

Impact of Femoral Neck and Lumbar Spine BMD Discordances on FRAX Probabilities in Women: A Meta-analysis of International Cohorts

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Abstract There are occasional marked discordances in BMD T-scores at the lumbar spine (LS) and femoral neck (FN). We investigated whether such discordances could contribute independently to fracture prediction using FRAX. We studied 21,158 women, average age 63 years, from 10 prospective cohorts with baseline FRAX variables as well as FN and LS BMD. Incident fractures were collected by self-report and/or radiographic reports. Extended Poisson regression examined the relationship between differences in LS and FN T-scores (Δ LS–FN) and fracture risk, adjusted for age, time since baseline and other factors including FRAX 10-year probability for major osteoporotic

fracture calculated using FN BMD. To examine the effect of an adjustment for Δ LS–FN on reclassification, women were separated into risk categories by their FRAX major fracture probability. High risk was classified using two approaches: being above the National Osteoporosis Guideline Group intervention threshold or, separately, being in the highest third of each cohort. The absolute Δ LS–FN was greater than 2 SD for 2.5 % of women and between 1 and 2 SD for 21 %. Δ LS–FN was associated with a significant risk of fracture adjusted for baseline FRAX (HR per SD change = 1.09; 95 % CI = 1.04–1.15). In reclassification analyses, only 2.3–3.2 % of the women

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moved to a higher or lower risk category when using FRAX with Δ LS–FN compared with FN-derived FRAX alone. Adjustment of estimated fracture risk for a large LS/FN discrepancy ($>2SD$) impacts to a large extent on only a relatively small number of individuals. More moderate (1–2SD) discordances in FN and LS T-scores have a small impact on FRAX probabilities. This might still improve clinical decision-making, particularly in women with probabilities close to an intervention threshold.

Keywords FRAX · BMD · Discordance · Reclassification · Fracture risk

Introduction

FRAX[®] calculates 10-year fracture probability from readily obtainable clinical risk factors (CRFs) in men and women (<http://www.shef.ac.uk/FRAX>) [1–3]. The fracture risk calculation can be enhanced by the optional entry of bone mineral density (BMD) measured at the femoral neck (FN), the only skeletal region of interest currently validated for use with FRAX [1]. The principal reason for the inclusion of FN BMD into FRAX was its wide availability in the development cohorts; lumbar spine (LS) BMD was available in only about half the number of individuals compared to femoral neck BMD, with peripheral BMD available in even fewer. FN BMD also has the advantage that for any given age and BMD, the fracture risk is approximately the same in men and women so that the T-score used in FRAX is derived from a single reference standard (i.e. the NHANES III database for female Caucasians aged 20–29 years) [4, 5]. Additionally, FN BMD is associated with a higher gradient of risk for hip fracture than BMD measurements at other sites, with similar or better prediction of major fractures when appropriate adjustment is made to the units of BMD [6, 7]. Notwithstanding, measurements of BMD at sites other than the FN provide significant information on fracture risk [4, 6, 7].

In clinical practice, LS BMD is frequently measured by dual-energy X-ray absorptiometry (DXA) at the same visit as FN BMD. Indeed, LS BMD is incorporated into several clinical guidelines and is the preferred measurement site

for monitoring treatment [8–10]. Although the combination of these two skeletal sites does not improve the general predictive ability (sensitivity/specificity) for future fractures, there are situations when a large discordance in the T-score at the two sites in a given individual may enhance the accuracy for risk characterisation [11–13]. In a recent analysis of a large referral cohort, there was approximately a 10 % change in fracture probability for each unit of T-score discordance, and the authors proposed that the clinician may “Increase/decrease FRAX estimate for a major fracture by one-tenth for each rounded T-score difference between the lumbar spine and femoral neck” [14]. We wished to determine the impact of a T-score discordance in independent population-based cohorts and to examine the impact of the discordance on reclassification of patients across risk thresholds.

Materials and Methods

We studied women in whom FRAX variables and BMD at both the FN and LS were recorded at baseline with subsequent follow-up fracture data from 10 prospective population-based cohorts from North America, Europe, Asia and Australia as follows:

Women’s Health Initiative (WHI) Study

The study comprises three overlapping randomised controlled studies and an observational study in post-menopausal women aged 50–79 years [15, 16]. Women on HRT or other bone-active medications were excluded from the analysis. Bone mineral density measurements at the FN and LS were measured using the Hologic QDR2000. Incident hip fractures were documented from medical records and adjudicated at a central facility, while non-hip fractures were locally adjudicated. For this analysis, BMD, FRAX estimation and validated fracture follow-up were available for 4,039 women.

Canadian Multicentre Osteoporosis Study (CaMOS)

This is an on-going prospective age-stratified cohort documenting risk factors and the incidence of fractures in a random sample of 9,424 men and women aged 25 years or more selected by telephone listings [17]. Family history of fracture captured any fracture, not just hip fracture. BMD was measured by DXA at the FN and LS by Hologic QDR or Lunar DPX equipment. Machines were cross-calibrated using the same European Spine Phantom. For this analysis, BMD, FRAX and validated fracture follow-up data were available for 4,871 women.

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Osteoporosis and Ultrasound Study (OPUS)

OPUS comprises five age-stratified population-based female cohorts drawn from different European centres (Sheffield and Aberdeen (UK), Berlin and Kiel (Germany), and Paris (France)) [18, 19]. 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 BMD at both skeletal sites and FRAX estimates were available in 2,176 women. Incident fractures were documented from hospital, general practitioner or individual imaging databases.

Rochester Cohorts

These comprised two random population samples stratified by decade of age, one followed for up to 20 years and the other for 8 years [20, 21]. Current smoking was captured as ever use of smoking. Data on rheumatoid arthritis and alcohol intake were absent and set to “No” in the analysis of FRAX. BMD of the right femoral neck was measured by dual photon absorptiometry in the first cohort (cross-calibrated to DXA) and by DXA (Hologic QDR 2000) in the second group. Fractures were ascertained by periodic interview combined with review of the in-patient and outpatient medical records of all local care providers. For this analysis, BMD, FRAX probabilities and validated fracture follow-up were available for 487 women.

Dubbo Osteoporosis Epidemiology Study (DOES)

This is a population-based study with multiple assessments of skeletal status in men and women aged 60 years or more from Dubbo, Australia [22, 23]. A family history of osteoporosis was used instead of a parental history of hip fracture. Baseline measurements included BMD at the FN and LS assessed using DXA (GE-Lunar DPX and Prodigy). Fractures were identified through radiologists’ reports. For this analysis, BMD, FRAX and validated fracture follow-up were available for 1,221 women.

Adult Health Study (AHS)

The AHS was established in 1958 and documents the late health effects of radiation exposure among atomic bomb survivors in Hiroshima and Nagasaki, originally comprising about 15,000 survivors and 5,000 controls. Data on family history, rheumatoid arthritis and alcohol intake were not captured and set to “no” in FRAX calculations. BMD was measured at the both skeletal sites by DXA in 1994 (Hologic QDR 2000) [24, 25]. For this analysis, BMD, FRAX and validated fracture follow-up were available for 1,318 women.

European Vertebral Osteoporosis Study/European Prospective Osteoporosis Study (EVOS/EPOS)

These two linked studies comprised age- and sex-stratified random samples from multiple centres in 19 European countries [26–28]. Alcohol intake was entered as “yes” in FRAX, where the intake was documented as at least 5 days per week. BMD was measured at 13 centres by DXA at the FN and LS using pencil beam machines that were cross-calibrated using the European Spine Phantom. For this analysis, BMD, FRAX and validated fracture follow-up were available for 1,550 women.

Osteoporosis Risk Factor and Prevention Study (OSTPRE)

In a sub-study of this study [29], a prospective population sample of women aged 47–56 years who were residents of Kuopio province in 1989, 3,222 women underwent bone densitometry by DXA using the Lunar DPX. Incident fractures were captured by questionnaire on a yearly basis, but only validated fractures reviewed from medical records or X-rays were included in the analysis. For this analysis, BMD, FRAX and validated fracture follow-up were available for 2,711 women.

Aberdeen Prospective Osteoporosis Screening Study (APOSS)

5,119 women 45–54 years of age were randomly selected from a community-based register and attended a baseline visit between 1990 and 1994 [30]. All participants underwent bone densitometry of the LS and left FN by DXA using Norland scanners (Cooper Surgical, Trumbull, CT, USA). The mean time for follow-up was 9.7 years, ranging from a minimum of 7.5 years to a maximum of 12.2 years. For this analysis, BMD, FRAX and validated fracture follow-up were available for 1,154 women.

MsOS Hong Kong

This comprised a cohort of 2,000 Hong Kong Chinese women, 65 years of age or older [31]. 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. Trained interviewers conducted face-to-face interviews based on a structured and validated questionnaire. BMD of the LS and FN was measured using Hologic QDR-4500W densitometers. For this analysis, BMD, FRAX estimation and validated fracture follow-up were available for 1,631 women.

Table 1 Baseline characteristics of the cohorts included in the analysis of lumbar spine and femoral neck T-score offset

Cohort	N	Age (y)	BMI	Risk factor prevalence (%)				FRAX	FN T-score	Δ LS-FN T-score	Follow up (y; mean, total person years)	Incident fractures (total, hip, total/100 person years))		
				Prior fracture	Family history	Smoking	GC						RA	Alcohol
Aberdeen	1154	48 ± 1	25 ± 4	13	8	26	4	1	3	4.3 ± 2.2	-0.6 ± 1.1	0.1 ± 0.8	9.9, 11450	47, 1, (0.41)
Dubbo	1221	70 ± 7	26 ± 5	14	20	7	7	4	8	9.4 ± 8.7	-1.8 ± 1.0	-0.0 ± 0.9	8.1, 9867	237, 76, (2.40)
CaMOs	4871	63 ± 10	27 ± 5	41	36	14	1	7	1	13.8 ± 10.3	-1.4 ± 1.1	0.0 ± 0.8	6.2, 30299	340, 59, (1.12)
EVOS	1550	63 ± 8	27 ± 5	34	9	13	7	-	9	9.6 ± 8.1	-1.4 ± 1.1	0.1 ± 0.9	3.0, 4395	117, 4, (2.66)
Hiroshima	1318	65 ± 10	23 ± 4	27	-	9	3	-	-	10.1 ± 6.5	-1.5 ± 1.1	0.0 ± 0.9	4.0, 5211	55, 16, (1.06)
Kuopio	2711	52 ± 3	26 ± 4	19	7	11	3	5	3	4.2 ± 3.1	-0.9 ± 1.0	0.3 ± 0.9	12.2, 33101	314, 10, (0.45)
Rochester	487	64 ± 14	26 ± 5	21	52	41	4	-	-	16.0 ± 11.9	-1.4 ± 1.2	-0.0 ± 1.0	8.5, 4148	165, 41, (3.98)
MsOs HK	1631	72 ± 5	24 ± 3	19	5	2	0	2	0	12.2 ± 7.4	-1.9 ± 1.0	-0.1 ± 1.0	3.5, 5719	81, 15, (1.42)
Opus	2176	67 ± 7	27 ± 5	43	11	14	3	7	1	11.7 ± 8.4	-1.5 ± 1.0	0.0 ± 0.9	6.0, 9568	89, 8, (0.93)
WHI	4039	66 ± 6	28 ± 6	18	13	8	1	6	3	11.9 ± 8.2	-1.6 ± 1.0	0.0 ± 0.8	7.8, 31312	399, 77, (1.27)
Total	21158	63 ± 10	26 ± 5	27	17	12	3	4	3	10.6 ± 8.7	-1.4 ± 1.1	0.1 ± 0.9	7.1, 145069	1844, 307, (1.27)

Continuous variables are shown as mean ± SD unless otherwise stated

BMI body mass index (kg/m²); GC glucocorticoids; RA rheumatoid arthritis; FRAX 10 year probability of major osteoporotic fracture calculated with BMD; FN femoral neck; LS lumbar spine; Δ LS-FN difference between LS and FN T-score

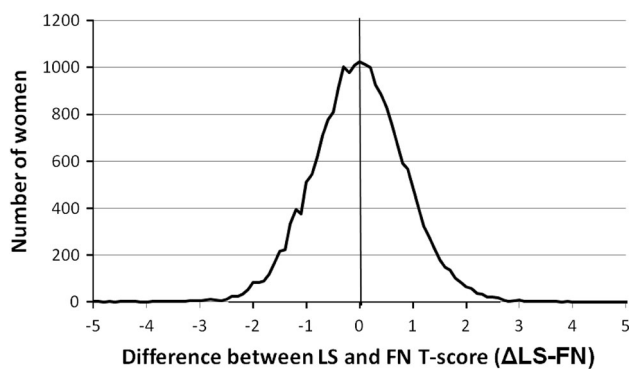


Fig. 1 Distribution of differences between lumbar spine (LS) and femoral neck (FN) BMD T-scores. Standard deviation values to the left of zero represent individuals in whom the LS T-score was lower than FN, and vice versa

Statistical Analysis

FRAX probabilities were computed using the appropriate country models for the study cohorts. Differences in scanning equipment between cohorts were accommodated by the use of cohort-specific z -scores for BMD prior to conversion to T-scores using NHANES III reference data for the femoral neck and Hologic reference data for the lumbar spine. We have been able to compare this approach to actual reported T-scores in a small sample of the cohorts that also provided original T-scores to us. The mean difference in T-score was -0.3 suggesting that our calculated T-score values were slightly lower than those produced locally by the manufacturer's reference range. The difference between LS and FN T-scores ($\Delta\text{LS-FN}$) was calculated by simply subtracting the FN T-score from that at the LS.

Risk for major osteoporotic fracture, including clinical vertebral fracture, hip fracture, forearm or humerus fracture, was investigated using an extended Poisson model applied to each cohort, with subsequent merging of the β -coefficients from each cohort, weighted according to the variance. The gradient of risk was estimated as the hazard ratio (HR) for a 1SD decrease in $\Delta\text{LS-FN}$. Adjustment was made for age, time from baseline and FRAX probabilities. As LS BMD can be artefactually increased with advancing age due to disorders such as degenerative changes and aortic calcification, we also explored if the HR differed for those with higher LS than FN T-scores and those where the LS T-score was lower than that at the FN.

Finally, we examined the impact of taking account of the discordance by looking at the proportion of patients reclassified using two approaches; first, we utilised the National Osteoporosis Guideline Group (NOGG) intervention thresholds as utilised in European guidance [32,

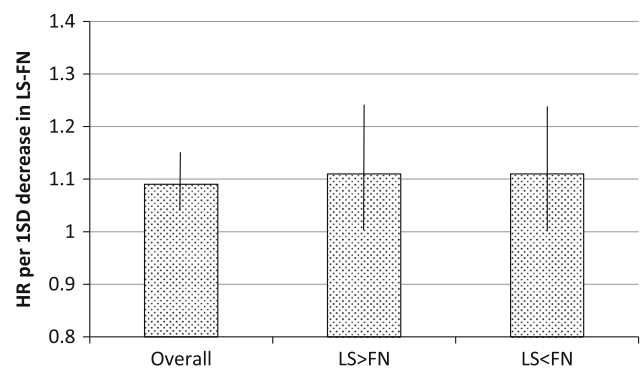


Fig. 2 Hazard ratios (HR) per 1SD decrease in $\Delta\text{LS-FN}$ with 95 % confidence intervals in the whole population (overall) and in the subgroups, where the LS T-score was greater than FN T-score and vice versa. The HRs are adjusted for age, time since baseline and FRAX major osteoporotic fracture probability

33] and the UK [34] and secondly, given the fact that different country models were used, we also derived cohort-specific thresholds that categorised the highest third of FRAX probabilities to be “at risk” within each cohort.

Results

The analysis population comprised 21,158 women, ranging in age from 40–90 years with an average age of 63 years (SD 10 years) (Table 1). During a mean follow-up of 7.4 years, 1,844 women sustained one or more major osteoporotic fracture.

Discordance Between LS and FN T-Scores

The mean T-score was similar at the FN (-1.40 , SD 1.11) and LS (-1.35 , SD, 1.21) with a mean T-score offset ($\Delta\text{LS-FN}$) of $+0.05$ (SD 0.89). Discordances between T-scores at the two measurement sites showed a near normal distribution (Fig. 1). Major discrepancies (>2 SD) in T-scores between the two sites were uncommon, comprising 2.5 % of all the participants. Those with major discrepancies were of similar mean age to the cohort as a whole (mean 63, 63 and 66 years for the whole cohort, those with FN lower than LS and those with FN higher than LS, respectively). Moderate discordances (between 1 and 2 SDs) were more frequent but still comprised a minority of the study population (21 %).

Impact of Spine and Femoral Neck Discordance ($\Delta\text{LS-FN}$) on Fracture Prediction

In multivariate models, adjusted for age, time since baseline and FN-BMD, $\Delta\text{LS-FN}$ was a significant independent

Table 2 Analysis of reclassification across National Osteoporosis Guideline Group (NOGG; www.shef.ac.uk/NOGG) intervention thresholds following adjustment of FRAX probabilities for LS–FN discordance in women aged >50 years (% of total number)

FRAX	FRAX adjusted for Δ LS–FN	
	Below threshold	Above threshold
Below threshold	15,161 (82.9)	166 (0.9)
Above threshold	262 (1.3)	2,904 (14.9)

Table 3 Analysis of reclassification across cohort-specific thresholds (highest third) following adjustment of FRAX probabilities for LS–FN discordance in all women (% of total number)

FRAX	FRAX adjusted for Δ LS–FN	
	Below threshold	Above threshold
Below threshold	13,730 (64.9)	286 (1.4)
Above threshold	393 (1.9)	6,749 (31.9)

predictor of major osteoporotic fracture risk (GR 1.20, 95 % CI 1.07–1.35, $p < 0.001$) but not of hip fracture risk (GR 1.04, 95 % CI 0.92–1.17, $p > 0.30$).

In a further multivariate model, adjusted for age, time since baseline and the 10-year probability of a major osteoporotic fracture, Δ LS–FN still remained a significant predictor of major osteoporotic fracture risk. This suggests that low BMD at the LS, relative to that at the FN, is a predictor of increased fracture risk. Each 1SD decrease in Δ LS–FN was associated with a 9 % increase in fracture risk (GR 1.09, 95 % CI 1.04–1.15) (Fig. 2).

When the study population was dichotomised into those with lower LS than FN T-scores versus those with higher LS T-scores, the gradient of risk in each group was similar in both groups (HR 1.11, 95 % CI 1.00–1.24) to that observed when the whole population was included in a single analysis (Fig. 2).

Impact of Discordance on Reclassification

In this analysis, the original FRAX probability for each individual was adjusted as follows. Where the Δ LS–FN was between -1 and $+1$ SDs, no adjustment was made; where Δ LS–FN was between 1 and 2 SDs, the FRAX probability was increased or decreased by 10 % in those where the LS T-score was lower or higher, respectively; for those with Δ LS–FN between 2 and 3 SDs, the FRAX probability was increased or decreased by 20 % and so on.

The outcomes of the reclassification analyses using the NOGG intervention thresholds or the cohort-specific thresholds (highest third) are shown in Tables 2 and 3, respectively. A total of 2.2 % of the women were reclassified across the NOGG thresholds with more women

moving from above the threshold to below it compared to the converse movement (Table 2). A similar, small proportion (3.3 %) was reclassified using the cohort-specific thresholds, again with the majority moving from above to below the threshold (Table 3).

Discussion

The current study involving multiple international cohorts suggests that discordance between LS and FN BMD T-scores can contribute to fracture risk, independently of FRAX probabilities that incorporate FN BMD alone. The effect is small, however, with only a 9 % change in fracture risk for each 1SD difference in T-score between the two sites.

The present study has a number of limitations. We did not have access to the original scans and were unable to determine, therefore, whether vertebrae were excluded from analysis of LS BMD where there was evidence of significant confounding pathology, such as osteoarthritis, aortic calcification, facet joint arthritis or vertebral fracture. The fact that the discordant T-scores showed a near normal distribution, with an identical gradient of risk for those with higher or lower LS T-scores, suggests that this was not a significant limitation. A further limitation is the lack of consensus over an international reference standard for LS BMD. Recently, LS BMD values have also been published from NHANES III and it would be possible to re-compute our LS T-scores using these data [35]. It should be noted, however, that whilst the absolute LS T-score values may differ slightly, as long as the variance is similar this would have little or no impact on the gradient of risk analysis that examines the risk associated with a 1 SD decrease in the difference between T-scores (Δ LS–FN). The present analysis has been confined to the impact of discordance on the risk of future major osteoporotic fractures in women. Whether a similar conclusion would be reached for the hip fractures remains untested, but is unlikely given the fact that there is no incremental benefit of LS BMD over FN BMD alone for the prediction of hip fractures [36]. It is not clear if a similar result would be obtained in men. Finally, the current analysis does not take into account potential interactions between Δ LS–FN and individual variables within FRAX or its potential interaction with mortality.

Our findings are in keeping with the report from the Manitoba cohort [14] that also demonstrated that discordances between FN and LS BMD T-scores can contribute to fracture risk. Bearing in mind some of the limitations of the analysis, the gradient of risk for the discordance between the two sites in the present analysis (1.09/SD) is very similar to that reported by Leslie and colleagues (1.12/SD) [14]. Indeed, we observed a gradient of risk of 1.11/SD

when the analysis was restricted to those subjects where the LS T-score was lower or higher than the FN. Leslie et al. have suggested that a relatively simple adjustment (approximately 10 % per SD) for major osteoporosis fracture probability may be an appropriate clinical tool to take such discordances into account. It is, however, important to note that the number of individuals who were reclassified following adjustment was small (2.3 % and 3.3 % for the NOGG and cohort-specific thresholds). At first glance, these values seem somewhat lower than the 8.3 % reclassification reported by Leslie [14]. This reflects a slight difference in the method of utilising Δ LS–FN for the estimation of the offset; in this study, for example, we applied the same weight to Δ LS–FN between -1 and -2 , whereas Leslie used rounding to the nearest integer. While this will have a small impact to decrease the reclassification in our study, it is important to recall that the analysis of reclassification in the Manitoba study used movement across two thresholds (low-, medium- and high-risk groups). This would have been approximately halved with the use of a single threshold as in the NOGG approach that we have used. The small increment in risk stratification almost certainly reflects the modest, but significant, correlations between measurements of BMD at both sites ($r = 0.5\text{--}0.7$) [37, 38].

In summary, major discordances between LS and FN BMD T-scores are relatively uncommon but recognition of this issue may enhance the assessment of fracture risk where they exist. Our findings in a number of international cohorts are similar to that reported from a single cohort previously. It is important to note that adjustment of FRAX for these discrepancies impacts to a large extent on only a relatively small number of individuals in the context of clinical practise, but our results do provide some guidance for physicians, particularly those that report on the output of DXA to primary care.

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Conflict of Interest There are no conflicts of interest to declare.

Human and Animal Rights and Informed Consent Participants in the cohorts included in this analysis provided informed consent at enrolment to the individual cohort studies.

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