Comparing results from one and two stage meta-analytic joint models

Maria Sudell[1]*, Ruwanthi Kolamunnage-Dona[1] and Catrin Tudur-Smith[1]

[1]Department of Biostatistics, University of Liverpool

mesudell@liverpool.ac.uk @mesudelll

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1: Background

Joint models[1,2] are methods to simultaneously model potentially related longitudinal and time-to-event data. A sub-model is fitted for each of the longitudinal and time-to-event components. The relationship between the two sub-models is represented through an association structure.

Meta-analysis (MA) is the numerical pooling of data from multiple studies and can be one-stage (where data from all studies is analysed in one model) or two stage (where data from each study is analysed separately, and then the study specific results are pooled).

In most cases, results from one and two stage MA are similar, however recent work by Burke et al[3] identified 10 reasons why results may differ. This investigation aims to establish the extent to which these reasons could cause results from one and two stage joint MA to differ.

This poster focuses on the following reasons for discrepancy (discussed fully in Burke et al[3]):

1. **Exact one-stage likelihood versus approximate two-stage likelihood**
   - *Two stage MA assume study specific treatment effects have a normal sampling distribution, and that their variances are known (i.e. that the central limit theory holds, and the variances have been accurately estimated)*
   - *This might not hold for small datasets (<30 people), or rare/common events in time-to-event data*
2. **Clustering and choice of specification for the intercept**
   - *Naïve to ignore clustering within studies*
   - *Two stage MA automatically account for clustering within studies*
   - *Range of methods to account for clustering in one-stage MA*
3. **Accounting for correlation amongst parameters**
   - *One stage methods automatically account for correlation between model parameters*
   - *Two stage approaches don't automatically account for this, unless multivariate meta-analyses are employed*

2: Data Simulation

- The above reasons for potential discrepancies will be assessed through simulations
- Data was simulated in R[5] under the proportional association structure[1,2]
- Each scenario consisted of data from 10 simulated studies. 1000 meta-datasets generated for each scenario.
- Longitudinal data simulated under linear mixed effects model with variability at individual and study level, time-to-event data simulated under Gompertz distribution[4].
- As treatment effect would be a measure of interest in the meta-analysis, individuals were allocated 1:1 to a binary treatment variable, which was included as a covariate in both sub-models.
- To test reason 1 (above) data was simulated under cases where
  - all 10 studies included are normal sized (n=200), or all are small (n=25).
  - Event is rare (10% of population experienced event) or equal (50% of population experienced event)

3: Methods

- Standard joint model takes format (for individual i in study k at time j) :

  Longitudinal sub-model: $Y_{kij} = \boldsymbol{X_{1kij}\beta_1} + \boldsymbol{Z^{(2)}_{kij}b^{(2)}_{ki}} + \boldsymbol{Z^{(3)}_{kij}b^{(3)}_{k}} + \varepsilon_{kij}$

  Time-to-event sub-model: $\lambda_{ki}(t) = \lambda_0(t)\, exp(\boldsymbol{X_{2ki}\beta_2} + W_{2ki}(t))$

  Association structure: $W_{2ki(t)} = \alpha^{(2)}\left(\boldsymbol{Z^{(2)}_{kij}b^{(2)}_{ki}}\right) + \alpha^{(3)}\left(\boldsymbol{Z^{(3)}_{kij}b^{(3)}_{k}}\right)$

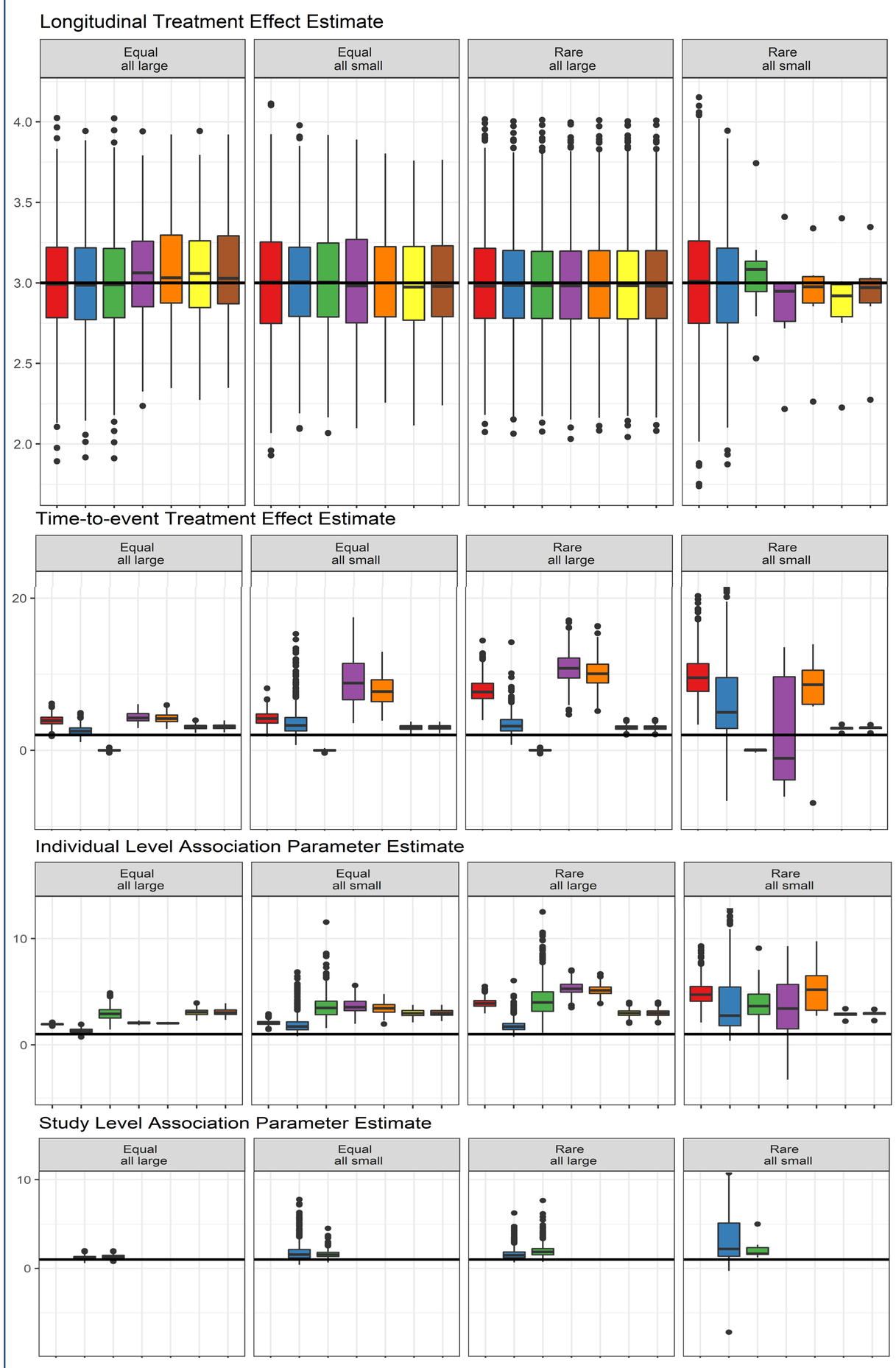
- Once data had been simulated the methods shown in the table below were fitted to the data
  - Reason 2 (above) for one and two-stage results differing was examined through the range of one-stage methods examined
  - Reason 3 (above) for one and two-stage results differing was examined through fitting both standard and multivariate two-stage MA
  - Parameters of interest extracted were longitudinal and time-to-event treatment effects, and association parameters.

Two stage MA methods examined		One stage MA methods examined	
Fixed effect standard MA		Naïve (ignoring clustering – no fixed study effect, or study level random effects)	
Random effect standard MA		Clustering modelled through study level random effects $\boldsymbol{b^{(3)}_k}$	
Fixed effect multivariate MA		Clustering modelled mix of study level random effects $\boldsymbol{b^{(3)}_k}$ and stratified baseline hazard by study $\lambda_{0k}(t)$	
Random effect multivariate MA			

- *Notes:*
  - *Two stage MA methods would not contain study fixed effects, or study level random effects, or baseline hazard stratified by study*
  - *One stage methods accounting for between study heterogeneity using fixed effects planned but long running, results not presented here*
  - *The joineR[6], metafor[7] and joineRmeta packages were used in these simulations. Data was simulated under code to be released soon in joineRsim (new package)*

4: Results

- "True" value of parameter shown by black line



- Joint models appear to perform poorly for cases where the studies are all small, and the event rate is rare (right hand column)
- Issue most noticeable for association parameters, and time-to-event treatment coefficient (bottom 3 rows of graphs) – under scenarios investigated, results for longitudinal treatment coefficient treatment was more robust (top row)
  - Would be useful to see finer continuum of levels of event rates to examine problem in greater detail (ongoing – see further work)
- In reality, there would be concerns fitting a joint model to a dataset containing only 25 individuals (e.g. in two stage approach) as there is unlikely to be sufficient information to properly estimate model parameters – however important to determine whether a one stage approach for 10 studies of 25 individuals is feasible.

5: Discussion & Conclusions

- Evidence that discrepancies identified by Burke et al[3] for time-to-event data extends to joint data analyses especially for rare events, and small datasets
- Important to assess before undertaking meta-analysis (or normal analysis) of joint data the event rate, and it's potential impact on coefficient estimates
- Recommendation to perform both one and two stage analyses to compare the results
- Future work
  - Completion of simulations evaluating other reasons presented in Burke et a
  - Simulations evaluating varying follow up and event rate defined per year rather than "overall" event rate
  - Completion of one-stage simulations accounting for between study heterogeneity using fixed interaction terms with study membership
  - Comparison of Bayesian and frequentist approaches

References

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