Joint Models with Multiple Longitudinal Outcomes

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Outcomes in Follow-up Studies

- Often in follow-up studies different types of outcomes are collected
  - multiple longitudinal responses (e.g., markers, blood values)
  - time-to-event(s) of particular interest (e.g., death, relapse)

- Depending on the questions of interest, different types of statistical analysis are required

Outcomes in Follow-up Studies (cont'd)

- Focus *simultaneously* on multiple outcomes
  - association between longitudinal outcomes
  - which features of the longitudinal profiles are associated with the risk of death

Illustrative Case Study

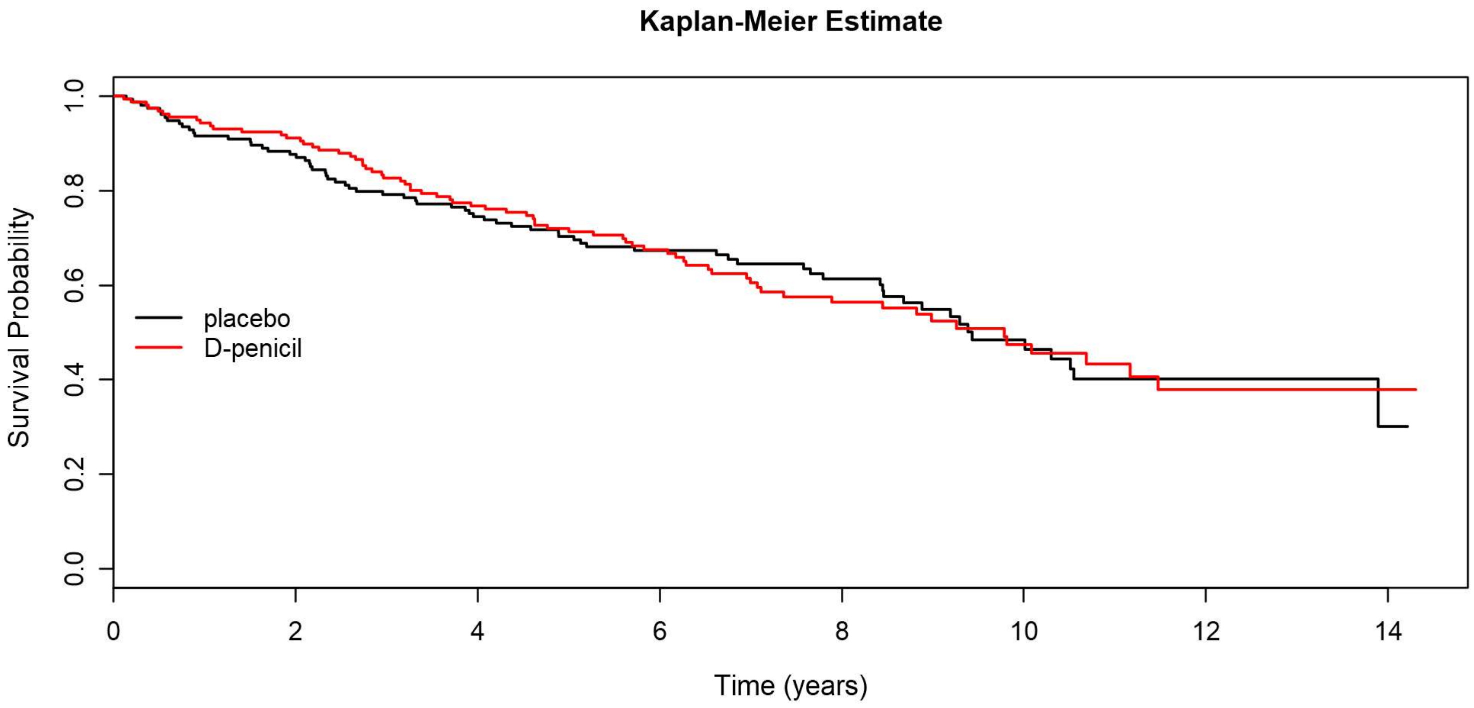
- Mayo Clinic PBC data: Primary Biliary Cirrhosis
  - a chronic, fatal but rare liver disease
  - characterized by inflammatory destruction of the small bile ducts within the liver

- Outcomes of interest:
  - time to death and/or liver transplantation
  - longitudinal
    - bilirubin, cholesterol, prothrombin time (continuous)
    - ascites, hepatomegaly, spiders (dichotomous)

Illustrative Case Study (cont'd)

Outcome:

survival



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Illustrative Case Study (cont'd)

- Research Questions:
  - How strong is the association between the longitudinal biomarkers and the risk of death?
  - How the observed biomarker levels could be utilized to provide predictions of survival probabilities?

Time-varying Covariates

- To answer these questions we need to link
  - the survival outcome
  - the longitudinal biomarkers

- Biomarkers are *endogenous* time-varying covariates

Time-varying Covariates (cont'd)

To account for endogeneity we use the framework of

Joint Models for Longitudinal & Survival Data

Multivariate Joint Models

- **We want to simultaneously model all outcomes**
  - K possible longitudinal outcomes, i.e., $\mathbf{Y}_{1i}, \ldots, \mathbf{Y}_{Ki}$
  - multivariate generalized linear mixed model

$$\left\{\begin{array}{l} g_k \big[E\{y_{ki}(t) \mid \mathbf{b}_{ki}\} \big] = \eta_{ki}(t) = \mathbf{x}_{ki}^\top(t)\beta_k + \mathbf{z}_{ki}^\top(t)\mathbf{b}_{ki} \\ \\ h_i(t) = h_0(t) \exp\Big\{ \gamma^\top \mathbf{w}_i + \sum_{k=1}^K \alpha_k \eta_{ki}(t) \Big\} \end{array}\right.$$

Multivariate Joint Models (cont'd)

- The association between the longitudinal outcomes is build via random effects

$$\mathbf{b} = \begin{bmatrix} \mathbf{b}_{1i} \\ \mathbf{b}_{2i} \\ \vdots \\ \mathbf{b}_{Ki} \end{bmatrix} \sim \mathcal{N}(\mathbf{0}, \mathbf{D})$$

- **(very) high-dimensional random effects**

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Multivariate Joint Models (cont'd)

- Several papers on multivariate joint models
  - a couple under (pseudo) maximum likelihood
  - but mainly under the Bayesian approach or two-stage approaches
- Why?
  - high dimensional random effects
  - MCMC more robust than Gaussian quadrature

Multivariate Joint Models (cont'd)

- Even though in the majority of these papers the model is written for K longitudinal outcomes

- In practice it is only fitted for 2 or 3 outcomes …

Multivariate Joint Models (cont'd)

Hence, a practical deadlock!

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Multivariate Joint Models (cont'd)

- To overcome these difficulties some papers have proposed to work with **two-stage approaches**
  - fit the longitudinal outcomes in the first stage, and
  - then combine them with the survival one

- Computationally easier
  - it could be done with standard software
  - **however biased results!**

IS Two-Stage

- Why does the 2-stage approach give biased results?
  - because it **does not** work with the joint likelihood

- **Hence, to correct the two-stage approach we need the full likelihood**

- However, it is *not efficient* to work with the full joint likelihood due to the aforementioned computational problems

IS Two-Stage (cont'd)

- However, under a Bayesian approach there is a possible solution, namely

Importance Sampling (IS)

- IS allows to use a sample from a *wrong* distribution, and adjust it to look like a sample from the *correct* one

IS Two-Stage (cont'd)

- **Stage I:**
  - Fit a multivariate mixed effects model to the longitudinal outcomes alone
  - We obtain an MCMC sample from the distribution

$$\{\theta_y^{(m)}, \mathbf{b}^{(m)};\ m = 1, \ldots, M\}\ \sim\ [\theta_y, \mathbf{b} \mid \mathbf{y}_{1i}, \ldots, \mathbf{y}_{Ki}]$$

- **Stage II:**
  - For each MCMC realization from the first stage we obtain a value for the parameters of the survival model

$$\{\theta_t^{(m)};\ m = 1, \ldots, M\}\ \sim\ [\theta_t \mid T_i, \delta_i, \mathbf{b}^{(m)}, \theta_y^{(m)}]$$

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IS Two-Stage (cont'd)

- The combined MCMC sample from the two-stage approach can be corrected with the weights

$$\widetilde{w}^{(m)} = \frac{p(\theta_t^{(m)}, \theta_y^{(m)}, \mathbf{b}^{(m)} \mid T_i, \delta_i, \mathbf{y}_{1i}, \ldots, \mathbf{y}_{Ki})}{p(\theta_t^{(m)} \mid T_i, \delta_i, \theta_y^{(m)}, \mathbf{b}^{(m)}) \; p(\theta_y^{(m)}, \mathbf{b}^{(m)} \mid \mathbf{y}_{1i}, \ldots, \mathbf{y}_{Ki})}$$

$$w^{(m)} = \widetilde{w}^{(m)} \Big/ \sum_{m=1}^{M} \widetilde{w}^{(m)}$$

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IS Two-Stage (cont'd)

- If you do the math …

$$\widetilde{w}^{(m)} = p(T_i, \delta_i \mid \mathbf{b}^{(m)}, \theta_y^{(m)})$$

$$= \int p(T_i, \delta_i \mid \theta_t, \mathbf{b}^{(m)}, \theta_y^{(m)}) p(\theta_t) \; d\theta_t$$

  - Hence, a marginal likelihood calculation

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IS Two-Stage (cont'd)

- Approaches to estimate marginal likelihoods
  - Power posteriors
    - more accurate estimate of marginal likelihood
    - but computationally intensive

  - **Laplace approximation**

IS Two-Stage (cont'd)

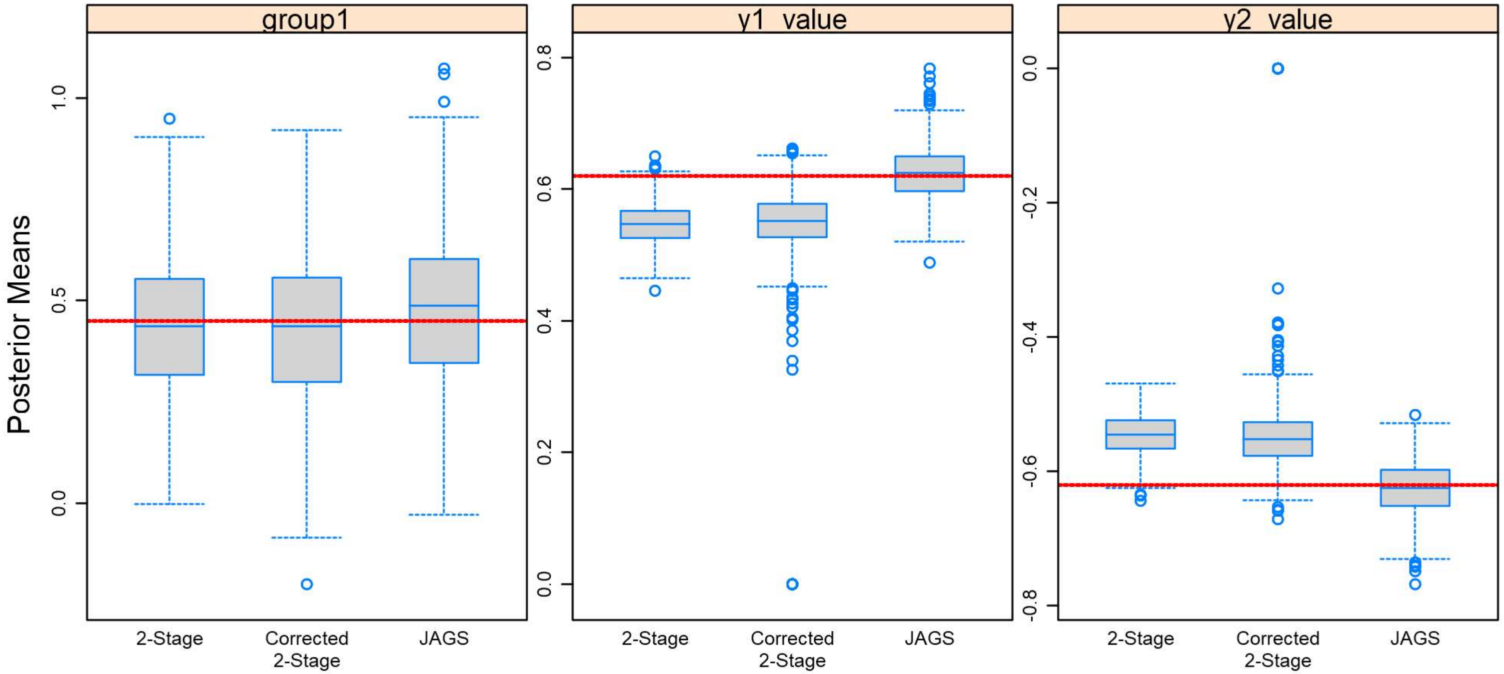
- *OK, how does it perform?*

- Simulation study
  - 2 longitudinal outcomes (both normal)
  - compare corrected two-stage approach with full Bayesian
  - Stage I: JAGS 2 chains run in parallel
  - Stage II: run in parallel using 4 cores

IS Two-Stage (cont'd)

Performance:

- Time
- Bias



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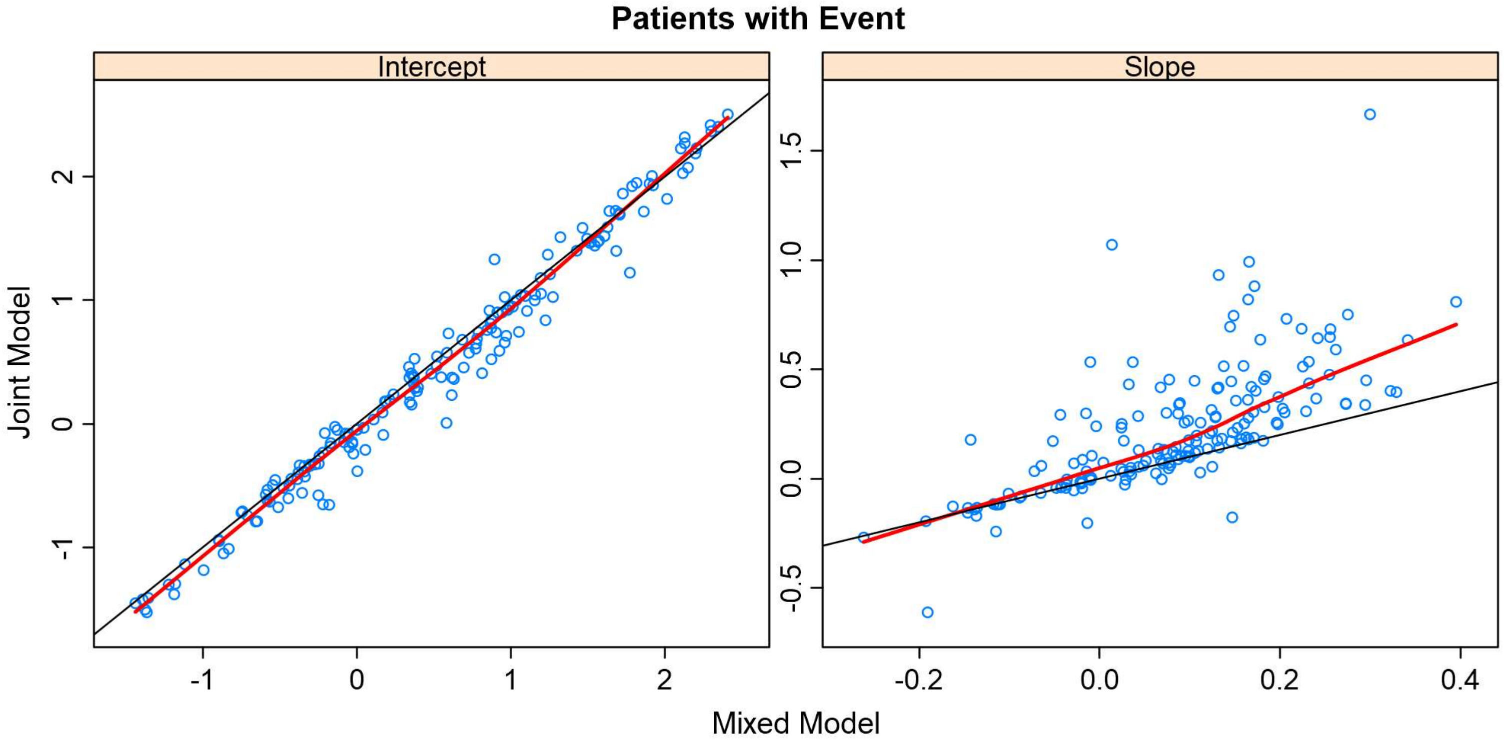
IS Two-Stage (cont'd)

- The correction does not seem to help much!!
- Why is that?
    - detective work …

IS Two-Stage (cont'd)

Sub-group:
- All
- Event-free
- Event (selected)



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IS Two-Stage (cont'd)

- **Stage I:**
  - Fit a multivariate mixed effects model to the longitudinal outcomes alone
  - We obtain an MCMC sample from the distribution

$$\{\theta_y^{(m)}, \mathbf{b}^{(m)};\ m = 1, \ldots, M\}\ \sim\ [\theta_y, \mathbf{b} \mid \mathbf{y}_{1i}, \ldots, \mathbf{y}_{Ki}]$$

- **Stage II:**
  - For each MCMC realization from the first stage we obtain a value for the parameters of the survival model **and** the random effects

$$\{\theta_t^{(m)}, \mathbf{b}^{(m)};\ m = 1, \ldots, M\}\ \sim\ [\theta_t, \mathbf{b} \mid T_i, \delta_i, \mathbf{y}_{1i}, \ldots, \mathbf{y}_{Ki}, \theta_y^{(m)}]$$

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IS Two-Stage (cont'd)

- Now Stage II is more challenging
  - Stage II-a: $\mathbf{b}^* \;\sim\; [\mathbf{b} \mid T_i, \delta_i, \mathbf{y}_{1i}, \ldots, \mathbf{y}_{Ki}, \theta_y^{(m)}, \theta_t^*]$
  - Stage II-b: $\theta_t^* \;\sim\; [\theta_t \mid T_i, \delta_i, \theta_y^{(m)}, \mathbf{b}^*]$

- Stage II-a: entails calculating the multivariate density of *all* longitudinal outcomes

IS Two-Stage (cont'd)

- The combined MCMC sample from the two-stage approach can be corrected with the weights

$$\widetilde{w}^{(m)} = \frac{p(\theta_t^{(m)}, \theta_y^{(m)}, \mathbf{b}^{(m)} \mid T_i, \delta_i, \mathbf{y}_{1i}, \ldots, \mathbf{y}_{Ki})}{p(\theta_t^{(m)}, \mathbf{b}^{(m)} \mid T_i, \delta_i, \mathbf{y}_{1i}, \ldots, \mathbf{y}_{Ki}, \theta_y^{(m)}) \; p(\theta_y^{(m)}, \mathbf{b}^{(m)} \mid \mathbf{y}_{1i}, \ldots, \mathbf{y}_{Ki})}$$

$$w^{(m)} = \widetilde{w}^{(m)} \Big/ \sum_{m=1}^{M} \widetilde{w}^{(m)}$$

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IS Two-Stage (cont'd)

- Again we obtain a marginal likelihood computation

$$\widetilde{w}^{(m)} = \frac{p(\mathbf{y}_{1i}, \ldots, \mathbf{y}_{Ki}, T_i, \delta_i \mid \theta_y^{(m)})}{p(\mathbf{y}_{1i}, \ldots, \mathbf{y}_{Ki} \mid \mathbf{b}_i^{(m)}, \theta_y^{(m)}) \, p(\mathbf{b}_i^{(m)} \mid \theta_y^{(m)})}$$

where

$$p(\mathbf{y}_{1i}, \ldots, \mathbf{y}_{Ki}, T_i, \delta_i \mid \theta_y^{(m)}) =$$

$$\int\int p(\mathbf{y}_{1i}, \ldots, \mathbf{y}_{Ki} \mid \mathbf{b}_i, \theta_y^{(m)}) p(T_i, \delta_i \mid \mathbf{b}_i, \theta_t, \theta_y^{(m)}) p(\mathbf{b}_i \mid \theta_y^{(m)}) p(\theta_t) \; d\mathbf{b}_i d\theta_t$$

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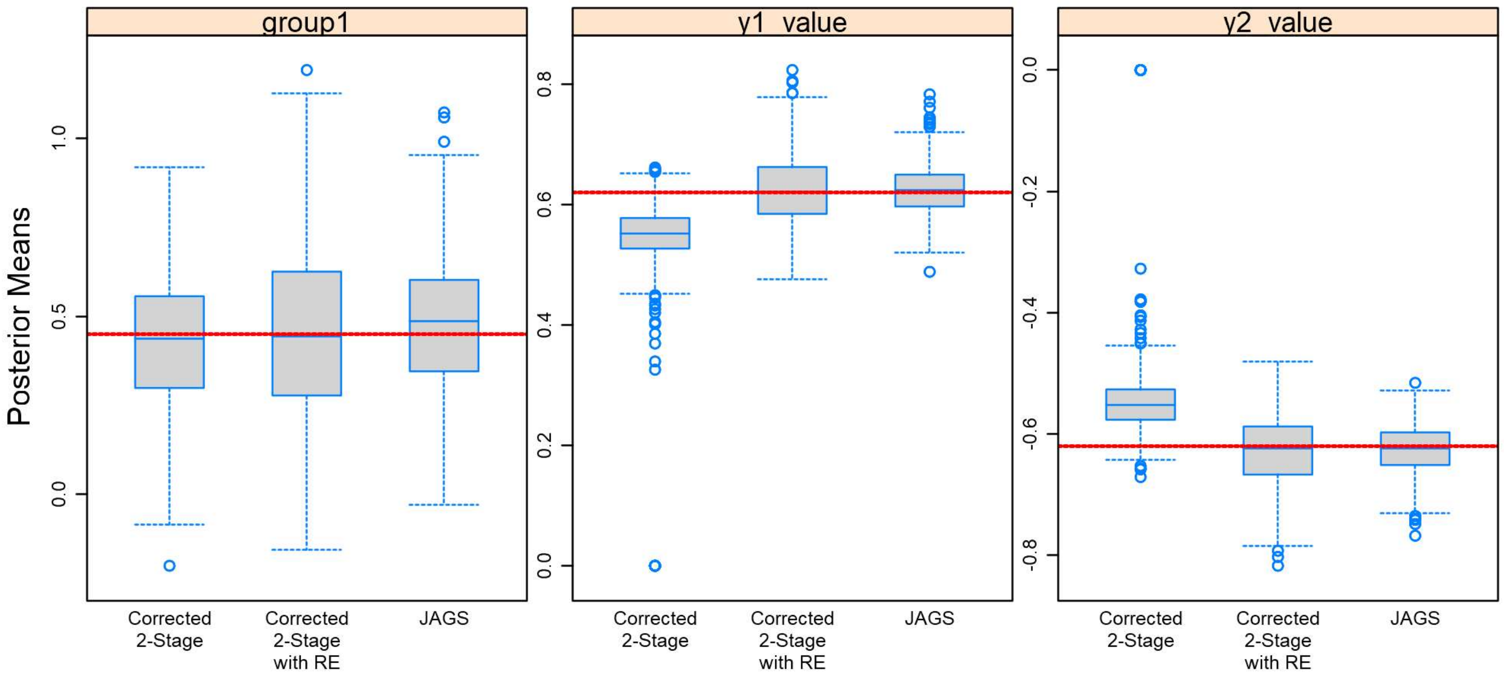
IS Two-Stage (cont'd)

Performance:
- Time ○
- Bias ◉



Conclusion & Software

- We have evaluated the IS-corrected 2-stage approach is more challenging settings
  - 6 longitudinal outcomes
  - mix of continuous, count & binary

- Promising results

- Software implementation in the R package **JMbayes**

Thank you for your attention!

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