

Background:

- Observational data are increasingly used to evaluate the effectiveness of medical interventions. However, estimates may be biased when follow-up is informative.
- Unlike trials, where measurements are collected according to a schedule, observational data often has irregular follow-up.
- For example, patients on different blood pressure treatments may be seen for follow-up at different rates due to reasons unrelated to the trial, such as poor health or differing co-morbidities.
- Joint modelling provides a framework for modelling the longitudinal outcome and observation process jointly, this can account for the visitation process [1].

Objective:

We conducted a simulation study to assess whether joint modelling is necessary to account for the observation process. We considered two scenarios:

- a scenario replicating the ASCOT-BPLA trial, a trial comparing two blood-pressure lowering treatments [2]
- a scenario with exaggerated associations between visitation, blood pressure, and treatment arm

We compared longitudinal mixed-effects models with joint models incorporating visitation and mortality processes.

Methods:

Five models were then fit using INLAjoint [3]:

Model 1 is a mixed-effects model with blood pressure $x_i(t)$ and random intercept μ_{i0} and slope μ_{i1} .

$$\log(x_i(t)) = \alpha_0 + (\alpha_1 + \alpha_2 A_i)t + \mu_{i0} + \mu_{i1}t$$

$$\begin{pmatrix} \mu_{i0} \\ \mu_{i1} \end{pmatrix} \sim \mathcal{N}(\mathbf{0}, \Sigma_\mu)$$

Model 2 is a joint longitudinal-survival model with a mortality sub-model with Weibull baseline-hazard λ_0^M and association parameter b :

$$\log(x_i(t)) = \alpha_0 + (\alpha_1 + \alpha_2 A_i)t + \mu_{i0} + \mu_{i1}t$$

$$\lambda_i^M(t) = \lambda_0^M(t) \exp(\beta_1^M A_i + b \log(m_i(t)))$$

$$\begin{pmatrix} \mu_{i0} \\ \mu_{i1} \end{pmatrix} \sim \mathcal{N}(\mathbf{0}, \Sigma_\mu)$$

Model 3 includes a sub-model for visitation instead of mortality, with a Weibull baseline hazard λ_0^V and visitation random-effect v_i :

$$\log(x_i(t)) = \alpha_0 + (\alpha_1 + \alpha_2 A_i)t + \mu_{i0} + \mu_{i1}t + \gamma_0 v_i + \gamma_1 v_i t,$$

$$\lambda_i^V(t) = \lambda_0^V(t) \exp(\beta_1^V A_i + v_i)$$

$$\begin{pmatrix} \mu_{i0} \\ \mu_{i1} \end{pmatrix} \sim \mathcal{N}(\mathbf{0}, \Sigma_\mu), \quad v_i \sim \mathcal{N}(0, \sigma_v^2)$$

Model 4 then combines both mortality and visitation:

$$\log(x_i(t)) = \alpha_0 + (\alpha_1 + \alpha_2 A_i)t + \mu_{i0} + \mu_{i1}t + \gamma_0 v_i + \gamma_1 v_i t$$

$$\lambda_i^V(t) = \lambda_0^V(t) \exp(\beta_1^V A_i + v_i)$$

$$\lambda_i^M(t) = \lambda_0^M(t) \exp(\beta_1^M A_i + b \log(m_i(t)))$$

$$\begin{pmatrix} \mu_{i0} \\ \mu_{i1} \end{pmatrix} \sim \mathcal{N}(\mathbf{0}, \Sigma_\mu), \quad v_i \sim \mathcal{N}(0, \sigma_v^2)$$

Model 5 then simplifies this model, by removing the longitudinal random-slope. This assumes that the variability over time in the longitudinal blood pressure measurement is solely affected by the fixed effects and the effect of visitation via the random-effect v_i .

$$\log(x_i(t)) = \alpha_0 + (\alpha_1 + \alpha_2 A_i)t + \mu_{i0} + \gamma_0 v_i + \gamma_1 v_i t,$$

$$\lambda_i^V(t) = \lambda_0^V(t) \exp(\beta_1^V A_i + v_i)$$

$$\lambda_i^M(t) = \lambda_0^M(t) \exp(\beta_1^M A_i + b \log(m_i(t)))$$

$$\mu_{i0} \sim \mathcal{N}(0, \sigma_{\mu_0}^2), \quad v_i \sim \mathcal{N}(0, \sigma_v^2)$$

Results:

Under the scenario replicating the ASCOT-BPLA trial, there was little association between visitation and blood pressure, hence all five models performed similarly. In the exaggerated association scenario, there was some difference in estimate uncertainty for the simplified Model 5.

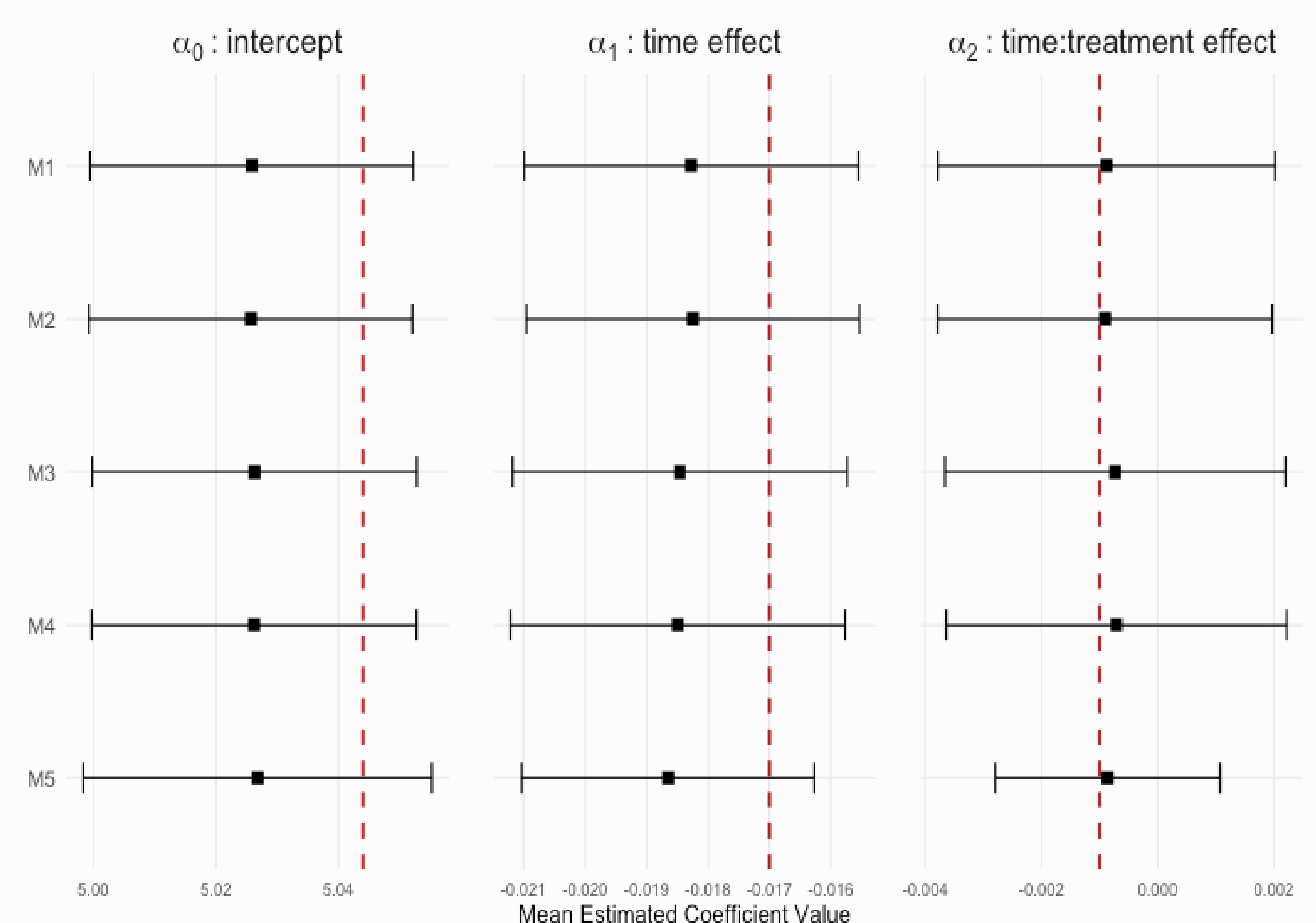


Figure 1: Forest plot of fixed-effects estimates in the exaggerated visitation scenario, the red-dashed line represents the true parameter values.

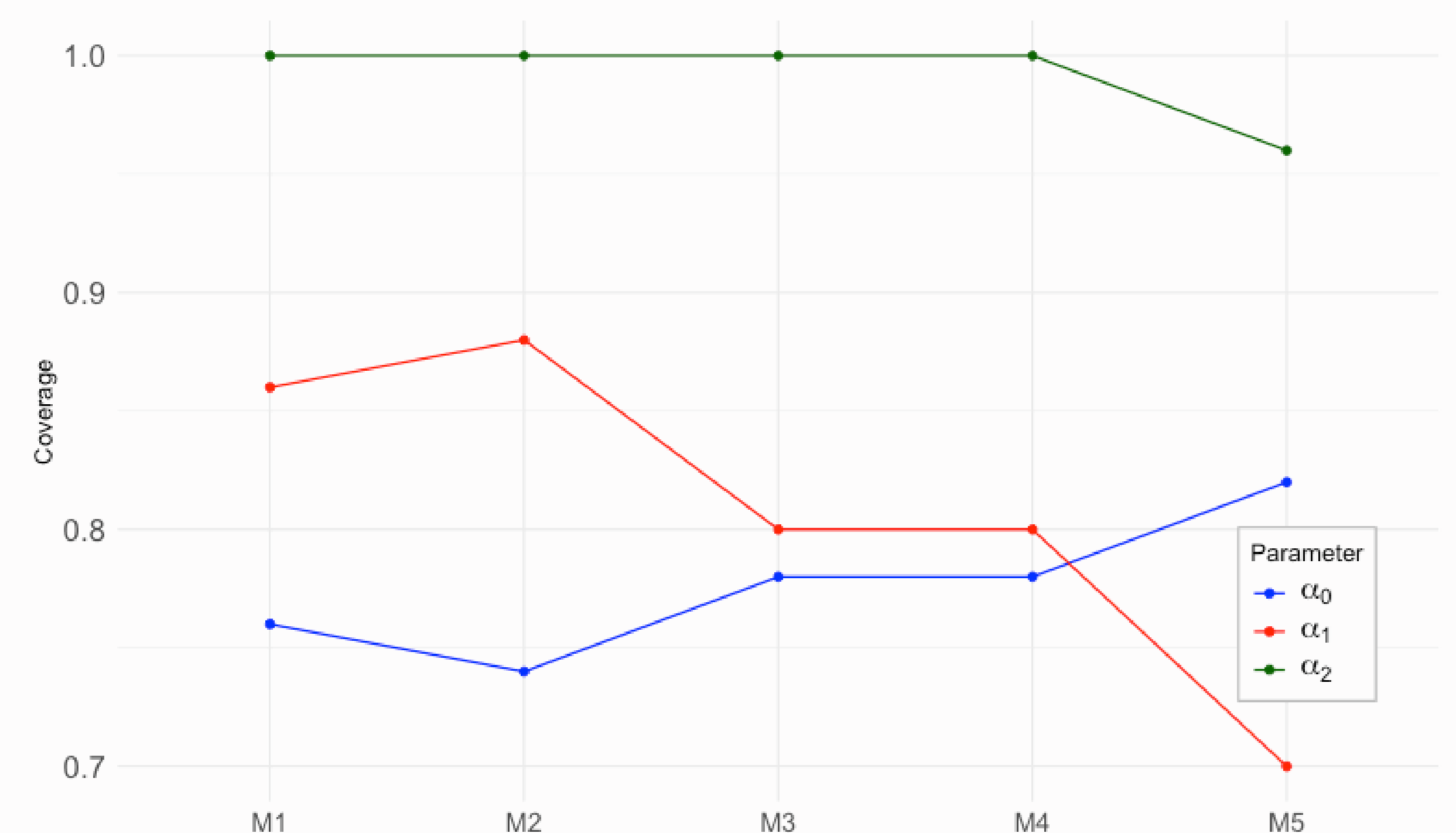


Figure 2: Coverage plot of parameters across all five models in exaggerated visitation scenario.

Conclusion:

For the scenarios considered, joint longitudinal-survival models reduce uncertainty in the estimated treatment-effect, while traditional mixed-effects models produced similar point estimates under the presence of an informative observation process.

