







# Joint models of longitudinal and time-to-event data: extensions and recent developments

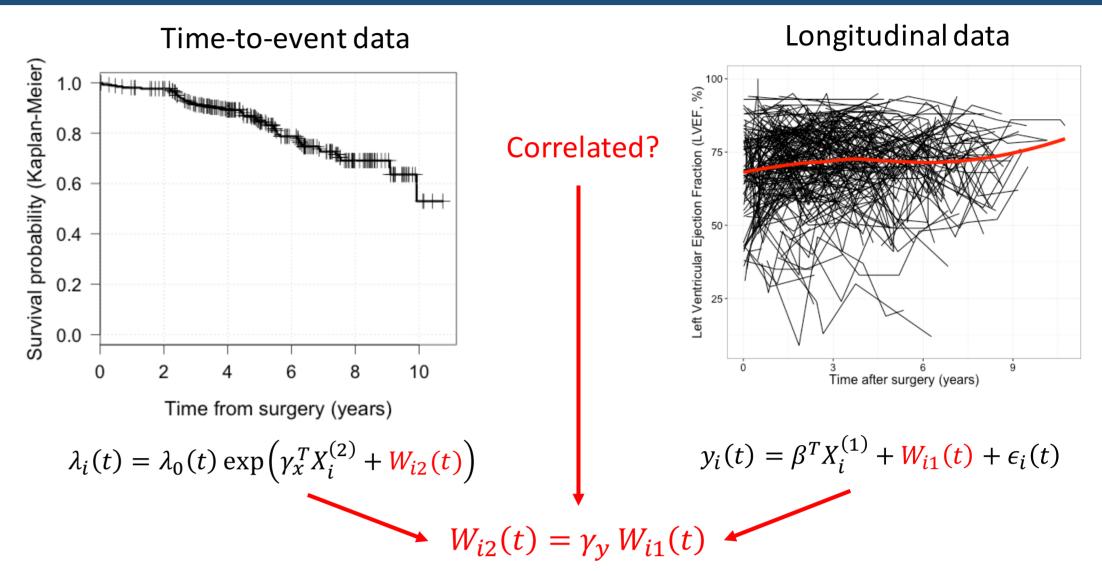
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# WHAT IS JOINT MODELLING?

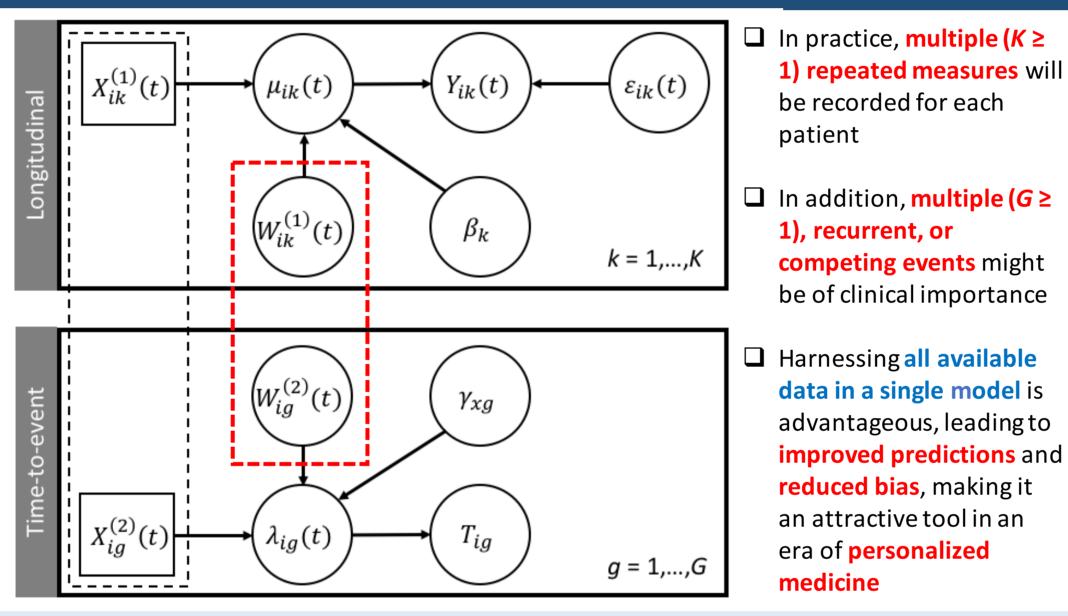
- In clinical trials or cohort studies, measurements are repeatedly measured over time (e.g. cardiac ejection fraction), which we call longitudinal data
- In addition, the time to one or more clinical endpoints (e.g. death) is recorded, which we call **time-to-event data**
- Historically, these data have been **analysed separately**

#### **Problems with standard models?**

- Sickest patients more likely to drop out of study  $\rightarrow$  informative missingness
- Repeated outcomes measured with error  $\rightarrow$  estimator attenuation
- Time-varying covariates treated as constant between follow-up time in event-time model  $\rightarrow$  unrealistic



#### **EXTENSION TO MULTIVARIATE DATA**

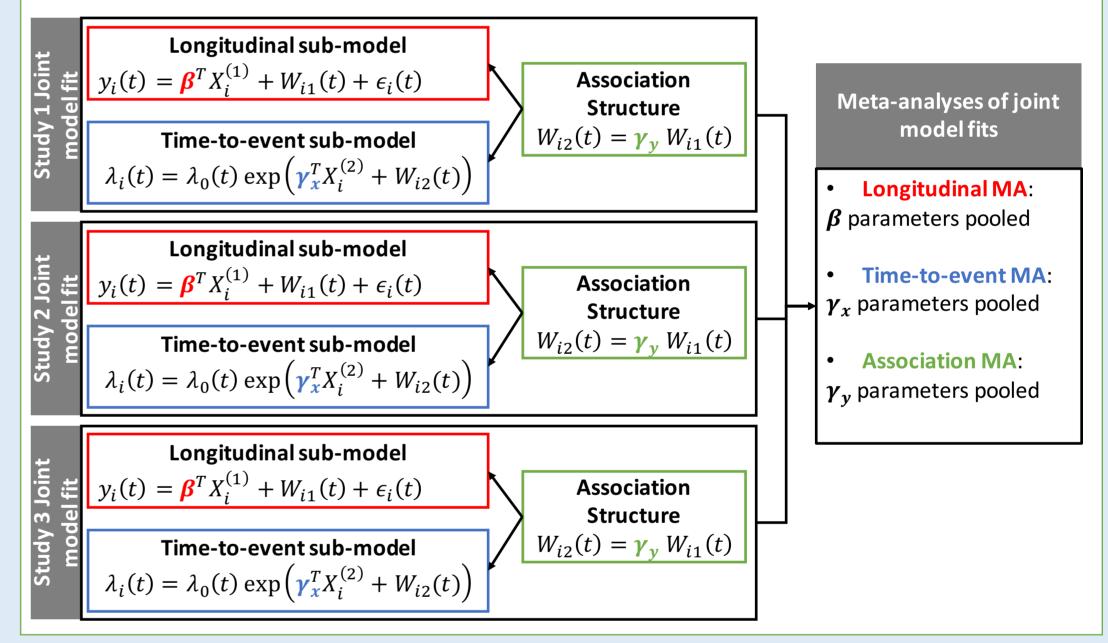


## **RECENT METHODOLOGICAL DEVELOPMENTS**

- Research has **predominantly focused on univariate data**, but a review identified a growing methodological literature on multivariate data
- Majority of articles only considered **either** multivariate longitudinal or time-to-event data, not both
- Numerous innovations in models, distributional assumptions, estimation methodologies
- Diverse range of association structures (red box in model graph above) linking sub-models

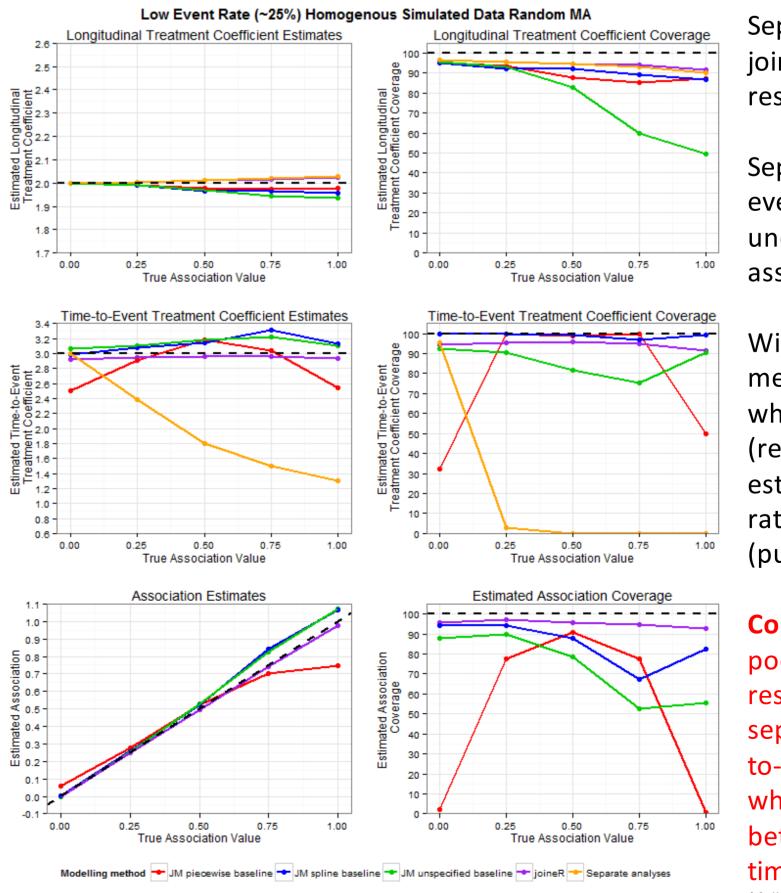
### META-ANALYSIS (MA) OF JOINT OUTCOMES

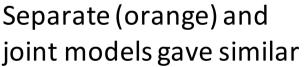
- Investigation to examine the benefits of joint models in a multi study ulletcase
- Considering two stage MA where models are fitted to each study then • study coefficients pooled using standard MA methods



#### JOINT OUTCOME MA – SIMULATION STUDY

#### Findings\*





**Limited clinical applications**, with methodological papers concentrating mostly on cardiovascular, neurodegenerative, lung, cancer, and HIV/AIDs diseases

## SOFTWARE

- Currently **no statistical software available** to fit joint models to multivariate longitudinal data
- A number of software options for fitting joint models to **competing risks data**, each incorporating different sub-models and association structures
- Multivariate data increases number of random effects in model, leading to exponential increase in computational time
- **joineR** package freely available for installation in R software for fitting joint models to univariate data
- Development of joineR to incorporate multivariate outcomes is on-going

results in longitudinal MA

Separate analysis time-toevent MA increasingly underestimated as association increased

Within joint modelling methods, worse coverage where profile likelihood (red, blue, green) estimated standard errors rather than bootstrapping (purple)

**Conclusion:** Benefit of pooling joint modelling results in MA over separate results for timeto-event coefficients where association exists between longitudinal and time-to-event outcomes \*full results available from author

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