisense mQUS in a moderate-sized cohort (n=268) of patients with osteoporosis or osteopenia as defined by BMD and found that there was a poor level of agreement among the techniques as demonstrated by the kappa scores of the QUS devices to DXA BMD (0.02-0.20). Another investigation from Damilakis et al. (27) reported a correlation between FN BMD and Sunlight mQUS phalangeal SOS of 0.35 (shared variance of 12%). Similar low correlations were reported by Drake et al. (28) (r=-0.08 to 0.22). Another investigation found that while there were significant correlations between BMD and mQUS measures (r=0.21-0.41; $p<0.001$)), the shared variance was below 17% in the best circumstance (19).

Ideally, the combination of SOS and BMD may increase predictive ability. However, Bauer et al. (43) reported that when models combined the two measures there was little gained with respect to hip fracture predictive ability – the current investigation came to a similar conclusion with respect to hip fractures, but when all the FRAX variables were included in the fracture prediction models rather than just BMD. This finding demonstrates that the inclusion of mQUS measures to the FRAX clinical risk factors and FN BMD did not explain a significantly greater amount of the variance with respect to hip fracture prediction. However, this investigation found that some mQUS measures did predict all clinical and non-vertebral fractures in women. Perhaps the FRAX variables captured a large proportion of the variance associated with hip fracture, but not as much of the variance with clinical or non-vertebral fracture in which mQUS added important prognostic utility.

Muller et al. (34) tested three QUS devices against information provided from high-resolution peripheral quantitative computerized tomography. Human radii from cadavers were assessed with all devices and then subjected to mechanical testing until failure. BeamMed mQUS SOS was significantly correlated to Young's modulus, a measure of the elastic stiffness of bone ($r=0.45$; $p<0.01$), although there was no other significant correlation with any other assessed mechanical measure or failure load.

One major hurdle in the use of mQUS to assess fracture risk in patients is that almost all therapies that have been tested for the treatment of osteoporosis have been tested on patients selected for the trials based on their DXA BMD. Thus, it is relatively unknown if patients selected on the basis of their mQUS risk will benefit from these therapies in the expected manner. Studies are needed to investigate whether monitoring of therapy is possible with mQUS as it is with DXA. Prior studies have largely suggested that it is of use when monitoring women on hormone therapy (31;38) or alendronate (39), although these findings need to be replicated over a longer duration and with larger cohorts as there have been conflicting analyses (28).

There are a few limitations of this investigation. First, clinical fractures were self-reported and this may be subject to bias. However, all fractures were verified with treating physicians and radiographs verified if available. Second, the low numbers of hip fractures in both the women's and men's groups as well as the low overall low numbers of fractures in the men's group limits the robustness of the findings here. The relatively

healthy population of patients included in these analyses may have limited the findings. Third, no analyses were made for the inclusion of non-clinical vertebral fractures. Lastly, in CaMos all incidences of rheumatoid arthritis were self-reported and not corroborated by investigators.

In conclusion, the BeamMed Omnisense mQUS provides significant five-year clinical fracture prediction, independent of BMD and other significant risk factors for fracture, when measured at the distal radius and tibia sites in women. Further investigation into the use of mQUS for inclusion in 10-year fracture risk models and for its use in monitoring therapy is warranted.

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Table 1. Basic demographic information of cohort.

Variable	Men Mean±SD	Women Mean±SD	P-value*
Distal radius SOS in m/s	4073±126.7	4031±156.9	<0.0001
Tibia SOS in m/s	3935±117.5	3839±145.1	<0.0001
Phalanx SOS in m/s	3883±192.5	3791±218.5	<0.0001
Age in years	63.3±12.9	66.1±11.5	<0.0001
Femoral neck BMD T-score	-0.50±0.96	-1.25±0.95	<0.0001
Number of other diseases	0.66±0.92	0.91±1.05	<0.0001
Standardized physical summary	49.1±8.9	46.5±10.2	<0.0001
Body mass index in kg/m^2	27.6±3.9	27.3±5.3	0.137
Mass in kg	83.2±13.7	69.6±14.4	<0.0001
Height in cm	173.7±7.0	159.7±6.8	<0.0001

*Differences between men and women.

Table 2. Frequency of variables included in multivariate models.

Variable	Men percent yes	Women percent yes	P-value*
Anti-resorptive use	1.0	8.1	<0.0001
Prior fracture	15.4	22.0	<0.0001
History of hip fracture in parents	8.7	11.6	0.01
Currently smoking tobacco	14.3	10.9	0.003
Currently drinking 3 or more drinks/d	4.0	0.6	<0.0001
Currently taking glucocorticoids	0.9	1.2	0.461
Diagnosed with rheumatoid arthritis	2.5	5.1	0.0006

*Differences between men and women.

Table 3. Results of univariate proportional hazards model for all fracture types (unadjusted model) assuming a one standard deviation decrease in speed of sound.

Fracture grouping	Measurement site	Women HR[a]	Men HR[a]
Any clinical fracture	Distal radius	1.83 (1.56, 2.17)[b]	1.12 (0.74, 1.69)[c]
	Tibia	1.65 (1.41, 1.92)[b]	1.37 (0.93, 2.04)[c]
	Phalanx	1.52 (1.30, 1.79)[b]	1.26 (0.86, 1.82)[c]
Hip fracture	Distal radius	2.00 (1.39, 2.86)[b]	1.37 (0.57, 3.33)[c]
	Tibia	2.00 (1.41, 2.86)[b]	1.03 (0.47, 2.27)[c]
	Phalanx	2.30 (1.59, 3.33)[b]	1.47 (0.74, 2.94)[c]
Non-vertebral fracture	Distal radius	1.85 (1.56, 2.17)[b]	1.06 (0.69, 1.63)[c]
	Tibia	1.67 (1.41, 1.96)[b]	1.35 (0.90, 2.00)[c]
	Phalanx	1.54 (1.30, 1.82)[b]	1.25 (0.85, 1.82)[c]

[a]Hazard ratio (95% confidence interval); [b]statistically significant at $p<0.05$; [c]not statistically significant at $p<0.05$.

Table 4. Results of adjusted[a] proportional hazards model for all fracture types one standard deviation decrease in speed of sound.

Fracture grouping	Measurement site	Women HR[b]	Men HR[b]
Any clinical fracture	Distal radius	1.30 (1.06, 1.59)[c]	0.96 (0.63, 1.47)[d]
	Tibia	1.25 (1.05, 1.49) [c]	1.08 (0.70, 1.67)[d]
	Phalanx	1.05 (0.88, 1.27)[d]	0.93 (0.61, 1.41)[d]
Hip fracture	Distal radius	0.93 (0.62, 1.39)[d]	0.88 (0.35, 2.22)[d]
	Tibia	1.29 (0.88, 1.89)[d]	0.46 (0.18, 1.18)[d]
	Phalanx	1.23 (0.81, 1.85)[d]	0.53 (0.23, 1.23)[d]
Non-vertebral fracture	Distal radius	1.31 (1.06, 1.61)[c]	0.93 (0.60, 1.43)[d]
	Tibia	1.26 (1.05, 1.52)[c]	1.06 (0.68, 1.67)[d]
	Phalanx	1.06 (0.88, 1.28)[d]	0.93 (0.61, 1.45)[d]

[a]Adjusted for age, anti-resorptive use, femoral neck BMD, number of diseases, previous fractures, BMI, sex (in combined model), parental history of hip fracture, current smoking, current alcoholic drinks >3 per day, current use of glucocorticoids, and diagnosis of rheumatoid arthritis; [b]Hazard ratio (95% confidence interval);); [c]statistically significant at $p<0.05$; [d]not statistically significant at $p<0.05$.