

# A methodological review of joint modelling of multivariate time-to-event data and longitudinal outcomes

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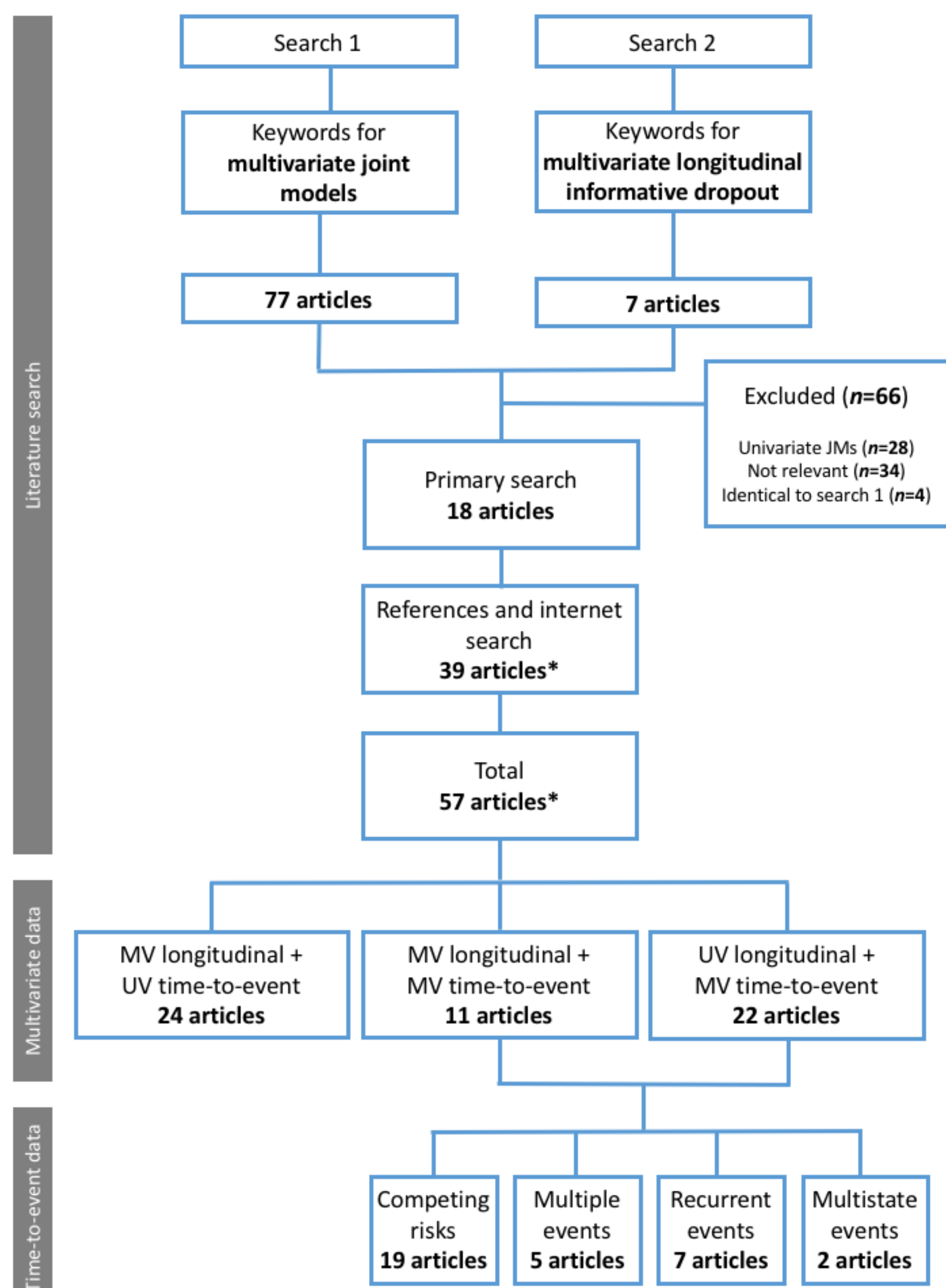
## Introduction

- Joint models of longitudinal and time-to-event data have predominantly focused on a univariate longitudinal measure and a single event time
- However, clinical studies are likely to record multiple longitudinal outcomes and/or multiple, recurrent or competing events
- Incorporating all sources of data will improve the predictive capability of any model and lead to more informative inferences for the purpose of medical decision-making
- Our **study objective** is to review the literature for implementations of joint modelling for multivariate data

## Methods

- Search of Ovid MEDLINE (1946 to August 2015)
- Keywords included 'multivariate', 'time-to-event', 'longitudinal', etc.
- Web search and scan of reference sections
- Information extracted on multivariate features, data types, submodels, distributional assumptions, estimation methods, applications, diagnostics, software

## Search



\* 3 articles from a single source

## Highlights

- Majority of articles only considered either multivariate longitudinal or time-to-event data
- Numerous innovations in models, distributional assumptions, estimation methodologies
- Diverse range of association structures linking submodels
- Limited clinical application, with methodological papers concentrating most on cardiovascular, neurodegenerative, lung, cancer, and HIV/AIDs diseases
- A lack of software implementations that allow researchers to easily exploit novel methodology, with R the most reported software used for analyses
- A number of novel developments in the field of diagnostics to measure benefit and assess model assumptions

## Future research

- Development of the R package `joiner` to incorporate multivariate outcomes – longitudinal and event times
- Explore techniques for overcoming intractable numerical integration with multiple longitudinal outcomes

### Association structure

Current value, Random effects, JLCM, Correlated random effects, Other (function of imputed longitudinal data profile, cumulative effects, time-dependent slopes, lagged effects, previous values, PMM)

### Time-to-event data

Continuous, Discrete, Right-censored, Interval-censored, Left-censored

### Longitudinal data

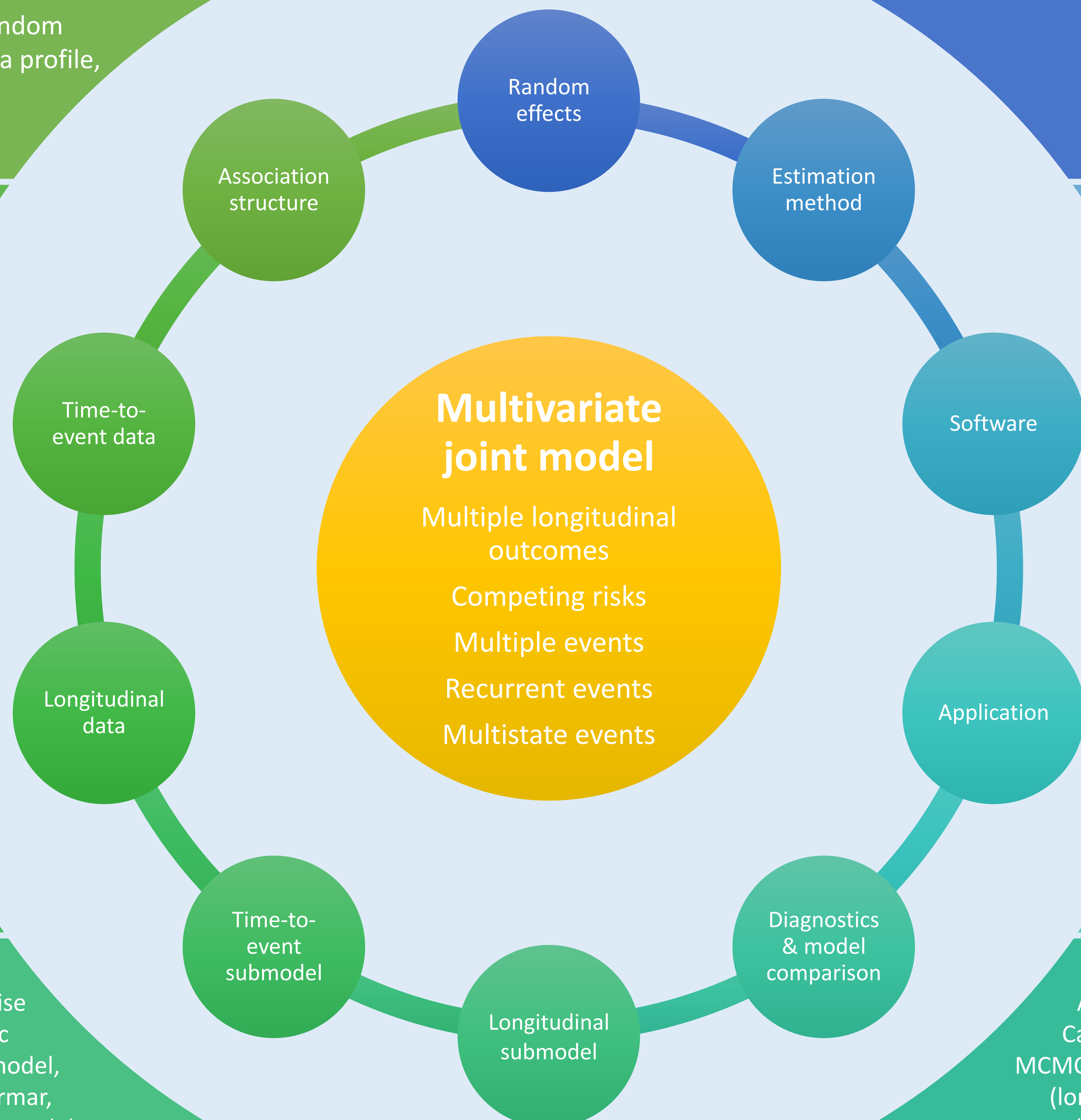
Continuous (incl. censored, bounded), Discrete, Ordinal, Combinations of types for multivariate models

### Longitudinal submodel

LMM, GLMM, NLMM, Item response theory models, Continuation ratio mixed effects, Mixed effects partial proportional odds model, Zero-inflated Beta regression model, Random change-point mixed model

### Time-to-event submodel

PH (Cox [incl. cause-specific + sub-distribution], piecewise constant), Discrete time hazard log-linear, Cure fractions model, Parametric (log-logistic, log-normal, other), Royston-Parmar, Kaplan-Meier, Truncated-geometric distribution-logistic model, Two-step mixture model, Transformation models, Multistate models



### Random effects

Longitudinal: Multivariate/independent normal, Semi-parametric, Discrete, Multivariate- $t$   
Frailty: Log-normal, Gamma, Positive stable law

### Estimation method

MLE, NP-MLE, Bayesian MCMC, Conditional score estimation, Two-stage regression calibration, Generalised estimating equations, Multiple imputation

### Software

C/C++, Fortran, Matlab, S-Plus, R, OpenBUGS, WinBUGS, JAGS, SAS, Stata, MLn

### Application

Cancer, Cardiovascular disease, Lung disease, HIV / AIDS, Mental health, Neurodegenerative disease, Renal disease, Hepatic disease, Cognitive function, ITU care, Neurological disease

### Diagnostics & model comparison

AIC, BIC, DIC, LRT, LPML, CPO, Local influence measures, Case-deletion diagnostics, Graphical methods, Score tests, MCMC diagnostics, Multivariate  $L$ -measure, Residual analysis (longitudinal, time-to-event), Predictive ability assessment (Harrell's  $C$ -statistic, dynamic AUC, dynamic Brier score), Two-group comparison tests, Measures of relative benefit

