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

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Aims of Talk

• Overview of methodology for
  • Two stage meta-analysis of multi-study joint longitudinal and time-to-event data
  • One stage meta-analysis of multi-study joint longitudinal and time-to-event data

• Review of current reporting of single study joint models applied to medical datasets

• Introduction of software package in R to implement methods
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

Longitudinal Sub-model
\[ Y_{ij} = g(W_1, \theta_1) + \varepsilon_{ij} \]
\[ Y_{ij} = X_1 \beta_1 + Z_i^{(2)} b_i^{(2)} + \varepsilon_{ij} \]

Association Structure
\[ W_1 \propto W_2 \]

Time-to-event Sub-model
\[ \lambda_i(t) = h(W_2, \theta_2) \]
\[ \lambda_i(t) = \lambda_0(t) \exp(X_2 \beta_2 + W_2) \]
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)

Longitudinal Sub-model

\[
Y_{kij} = g(W_1, \theta) + \varepsilon_{kij} \\
Y_{kij} = X_1\beta_1 + Z_{ki}^{(2)} b_{ki}^{(2)} + Z_{ki}^{(3)} b_{k}^{(3)} + \varepsilon_{kij}
\]

<table>
<thead>
<tr>
<th>Study 1 Longitudinal Data</th>
<th>Study 2 Longitudinal Data</th>
<th>Study k Longitudinal Data</th>
</tr>
</thead>
</table>

Time-to-event Sub-model

\[
\lambda_{ki}(t) = h(W_2, \alpha) \\
\lambda_{ki}(t) = \lambda_0(t) \exp(X_2\beta_2 + W_2)
\]

<table>
<thead>
<tr>
<th>Study 1 Event time Data</th>
<th>Study 2 Event time Data</th>
<th>Study k Event time Data</th>
</tr>
</thead>
</table>

Association Structure

\[ W_1 \propto W_2 \]
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

• Using subset with data for longitudinal outcome systolic blood pressure (SBP) and time to death, data available from 6 studies. Proportions of individuals from each study, and proportions events/censored within each study kept same as full dataset. Full analysis using entire dataset currently running.

• Evidence of a changepoint in the data at 6 month, so $\exp(-3 \times \text{time})$ 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

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

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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**Time-to-event Treatment Effect Coefficient**

**Separate Time-to-event model**

<table>
<thead>
<tr>
<th>Study</th>
<th>TE</th>
<th>seTE</th>
<th>Mean difference</th>
<th>MD</th>
<th>95%-CI</th>
<th>Weight (fixed)</th>
<th>Weight (random)</th>
</tr>
</thead>
<tbody>
<tr>
<td>COOP</td>
<td>-0.04</td>
<td>0.1790</td>
<td></td>
<td>-0.04</td>
<td>[-0.38, 0.31]</td>
<td>6.2%</td>
<td>6.5%</td>
</tr>
<tr>
<td>EWP</td>
<td>-0.10</td>
<td>0.1189</td>
<td></td>
<td>-0.10</td>
<td>[-0.33, 0.13]</td>
<td>13.7%</td>
<td>14.0%</td>
</tr>
<tr>
<td>MRC1</td>
<td>-0.03</td>
<td>0.0094</td>
<td></td>
<td>-0.03</td>
<td>[-0.20, 0.15]</td>
<td>24.2%</td>
<td>24.0%</td>
</tr>
<tr>
<td>MRC2</td>
<td>-0.04</td>
<td>0.0098</td>
<td></td>
<td>-0.04</td>
<td>[-0.19, 0.12]</td>
<td>20.7%</td>
<td>22.1%</td>
</tr>
<tr>
<td>SHEP</td>
<td>-0.13</td>
<td>0.0940</td>
<td></td>
<td>-0.13</td>
<td>[-0.32, 0.06]</td>
<td>21.9%</td>
<td>21.9%</td>
</tr>
<tr>
<td>STOP</td>
<td>-0.51</td>
<td>0.2109</td>
<td></td>
<td>-0.51</td>
<td>[-0.92, -0.10]</td>
<td>4.3%</td>
<td>4.6%</td>
</tr>
</tbody>
</table>

**Fixed effect model**

-0.08 [-0.17; 0.00] 100.0% --

**Random effects model**

-0.09 [-0.17; 0.00] -- 100.0%

Heterogeneity: $I^2 = 4\%$, $t^2 = 0.0006$, $p = 0.39$

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**Time-to-event Treatment Effect Coefficient**

**Joint model**

<table>
<thead>
<tr>
<th>Study</th>
<th>TE</th>
<th>seTE</th>
<th>Mean difference</th>
<th>MD</th>
<th>95%-CI</th>
<th>Weight (fixed)</th>
<th>Weight (random)</th>
</tr>
</thead>
<tbody>
<tr>
<td>COOP</td>
<td>-0.05</td>
<td>0.1790</td>
<td></td>
<td>-0.05</td>
<td>[-0.43, 0.34]</td>
<td>4.9%</td>
<td>5.6%</td>
</tr>
<tr>
<td>EWP</td>
<td>-0.06</td>
<td>0.1225</td>
<td></td>
<td>-0.06</td>
<td>[-0.30, 0.18]</td>
<td>12.8%</td>
<td>13.8%</td>
</tr>
<tr>
<td>MRC1</td>
<td>0.02</td>
<td>0.0682</td>
<td></td>
<td>0.02</td>
<td>[-0.15, 0.20]</td>
<td>24.6%</td>
<td>24.5%</td>
</tr>
<tr>
<td>MRC2</td>
<td>-0.04</td>
<td>0.0760</td>
<td></td>
<td>-0.04</td>
<td>[-0.19, 0.11]</td>
<td>33.4%</td>
<td>31.2%</td>
</tr>
<tr>
<td>SHEP</td>
<td>0.11</td>
<td>0.0665</td>
<td></td>
<td>0.11</td>
<td>[-0.10, 0.15]</td>
<td>20.7%</td>
<td>21.0%</td>
</tr>
<tr>
<td>STOP</td>
<td>-0.56</td>
<td>0.2382</td>
<td></td>
<td>-0.56</td>
<td>[-1.03, 0.00]</td>
<td>3.4%</td>
<td>3.0%</td>
</tr>
</tbody>
</table>

**Fixed effect model**

-0.06 [-0.15; 0.03] 100.0% --

**Random effects model**

-0.06 [-0.16; 0.03] -- 100.0%

Heterogeneity: $I^2 = 11\%$, $t^2 = 0.0015$, $p = 0.35$
Two stage methods – real data

### Association parameter

#### Joint model

<table>
<thead>
<tr>
<th>Study</th>
<th>TE</th>
<th>seTE</th>
<th>Mean difference</th>
<th>MD</th>
<th>95% CI</th>
<th>Weight (fixed)</th>
<th>Weight (random)</th>
</tr>
</thead>
<tbody>
<tr>
<td>COOP</td>
<td>-0.00</td>
<td>0.0080</td>
<td>-0.00</td>
<td>-0.00</td>
<td>[-0.02; 0.01]</td>
<td>8.8%</td>
<td>15.7%</td>
</tr>
<tr>
<td>EWPH</td>
<td>0.01</td>
<td>0.0054</td>
<td>0.01</td>
<td>0.01</td>
<td>[0.00; 0.02]</td>
<td>19.4%</td>
<td>18.2%</td>
</tr>
<tr>
<td>MRC1</td>
<td>0.03</td>
<td>0.0050</td>
<td>0.03</td>
<td>0.03</td>
<td>[0.02; 0.04]</td>
<td>22.6%</td>
<td>18.6%</td>
</tr>
<tr>
<td>MRC2</td>
<td>-0.00</td>
<td>0.0064</td>
<td>-0.00</td>
<td>-0.00</td>
<td>[-0.01; 0.01]</td>
<td>13.8%</td>
<td>17.3%</td>
</tr>
<tr>
<td>SHEP</td>
<td>0.01</td>
<td>0.0042</td>
<td>0.01</td>
<td>0.01</td>
<td>[0.00; 0.02]</td>
<td>32.1%</td>
<td>19.2%</td>
</tr>
<tr>
<td>STOP</td>
<td>-0.01</td>
<td>0.0131</td>
<td>-0.01</td>
<td>-0.01</td>
<td>[-0.04; 0.01]</td>
<td>3.3%</td>
<td>11.0%</td>
</tr>
</tbody>
</table>

Fixed effect model

Random effects model

Heterogeneity: \( I^2 = 84\% \), \( t^2 = 0.0002 \), \( p < 0.01 \)

- Treatment coefficient

\[ \text{TE} = \text{Effect size} \]

\[ \text{seTE} = \text{Standard error of effect size} \]

\[ \text{MD} = \text{Mean difference} \]

\[ \text{95% CI} = \text{Confidence interval} \]

\[ \text{Weight (fixed)} = \text{Weight for fixed model} \]

\[ \text{Weight (random)} = \text{Weight for random model} \]
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.
Current reporting standard of joint models
Review of standard of published joint data analyses
## Review of standard of published joint data analyses

<table>
<thead>
<tr>
<th></th>
<th>Longitudinal MA</th>
<th>Time-to-event MA</th>
<th>Association MA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coefficients reported (%)</td>
<td>45 (69.2)</td>
<td>46 (70.8)</td>
<td>51 (78.5)</td>
</tr>
<tr>
<td>Precision reported (%)</td>
<td>44 (67.7)</td>
<td>45 (69.2)</td>
<td>50 (76.9)</td>
</tr>
<tr>
<td>Standard Errors reported (%)</td>
<td>22 (33.8)</td>
<td>23 (35.4)</td>
<td>25 (38.5)</td>
</tr>
<tr>
<td>Confidence Intervals (CI)</td>
<td>30 (46.2)</td>
<td>32 (49.2)</td>
<td>36 (55.4)</td>
</tr>
<tr>
<td>Significance level reported</td>
<td></td>
<td>57 (87.7)</td>
<td></td>
</tr>
<tr>
<td>Sample size reported (%)</td>
<td></td>
<td>64 (98.5)</td>
<td></td>
</tr>
<tr>
<td>MA possible given reported information (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All identified studies (N=65)</td>
<td>44 (67.7)</td>
<td>45 (69.2)</td>
<td>50 (76.9)</td>
</tr>
<tr>
<td>Studies using joint models to account for dropout (N=22)</td>
<td>18 (81.8)</td>
<td>14 (63.6)</td>
<td>15 (68.2)</td>
</tr>
<tr>
<td>Studies using joint models to include time varying covariate in time-to-event sub-model (N=4)</td>
<td>2 (50.0)</td>
<td>3 (75.0)</td>
<td>3 (75.0)</td>
</tr>
</tbody>
</table>
One stage methods
One stage methods - overview

- **Longitudinal sub-model**: linear mixed effects model with zero mean random effects.
- **Time-to-event sub-model**: Proportional hazards model with unspecified baseline hazard
- **Association structure**: random effects proportional association structure
- **Aim** was not to assess affect of range of covariates, only to assess the different model groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Method to account for between study heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Between study heterogeneity ignored</td>
</tr>
<tr>
<td>1</td>
<td>Fixed interaction term between treatment and study in each sub-model</td>
</tr>
<tr>
<td>2</td>
<td>Fixed study indicator in longitudinal sub-model, study level random treatment effect</td>
</tr>
<tr>
<td>3</td>
<td>Study level random intercept and random treatment effect</td>
</tr>
<tr>
<td>4</td>
<td>Fixed interaction term between treatment and study in longitudinal sub-model, baseline hazard stratified by study</td>
</tr>
<tr>
<td>5</td>
<td>Fixed study indicator in longitudinal sub-model, study level random treatment effect, baseline hazard stratified by study</td>
</tr>
</tbody>
</table>
One stage methods – real data

Longitudinal Treatment Effect

Joint Models

Separate Models

Model Group

Model Group

Estimate Type

- Overall
- COOP
- EWPHE
- MRC1
- MRC2
- SHEP
- STOP
One stage methods – real data

Time-to-Event Treatment Effect

Joint Models

Separate Models

Model Group

Estimate Type
- Overall
- COOP
- EWPHE
- MRC1
- MRC2
- SHEP
- STOP
One stage methods – real data
One stage methods – simulation work

- Ongoing
- Scenarios designed to investigate behaviour of different model groups under e.g.
  - Varying association levels
  - Low (~25%) or high (~75%) event rate
  - Varying numbers of included studies
Software – joineRmeta package

- Currently available from GitHub - https://github.com/mesudell/joineRmeta/

- Functions to:
  - Easily plot multi-study joint data
  - To automatically extract and meta-analyse specified model parameters from supplied joint model fits
  - Model three level joint data allowing for
    - Random effects only association structure
    - Individual level and study level random effects
    - Un-stratified or stratified baseline hazard
  - Simulation of multi-study joint data
Discussion

• One stage methods
  • Use of study level random effects may be unwise unless number of studies is over a certain threshold
  • Interaction terms between covariates and study membership would quickly become cumbersome with large numbers of studies
  • Allows in depth investigation of between study heterogeneity
• Two stage methods
  • Faster than one stage methods
  • Increasing difference between coefficient estimates in separate time-to-event models compared to joint models as association increases in magnitude
  • Multivariate meta-analysis of results rather than separate meta-analyses of each coefficient might be beneficial – future research
• Time commitment to bootstrap models is a concern
Conclusions

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

• Current reporting of joint models may hamper an aggregate data meta-analysis of joint data given current reporting standards

• 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
Thank you for listening.
Any questions?