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Multiple imputation of systematically missing predictors in an individual participant data meta-analysis

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Prediction models

Aim to predict…

- presence of a certain outcome (**diagnosis**)
- future occurrence of a certain outcome (**prognosis**)

Are based on…

- Individual characteristics
- Signs and symptoms
- More invasive or costly measures (e.g. imaging)

Are developed from…

- A set with individual participant data (IPD)
- Increasingly: multiple individual participant datasets
  Individual participant data meta-analysis (**IPD-MA**)

IPD meta-analysis

Between-study heterogeneity

- Differences in outcome prevalence/incidence
- Differences in predictor-outcome associations
- Should be avoided/mitigated in prediction models!!
- Missing data: impute datasets separately
- Problematic when some predictors are not measured in each individual dataset
  - Exclusion of entire studies or missing predictors
  - Use of imputation strategies ignoring heterogeneity

Imputation strategies are needed to account for systematically missing data in an IPD-MA

Imputation of continuous systematically missing predictors

Previously, *Resche-Rigon* et al. developed a multiple imputation approach that[1]:

- Is based on MICE
- Imputes systematically missing continuous predictors
- Adopts linear mixed effect model with random intercept term and slopes
- Relies on standard error around estimated between-study covariance parameters

Although promising, this approach is problematic for non-continuous predictors.

[1] Resche-Rigon M et al. Multiple imputation for handling systematically missing confounders in meta-analysis of individual participant data. Stat Med. 2013 Dec 10;32(28):4890-905.

Imputation of systematically missing predictors

- Standard errors of between-study covariance parameters are unreliable:
  - Likelihood of non-linear mixed effects models often lack a closed-form expression -> second-order derivatives become unreliable
  - Standard errors tend to be heavily skewed (even if log-transformed)
- Standard errors of between-study covariance parameters are not always reported (e.g. lme4)

Imputation of non-continuous systematically missing predictors

- MICE procedure (assuming MAR)
- Generalized linear mixed effect model with
  - Fixed effects parameters ($\boldsymbol{\gamma}$)
  - Between-study covariance parameters ($\boldsymbol{\psi}$)
  - Dispersion parameter(s) ($\boldsymbol{\sigma}^2$)
    (only for imputation of continuous predictors)
- Diffuse prior distributions for $\boldsymbol{\gamma}$
- Prior distribution of $\boldsymbol{\sigma}^2$ with density proportional to σ^{-2}
- Reference prior for $\boldsymbol{\psi}^{-1}$

The imputation procedure

Let M = number of studies where *x* is observed

1. Use MLE to estimate **γ**, **ψ** and $\boldsymbol{\sigma}^2$ in studies where x is observed
2. Draw **γ*** from MVN(**γ**, var(**γ**))
3. Obtain random effects **b** and calculate $\Lambda = \text{sum}(\mathbf{b^* b}^T)$
4. Draw $\boldsymbol{\psi}^{*-1}$ from a Wishart distribution with df=M and scale matrix Λ^{-1}
5. For studies where *x* is missing: draw **b*** from MVN(0,**ψ***)
6. For binary *x*: draw *x** using $\text{logit}^{-1}(z\boldsymbol{\gamma}^* + zb^*)$
7. For continuous *x*:
   draw $\boldsymbol{\sigma}^{*2}$ using σ^2 (based on X^2 distribution)
   draw $x^* = z\boldsymbol{\gamma}^* + zb^* + \varepsilon^*$ where $\varepsilon^* \sim N(0, \boldsymbol{\sigma}^{*2})$

Empirical example

Diagnosis of deep vein thrombosis (DVT) I patients with a suspected DVT

- IPD meta-analysis of 13 studies (N=10,002)
- 11 predictors measured in all studies
- 4 (binary) predictors systematically missing
  - Results D-dimer test (***ddimmd***)
  - Family history of thrombofilia (*coag*)
  - Leg trauma presence (***notraum***)
  - Use of oral contraceptives (***oachst***)
- Estimation of coefficients *Oudega* model (8 predictors + intercept term)

Methods

- Complete case analysis (**CCA**)
  exclude studies with missing predictor

- Traditional multiple imputation (**TMI**)
  imputation model ignoring between-study heterogeneity

- Multilevel multiple imputation (**MLMI**)
  imputation model accounting for between-study heterogeneity

Empirical example results

Method		CCA	TMI	MLMI
(intercept)	β	-4.96	-5.00	-4.42
	SE(β)	0.24	0.21	0.28
	τ	0.29	0.46	0.77
(…)				
ddimd	β	2.68	2.69	2.06
	SE(β)	0.18	0.15	0.34
	τ	0.17	0.26	1.07
notraum	β	0.53	0.54	0.40
	SE(β)	0.12	0.11	0.13
	τ	0.00	0.03	0.18

CCA = complete case analysis
TMI = traditional multiple imputation
MLMI = multilevel multiple imputation

Empirical example results

- Results CCA
  - Low degree of between-study heterogeneity
  - Solely based on Dutch studies
  - Poor transportability: MCAR not plausible (remaining studies are from different countries)
- Results TMI
  - Lowest standard errors
  - Medium levels of between-study heterogeneity
- Results MLMI
  - Largest standard errors
  - Largest degree of between-study heterogeneity

Simulation study

- Based on DVT case study, but using 2 predictors that were measured in all studies
- Introduction of systematically missing predictors according to MCAR

Results (not shown)

- Fixed effect estimates similar for all methods
  - Problematic coverage for TMI and CCA
- Substantial differences for between-study heterogeneity
  - Downward bias for CCA and TMI
  - MLMI sometimes yield extreme estimates when few studies were available

Discussion

- CCA
  - Underestimates actual degree of heterogeneity
  - Problematic when MCAR not justified
  - Problematic when multiple predictors are missing, and almost all studies need to be excluded
- TMI
  - Underestimates actual degree of heterogeneity
- MLMI
  - Optimal coverage (predictor effects)
  - Lowest bias (between-study heterogeneity)
  - Possible issues: convergence & model complexity

Discussion

CCA and TMI problematic during

- model development
  - Cannot properly identify homogeneous predictors
  - Detrimental selection of important predictors
- Model validation
  - Mask between-study heterogeneity, and therefore…
  - show overoptimistic model performance

MLMI recommended to avoid bias in heterogeneity parameters and improve insight into potential model generalizability