Bayesian Joint Modeling of Bone Mineral Density And Repeated Time-To-Fracture Event For Multiscale Bone Systems Model Extension


Background
- Physiologically-based multiscale systems (PBMS) model describes cellular mechanisms and bone dynamics in bone-related diseases.
- Fracture rate considered as most meaningful endpoint affected by disease progression and drug intervention.

Objectives
To develop a model simultaneously characterizing bone mineral density (BMD) and fracture risk based on time since final menstrual period (FMP).

Methods
Data
- 2005-2008 NHANES demographics, dual energy X-ray absorptiometry, body measures, osteoporosis, and reproductive health datasets.
- 1605 postmenopausal \( \xi \) of 63 (95% inter-percentiles (IP) 27–85) yr mean age and 45 (95% IP 26–57) yr mean FMP age; 1 femoral neck BMD measure and 0–5 (204 total) fracture events each.

Models
BMD: Piecewise linear model from literature\(^5\)
\[ \text{BMD}(t) = b + s_1 \times t + s_2 \times t^2 + s_3 \times t^3 + s_4 + s_5 \times t^5 \]
Included covariates: BMI, ethnicity, and FMP\(_{\text{Age}}\).

Fracture risk: Repeated time-to-event model\(^6,7\)
\[ S(t) = e^{-(t - \xi)^2/2\sigma^2} \]
Investigated covariates: observed BMD, BMD(t), FMP\(_{\text{Age}}\), and time (\(\alpha = 1\), Weibull distribution).

Software
WinBUGS, BlackBox\(^8\), R (deSolve, mrgSim).

Results
Evaluation w.r.t. NHANES data
BMD: Retrospective prediction, from examination time to FMP through fracture time point(s).
Structural parameter estimates:
\[ b = 0.84, s_1 = -1.66, s_2 = -0.85, s_3 = -0.34 \]
(close to reported literature values\(^5\)).
Centered covariate effects added on all parameters.
Random effect included as residual variability:
\[ \sigma = 0.151 \] (95% credible interval (CI) 0.127–0.136).

Fracture risk: Time-varying hazard reflects increase due to time-dependent BMD decline in final model.
\[ h(t) = e^{\theta_1 + 1 + \theta_0} \times \text{BMD}(t)^{-1} \]
\[ \text{BMD} = 0.8 \text{ g/cm}^2, \ a = 1 \]
\[ \theta_0 = -5.5 \] (95%CI –5.49 – –5.54), \[ \theta_{\text{BMD}} = 1.5 \] (95%CI 1.49–1.52)
\[ h(t) \] accumulates from \( t_0 = \text{FMP} \)
\[ \Delta \text{DIC} = \text{DIC}(\text{constant}) - \text{DIC}(\text{varying}) \]
\[ = 30 \]
\[ \text{FMP}_{\text{Age}} \] and time indirect covariates with dynamically predicted BMD vs. direct with observed BMD.

Simulation with PBMS model

Conclusions
- Simultaneous modeling of BMD time-course and repeated time-to-fracture events from publicly available data enabled the characterization of the fracture risk in > 1500 postmenopausal \( \xi \).
- Next steps include, among others, testing drug effects from previously explored therapies, performing external evaluation with estrogen therapy, and including uncertainty in deterministic model.
- This model will be made available in the data and model library METAMODL\(^\circ\).

References
8. WinBUGS2Library, PBMG Model Library for WinBUGS. Gelehrter Software.

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