Practical methods to pool multi-study joint longitudinal and time to event data

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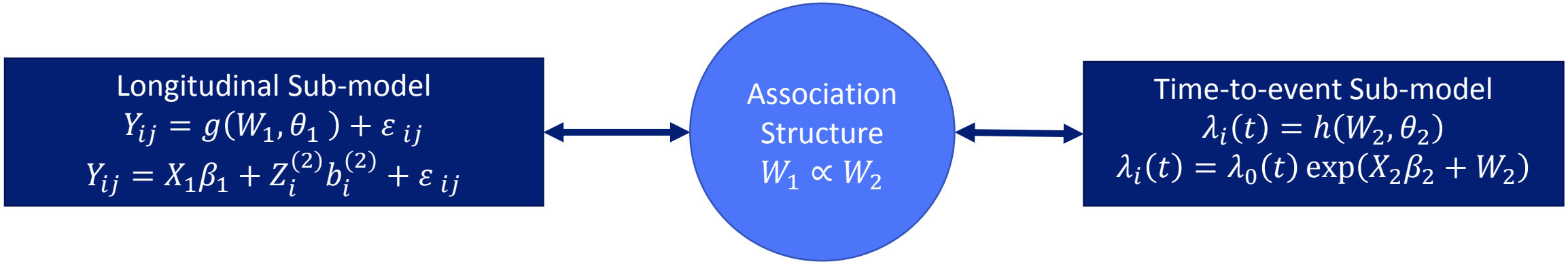
Joint longitudinal and time-to-event data (single study)

- Methods to simultaneously model potentially related longitudinal and time-to-event data
- Can produce less biased more efficient results than standalone cases where linked longitudinal and time-to-event data exists

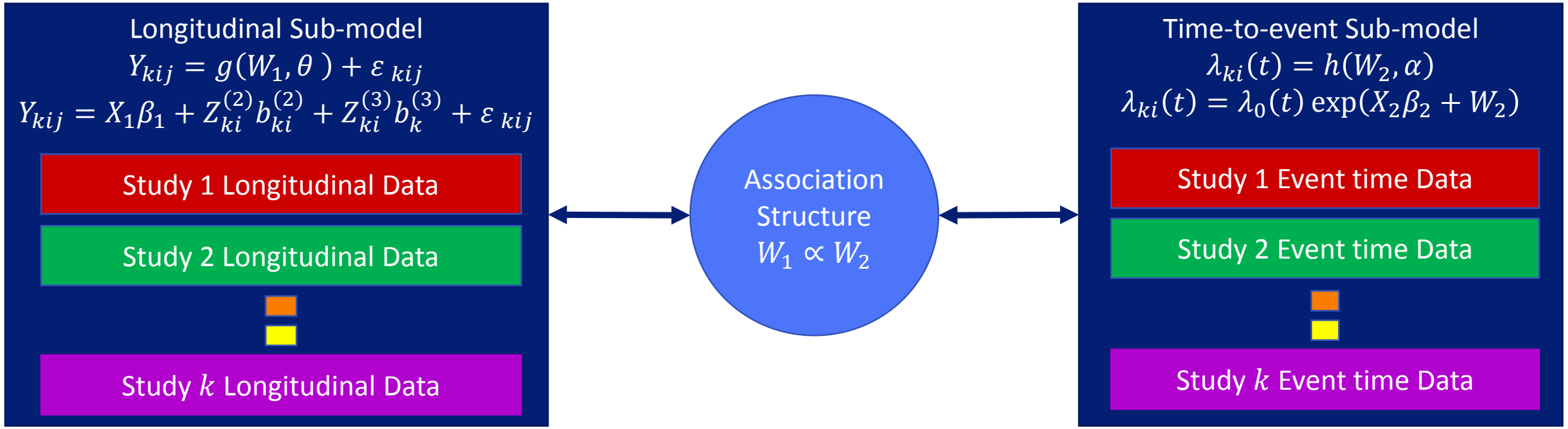


Meta-Analysis (MA)

- Systematic pooling of results from multiple studies
- Allows increased precision, identification of effect sizes too small to be identified in single studies, and allows questions additional to those originally posed in the data to be answered
- Gold standard – Individual Participant/Patient Data (IPD) meta-analyses, where data for each individual recorded in studies identified in the meta-analysis is available.

Joint longitudinal and time-to-event data (multi-study)

- Data available from multiple studies
- Clustering of data within studies must be accounted for (e.g. through random effects, interaction terms, stratified baseline hazard)



Approaches to modelling multi-study IPD joint data

- Two main approaches – one stage or two stage

- Two stage approaches
  - Separate joint models fitted to data from each study
  - Results from each study pooled using standard meta-analytic techniques

- One stage approaches
  - Joint model fitted to meta-dataset (containing data from all studies)
  - Clustering of data must be accounted for

Real Data – subset of the INDANA dataset

- IPD from multiple studies investigating the effect of no treatment versus any treatment for hypertensive patients

- Longitudinal data measured at baseline, 6 months, then annually thereafter to maximum of 7 years. Measurement patterns varied between studies

- Examining longitudinal outcome systolic blood pressure and time-to-event outcome time to death

- Evidence of a changepoint in the data at 6 month, so $\exp(-3 * time)$ term included in the model

Two stage methods

Two stage methods - overview

Stage 1: Joint model fitted to data from each study

Longitudinal Sub-model

$$Y_{kij} = \beta_{10} + \beta_{11} time_{kij} + \beta_{12} \exp(-3 * time_{kij}) + \beta_{13} treat_{ki} + b_{0ki}^{(2)} + b_{1ki}^{(2)} time_{kij} + \varepsilon_{kij}$$

Association Structure

$$W_{ki}^{(2)} = \alpha^{(2)}(b_{0ki}^{(2)} + b_{1ki}^{(2)} time_{kij})$$

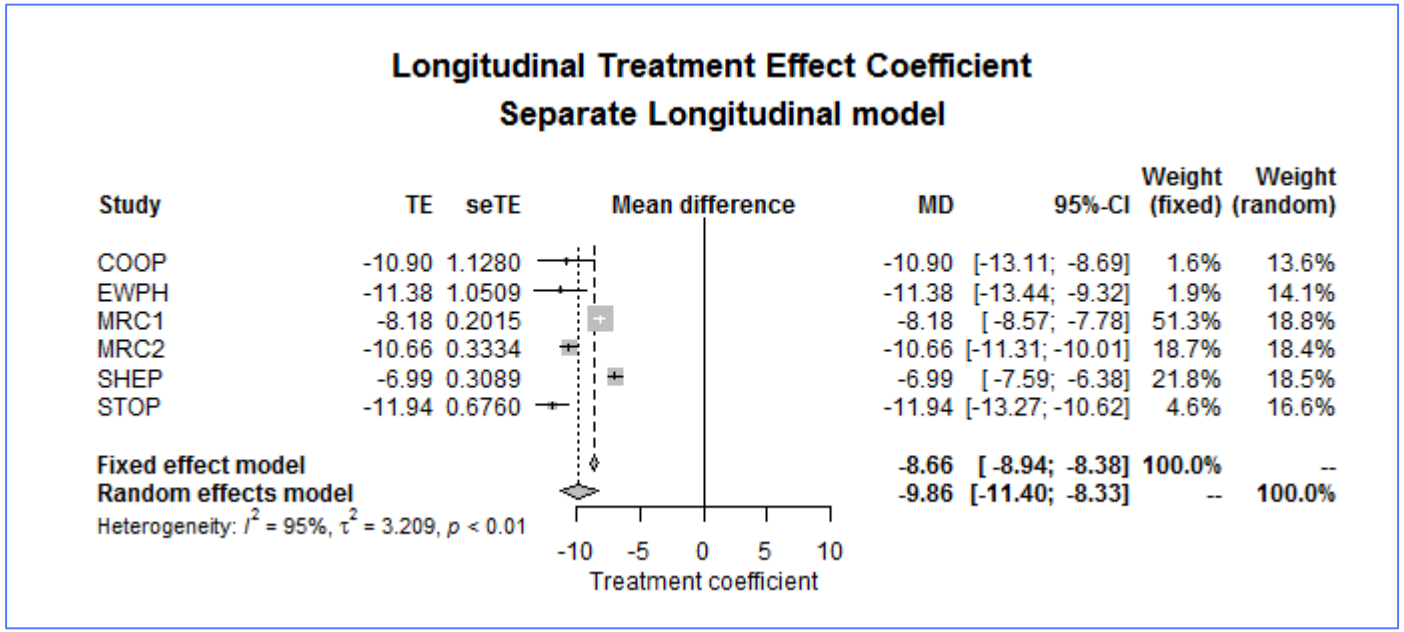
Time-to-event Sub-model

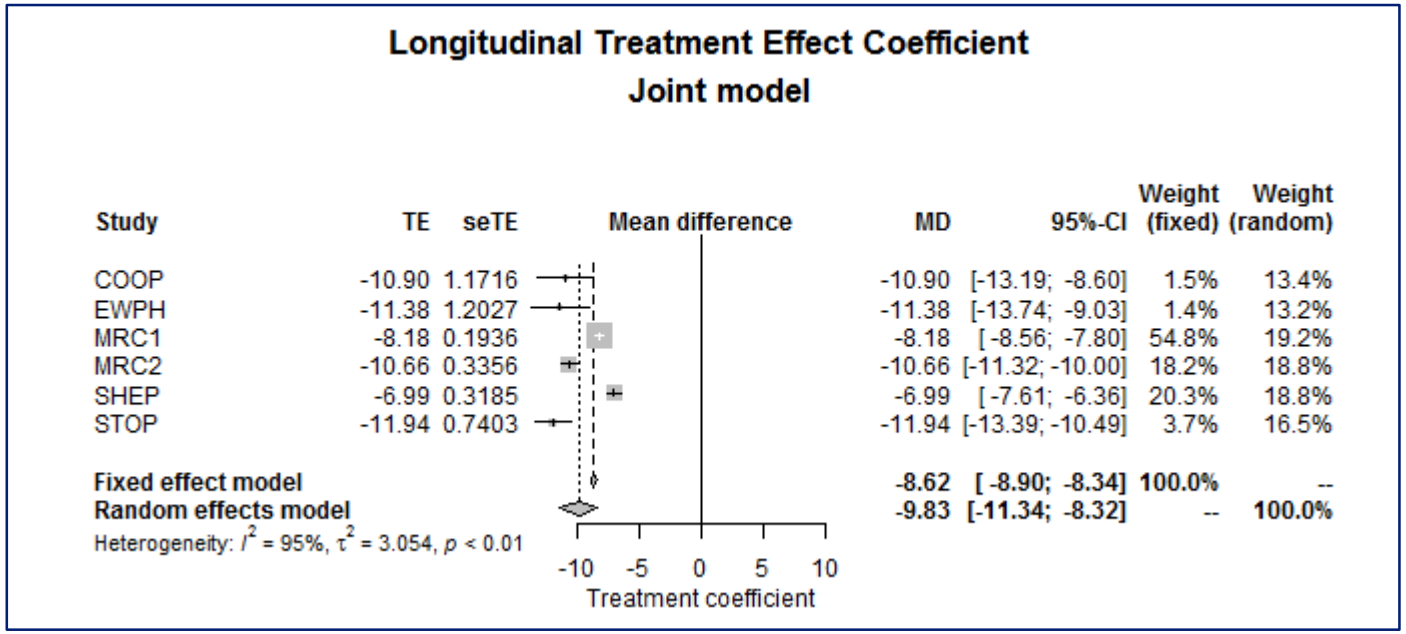
$$\lambda_{ki}(t) = \lambda_0(t) \exp(\beta_{21} treat_{ki} + W_{ki}^{(2)})$$

Stage 2: Study specific parameters pooled using standard meta-analytic techniques

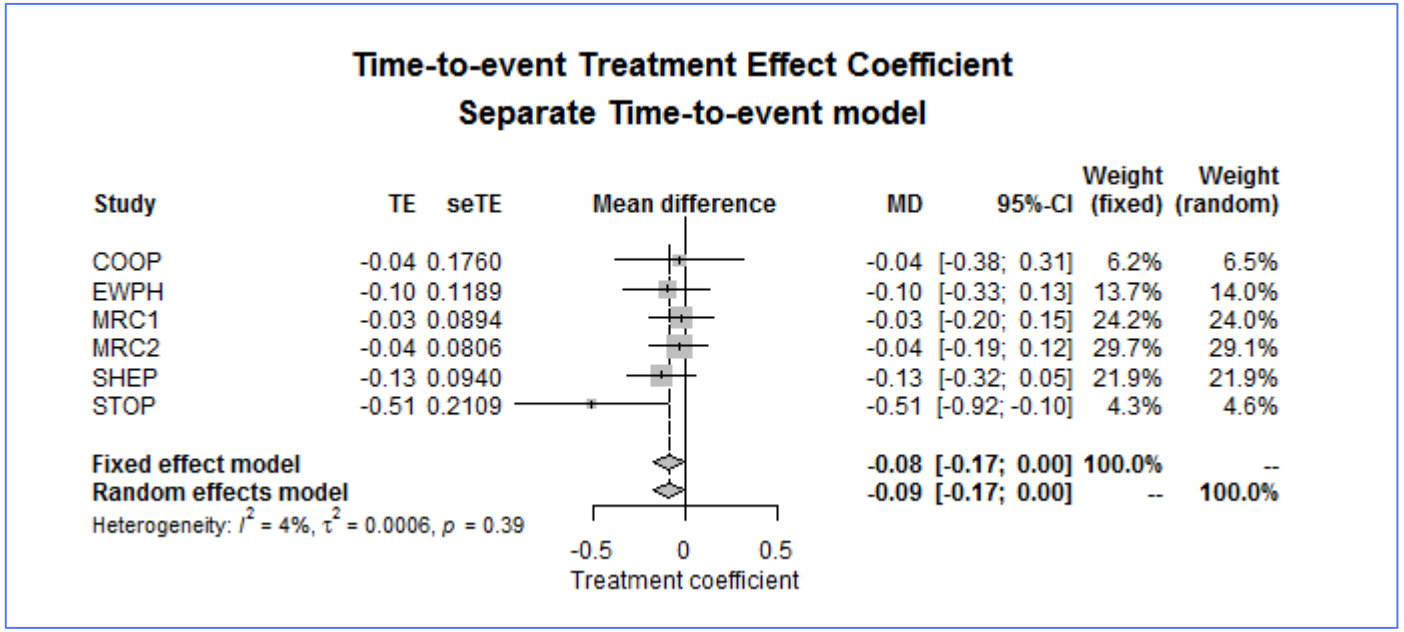
- Inverse variance method used (DerSimonian method used for random meta-analyses)
- Both fixed and random effects meta-analyses fitted and compared
- Separate meta-analyses for each parameter of interest

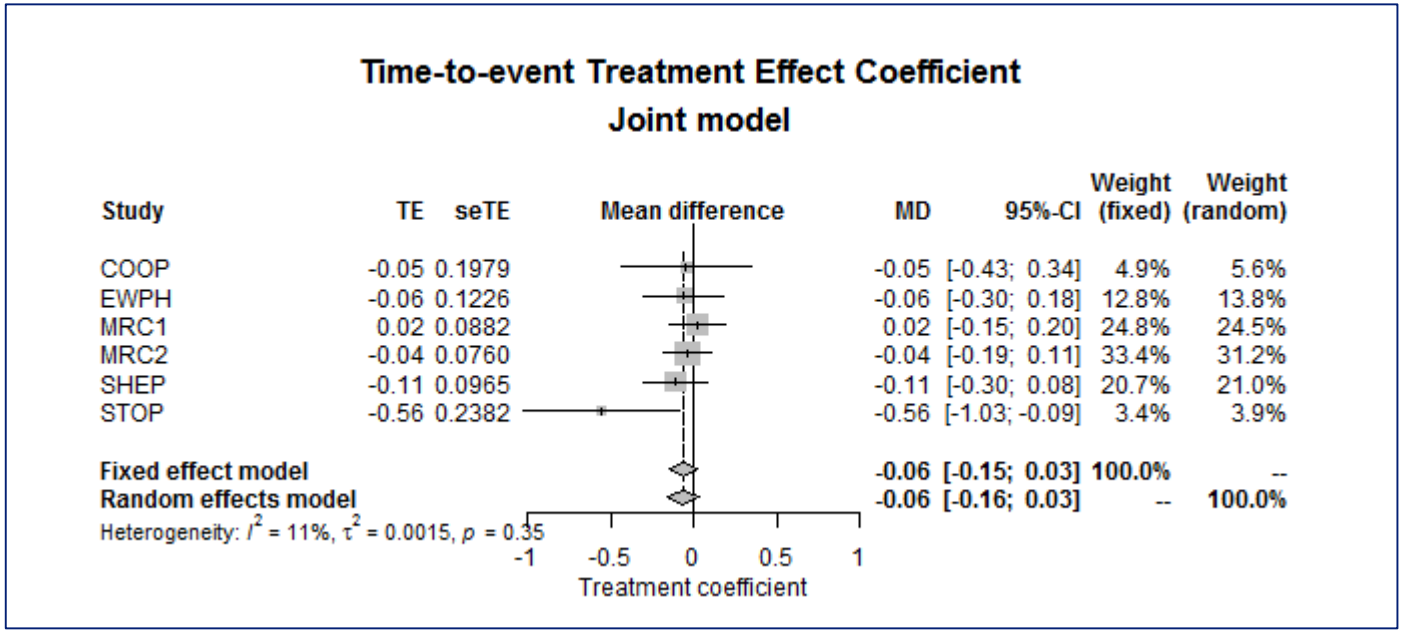
Two stage methods – real data





Two stage methods – real data





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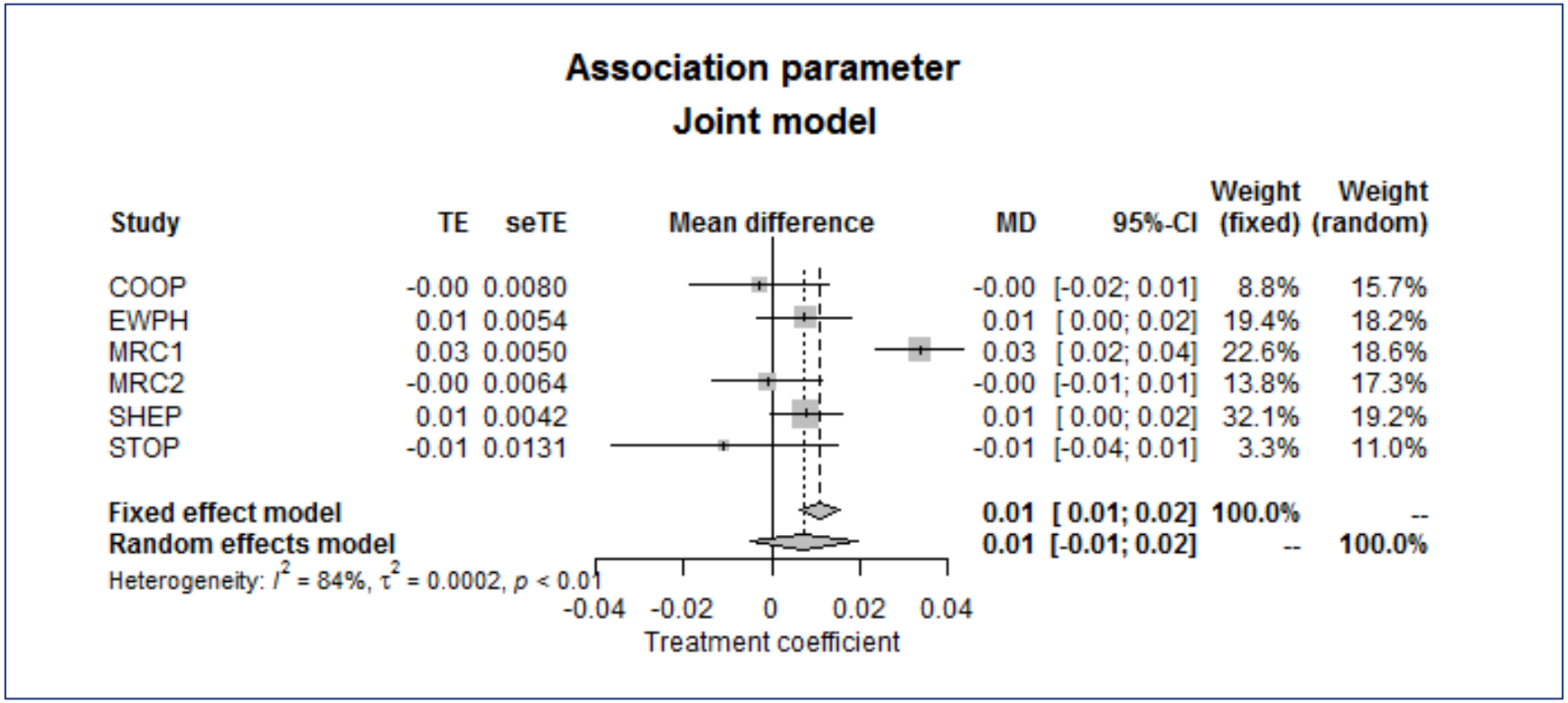
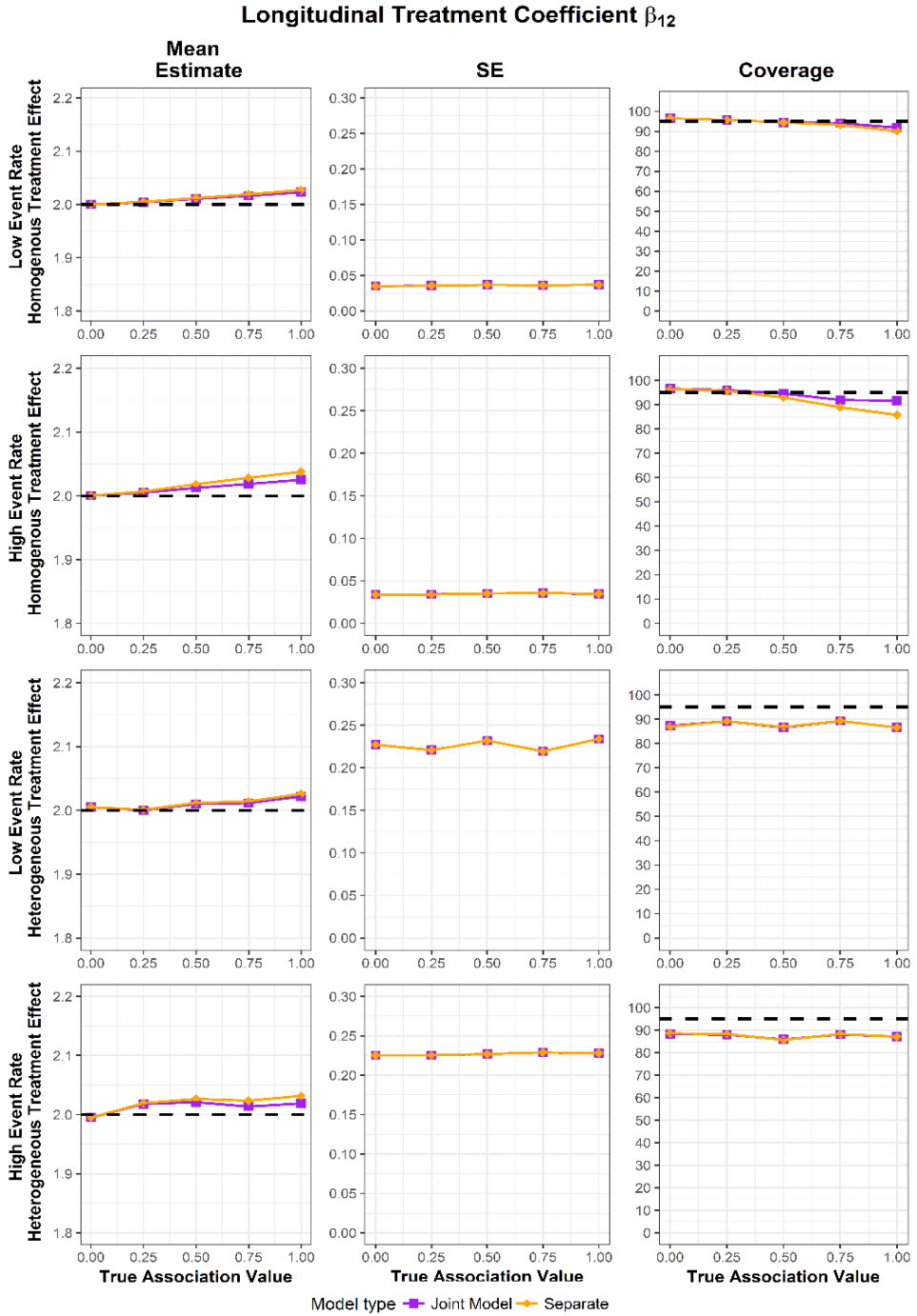
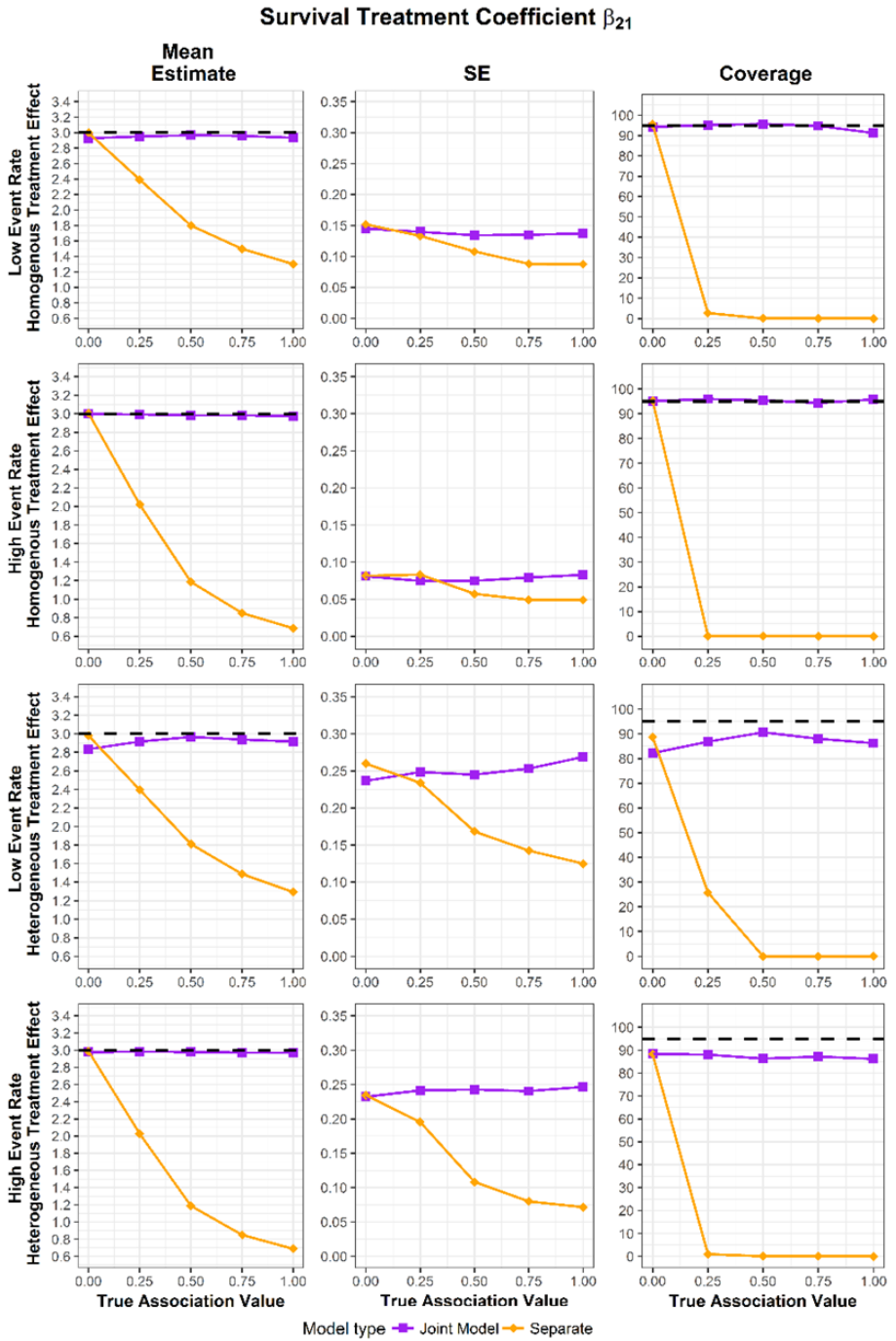


Two stage methods – simulations (longitudinal treatment effect coefficient)



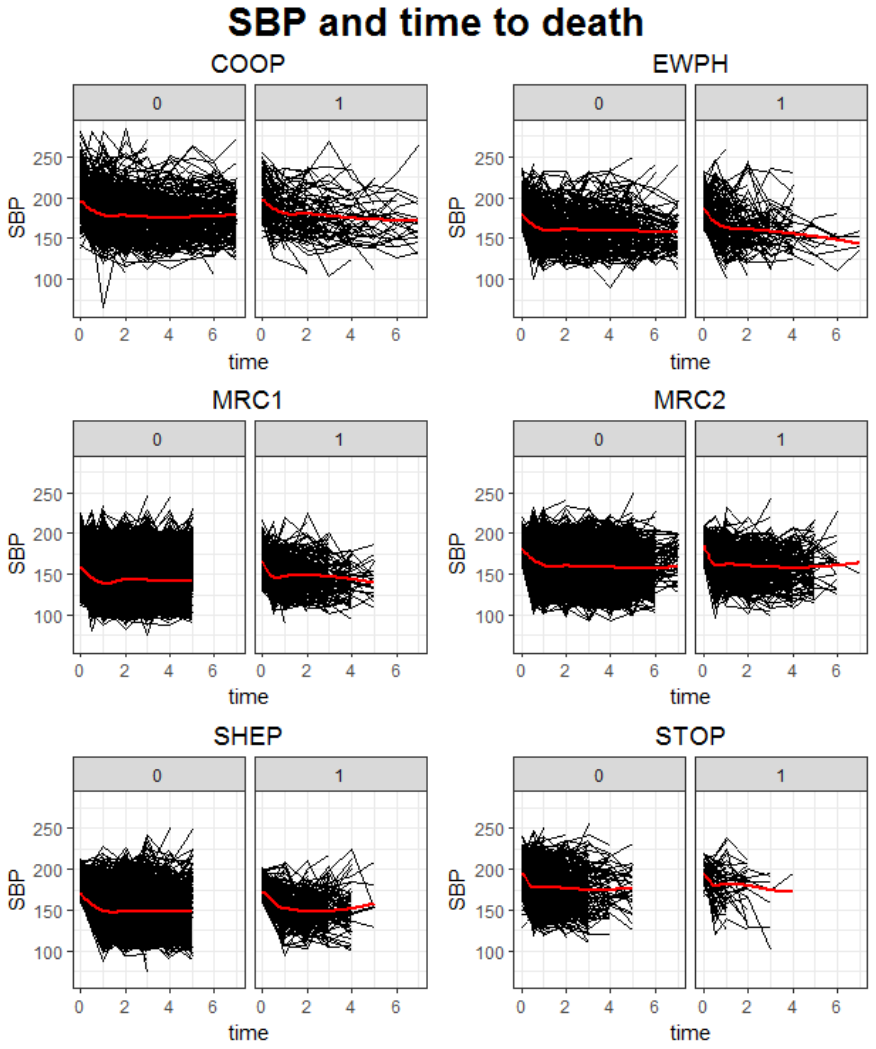
Two stage methods – simulations (time-to-event treatment effect coefficient)



Two stage methods - recommendations

Preliminary work

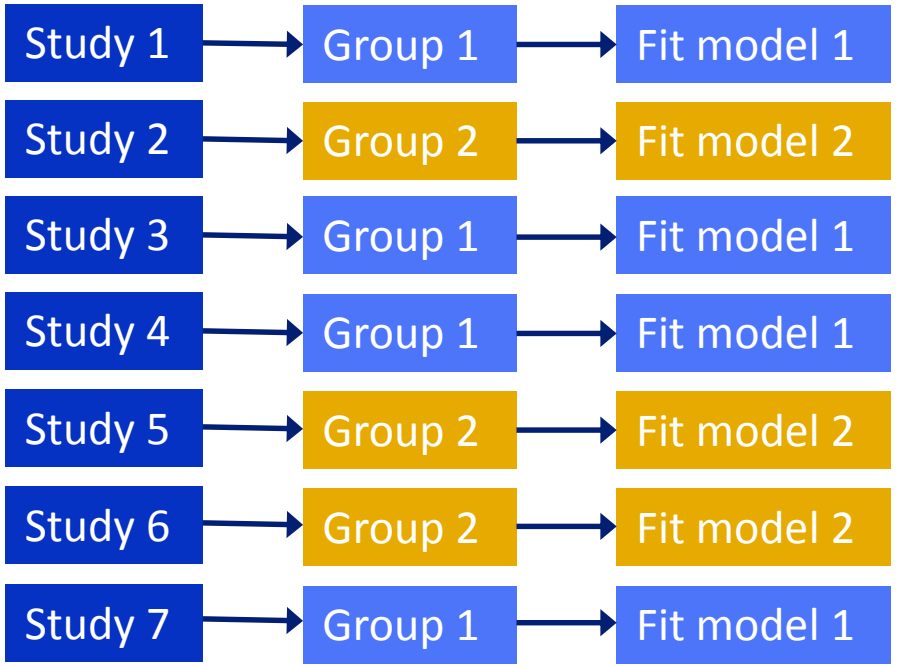
- For each study:
  - Plot longitudinal trajectories separately for those experiencing an event and those censored.
  - Produce Kaplan-Meier plots for e.g. each treatment group
- Use plots to assess whether an association between longitudinal and time-to-event outcomes is feasible
- Use plots and clinical background of the data to select:
  - Longitudinal sub-model
  - Time-to-event sub-model
  - Association structure



Two stage methods - recommendations

First Stage

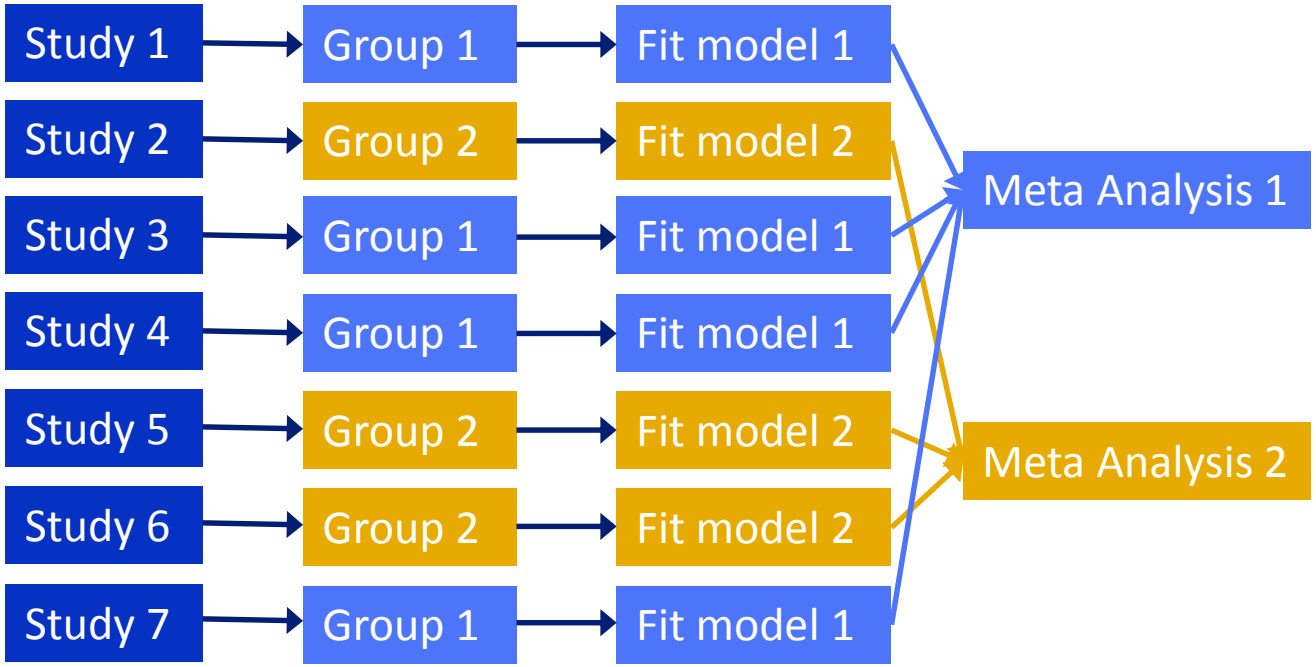
- Group studies such that chosen model structure within each group is identical.
- Within each group, fit identical joint models to data from each study. Model structures can differ between groups.



Two stage methods - recommendations

Second Stage

- For each study extract model parameters, precision estimates and sample size
- Pool estimates within groups using standard MA techniques.



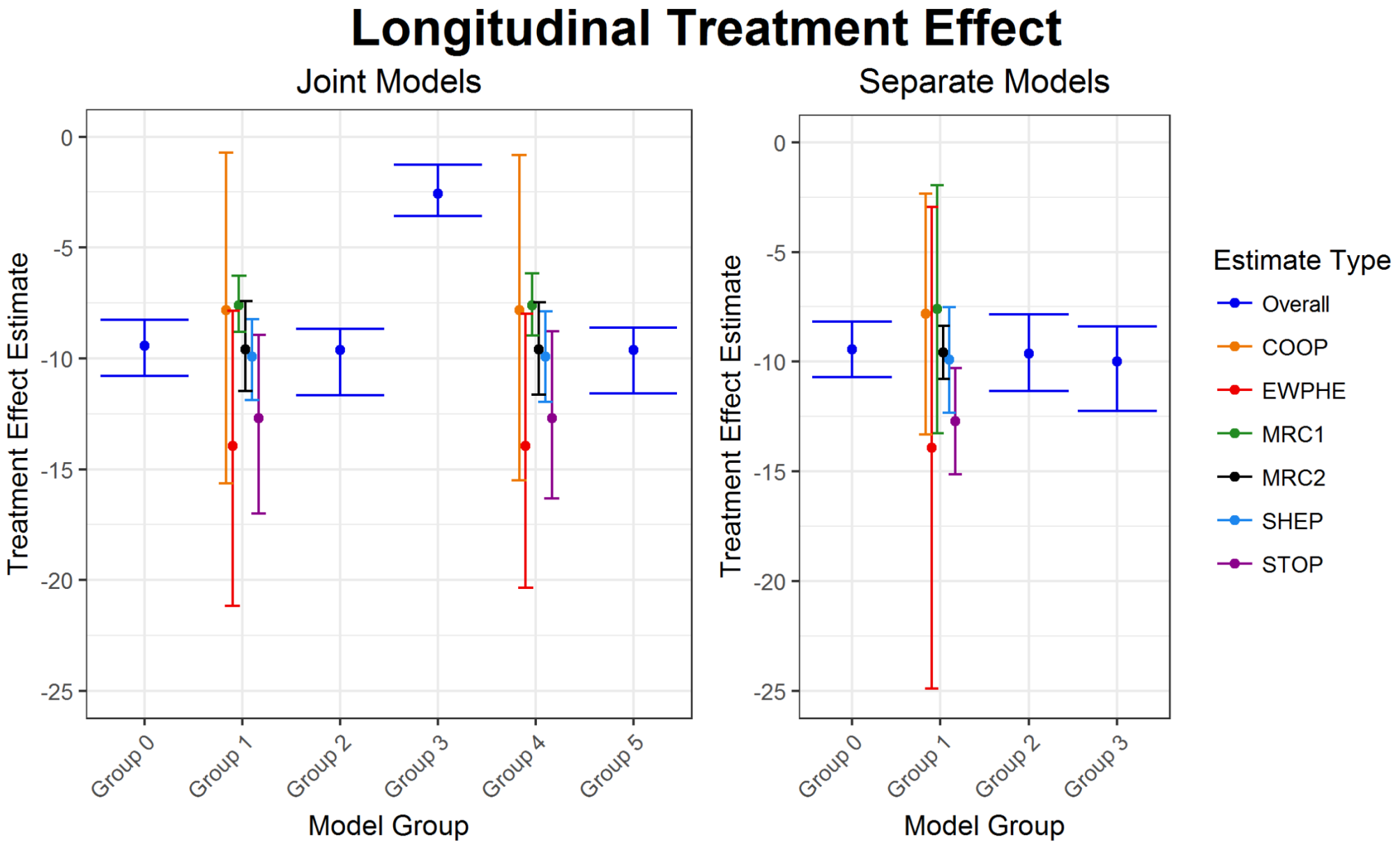
One stage methods

One stage methods - overview

- Same model basic model specification as first stage of two stage work, but now additional terms included to account for between study heterogeneity

Group	Method to account for between study heterogeneity
0	Between study heterogeneity ignored
1	Fixed interaction term between treatment and study in each sub-model
2	Fixed study indicator in longitudinal sub-model, study level random treatment effect
3	Study level random intercept and random treatment effect
4	Fixed interaction term between treatment and study in longitudinal sub-model, baseline hazard stratified by study
5	Fixed study indicator in longitudinal sub-model, study level random treatment effect, baseline hazard stratified by study

One stage methods – real data



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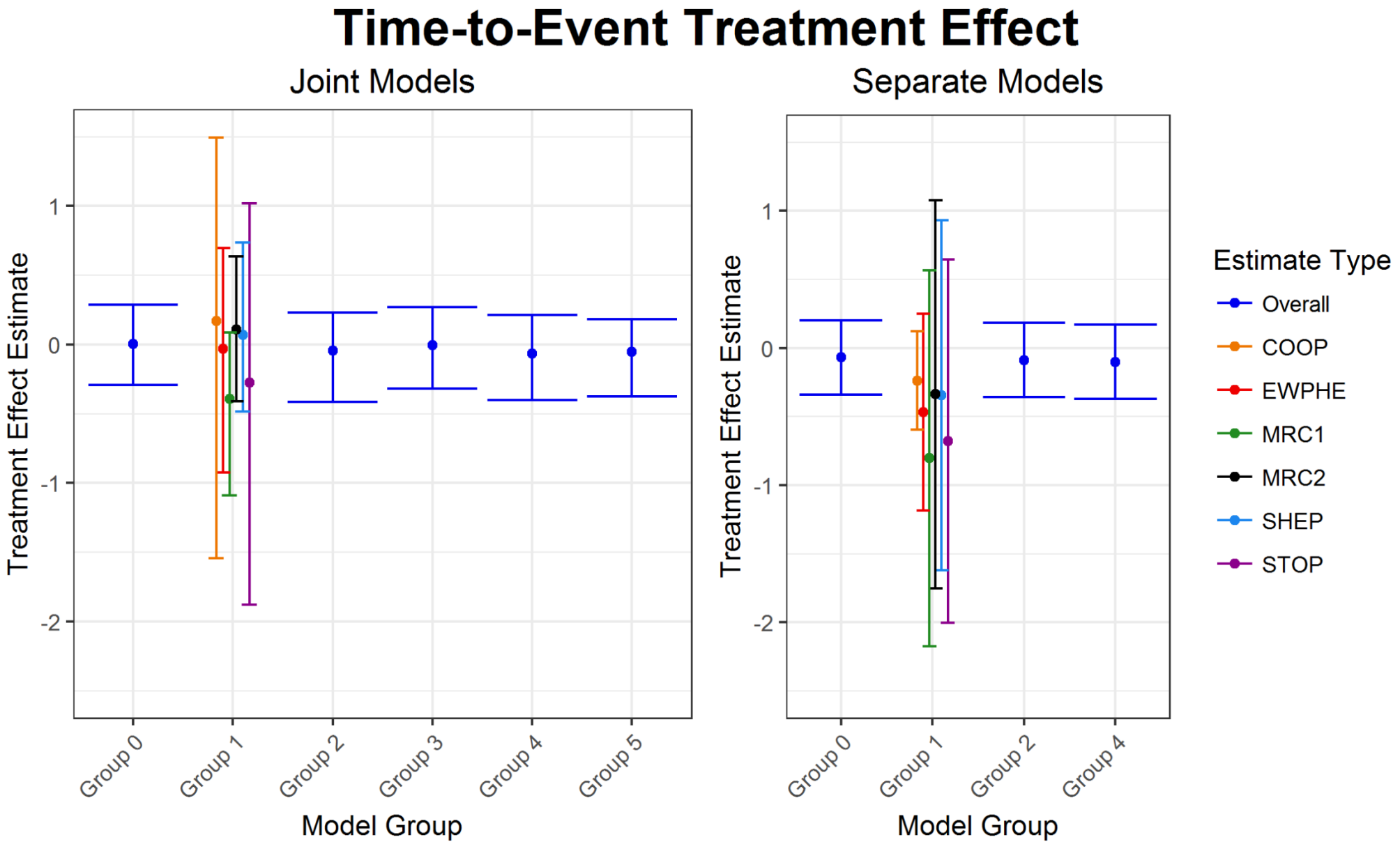
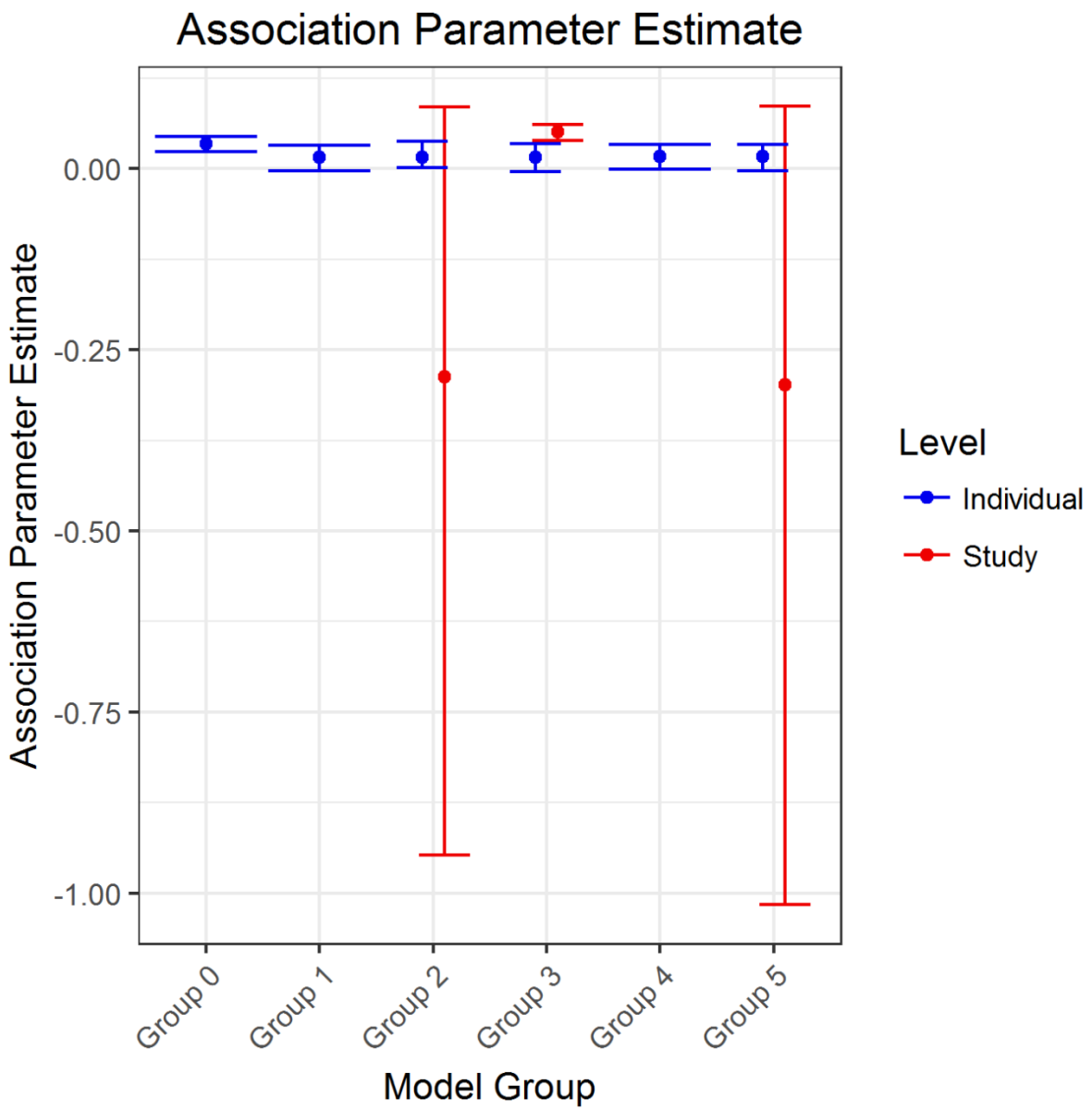


One stage methods – real data



Conclusions

- Care must be taken during two stage meta-analyses of joint data to pool only parameters with comparable interpretations

- A variety of methods exist to model multi-study joint data in a one stage analyses, however some may not be appropriate unless the number of studies in the meta-analysis is over a given threshold

- Functions for analysis of multi-study joint data available in R package joineRmeta

Thank you for listening.
Any questions?