

Multiple imputation for multilevel data with continuous and binary variables

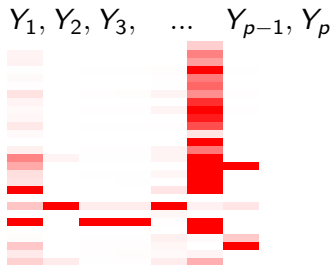
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Motivation: GREAT data (GREAT Network, 2013)

- 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)

$$y_{ik}^{LVEF} = \beta^0 + \beta^1 y_{ik}^{BNP} + \beta^2 y_{ik}^{AFIB} + b_k^0 + b_k^1 y_{ik}^{BNP} + \varepsilon_{ik}$$

$$b_k \sim \mathcal{N}(0, \Psi) \quad \varepsilon_{ik} \sim \mathcal{N}(0, \sigma^2)$$

$\hat{\beta}$ and associated variability $var(\hat{\beta})$

Outline

① Introduction

Handling missing values

Multiple imputation

② MI methods for multilevel data

Continuous variables

Binary variables

③ Comparisons

Simulations

Application

④ Conclusion

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

→ not always feasible

→ specific to the **analysis model**
- **Multiple imputation**

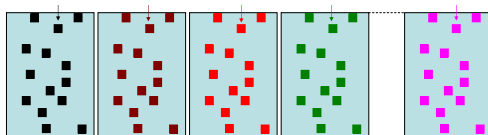
→ leads to unbiased estimates

→ can be used for several **analysis models**

Multiple imputation (Rubin, 1987)

- 1 Generate a set of M parameters $(\theta_m)_{1 \leq m \leq M}$ of an **imputation model** to generate M plausible imputed data sets

$$P(Y^{miss} | Y^{obs}, \theta_1) \quad \dots \quad P(Y^{miss} | Y^{obs}, \theta_M)$$



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

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

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

⇒ **Provide estimation of the parameters and of their variability**

Imputation model 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

- account for the **heterogeneity** between clusters
- account for the **types** of variables (continuous and binary)
- be identifiable with **sporadically and systematically** missing values

MI for multilevel data

Method (type - name)	deal with missing values:				Coded in R
	Spor.?	Syst.?	continuous ?	binary?	
JM-pan	yes	yes	yes	no	yes
JM-REALCOM	yes	yes	yes	yes	no
JM-jomo	yes	yes	yes	yes	yes
JM-Mplus	yes	yes	yes	yes	no
JM-RCME	yes	yes	yes	no	no
FCS-pan	yes	yes	yes	no	yes
FCS-2lnorm	yes	no	yes	no	yes
FCS-GLM	yes*	yes	yes	yes	yes
FCS-2stage	yes	yes	yes	yes*	yes

* using variant reported in this work

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FCS-GLM (Jolani, 2017)

Conditional imputation models

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

For each incomplete variable

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

$$\sigma^2 | Y, b \sim \text{Inv-}\Gamma\left(\frac{n-p}{2}, \frac{(n-p)\widehat{\sigma}^2}{2}\right)$$

$$\beta | Y, b, \sigma^2 \sim \mathcal{N}(\widehat{\beta}, \widehat{\text{var}}(\widehat{\beta}))$$

$$\Psi^{-1} | Y, b \sim \mathcal{W}(K, \widehat{bb}^\top)$$

- 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-GLM (Jolani, 2017)

Conditional imputation models

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

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

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

Conditional imputation models

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

- generate $\theta_m = (\beta_m, \Psi_m, (\sigma_1^2, \dots, \sigma_K^2)_m)$
 - estimate θ and $\text{var}(\hat{\theta})$ with a **two-stage estimator**
 - fit $y_{ik} = \mathbf{z}_{ik}\beta_k + \varepsilon_{ik}$ to each cluster
 - combine the $\hat{\beta}_k$ (and $\hat{\sigma}_k^2$) with a random intercept model:
$$\hat{\beta}_k = (\beta + b_k) + \varepsilon'_k \quad b_k \sim \mathcal{N}(0, \Psi) \quad \varepsilon'_k \sim \mathcal{N}(0, \text{var}(\hat{\beta}_k))$$
 - draw θ_m from the **asymptotic** distribution of the estimator with expectation $\hat{\theta}$ and variance $\widehat{\text{var}}(\hat{\theta})$
- 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)

Conditional imputation models

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

- generate $\theta_m = (\beta_m, \Psi_m, (\sigma_1^2, \dots, \sigma_K^2)_m)$
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 - fit $y_{ik} = \mathbf{z}_{ik}\beta_k + \varepsilon_{ik}$ to each cluster
 - combine the $\hat{\beta}_k$ (and $\hat{\sigma}_k^2$) with a random intercept model:
$$\hat{\beta}_k = (\beta + b_k) + \varepsilon'_k \quad b_k \sim \mathcal{N}(0, \Psi) \quad \varepsilon'_k \sim \mathcal{N}(0, \text{var}(\hat{\beta}_k))$$
 - draw θ_m from the **asymptotic** distribution of the estimator with expectation $\hat{\theta}$ and variance $\widehat{\text{var}}(\hat{\theta})$
- impute in each cluster k with **sporadically missing data**
 - draw b_k **conditionally to** $\hat{\beta}_k$ from step 2
 - impute data according to the imputation model

JM-jomo (Quartagno and Carpenter, 2016a)

$$\mathbf{Y}_{ik} = \mathbf{z}_{ik}\beta + \mathbf{w}_{ik}b_k + \varepsilon_{ik} \quad b_k \sim \mathcal{N}(0, \Psi) \quad \varepsilon_{ik} \sim \mathcal{N}(0, \Sigma_k)$$

1 Bayesian formulation to generate

$$\theta_m = (\beta_m, \Psi_m, (\Sigma_1, \Sigma_2, \dots, \Sigma_K)_m)_{1 \leq m \leq M}$$

- (conjugate) prior:

$$\beta \propto \mathbf{1}, \quad \Psi^{-1} \sim W(\nu_1, \Lambda_1), \quad \Sigma_k^{-1} | \nu_2, \Lambda_2 \sim W(\nu_2, \Lambda_2)$$

- posterior: unknown explicitly **but...**
 - conditional posterior distributions are known without missing values \rightarrow **Gibbs sampler**
 - with missing values, alternate imputation and draw from the posterior (**Data augmentation**)

2 Imputation (given by step 1)

Binary variables

- **FCS-GLM** (Jolani et al., 2015)
 - fit a logistic model with mixed effect to all clusters
 - sporadically missing values not properly handled
- **FCS-2stage** (Resche-Rigon and White, 2016)
 - fit a logistic model with fixed effect to each cluster
 - combine estimates using a random intercept model
 - large clusters are required
- **JM-jomo** (Quartagno and Carpenter, 2016a)
 - probit link: outcomes are latent normal variables, variance for errors are fixed to 1
 - draw latent normal variables
 - derive categories
 - potentially more time consuming

Differences between MI methods

	Prior	heteroscedasticity link assumption	binary
FCS-GLM	Jeffrey	no	logit
FCS-2stage		yes	logit
JM-jomo	conjugate	yes	probit

- conjugate prior distributions are known to very informative in GLMM
- heteroscedastic assumption is more flexible
- logit link does not allow imputation of sporadically binary variables for FCS-GLM

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Simulation design: data generation

500 incomplete data sets are independently simulated

- a multilevel structure
- 4 variables (1 binary, 3 continuous)
- sporadically and systematically missing data
- parameters are tuned to mimic GREAT data

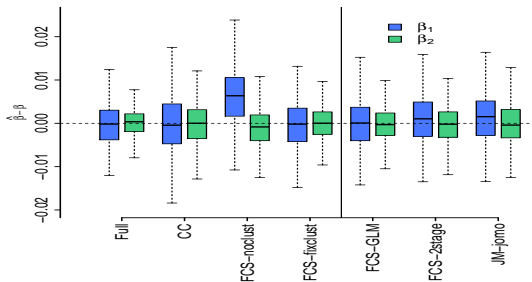
More precisely,

- $\mathbf{x}_{ik}^{(1)} : \mathcal{N}(2.9 + \mu_k, .36)$
- $\mathbf{x}_{ik}^{(2)} : \text{logit} \left(P \left(\mathbf{x}_{ik}^{(2)} = 1 \right) \right) = 4.2 + \nu_k \quad (\mu_k, \nu_k, \xi_k) \sim \mathcal{N} \left(0, \begin{bmatrix} .12 & .001 & .001 \\ .001 & .12 & .001 \\ .001 & .001 & .12 \end{bmatrix} \right)$
- $\mathbf{x}_{ik}^{(3)} : \mathcal{N}(2.9 + \xi_k, .36)$
- $y_{ik} = \beta^0 + \beta^1 \mathbf{x}_{ik}^{(1)} + \beta^2 \mathbf{x}_{ik}^{(2)} + b_k^0 + b_k^1 \mathbf{x}_{ik}^{(1)} + \varepsilon_{ik}$
with $\beta = (.72, -.11, .03)$, $\Psi = \begin{bmatrix} .0077 & .0015 \\ .0015 & .0004 \end{bmatrix}$, $\sigma = .15$
- add missing values on $\mathbf{x}^{(1)}, \mathbf{x}^{(2)}$ with $\pi_{\text{sys}} = .25$ and $\pi_{\text{spor}} = .25$

Simulation design: evaluation

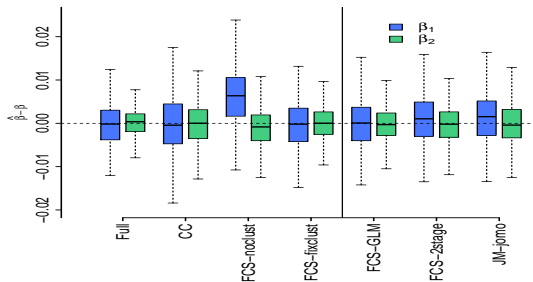
- **Methods**
 - JM-jomo, FCS-GLM, FCS-2stage
 - Full, CC, FCS-fixclust, FCS-noclust
 - $M = 5$ imputed arrays
- **Estimands:** β and $var(\hat{\beta})$
- **Criteria:** bias, rmse, variance estimate, coverage

Results for base-case configuration



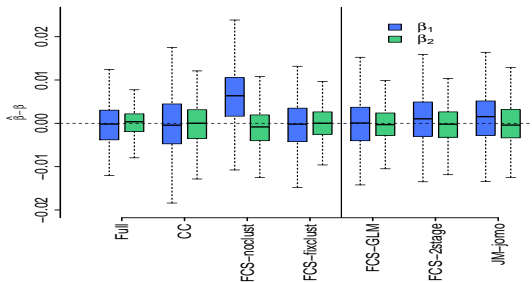
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	β_1	β_2	β_1	β_2	β_1	β_2	
Full	0.0047	0.0029	0.0048	0.0030	93.8	94.2	
CC	0.0070	0.0053	0.0071	0.0053	92.2	94.4	
FCS-noclust	0.0041	0.0043	0.0067	0.0045	58.2	92.0	0.9
FCS-fixclust	0.0043	0.0043	0.0058	0.0042	87.0	94.6	1.1
FCS-GLM	0.0047	0.0046	0.0057	0.0043	89.7	95.8	103.3
FCS-2stage	0.0059	0.0049	0.0058	0.0044	95.0	96.2	0.9
JM-jomo	0.0066	0.0069	0.0056	0.0049	98.4	97.6	7.8

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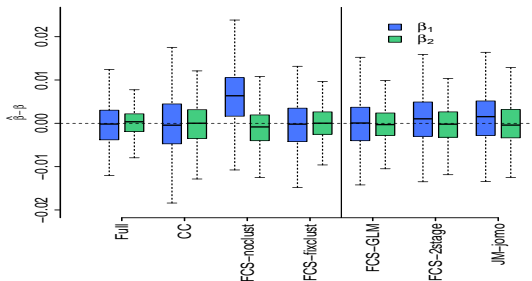
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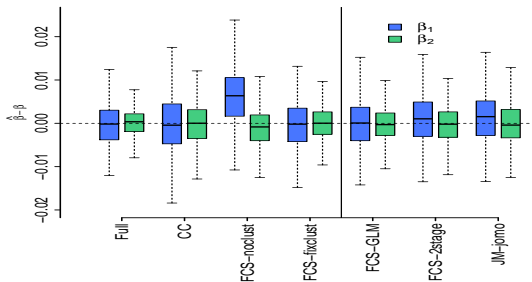
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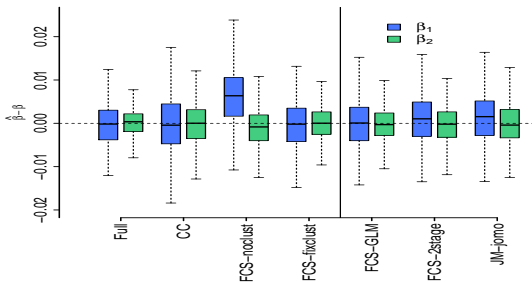
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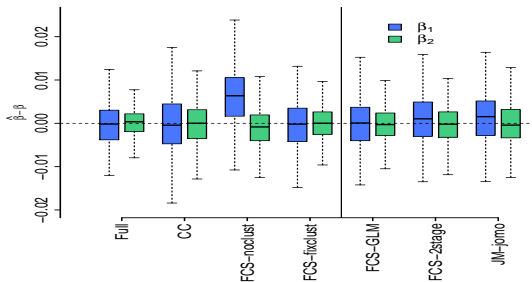
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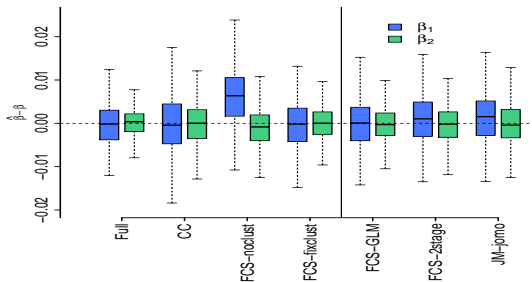
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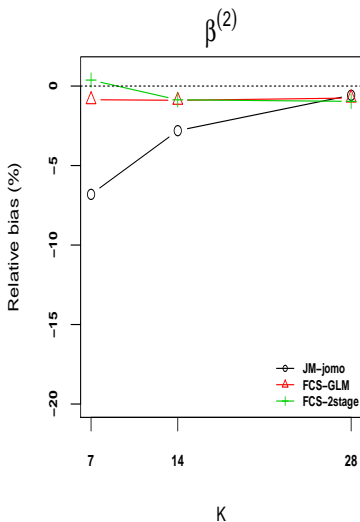
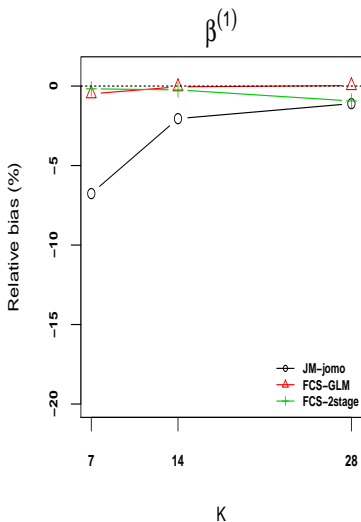
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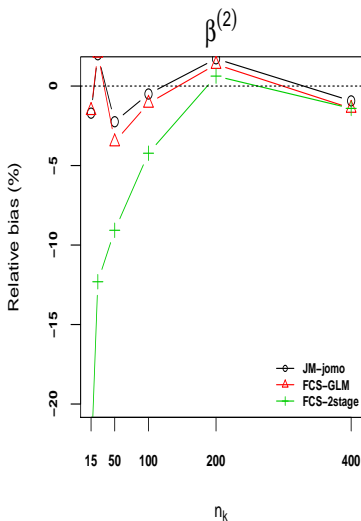
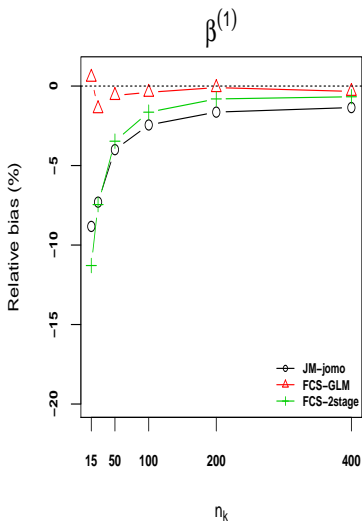


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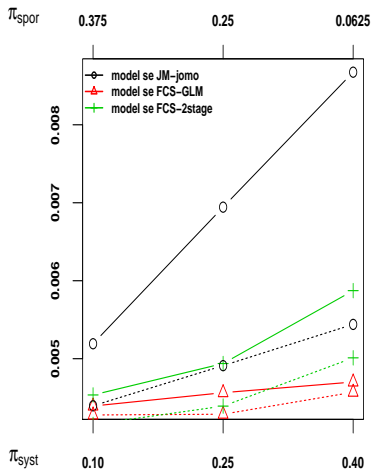
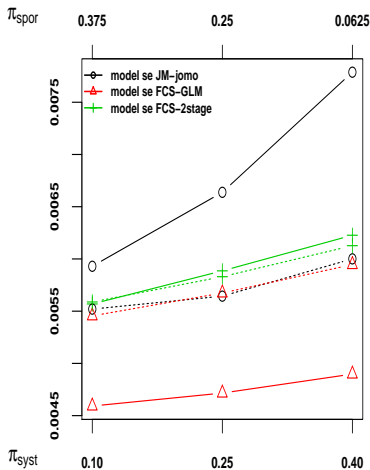
Influence of the number of clusters



Influence of the cluster size

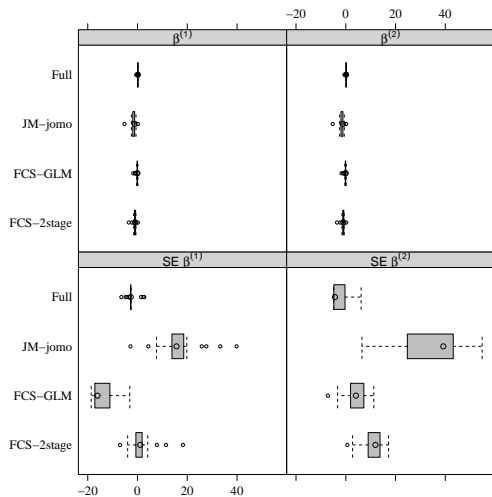


Influence of the proportion of systematically missing values



Other configurations

- 19 configurations
 - MAR mechanism
 - binary outcome
 - probit model for covariates
 - ...
- similar behaviours to base-case configuration

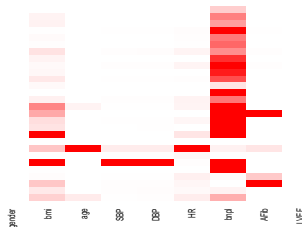


Application to GREAT data

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

$$\begin{aligned}
 y_{ik}^{LVEF} &= \beta^0 + \beta^1 y_{ik}^{BNP} + \beta^2 y_{ik}^{AFIB} \\
 &+ b_k^0 + b_k^1 y_{ik}^{BNP} + \varepsilon_{ik} \\
 b_k &\sim \mathcal{N}(0, \Psi) \quad \varepsilon_{ik} \sim \mathcal{N}(0, \sigma^2)
 \end{aligned}$$

- MI using $M = 20$ imputed arrays



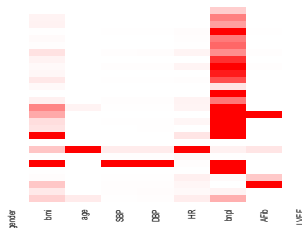
		CC	JM-jomo	FCS-GLM	FCS-2stage
β_{BNP}	est	-0.1132	-0.0891	-0.1002	-0.1009
	model se	0.0108	0.0078	0.0163	0.0112
β_{AFIB}	est	0.0268	0.0216	0.0218	0.0273
	model se	0.0071	0.0046	0.0066	0.0045
time (min)			94.0	30819.5	31.8

Application to GREAT data

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

$$\begin{aligned}
 y_{ik}^{LVEF} &= \beta^0 + \beta^1 y_{ik}^{BNP} + \beta^2 y_{ik}^{AFIB} \\
 &+ b_k^0 + b_k^1 y_{ik}^{BNP} + \varepsilon_{ik} \\
 b_k &\sim \mathcal{N}(0, \Psi) \quad \varepsilon_{ik} \sim \mathcal{N}(0, \sigma^2)
 \end{aligned}$$

- MI using $M = 20$ imputed arrays



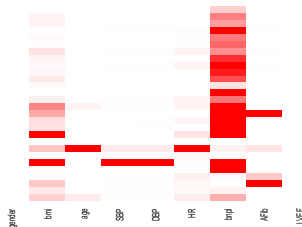
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Conclusion

An overview of MI methods for multilevel data

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

FCS-2stage

- provides a quick way to obtain first results
- for large clusters

FCS-GLM

- tends to underestimate the variance of the estimator because of the homoscedastic assumption
- recommended with small clusters
- time consuming (with binary variables)

JM-jomo

- tends to overestimate the variance of the fixed coefficients because of unsuitable prior distributions
- recommended for large clusters when the proportion of binary variables is high

Methods are implemented in R (mice, micemd, jomo)

Limits and perspectives

Limits

- congeniality (**analysis model** vs **imputation model**)
- choice of random and fixed effects in the imputation models
- binary variables are challenging

Perspectives

- imputation using machine learning
- large number of variables
- ordinal and nominal variables
- MNAR mechanism

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