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A Bayesian path analysis to estimate causal effects of bazedoxifene acetate on incidence of vertebral fractures, either directly or through non-linear changes in bone mass density

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Abstract

Background/Aims: Bone mass density values have been related with risk of vertebral fractures in post-menopausal women. However, bone mass density is not perfectly accurate in predicting risk of fracture, which decreases its usefulness as a surrogate in clinical trials. We propose a modeling framework with three interconnected parts to improve the evaluation of bone mass density accuracy in forecasting fractures after treatment.

Methods: The modeling framework includes: (1) a piecewise regression to describe non-linear temporal BMD changes more accurately than crude percent changes, (2) a structural equation model to analyze interdependencies among vertebral fractures and their potential risk factors in preference to regression techniques that consider only directional associations, and (3) a counterfactual causal interpretation of the direct and indirect relationships between treatment and occurrence of vertebral fractures. We apply the methods to BMD repeated measurements from a study of the effect of bazedoxifene acetate on incident vertebral fractures in three different geographical regions.

Results: We made four observations: (1) bone mass density changes varied largely across participants, (2) baseline age and body mass index influenced baseline bone mass density that, in turn, had an effect on prevalent fractures, (3) direct and/or indirect effects of bazedoxifene acetate on incident fractures were different across regions, and (4) estimates of indirect effects were sensible to the presence of post-treatment unmeasured confounders. In one region, around 40% of the bazedoxifene acetate effect on the occurrence of fracture is explained by its effect on bone mass density. Under the counterfactual approach, these 40% represent the average difference in the occurrence of fracture observed for untreated individuals when their bone mass density values are set at the value under bazedoxifene acetate versus under placebo.

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Conclusions: Computational methods are available to evaluate and interpret the surrogacytic capability of a biomarker of a primary outcome.

Keywords
Causal analysis, structural equation model, piecewise regression, bone mineral density, vertebral fracture, bazedoxifene acetate

1 Introduction

Vertebral fracture in post-menopausal women is a serious public health issue. In 2000, there were an estimated 9 million new osteoporotic fractures, of which 1.4 million were clinical vertebral fractures. As much as 51% of all these fractures are found in Europe and the Americas.[1] Many factors are known to increase the risk for vertebral fractures in post-menopausal women, among which decreased bone mineral density (BMD), advanced age, preexisting vertebral fractures, early menopause, ethnicities, current smoking and maternal fracture history.[2,3]

Values of BMD, measured either at a single point in time[4] or as percent changes across time[5] have been related with the risk of fracture. The risk of multiple vertebral fractures in post-menopausal women increased by 2.1 (95% CI: 1.2–3.9) and 2.4 (95% CI: 1.3−4.3) for each standard deviation decrease in BMD measured by dual-energy X-ray absorptiometry (DXA) lumbar spine and DXA total hip, respectively.[6] Values of BMD have also been associated with bone stiffness and strength[7] and with vertebral mechanical behavior.[8] Because of these properties, BMD measurements have been incorporated in the WHO Fracture Risk Assessment Tool (FRAX®) to estimate 10-year probability of osteoporotic fracture.[9]

However, BMD is not perfectly accurate in predicting risk of fracture. There is no exact BMD cut-off point to characterize absolutely a person who will fracture from one who will not. A meta-analysis of treatment osteoporosis trials revealed that increased spinal BMD accounted for less than 25% of the overall reduction in fracture risk.[10] Others observed that the proportion of fracture risk reduction explained by BMD change is around 4% for raloxifene, varies from 16% to 28% for bisphosphonates[11] and up to 75% for strontium ranelate.[5] Such proportions, often called proportions of treatment effect explained by a surrogate (PTE), are typically obtained as the ratio of regression coefficients for the treatment effect on fracture risk from models with or without the surrogate.[12,13] Unfortunately, the PTE is variable and can fall outside the allowed range [0, 1] for a proportion. Also, models do not allow for an interaction between biomarker and treatment, and there is no guarantee they both fit equally well the data.[14,15]

In this study, we propose a modeling framework with three interconnected parts to evaluate BMD accuracy in forecasting fractures after treatment. Treatment is bazedoxifene acetate (BZA), BMD are measured repeatedly, and fractures are vertebral but the methodology may be applied to other experiments and drugs.

In the first part of the framework (Part 1), we suggest modeling BMD changes after treatment with piecewise regressions. Traditionally, repeated measures of BMD are synthesized in BMD percent changes from baseline to a predetermined point in time but BMD temporal changes are often non-linear across the menopause transition period or after treatment.[16] For example, in post-menopausal women receiving BZA, BMD mean percent changes from baseline increased linearly until they reached a plateau.[11,17] In such a case, percent changes computed between baseline and a time-point occurring before (or after) the time plateau is reached, is higher (or

lower) than the real BMD changes observed after taking the drug. Piecewise regression models are an interesting alternative because they are broken-stick models with two or more lines joined at breakpoints. The nonlinear trend is constructed out of these linear lines. Slopes for the different lines and breakpoints therefore characterize more correctly BMD fluctuations than percent changes.

In the second part of the framework (Part 2), we propose using structural equation models (SEM) to explore the web of relationships between treatments, risk of fracture and potential risk factors among which BMD changes quantified with piecewise regressions. Usually, effects of treatment and risk factors on vertebral fractures are identified by Poisson or logistic regressions.[9,18] Such regression models assume only directional associations between the risk factors and occurrence of vertebral fractures and ignore all possible inter-relationships. Conversely, SEMs are techniques appropriate to evaluate complex networks of relationships among variables.[19] In SEM, risk factors and treatment can be both independent and dependent variables so alternative hypotheses can be tested regarding their direct and indirect (or mediated) relationships with the outcome of interest.[20] Here, the Bayesian approach to SEM is privileged over classical inference methods (e.g. maximum likelihood, generalized or weighted least squares) because the approach allows the incorporation of prior knowledge about the parameters and is computationally faster and more tractable (e.g. singularities in the likelihood surface).

In the third part of the framework (Part 3), we convey counterfactual causal analyses to interpret the direct and indirect relationships between BMD and vertebral fracture as identified within the SEM framework. Usually, candidate surrogates, such as BMD, are evaluated in models that assumed no sequential ignorability (i.e. no unmeasured confounders of the BMD–fracture relationships such that BMD is randomly assigned to individuals in addition to the treatment) and no interaction between effects and treatment status.[21] When these assumptions are violated, significant associations do not reflect causality.[22] Fortunately, both assumptions may be partially released in methods based on counterfactual experimental conditions in which BMD is theoretically measured on each participant as if he/she received both treatment and placebo.[23,24] In this context, the direct and indirect effect of a treatment on the risk of fracture is defined as the population mean of individual direct and indirect effects. An individual direct effect is the difference between fracture occurrence when an individual is treated and BMD is set at its value under treatment, and fracture occurrence when the same individual is not treated. An individual indirect effect is the difference between occurrence of fracture when an individual is untreated and BMD is set at its value under treatment, and occurrence fracture when BMD of the same individual is set at its value under placebo.[25]

2 Subjects and methods

Data on 3776 Caucasian post-menopausal women (age 50–85) were retrieved from a 3-year, randomized, double-blind, placebo- and active-controlled study, healthy postmenopausal women with osteoporosis. Femoral neck and total hip BMD were measured by DXA at baseline, 6, 12, 18, 24 and 36 months, or at early termination in subjects who withdrew. Vertebral fractures were diagnosed using both semi-quantitative and quantitative morphometric assessment approaches on participants at baseline, and once during the follow-up period. Subjects were randomized to receive BZA (20 or 40 mg/day) or placebo. All subjects received oral daily calcium (up to 1200 mg) and vitamin D (400–800 IU) supplementation.[26]

Analyses concerned 21,134 total hip and 21,166 femoral neck BMD measurements on post-menopausal women in sites located in three distinct geographical regions (Europe, North and South Americas). For each ith participant, three dependent variables are considered: the measure of BMD at time $T_t(y_{it})$, the binary variable F_i with $F_i = 1$ if the participant presents a

fracture at baseline, and 0 if not, and the binary variable z_i with $z_i = 1$ if the participant presents a fracture during the follow-up period, and 0 if not. The time at which the event occurs is denoted T_t ($T_t = 0$, 6, 12, 18, 24, 36 months for $t = 1$ to 6) and $i = 1, 2, \ldots, n_k$ patients in the geographical region k ($k = 1$, 2, 3).

In Part 1, BMD measures are distributed as:

$$y_{it} \sim \text{Normal}\,(\mu_{1i} + \beta_{1i} T_t, \sigma_i^2) \quad \text{for } T_t \leq K_i$$
$$y_{it} \sim \text{Normal}\,(\mu_{2i} + \beta_{2i} T_t, \sigma_i^2) \quad \text{for } T_t > K_i.$$

The lines describe the changes in BMD before and after the breaking point (K_i). Intercepts and regression coefficients for the lines before (and after) K_i are μ_{1i} and β_{1i} (and μ_{2i} and β_{2i}), respectively. Both lines meet at K_i hence the BMD value at K_i is given by: $\mu_{2i} = K_i(\beta_{1i} - \beta_{2i}) + \mu_{1i}$.

After discussion with experts (authors of the paper) in osteoporosis, the model for the SEM analyses was set (Part 2). Baseline age and body mass index were considered as potential predictors of baseline BMD (μ_{1i}) and treatment of BMD initial increase (β_{1i}). In turn, baseline BMD was tentatively associated with prevalent and incident fractures whereas BMD initial increase, treatment and prevalent fractures were linked with incident fractures. The corresponding equations are:

$$\begin{aligned}
\mu_{1i} &\sim \text{Normal}(\gamma_{0m} + \gamma_{1m} A_i + \gamma_{2m} B_i, \sigma_a^2),\\
\beta_{1i} &\sim \text{Normal}(\gamma_{0b} + \gamma_{1b} R_i, \sigma_b^2),\\
F_i &\sim \text{Bernoulli}(p_i); \quad \text{logit}(p_i) = g_0 + g_1 \mu_{1i}\\
z_i &\sim \text{Bernoulli}(q_i); \text{logit}(q_i) = h_0 + h_1 \beta_{1i} + h_2 \mu_{1i} + h_3 R_i + h_4 F_i + h_5 (\beta R)_{1i}
\end{aligned}$$

where A_i is the age in years of the patient at baseline; B_i is the body mass index (BMI; kg/m^2) of the patient at baseline; R_i is 1 if the patient received the BZA, and 0 if he/she received a placebo; $(\beta R)_{1i}$ is the interaction between β_{1i} and R_i. Then, γ_{0m} = baseline BMD adjusted for age and BMI; γ_{1m} = linear change in baseline BMD by year increase in age; γ_{2m} = linear change in baseline BMD by unit increase in BMI; γ_{0b} = BMD slope for women in the placebo group; γ_{1b} = difference in the BMD slope between women receiving BZA versus placebo; g_0 = logit of prevalent fracture adjusted for μ_{1i}; g_1 = linear change in the logit of prevalent fracture by unit increase in baseline BMD; h_0 = logit of incident fracture adjusted for the effects in the model; h_1 = linear change in the logit of incident fracture by unit increase in β_{1i}; h_2 = linear change in the logit of incident fracture by unit increase in μ_{1i}; h_3 = difference in the logit of incident fracture between subjects receiving BZA versus placebo; h_4 = difference in the logit of incident fracture between subjects receiving with versus without prevalent fracture; h_5 = linear change in the logit of incident fracture by unit increase in BMD slope in subject with BZA versus placebo.

In Part 3, a counterfactual approach was used to explicitly formalize the direct and indirect effects of BZA on occurrence of fracture, based on results from Part 1 and Part 2. To do so, we firstly defined ϕ_i^0 as the value of the BMD slope (β_{1i}) when the subject was assigned to the control group ($\phi_i^0 = \gamma_{0b}$) and ϕ_i^1 when the subject was assigned to the BZA group ($\phi_i^1 = \gamma_{0b} + \gamma_{1b}$). Next, we computed four logits ($\eta_i^{00}, \eta_i^{01}, \eta_i^{10}, \eta_i^{11}$) for each participant: the logit of the probability of fracture when the participant received the placebo under ϕ_i^0 (η_i^{00}) and ϕ_1^1 (η_i^{10}), and when the participant received BZA under ϕ_i^0 (η_i^{01}) and under ϕ_i^1 (η_i^{11}). Then, average direct (δ) and indirect (ζ) effects[23,24] were

$$\delta = E[\eta_i^{11} - \eta_i^{10}] = h_5(\gamma_{0b} + \gamma_{1b}) + h_3 \text{ and } \zeta = E[\eta_i^{10} - \eta_i^{00}] = h_1 \gamma_{1b}$$

Table 1. Demographic and baseline characteristics: mean and standard deviation in parentheses

Mean (SD)	Region 1 ($n = 599$)	Region 2 ($n = 1850$)	Region 3 ($n = 1327$)
Age (years)	65.95 (7.44)	66.42 (6.37)	66.23 (6.51)
BMI (kg/m^2)	26.57 (4.11)	26.28 (3.62)	26.79 (3.81)
Prevalent fracture (%)	70.78 (45.51)	56.70 (49.56)	45.74 (49.84)
Total hip BMD (cg/cm^2)	79.30 (12.27)	80.02 (11.12)	80.04 (11.92)
Neck femoral BMD (cg/cm^2)	68.75 (12.84)	71.19 (11.89)	72.07 (12.49)

BMI: body mass index; BMD: bone mass density.

A counterfactual equivalent of the PTE is: $E[\eta_i^{10} - \eta_i^{00}]/E[\eta_i^{11} - \eta_i^{00}]$. The numerator is the indirect effect of BZA on incidence of vertebral fracture and the denominator is its total effect, i.e. the difference in incident fractures between participants with or without BZA, at the observed levels of BMD.

Bayesian estimates of all parameters in the framework were obtained after 20 000 MCMC iteration runs with 2000 iterations burn-in (OpenBUGS[30]). We chose inverse-gamma priors for the variance components parameters (σ_i^2, σ_a^2 and σ_b^2), normal priors for the coefficients μ, β, γ, η, g and h, and truncated normal priors for K_i, which was known in advance to fall within the time range, i.e. 0 to 36 months. Initial values for the mean and precision of all normal priors were set at 0 and 10^{-5}, respectively, with the exception of the prior means for γ_{0m}, h_0 and g_0 that were obtained from the data (empirical Bayesian estimates). The initial value of γ_{0m} was the observed average BMD value at baseline (Table 1). The initial values of g_0 and h_0 were the logit of the average prevalent and incident fracture rates, respectively.

At the end of all iterations, a sensitivity analysis[23] was performed because the assumption of sequential ignorability (i.e. slopes β_{1i} are randomized across participants) could not be verified. Different values for the average causal indirect effects were computed for different values of the sensitivity parameter (∂) as

$$h_1 = h_3' - \left[\frac{\partial}{s}\sqrt{\frac{1}{1-\partial^2}\left(q(1-q) - h_3'^2 s^2\right)}\right]$$

where h_3' is the regression coefficient of the treatment on logit of z_i without adjusting for β_{1i}; ∂ is the correlation between error terms in the models for β_{1i} and z_i (Part 2); q is the incident rate of fracture; and s is the standard deviation of β_{1i}. Imai et al.[23] showed $\partial = 0$ under sequential ignorability and the magnitude of ∂ represents the departure from the assumption.

The same framework was applied to each BMD site (femoral neck and total hip) and to participants in each geographical region, separately. Indeed, geographic variation in vertebral fracture occurrence has been shown, for example, across regions within Europe and between South and North Americas.[27,28] Risk of vertebral fracture depends also upon the site of BMD measurement.[29]

3 Results

Demographic and baseline characteristics can be found in Table 1 for each geographic region. Baseline BMI ranged from 15 to 38 kg/m^2, with an average of 26.5 kg/m^2 (SD = 3.77). At baseline, average femoral and total hip BMD were 71.11 g/cm^2 (SD = 12.30) and 79.92 g/cm^2

(SD = 11.59), respectively. The prevalent rate of vertebral fracture was 55.97% and 54.64% in the placebo and BZA groups, respectively. While average BMI and BMD measurements were not different across regions, averages for age and prevalent fracture in region 1 were different from averages observed in the other two regions (test t student; $p < 0.01$). A description of the non-linear trend in BMD is given in Figure 1 where crude percent changes from baseline up to 36 months in total hip (left panel) and femoral neck (right panel) BMD are shown for participants in both groups and each region. As expected, they were positive in the BZA group with a tendency to increase until a maximum was reached at which they stabilized before declining slowly. In the placebo groups, they decreased across time and became negative or close to null in regions 1 and 2 while remaining positive in region 3.

Bayesian estimates of the parameters of the SEM (Part 2) are given for each region in Table 2 for total hip BMD, and in Table 3 for femoral neck BMD. Results were similar in both tables and across the 3 regions, as suggested by the overlapping 95% credibility intervals for all parameters of the piecewise regression. Looking more closely at hip BMD, we observed average baseline values for hip BMD (μ_b) close to 80 cg/cm^2 in all regions. No significant changes were observed across time (95% credibility intervals for γ_{0b} include 0) in the placebo groups. On the other hand, BMD increased in participants receiving BZA with a positive slope (95% credibility intervals for γ_{1b} greater than 0) before the break point K_i was reached. The expected time at which the plateau was reached (μ_K) was close to 29 months. At that time, average percent changes in BMD were estimated at 1.09%, 1.98% and 1.89% for participants in the BZA group in region 1, 2 and 3, respectively. These values were obtained from equations in Part 1, using the fact that segmented lines meet at K_i.

Basal hip BMD increased with BMI and decreased with age at baseline. Their effects were estimated by substituting the values for μ_{1i}, which gives $\text{logit}(p_i) = g_0 + g_1\mu_{1i} = g_0 + g_1(\gamma_{0m} + \gamma_{1m} A_i + \gamma_{2m} B_i)$. Then, the frequencies of prevalent fractures for a woman of 65 years with a BMI of 26 kg/m^2 were estimated at 72.67%, 57.15% and 44.95% in region 1, 2 and 3, respectively. Likewise, the probability of occurrence of a new fracture during the study period was computed as $\text{logit}(q_i) = h_0 + h_1\gamma_{0b} + h_2(\gamma_{0m} + \gamma_{1m}A_i + \gamma_{2m}B_i)$ in the placebo group, and $\text{logit}(q_i) = h_0 + h_1 \gamma_{0b} + h_2(\gamma_{0m} + \gamma_{1m}A_i + \gamma_{2m}B_i)\ h_3 + h_1\gamma_{1b} + h_5(\gamma_{0b} + \gamma_{1b})$ in the BZA group. Then, frequencies of new fractures for a woman with age of 65 years and BMI of 26 kg/m^2 were 0.78%, 0.81% and 0.46% in the BZA groups, and 2.11%, 1.36% and 1.84% in placebo groups (regions 1, 2 and 3).

Average direct and indirect effects of BZA on the logit of incident fractures are given in Table 4 for total hip and neck femoral BMD. Effects of BZA on incident vertebral fractures were mostly direct in region 3 and indirect in region 2 (95% credibility intervals for δ and ζ limited by negative values). In region 1, estimates for both direct and indirect effects showed large variation and were not significantly different from null (largest SD). These differences between regions are illustrated in Figure 1. Indeed, in region 3, percent changes in BMD had a tendency to increase and remained positive in both BZA and placebo groups and this suggests BZA did not influence BMD. Inversely, in the other two regions, BMD decreased and became negative for participants receiving the placebo. The counterfactual equivalent of PTE in region 2, where indirect effects were not null, was estimated at 41.57% for hip BMD and 43.97% for neck femoral BMD (Table 4). Results from the sensitivity analyses are shown in Figure 2 for hip and neck femoral BMD in the 3 regions. One can see that estimates of indirect effects varied greatly, with higher departures from the current estimates of the indirect effects when the sensitivity parameter increased towards its absolute maximum.

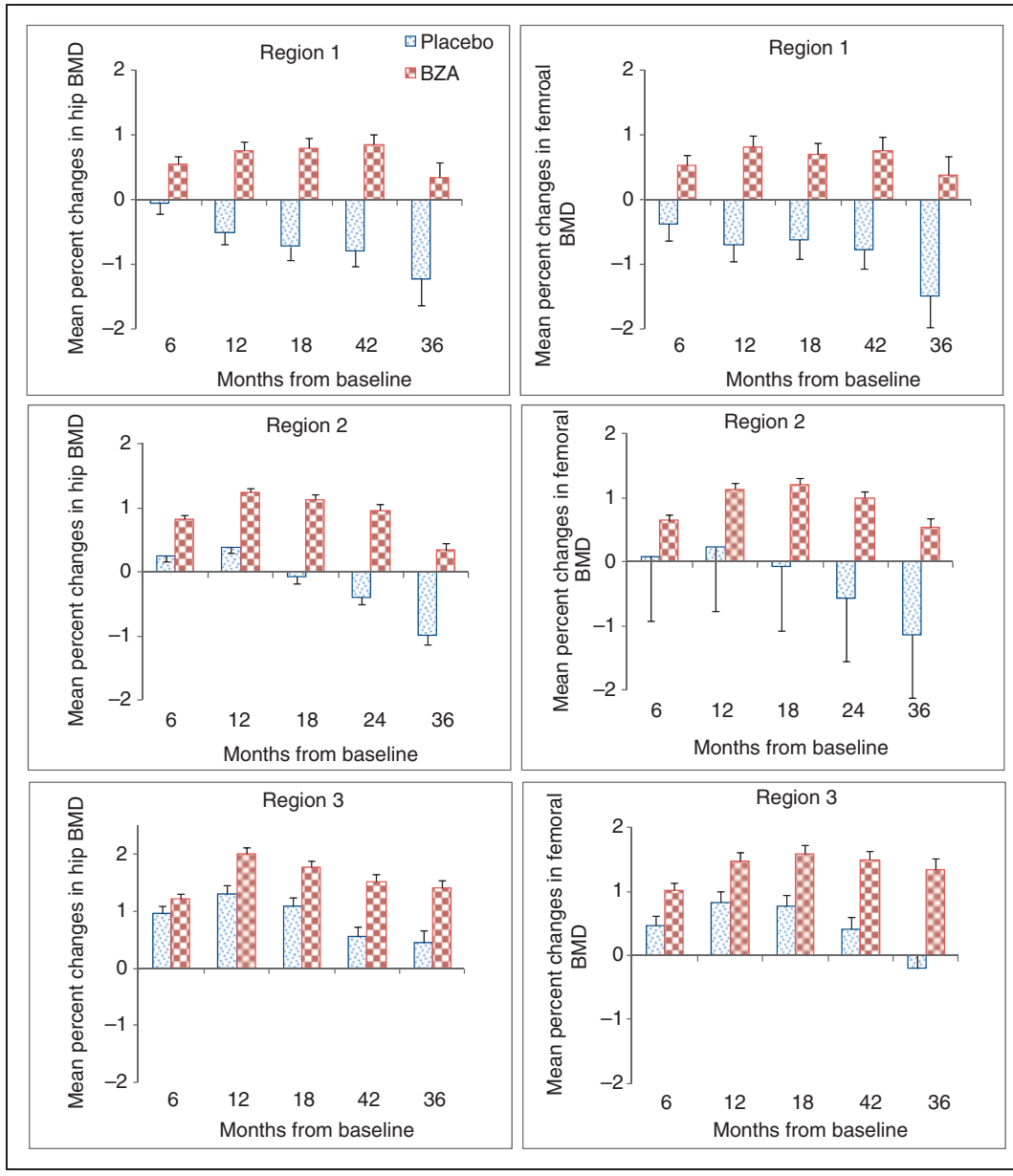

Figure 1. Average percent changes in total hip (left panel) and neck femoral (right panel) BMD from baseline to 36 months for women receiving BZA (hatched blocks) or placebo (dotted blocks) in the 3 regions. Vertical bars are the standard errors.

BMD: bone mass density; BZA: bazedoxifene acetate.

Table 2. Bayesian estimates of the parameters of the structural equation model for total hip BMD in the three regions. Symbols refer to equation (1) in the text

Mean (SD) Lower and upper bounds of the 95% credibility intervals	Region 1	Region 2	Region 3
Average of expected individual basal BMD ($\mu_b = \Sigma\mu_{1i}/n$)	79.39 (0.45) 78.51 to 80.28	80.20 (0.24) 79.73 to 80.66	80.42 (0.27) 79.89 to 80.96
Expected BMD slope after the break-point (μ_a)	−2.99 (5.08) −12.92 to 6.94	−5.52 (2.76) −10.91 to −0.12	−5.14 (3.13) −11.28 to 1.00
Expected time at the break−point (μ_K)	28.65 (3.79) 21.19 to 36.06	29.18 (2.27) 24.72 to 33.63	28.97 (2.65) 23.73 to 34.14
Baseline BMD adjusted for the effects in the model (γ_{0m})	62.30 (4.73) 53.01 to 71.57	65.38 (2.95) 59.61 to 71.14	71.74 (3.33) 65.20 to 78.29
Linear change in baseline BMD by year increase in BMI (γ_{1m})	1.25 (0.11) 1.04 to 1.46	1.15 (0.06) 1.03 to 1.28	1.54 (0.07) 1.40 to 1.68
Linear change in baseline BMD by unit increase in age (γ_{2m})	−0.24 (0.06) −0.36 to −0.13	−0.23 (0.04) −0.31 to −0.16	−0.49 (0.04) −0.57 to −0.41
BMD slope for women in the placebo group ($100^*\gamma_{0b}$)	−3.37 (2.54) −8.36 to 1.61	0.78 (1.45) −2.08 to 3.63	1.71 (1.66) −1.55 to 4.95
Difference in the BMD slope between women receiving BZA vs placebo ($100^*\gamma_{1b}$)	7.36 (0.93) 4.54 to 8.20	4.66 (0.48) 3.73 to 5.60	3.49 (0.66) 2.22 to 4.78
Logit of prevalent fracture adjusted for the effects in the model (g_0)	−4.10 (0.73) −5.59 to −2.71	−3.20 (0.38) −3.95 to −2.45	−3.49 (0.40) −4.30 to −2.71
Linear change in the logit of prevalent fracture by unit increase in baseline BMD (g_1)	0.06 (0.01) 0.05 to 0.08	0.04 (0.00) 0.03 to 0.05	0.04 (0.00) 0.03 to 0.05
Logit of incident fracture adjusted for the effects in the model (h_0)	2.62 (3.08) −3.44 to 8.65	−1.71 (1.23) −4.14 to 0.68	−0.85 (1.70) −4.20 to 2.49
Linear change in the logit of incident fracture by unit increase in BMD slope (h_1)	−7.28 (9.41) −27.14 to 10.45	−7.91 (4.19) −16.35 to −1.12	−1.92 (4.59) −10.96 to 7.13
Linear change in the logit of incident fracture by unit increase in baseline BMD (h_2)	−0.08 (0.04) −0.17 to −0.01	−0.03 (0.02) −0.06 to −0.00	−0.04 (0.02) −0.08 to 0.01
Difference in the in the logit of incident fracture between subjects receiving BZA vs placebo (h_3)	−0.79 (1.17) −2.89 to 1.77	−0.49 (0.40) −1.27 to 0.30	−0.95 (0.55) −2.08 to −0.19
Difference in the logit of incident fracture between subjects receiving with vs without prevalent fracture (h_4)	−1.44 (0.82) −3.15 to 0.08	0.82 (0.37) 0.11 to 1.58	0.09 (0.51) −0.93 to 1.08
Interaction – Linear change in the logit of incident fracture by unit increase in BMD slope in subject with BZA (h_5) versus placebo	8.35 (11.79) −14.19 to 32.29	6.19 (6.05) −5.58 to 18.16	−7.13 (7.74) −22.45 to 7.95

BMD: bone mass density; BZA: bazedoxifene acetate.

4 Discussion

To our knowledge, this is the first attempt to quantify temporal changes in BMD with piecewise regression and effects of BZA on incidence of vertebral fractures using counterfactual concepts and structural equations.

Table 3. Bayesian estimates of the parameters of the structural equation model for femoral neck BMD in the three regions. Symbols refer to equation (1) in the text

Mean (SD) Lower and upper bounds of the 95% credibility intervals	Region 1	Region 2	Region 3
Average of expected individual basal BMD ($\mu_b = \Sigma\mu_{1i}/n$)	68.80 (0.49) 67.82 to 69.76	71.34 (0.27) 70.82 to 71.87	72.29 (0.30) 71.69 to 72.88
Expected BMD slope after the break−point (μ_a)	−2.02 (5.05) −11.89 to 7.85	−3.99 (2.74) −9.33 to 1.41	−4.07 (3.19) −10.43 to 2.12
Expected time at the break−point (μ_K)	28.79 (3.79) 21.35 to 36.19	29.57 (2.27) 25.14 to 34.02	29.54 (2.64) 24.36 to 34.74
Baseline BMD adjusted for the effects in the model (γ_{0m})	62.05 (5.16) 51.98 to 72.29	58.91 (3.33) 52.39 to 65.48	77.51 (3.66) 70.36 to 84.71
Linear change in baseline BMD by year increase in BMI (γ_{1m})	0.93 (0.12) 0.69 to 1.16	0.78 (0.07) 0.64 to 0.93	1.23 (0.08) 1.07 to 1.38
Linear change in baseline BMD by unit increase in age (γ_{2m})	−0.27 (0.07) −0.40 to −0.14	−0.12 (0.04) −0.20 to −0.04	−0.57 (0.05) −0.67 to −0.48
BMD slope for women in the placebo group ($100^*\gamma_{0b}$)	−2.61 (0.77) −4.13 to −1.08	−1.27 (0.39) −2.03 to −0.50	1.34 (0.50) −0.37 to 2.31
Difference in the BMD slope between women receiving BZA vs placebo ($100^*\gamma_{1b}$)	4.55 (0.94) 2.70 to 6.39	4.58 (0.48) 3.63 to 5.51	3.30 (0.62) 2.08 to 4.52
Logit of prevalent fracture adjusted for the effects in the model (g_0)	−3.11 (0.60) −4.26 to −1.92	−2.90 (0.32) −3.55 to −2.29	−2.72 (0.34) −3.36 to −2.04
Linear change in the logit of prevalent fracture by unit increase in baseline BMD (g_1)	0.06 (0.01) 0.04 to 0.08	0.04 (0.00) 0.04 to 0.05	0.03 (0.00) 0.02 to 0.04
Logit of incident fracture adjusted for the effects in the model (h_0)	−0.47 (2.43) −5.02 to 4.39	−1.79 (1.10) −3.88 to 0.39	−0.68 (1.51) −3.53 to 2.51
Linear change in the logit of incident fracture by unit increase in BMD slope (h_1)	3.42 (14.31) −23.66 to 33.36	−11.16 (5.61) −22.87 to −1.65	−5.27 (5.76) −16.69 to 6.07
Linear change in the logit of incident fracture by unit increase in baseline BMD (h_2)	−0.04 (0.04) −0.12 to 0.03	−0.04 (0.01) −0.07 to −0.01	−0.05 (0.02) −0.09 to −0.00
Difference in the in the logit of incident fracture between subjects receiving BZA vs placebo (h_3)	−1.09 (1.16) −3.39 to 1.23	−0.48 (0.51) −1.44 to 0.58	−0.99 (0.58) −2.21 to −0.17
Difference in the logit of incident fracture between subjects with vs without prevalent fracture (h_4)	−1.70 (0.85) −3.50 to −0.16	0.92 (0.38) 0.21 to 1.70	0.11 (0.51) −0.90 to 1.09
Interaction – Linear change in the logit of incident fracture by unit increase in BMD slope in subject with BZA (h_5) vs placebo	−1.52 (16.52) −34.78 to 31.07	14.06 (7.31) −0.01 to 28.61	−2.79 (9.99) −22.09 to 17.35

Piecewise regression models (Part 1) were valuable in this study because BMD values increased linearly until they reached a plateau in participants receiving BZA (Figure 1). This was also shown by others.[11,17] The time when the plateau was reached and the magnitude of the BMD change were very different across participants. Indeed, credibility intervals observed around the median values for γ_{1b} and μ_k were very large (Tables 2 and 3). This suggests that fixing, for all participants the same moment at which percent BMD change from baseline should be measured may not be adequate to

Table 4. Direct and indirect effects of BZA on the logit of incident fractures in the 3 regions for total hip and neck femoral BMD.

	Region 1	Region 2	Region 3
Hip BMD			
Direct (δ)	−1.10 (1.11)[a]	−0.52 (0.40)	−1.13 (0.57)
	−3.34 to 1.09[b]	−1.32 to 0.27	−2.32 to −0.07
Indirect (ζ)	−0.56 (0.60)	−0.37 (0.20)	−0.07 (0.16)
	−1.78 to 0.64	−0.78 to −0.01	−0.39 to 0.26
Neck femoral BMD			
Direct (δ)	−1.06 (1.30)	−0.65 (0.50)	−1.03 (0.59)
	−3.80 to 1.39	−1.66 to 0.34	−2.25 to −0.08
Indirect (ζ)	0.14 (0.66)	−0.51 (0.26)	−0.17 (0.20)
	−1.14 to 1.54	−1.07 to −0.03	−0.58 to 0.20

[a]Mean (SD).
[b]Lower and upper credibility interval.
BMD: bone mass density; BZA: bazedoxifene acetate.

evaluate the efficacy of BZA. A same percent BMD change after a fixed amount of time may indeed represent BMD value that reached a low plateau before or a high plateau after the fixed time, both with possible different impact on the risk of incident fracture. Note our model was very simple (i.e. two linear segments with a single join point) and more complex models could improve this and other settings.

We next proposed a SEM to study the interdependencies between age, BMI, BMD parameters, and occurrence of vertebral fractures (Part 2). Indeed, SEMs are adequate to model complex relationships between variables and to study direct and indirect effects of variables on one another.[20] The SEM was based on our current (partial) understanding of the relationships between variables but other SEMs could also be suggested. For example, we may have considered baseline age and BMI affect the frequency of incident vertebral fractures, with or without influencing BMD. Fortunately, relationships are clearly specified in SEMs and this allows transparent understanding and discussion of the results, knowing the assumptions of the SEM. Here, we observed age decreased and BMI increased baseline BMD. In turn, baseline BMD had small effects on frequency of baseline and incident vertebral fractures. Prevalent fractures had no effect on incident fractures, with the exception of region 2. These results were confirmed in some[31–33] but not[34,35] previous studies.

In the last part of the study (Part 3), we presented a causal interpretation of the relationship between BZA, BMD and incident fractures. Understanding causality is a real issue when one has to judge the worth of a treatment based on its impact on a biomarker. For example, we observed the counterfactual equivalent of the PTE obtained with conventional (linear or logistic) regression techniques is the ratio $E[\eta_i^{10} - \eta_i^{00}]/E[\eta_i^{11} - \eta_i^{00}]$. The denominator is the difference in the logit of the occurrence of fracture for individuals under BZA and placebo at their observed BMD values. The numerator compares occurrence of fracture for individuals receiving the placebo, with BMD values under BZA versus placebo. An alternative would be to compute PTE as the ratio $E[\eta_i^{11} - \eta_i^{01}]/E[\eta_i^{11} - \eta_i^{00}]$. Here, the numerator compares the occurrence of fracture for individuals under BZA, with BMD values under BZA versus placebo. The difference between both PTEs resides in the interaction term between treatment and BMD (h_5). In this study, BZA and BMD didn't

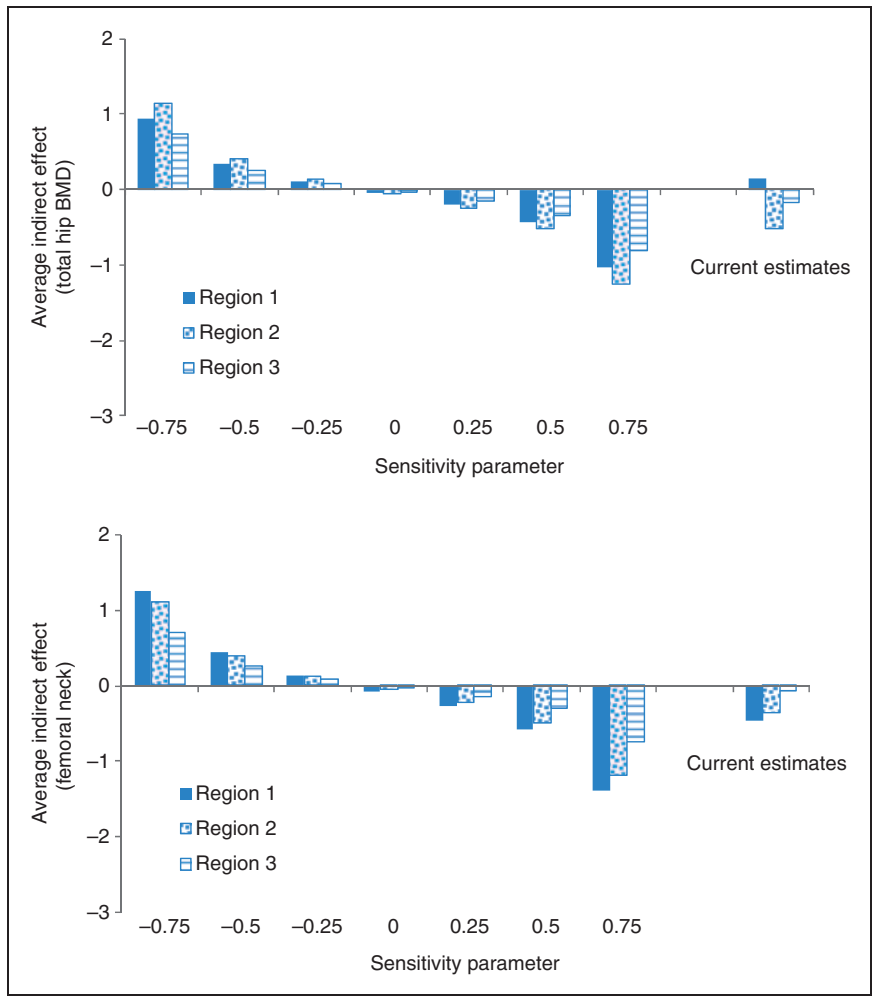

Figure 2. Sensitivity analyses of the indirect effects for total hip (left panel) and femoral neck (right panel) BMD. BMD: bone mass density.

interact to cause fracture (95% credibility intervals for h_5 include 0) so both PTEs were equivalent. But it is not always the case and the choice between PTEs will depend upon the research question.[15,25]

Effects of BZA on incidence of fracture were different across regions. In region 2, part of its impact was via changes in BMD. In the other two regions, indirect effects were not significantly different from null (Table 4): BZA induced only direct effects in region 3 while no effects were found in region 1. These differences between regions may be due to a combination of biological and socio-economic factors that could have influenced differently individuals in the placebo and BZA groups.[36] Osteoporosis is indeed a multi-factorial disease, submitted to genetic and environmental influences. Incidence of fracture in Canadian post-menopausal women has been associated with dietary patterns.[37] Variations in genes such as those involved in the RANK/RANKL/OPG pathway may also explain part of the variation in the pathogenesis of postmenopausal

osteoporosis.[38] Pharmacogenetics is another possible source of variation in individual responses to BZA although, so far, no gene variations have been conclusively shown to be responsible for the regulation of anti-osteoporosis drug response. Note, however, that most data on post-menopausal women available in the literature has been obtained from Caucasian populations aged 65 or over, and that information from other ethnic groups is limited.[39]

Finally, we considered whether unmeasured confounders may have introduced spurious associations between BMD and incident fracture. Indeed, the assumption of sequential ignorability was probably not met in this study because BMD slopes were observed after participants were randomly allocated to placebo and BZA groups. The sensitivity analysis showed that our estimates of indirect effects were not very robust to violation of this assumption (Figure 2). This highlights one important limitation of our work: our estimates are only valid in the absence of post-treatment unmeasured variables that confound the relationships between BMD and incident fracture. We hypothesize that estimates in previous studies with the same design were sensitive to similar biases and may explain changeable results. Given the importance of the matter, researchers are currently suggesting different methods to estimate unmeasured confounding, as recently reviewed.[40]

5 Conclusions

Our objective was to illustrate the use of piecewise regression, SEM and counterfactual to repeated measurements of BMD from a study of BZA and vertebral fractures in three geographical regions. We observed large individual variation in BMD temporal changes which suggests percent changes from baseline up to a fixed point in time may not be optimal in describing the non-linear trend in BMD. Risk factors influenced directly or indirectly on one another: Baseline age and BMI influenced baseline BMD that, in turn, had an effect on the frequency of vertebral fractures. Depending on the region, BZA acted either directly on the frequency of incident fractures or indirectly through an effect on BMD temporal changes (before the plateau). A causal interpretation of the proportion of treatment explained is provided for one region: around 40% of average difference in occurrence of fracture between BZA versus placebo individuals is due to average difference observed for untreated individuals with BMD set at the value under BZA versus under placebo. Estimates of indirect effects can be biased in the presence of unmeasured post-treatment variable. Fortunately, new research explores alternative statistical methods and experimental designs to identify causal mediation effects with weaker assumptions.

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