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ORIGINAL PAPER

A model of fracture risk used to examine the link between bone mineral density and the impact of different therapeutic mechanisms on fracture outcomes in patients with osteoporosis

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Abstract A hazard model of fracture was developed using individual patient data (IPD) from the NHANES (2005–2008) database and summary-level data from an aggregate dataset (AD). The AD was built by performing a comprehensive and systematic literature search of clinical studies published from 1995 to 2015, recording fracture rate and bone mineral density (BMD) for both treatment and placebo arms. The search resulted in a metadata set comprised of 21 studies investigating the effects of various bisphosphonates, teriparatide, denosumab, and raloxifene in 65,254 patients over a cumulative 56.75 years of study. The IPD was used to augment an AD in a model-based meta-analysis (MBMA) hierarchical modeling approach. The resulting model predicts the probability of fracture events in patients with osteoporosis. The object of model building using this approach was to promote understanding of the impact of therapeutic drug effects on the probability of fracture together with, or independent of their effects on BMD. Candidate models were evaluated by deviance information criteria and posterior predictive check. The model with covariates for lumbar spine BMD with interaction with a drug effect on BMD, and patient body mass index, years post-menopause, fracture measure method (clinical or radiological) and an additional drug effect outperformed those models without interaction and without additional drug effects. The model quantitatively supports the widely held notion that changes in bone microarchitecture, which cannot be measured by areal BMD elicited by therapy contribute in a significant way to a reduction in fracture. Furthermore, this model can be used to simulate fracture risk in a clinical cohort similar to those contained in the MBMA.

Keywords Bone mineral density · Fracture · Osteoporosis · Hazard model · MBMA

Introduction

The aging global population has lead to significant increases in osteoporosis diagnoses. Patients with the progressed form of this disease suffer significant loss of quality of life due to fractures resulting from bone fragility. There are a number of therapies that have been shown to increase bone mineral density (BMD) at various skeletal sites and reduce the rate of fracture [1–3]. As newer therapies are developed, it is important to establish the relationship between changes in BMD, which can be measured in early-phase clinical trials, and fracture risk. The value of predictive tools is the ability to quantitatively link an outcome that can be precisely measured, such as BMD, to one that cannot be measured directly, such as fracture risk. It is also important to identify and determine the degree to which patient characteristics are implicated in the occurrence of fracture.

Much work has already been done to establish risk factors associated with fracture. The FRAX® [4] online calculator was developed by the World Health Organization (WHO) and is used to calculate the 10-year probability of fracture using information about individual-level patient demographics, physical traits, family history,

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glucocorticoid use, whether or not the patient has experienced a previous fracture, smoking habits and alcohol consumption. Unfortunately the FRAX model structure and parameter values are not published and it would require extensive groundwork to use this tool to simulate probability of fracture risk in a clinical cohort, for example. Instead, FRAX was used to guide the choice of parameters and covariates in model development but it was not an adequate foundation for working towards the objective of understanding therapeutic impact on fracture outcomes.

This work involves the development of a time-to-event (TTE)/hazard model using a compilation of historic clinical data recording fracture incidence in osteoporosis patients. This model-based meta-analysis (MBMA) approach makes inferences about fracture based on a large body of evidence available from published works and databases. Because it leverages information from many heterogeneously designed trials, this approach is well suited for making inferences regarding comparative effects of different classes of therapeutic intervention [5].

It has been shown in the literature that a reduction in fracture events can be predicted by changes in BMD mediated by therapy [6]. Taken one step further, the primary objective of this work was to understand how effects of therapy, with or independent of, effects on BMD may impact fracture risk. In the model development process a large body of data used to compare marketed therapies for osteoporosis was incorporated (aggregate data, AD). Individual patient-level data (IPD) was combined with the AD to inform the model covariates that have historically been influential to assess the quantitative impact of these factors on fracture.

Materials and methods

Data collection

The IPD was taken from a subset of data in the NHANES database. These observational data were collected from 2005 to 2008 and the selected patients fulfilled the following criteria:

- Post-menopausal women above 20 years of age
- Patients who had BMD measurements taken at the time of the interview
- Patients who were at least 2 years post-menopause at screening

Only a fracture event (vertebral or non-vertebral) that was recorded either 2 years post-menopause or 10 years prior to screening (whichever was less) was included in the dataset. In NHANES, the fracture incidence was assessed retrospectively and reported as the year in which it occurred. Fractures that occurred in the same year as screening were not recorded. After filtering, there were 1925 total patients out of the original 20,497 in the NHANES dataset (9.4%) which were included in the model dataset. This dataset was comprised of BMD, fracture data and characteristics (age, years post-menopause, race and body mass index (BMI)) within individuals and contributed information about how these individual-level patient characteristics affect outcomes, but contained no specific information about therapy (except whether the patient had received osteoporosis medication of any kind).

In contrast, AD for the fracture model was compiled from a PubMed search conducted on or around Dec 11, 2015 using keywords "vertebral fracture", "prevent", "risk", "occur", "humans", "clinical trial", "randomized controlled trial", "osteoporosis", "zoledronic acid", "teriparatide", "alendronate", risedronate", denosumab", "PTH1-34", "strontium ranelate," "minodronate," "raloxifene," "ibandronate," "BMD," "bone mineral density", or "spine" published from 1995 to 2015 [1–3, 7–27]. Graphically presented data from these publications were digitized using GraphClick (v3.0 Arizona Software). These data are summarized in Supplementary Table I. Only studies having fractures as a primary endpoint were included in the dataset. Because vertebral fractures were the dominant type of measured fracture in most of the clinical trials, studies that did not include vertebral fractures were excluded from the dataset. If non-vertebral and vertebral fractures were reported as separate measures, these were combined and recorded as total fracture events. Studies that did not include at least one post-baseline measurement of lumbar spine (LS) BMD also were excluded from the dataset. Patient baseline characteristics including age, race, BMI, years post-menopause, height, weight, prior fracture, LS BMD, and current smoking status, summarized by arithmetic mean, were also recorded. Whether or not fractures were routinely evaluated via radiograph or classified as 'clinical fractures' was indicated in the dataset. Study extensions were recorded as separate trials, because the extension population typically had its own set of baseline characteristics and therefore potentially could influence parameter estimation differently. Supplementary Fig. 1 shows longitudinal changes in LS BMD for each study included in the AD (A), and the corresponding rate of fracture for each study arm (B).

Data standardization and missing data imputation

In the IPD, BMD measurements were taken at screening, so the BMD time course over the period when the patient was at risk of fracture had to be imputed. The following equation was used to impute BMD for four different groups. These were grouped by screening BMD quartiles

so that the distribution of imputed BMDs over the period of fracture risk was the same as the distribution at screening (and no additional bias introduced). The coefficients were estimated by multiple linear regression:

$$\begin{aligned} BMD_{pred,i} = {} & \beta_0 + \beta_1(post\ menopausal\ age_i - 20) \\ & + \beta_2(BMI_i - 27.1) \\ & + \beta_3(age\ at\ last\ menstrual\ period_i - 51.7) \\ & + \beta_4 I_{afro-american} \end{aligned} \quad (1)$$

for the *i*th individual in the IPD.

Imputed values for BMD were used in the equation for hazard (Eq. 5). BMD in the AD was calculated using linear interpolation of the observed longitudinal data.

For both IPD and AD, missing BMI (kg/m^2) was computed from weight and height. If neither BMI nor height and weight were reported, it was imputed by linear regression, where the coefficients were estimated separately for each dataset:

$$BMI_i = \beta_5 + \beta_6 * (age_i - \widehat{age}) \quad (2)$$

for the *i*th individual (IPD) or *i*th treatment arm (AD).

Linear regression models were used due to a lack of more descriptive data that would have been required to inform a more complex interpolation. Six patients in the NHANES dataset and five studies (9085 patients) in the AD had missing BMI data and had to be imputed. In the IPD all BMD were reported as T-scores. These, and the values of BMD in the AD reported as T-scores, were converted to units of g/cm^2 using the reference BMD and standard deviation (SD) parameters for a white female [28].

$$BMD_{g/cm^2} = 0.106 * BMD_{T-Score} + 1.064 \quad (3)$$

If post-menopausal age was not reported in the aggregate dataset, it was computed using the average age of the treatment arm and subtracting a weighted average of post-menopausal ages of the treatment arms that were reported, using number of individuals in the respective treatment arms as weights. Seven studies (12,342 patients) had missing postmenopausal age and had to be imputed. Baseline characteristics of patients in both datasets are summarized in Table 1.

Hazard model of fracture

As mentioned previously, supplementing AD with IPD overcomes some biases imposed by clinical trial design and patient selection. Summary-level data in the MBMA was collected with specific study aims in mind, and may or may not be representative of the individuals that make up a disease population. Both datasets therefore contributed to parameter estimates and informed covariate effects in this analysis. However, the structure of the IPD necessitated a different form of the likelihood equation to account for inter-subject variability (not inter-arm), additional covariate information as it pertains to changes in BMD within an individual, and the possibility of a patient dropping out of the study prior to the end of the 10-year observation period (censoring). To address this, the equation for the likelihood of fracture describing the IPD was structured differently than the equation describing the probability of fracture in the aggregate dataset. In calculating the likelihood of fracture for the aggregate dataset, the IPD was incorporated as a single trial arm, with a random effect on baseline hazard allowing flexibility for differences between study arms. In particular, inter-trial variability in $\log(h_0)$ was described by a normal distribution with mean 0 and variance Ω^2. The parameters describing the covariate effects were shared (i.e., the coefficients were estimated simultaneously) using a Bayesian approach implemented in OpenBUGS v. 3.2.2. The covariates included in both models were preselected based upon the those examined in the FRAX project [4] and those available in the literature. It was determined from a previous analysis that LS BMD was more predictive of fracture outcomes than either total hip or femoral neck BMD (data not shown) and no formal covariate selection process was performed.

Likelihood and hazard equations describing the IPD

The likelihood for the time to first fracture in the *i*th patient ($t_{frac,i}$) took the form:

Table 1 Comparing baseline characteristics between datasets

	NHANES (mean, SE)	Aggregate (mean, SE)
Age (years)	64.7 (10.8)	69.5 (3.85)
Post-menopausal age (years)	11.8 (10.0)	22.3 (2.84)
BMI (kg/m^2)[a]	29.0 (6.20)	25.5 (1.51)
BMD (g/cm^2)[b]	0.951 (0.159)	0.787 (0.0644)

[a]BMI calculated at screening for NHANES dataset

[b]BMD imputed from screening for NHANES at time = 0 using Eq. 1

$$L(\theta|t_{frac,i},censor_i,X_i) = \begin{cases} e^{-\int_0^{t_{frac,i-1}} h_i(u|\theta,X_i)du} - & \text{Fracture occurred in } (t_{frac,i-1},t_{frac,i}) \\ e^{-\int_0^{t_{frac,i}} h_i(u|\theta,X_i)du}, & \\ e^{-\int_0^{t_{end,i}} h_i(u|\theta,X_i)du} & \text{No fracture occurred} \end{cases} \quad (4)$$

where $t_{frac,i}$ is the end of a 1-year period during which a fracture occurred. If fracture is right censored, $t_{end,i}$ corresponds to the time of last observation during the observation period. X_i corresponds to the observed covariates. h_i represents the hazard equation. Observation period (beginning at t = 0) was defined as beginning 10 years before the interview or 2 years post-menopause, whichever occurred last.

The hazard equation (h_i) for the IPD model took the form:

$$h_i = h_0 \exp(\beta_{BMD} * \log(\mathrm{BMD}_{pred,i}/\widehat{BMD}) + \beta_{postMenoAge}(time + postMenoage_{0,i} + \widehat{postMenoAge}) + \beta_{BMI}(BMI_i - \widehat{BMD})) \quad (5)$$

in the ith individual, h_0 is the estimated hazard when all covariates are at their reference values, $postMenoage_{0,i}$ indicates years post-menopause for the ith individual at the start of the observation period, and time = years from the start of the observation period. The reference values (designated by $\bigwedge$) are the mean population baseline values for each covariate.

The BMD portion of the hazard was log-transformed because prior model development resulted in better fits to clinical data under this transformation.

Probability of fracture and hazard equation describing all metadata

The number of patients experiencing a fracture from the AD followed a binomial distribution with probability of fracture, $p_{frac,ij}$ for n_{ij} patients at risk for fracture, where

$$p_{frac,ij} = 1 - e^{-\int_0^{t_{ij}} h_{ij}(u|\theta,X_{ij})du} \quad (6)$$

in the ith treatment arm of the jth trial, X_{ij} represent the model covariates, h_{ij} represents the calculated hazard and t_{ij} = duration of observation in trial.

The modeling objective was to determine whether the drug- mediated changes in BMD fully account for changes in fracture outcomes regardless of therapeutic mechanism, or if a fracture event can be better predicted by incorporating a specific therapeutic effect. To this end, three different hazard models, which were variations of a proportional hazard model (Eq. 7), were evaluated on the basis of which application of the drug effect best predicted the proportion of patients experiencing fracture in the aggregate dataset. The drug effect was applied either in interaction with or independent of BMD differently to determine which structure resulted in improved predictions of fracture rate. An additional model with no drug effect was added for comparison.

$$h(t) = h_0 e^{[\Sigma\beta_{x_i}(x_i - \widehat{x_i})]} \quad (7)$$

where each x_i is a covariate and h_0 is the estimated baseline hazard.

Covariates consistent across all the model candidates included post-menopausal age, method of vertebral fracture identification ($I_{radFracture1}$, $I_{radFracture2}$ = 0, 0 if all clinical fractures were recorded, 1, 0 if radiologically-assessed vertebral and non-vertebral fractures were reported and 0, 1 if only radiologically-assessed vertebral fractures were reported), and body mass index (BMI).

The three candidate model structures for the BMD covariate(s) were as follows:

(1) BMD + drug interaction

$$h_{ij} = h_{0j} \exp\left((\beta_{BMD} + \beta_{E_{Drug_k}}) \log\left(\frac{BMD_{ij}(t)}{\widehat{BMD}}\right) + \beta_{postMenoAge}(postMenoAge_{ij}(t) - \widehat{postMenoAge}) + \beta_{radFracture,l} I_{radFracture,ij} + \beta_{BMI}(BMI_{ij} - \widehat{BMI}) \right) \quad (8)$$

(2) BMD + drug interaction + additional drug effect

$$h_{ij} = h_{0j} \exp\left((\beta_{BMD} + \beta_{E_{Drug_k}}) \log\left(\frac{BMD_{ij}(t)}{\widehat{BMD}}\right) + \beta_{postMenoAge}(postMenoAge_{ij}(t) - \widehat{postMenoAge}) + \beta_{radFracture,l} I_{radFracture,ij} + \beta_{BMI}(BMI_{ij} - \widehat{BMI}) + E_{Drug_k} \right) \quad (9)$$

(3) Additional drug effect only

$$h_{ij} = h_{0j} \exp\left(\beta_{BMD} \log\left(\frac{BMD_{ij}(t)}{\widehat{BMI}}\right) + \beta_{postMenoAge}(postMenoAge_{ij}(t) - \widehat{postMenoAge}) + \beta_{radFracture,l} I_{radFracture,ij} + \beta_{BMI}\left(BMI_{ij} - \widehat{BMI}\right) + E_{Drug_k} \right) \quad (10)$$

for ith arm, jth trial, kth drug class (1 = placebo, 2 = bisphosphonates, 3 = PTH/teriparatide, 4 = denosumab, 5 = SERM), and lth type of fracture reported, t is the time interval over which the cumulative hazard is integrated. The reference values (designated by Λ) are the same mean population baseline values for each covariate from Eq. 5.

Markov Chain Monte Carlo (MCMC) simulations generated vectors of parameters whose empirical distribution approximates their joint posterior distribution. Four chains of 100,000 iterations are generated, with the first 50,000

being discarded and every 50th sample retained, resulting in 4000 samples for statistical inference. Weakly informative prior distributions for covariate parameters and variance parameters were used in all versions of the model to allow the data to dominate parameter estimation (Supplementary Material Table II). Model selection was based on values of mean deviance, deviance information criteria (DIC), and posterior predictive checks (PPCs).

A hazard ratio for each class of drug in the model was calculated using the interpolated mean BMD after 1 year of treatment for each drug class and the estimated drug effect. This ratio is the overall drug effect compared to placebo in terms of the relative hazard. Because the analysis does not directly model the effect of the drug on BMD, the ratio is calculated using a combination of observed BMD data and the model predicted effect of the drug not explained by changes in BMD. A ratio much less than one indicates a large combined effect of drug both on BMD and independent of BMD contributing to hazard reduction.

$$Hazard\ ratio = \exp\left((\beta_{BMD} + \beta_{E_{Drug_k}}) \log\left(\frac{BMD_{1yr,Drug_k}}{\widehat{BMD}}\right) + E_{Drug_k}\right) / \exp\left(\beta_{BMD} \log\left(\frac{BMD_{1yr,PBO}}{\widehat{BMD}}\right)\right). \quad (11)$$

Table 3 The model that yielded the lowest DIC score (indicated by bold text) included the model with both BMD–drug interaction and an additional drug effect

Drug effect covariate structure	DIC
BMD + drug interaction	1634.67
BMD + drug interaction + additional drug effect	**1541.51**
Additional drug effect only	1546.33
BMD only (no drug effects)	1649.90

Results

Covariate structures and parameter estimates

The parameter estimates used to generate time-dependent BMD and missing quantities for BMI are shown in Table 2.

Each of the three model candidates was tested with and without a drug effect and yielded the following results for DIC (Table 3).

The model that yielded the lowest DIC score included the model with both BMD–drug interaction and an additional drug effect. The mean parameter estimates for this model are shown in Table 4. Figure 1 shows both individual-level and population-level post-predictive checks

Table 2 Parameter estimates used to generate missing quantities for BMD and BMI

Parameter	Mean (95% CI)			
	Strata 1	Strata 2	Strata 3	Strata 4
β_0 (unitless)	0.756 (0.746; 0.766)	0.894 (0.890; 0.899)	0.989 (0.985; 0.994)	1.14 (1.12; 1.16)
β_1 (unitless)	− 1.42e−3 (− 2.17e−3; − 6.74e−4)	− 7.16e−5 (− 3.65e−4; 2.22e−4)	5.73e−5 (− 2.37 e−4; 3.52e−4)	2.29e−4 (− 7.25 e−4; 1.18e−3)
β_2 (unitless)	− 4.04e−4 (1.15e−3; 3.70e−3)	5.78e−4 (3.67e−5; 1.12e−3)	− 1.64e−4 (4.98e−3; 5.89e−3)	1.71e−3 (1.86e−4; 3.24e−3)
β_3 (unitless)	2.43e−3 (− 1.48e−3; 6.71e−4)	− 1.78e−4 (− 5.97e−4; 2.41e−4)	4.38e−4 (− 5.55e−4; 2.26e−4)	− 8.80e−4 (− 2.14e−3; 3.77e−4)
β_4 (unitless)	1.33e−2 (− 1.05e−2; 3.71e−2)	3.05e−3 (− 4.73e−3; 1.08e−2)	3.18e−3 (− 3.72e−3; 1.01e−2)	1.89e−2 (− 1.35e−3; 3.92e−2)
β_5 (unitless)	26.6 (25.9; 27.2)	27.9 (27.2; 28.6)	29.5 (28.7; 30.4)	30.6 (29.8; 31.4)
β_6 (unitless)	− 0.0524 (−0.116; 1.08e−2)	− 3.04e−2 (− 9.06e−2; 2.87e−2)	− 6.55e−2 (− 0.123; − 7.60e−3)	− 8.31e−2 (− 0.139; − 2.61e−2)
Aggregate data				
β_5 (unitless)	25.5 (25.2; 25.8)			
β_6 (unitless)	5.74e−2 (− 2.75e−2; 0.141)			

Estimates are mean and 95% CI around the mean

Table 4 Parameter estimates and 95% CI around the mean

Parameter	Mean	95% CI
Reference hazard, h_0 (1/years)	0.0404	(0.0292; 0.0554)
BMD covariate, β_{BMD} (1/gm/cm^2)	−1.00	(−2.11; 0.161)
Drug interaction term, $\beta_{BMD+bisphos}$ (1/gm/cm^2)	0.931	(0.209; 1.69)
Drug Interaction term, $\beta_{BMD+teripar}$ (1/gm/cm^2)	−1.13	(−5.64; 3.49)
Drug interaction term, $\beta_{BMD+denos}$ (1/gm/cm^2)	3.90	(−0.324; 8.16)
Drug interaction term, $\beta_{BMD+SERM}$ (1/gm/cm^2)	60.3	(−144; 314)
Fracture Assessment, $\beta_{radFracture1}$ (unitless)	0.185	(−0.408; 0.769)
Fracture Assessment, $\beta_{radFracture2}$ (unitless)	0.603	(0.0888; 1.14)
Years post-menopause covariate, $\beta_{postMenoAge}$ (1/years)	0.0225	(0.00658; 0.0387)
BMI covariate, β_{BMD} (kg/m^2)	−0.0141	(−0.0476; 0.0197)
Additional drug effect parameter, $\beta_{biophosphonates}$ (unitless)	−0.310	(−0.386; −0.235)
Additional drug effect parameter, $\beta_{PTH/teriparatide}$ (unitless)	−0.884	(−1.32; −0.48)
Additional drug effect parameter, $\beta_{denosumab}$ (unitless)	−0.450	(−0.619; −0.292)
Additional drug effect parameter, β_{SERM} (unitless)	−2.78	(−12.3; 3.54)
Random effect parameter on baseline hazard, Ω (unitless)	0.745	(0.626; 0.898)

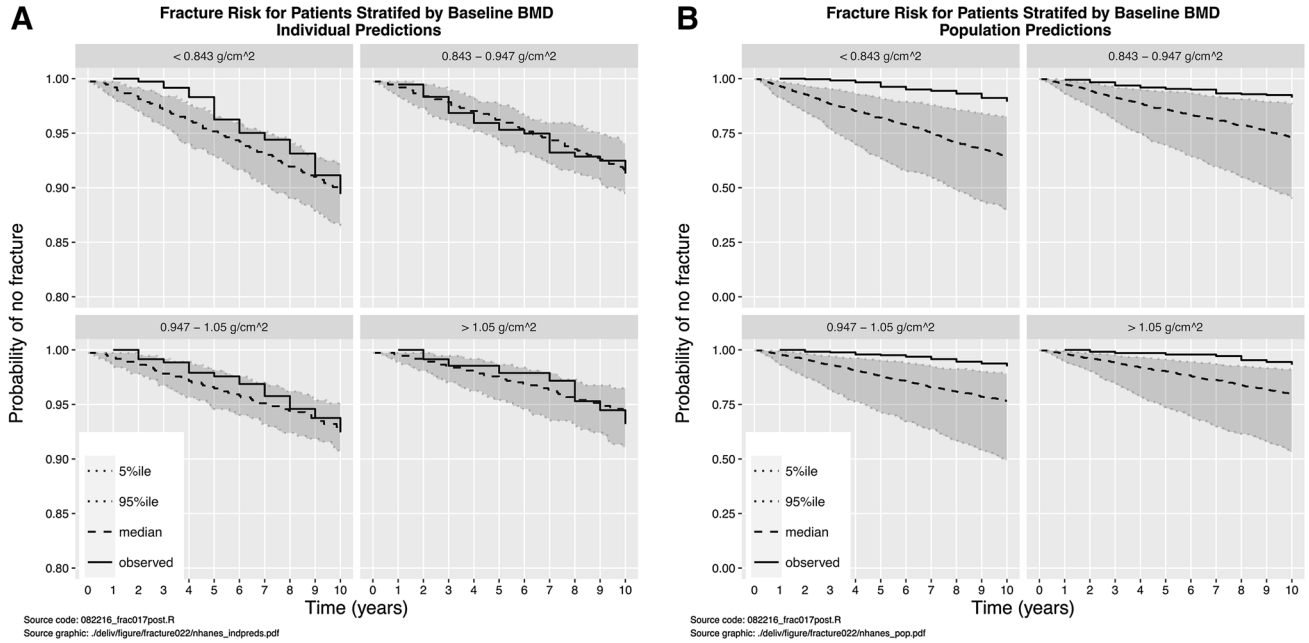

Fig. 1 Individual (**a**) and population-level (**b**) PPCs for the IPD, stratified by baseline BMD. Individual-level predictions estimate fracture probability in the same trial with the same patient covariates. Predictions at the population-level reflect probability of fracture in a new trial, but same patient covariates

(PPC) of the model, with the IPD and predictions stratified by screening BMD. Figure 2 shows PPCs of the AD-driven hazard model at both the individual and population (trial) levels. Simulations were performed by taking 100 random draws of the posterior and calculating the respective mean and 95% CI for calculated likelihood of fracture in the individual for IPD and proportion of patients experiencing fracture in the AD. Simulations use a random draw from a normal distribution with mean equal to the estimated population mean h_0, and standard deviation equal to Ω.

Discussion

Prior to the development of this hazard model of fracture, there was no published model relating the effect of therapy, independent of the effect on BMD, to probability of fracture in patients with osteoporosis. This work leverages a large amount of summary-level metadata, as well as IPD (NHANES), including BMD and fracture measures, in order to provide a framework for linking effects of drug therapy to fracture risk. Changes in BMD patient

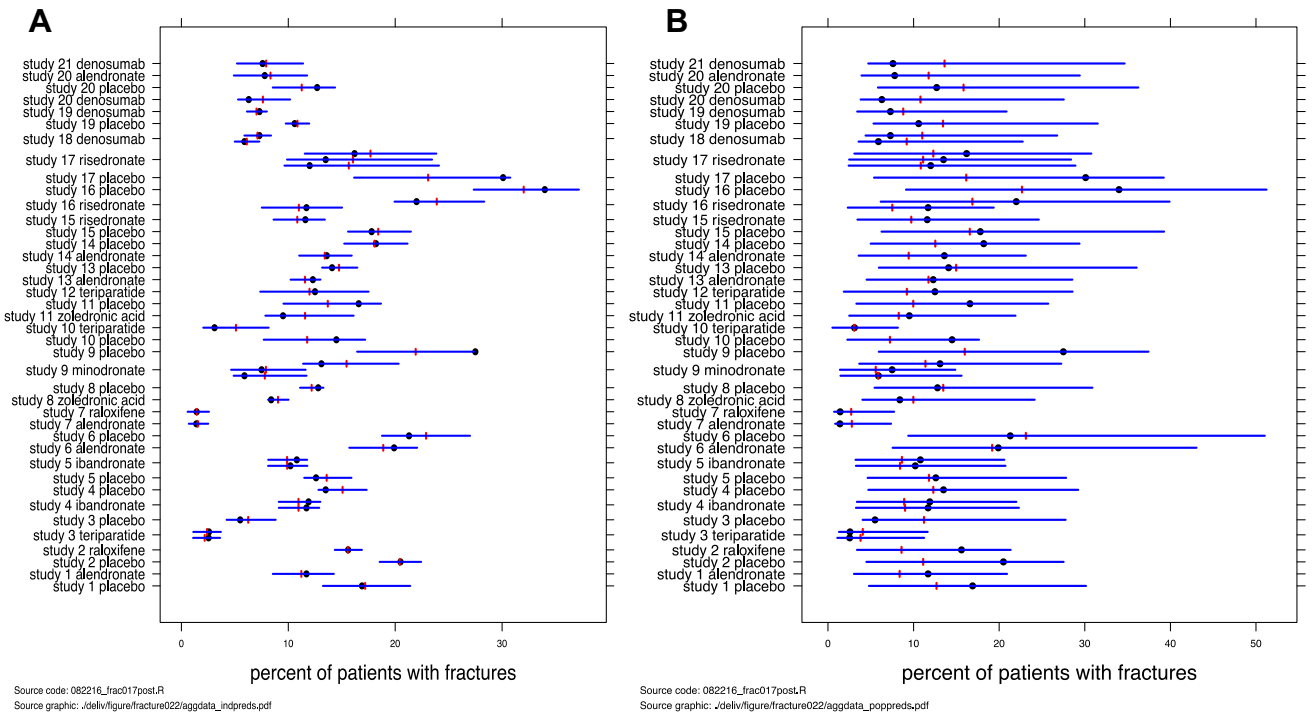

Fig. 2 Individual (**a**) and population (**b**)-level PPCs for the AD, grouped by study arm. The bullet symbol indicates the mean percentage of patients with fracture from the aggregate dataset, the red line indicates predicted median, and blue lines indicate 90% CI around the prediction. Individual-level predictions estimate fracture probability in the same trial with the same patient covariates. Predictions at the population-level reflect probability of fracture in a new trial, but same patient covariates (Color figure online)

characteristics were also included in the MBMA to quantify their contribution to fracture risk. The model that generated fracture predictions most closely resembling the MBMA dataset was the model that had both a drug-BMD interaction term and additional drug effect that was independent of drug effects on BMD.

A hierarchical modeling approach, as described in Jackson et al. [29] and Haneuse et al. [30] was used to model pooled AD and IPD. There are benefits and drawbacks to this approach. Adding IPD to extend and enhance AD allows correlations between individual level outcomes and covariates (such as influence of age, BMD, body mass index [BMI] and race) to be estimated, and effects of these covariates to be quantified. Bias due to an imbalance in patient-level characteristics across comparisons can be minimized by accounting for within-group variability, which requires supplementation of group-level data with individual-level data [29, 31]. A drawback to pooling IPD and AD is that adding these data still does not allow inferences about covariates at the group-data level to be interpreted at the individual level [29] and can potentially introduce selection bias.

While AD is useful for distinguishing effects of assigned intervention across summary-level treatment arms, it is less useful for quantifying the effects of individual-level patient characteristics on outcome. Incorporating IPD into AD in model development informs how BMD, BMI, postmenoage and nominal age influence risk of fracture at the individual level. Using linear models to describe both datasets also avoids bias introduced when the functions are non-linear with respect to individual-specific parameters [32]. Because there is no treatment information contained in the individual-level data, a limitation of the model is that it cannot be used to predict the effect of treatment in individual patients in a clinical setting.

The final model over-predicted the probability of fracture over time in patients in the IPD dataset at the population level (Fig. 1b), but described individual-level hazard well (Fig. 1a). This points to high levels of inter-trial variability at the level of the base hazard, (h_0) and underlying differences in two datasets. For example, the information contained in the IPD originates from an observational study and is reflective of a highly heterogeneous population. Fracture events recorded in this dataset were assessed by patient interview and subject to errors in human memory. This is in contrast to the metadata set that was made up of mostly prospective trials conducted in-house and subject to a greater level of control. Population-level estimates for the AD were also more variable, again due to high inter-trial variability in the baseline hazard. Precision around some of the parameter estimates was poor (C.I. included the null in some cases; see Table 4). In the

case of the BMD–drug interaction term, this can be explained by amount of data for each drug class included in the aggregate dataset or the BMD response to the drug being highly variable. Diagnostic differences contribute to high variability in BMD response. Areal BMD is typically measured with a DEXA scanners but there have been documented discrepancies in measurements taken with the different types of scanners (Hologic, Lunar, Norland) [33].

Hazard models with and without a drug–BMD interaction term and an additional drug effect covariate were compared. It was determined that there is an additional hazard-lowering effect of some classes of therapies, which in most cases is independent of the contribution of changes in BMD elicited by the therapy.

Hazard ratios were computed comparing drug effect relative to placebo (Fig. 3). Posterior distributions of hazard ratios calculated from the model with both drug–BMD interaction and an additional drug effect indicate significant benefits of all classes of therapies in fracture reduction over placebo. This analysis indicates bisphosphonates have the least significant effect over placebo after 1 year of treatment (indicated by a large portion of the distribution laying in the alpha-region) however, there is a large amount of uncertainty around both the denosumab and teriparatide effects (indicated by wide distributions). The inclusion of an additional drug effect may be highlighting the differential effects of therapy on regional areal BMD (aBMD, the type recorded in the metadata set) and bone microarchitecture. BMD and bone microarchitecture have been shown to be loosely associated in clinical reports. For example, changes in 1/3rd radius BMD are linked to changes in the microarchitecture of the cortical bone compartment and distal radius BMD is descriptive of changes at intracortical sites [34]. However, development of this model supports the widely held notion that BMD response to therapy only partially contributes to a reduction in fracture risk and does not represent the full benefit of therapy on fracture reduction. This indicates that there are affects of therapy on bone composition and strength, independent of BMD- at least BMD measured at the lumbar spine. A study by Sornay-Rendu et al. [35], demonstrated that changes in microarchitecture associated with fracture are partially independent of changes in aBMD, as measured at the radius and hip. Given the results of this study and the findings that the measures of trabecular number, trabecular distribution and separation of distribution were the significant measures distinguishing osteoporotic women with and without fracture, one could make the argument that measuring changes in bone microarchitecture would be more clinically useful in measuring drug efficacy and should be more routinely used, when possible. However in this study, the authors did not consider lumbar spine or femoral neck BMD, two of the routinely examined sites in clinical efficacy studies. A recent study found trabecular bone score (TBS), a measure of the quality of bone microarchitecture, to be a significant, independent predictor for fracture, further supporting the clinical utility of these measures [36].

There is much evidence for different classes of therapy having differential effects on bone microarchitecture in the published literature. Seeman, et al. [37] published a study looking at the different effects of denosumab and alendronate on bone microarchitecture. The authors speculated that treatment-specific changes in total and cortical BMD might point to drug mechanisms at the level of the bone multicellular unit (BMU). Because denosumab inhibits osteoclast synthesis there is a rapid reduction in newly excavated resorption cavities and simultaneous filling of

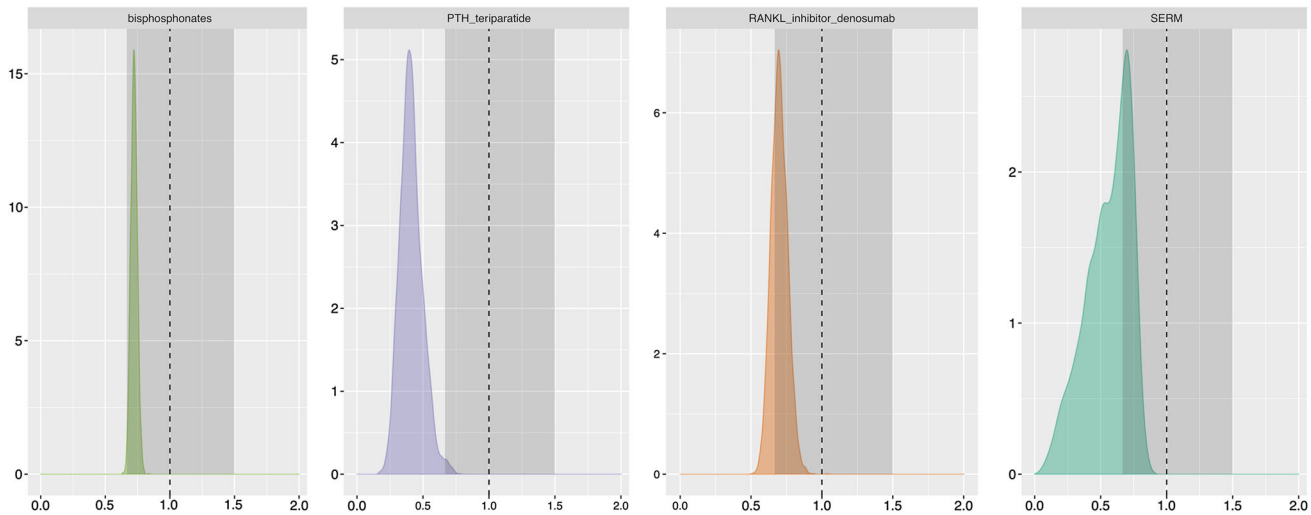

Fig. 3 Hazard ratios for each treatment relative to placebo calculated and density plots for this calculation over the posterior distribution of parameter estimates are represented, for the model with both drug–BMD interaction and additional drug effect

existing cavities, in contrast with alendronate, which does not elicit the same CTX response (marker of resorption activity) at comparable doses. It has also been suggested that the anti-resorptive effect of bisphosphonates is mediated by the distribution of the drug, because the strong affinity of bisphosphonates for hydroxyapatite and bone mineral may limit distribution [34]. It is possible that osteoclasts may not commence remodeling activity until the entire matrix containing the bisphosphonate is resorbed. This process may not be linear or uniform throughout the skeleton.

In contrast to anti-resorptive therapies, teriparatide has been shown to decrease cortical thickness in the tibia and radius while increasing cortical porosity and significantly increasing trabecular number in the tibia [38]. The authors of this study conjecture that the anabolic mechanism of action of PTH is to accelerate intracortical and endosteal remodeling. Zoledronic acid was used as a comparator in this study and did not have an impact on cortical porosity, but did increase cortical thickness, consistent with bisphosphonate activity seen in the Seeman et al. study. Considering the variable effects of different agents on microarchitecture, differences in drug effects between classes of therapy, as they pertain to probability of fracture, may be due to the changes in bone composition that are not fully represented by regional areal BMD measures. This evidence quantitatively supports that a model including BMD-independent therapeutic effects may more accurately predict the probability of fracture.

Future development of the model may include investigation of the relationship between BMD, therapeutic drug effects, and fractures at specific sites. The major limitation to this endeavor is a lack of clinical trials reporting site-specific fracture events. Coupling MBMA developed by a comprehensive, systematic literature search with individual-level data from the NHANES database allowed for a comparison of effects of different drug classes on probability of fracture, and demonstrated the influence of patient characteristics on this probability. Still, more clinical data at the level of the individual patient is also desired in order to describe effects of patient characteristics on fracture risk more precisely.

Conclusion

In the development of a hazard model of fracture, the best predictions of fracture events came from a model that included both drug–BMD interaction and additional drug covariates representing different classes of therapy for osteoporosis. This indicates that with some classes of therapy there is a significant contribution of the therapy contributing to fracture reduction, independent of LS BMD changes elicited by therapy. This additional drug effect likely reflects changes in the bone microarchitecture that are not being represented by areal BMD endpoints typically measured in a clinical trial. This fracture model is a public and expandable framework for quantifying the extent to which patient characteristics and different therapeutic mechanisms contribute to fracture reduction.

As more clinical data become available and therapies with different mechanisms of action are developed, the model can be updated to allow for further exploration of the extent to which therapeutic mechanism of action influences changes in bone microarchitecture and lower fracture risk. A feature of this model that distinguishes it from other documented fracture models in the literature is it can be used to make inferences about how variability affects outcome in a clinical population. This utility for prediction into a clinical study paradigm is relevant for development of new therapies for osteoporosis.

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