

Predictive ability of heel quantitative ultrasound for incident fractures: an individual-level meta-analysis

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Abstract

Summary The relationship between bone quantitative ultrasound (QUS) and fracture risk was estimated in an individual level data meta-analysis of 9 prospective studies of 46,124 individuals and 3018 incident fractures. Low QUS is associated with an increase in fracture risk, including hip fracture. The association with osteoporotic fracture decreases with time.

Introduction The aim of this meta-analysis was to investigate the association between parameters of QUS and risk of fracture.

Methods In an individual-level analysis, we studied participants in nine prospective cohorts from Asia, Europe and North America. Heel broadband ultrasonic attenuation (BUA dB/MHz) and speed of sound (SOS m/s) were measured at baseline. Fractures during follow-up were collected by self-report

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and in some cohorts confirmed by radiography. An extension of Poisson regression was used to examine the gradient of risk (GR, hazard ratio per 1 SD decrease) between QUS and fracture risk adjusted for age and time since baseline in each cohort. Interactions between QUS and age and time since baseline were explored.

Results Baseline measurements were available in 46,124 men and women, mean age 70 years (range 20–100). Three thousand and eighteen osteoporotic fractures (787 hip fractures) occurred during follow-up of 214,000 person-years. The summary GR for osteoporotic fracture was similar for both BUA (1.45, 95 % confidence intervals (CI) 1.40–1.51) and SOS (1.42, 95 % CI 1.36–1.47). For hip fracture, the respective GRs were 1.69 (95 % CI, 1.56–1.82) and 1.60 (95 % CI, 1.48–1.72). However, the GR was significantly higher for both fracture outcomes at lower baseline BUA and SOS ($p < 0.001$). The predictive value of QUS was the same for men and women and for all ages ($p > 0.20$), but the predictive value of both BUA and SOS for osteoporotic fracture decreased with time ($p = 0.018$ and $p = 0.010$, respectively). For example, the GR of BUA for osteoporotic fracture, adjusted for age, was 1.51 (95 % CI 1.42–1.61) at 1 year after baseline, but at 5 years, it was 1.36 (95 % CI 1.27–1.46).

Conclusions Our results confirm that quantitative ultrasound is an independent predictor of fracture for men and women particularly at low QUS values.

Keywords Bone densitometry · Bone ultrasound · Fractures · Meta-analysis · Osteoporosis

Introduction

Identifying individuals at high risk of osteoporotic fractures is the cornerstone of good clinical practice in osteoporosis management [1]. Several skeletal and extra-skeletal risk factors contribute to fracture risk and have been incorporated into widely used assessment tools such as FRAX [1–4]. The measurement of bone mineral density (BMD) by dual X-ray absorptiometry (DXA), particularly at the femoral neck, is the usual measure of skeletal strength incorporated into diagnostic and/or risk algorithms, but access to central skeleton DXA varies widely within and across geographical regions and countries [5, 6]. Where provision of DXA is poor, other techniques that assess the peripheral skeleton may be used. A substantial number of prospective studies have used quantitative bone ultrasound (QUS) [7–21], as it has the potential to provide a low-cost, radiation-free measurement of heel bone that may aid the identification of individuals at risk for fracture in a primary or secondary care setting. There are also limitations to the use of QUS devices; for example, results cannot be

compared across devices, there is no agreed definition of osteoporosis using QUS, and the response of QUS to treatment is not as well studied as that of BMD [22].

The common QUS parameters that are measured include speed of sound (SOS) and broadband ultrasound attenuation (BUA) with these values being combined into composite parameters such as stiffness index [23–26]. Systematic reviews of prospective cohort studies have confirmed that QUS was predictive of hip and other fractures [18, 19]. As is the case for BMD, it is likely that the utility of QUS can be enhanced by combining QUS measurements with other independent fracture risk factors, including age [27]. Although the relationship between QUS and fracture risk has been reasonably well characterised and appears similar in men and women [19], it is not yet clear whether the relationship is similar across the full range of age and QUS values, or if it remains constant with time after assessment. For these reasons, we wished to characterise the predictive ability of QUS measurements by age, gender, time since assessment and absolute value of QUS for different fracture outcomes on an international basis.

Methods

We studied men and women in whom ultrasound measurements were recorded at baseline with subsequent follow-up fracture data from nine prospective cohorts from North America, Europe and Asia. The majority of studies were population based (6/9), and seven cohorts included baseline measurements of BMD as well as QUS. The studies are described briefly below and summarised in Table 1.

The Ecografía Osea en Atención Primaria (ECOSAP) study recruited in 58 primary care centres throughout Spain, regardless of the reason for consultation [10]. For this analysis, QUS and validated fracture follow-up were available for 4711 women. Fractures were documented by self-report and confirmed by investigator by X-ray or radiological or surgical report.

The Norfolk cohort of the European Prospective Investigation into Cancer (EPIC-Norfolk), started in 1992–1993, comprised men and women aged 40–79 years who were resident in Norfolk, UK, and were recruited from general practices [16]. For this analysis, heel ultrasound and validated fracture follow-up were available for 15,667 men and women. Fractures were documented by hospital record linkage.

The Epidemiologie de l'osteoporose (EPIDOS) study comprises a population-based cohort from five French centres (Amiens, Lyon, Montpellier, Paris and Toulouse) [28]: women were recruited through mailings using large population-based listings such as voter registration rolls. For this analysis, ultrasound and validated fracture follow-up were available for 5978 women. Fractures were documented by self-report, family report or physician report.

Table 1 Details of cohorts studied

Cohort	Number	Length of follow-up (years) Mean (max)	Age (years) Mean (range)	Female (%)	Femoral neck BMD (<i>n</i>)	DXA equipment	QUS equipment
ECOSAP ^a	4711	2.9 (4.1)	72 (65–100)	100	–	–	Sahara ^b
EPIC-Norfolk	15,667	5.4 (6.9)	62 (42–82)	56	–	–	CubaClinical ^c
EPIDOS	5978	3.4 (5.0)	80 (70–100)	100	5956	DPX ^d	Achilles ^d
EVOS/EPOS	178	2.7 (3.5)	62 (50–85)	48	121	?	Achilles ^d
MrOS/MsOS HK ^a	3990	3.7 (5.4)	72 (65–98)	50	3990	QDR4500 ^b	Sahara ^b
MrOS US ^a	5205	8.6 (11.6)	74 (64–100)	0	5204	QDR4500 ^b	Sahara ^b
OPUS	1632	6.1 (8.2)	62 (20–81)	100	1610	QDR 4500 ^b /Expert ^d	QUS-2 (BUA) ^c Achilles Plus (SOS) ^d
SEMOF	7062	2.8 (4.9)	75 (70–91)	100	908	QDR4500 ^b	Sahara ^b
Sheffield	1701	3.9 (5.8)	80 (74–96)	100	1684	QDR4500 ^b	CubaClinical ^c
Total	46,124	4.7 (11.6)	70 (20–100)	69	19,473	–	–

^a Denotes that the cohort was not population based

^b Hologic, Bedford, MA

^c McCue

^d GE-Lunar Corp

^e Metra/Quidel

The European Vertebral Osteoporosis Study/European Prospective Osteoporosis Study (EVOS/EPOS) comprised age- and sex-stratified random samples from multiple centres in 19 European countries [29–31]. For this analysis, ultrasound and validated fracture follow-up were available for 178 women from Cambridge, UK. Fractures were documented by self-report and were confirmed where possible by radiograph, attending physicians or subject interview.

MrOS and MsOS Hong Kong comprised a cohort of 2000 Hong Kong Chinese men and women, 65 years of age or older [32]. Stratified sampling was used in order to obtain approximately one third of the subjects in each of the following age groups: 65–69, 70–74 and ≥ 75 years. All eligible subjects were community-dwelling and ambulatory. For this analysis, ultrasound and validated fracture follow-up were available for 3990 men and women. Fractures were documented by self-report and confirmed by X-ray or medical record.

MrOS USA is a multicentre prospective study of risk factors for vertebral and all non-vertebral fractures in 5995 community-dwelling men [33, 34] aged 65 years or older. For this analysis, ultrasound and validated fracture follow-up were available for 5205 men. Fractures were documented by self-report and confirmed by X-ray or medical record.

The Osteoporosis and Ultrasound Study (OPUS) comprised five age-stratified population-based female cohorts drawn from different European centres (Sheffield and Aberdeen (UK), Berlin and Kiel (Germany) and Paris (France)) [35, 36]. Participants completed a questionnaire at baseline, and BMD was measured by DXA using the Hologic QDR 4500 (Kiel, Paris and Sheffield) or the Lunar Expert (Aberdeen and Berlin). Baseline estimates for ultrasound were

available in 1632 women, and incident fractures were documented from hospital, general practitioner or individual imaging databases.

The Osteoporotic Fracture Risk (SEMOF) study is a prospective study based in 10 Swiss centres with women randomly selected from an address register [37]. For this analysis, ultrasound and validated fracture follow-up were available for 7062 women, and fractures were documented by questionnaire and confirmed from medical records.

The Sheffield cohort comprised women aged 75 years or more selected randomly from the population of Sheffield, UK, and surrounding districts identified from general practitioner listings. Willing participants fulfilling the inclusion criteria were randomly allocated to treatment with placebo or the bisphosphonate, clodronate, to study its effects on fracture risk; this analysis comprised women allocated to treatment with placebo only [38, 39]. For this analysis, ultrasound and validated fracture follow-up were available for 1701 women, and fractures were documented by self-report and confirmed by radiological reports.

The heel ultrasound devices provide two QUS parameters, namely broadband ultrasonic attenuation (BUA in dB/MHz) and speed of sound (SOS in m/s). We did not analyse machine specific outputs, such as stiffness (GE Lunar) or Est. BMD (Hologic), as such variables are not shared across all manufacturers. The contact for the devices could be water based (Achilles) or gel based (QUS-2, Sahara and CUBAClinical). We conducted an initial analysis of water- and gel-based devices; since the results were similar (data not presented), a single meta-analysis using both water- and gel-based measurements was made and presented in this paper. If data from both

Table 2 Details of incident fractures by cohort

Cohort	Person-years	Incident fracture						
		Osteoporotic	Hip	Vertebral	Distal forearm	Humerus/elbow	Rib	Pelvis
ECOSAP	13,655	261	49	–	98	48	23	13
EPIC-Norfolk	84,401	238	112	50	92	–	–	–
EPIDOS	20,578	838	244	–	256	192	174	60
EVOS/EPOS	431	11	0	–	2	0	–	–
MrOS/MsOS HK	14,616	147	42	33	58	16	18	5
MrOS US	44,740	657	168	160	76	85	187	46
OPUS	9886	90	13	7	54	21	–	–
SEMOF	19,639	534	80	99	184	104	37	42
Sheffield	6542	242	79	29	89	31	8	21
Total	214,488	3018	787	378	909	497	447	187

– Site of fracture not given

water and gel-based equipment were available in the same cohort, the gel-based measurement was chosen. Only the measurements of BUA and SOS in the EPIDOS and EVOS/EPOS studies, as well as the SOS measurements in OPUS, were exclusively water based.

Femoral neck BMD values and/or T-scores were available in subsets of patients by a variety of DXA equipment, including Hologic and GE Lunar scanners (Table 1). Within each cohort and scanner type, cohort specific z-scores were derived dependent on age and sex.

For fracture outcomes, we used information on fractures only at sites considered to be associated with osteoporosis [40], i.e. fractures of the spine, coccyx, ribs, pelvis, humerus, forearm, elbow, hip, other femoral, clavicle, scapula and sternum. Fractures of the skull, face, hands and fingers, feet and toes, distal tibia and fibula and ankle and patella were excluded. In addition to ‘osteoporotic fractures’, incident hip, distal forearm, upper arm (humerus and/or elbow), rib, pelvic and clinical vertebral fractures were considered separately.

Statistical methods

The analysis was conducted using individual-level data from within each cohort. For ultrasound measures and BMD a cohort specific z-score was calculated adjusted for age within each cohort. Thus, the mean BUA and SOS were 0 and the standard deviation 1. The association between these measures and the risk of fracture was examined using an extension of the Poisson regression model [41] in each cohort. The observation period of each participant was divided in intervals of 1 month. The first fracture per person was counted for each relevant outcome. Covariates included current age and time since start of follow-up, and analyses were performed with and without adjustment for BMD. The interaction between ultrasound and gender, ultrasound and age and also between ultrasound and time since baseline was studied. The β -coefficients from each cohort were weighted according to the variance and then merged to determine the weighted mean of the coefficient and its standard deviation. The associations

Table 3 Hazard ratios per 1 SD (GR) for fracture and 95 % confidence intervals (CI), according to different fracture outcomes adjusted for age

Fracture outcome	Not adjusted for BMD (<i>n</i> =46,124)		Adjusted for BMD (<i>n</i> =19,473)	
	BUA GR (95 % CI)	SOS GR (95 % CI)	BUA GR (95 % CI)	SOS GR (95 % CI)
Osteoporotic	1.45 (1.40, 1.51)	1.42 (1.36, 1.47)	1.22 (1.16, 1.28)	1.19 (1.13, 1.25)
Hip	1.69 (1.56, 1.82)	1.60 (1.48, 1.72)	1.21 (1.10, 1.33)	1.20 (1.09, 1.32)
Vertebral	1.40 (1.26, 1.55)	1.45 (1.30, 1.63)	1.25 (1.09, 1.43)	1.27 (1.10, 1.47)
Distal forearm	1.44 (1.34, 1.54)	1.41 (1.31, 1.51)	1.29 (1.18, 1.42)	1.21 (1.10, 1.32)
Humerus/elbow	1.45 (1.31, 1.59)	1.40 (1.27, 1.54)	1.24 (1.10, 1.40)	1.19 (1.06, 1.34)
Rib	1.24 (1.12, 1.37)	1.18 (1.07, 1.30)	1.09 (0.98, 1.22)	1.03 (0.93, 1.15)
Pelvis	1.52 (1.30, 1.78)	1.37 (1.17, 1.59)	1.26 (1.04, 1.53)	1.12 (0.93, 1.35)

HRs are adjusted for age and time since baseline

between ultrasound and risk of fracture were described as the hazard ratio (HR) for fracture per 1 SD change in ultrasound (gradient of risk (GR)) together with 95 % confidence intervals (CI).

Heterogeneity between cohorts was tested by means of the I^2 statistic [42]. A fixed effects rather than a random effects model was used. In order to study the association between ultrasound and fracture risk in more detail, a spline Poisson regression model was fitted using cohort specific knots at the 10th, 50th and 90th percentiles of z-score of ultrasound (i.e. -1.28, 0.00, 1.28), as recommended by Harrell [43]. The splines were second-order functions between the breakpoints and linear functions at the tails resulting in a smooth curve. When the HR per 1 SD (GR) below and above 0 was studied, a piecewise linear Poisson regression model was fitted using 0 (the mean of the z-score) as a specific knot. As an internal control, the association between femoral neck BMD and fracture outcome was studied.

Results

The cohorts comprised 46,124 men and women aged 20–100 years with an average age of 70 years, who were followed for approximately 214,000 person-years (Tables 1 and 2). During an average follow-up of 4.7 years, 3018 osteoporotic fractures were documented of which 787 were at the hip (Table 3).

Heterogeneity was found for the osteoporotic fracture and hip fracture outcomes for SOS ($I^2=80$ %, 95 % CI 60–88 and $I^2=79$ %, 95 % CI 62–89, respectively). For BUA, there was no significant heterogeneity between cohorts either for osteoporotic or hip fracture ($I^2=43$ %, 95 % CI 0–71 and $I^2=27$ %, 95 % CI 0–65, respectively). When the interaction between ultrasound and time since baseline was included, there was no longer a significant heterogeneity between cohorts for SOS

($I^2=3$ %, 95 % CI 0–31 for osteoporotic fracture and $I^2=30$ %, 95 % CI 0–67 for hip fracture).

Prediction of osteoporotic and hip fractures

There was a significant inverse association between QUS and fracture risk. For future osteoporotic fractures, the GR for BUA was 1.45 (95 % CI=1.40–1.51) and 1.69 (95 % CI=1.56–1.82) for hip fractures (Table 3), both adjusted for age. The HRs per 1 SD were similar and also statistically significant for SOS (1.42 and 1.60 for osteoporotic and hip fractures, respectively). For femoral neck BMD, the weighted GR was 1.6 (95 % CI 1.5–1.7) per SD decrease for the outcome of osteoporotic fracture and 2.3 (95 % CI 2.1–2.6) for incident hip fractures, both adjusted for age. The GRs for QUS were attenuated after adjustment for femoral neck BMD, but were still significant (GRs 1.19–1.22 for both BUA and SOS and the outcomes of osteoporotic fracture and hip fracture (Table 3)).

Figure 1 shows the association between ultrasound and fracture outcomes when spline curves were used. When using piecewise linear models with a breakpoint in ultrasound at z-score=0, there was a significant difference between the predictive power of ultrasound above and below 0 ($p<0.001$, for both BUA and SOS for outcomes of osteoporotic and hip fracture) (Table 4). For the outcome of osteoporotic fracture, the HR per 1 SD for SOS was 1.60 when ultrasound z-score was below 0 and 1.24 when ultrasound z-score was above 0, with similar results for the GR of SOS. For the outcome of hip fracture, the HR per 1 SD for SOS was 2.03 when ultrasound z-score was below 0 and 1.16 when ultrasound z-score was above 0, and again the GRs for SOS were similar.

Prediction of fracture at specific sites

The performance of QUS to predict fractures at specific sites was similar to that for all osteoporotic fractures, whether

Fig. 1 Relationship between BUA and risk of osteoporotic fracture (solid line) and hip fracture (dashed line) adjusted for age and time since baseline (The hazard ratio (HR) compares the risk at a given z-score of BUA with a z-score of 0)

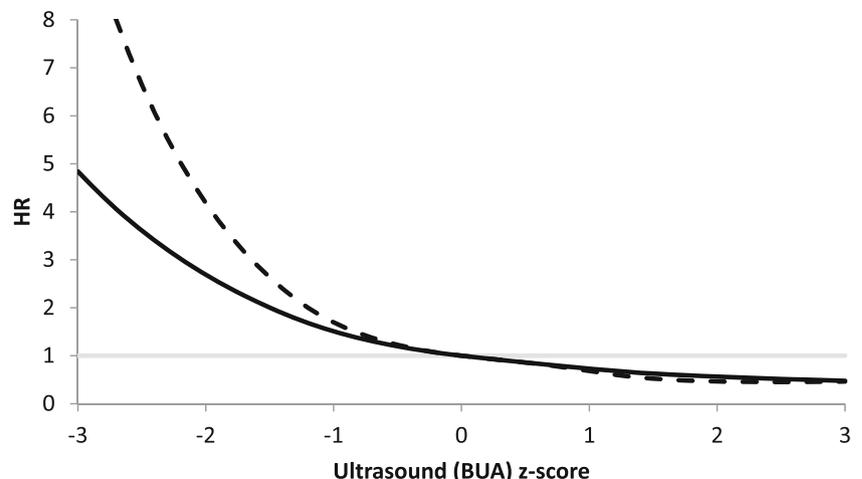


Table 4 Hazard ratios per 1 SD (GR) for fracture and 95 % confidence intervals (CI), according to different fracture outcomes adjusted for age (piecewise linear with breakpoint in ultrasound z-score 0)

Fracture outcome	BUA		SOS	
	Below 0 GR (95 % CI)	Above 0 GR (95 % CI)	Below 0 GR (95 % CI)	Above 0 GR (95 % CI)
Osteoporotic	1.60 (1.50, 1.71)	1.24 (1.14, 1.34)	1.69 (1.58, 1.80)	1.12 (1.04, 1.21)
Hip	2.03 (1.81, 2.28)	1.16 (0.99, 1.36)	2.05 (1.83, 2.31)	1.04 (0.90, 1.20)

HRs are adjusted for age and time since baseline

adjusted for femoral neck BMD or not (Table 3), apart from rib fractures where the predictive power was somewhat lower; when adjusted for BMD, the association with rib fracture was no longer significant.

Prediction of fracture in men and women

When comparing predictive ability in men and women, there were no significant differences (Fig. 2) in the gradients of risk of QUS for the outcomes of osteoporotic fracture and hip fracture ($p=0.10$ and $p=0.17$, respectively for BUA). For example, for the outcome of osteoporotic fracture, the GR for BUA, unadjusted for BMD, was 1.38 (95 % CI 1.28–1.48) for men and 1.48 (1.42–1.55) for women. When adjusted for BMD, there were no significant differences between genders in GRs for osteoporotic fracture and hip fracture ($p=0.10$ and $p=0.13$, respectively). For example, for the outcome of osteoporotic fracture, the GR for BUA was 1.16 (95 % CI 1.07–1.25) for men and 1.26 (1.18–1.34) for women.

Interactions of age and time since baseline with heel QUS

There was no significant interaction between QUS and age for either BUA or SOS for osteoporotic or hip fracture outcomes ($p>0.20$), i.e. the predictive value of ultrasound was the same

for all ages. There was no significant interaction between QUS and time since baseline for either BUA or SOS for the outcome of hip fracture ($p=0.28$ and $p>0.30$, respectively). There were, however, significant interactions between QUS and time since baseline for BUA and SOS for the outcome of osteoporotic fracture ($p=0.018$ and $p=0.010$, respectively), such that the predictive power of QUS decreased with time (Fig. 3). For example, the GR of BUA for osteoporotic fracture, adjusted for age, was 1.51 (95 % CI 1.42–1.61) at 1 year after baseline, but at 5 years after baseline, it was 1.36 (95 % CI 1.27–1.46). For SOS, the corresponding GRs were 1.46 and 1.31, respectively. For comparison, there was no significant interaction between time since baseline and femoral neck BMD for hip fracture or osteoporotic fracture ($p>0.30$ for both). The GR of BMD for osteoporotic fracture was 1.6 (95 % CI: 1.5–1.8) at 1 year after baseline and was still 1.6 (95 % CI: 1.3–1.9) at 5 years after baseline. For hip fracture, the respective GRs were 2.4 (95 % CI 1.3–4.4) and 2.2 (95 % CI 1.2–3.9).

Discussion

This meta-analysis of individual-level data from over 46,000 individuals in nine prospective cohort studies has

Fig. 2 Hazard ratio per 1 SD for fracture outcome (osteoporotic fracture and hip fracture) and 95 % confidence interval, adjusted for age and time since baseline

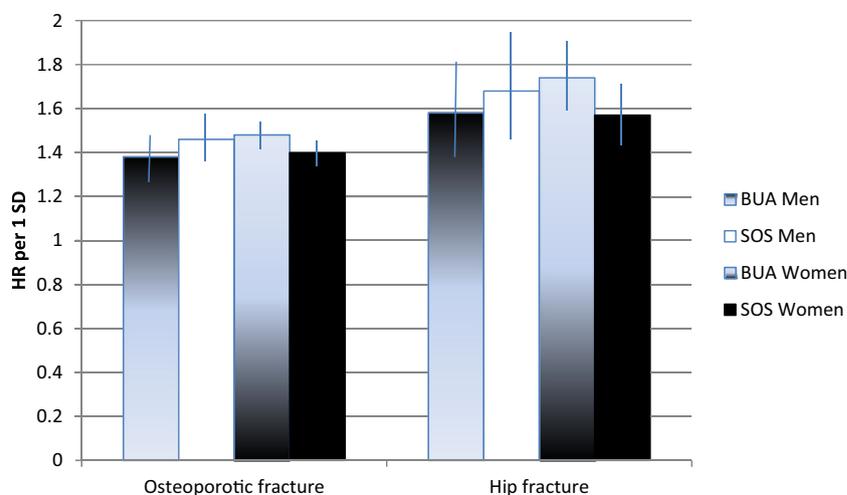
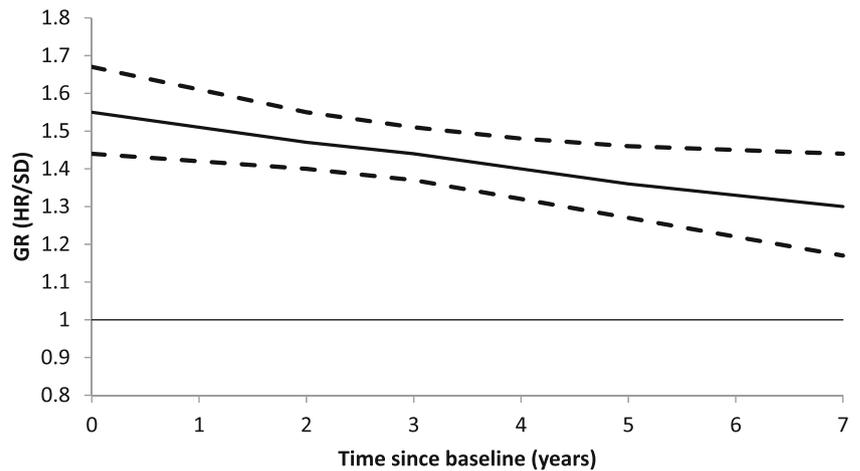


Fig. 3 Gradient of risk per 1 SD (95 % confidence interval) for the association between ultrasound BUA and the risk of osteoporotic fracture adjusted for age and current time



demonstrated a significant relationship between low heel QUS values and increased future fracture risk, independently of age and other covariates. Depending on the QUS parameter and the type of fracture, the estimated relative risks were all statistically significant and ranged between 1.23 and 1.94 for each SD decrease in QUS measurements. The current analysis adds two new pieces of information about the relationship between QUS and fracture risk; firstly, the GR is much lower at higher values of QUS than at lower values (below the population mean). Furthermore, there is a significant waning of the predictive ability of QUS for osteoporotic fractures, but not hip fractures, with increasing time of follow-up.

The gradients of risk for osteoporotic or hip fractures are similar to those reported for peripheral or axial DXA [44–46] and our results are very consistent with those reported for QUS in previous meta-analyses undertaken using summary statistics [18, 19]. The strength of the current analysis, by virtue of access to the primary data, is the ability to look for nonlinearity in its predictive ability to undertake adjustment of QUS for other variables at the individual level and to examine for nuances such as the interaction of the predictive ability of QUS with time since measurement. It demonstrates several features that would impact on the clinical implementation of QUS in predictive tools such as FRAX. For example, like femoral neck BMD, it appears that QUS has a similar predictive ability for fractures in both men and women. While male subjects were only available within some of the cohorts, our conclusion is consistent with a larger meta-analysis using summary statistics by Moayyeri and colleagues [19]. In addition, the predictive ability as expressed by the GR is not constant across the range of values observed in populations; the assumption of linearity in statistical analyses would therefore tend to underestimate the GR for QUS in those at highest risk of fracture and overestimate the risk in those at lower risk. A similar increase in GR for osteoporotic fractures has been observed at lower values of femoral neck BMD [44]. Finally, the novel finding that the predictive ability of QUS for

osteoporotic fracture decreases with time has important implications for the incorporation of QUS into fracture risk prediction models. The cause of the slow but significant decline in predictive ability remains speculative. Fluctuations in measurements may contribute, but the natural history of changes in QUS parameters over time within individuals is poorly documented. The decreasing effect with time is not unexpected. Indeed, the risk of a subsequent fracture following a previous fracture appears to diminish with time [47, 48]. Similar observations have been reported for other risk variables including adiponectin when used to predict fracture risk in men [49] and for serum vitamin D when used to predict mortality [50]. With relatively short observation times, a decreasing effect may be due to heterogeneity in the natural history of disease as reported for some of the biochemical markers of bone turnover [51, 52]. If the interaction that we observe with QUS is implemented in fracture prediction models, the accuracy of the prediction will be improved but may also demonstrate that QUS has a significant role in the short-term assessment of fracture risk but a more limited role over a 10-year time horizon.

A limitation of the study is that BMD was only available in a subset of participants, but its availability provided a good internal control within the analysis. As noted above, the association between femoral neck BMD and fracture risk, particularly hip fracture risk, was similar in this subset to that reported in a previous meta-analysis [44]. It is important to note that the GRs for QUS were still somewhat lower than those observed for femoral neck BMD for osteoporotic and hip fractures. Nonetheless, QUS remained a significant predictor of osteoporotic and hip fractures following adjustment for femoral neck BMD, though the GRs were somewhat attenuated. It remains unclear whether this relates to differences in the bone parameters captured by QUS and BMD or is a result of measuring two different skeletal sites. A further limitation is that our analysis did not have access to other skeletal sites of BMD to determine whether this independence was observed

with identical technologies at different sites. Furthermore, despite a good representation of studies, a number of other, relatively large studies of QUS and fracture risk have not been included; for example, data from the National Osteoporosis Risk Assessment study [53] or the Fracture Risk Epidemiology in the frail Elderly (FREE) study [54, 55] were not available to us at the time of the analysis.

In conclusion, QUS is a significant predictor of osteoporotic fractures and hip fractures similar to other axial or peripheral measures of bone strength, but is a weaker predictor than femoral neck BMD for hip fractures. The predictive value is greater at lower values of QUS and decreases slowly over time, at least for osteoporotic fractures. In a clinical setting, there is a need to integrate QUS with clinical risk factors for the assessment of fracture risk and this will be the subject of subsequent analyses, including reclassification analyses.

Conflicts of interest None.

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