**Article:**
Schini, M. orcid.org/0000-0003-2204-2095, Lui, L.-Y., Vilaca, T. orcid.org/0000-0002-9227-6076 et al. (6 more authors) (2025) The relationship between baseline bone mineral density and fracture incidence in the placebo groups of randomized controlled trials using individual patient data from the FNIH-ASBMR-SABRE project. Journal of Bone and Mineral Research, 40 (3). pp. 307-314. ISSN 0884-0431

https://doi.org/10.1093/jbmr/zjae201

*Journal of Bone and Mineral Research*, 2025, **00**, 1–8
https://doi.org/10.1093/jbmr/zjae201
Advance access publication: December 16, 2024
**Research Article**

# The relationship between baseline bone mineral density and fracture incidence in the placebo groups of randomized controlled trials using individual patient data from the FNIH-ASBMR-SABRE project

**Marian Schini[1,*], Li-Yung Lui[2], Tatiane Vilaca[1], Susan K. Ewing[3], Austin Thompson[3], Douglas C. Bauer[3,4], Mary L. Bouxsein[5], Dennis M. Black[3], Richard Eastell[1]**

[1]Division of Clinical Medicine, School of Medicine and Population Health, University of Sheffield, S10 2TN, Sheffield, United Kingdom
[2]California Pacific Medical Center Research Institute, San Francisco, 94158, CA, United States
[3]Department of Epidemiology and Biostatistics, University of California, San Francisco, 94158, CA, United States
[4]Department of Medicine, University of California, San Francisco, 94158, CA, United States
[5]Department of Orthopedic Surgery, Harvard Medical School, Center for Advanced Orthopedic Studies, Beth Israel Deaconess Medical Center, Boston, 02215, MA, United States

*Corresponding author: Marian Schini, Metabolic Bone Centre, Northern General Hospital, Herries Road, Sheffield S5 7AU, United Kingdom (m.schini@sheffield.ac.uk).

## Abstract

We have proposed to the Food and Drug Administration (FDA) that treatment-related increases in total hip BMD (TH BMD) at 2 yr could be a surrogate endpoint for fracture risk reduction in clinical trials. The qualification of a surrogate includes a strong association of the surrogate with the clinical outcome. We compiled a large database of individual patient data (IPD) through the Foundation for the National Institutes of Health-American Society for Bone and Mineral Research- A Study to Advance BMD as a Regulatory Endpoint (FNIH-ASBMR-SABRE) project, and this analysis aimed to assess the relationship between baseline BMD and fracture risk in the placebo groups. We estimated the association of baseline TH, femoral neck (FN), and lumbar spine (LS) BMD with fracture risk using IPD from the combined placebo groups, which included data from 46 666 placebo participants in 25 RCTs. We estimated the relative risk (RR) of fracture per SD decrease in baseline BMD using logistic regression models for radiographic vertebral fractures and proportional hazards models for hip, non-vertebral, "all," and "all clinical" fractures. Total person-years in the combined placebo groups was 250 662 (mean baseline age 70.2 ± 7.2 yr, mean TH BMD *T*-score −1.97 ± 0.90). We observed significant relationships between baseline TH BMD and vertebral (RR = 1.55/SD), hip (RR = 2.27), non-vertebral (RR = 1.31), all (RR = 1.43), and all clinical (RR = 1.35) fracture risk. Fracture risk estimates were similar for FN BMD and after adjustment for age, race, and study. Fracture incidence increased with decreasing TH BMD quintile, confirming the strong graded association between TH BMD and fracture risk. There was a strong relationship between LS BMD and vertebral fracture risk (RR = 1.56/SD), but only a weak association with non-vertebral (RR = 1.07) and no association with hip (RR = 1.01) fracture risk. These data support the very strong relationship between hip BMD and fracture risk and provide supporting rationale for change in TH BMD as a surrogate for fracture risk reduction in future RCTs.

**Keywords:** Bone mineral density, baseline BMD, SABRE, fracture risk, osteoporosis

## Lay summary

Bone mineral density (BMD) is the standard of care for the diagnosis of osteoporosis. In this study, we analyzed data from more than 40 000 placebo participants in 25 RCTs of medications used for osteoporosis. We showed that there is a strong relationship between low total hip BMD (TH BMD) and high risk of fractures.

## Introduction

We have proposed that treatment-related changes in total hip (TH) BMD at 2 yr could be a surrogate for fracture risk reduction in clinical trials, and a formal application for qualification of treatment-related changes in TH BMD as a surrogate endpoint in future trials is pending with the Food and Drug Administration (FDA).[1,2] One of the four pieces of support for using a surrogate to replace a clinical one in trials is to show that a single measurement of the proposed surrogate is strongly related to the clinical outcome in observational studies.[3] BMD has been shown in observational studies to be a very strong predictor of fracture, justifying its use in clinical practice for the diagnosis of osteoporosis. However, most previously published studies have assessed the femoral neck (FN) BMD rather than TH BMD.[4–9] Moreover, previously published studies do not have consistent definitions of fracture outcomes, and they mainly assess hip and/or all fractures, so more fracture categories need to be assessed to support this application.

We have compiled a very large database of individual patient data (IPD) from randomized trials of osteoporosis medications through the FNIH-ASBMR-SABRE project. This

**Received:** September 12, 2024. **Revised:** November 24, 2024. **Accepted:** December 13, 2024

analysis aimed to assess the relationship between BMD and fracture risk using data from pooled placebo groups in the randomized trials. We estimated the association between baseline TH BMD, FN BMD, and lumbar spine (LS) BMD and the risk of radiographic vertebral fractures, hip, non-vertebral, "all," and "all clinical" fractures.

## Materials and methods

The details of the FNIH-ASBMR-SABRE project have been previously described.[10,11]

Our analysis utilized five fracture endpoints: radiographic vertebral, non-vertebral, hip, all clinical (a combination of non-vertebral and clinical vertebral fractures), and all fractures (a combination of non-vertebral, clinical vertebral, and radiographic vertebral fractures). All non-vertebral fractures were included except for fractures of the skull, face, fingers, toes, and cervical spine, as well as fractures due to major trauma (ie, trauma sufficient to cause a fracture in a young, normal individual). For studies where trauma information was not available, all adjudicated fractures were included.

Bone mineral density (BMD) at the TH, FN, and LS were measured using various devices across studies (Hologic, GE Lunar, and Norland Corporation). Unstandardized hip BMD values for Lunar and Norland participants were converted to Hologic BMD values using equations provided in Lu et al.,[12] while spine BMD values were converted to Hologic values using equations provided in Hui et al.[13] This created Hologic-converted BMD values comparable across DXA devices. When available, the LS vertebrae L1-L4 were used; otherwise, L2-L4 were used. Reference values for young non-Hispanic white females from the NHANES III database were used to calculate the TH and FN BMD *T*-scores,[14] and Hologic reference values for young non-Hispanic white females were used to calculate the LS BMD *T*-score.

We included IPD from 25 RCTs (Table S1). Participants who were assigned to study treatment were excluded from all analyses since the objective of this analysis was to estimate the association between baseline BMD and fracture risk among untreated participants. Not all 25 trials had data for all 3 BMD sites and all 5 fracture outcomes; trials were included only in analyses for which data existed for a specific combination of BMD site and fracture outcome. Details about data availability for the 3 BMD sites and 5 fracture types for each study can be found in Table S1.

Baseline characteristics of the placebo participants included in the analysis were summarized using means and SDs for continuous measures and percentages for categorical measures.

We estimated the RR of fracture per SD decrease in baseline BMD using logistic regression models for radiographic vertebral fractures, where time to event is unknown, and proportional hazards models for non-vertebral, hip, "all" fractures, and all clinical fractures, where time to event is known. Since the "all" fractures outcome involves radiographic vertebral fractures, where exact time to event is unknown, and clinical fractures, where time to fracture is known, we applied an algorithm for determining time to first "all" fracture. In brief, each participant was assigned a random number between 0 and 1, and that number was applied to the time interval when a radiographic vertebral fracture occurred as an estimate of follow-up time for those who had a radiographic vertebral fracture. If a participant had both a clinical fracture and a radiographic vertebral fracture in the same time interval, we used the earliest of the two times as the time to first "all" fracture. Logistic regression models were performed using the PROC LOGISTIC procedure, with results reported as odds ratios (ORs) and 95% CIs, and proportional hazards models were performed using the PROC PHREG procedure, with results reported as hazard ratios (HRs) and 95% CIs per SD decrease in baseline TH, FN, or LS BMD. The SD for each BMD site was determined using all placebo participants with available BMD. The modeling was carried out both unadjusted and adjusted for baseline age, race (White vs others), and study (using dummy variables for the studies).

We provided bar charts displaying the fracture incidence rate per 1000 person-years by baseline BMD quintile. To estimate incidence for the vertebral fracture outcome, follow-up time was set to overall study follow-up for participants who did not fracture. For those who had an incident vertebral fracture, follow-up time was estimated as the number of years from baseline to the last negative vertebral radiograph. Estimation of follow-up time depended on the timepoints when each study assessed incident vertebral fracture status. To illustrate the interaction with age, we determined hip fracture incidence and vertebral fracture incidence according to the combination of baseline age (<65, 65-74, and ≥75 yr) and BMD quintile. We determined the risk of fracture per SD decrease in baseline BMD according to baseline age group, using logistic regression models for the vertebral fracture outcome and proportional hazards models for all other outcomes. Finally, we included both TH BMD and LS BMD in the same model to determine if the BMD associations were independent of one another.

We used SAS software to perform these analyses (version 9.4, SAS Institute Inc.).

**Table 1.** Baseline characteristics of the participants in the placebo groups of the 25 RCTs included in the analysis.

| | *N* = 46 666 |
|---|---|
| **Female, %** | 99.3 |
| **Age, yr (mean ± SD)** | 70.2 ± 7.2 |
| **Race, %** | |
| **White** | 75.3 |
| **Hispanic** | 14.3 |
| **Asian** | 8.2 |
| **Other** | 2.2 |
| **BMI (kg/m$^2$) (mean ± SD)** | 25.7 ± 4.4 |
| **Current smoker, %** | 10.7 (*n* = 42 337) |
| **FN BMD *T*-score (mean ± SD)** | −2.28 ± 0.74 |
| **TH BMD *T*-score (mean ± SD)** | −1.97 ± 0.90 |
| **LS BMD *T*-score (mean ± SD)** | −2.61 ± 1.15 |
| **Prevalent vertebral fracture, %** | 38.3 (*n* = 43 384) |
| **Prevalent non-vertebral fracture, %** | 33.0 (*n* = 16 957) |
| **History of falls in the past 12 mo, %** | 28.2 (*n* = 11 630) |
| **Maternal history of hip fracture, %** | 9.5 (*n* = 20 947) |

*n* refers to the number of people for whom we have information. Abbreviations: SD, standard deviation; BMI, body mass index; BMD, bone mineral density; FN, femoral neck; TH, total hip; LS, lumbar spine.

## Results

We included IPD from 25 RCTs (Table S1) (46 666 participants, 99.3% female, baseline age 70.2 ± 7.2 yr) (Table 1). We

**Table 2.** Number of individuals who fractured among those with available BMD measurements.

| Fracture events | TH hBMD | FN hBMD | LS hBMD |
|---|---|---|---|
| **Vertebral** | 2489 | 2817 | 2332 |
| **Hip** | 572 | 607 | 390 |
| **Non-vertebral** | 3540 | 3834 | 3013 |
| **All fracture** | 5810 | 6400 | 5117 |
| **All clinical** | 4109 | 4446 | 3501 |

Abbreviations: hBMD, Hologic-converted bone mineral density; FN, femoral neck; TH, total hip; LS, lumbar spine.

**Table 3.** Association between baseline BMD and incident fracture in the placebo group from combined studies: odds ratio or hazard ratio (95% CI) per 1 SD decrement.

| Fracture outcome | TH hBMD (per 1 SD [110 mg/cm$^2$] decrease) $N = 42\,847$[a] | | FN hBMD (per 1 SD [89 mg/cm$^2$] decrease) $N = 46\,125$[a] | | LS hBMD (per 1 SD [129 mg/cm$^2$] decrease) $N = 38\,669$ | |
|---|---|---|---|---|---|---|
| | **Unadjusted** | **Adjusted**[b] | **Unadjusted** | **Adjusted**[b] | **Unadjusted** | **Adjusted**[b] |
| **Vertebral** | 1.55 (1.48, 1.62) | 1.54 (1.46, 1.62) | 1.46 (1.40, 1.53) | 1.47 (1.39, 1.54) | 1.56 (1.48, 1.64) | 1.60 (1.52, 1.68) |
| **Hip** | 2.27 (2.09, 2.47) | 1.94 (1.78, 2.12) | 2.20 (2.01, 2.40) | 1.94 (1.77, 2.13) | 1.01 (0.92, 1.12) | 1.00 (0.90, 1.10) |
| **Non-vertebral** | 1.31 (1.27, 1.36) | 1.32 (1.28, 1.37) | 1.29 (1.25, 1.33) | 1.32 (1.28, 1.37) | 1.07 (1.03, 1.10) | 1.10 (1.05, 1.14) |
| **All** | 1.43 (1.39, 1.47) | 1.39 (1.35, 1.44) | 1.40 (1.36, 1.44) | 1.37 (1.33, 1.41) | 1.27 (1.23, 1.31) | 1.29 (1.25, 1.33) |
| **All clinical** | 1.35 (1.31, 1.39) | 1.34 (1.30, 1.39) | 1.31 (1.27, 1.35) | 1.33 (1.29, 1.38) | 1.13 (1.09, 1.17) | 1.16 (1.11, 1.20) |

SDs determined from all placebo participants. [a] $N = 33\,916$ for TH, $N = 36\,176$ for FN, and $N = 32\,502$ for LS among the subset of participants in the vertebral fracture analysis. [b] Adjusted for age, race (white vs others), and study. Abbreviations: hBMD, Hologic-converted bone mineral density; TH, total hip; FN, femoral neck.

had 541 184 person-years of observation among all participants while the total person years for the 46 666 placebo participants with at least one BMD measurement was 143 490. The number of placebo participants included in TH BMD analyzes was 33 916 for vertebral fractures and 42 847 for the other fracture categories (Table 2). The number of placebo participants included in the FN BMD analyzes was 36 176 for vertebral fractures and 46 125 for the other fracture categories (Table 2). Finally, for LS BMD, we included 32 502 participants for vertebral fractures and 38 669 for the other fracture categories (Table 2).

We observed strong and significant relationships between lower baseline hip BMD and increased fracture risk within the combined placebo groups for all five fracture types (Table 3). For each SD decrease in TH BMD, the unadjusted HRs ranged from 1.31 (95% CI 1.27, 1.36) for non-vertebral fractures to 2.27 (2.09, 2.47) for hip fractures. The respective associations for FN BMD were 1.29 (1.25, 1.33) and 2.20 (2.01, 2.40) (Table 3). The HRs for LS BMD were much smaller for the clinical fracture outcomes, as this site was not a good predictor for hip or non-vertebral fracture risk, and the CIs did not overlap those from TH or FN BMD. LS BMD was, however, a good predictor for vertebral fractures (unadjusted OR 1.56 [1.48, 1.64]), similar to the HRs for TH and FN BMD. Adding both LS and TH BMD in the same model for the prediction of vertebral fractures lowered the HR for TH, but this association still remained significant: the unadjusted HR for TH was 1.32 (1.25, 1.40). Additional adjustments for age, race, and study had little effect on the associations.

We also present the association between baseline BMD and incident fracture by age groups in the appendix (Table S2).

Fracture incidence increased with decreasing TH BMD quintile, confirming the strong graded association between TH BMD and fracture risk (Figure 1, Figure S1). For example, the incidence of hip fracture increased 10-fold from the highest to lowest TH BMD quintiles. Similarly, the incidence of vertebral and all clinical fractures was 2.7 and 2.4 times higher, respectively, in the lowest versus highest TH BMD quintiles. Relationships were similar for FN BMD (Figure S2). Vertebral fracture incidence increased 2.7-fold from the highest to lowest LS BMD quintiles, confirming the strong association between LS BMD and vertebral fracture risk (Figure 1). However, the grade was much weaker across the LS BMD quintiles for non-vertebral and all clinical fracture incidence, and there was a U-shaped association with hip fracture incidence (Figure 1, Figure S1).

When participants were grouped both by baseline BMD quintile and age group, the independent predictive strength of TH BMD remained strong for hip fractures (Figure 2) and vertebral fractures (Figure 3), with incidence generally increasing with decreasing BMD quintile within each age group. When the LS BMD quintile results were further stratified by age, the independent predictive strength of LS BMD remained strong for vertebral fractures, with incidence steadily increasing with decreasing LS BMD quintile within each age group (Figure 3). Stratification by age showed no relationship between LS BMD and hip fracture risk in any age group (Figure 2).

## Discussion

Using IPD data from 25 RCTs, we have shown that baseline hip BMD is a strong predictor of fracture risk. This large database was assembled to support an FDA application to qualify change in TH BMD as a surrogate biomarker, replacing fracture incidence as the primary endpoint for future

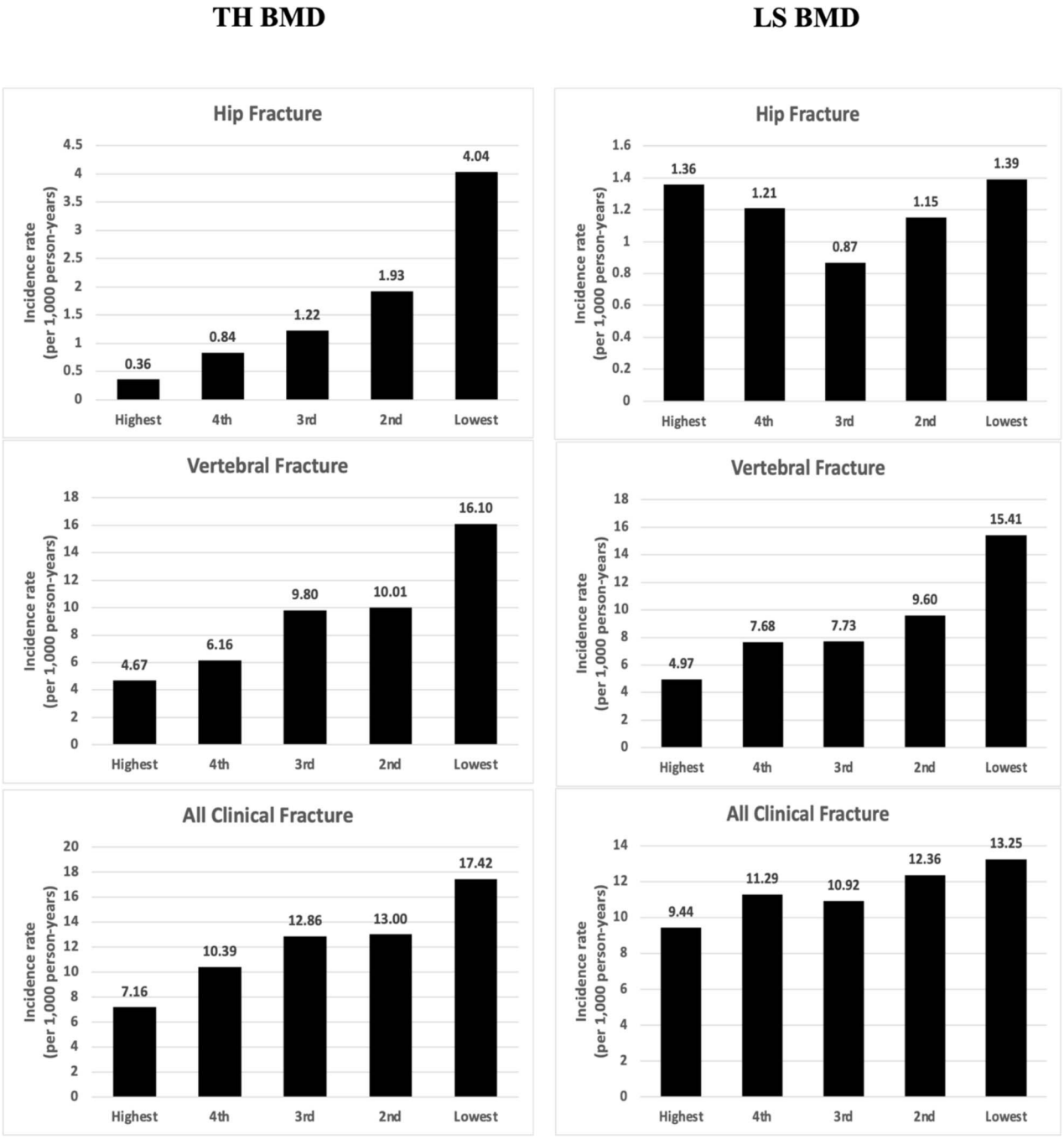


**Figure 1.** Left: Association between baseline total hip BMD and incident fracture risk, unadjusted. Fracture incidence is shown as rate per 1,000 person-years by baseline TH BMD quintile. For the vertebral fracture outcome incidence is the percentage of participants who fractured during follow-up. Right: Association between baseline LS BMD and incident fracture risk, unadjusted.TH BMD quintiles (mg/cm$^2$): first quintile (<612.9), second quintile (≥612.9< and <667.4), third quintile (≥667.4 and <721.8), fourth quintile (≥721.8 and <788.9), and fifth quintile (≥788.9). LS BMD quintiles: first (<665.0), second (≥665.0 and <724.2), third (≥724.2 and <774.4), fourth (≥774.34 and <857.3), and fifth (≥857.3).

randomized trials of new osteoporosis treatments. One of the FDA requirements for surrogate biomarker qualification is to show a strong relationship between the proposed surrogate (TH BMD) and clinical endpoint (fracture). This study supports using TH BMD as a surrogate marker for future clinical trials.

The results from this analysis of placebo participants in randomized trials are generally consistent with several large observational studies that have been previously published (Table 4). Note that there are more studies that assessed the relationship between BMD and fracture risk, but we only included the ones that assessed the risk per 1 SD decrease in BMD. Qualitatively, our results agree with the large observational studies that TH BMD is more strongly predictive for hip fractures and less so for vertebral fractures and other fractures.

Quantitatively, comparing our results for hip fracture to those from the observational studies, the results are largely consistent with the observational studies. For example, in relating FN BMD to hip fracture risk, the Rochester study showed a RR/SD of 2.4 (95% CI: 1.2-4.5),[5] the Study of

**Table 4.** Summary of observational studies reporting fracture risk (age adjusted RR) per SD decrease in BMD at the LS, FN, or TH.

| Author Year Study | Total number of participants | Follow-up | BMD site | Hip fractures | | Vertebral fractures | | Non vertebral fractures | | All clinical fractures | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | *n* | RR | *n* | RR | *n* | RR | *n* | RR |
| Black[a,6] (1992) Study of Osteoporotic Fractures (SOF) | 8134 women older than 65 yr | Mean 0.72 yr (range 0.1-1.9) | FN and TH | | | | | 208 | TH 1.40 (1.20-1.63) FN 1.41 (1.20-1.66) | | |
| | | | LS | | | | | 208 | 1.35(1.15-1.58) | | |
| Cummings et al.[a 15] (1993) SOF | 8134 women older than 65 yr | Mean 1.8 yr (range 0.4-3.1) | FN | 65 | 2.6 (1.9-3.6) | | | | | | |
| | | | TH | | 2.7 (2.0-3.6) | | | | | | |
| | | | LS | 65 | 1.6 (1.2-2.2) | | | | | | |
| Melton[a,5] (1993) | 304 women 30-94 yr | Mean 7.8 yr (range 0.1-10.2) | FN | 16 | 2.4 (1.2-4.5) | 52 clinical spine | 1.8 (1.1-2.7) | | | 163 | 1.3 (1.01-1.8) |
| Rochester, Minnesota | | | LS | 16 | 1.9 (0.9-3.7) | | 1.9 (1.3-3.0) | | | 163 | 1.4 (1.1-1.8) |
| Nguyen[a,7] (1993), City of Dubbo, New South Wales | 1789 subjects ≥60 yr | 1989-1992 | FN | | | | | | | | 2.39 (1.92-2.97) for women[b] |
| Marshall et al.[9] (1996) Meta-analysis | 11 studies 90 000 person yr | Range 1.8-24 yr | Hip BMD, includes FN, TH and trochanteric | | 2.6 (2.0-3.5) | | 1.8 (1.1-2.7) | | | >2000 | 1.6 (1.4-1.8) |
| | | | LS | | 1.6 (1.2-2.2) | | 2.3 (1.9-2.8) | | | | 1.5 (1.4-1.7) |
| Taylor (2004) SOF | 6787 women aged 66 yr and older | Mean 10.1 yr | TH | 602 | 1.84 (1.66-2.05)[c] | | | | | | |
| Johnell et al.[8] (2005) IPD study (FRAX) | 12 studies 168 366 person-years | up to 16.3 yr | FN | 971 | 2.07 (1.91-2.24) | | | | | 3694 | 1.45 (1.39-1.51)[d] |
| Leslie et al.[16] (2007) Manitoba, Canada | 16 505 women aged 50 yr or older | 3.2 ± 1.5 yr | TH | 189 | 2.87 (2.40-3.43) | 209 clinical spine | 1.73 (1.47-2.03) | | | | |
| | | | FN | | 2.49 (2.07-3.01) | | 1.70 (1.44-2.01) | | | | |
| | | | LS | | 1.37 (1.17-1.59) | | 1.80 (1.54-2.10) | | | | |
| Black et al.[17] (2018) SOF | 7959 women ≥67 yr | 25 yr for hip fracture 20 yr for any nonvertebral fracture | FN | | 2.6 (2.2-3.0) For 0-5 yr | | | | 1.4 (1.3-1.5) For 0-5 yr | | |

Note that vertebral fractures were not obtained by regular spinal radiographs and that non-vertebral and all clinical fractures were not defined consistently. [a]Studies with superscript "a" were included in the Marshall et al.[9] (1996) meta-analysis. Melton et al.[5] (1993). The spine radiographs were not taken regularly, nor were they assessed by a recognized method, such as QM or SQ. [b]Odds ratio. [c]Taylor[18] et al. (2004). HR adjusted for age, previous fracture, Parkinson's disease, type 2 diabetes, lowest quartile for distant depth perception, body mass index, height at age 25, nulliparous, walking speed, digit symbol test number completed. Johnell et al.[8] (2005). FRAX analysis included 12 cohorts comprised of EVOS/EPOS, EPIDOS, OFELY, CaMos, Rochester, Sheffield, Rotterdam, Kuopio, DOES, Hiroshima, and 2 cohorts from Gothenburg. [d]Not clear if RR is adjusted. Abbreviations: FN, femoral neck; TH, total hip; LS, lumbar spine; BMD, bone mineral density; RR, relative risk; SD, standard deviation; IPD, individual patient data.

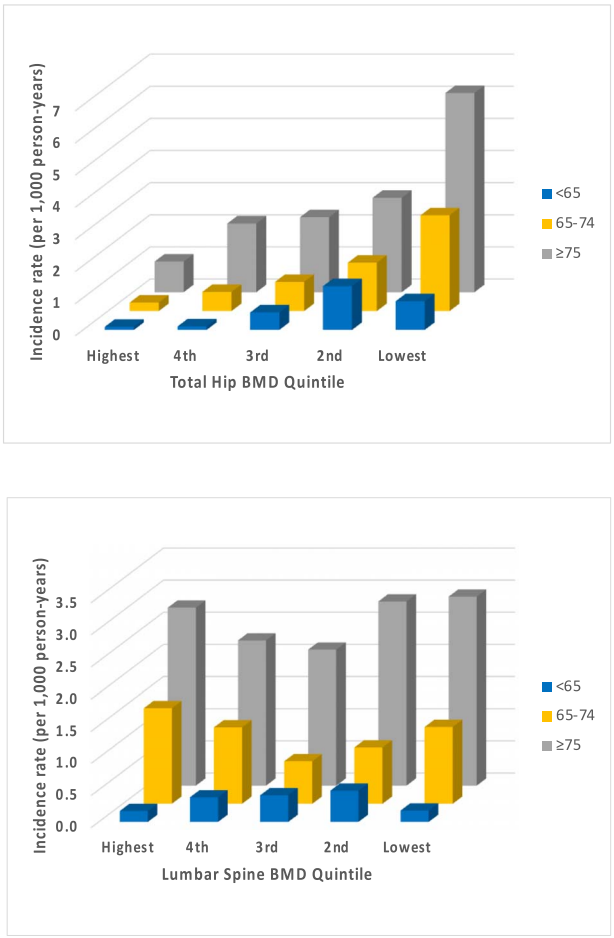


**Figure 2.** Top: Hip fracture risk according to baseline age and TH BMD quintile, unadjusted. Bottom: Hip fracture risk according to baseline age and LS BMD quintile, unadjusted. TH BMD quintiles (mg/cm$^2$): first quintile (<612.9), second quintile (≥612.9 and <667.4), third quintile (≥667.4 and <721.8), fourth quintile (≥721.8< and <788.9), and fifth quintile (≥788.9). LS BMD quintiles: first (<665.0), second (≥665.0 and <724.2), third (≥724.2 and <774.4), fourth (≥774.4 and <857.3), and fifth (≥857.3).

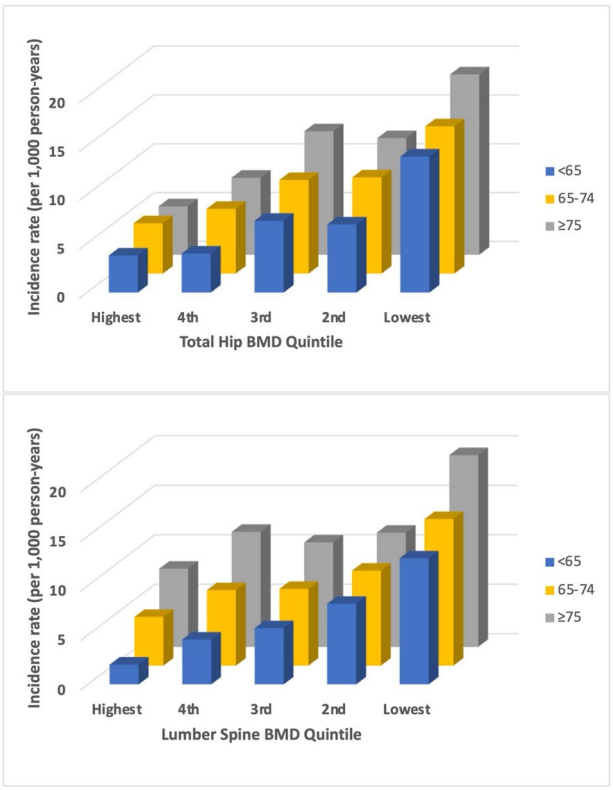


**Figure 3.** Top: Vertebral fracture risk according to baseline age and TH BMD quintile, unadjusted. Bottom: Vertebral fracture risk according to baseline age and LS BMD quintile, unadjusted. TH BMD quintiles (mg/cm$^2$): first quintile (<612.9), second quintile (≥612.9 and <667.4), third quintile (≥667.4 and <721.8), fourth quintile (≥721.8< and <788.9), and fifth quintile (≥788.9). LS BMD quintiles: first (<665.0), second (≥665.0 and <724.2), third (≥724.2 and <774.4), fourth (≥774.4 and <857.3), and fifth (≥857.3).

Osteoporotic Fractures (SOF) 2018 showed RR/SD of 2.6 (2.2-3.0)[17] and the FRAX analysis combining 12 large cohorts showed a RR/SD of 2.07 (1.91-2.24).[8] Importantly, all CIs overlap supporting consistency. There are several reasons why some variation between SABRE and the observational studies would be expected, one being that follow-up duration varied. The study by Black et al.[17] compared the ability of a single BMD measurement to predict fracture risk over increasing follow-up periods—for 5, 10, 15, 20, and 25 yr of follow-up—and showed that, as expected, RR decreased with longer duration between the BMD measurement and longer follow-up.[17] Other reasons for variation in results include that the populations varied with respect to nationality, age, and densitometry manufacturer. Additionally, since most of the trials in SABRE excluded women with higher BMDs, the range of BMD values would be smaller. For non-vertebral and spine fractures, methods of fracture ascertainment varied, adding another source of potential variation. Despite these differences, the relationships from the observational studies are similar to those that we found using data from the RCTs in SABRE.

Our study has important strengths. We used IPD from all major osteoporosis trials to create a large database including many participants. In general, because these studies were planned to be submitted for regulatory approvals, the conduct of the study was closely scrutinized by the study sponsors. For example, all studies had some level of central quality assurance for BMD assessment, a practice not generally done in observational studies, which tend to be less rigorously conducted. We also harmonized fracture definitions across the trials and standardized the BMD measurements. Fracture assessment, like BMD, would have been carefully overseen by the sponsors. For vertebral fractures, we studied incident fractures assessed by radiographic criteria comparing baseline to follow-up radiographs. We also assessed vertebral fractures in radiographs taken regularly and with definitions based on defined criteria. Most observational studies rely on the identification of clinical vertebral fractures. There are data to suggest that clinical fractures are 23% of the radiographic fractures.[19] Our SABRE project combined data from 25 randomized trials resulting in a large number of fractures. In terms of limitations, the majority of the participants were women, so results might be different in men (lower risk of osteoporotic and hip fracture per 1 SD decrease in BMD).[20] We also did not have many non-white participants. Also, our subjects were in the placebo group, but subjects in most trials received calcium and vitamin D, which might have

attenuated the fracture risk,[21] although that may not have impacted the relationship between BMD and fracture risk. LS measurements were based upon L1-L4 or L2-L4. We could not check each patient and exclude any artifact. Finally, previous studies included population-based samples, while our studies are based on participants at high risk of fracture.

In summary, the relationships between BMD and fracture risks computed from the pooled placebo groups in these randomized trials were similar to the much larger population-based observational studies. The number of fracture events in the observational studies is smaller than SABRE. Our results add further evidence showing the strong relationship between BMD, especially hip BMD, and fracture risk, which provides additional rationale for the use of TH BMD change as a surrogate for fracture in future trials of new osteoporosis fractures.

## Author contributions

Marian Schini (Conceptualization, Investigation, Supervision, Visualization, Writing—original draft, Writing—review & editing), Li-Yung Lui (Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Validation, Visualization, Writing—original draft, Writing—review & editing), Tatiane Vilaca (Writing—original draft, Writing—review & editing), Susan K. Ewing (Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Validation, Visualization, Writing—original draft, Writing—review & editing), Austin Thompson (Project administration, Writing—original draft, Writing—review & editing), Douglas C. Bauer (Conceptualization, Project administration, Writing—original draft, Writing—review & editing), Mary L. Bouxsein (Conceptualization, Funding acquisition, Project administration, Supervision, Visualization, Writing—original draft, Writing—review & editing), Dennis M. Black (Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Writing—original draft, Writing—review & editing), and Richard Eastell (Conceptualization, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing—original draft, Writing—review & editing)

## Supplementary material

Supplementary material is available at *Journal of Bone and Mineral Research* online.

## Funding

Food and Drug Administration (FDA) (Grant No.1U01FD007772-01). Grant from the American Society for Bone Mineral Research.

## Conflicts of interest

M.S. received consultancy from Kyowa Kirin International and UCB. T.V. received consultancy funding from Pharmacosmos. M.L.B. Advisory Board/Consulting: Angitia, Beryl Therapeutics. Lecture honoraria: Alexion. D.M.B. Denosumab membership for Eli Lilly. R.E. receives consultancy funding from Immunodiagnostic Systems, Sandoz, Samsung, CL Bio, CureTeQ, Biocon, Takeda, UCB, meeting presentations for Pharmacosmos, Alexion, UCB and Amgen, and grant funding from Alexion and Osteolabs.

## Data availability

All study data were acquired by requesting IPD from study sponsors. An overarching data use agreement was created between all parties and individual data use agreements were created between individual study sponsors, FNIH, and University of California, San Francisco (UCSF). Per the data sharing agreements that we have with each sponsor, the data can be used for surrogate marker analyses, including any surrogate qualification processes with regulatory authorities. However, other uses of the data are restricted by this agreement, and UCSF is not allowed to share the data.

## References

1. Black DM, Bauer DC, Vittinghoff E, et al. Treatment-related changes in bone mineral density as a surrogate biomarker for fracture risk reduction: meta-regression analyses of individual patient data from multiple randomised controlled trials. *Lancet Diabetes Endocrinol*. 2020;8(8):672-682. https://doi.org/10.1016/S2213-8587(20)30159-5
2. Eastell R, Vittinghoff E, Lui LY, et al. Validation of the surrogate threshold effect for change in bone mineral density as a surrogate endpoint for fracture outcomes: the FNIH-ASBMR SABRE project. *J Bone Miner Res*. 2022;37(1):29-35. https://doi.org/10.1002/jbmr.4433
3. Ciani O, Buyse M, Drummond M, Rasi G, Saad ED, Taylor RS. Time to review the role of surrogate end points in health policy: state of the art and the way forward. *Value Health*. 2017;20(3):487-495. https://doi.org/10.1016/j.jval.2016.10.011
4. Cummings SR, Nevitt MC, Browner WS, et al. Risk factors for hip fracture in white women. *N Engl J Med*. 1995;332(12):767-773. https://doi.org/10.1056/nejm199503233321202
5. Melton LJ, Atkinson EJ, O'Fallon WM, Wahner HW, Riggs BL. Long-term fracture prediction by bone mineral assessed at different skeletal sites. *J Bone Miner Res*. 1993;8(10):1227-1233. https://doi.org/10.1002/jbmr.5650081010
6. Black DM, Cummings SR, Genant HK, Nevitt MC, Palermo L, Browner W. Axial and appendicular bone density predict fractures in older women. *J Bone Miner Res*. 1992;7(6):633-638. https://doi.org/10.1002/jbmr.5650070607
7. Nguyen T, Sambrook P, Kelly P, et al. Prediction of osteoporotic fractures by postural instability and bone density. *BMJ*. 1993;307(6912):1111-1115. https://doi.org/10.1136/bmj.307.6912.1111
8. Johnell O, Kanis JA, Oden A, et al. Predictive value of BMD for hip and other fractures. *J Bone Miner Res*. 2005;20(7):1185-1194. https://doi.org/10.1359/JBMR.050304
9. Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. *BMJ*. 1996;312(7041):1254-1259. https://doi.org/10.1136/bmj.312.7041.1254
10. Bouxsein ML, Eastell R, Lui L-Y, et al. Change in bone density and reduction in fracture risk: a meta-regression of published trials. *J Bone Miner Res*. 2019;34(4):632-642. https://doi.org/10.1002/jbmr.3641
11. Bauer DC, Black DM, Bouxsein ML, et al. Treatment-related changes in bone turnover and fracture risk reduction in clinical trials of anti-resorptive drugs: a meta-regression. *J Bone Miner Res*. 2018;33(4):634-642. https://doi.org/10.1002/jbmr.3355
12. Lu Y, Fuerst T, Hui S, Genant HK. Standardization of bone mineral density at femoral neck, trochanter and Ward's triangle. *Osteoporos Int*. 2001;12(6):438-444. https://doi.org/10.1007/s001980170087
13. Hui SL, Gao S, Zhou XH, et al. Universal standardization of bone density measurements: a method with optimal properties for calibration among several instruments. *J Bone Miner Res*. 1997;12(9):1463-1470. https://doi.org/10.1359/jbmr.1997.12.9.1463
14. Looker AC, Wahner HW, Dunn WL, et al. Updated data on proximal femur bone mineral levels of US adults. *Osteoporos Int*. 1998;8(5):468-490. https://doi.org/10.1007/s001980050093

15. Cummings SR, Black DM, Nevitt MC, et al. Bone density at various sites for prediction of hip fractures. The Study of Osteoporotic Fractures Research Group. *Lancet*. 1993;341(8837):72-75.
16. Leslie WD, Tsang JF, Caetano PA, Lix LM, Program MBD. Effectiveness of bone density measurement for predicting osteoporotic fractures in clinical practice. *J Clin Endocrinol Metab*. 2007;92(1):77-81.
17. Black DM, Cauley JA, Wagman R, et al. The ability of a single BMD and fracture history assessment to predict fracture over 25 years in postmenopausal women: the study of osteoporotic fractures. *J Bone Miner Res*. 2018;33(3):389-395. https://doi.org/10.1002/jbmr.3194
18. Taylor BC, Schreiner PJ, Stone KL, et al. Long-Term Prediction of Incident Hip Fracture Risk in Elderly White Women: Study of Osteoporotic Fractures. *Journal of the American Geriatrics Society*. 2004;52(9):1479-1486.
19. Lindsay R, Silverman SL, Cooper C, et al. Risk of new vertebral fracture in the year following a fracture. *JAMA*. 2001;285(3):320-323. https://doi.org/10.1001/jama.285.3.320
20. Melton LJ, Orwoll ES, Wasnich RD. Does bone density predict fractures comparably in men and women? *Osteoporos Int*. 2001;12(9):707-709. https://doi.org/10.1007/s001980170044
21. Yao P, Bennett D, Mafham M, et al. Vitamin D and calcium for the prevention of fracture. *JAMA Netw Open*. 2019;2(12):e1917789. https://doi.org/10.1001/jamanetworkopen.2019.17789




*Journal of Bone and Mineral Research*, 2025, 00, 1–8
https://doi.org/10.1093/jbmr/zjae201
Research Article