

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

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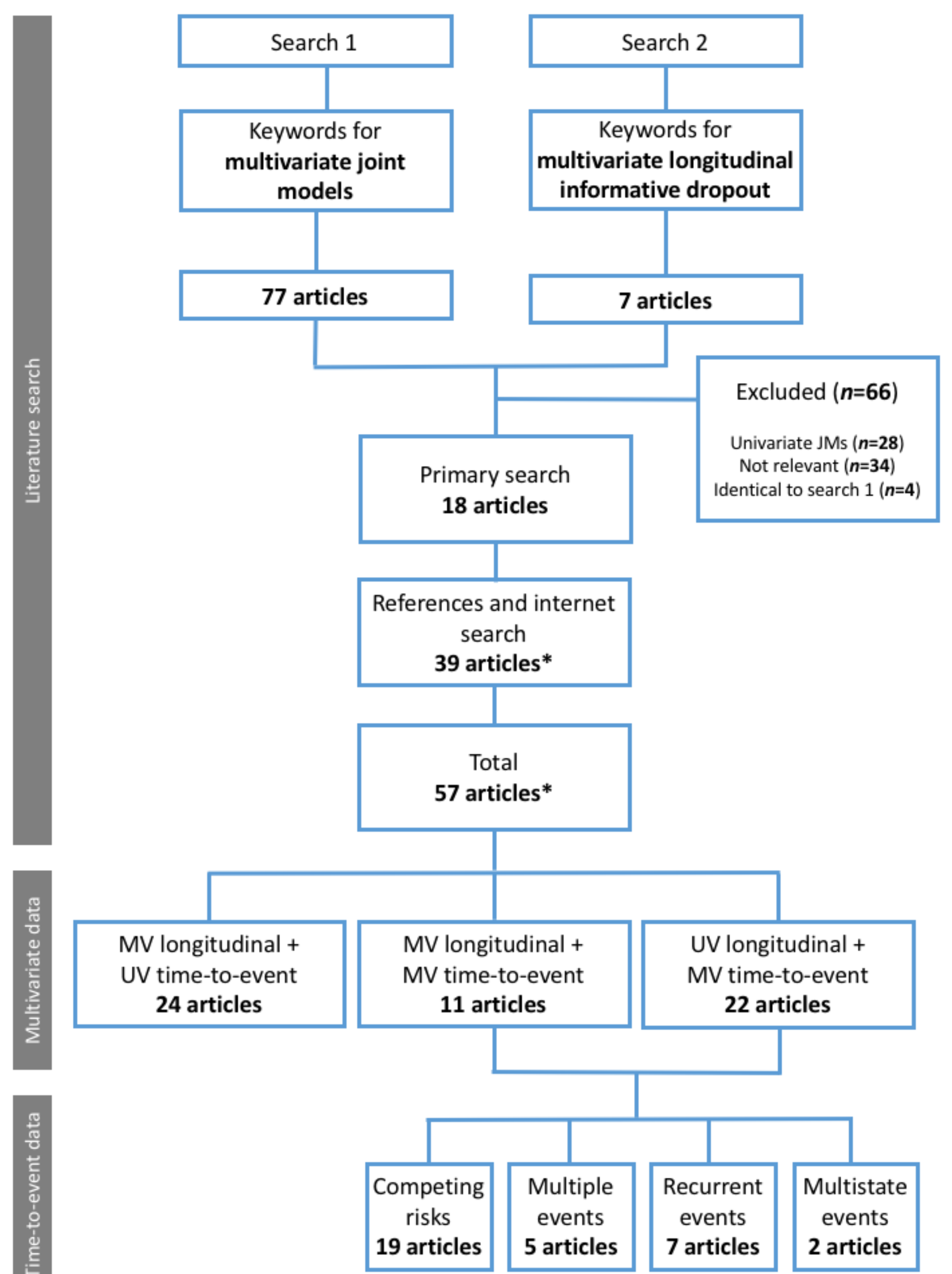
Introduction

- 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

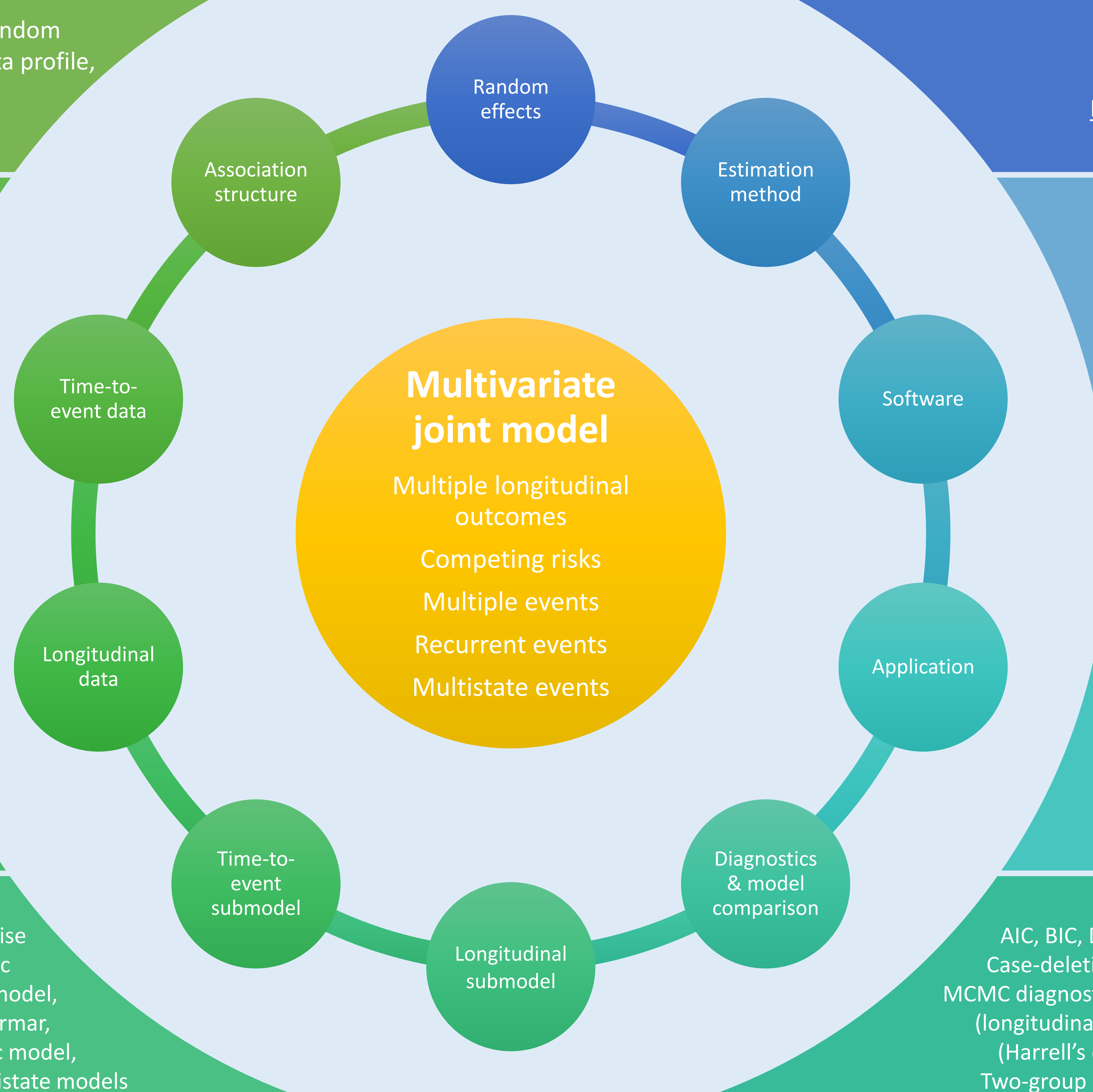
Continuous (incl. censored, bounded), Discrete, Ordinal, Combinations of types for multivariate models

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, M-splines, Weibull, Gompertz, restricted cubic spline), 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 test, MCMC diagnostics, Multivariate L -measure, Residual analyses (longitudinal, time-to-event), Predictive ability assessment (Harrell's C -statistic, dynamic AUC, dynamic Brier score), Two-group comparison tests, Measures of relative benefit

