Meta-Analysis Methods for Joint Longitudinal and Time-to-Event Data

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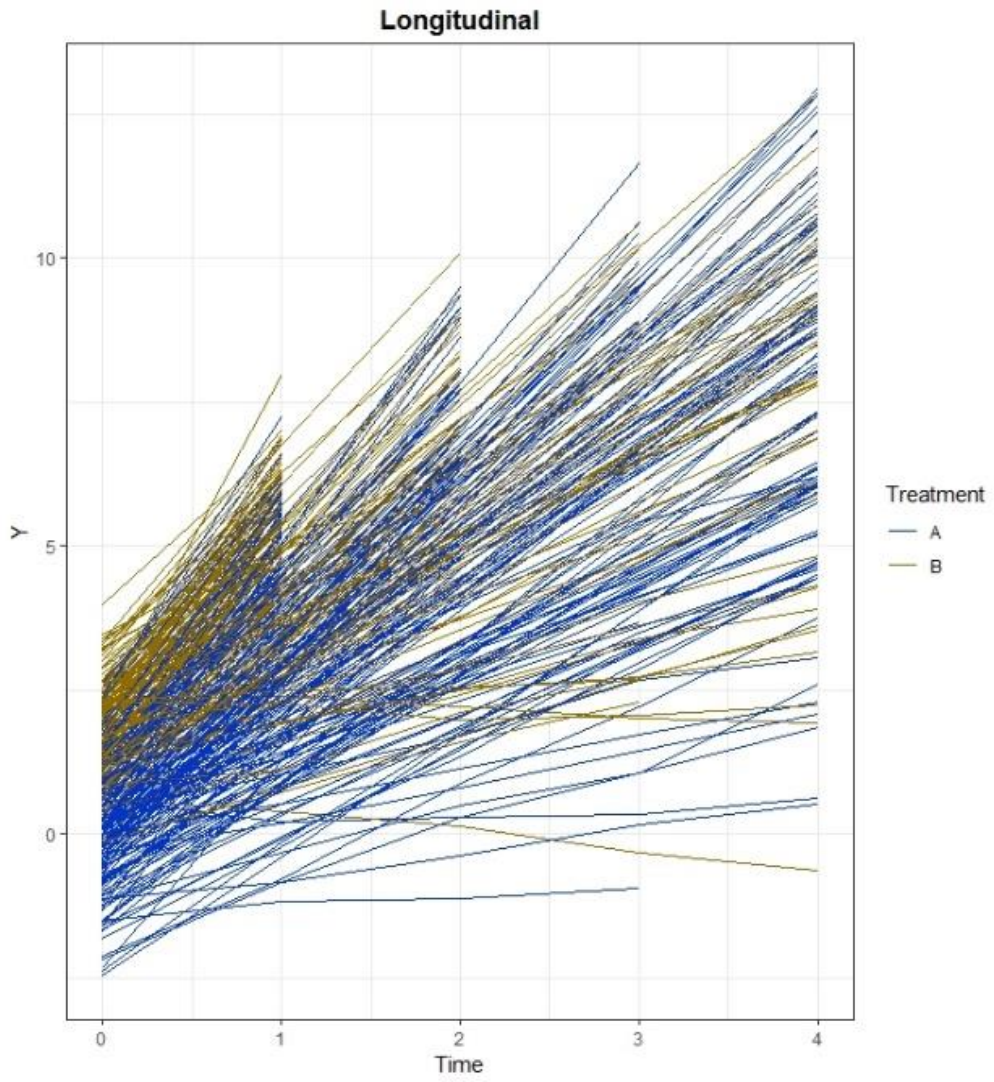
Outline of Webinar

- Introduction to joint modelling methodology
- Aggregate Data Meta-Analysis (AD-MA) of joint data
- Individual Participant Data Meta-Analysis (IPD-MA) of joint data
  - Illustrative example
  - Two stage IPD-MA of joint data
  - One stage IPD-MA of joint data
- Conclusions

Introduction to joint modelling methodology

Longitudinal Data

- Data measured repeatedly over time
- Examples
  - Weekly blood pressure measurements
  - Repeated biomarker measurements
  - Results of repeatedly performed test
- Multiple measurements per individual
  - Measurements within individuals more similar than measurements across individuals
- Commonly modelled using (generalised) linear mixed effects models



Meta Analyses of Longitudinal Data

- **Aggregate Data Meta-Analysis (AD-MA) of longitudinal data has issues:**
  - Commonly, separate MA performed at each time point of interest – *not advised as correlation ignored*
  - Different times reported across studies – a form of publication bias

- **Individual Participant Data Meta-Analysis (IPD-MA) of longitudinal data is more flexible**
  - Hierarchical (generalised) linear mixed effects models can be performed in standard software
  - Allows proper modelling of correlation structures and trends over time

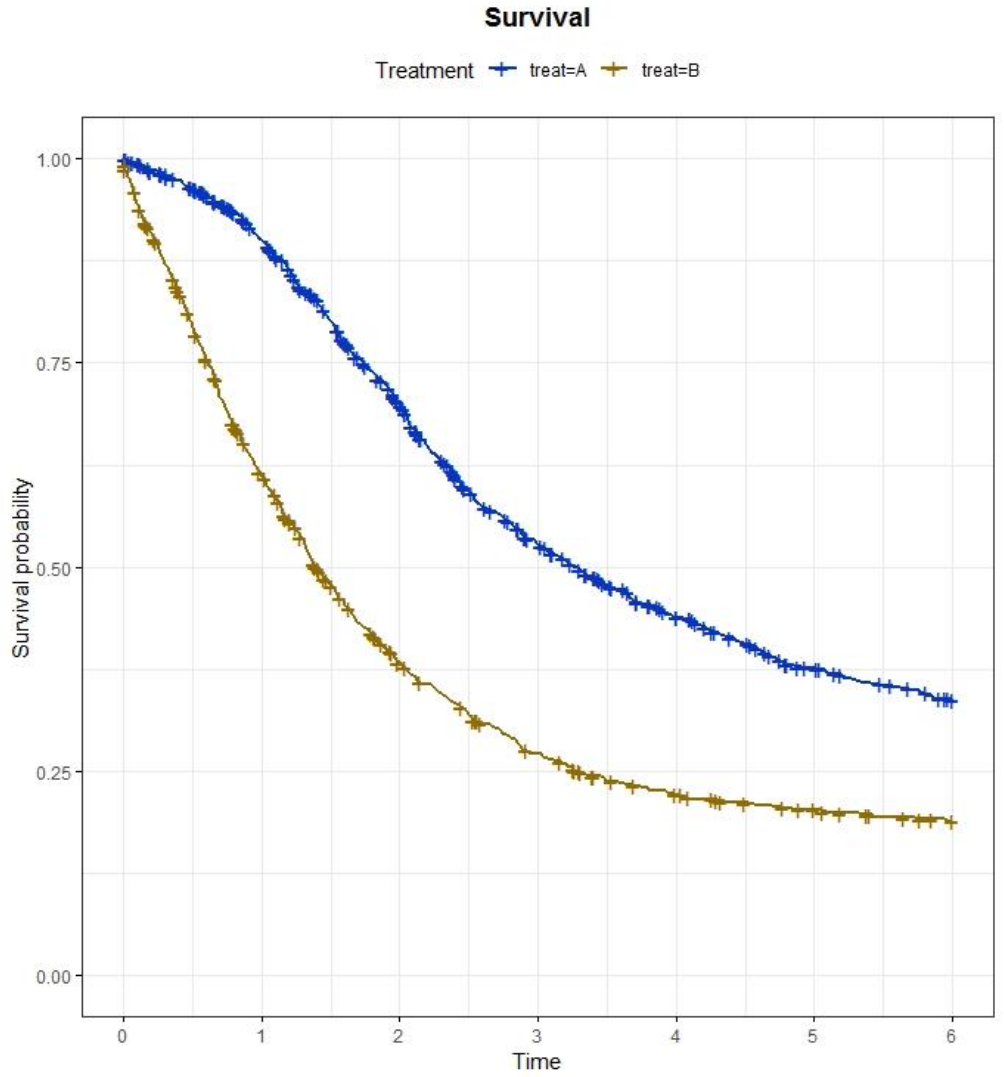
- **Key References**
  - IPD-MA of longitudinal data: Jones et al 2007, Gurrin and Turkovic 2012
  - AD-MA of longitudinal data: Ishak et al 2007, Maas et al 2004 , Peters and Mengersen 2008

Time-to-event Data

- Time until some event occurs

- Not all individuals will experience the event
  - Some will drop out for reasons unrelated to the event
  - Some will reach end of study without experiencing the event

- These individuals are censored
  - Still provide information – that event has not occurred up to this point



Meta-analyses of Time-to-event Data

- Aggregate Data Meta-Analysis (AD-MA) of time-to-event data
  - Care must be taken to ensure methods in each study are appropriate e.g. take into account censoring
  - Again, potential issues with data not being reported at all time points

- Individual Participant Data Meta-Analysis (IPD-MA) of time-to-event data
  - Often recommended to ensure correct modelling of the complex data
  - Commonly extensions to standard proportional hazards models proposed in literature are used

- Key references
  - IPD-MA: Tudur Smith 2005, Crowther et al 2014, Crowther et al 2012, Katsahian et al 2008, Michels et al 2005, Rondeau et al 2008, Thompson et al 2010
  - AD-MA: Parmar et al 1998, Tudur Smith et al 2001, Tierney et al 2007, Williamson et al 2002, Duchateau et al 2000, Arends et al 2008, Bennett et al 2013

Joint Data

- In some circumstances data will contain both longitudinal and time-to-event information – this is termed joint longitudinal and time-to-event data, or joint data.

- Joint modelling techniques might be employed when:
  - A longitudinal study is complicated by outcome related dropout
  - A time-to-event study involves time varying covariates
  - The longitudinal and time-to-event outcomes are both of interest, as well as the relationship between them

- When you have potentially related longitudinal and time-to-event data, it is important to model and investigate the relationship between them
  - *Modelling longitudinal and time-to-event outcomes separately when they are related could lead to biases*

Joint Model

- First proposed in 1997 by Wulfsohn and Tsiatis, but many papers since then have expanded methods to a range of areas (multivariate models, competing risks, cure rate…)

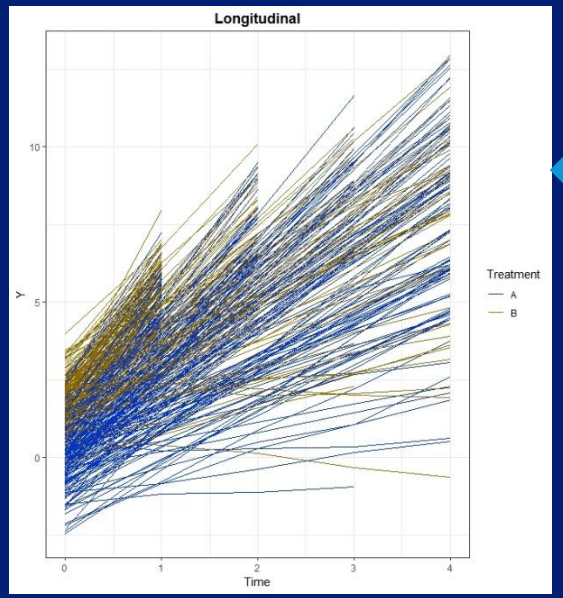
- Joint models consist three main components
  - Longitudinal sub-model
  - Time-to-event sub-model
  - Association / linking structure

- They simultaneously model both the longitudinal and time-to-event outcomes, rather than performing a two stage analysis (modelling of longitudinal, followed by modelling of time-to-event)

- Key references: Rizopoulos et al 2012, Elashoff et al 2017, Davidian et al 2004, Gould et al 2015, Ibrahim et al 2010, Tsiatis and Davidian 2004

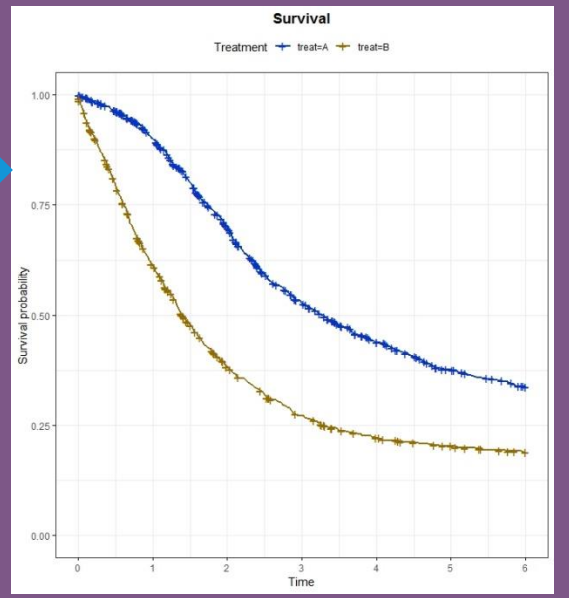
Joint Model – basic structure

Longitudinal Sub-model

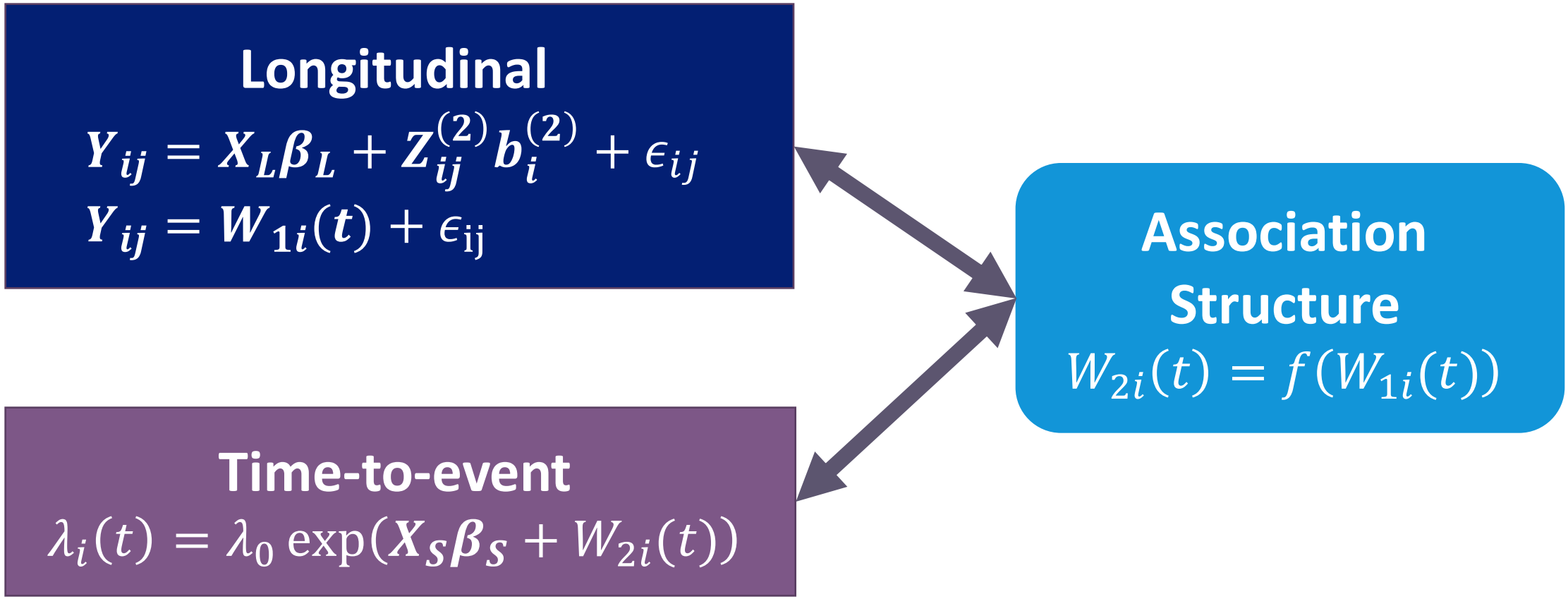


Association Structure

Time-to-event sub-model



Joint Model – algebraic notation



Association structures

Structure	Notation
Random proportional	$\alpha_{ind}\left(Z_i^{(2)} b_i^{(2)}\right)$
Current value	$\alpha_c(W_{1i}(t))$
Slope	$\alpha_s\left(\frac{d}{dt}\{W_{1i}(t)\}\right)$
Weighted cumulative	$\alpha_{wcum}\left(\int_0^t \varpi(t-s)_+ W_{1i}(s)ds\right)$
Interaction	$\alpha_c(W_{1i}(t)) + \alpha_{int}(x * W_{1i}(t))$
Lagged	$\alpha_{lag}(W_{1i}(\max(t-s,0)))$

Association structures

Structure	Interpretation
Random proportional	Difference between individual and population average longitudinal outcome has effect on risk of event
Current value	Current value of longitudinal marker has effect on risk of event
Slope	Rate of change of longitudinal marker has effect on risk of event
Weighted cumulative	History of longitudinal marker has an effect on risk of event
Interaction	Longitudinal has different effect across groups on risk of event
Lagged	Lagged effect of longitudinal on risk of an event

Joint Model – How common are they?

- In 2016 a review was conducted to assess current use of joint models applied to medical datasets
- Only applied papers, not those developing methodology were included
- Clear trend over time of increasing number of joint analyses, in a range of areas (Cancer, HIV, transplant studies, Cognitive decline,…)

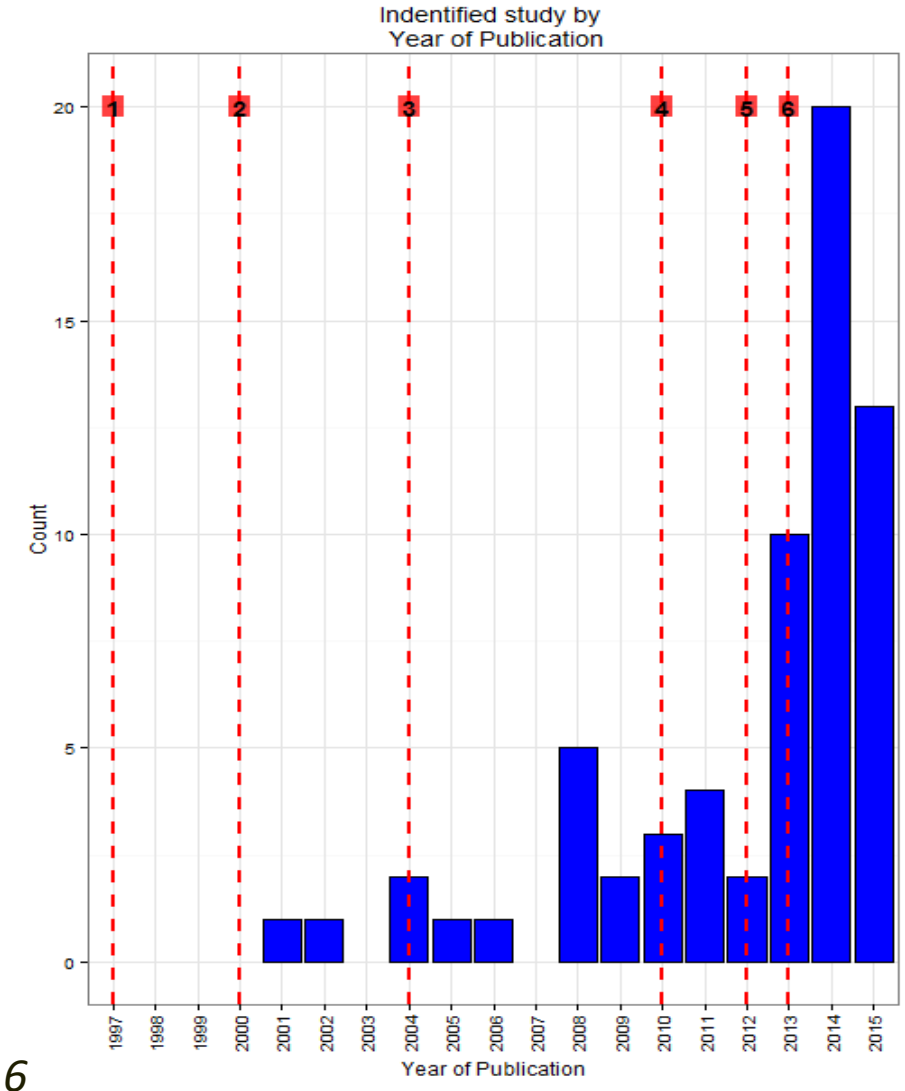


Fig. from Sudell et al 2016

AD-MA of joint data

Aggregate Data Meta-Analysis (AD-MA) of Joint Data

- ***How feasible is it to perform AD-MA of joint data?***

- Review by Sudell et al (2016) assessed reporting of joint analyses in 65 studies that applied joint models to medical datasets

- Assessed whether information currently reported in applied joint modelling papers was sufficient to extract necessary information to conduct separate meta-analyses for each parameter of interest

Aggregate Data Meta-Analysis (AD-MA) of Joint Data

	Longitudinal MA	Time-to-event MA	Association MA
MA possible given reported information (%)			
All identified studies (N=65)	44 (67.7)	45 (69.2)	50 (76.9)
Studies using joint models to account for dropout (N=22)	18 (81.8)	14 (63.6)	15 (68.2)
Studies using joint models to include time varying covariate in time-to-event sub-model (N=4)	2 (50.0)	3 (75.0)	3 (75.0)

The reason for joint model use appeared linked to reporting of joint models

Aggregate Data Meta-Analysis (AD-MA) of Joint Data

- Potential issues with reporting of joint models in literature might effect AD-MA of joint data
  - *Potential Reporting Bias*
  - *Reporting appeared linked to reason for joint modelling use*

- Differences in models used (longitudinal sub-model, time-to-event sub-model, association structure could make it difficult to pool results

- Recommendation to seek IPD if performing a meta-analysis of joint data
  - *Standardisation of models across included studies*
  - *Proper modelling of effects over time*
  - *Proper modelling of complex data*

IPD-MA of joint data

Illustrative example – subset of INDANA data

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

- Longitudinal outcome systolic blood pressure (SBP) measured at baseline, 6 months, then annually thereafter to maximum of 7 years. Measurement patterns varied between studies

- 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

- Example is only illustrative – in a real analysis further covariates known to be important for hypertension should be considered (Smoking status, age,….)

Preliminary Steps

- There are a range of graphs which are useful to produce when performing a IPD-MA of joint data before analysing the data

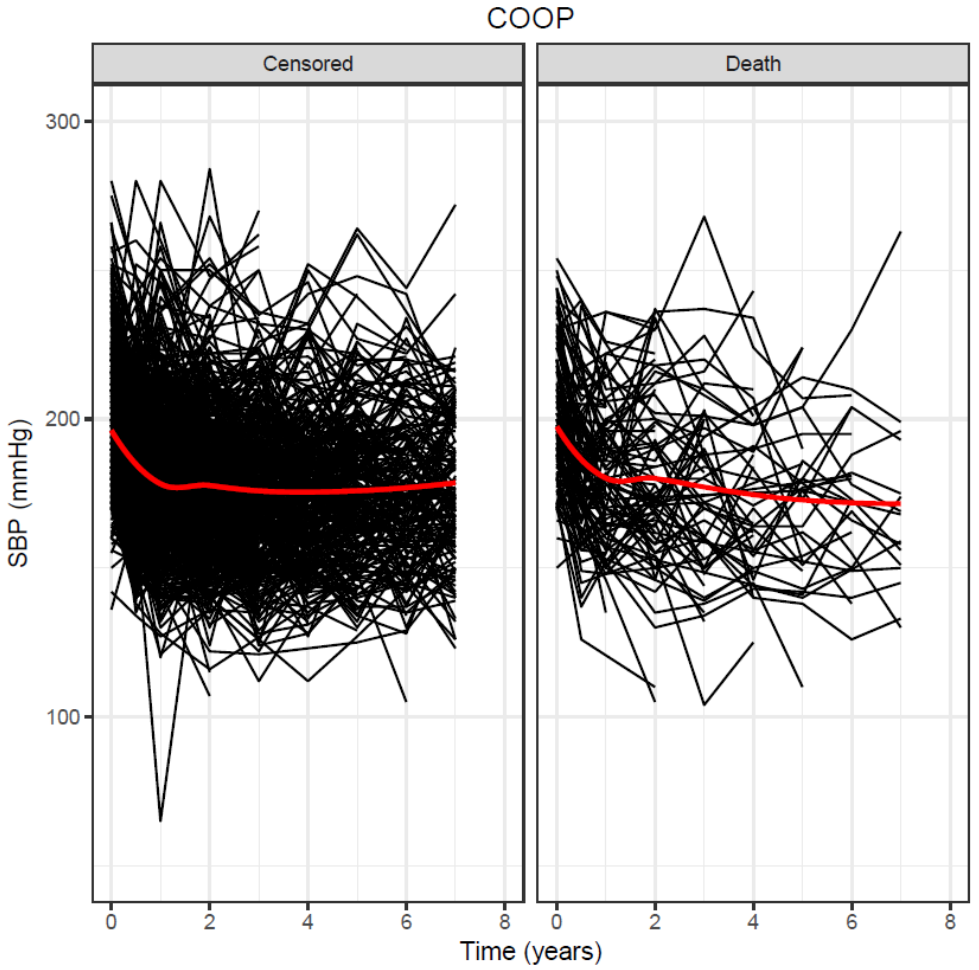
- These graphs should be produced regardless of the IPD-MA approach (one-stage, two-stage)

- These graphs give an initial assessment of modelling approaches in each sub-model (*e.g. is the longitudinal trajectory linear or non-linear?*) and can show evidence of the relationship between the longitudinal and time-to-event components

- Plots should be made of both the longitudinal trajectory and the time-to-event outcome.
  - Time-to-event plots are the same as for separate time-to-event analyses
  - Longitudinal plots show some additional useful components, which we will now discuss

Preliminary Steps – plots of longitudinal trajectory

- Plot of the longitudinal outcome Y_{ki} by longitudinal time t_{kij} (termed the trajectory) panelled by whether the individual experienced the event should be produced for each study within the MA
- Example for COOPE – the mean trajectories for those censored and those experiencing an event show an initial drop in SBP.
- However it appears that those censored remain steady at a higher SBP than those experiencing the event.
- Examine alternative graph, adjusted by survival time (next slide)

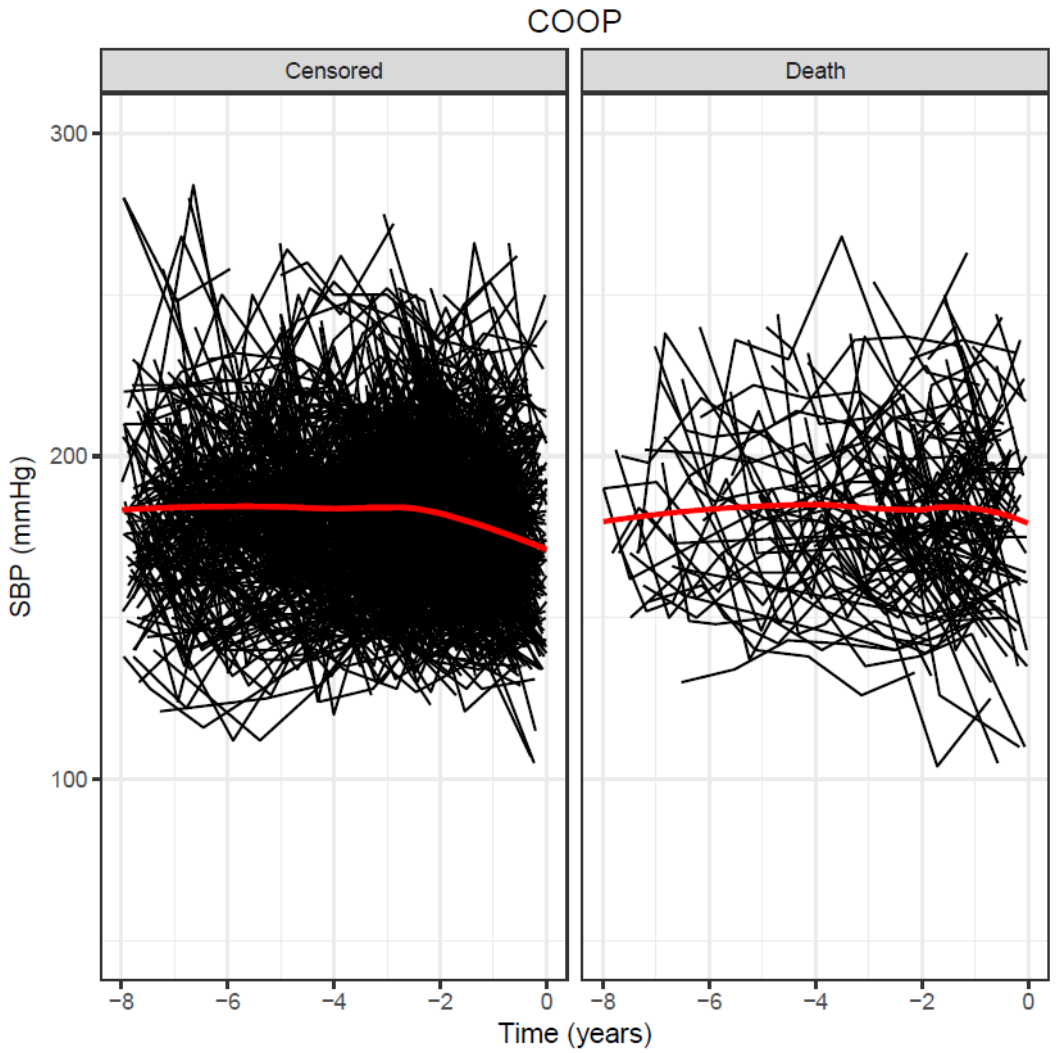


Preliminary Steps – plots of longitudinal trajectory

- Now longitudinal outcomes Y_{ki} for individuals i within study k are plotted against $t_{kij} - T_{ki}$ i.e. against longitudinal time adjusted by the individual's survival time

- The mean longitudinal trajectory for those censored drops shortly before time zero (before the survival time). However, the mean SBP trajectory for those experiencing the event remains higher

- Evidence of a relationship between longitudinal outcome and the event of interest – motivation for use of a joint model



Two stage IPD-MA of joint data

Two Stage Individual Participant Data Meta-Analysis (IPD-MA) of Joint Data

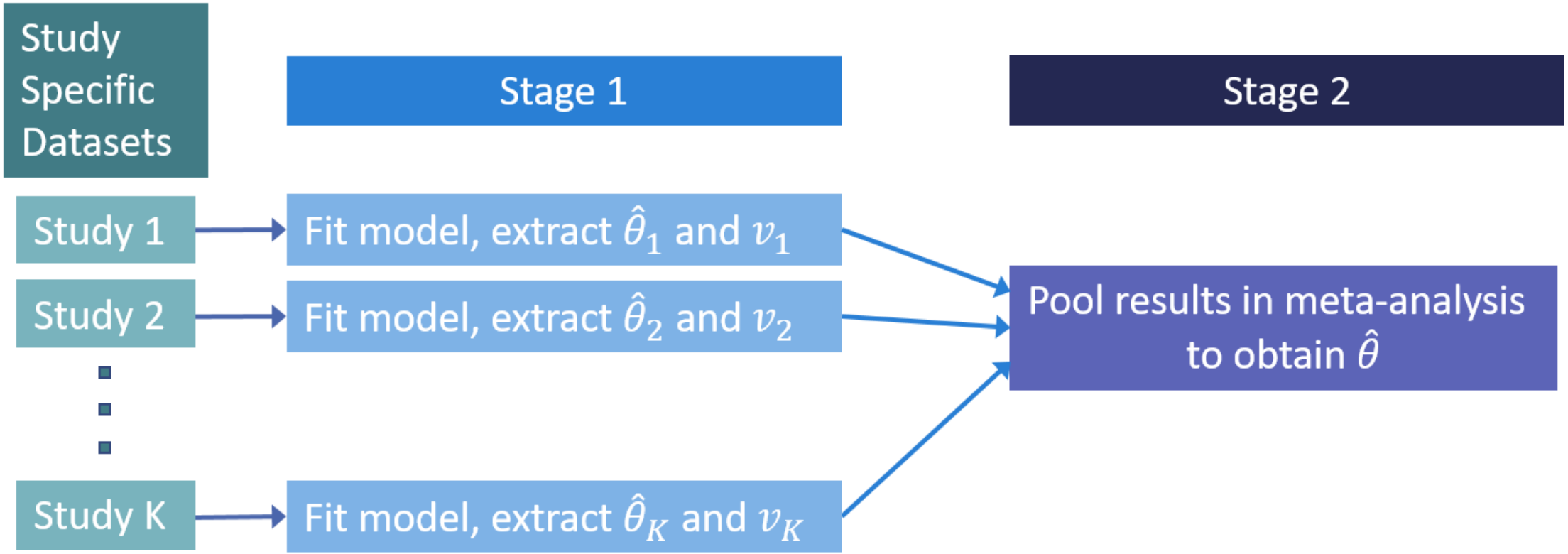
Process

- For the data from each study k in $1, \ldots, K$ where K is the total number of studies in the meta-analysis, fit a joint longitudinal and time-to-event model

- Extract parameters of interest from the study specific joint model fits, for example treatment effect parameters and/or association parameters. Also extract measure of variability (standard error) for each parameter of interest

- Pool the extracted study specific information using standard meta-analytic techniques

Two Stage Individual Participant Data Meta-Analysis (IPD-MA) of Joint Data



Two Stage IPD-MA of Joint Data – First Stage

For example: For k in $1, \ldots, K$, using the INDANA data fit the following joint model to the data from study k, and extract estimates and standard errors for the highlighted parameters of interest

Longitudinal

$$\boldsymbol{Y_{kij}} = \beta_{L0k} + \beta_{L1k} t_{kij} + \beta_{L2k} trt_{ki} + \beta_{L3k} \exp(-3 * t_{kij}) + b_{ki0}^{(2)} + b_{ki1}^{(2)} t_{kij} + \epsilon_{kij}$$

$$\boldsymbol{Y_{kij}} = \boldsymbol{W_{1ki}(t)} + \boldsymbol{\epsilon_{kij}}$$

Time-to-event

$$\lambda_{ki}(T_{ki}) = \lambda_{0k} \exp(\beta_{S1k} trt_{ki} + W_{2ki}(T_{ki}))$$

Association Structure

$$W_{2ki}(t) = \alpha_k^{(2)} \left(b_{ki0}^{(2)} + b_{ki1}^{(2)} t \right)$$

Note: $\exp(-3 * t_{kij})$ *term included to model initial drop in longitudinal trajectory*

Two Stage IPD-MA of Joint Data – Second Stage

Example continued:

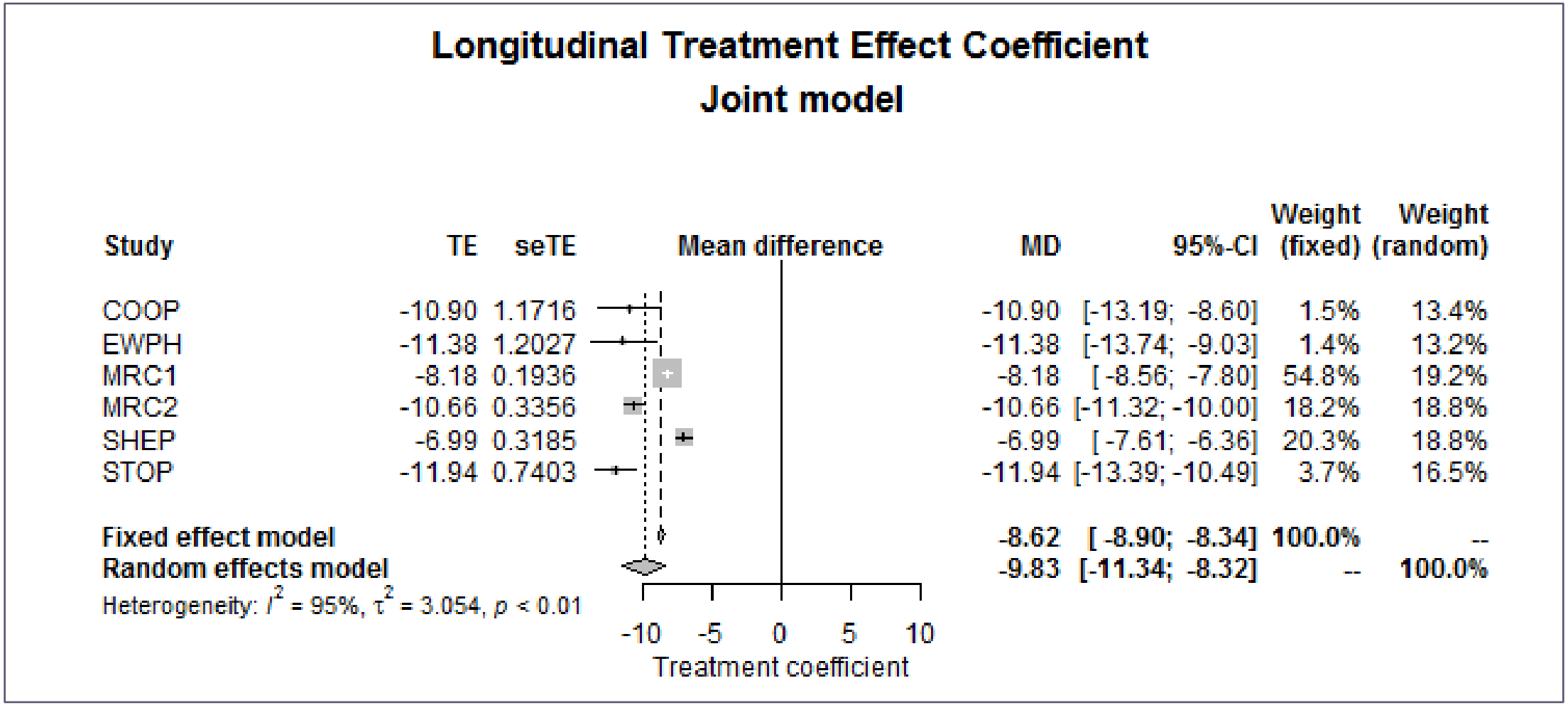
- Once estimates and standard errors for the parameters of interest have been extracted (*here the longitudinal treatment effect β_{L2}, the time-to-event treatment effect β_{S1} and the association parameter $\alpha^{(2)}$*), pool parameters using standard meta-analytic techniques.

- For example, an inverse variance approach:

$$\hat{\alpha}^{(2)} = \frac{\sum_{k=1}^{K} w_k \hat{\alpha}_k^{(2)}}{\sum_{k=1}^{K} w_k}$$

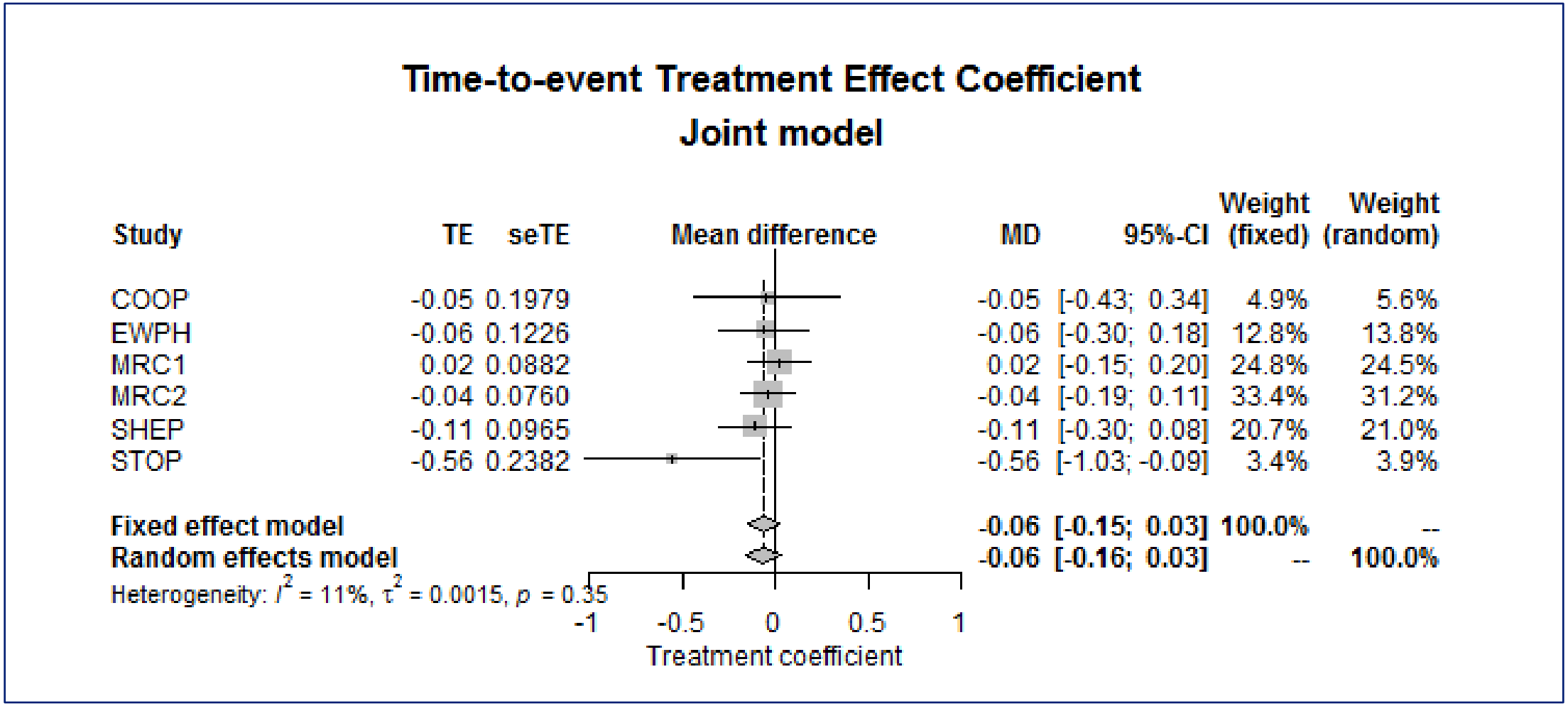
Where $w_k = 1/\left(var\left(\hat{\alpha}_k^{(2)}\right)\right)$ for the fixed effects approach, and $w_k = 1/\left(var\left(\hat{\alpha}_k^{(2)}\right) + \tau^2\right)$ for the random effects approach (DerSimonian and Laird 1986), where τ^2 represents the between study heterogeneity

Two Stage IPD-MA of Joint Data – Second Stage



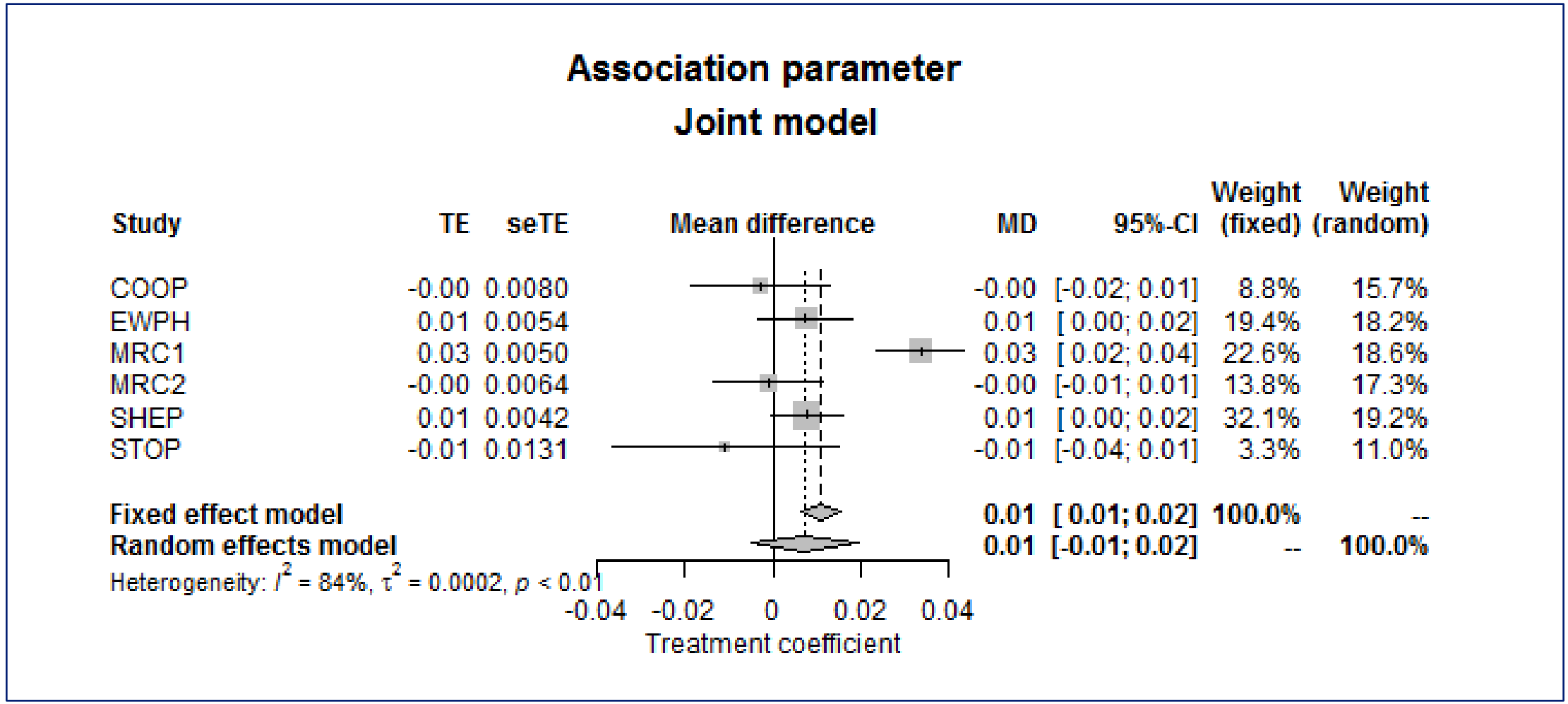
Analysis from Sudell et al 2017

Two Stage IPD-MA of Joint Data – Second Stage



Analysis from Sudell et al 2017

Two Stage IPD-MA of Joint Data – Second Stage



Analysis from Sudell et al 2017

Two Stage IPD-MA of Joint Data – Considerations

What if different association structures were used in different studies?

If one study used the current value association structure:

$$W_{2ki}(t) = \alpha_{ck}\left(\beta_{L0} + \beta_{L1}t + \beta_{L2}trt_{ki} + \beta_{L3}\exp(-3 * t) + b_{ki0}^{(2)} + b_{ki1}^{(2)}t\right)$$

In this study, the association parameter would represent the effect of the currently recorded longitudinal outcome on the risk of an event

If another study used the random proportional association structure

$$W_{2ki}(t) = \alpha_{k}^{(2)}\left(b_{ki0}^{(2)} + b_{ki1}^{(2)}t\right)$$

The association parameter from this study represents the effect of the difference between the recorded value and the population average value in longitudinal outcome for a particular individual on the risk of an event

Care should be taken to pool only parameters whose interpretation is comparable

Two Stage IPD-MA of Joint Data – Considerations

Same problem occurs if terms involved in the association structure differ between studies.

If one study employed an individual level random intercept and slope:

$$W_{2ki}(t) = \alpha_k^{(2)}\left(b_{ki0}^{(2)} + b_{ki1}^{(2)}t\right)$$

Whilst another study employed only an individual level random intercept

$$W_{2ki}(t) = \alpha_k^{(2)}\left(b_{ki0}^{(2)}\right)$$

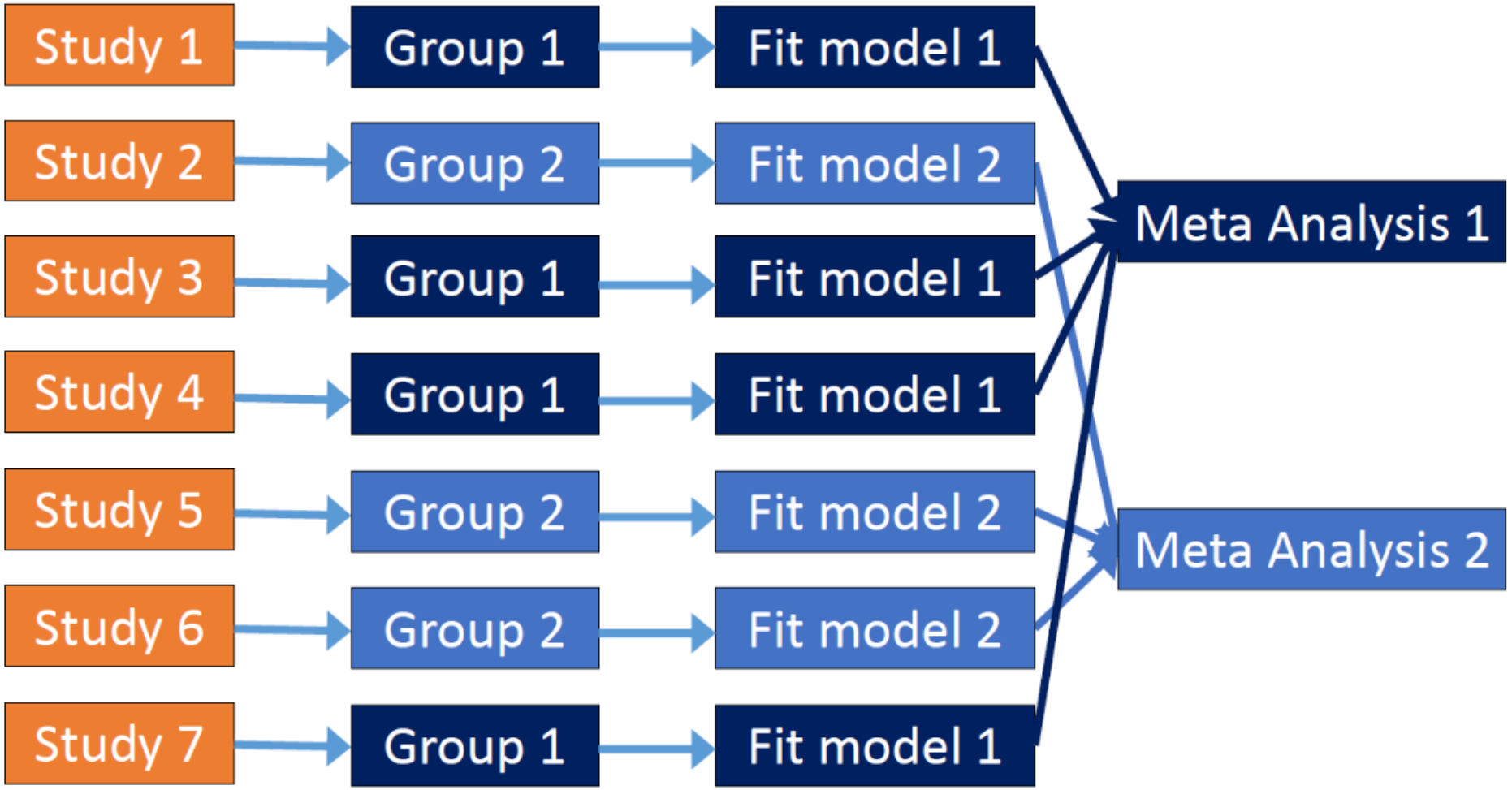
The association parameter again would represent different things - the first represents the effect of the sum of the individual specific random intercept and slope on the risk of the event. The second represents only the effect of the individual specific random intercept on the risk of an event

Care should be taken to pool only parameters whose interpretation is comparable

Two Stage IPD-MA of Joint Data – Recommendations

- Evaluate each study separately using e.g. graphical techniques
- Assess the most appropriate joint modelling structure for each study
- If parameters have different interpretations between studies (for example different association parameter interpretations), pool only parameters whose interpretations are comparable

Two Stage IPD-MA of Joint Data – Recommendations



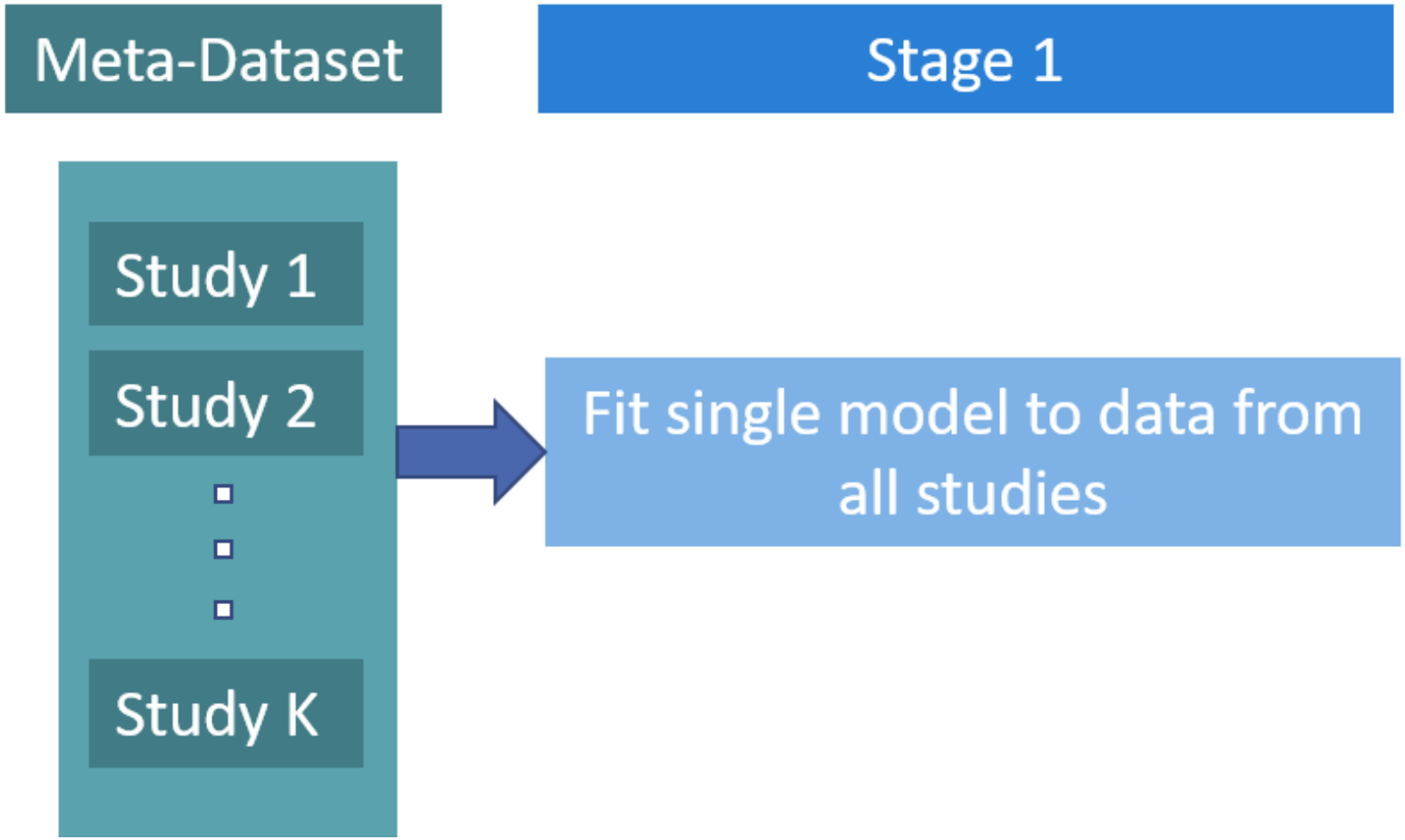
One-stage IPD-MA of joint data

One Stage Individual Participant Data Meta-Analysis (IPD-MA) of Joint Data

Process

- Hold the data from each study k in $1, \ldots, K$ where K is the total number of studies in the meta-analysis in a single large meta-dataset
- Fit a single large joint model to the meta-dataset
- Ensure clustering of data within studies is accounted for e.g. using
  - Study level random effects
  - Fixed interactions between study membership and other covariates in either sub-model
  - Baseline hazard stratified by study
  - *Do not ignore clustering*

One Stage Individual Participant Data Meta-Analysis (IPD-MA) of Joint Data



One Stage IPD-MA of Joint Data – Accounting for Clustering

Option 1: Accounting for clustering using **study level random effects**

Longitudinal

$$Y_{kij} = \beta_{L0} + \beta_{L1} t_{kij} + \beta_{L2} trt_{ki} + \beta_{L1} \exp(-3 * t_{kij}) + b_{ki0}^{(2)} + b_{ki1}^{(2)} t_{kij} + b_{k0}^{(3)} + b_{k1}^{(3)} trt_{ki} + \epsilon_{kij}$$

Time-to-event

$$\lambda_{ki}(T_{ki}) = \lambda_0 \exp(\beta_{S1} trt_{ki} + W_{2ki}(T_{ki}))$$

Association Structure

$$W_{2ki}(t) = \alpha^{(2)} \left(b_{ki0}^{(2)} + b_{ki1}^{(2)} t \right) + \alpha^{(3)} \left(b_{k0}^{(3)} + b_{k1}^{(3)} trt_i \right)$$

Note: $\exp(-3 * t_{ij})$ *term included to model initial drop in longitudinal trajectory*

One Stage IPD-MA of Joint Data – Accounting for Clustering

Option 1: Accounting for clustering using **study level random effects**

Benefits of approach	Drawbacks of approach
Estimates a distribution for differences between studies	Random effects and their distribution poorly estimated if number of included studies is small
Ability to predict results for future studies	Study specific estimates not automatically produced
Doesn't become cumbersome as number of included studies increases	

One Stage IPD-MA of Joint Data – Accounting for Clustering

Option 2: Accounting for clustering using **fixed interactions with study membership**

Longitudinal

$$Y_{kij} = \beta_{L0} + \beta_{L1} t_{kij} + \beta_{L2} trt_{ki} + \beta_{L3} \exp(-3 * t_{kij}) + \beta_{L4} study_{ki} + \beta_{L5} study_{ki} * trt_{ki} + b_{ki0}^{(2)} + b_{ki1}^{(2)} t_{kij} + \epsilon_{kij}$$

Association Structure

$$W_{2ki}(t) = \alpha^{(2)} \left(b_{ki0}^{(2)} + b_{ki1}^{(2)} t \right)$$

Note: $\exp(-3 * t_{ij})$ *term included to model initial drop in longitudinal trajectory*

Time-to-event

$$\lambda_{ki}(T_{ki}) = \lambda_0 \exp(\beta_{S1} trt_{ki} + \beta_{S2} study_{ki} + \beta_{S3} study_{ki} * trt_{ki} + W_{2ki}(T_{ki}))$$

One Stage IPD-MA of Joint Data – Accounting for Clustering

Option 2: Accounting for clustering using **fixed interactions with study membership**

Benefits of approach	Drawbacks of approach
Exact estimation of study specific effects	Approach becomes cumbersome as number of included studies increases
Separate out study effects in each sub-model	Limited ability to predict results for future studies
Suitable if few studies included in meta-analysis	No distribution of studies produced
	No difference in association structure across included studies

One Stage IPD-MA of Joint Data – Accounting for Clustering

Option 3: Accounting for clustering using **baseline hazard stratified by studies, and fixed study membership terms**

Longitudinal

$$Y_{kij} = \beta_{L0} + \beta_{L1} t_{kij} + \beta_{L2} trt_{ki} + \beta_{L3} \exp(-3 * t_{kij}) + \beta_{L4} study_{ki} + b_{ki0}^{(2)} + b_{ki1}^{(2)} t_{kij} + b_{k1}^{(3)} trt_{ki} + \epsilon_{kij}$$

Association Structure

$$W_{2ki}(t) = \alpha^{(2)} \left(b_{ki0}^{(2)} + b_{ki1}^{(2)} t \right) + \alpha^{(3)} \left(b_{k1}^{(3)} trt_{ki} \right)$$

Time-to-event

$$\lambda_{ki}(T_{ki}) = \lambda_{0k}(t) \exp(\beta_{S1} trt_{ki} + W_{2ki}(T_{ki}))$$

Note: $\exp(-3 * t_{ij})$ *term included to model initial drop in longitudinal trajectory*

One Stage IPD-MA of Joint Data – Accounting for Clustering

Option 1: Accounting for clustering using **baseline hazard stratified by studies, and fixed study membership terms**

Benefits of approach	Drawbacks of approach
Fast to fit – baseline hazard involves only events from one study	Using fixed effects becomes cumbersome as number of included studies increases
	Limited applicability to future studies
	Stratified baseline hazard accounts for but doesn't explain between study heterogeneity
	Can be complex to interpret due to mix of approaches

One Stage IPD-MA of Joint Data – Illustrative example

- Obvious issue with option that accounts for between study heterogeneity only using study level random effects
  - due to small number of studies in meta-analysis
- Results from other approaches look comparable
- As with two stage MA difference between result for STOP trial and other trials

Model Option	Longitudinal Treatment Effect Parameter(s)	
Naïve – ignoring clustering	β_{L2}	**-9.52 (-9.92, -9.19)**
Fixed interaction with study membership (both sub-models)	β_{L2COOP}	**-10.04 (-12.39, -7.91)**
	$\beta_{L2EWPHE}$	**-13.15 (-15.24, -11.10)**
	β_{L2MRC1}	**-7.78 (-8.17, -7.42)**
	β_{L2MRC2}	**-10.72 (-11.33, -10.07)**
	β_{L2SHEP}	**-8.31 (-8.88, -7.75)**
	β_{L2STOP}	**-14.16 (-15.40, -12.93)**
Study level random effects	β_{L2}	**-2.70 (-3.09, -2.42)**
Baseline hazard stratified by study, and fixed interaction with study membership in longitudinal	β_{L2}	**-10.63 (-11.17, -10.06)**

Analysis from Sudell et al 2018

One Stage IPD-MA of Joint Data – Illustrative example

- Results from one stage comparable to results from two stage.
- Insignificant direct effect of treatment on risk of death
- Again results from STOP trial differ from other trials

Model Option	Time-to-event Treatment Effect Parameter(s)	
Naïve – ignoring clustering	β_{S1}	-0.02 (-0.13, 0.07)
Fixed interaction with study membership (both sub-models)	β_{S1COOP}	0.02 (-0.37, 0.41)
	$\beta_{S1EWPHE}$	-0.03 (-0.31, 0.25)
	β_{S1MRC1}	0.00 (-0.16, 0.15)
	β_{S1MRC2}	-0.01 (-0.16, 0.16)
	β_{S1SHEP}	-0.11 (-0.31, 0.09)
	β_{S1STOP}	**-0.49 (-0.95, -0.14)**
Study level random effects	β_{S1}	-0.05 (-0.14, 0.03)
Baseline hazard stratified by study, and fixed interaction with study membership in longitudinal	β_{S1}	-0.06 (-0.14, 0.03)

Analysis from Sudell et al 2018

One Stage IPD-MA of Joint Data – Illustrative example

- Significant association at individual level from all approaches
  - Interpretation – higher than population average SBP for an individual is linked to greater risk of an event
  - Indirect effect of treatment through SBP
- Difference between naïve approach and approaches that account for clustering
- Potential problems again where clustering solely account for using study level random effects

Model Option	Association Parameter(s)	
Naïve – ignoring clustering	$\alpha^{(2)}$	**0.032 (0.029, 0.035)**
Fixed interaction with study membership (both sub-models)	$\alpha^{(2)}$	**0.013 (0.009, 0.019)**
Study level random effects	$\alpha^{(2)}$	**0.011 (0.007, 0.016)**
	$\alpha^{(3)}$	**0.052 (0.049, 0.055)**
Baseline hazard stratified by study, and fixed interaction with study membership in longitudinal	$\alpha^{(2)}$	**0.013 (0.006, 0.017)**
	$\alpha^{(3)}$	0.000 (-0.039, 0.048)

Analysis from Sudell et al 2018

One Stage IPD-MA of Joint Data – Recommendations

- Perform same preliminaries as two-stage (e.g. graphical representations to assess link between longitudinal and time-to-event, and differences between studies
- Always account for clustering
- Take care not to account for “the same” heterogeneity in multiple ways in a joint model – be clear what parameters occur where given the association structure you are employing
- Consider whether there are sufficient studies to estimate the number of study level random effects

Key software

- Joint models can be fitted in many packages (SAS, Stata, WinBUGS,…) however analyses here done in R using

- **Single study joint modelling packages**
  - joineR
  - JM
- **Multi-study joint modelling packages**
  - joineRmeta
  - joineRmetaBayes (in progress)
- **Meta-analytic packages**
  - meta
  - metafor

Summary

- Joint models are growing in popularity as a way of simultaneously modelling related longitudinal and time-to-event data

- IPD is probably required for a meta-analysis of joint data

- Two stage IPD joint meta-analytic models
  - simple to be implemented
  - limited in terms of heterogeneity investigation

- One stage methods
  - more complex and time consuming
  - Allow greater investigation of heterogeneity
  - Care must be taken in modelling of clustering

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