Comparison of multiple imputation methods for systematically and sporadically missing multilevel data

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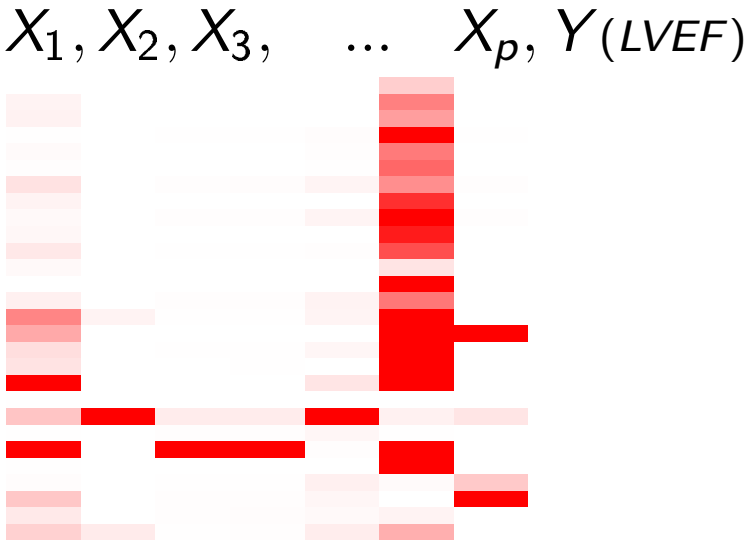
MODAL Seminar, November 22th, Lille

Motivation: GREAT data (Great Network, 2013)

- Risk factors associated with short-term mortality in acute heart failure
- 28 observational cohorts, 11685 patients, 2 **binary** and 8 **continuous** variables (patient characteristics and potential risk factors)
- sporadically and systematically **missing data**



Aim: explain the relationship between biomarkers (BNP, AFIB,...) and the left ventricular ejection fraction (LVEF)

$$y_{ik} = \mathbf{x}_{ik}\beta + \mathbf{z}_{ik}b_k + \varepsilon_{ik} \quad b_k \sim \mathcal{N}(0, \Psi) \qquad \varepsilon_{ik} \sim \mathcal{N}\left(0, \sigma^2\right)$$

$\hat{\beta}$ **and associated variability** $var\left(\widehat{\beta}\right)$

Methods to handle missing values

Missing data are often assumed to be missing at random (MAR)

Ad-hoc methods

- **Complete-case analysis**
  - → generally leads to biased estimates
  - → increases standard errors

- **Single imputation**
  - → leads to unbiased estimates
  - → standard errors are downwardly biased

Methods to handle missing values

Relevant methods

- **Likelihood approaches**
  - Frequentist framework: EM algorithm
  - Bayesian framework: Data Augmentation

  → leads to unbiased estimates
  → specific to the analysis model
  → not always feasible

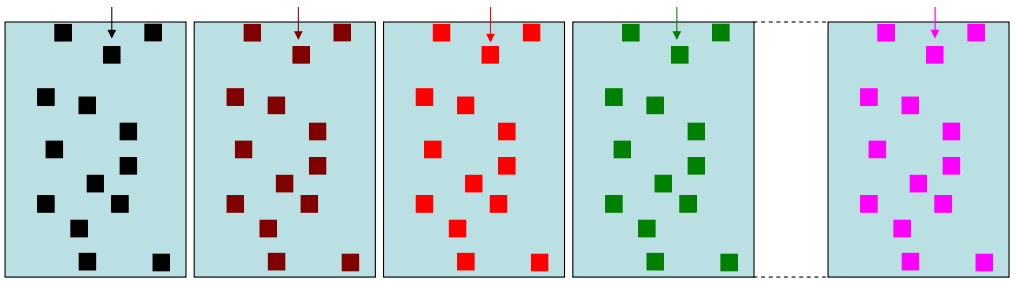
- **Multiple imputation**

  → leads to unbiased estimates
  → can be used for several analysis models

Multiple imputation (Rubin, 1987)

1. Generate a set of M parameters θ_m of an **imputation model** to generate M plausible imputed data sets

$$P\left(X^{miss}|X^{obs},\theta_1\right) \quad \ldots \quad \ldots \quad \ldots \quad P\left(X^{miss}|X^{obs},\theta_M\right)$$



2. Fit the **analysis model** on each imputed data set: $\hat{\beta}_m, \widehat{\text{Var}}\left(\hat{\beta}_m\right)$

3. Combine the results: $\hat{\beta} = \frac{1}{M}\sum_{m=1}^{M}\hat{\beta}_m$

$$T = \frac{1}{M}\sum_{m=1}^{M}\widehat{\text{Var}}\left(\hat{\beta}_m\right) + \left(1+\frac{1}{M}\right)\frac{1}{M-1}\sum_{m=1}^{M}\left(\hat{\beta}_m - \hat{\beta}\right)^2$$

$\Rightarrow$ **Provide estimation of the parameters and of their variability**

MI for multilevel data

Two standard ways to perform MI

- **Fully conditional specification** (FCS, MICE): a conditional imputation model for each variable
- **Joint modelling** (JM): a joint imputation model for all variables

The imputation model (joint or conditional) needs to be in line with the data

- need to account for the **heterogeneity** between clusters
- need to account for the **types** of data (continuous and binary)

MI for multilevel data

Type and name	Handles missing data:			Coded in R
	Sporadic?	Systematic?	in binary variable?	
JM-Pan	yes	yes	no	yes, (Pan)
JM-REALCOM	yes	yes	yes	no
JM-jomo	**yes**	**yes**	**yes**	**yes, (jomo)**
JM-Mplus	yes	yes	yes	no
FCS-2lnorm	yes	no	no	yes, (mice)
FCS-1stage	**yes using variant**	**yes**	**yes**	**yes**
FCS-2stage	**yes**	**yes**	**yes using variant**	**yes**

Outline

Continuous variables

Heteroscedastic random effect model as **imputation model**

$$\begin{aligned} \mathbf{y}_{ik} &= \mathbf{x}_{ik}\beta + \mathbf{z}_{ik}b_k + \varepsilon_{ik} \\ b_k &\sim \mathcal{N}(0, \Psi) \\ \varepsilon_{ik} &\sim \mathcal{N}(0, \Sigma_k) \end{aligned}$$

Multiple imputation under this model

1. generating M sets of parameters $\theta_m = \left(\beta^m, \Psi^m, (\Sigma_k^m)_{1\leq k\leq K}\right)$
   - $\rightarrow$ **Bayesian** formulation: draw θ_m from its posterior distribution
   - $\rightarrow$ **asymptotic** method: estimate θ_m, draw θ_m from the asymptotic distribution of the estimator
2. imputing the data according each set θ_m
   - draw $b_k^m | \mathbf{y}_k^{obs}, \theta_m$
   - draw $\mathbf{y}_{ik}^{miss} | \theta_m, b_k^m$

Continuous variables

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Specific issues

1. how to generate Σ_k without $\mathbf{y}_{ik}$? (systematic)
2. how to draw b_k^m without $\mathbf{y}_{ik}$ (systematic) or given $\mathbf{y}_{ik}$ (sporadic)?

FCS-1stage (Jolani et al., 2015)

Conditional imputation models

$$y_{ik} = \mathbf{x}_{ik}\beta + \mathbf{z}_{ik}b_k + \varepsilon_{ik} \quad b_k \sim \mathcal{N}(0, \Psi) \quad \varepsilon_{ik} \sim \mathcal{N}(0, \sigma^2)$$

For each incomplete variable

1. generate $\theta_m = (\beta_m, \Psi_m, \sigma^2{}_m) \qquad 1 \leq m \leq M$
   - prior: non-informative (Jeffreys)
   - posterior distribution

$$\beta_m \sim \mathcal{N}\left(\widehat{\beta}, var\left(\widehat{\beta}\right)\right) \quad \Psi_m^{-1} \sim \mathcal{W}\left(K, \widehat{bb}^{\top}\right) \quad \sigma_m^2 \sim \text{Inv-}\Gamma\left(\tfrac{n-p}{2}, \tfrac{(n-p)\widehat{\sigma^2}}{2}\right)$$

$\rightarrow$ **requires REML estimate**

2. impute in each cluster k with **systematically missing data**
   - draw $b_k \sim \mathcal{N}(0, \Psi_m)$
   - impute data according to the imputation model

FCS-1stage (Jolani et al., 2015)

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$\rightarrow$ **requires REML estimate**

2. impute in each cluster k with **sporadically missing data**
   - draw $b_k \sim \mathcal{N}\left(\mu_{b_k|y_k}, \Psi_{b_k|y_k}\right)$
   - impute data according to the imputation model

FCS-2stage (Resche-Rigon and White, 2016)

Conditional imputation models

$$y_{ik} = \mathbf{x}_{ik}\left(\beta + b_k\right) + \varepsilon_{ik} \qquad b_k \sim \mathcal{N}\left(0, \Psi\right) \qquad \varepsilon_{ik} \sim \mathcal{N}\left(0, \sigma_k^2\right)$$

$\rightarrow$ **the same imputation model, with heteroscedastic assumption**

1. generate $\theta_m = \left(\beta_m, \Psi_m, \left(\sigma_1^2, \ldots, \sigma_K^2\right)_m\right)$
   - estimate θ and var $\left(\widehat{\theta}\right)$ with **a two-stage estimator**
   - draw θ_m from the **asymptotic** distribution of the estimator with expectation $\widehat{\theta}$ and variance $\widehat{\text{var}}\left(\widehat{\theta}\right)$
2. impute in each cluster k

FCS-2stage (Resche-Rigon and White, 2016)

1. generate $\theta_m = \left(\beta_m, \Psi_m, \left(\sigma_1^2, \ldots, \sigma_K^2\right)_m\right)$

   stage 1 fit a linear model to each observed cluster

   $$\widehat{\beta}_k = \left(\mathbf{X}_k^\top \mathbf{X}_k\right)^{-1} \mathbf{X}_k^\top \mathbf{y}_k$$

   stage 2 combine the estimates

$$\widehat{\beta}_k = (\beta + b_k) + \varepsilon'_k \quad b_k \sim \mathcal{N}(0, \Psi) \quad \varepsilon'_k \sim \mathcal{N}\left(0, var\left(\widehat{\beta}_k\right)\right)$$

Two estimators available: **REML** or **method of moments**

$\rightarrow \widehat{\Psi}$, $\widehat{\beta}$ and their associated (asymptotic) variances

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   stage 2 combine the estimates

$$\log \widehat{\sigma}_k = (log\ \sigma + s_k) + \varepsilon_k'' \quad s_k \sim \mathcal{N}(0, \Psi_s) \quad \varepsilon_k'' \sim \mathcal{N}(0, var(log\widehat{\sigma}_k))$$

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   → $log\widehat{\sigma}, \widehat{\Psi}_s$ and their associated (asymptotic) variances

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2. impute in each cluster k with **systematically missing data**
   - draw b_k **from their marginal distribution**
   - impute data according to the imputation model

FCS-2stage (Resche-Rigon and White, 2016)

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   Two estimators available: **REML** or **method of moments**

   $\rightarrow$ $log\widehat{\sigma}, \widehat{\Psi}_s$ and their associated (asymptotic) variances

   $\rightarrow$ $\widehat{\Psi}$, $\widehat{\beta}$ and their associated (asymptotic) variances

2. impute in each cluster k with **sporadically missing data**
   - draw b_k **conditionally to** $\widehat{\beta_k}$
   - impute data according to the imputation model

JM-jomo (Quartagno and Carpenter, 2016)

$$y_{ik} = \mathbf{x}_{ik}\beta + \mathbf{z}_{ik}b_k + \varepsilon_{ik} \qquad b_k \sim \mathcal{N}(0, \Psi) \qquad \varepsilon_{ik} \sim \mathcal{N}(0, \Sigma_k)$$

1. Bayesian formulation to generate $\theta_m = (\beta_m, \Psi_m, \Sigma_m)_{1 \leq m \leq M}$
   - (informative) prior:
     $\beta \propto 1, \quad \Psi^{-1} \sim W(\nu_1, \Lambda_1), \quad \Sigma_k^{-1} | \nu_2, \Lambda_2 \sim W(\nu_2, \Lambda_2)$
   - posterior: unknown explicitly **but...**
     - most of conditional posterior distributions are known

       $\rightarrow$ **Gibbs sampler**
     - do not require REML estimate
     - unknown conditional distributions can be simulated by MCMC

2. Imputation (given by step 1)

Binary variables

- **FCS-1stage** (Jolani et al., 2015)
  - fit a logistic model with mixed effect to all clusters

  → sporadically missing values not handled

- **FCS-2stage** (Resche-Rigon and White, 2016)
  - fit a logistic model with fixed effect to each cluster
  - combine estimates using a meta-analysis

  → large clusters are required

- **JM-jomo** (Quartagno and Carpenter, 2016)
  - probit link: outcomes are latent normal variables, variance for errors are fixed to 1
  - draw latent normal variables
  - derive categories

  → more time consuming

Summary

method	Bayesian / asymptotic	prior for covariance matrices	heteroscedasticity assumption for errors	binary variables
FCS-1stage	Bayesian	Jeffrey	no	probit link
FCS-2tage	asymptotic		yes	logistic link
JM-jomo	Bayesian	Wishart	yes	logistic link

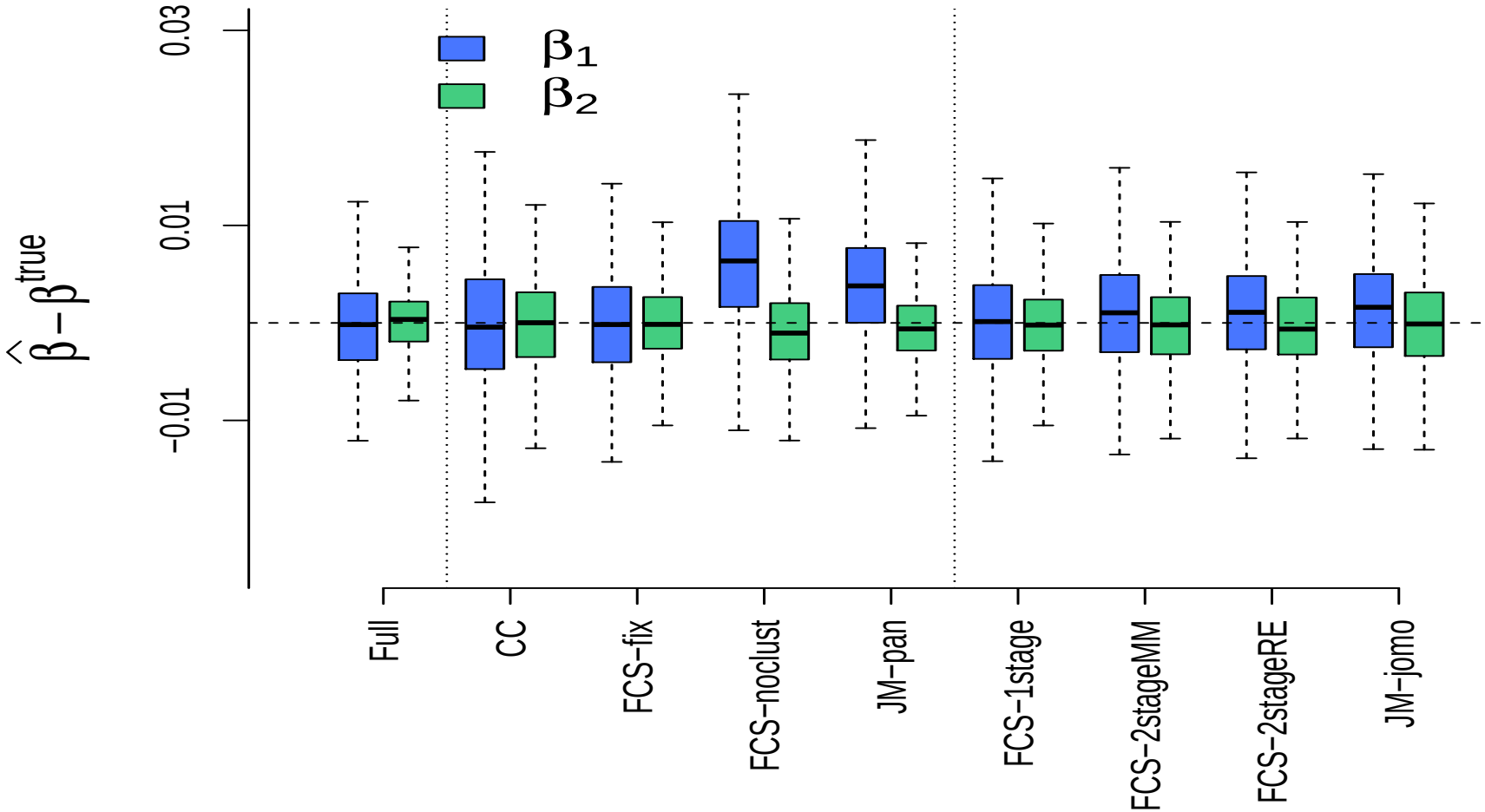
Simulation design

- **Data generation**: 500 incomplete data sets are independently simulated ($n = 11685, K = 28, 18 \leq n_k \leq 1834$)
  - $y_{ik} = \beta^{0} + \beta^{1}\mathbf{x}_{ik}^{(1)} + \beta^{2}\mathbf{x}_{ik}^{(2)} + b_k^0 + b_k^1\mathbf{x}_{ik}^{(1)} + \varepsilon_{ik}$ with $\beta = (.72, -.11, .03)$, $\Psi = \begin{bmatrix} .0077 & .0015 \\ .0015 & .0004 \end{bmatrix}$, $\sigma = .15$
  - $(\mu_k, \nu_k, \xi_k) \sim \mathcal{N}\left(0, \begin{bmatrix} .12 & .001 & .001 \\ .001 & .12 & .001 \\ .001 & .001 & .12 \end{bmatrix}\right)$
  - $\mathbf{x}_{ik}^{(1)} : \mathcal{N}(2.9 + \mu_k, .36)$
  - $\mathbf{x}_{ik}^{(2)} : logit\left(P\left(\mathbf{x}_{ik}^{(2)} = 1\right)\right) = 4.2 + \nu_k$
  - $\mathbf{x}_{ik}^{(3)}$: $\mathcal{N}(2.9 + \xi_k, .36)$
  - add missing values on $\mathbf{x}^{(1)}, \mathbf{x}^{(2)}$ with $\pi_{syst} = .25$ and $\pi_{spor} = .25$

Simulation design

- **Methods**
  - JM-jomo, FCS-1stage, FCS-2stage
  - Full, CC, FCS-fix, FCS-noclust, JM-pan
  - $M = 5$ imputed arrays
- **Estimands**: β and $var\left(\widehat{\beta}\right)$
- **Criteria**: bias, rmse, variance estimate, coverage

Base-case configuration



Base-case configuration

Method	$\sqrt{\widehat{var}\left(\widehat{\beta}\right)}$		$\sqrt{var\left(\widehat{\beta}\right)}$		95% Cover		Time (min)
	β_1	β_2	β_1	β_2	β_1	β_2	
Full	0.0047	0.0029	0.0048	0.0030	93.8	94.2	
CC	0.0070	0.0053	0.0071	0.0053	92.2	94.4	
FCS-fix	0.0043	0.0043	0.0058	0.0042	**85.6**	94.6	0.732
FCS-noclust	0.0041	0.0043	0.0067	0.0046	**59.6**	92.4	0.601
JM-pan	0.0048	0.0042	0.0058	0.0039	**83.0**	95.2	0.006
FCS-1stage	0.0049	0.0046	0.0056	0.0043	**90.4**	96.8	63.43
FCS-2stagemm	0.0059	0.0054	0.0058	0.0044	95.0	97.0	0.538
FCS-2stagere	0.0059	0.0049	0.0058	0.0044	95.0	96.2	1.304
JM-jomo	0.0066	0.0069	0.0057	0.0050	96.8	**97.6**	6.739

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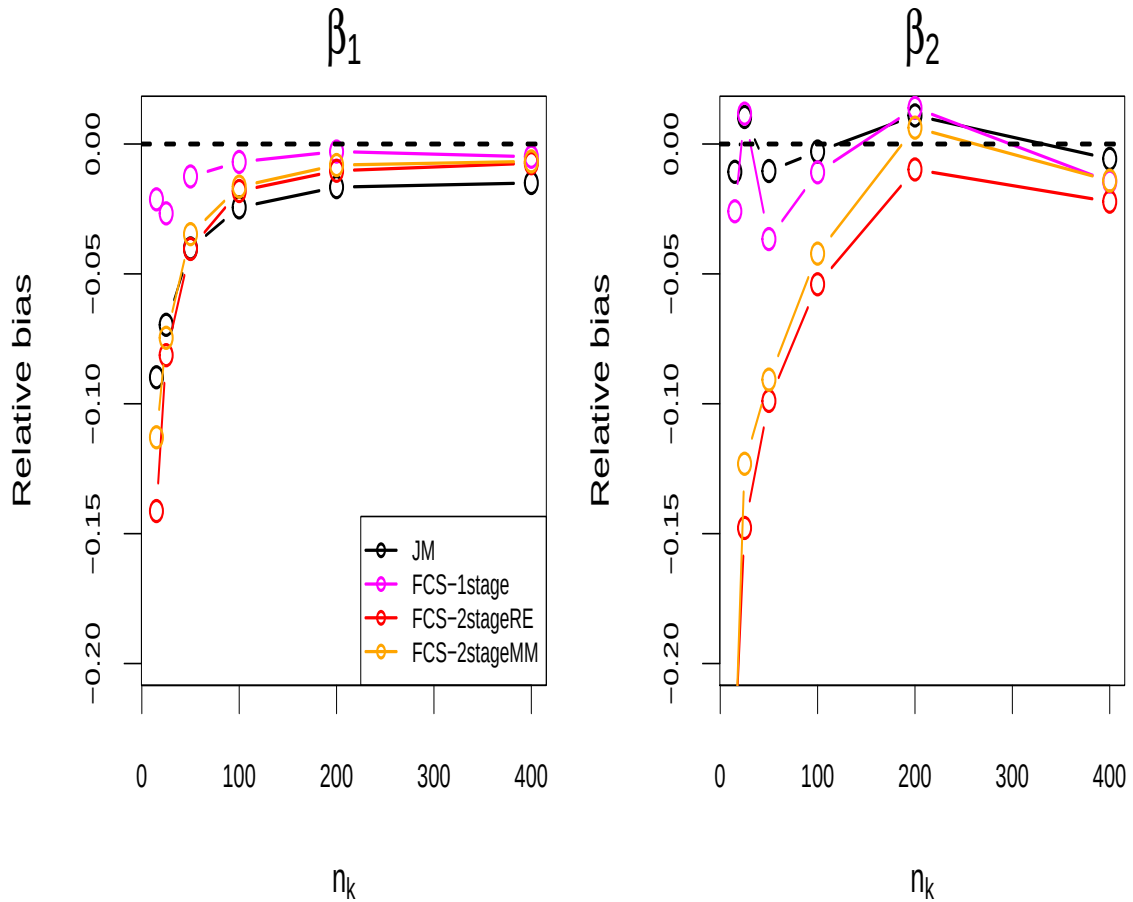
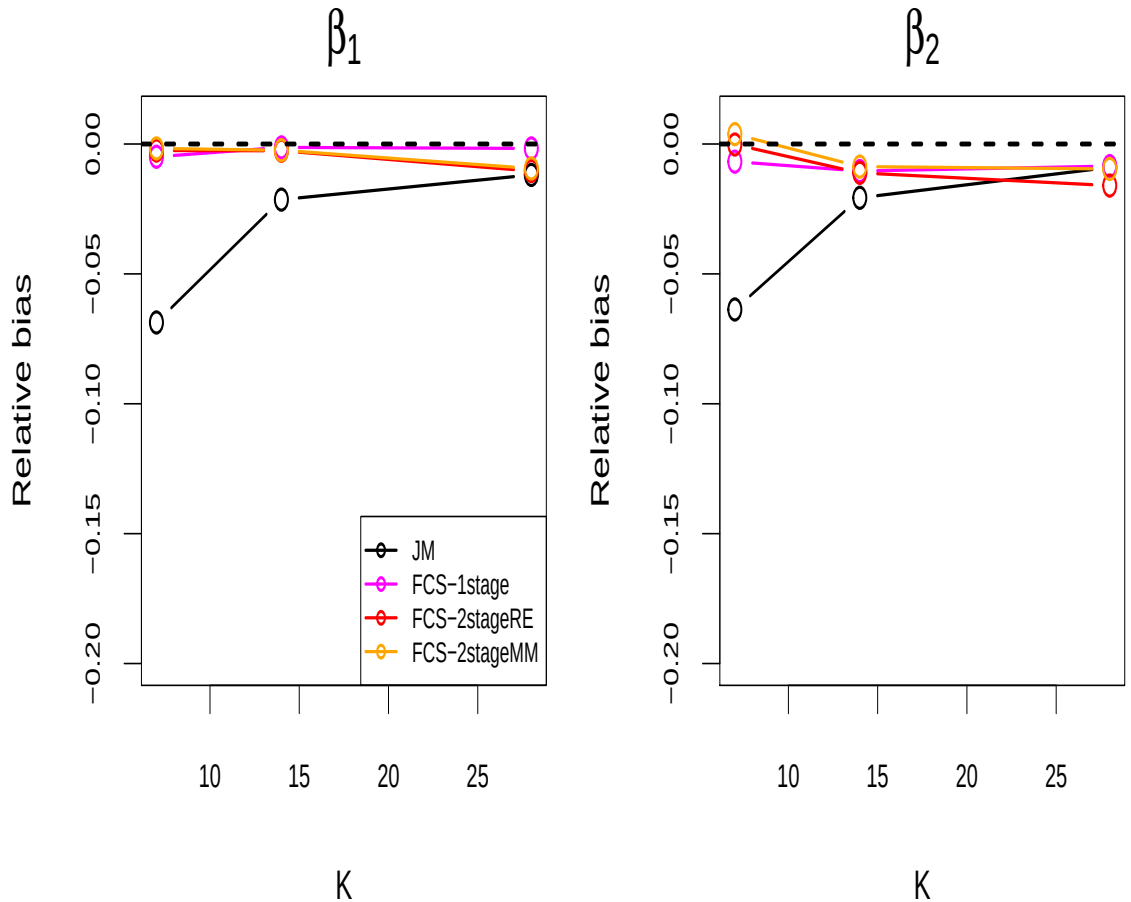
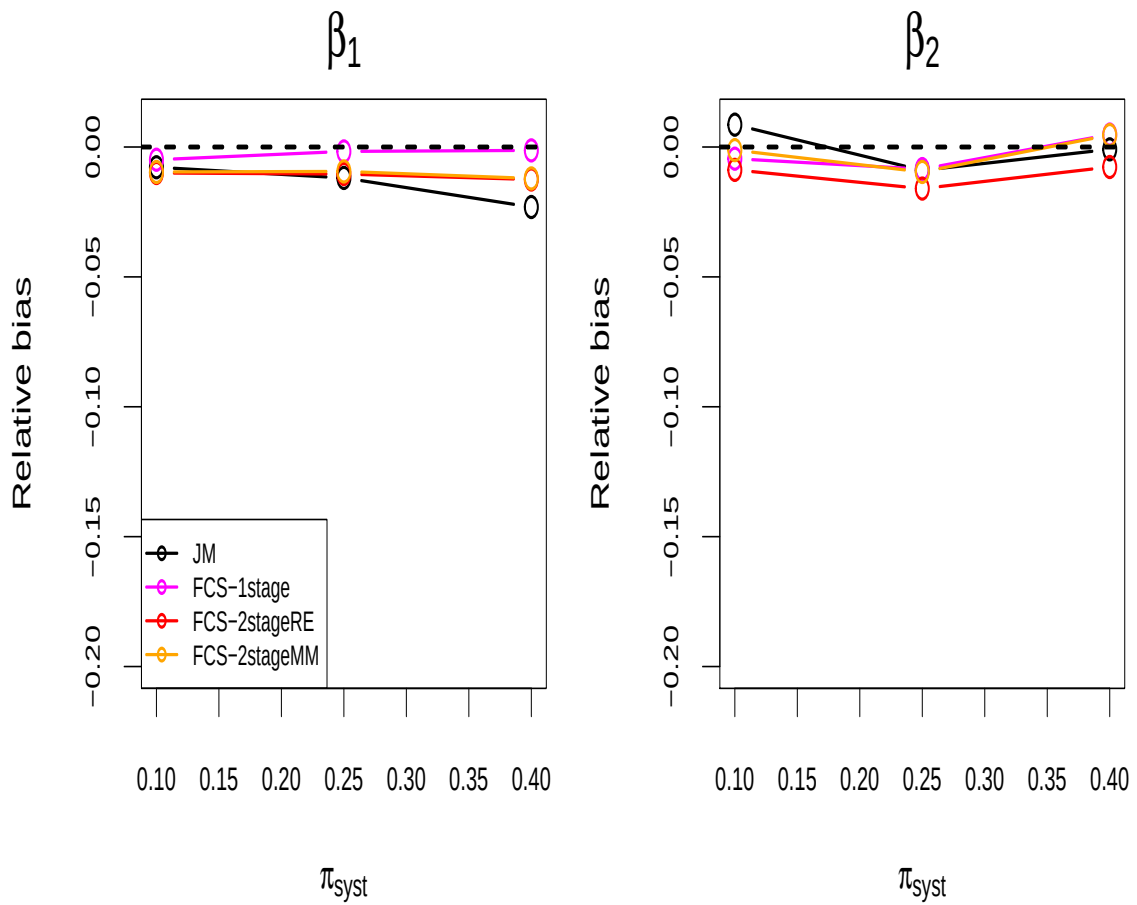
Robustness to the cluster size: point estimate



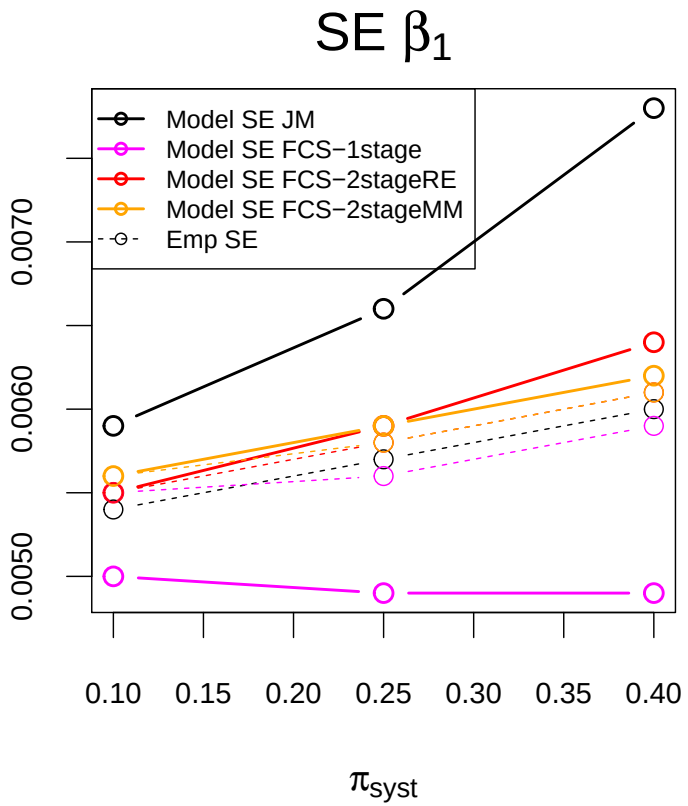
Robustness to the number of clusters: point estimate

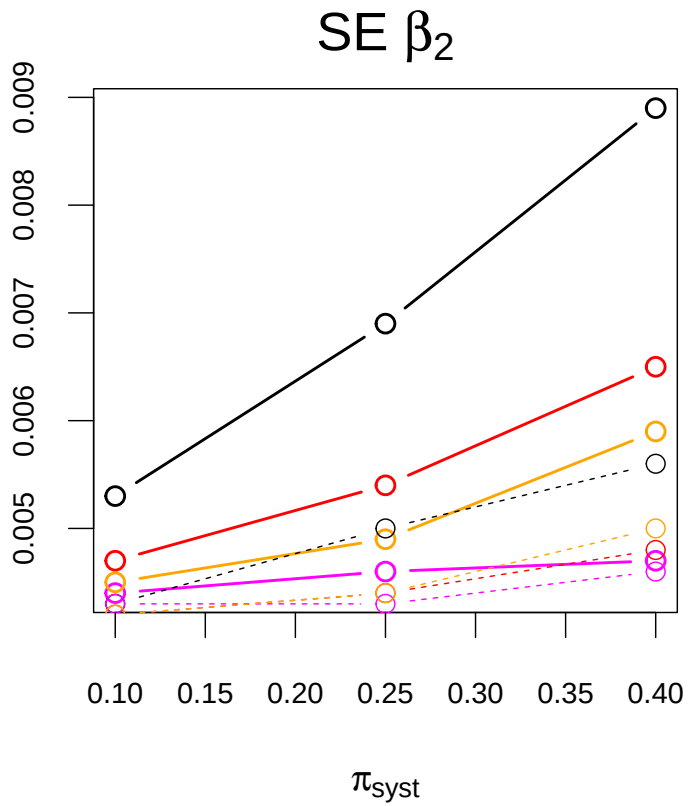


Robustness to π_{syst}: point estimate

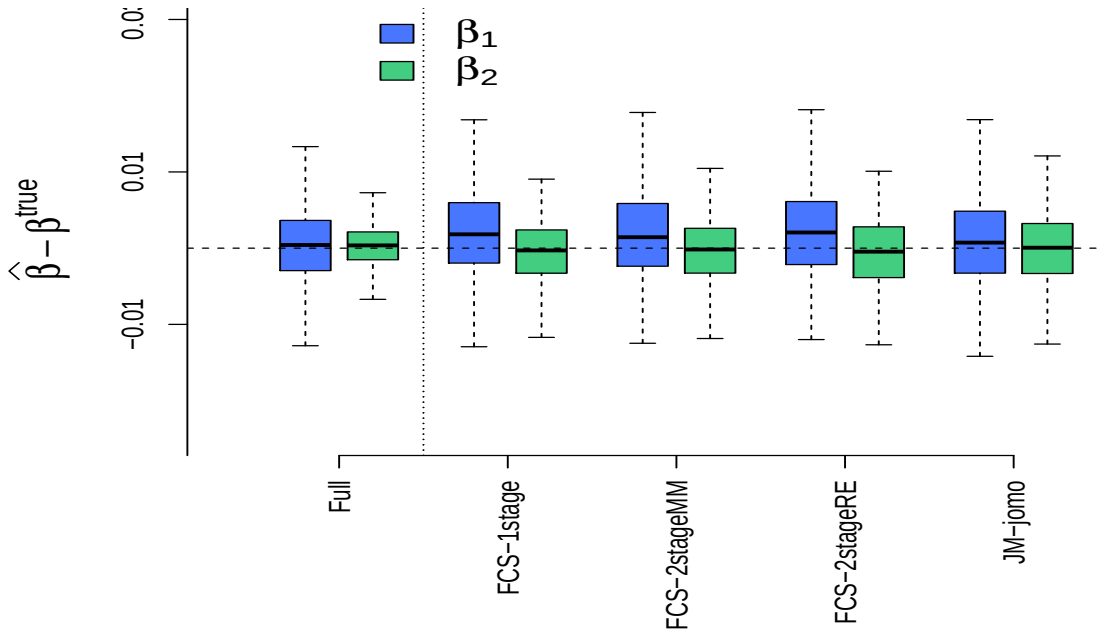


Robustness to π_{syst}: variance estimate





Robustness to the type of imputed variables



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FCS-2stagemm	0.0063	0.0051	0.0060	0.0044	94.0	96.2	0.652
FCS-2stagere	0.0056	0.0045	0.0061	0.0044	**90.4**	95.0	1.572
JM-jomo	0.0074	0.0072	0.0064	0.0047	97.0	98.6	5.612

Other configurations

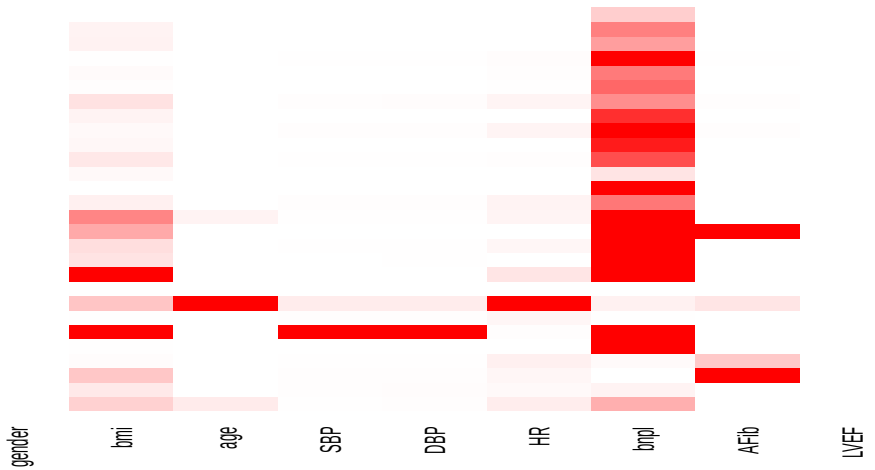
Methods have similar performances when

- the missing data mechanism is MAR
- the outcome of the analysis model is binary
- the variance of random effects is higher or smaller
- binary variables are generated using a probit link

Appplication to GREAT data

Explain the relationship between biomarkers easily measurable (BNP, AFIB) and the left ventricular ejection fraction

- **y**=LVEF,
  X = BNP, AFib
- MI using $M = 20$ imputed arrays



		CC	JM	FCS-1stage	FCS-2stagere	FCS-2stagemm
β_{BNP}	Est	**-0.1132**	**-0.0891**	**-0.0902**	**-0.0854**	**-0.1009**
	ModelSE	0.0108	0.0078	0.0153	0.0099	0.0112
β_{AFIB}	Est	0.0268	0.0216	0.0251	0.0215	0.0273
	ModelSE	0.0071	0.0046	0.0047	0.0040	0.0045
Time			94.0	18609.3	361.3	31.8

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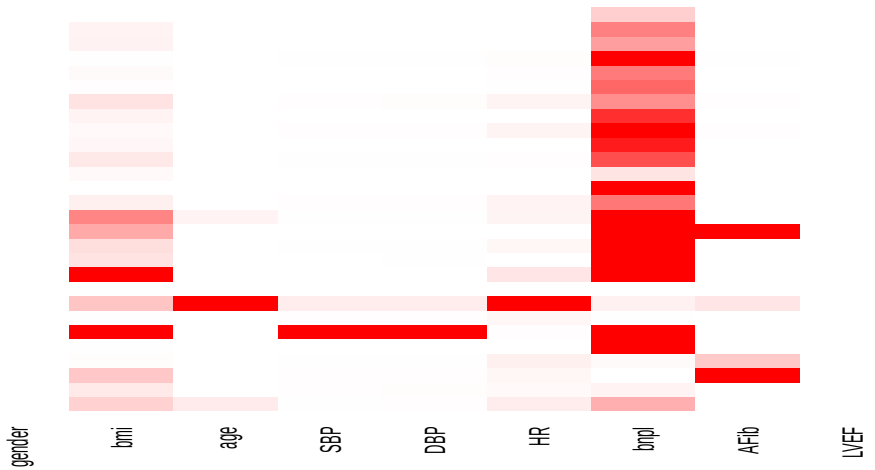

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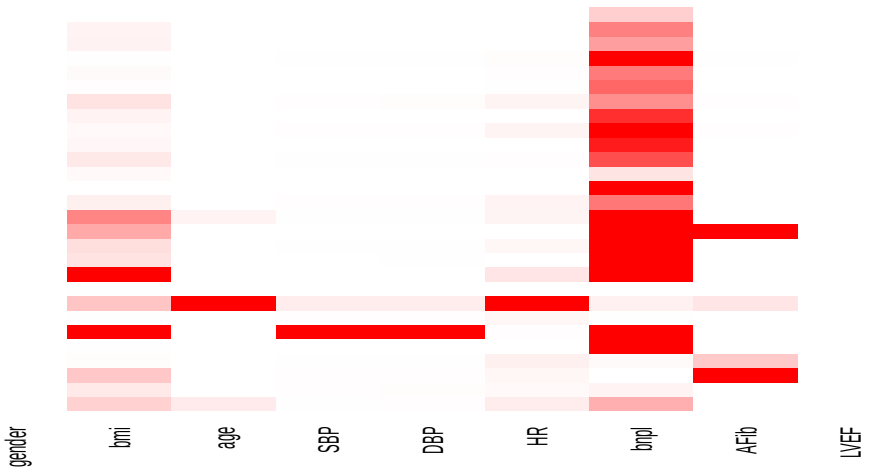
Appplication to GREAT data

Explain the relationship between biomarkers easily measurable (BNP, AFIB) and the left ventricular ejection fraction

- **y**=LVEF,
  X = BNP, AFib
- MI using $M = 20$ imputed arrays



		CC	JM	FCS-1stage	FCS-2stagere	FCS-2stagemm
β_{BNP}	Est	-0.1132	-0.0891	-0.0902	-0.0854	-0.1009
	ModelSE	0.0108	0.0078	**0.0153**	0.0099	**0.0112**
β_{AFIB}	Est	0.0268	0.0216	0.0251	0.0215	0.0273
	ModelSE	0.0071	0.0046	0.0047	0.0040	0.0045
Time			94.0	18609.3	361.3	31.8

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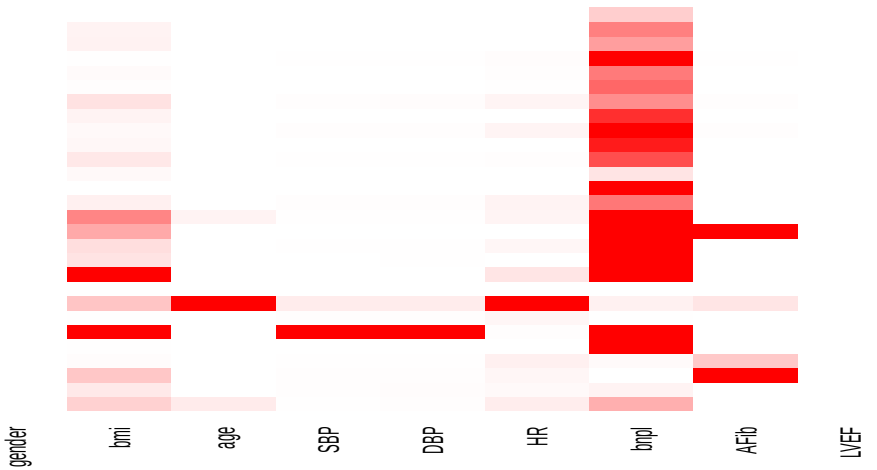

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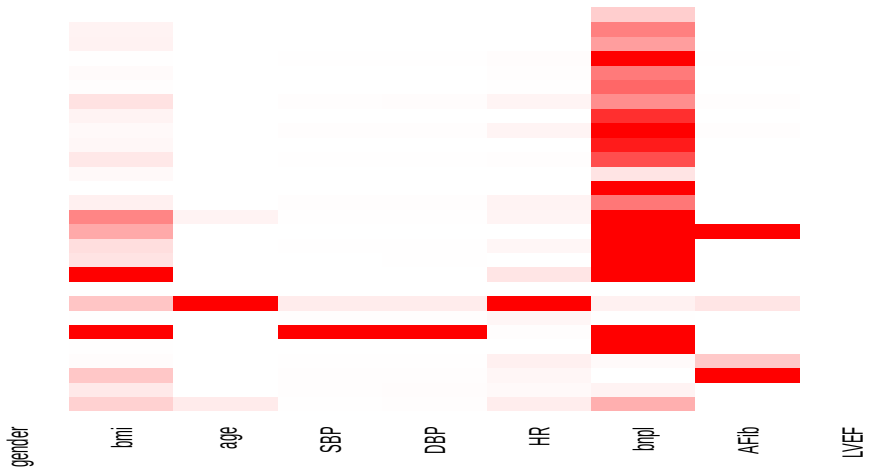

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Conclusion

An overview of MI methods for multilevel data

- FCS-1stage, FSC-2stage and JM-jomo all appear to perform well
- Outperform had-hoc methods

FCS-2stage	• MM version provides a quick way to obtain first results • for large clusters
FCS-1stage	• relevant with few systematically missing values • time consuming with binary variables
JM-jomo	• advised with a lot of incomplete categorical variables • be careful with few clusters

Methods are implemented in R

- mice package for FCS methods
- jomo package for JM-jomo

Limits and perspectives

Limits

- congeniality

$$y_{ik} = \beta^0 + \beta^1 \mathbf{x}_{ik}^{(1)} + \beta^2 \mathbf{x}_{ik}^{(2)} + b_k^0 + b_k^1 \mathbf{x}_{ik}^{(1)} + \varepsilon_{ik}$$

- convergence of the FCS approaches
- computational time

Perspectives

- correction for FCS-2stage with small clusters?
- handle logistic link for FCS-1stage?

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