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Imputation of Incomplete Multilevel Data with mice

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Abstract

This tutorial illustrates the imputation of incomplete multilevel data with the R pack-ackage **mice**. Footnotes in the current version show work in progress/under construction. The last section is not part of the manuscript, but purely for reminders. See also all of the TODOs that need to be worked out. We aim to submit at JSS, so there is no word count limit ("There is no page limit, nor a limit on the number of figures or tables"). [Just adding some text to get a better guess of what the actura abstract will look like: Lorem ipsum dolor sit amet, consectetur adipiscing elit, sed do eiusmod tempor incididunt ut labore et dolore magna aliqua. Ut enim ad minim veniam, quis nostrud exercitation ullamco laboris nisi ut aliquip ex ea commodo consequat. Duis aute irure dolor in reprehenderit in voluptate velit esse cillum dolore eu fugiat nulla pariatur. Excepteur sint occaecat cupidatat non proident, sunt in culpa qui officia deserunt mollit anim id est laborum.]

Keywords: missing data, multilevel, clustering, mice, R.

1. Introduction

Many datasets include individuals from multiple settings, geographic regions, or even different studies. In the simplest case, individuals (e.g., students) are nested within so-called clusters (e.g., school classes). More complex clustered structures may occur when there are multiple hierarchical levels (e.g., patients within hospitals within regions or countries), or when the clustering is non-nested (e.g., electronic health record data from diverse settings and populations within large databases). In general, individuals from the same cluster tend to be more similar than individuals from other clusters. In statistical terms, this implies that observations from the same cluster are correlated. If this correlation is left unaddressed, estimates of p values, confidence intervals even model parameters are prone to bias (Localio, Berlin, Ten Have, and Kimmel 2001). [TODO: make a link to imputation methods, which require adequate handling and propagation of variance; we are not recommending the adoption of multilevel models for data analysis here, but rather for imputation. VMTdJ: "I would only make that link after introducing missing data, and missing data is not mentioned yet, so I would do that in the next section" Statistical methods for clustered data typically adopt hierarchical models that explicitly describe the grouping of observations. These models are also known as 'multilevel models', 'hierarchical models', 'mixed effect models', 'random effect models', and in the context of time-to-event data as 'frailty models'. Table ?? provides an overview of some key concepts in multilevel modeling.

Table 1: Concepts in multilevel methods

Concept	Details
Sample unit	Units of the population from which measurements are taken in a sample.
Hierarchical levels	Data are grouped into clusters at different levels. A three-level
Fixed effect	Here we assume that the values of an independent variable are fixed, i.e.,
	the values observed in the study are representative of all values in the in the dependent variable y e.g., blood pressure between treatments A and B.
Random effect	The values of an independent variable are assumed to be randomly drawn from
	admission we might select only certain hospitals that are representative of the difference of y between individual hospitals, but rather the
ICC	variation of The variability due to clustering is often measured by means of the intraclass coefficient (ICC). The ICC can be seen as the percentage of variance that can be attributed to the cluster-level, where a high
	ICC would indicate that a lot of variability is due to the cluster structure.
Random effect	Multilevel models typically accommodate for variability by including a separate group mean for each cluster. In addition to random intercepts, multilevel models can also include random coefficients and heterogeneous residual error variances across clusters [see e.g.

	cluster	X_1	X_2	X_3	 X_p
1	1			NA	
2	1				
3	2		NA		
4	2		NA	NA	
5	3				
n	N				

Figure 1: Missingness in multilevel data

Concept	Details
	Gelman and Hill (2006), Hox, Moerbeek, and van de Schoot (2017) and de Jong, Moons, Eijkemans, Riley, and Debray (2021)]. [TODO:
	add stratification.]

1.1. Missingness in multilevel data

Like any other dataset, clustered datasets are prone to missing data. Several strategies can be used to handle missing data, including complete case analysis and imputation. We focus on the latter approach and discuss statistical methods for replacing the missing data with one or more plausible values. Afterwards, the completed data can be analyzed as if they were completely observed. In contrast to single imputation (where missing data are only replaced once), multiple imputation allows to preserve uncertainty due to missingness and is therefore recommended (c.f. Rubin 1976).

When clustered datasets are affected by missing values, we can distinguish between two types of missing data: sporadic missingness and systematic missingness (Resche-Rigon, White, Bartlett, Peters, and Thompson 2013). Sporadic missingness arises when variables are missing for some but not all of the units in a cluster (Van Buuren 2018; Jolani 2018). For example, it is possible that test results are missing for several students in one or more classes. [TODO: Provide an example for one of the case studies below.] When all observations are missing within one or more clusters, data are systematically missing. [TODO: Refer to Figure 1 and put interpretation in the figure caption. VMTdJ: "Mention in text that this is sporadic missingness?"]

Imputation of missing data requires consideration of the mechanism behind the missingness. Rubin proposed to distinguish between data that are missing completely at random (MCAR), data that are missing at random (MAR) and data that are missing not at random (MNAR; see Table ??). For each of these three missingness generating mechanisms, different imputation strategies are warranted Yucel (2008) and Hox, van Buuren, and Jolani (2015). We here consider the general case that data are MAR, and expand on certain MNAR situations.

Table 2: Concepts in missing data methods

Concept	Details
MCAR	Missing Completely At Random, where the probability to be missing is equal across all data entries
MAR	Missing At Random, where the probability to be missing depends on observed information
MNAR	Missing Not At Random (MNAR), where the probability to be missing depends on unrecorded information, making the missingness non-ignorable (Rubin 1976; Meng 1994). [TODO: add congeniality, but maybe in-text?]

The R package **mice** has become the de-facto standard for imputation by chained equations, which iteratively solves the missingness on a variable-by-variable basis. **mice** is known to yield valid inferences under many different missing data circumstances (Van Buuren 2018). However, commonly used imputation methods were not designed for use in clustered data and usually generate observations that are independent whereas multilevel data are dependent. For this reason, we discuss how the R package **mice** can be used to impute multilevel data.

[TODO: clarify why clustering is relevant during imputation, and why this exposes the need for specialized imputation methods and more attention during their implementation ("thou shall not simply run mice() on any incomplete dataset").] [TODO: Add that the more the random effects are of interest, the more you need multilevel imputation models.] [TODO: Add an overview of all possible predictor matrix values in manuscript or ggmice legend.]

1.2. Aim of this paper

This papers serves as a tutorial for imputing incomplete multilevel data with **mice** in R. We provide practical guidelines and code snippets for different missing data situations, including non-ignorable mechanisms. For reasons of brevity, we focus on multilevel imputation by chained equations with **mice** exclusively; other imputation methods and packages (e.g., **jomo** and **mdmb**) are outside the scope of this tutorial. [TODO: change this sentence because we do not assume familiarity: "Assumed knowledge includes basic familiarity with multilevel imputation (see e.g. Audigier, White, Jolani, Debray, Quartagno, Carpenter, van Buuren, and Resche-Rigon 2018, and Grund, Lüdtke, and Robitzsch (2018)) and the **lme4** notation for multilevel models (see Table ??)"].

Table 3: Notation

Formula lme4	Details
y ~ x1 + (1 g1)	Fixed x1 predictor with random
	intercept
	varying among g1
y~x1*x2+ (1 g1)	Interactions of $x1$ and $x2$ only in fixed
	effect
y ~ x1*x2+ (x2 g1)	Interactions of $x1$ and $x2$ only in fixed
	effect

Formula lme4	Details
y ~ x1*x2+ (x1*x2 g1)	with slope of x2 randomly varying among g1 variance-covariance matrix estimated only with
y ~ x1*x2+ (x1 g1)+ (x2 g1)	the variance terms of intercept, slope of x1, slope of x2 and interaction x1*x2 variance-covariance matrix estimated separately, i.e, one for intercept and x1 and another for
y ~ x1 + (x1 g1) or 1 + x1 + (1 + x1 g1)	intercept and x2 Fixed x1 with correlated random intercept and random slope of x
y ~ x1 + (x1 g1) or 1 + x1 + (1 g1) + (0 + x1 g1)	Fixed x1 with uncorrelated random intercept and random slope of x1
y ~ (1 g1) + (1 g2)	Random intercept varying among g1 and among g2 y ~ (1 [TODO: explain lme4 notation here

We illustrate imputation of incomplete multilevel data using three case studies:

- popmis from the mice package (simulated data on perceived popularity, n=2,000 pupils across N=100 schools with data that are MAR, van Buuren and Groothuis-Oudshoorn 2021);
- impact from the metamisc package (empirical data on traumatic brain injuries, n = 11,022 patients across N = 15 studies with data that are MAR, Debray and de Jong 2021);
- hiv from the GJRM package (simulated data on HIV diagnoses, n=6,416 patients across N=9 regions with data that are MNAR, Radice 2021).

For each of these datasets, we discuss the nature of the missingness, choose one or more imputation models and evaluate the imputed data, but we will also highlight one specific aspect of the imputation workflow.

This tutorial is dedicated to readers who are unfamiliar with multiple imputation. More experienced readers can skip the introduction (case study 1) and directly head to practical applications of multilevel imputation under MAR conditions (case study IMPACT) or under MNAR conditions (case study HIV).

TODO: explicit statement about not going into workings of the methods. Galimer 2l methods.

1.3. Setup

[TODO: Add environment info, seed and version number(s) somewhere.] Set up the R environment and load the necessary packages:

```
R> set.seed(2022)
                         # for imputation
R> library(mice)
R> library(miceadds)
                         # for imputation
R> library(ggmice)
                         # for visualization
R> library(ggplot2)
                         # for visualization
R> library(dplyr)
                         # for data wrangling
R> library(lme4)
                         # for multilevel modeling
R> library(mitml)
                         # for multilevel pooling
R> library(miceheckman) # for imputation
```

2. Case study I: popularity data

[TODO: explain case study]

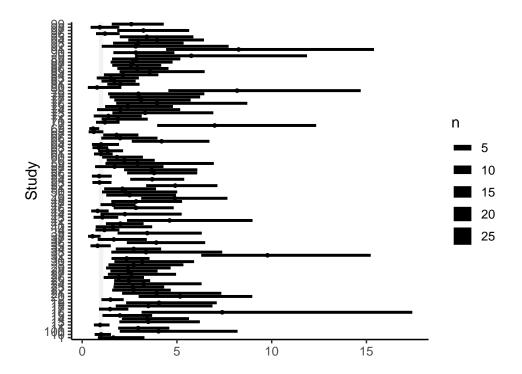
In this section we'll go over the different steps involved with imputing incomplete multilevel data with the R package mice. We consider the simulated popmis dataset, which included pupils (n=2000) clustered within schools (N=100). The following variables are of primary interest:

- school, school identification number (clustering variable);
- popular, pupil popularity (self-rating between 0 and 10; unit-level);
- sex, pupil sex (0=boy, 1=girl; unit-level);
- texp, teacher experience (in years; cluster-level).

The research objective of the popmis dataset is to predict the pupils' popularity based on their gender and the experience of the teacher. The analysis model corresponding to this dataset is multilevel regression with random intercepts, random slopes and a cross-level interaction. The outcome variable is popular, which is predicted from the unit-level variable sex and the cluster-level variable texp:

```
R> mod <- popular ~ 1 + sex + (1 | school)</pre>
```

The true effect is:



Load the data into the environment and select the relevant variables:

Plot the missing data pattern:

R> plot_pattern(popmis)

The missingness is univariate and sporadic, which is illustrated in the missing data pattern in Figure 2.

To develop the best imputation model for the incomplete variable popular, we need to know whether the observed values of popular are related to observed values of other variables. Plot the pair-wise complete correlations in the incomplete data:

R> plot_corr(popmis)

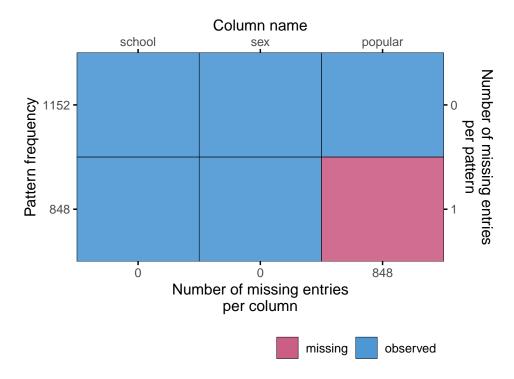
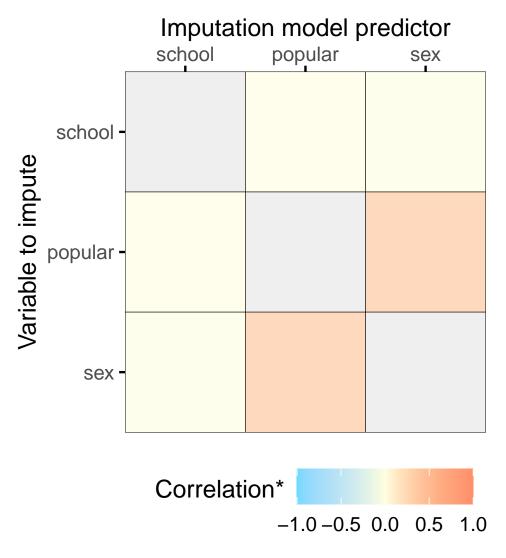
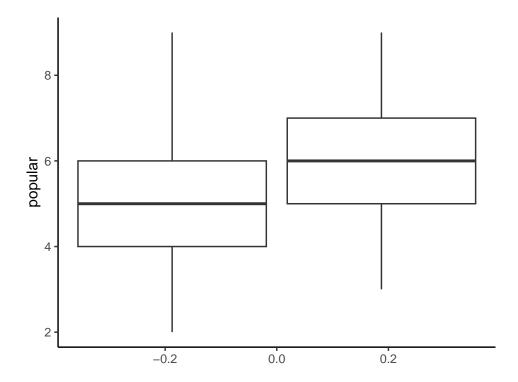


Figure 2: Missing data pattern in the popularity data



*pairwise complete observations

This shows us that sex may be a useful imputation model predictor. Moreover, the missingness in popular may depend on the observed values of other variables.

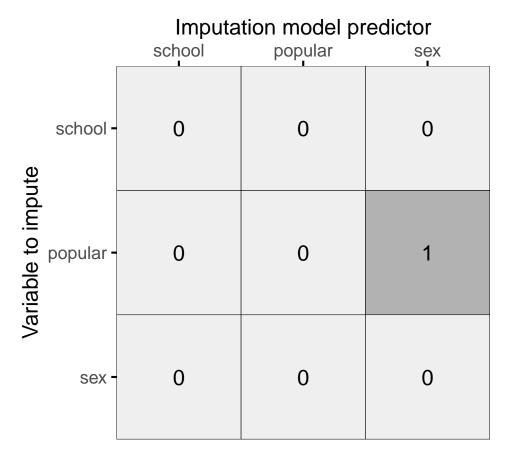


Imputation ignoring the cluster variable (not recommended)

The first imputation model that we'll use is likely to be invalid. We do <u>not</u> use the cluster identifier school as imputation model predictor. With this model, we ignore the multilevel structure of the data, despite the high ICC. This assumes exchangeability between units. We include it purely to illustrate the effects of ignoring the clustering in our imputation effort.

Create a methods vector and predictor matrix for popular, and make sure school is not included as predictor:

```
R> meth <- make.method(popmis) # methods vector
R> pred <- quickpred(popmis) # predictor matrix
R> plot_pred(pred)
```



Predictor used ___ no ___ yes

Impute the data, ignoring the cluster structure:

Analyze the imputations:

Print the estimates:

```
R> testEstimates(as.mitml.result(fit), extra.pars = TRUE)
```

Call:

```
testEstimates(model = as.mitml.result(fit), extra.pars = TRUE)
```

Final parameter estimates and inferences obtained from 5 imputed data sets.

	Estimate	Std.Error	t.value	df	P(> t)	RIV	FMI
(Intercept)	5.012	0.295	16.994	4.362	0.000	22.587	0.969
sex	0.695	0.251	2.768	4.287	0.047	28.390	0.975

	Estimate
<pre>Intercept~~Intercept school</pre>	0.266
Residual~~Residual	1.035
ICC school	0.208

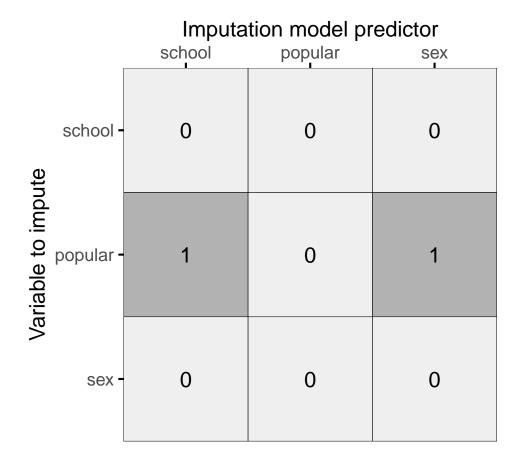
Unadjusted hypothesis test as appropriate in larger samples.

Imputation with the cluster variable as predictor (not recommended)

We'll now use school as a predictor to impute all other variables. This is still not recommended practice, since it only works under certain circumstances and results may be biased (Drechsler 2015; Enders, Mistler, and Keller 2016). But at least, it includes some multilevel aspect. This method is also called 'fixed cluster imputation', and uses N-1 indicator variables representing allocation of N clusters as a fixed factor in the model (Reiter, Raghunathan, and Kinney 2006; Enders et al. 2016). Colloquially, this is 'multilevel imputation for dummies'.

[TODO: Add that it doesn't work with systematic missingness (only with sporadic). There's some pros and cons, and it may not even differ much if the number of clusters is low.]

```
R> # adjust the predictor matrix
R> pred["popular", "school"] <- 1
R> plot_pred(pred)
```



Predictor used

yes

no

R> # impute the data, cluster as predictor
R> imp <- mice(popmis, pred = pred, print = FALSE)</pre>

Analyze the imputations:

Print the estimates:

R> testEstimates(as.mitml.result(fit), extra.pars = TRUE)

Call:

```
testEstimates(model = as.mitml.result(fit), extra.pars = TRUE)
```

Final parameter estimates and inferences obtained from 5 imputed data sets.

	Estimate	Std.Error	t.value	df	P(> t)	RIV	FMI
(Intercept)	4.915	0.217	22.642	4.926	0.000	9.110	0.926
sex	0.975	0.283	3.444	4.250	0.024	32.504	0.978

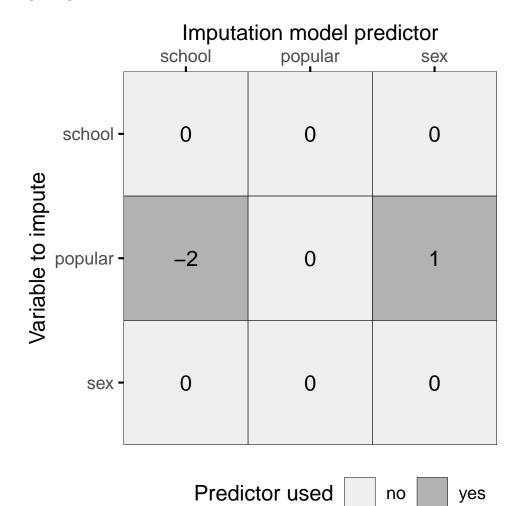
Estimate

<pre>Intercept~~Intercept school</pre>	0.351
Residual~~Residual	1.153
ICC school	0.233

Unadjusted hypothesis test as appropriate in larger samples.

 $Imputation\ with\ multilevel\ model$

R> # adjust the predictor matrix
R> pred["popular", "school"] <- -2
R> plot_pred(pred)



```
R> # impute the data, cluster as predictor
R> imp <- mice(popmis, pred = pred, print = FALSE)</pre>
```

Analyze the imputations:

Print the estimates:

```
R> testEstimates(as.mitml.result(fit), extra.pars = TRUE)
```

Call:

```
testEstimates(model = as.mitml.result(fit), extra.pars = TRUE)
```

Final parameter estimates and inferences obtained from 5 imputed data sets.

	Estimate	Std.Error	t.value	df	P(> t)	RIV	FMI
(Intercept)	5.011	0.410	12.222	4.226	0.000	35.955	0.980
sex	0.928	0.381	2.434	4.168	0.069	48.221	0.985

	Estimate
<pre>Intercept~~Intercept school</pre>	0.313
Residual~~Residual	1.428
ICC school	0.188

Unadjusted hypothesis test as appropriate in larger samples.

3. Case study II: IMPACT data (syst missingness, pred matrix)

[TODO: check if there is systematic missingness in this dataset, if not make Marshall Computerized Tomography classification (ct) systematically missing.]

We illustrate how to impute incomplete multilevel data by means of a case study: impact from the metamisc package (empirical data on traumatic brain injuries, n=11,022 units across N=15 clusters, Debray and de Jong 2021). [TODO: add more info about the complete data.] The impact data set contains traumatic brain injury data on n=11022 patients clustered in N=15 studies with the following 11 variables:

- name Name of the study,
- type Type of study (RCT: randomized controlled trial, OBS: observational cohort),
- age Age of the patient,
- motor_score Glasgow Coma Scale motor score,
- pupil Pupillary reactivity,

- ct Marshall Computerized Tomography classification, [TODO: make this one var? also shows that you don't always need random effects everywhere?]
- hypox Hypoxia (0=no, 1=yes),
- hypots Hypotension (0=no, 1=yes),
- tsah Traumatic subarachnoid hemorrhage (0=no, 1=yes),
- edh Epidural hematoma (0=no, 1=yes),
- mort 6-month mortality (0=alive, 1=dead).

The analysis model for this dataset is a prediction model with mort as the outcome. In this tutorial we'll estimate the adjusted prognostic effect of ct on mortality outcomes. The estimand is the adjusted odds ratio for ct, after including type, age motor_score and pupil into the analysis model:

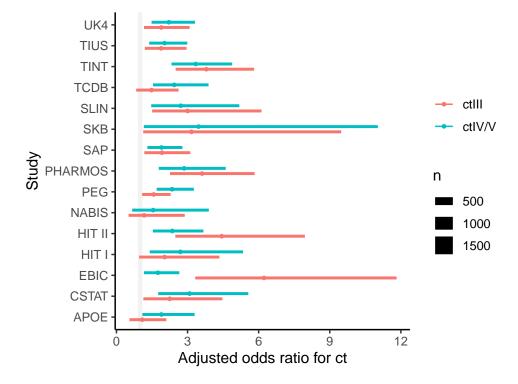
```
R> mod <- mort ~ 1 + type + age + motor_score + pupil + ct + (1 | name)
```

Note that variables hypots, hypox, tsah and edh are not part of the analysis model, and may thus serve as auxiliary variables for imputation.

The impact data included in the **metamisc** package is a complete data set. The original data has already been imputed once (Steyerberg et al, 2008). For the purpose of this tutorial we have induced missingness (mimicking the missing data in the original data set before imputation). The resulting incomplete data can be accessed from zenodo link to be created. Load the complete and incomplete data into the R workspace:

```
R> data("impact", package = "metamisc")  # complete data
R> dat <- read.table("link/to/the/data.txt") # incomplete data</pre>
```

The estimated effects in the complete data are visualized in Figure ??.



```
R> # fit <- glmer(mod, family = "binomial", data = impact) # fit the model
R> # tidy(fit, conf.int = TRUE, exponentiate = TRUE) # print estimates
```

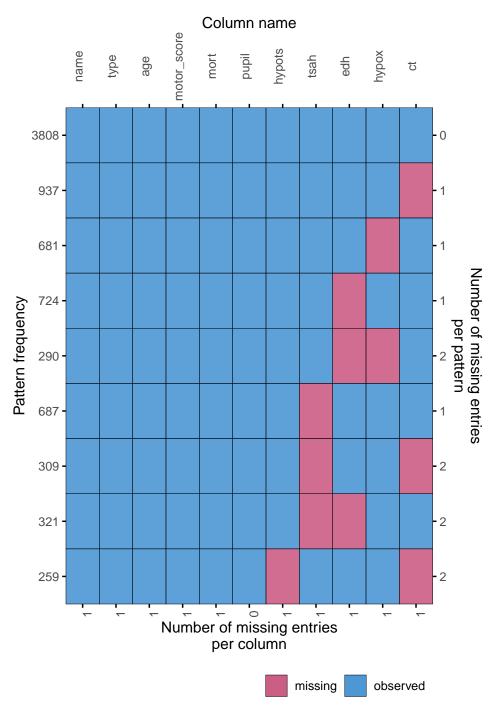
[TODO: show how much variance there is after different methods]

[TODO: add ICC before/after imputation and interpret: This tells us that the multilevel structure of the data should probably be taken into account. If we don't, we'll may end up with incorrect imputations, biasing the effect of the clusters towards zero.]

[TODO: add descriptive statistics of the complete and incomplete data.]

3.1. Missingness

To explore the missingness, it is wise to look at the missing data pattern:



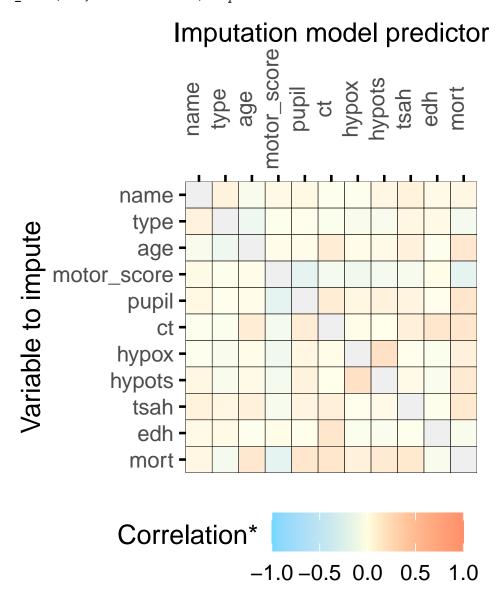
This shows... [TODO: fill in that we need to impute ct and pupil.]

To develop the best imputation model, we need to investigate the relations between the observed values of the incomplete variables and the observed values of other variables, and the relation between the missingness indicators of the incomplete variables and the observed values of the other variables. To see whether the missingness depends on the observed values of other variables, we... [TODO: fill in that we can test this statistically or use visual inspection (e.g. a histogram faceted by the missingness indicator).]

We should impute the variables ct and pupil and any auxiliary variables we might want to

use to impute these incomplete analysis model variables. We can evaluate which variables may be useful auxiliaries by plotting the pairwise complete correlations:

R> plot_corr(dat, rotate = TRUE) # plot correlations



*pairwise complete observations

This shows us that hypox and hypot would not be useful auxiliary variables for imputing ct. Depending on the minimum required correlation, tsah could be useful, while edh has the strongest correlation with ct out of all the variables in the data and should definitely be included in the imputation model. For the imputation of pupil, none of the potential auxiliary variables has a very strong relation, but hypots could be used. We conclude that we can exclude hypox from the data, since this is neither an analysis model variable nor an auxiliary variable for imputation:

R> dat <- select(dat, !hypox) # remove variable

3.2. Complete case analysis [TODO: remove this?]

As previously stated, complete case analysis lowers statistical power and may bias results. The complete case analysis estimates are:

```
R> fit <- glmer(mod, family = "binomial", data = na.omit(dat)) # fit the model
R> tidy(fit, conf.int = TRUE, exponentiate = TRUE) # print estimates
```

```
# A tibble: 11 x 9
  effect
           group term
                              estim~1 std.er~2 stati~3
                                                         p.value conf.~4 conf.~5
  <chr>
           <chr> <chr>
                                                                    <dbl>
                                <dbl>
                                         <dbl>
                                                 <dbl>
                                                           <dbl>
                                                                            <dbl>
 1 fixed
           <NA>
                                                -11.6
                                                        3.00e-31
                  (Intercept) 0.0863 0.0182
                                                                   0.0571
                                                                            0.130
2 fixed
           <NA> typeRCT
                               0.757
                                       0.137
                                                 -1.54 1.22e- 1
                                                                   0.531
                                                                            1.08
                                                        7.40e-38
3 fixed
           <NA> age
                               1.03
                                       0.00265
                                                 12.9
                                                                   1.03
                                                                            1.04
4 fixed
           <NA> motor_scor~
                                       0.0732
                                                 -3.82 1.34e- 4
                                                                   0.522
                                                                            0.811
                               0.651
5 fixed
           <NA> motor_scor~
                               0.489
                                       0.0555
                                                 -6.30
                                                        2.97e-10
                                                                   0.391
                                                                            0.611
6 fixed
           <NA> motor_scor~
                               0.274
                                       0.0321
                                                -11.0
                                                        2.28e-28
                                                                   0.218
                                                                            0.345
7 fixed
           <NA> pupilNone
                               3.20
                                       0.317
                                                 11.7
                                                        8.18e-32
                                                                   2.63
                                                                            3.88
8 fixed
           <NA> pupilOne
                               1.75
                                       0.195
                                                  5.06 4.27e- 7
                                                                   1.41
                                                                            2.18
            <NA> ctIII
                                                  7.89 3.05e-15
9 fixed
                               2.41
                                       0.268
                                                                   1.94
                                                                            2.99
10 fixed
            <NA>
                 ctIV/V
                               2.30
                                       0.214
                                                  8.95 3.56e-19
                                                                  1.92
                                                                            2.76
11 ran_pars name sd__(Inter~
                               0.230
                                      NA
                                                 NA
                                                       NA
                                                                 NA
                                                                           NA
# ... with abbreviated variable names 1: estimate, 2: std.error, 3: statistic,
   4: conf.low, 5: conf.high
```

As we can see... [TODO: fill in: This means that a higher ct (Marshall Computerized Tomography classification) is associated with a lower odds of 6-month mortality, given by the odds ratio $\exp(0.42)$, CI... to..., when controlling for...]

3.3. Imputation model

Mutate data to get the right data types for imputation (e.g. integer for clustering variable).

```
R> dat <- dat %>% mutate(across(everything(), as.integer))
```

Create a methods vector and predictor matrix, and make sure name is not included as predictor, but as clustering variable:

```
R> meth <- make.method(dat) # methods vector
R> pred <- quickpred(dat) # predictor matrix
R> plot_pred(pred)
```

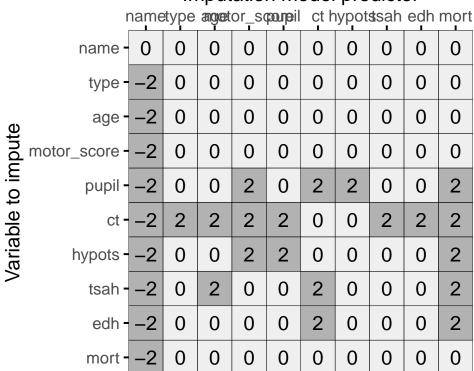
Imputation model predictor

	nametype ange tor_s coure il							ct hypotssah edh mort			
	name -	0	0	0	0	0	0	0	0	0	0
	type -	0	0	0	0	0	0	0	0	0	0
Φ	age -	0	0	0	0	0	0	0	0	0	0
put	motor_score -	0	0	0	0	0	0	0	0	0	0
Variable to impute	pupil -	0	0	0	1	0	1	1	0	0	1
ble t	ct -	0	1	1	1	1	0	0	1	1	1
aria	hypots -	0	0	0	1	1	0	0	0	0	1
>	tsah -	1	0	1	0	0	1	0	0	0	1
	edh -	1	0	0	0	0	1	0	0	0	0
	mort -	0	0	0	0	0	0	0	0	0	0

Predictor used no yes

```
R> pred[pred == 1] <- 2
R> pred["mort", ] <- 2
R> pred[, "mort"] <- 2
R> pred[c("name", "type", "age", "motor_score", "mort"), ] <- 0
R> pred[, "name"] <- -2
R> diag(pred) <- 0
R> plot_pred(pred)
```

Imputation model predictor



Predictor used no yes

```
R> meth <- make.method(dat)
R> meth
```

ct	pupil	motor_score	age	type	name
"pmm"	"pmm"	11 11	11 11	11 11	11 11
		mort	edh	tsah	hypots
		11 11	"mmg"	"mmg"	"mmg"

R> imp <- mice(dat, method = meth, predictorMatrix = pred, printFlag = FALSE)</pre>

Impute the incomplete data

```
R> fit <- imp %>%
+ with(glmer(mort ~ type + age + as.factor(motor_score) + pupil + ct + (1 | name), famil
R> tidy(pool(fit))
```

```
term estimate std.error statistic p.value

(Intercept) -2.35203726 0.340181747 -6.914061 4.994037e-12

type -0.41265892 0.180274846 -2.289054 2.209524e-02

age 0.03049023 0.001570162 19.418521 1.238416e-81
```

```
4 as.factor(motor score)2 -0.66764920 0.068737865 -9.712975 3.480413e-22
5 as.factor(motor_score)3 -1.05520001 0.070218940 -15.027285 2.540225e-50
6 as.factor(motor_score)4 -1.51238349 0.072304262 -20.916934 1.850073e-90
                    pupil 0.48421447 0.038982800 12.421234 6.772069e-17
                       ct 0.43474621 0.029968474 14.506785 2.342253e-36
8
                        df dfcom
                                                  lambda m
                                         fmi
                                                                    riv
1 5.281599e-04 10119.70041 11013 0.005673265 0.005476771 5 0.005506932
2 4.881699e-05 10893.89378 11013 0.001985736 0.001802528 5 0.001805783
3 3.335358e-08 6320.89582 11013 0.016545467 0.016234340 5 0.016502243
4 4.188703e-05 8327.24771 11013 0.010875748 0.010638213 5 0.010752602
5 5.135721e-05 7632.20045 11013 0.012757637 0.012498967 5 0.012657168
6 1.403058e-04 2831.75462 11013 0.032888241 0.032205434 5 0.033277139
7 3.571497e-04
                49.97295 11013 0.309130930 0.282023647 5 0.392803531
8 8.586645e-05
                294.69765 11013 0.120677044 0.114729598 5 0.129598366
          ubar
1 1.150898e-01
2 3.244044e-02
3 2.425385e-06
4 4.674630e-03
5 4.869071e-03
6 5.059539e-03
7 1.091079e-03
8 7.950697e-04
R> as.mitml.result(fit)
\lceil \lceil 1 \rceil \rceil
Generalized linear mixed model fit by maximum likelihood (Laplace
 Approximation) [glmerMod]
Family: binomial (logit)
Formula: mort ~ type + age + as.factor(motor_score) + pupil + ct + (1 |
    name)
      AIC
                BIC
                       logLik deviance df.resid
10495.423 10561.192 -5238.712 10477.423
                                            11013
Random effects:
 Groups Name
                    Std.Dev.
        (Intercept) 0.2843
Number of obs: 11022, groups: name, 15
Fixed Effects:
            (Intercept)
                                            type
                                                                       age
               -2.37195
                                        -0.41014
                                                                   0.03052
as.factor(motor_score)2 as.factor(motor_score)3 as.factor(motor_score)4
               -0.65802
                                        -1.04611
                                                                  -1.51245
                  pupil
                                              ct
                0.50405
                                         0.42496
optimizer (Nelder_Mead) convergence code: 0 (OK); 0 optimizer warnings; 1 lme4 warnings
```

```
[[2]]
Generalized linear mixed model fit by maximum likelihood (Laplace
  Approximation) [glmerMod]
 Family: binomial (logit)
Formula: mort ~ type + age + as.factor(motor score) + pupil + ct + (1 |
    name)
     AIC
              BIC
                    logLik deviance df.resid
10500.88 10566.65 -5241.44 10482.88
Random effects:
 Groups Name
                   Std.Dev.
        (Intercept) 0.2917
Number of obs: 11022, groups: name, 15
Fixed Effects:
            (Intercept)
                                            type
                                                                      age
               -2.37718
                                        -0.41511
                                                                  0.03067
as.factor(motor_score)2 as.factor(motor_score)3 as.factor(motor_score)4
               -0.66935
                                        -1.05211
                                                                 -1.49429
                  pupil
                0.49013
                                         0.43835
optimizer (Nelder_Mead) convergence code: 0 (OK); 0 optimizer warnings; 1 lme4 warnings
Generalized linear mixed model fit by maximum likelihood (Laplace
  Approximation) [glmerMod]
 Family: binomial (logit)
Formula: mort ~ type + age + as.factor(motor score) + pupil + ct + (1 |
    name)
                       logLik deviance df.resid
      AIC
                BIC
10505.026 10570.795 -5243.513 10487.026
                                            11013
Random effects:
 Groups Name
                   Std.Dev.
 name (Intercept) 0.2908
Number of obs: 11022, groups: name, 15
Fixed Effects:
            (Intercept)
                                            type
                                                                      age
               -2.32339
                                        -0.42359
                                                                  0.03023
as.factor(motor_score)2 as.factor(motor_score)3 as.factor(motor_score)4
               -0.67142
                                        -1.05776
                                                                 -1.51038
                  pupil
                                              ct.
                0.49756
                                         0.42474
optimizer (Nelder_Mead) convergence code: 0 (OK); 0 optimizer warnings; 1 lme4 warnings
[[4]]
Generalized linear mixed model fit by maximum likelihood (Laplace
  Approximation) [glmerMod]
 Family: binomial (logit)
Formula: mort ~ type + age + as.factor(motor_score) + pupil + ct + (1 |
```

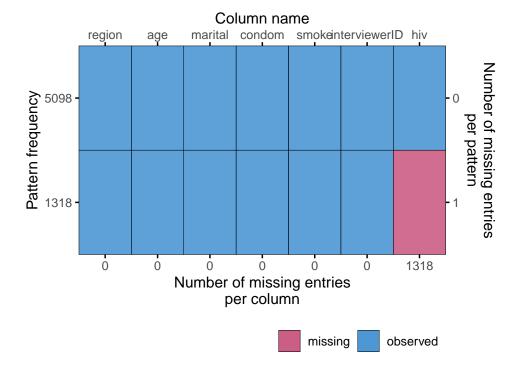
```
name)
      ATC
                BIC
                       logLik deviance df.resid
10519.511 10585.280 -5250.755 10501.511
                                            11013
Random effects:
 Groups Name
                   Std.Dev.
        (Intercept) 0.2961
Number of obs: 11022, groups: name, 15
Fixed Effects:
            (Intercept)
                                            type
                                                                      age
               -2.33581
                                        -0.40871
                                                                  0.03039
as.factor(motor_score)2 as.factor(motor_score)3 as.factor(motor_score)4
               -0.66477
                                        -1.05451
                                                                 -1.51858
                  pupil
                                              ct
                0.45928
                                         0.44419
optimizer (Nelder_Mead) convergence code: 0 (OK); 0 optimizer warnings; 2 lme4 warnings
Generalized linear mixed model fit by maximum likelihood (Laplace
  Approximation) [glmerMod]
 Family: binomial (logit)
Formula: mort ~ type + age + as.factor(motor_score) + pupil + ct + (1 |
    name)
      AIC
                BIC
                       logLik deviance df.resid
10522.038 10587.807 -5252.019 10504.038
                                            11013
Random effects:
                    Std.Dev.
 Groups Name
        (Intercept) 0.2955
Number of obs: 11022, groups: name, 15
Fixed Effects:
            (Intercept)
                                            type
               -2.35187
                                        -0.40574
                                                                  0.03064
as.factor(motor_score)2 as.factor(motor_score)3 as.factor(motor_score)4
               -0.67468
                                        -1.06551
                                                                 -1.52622
                  pupil
                                              ct
                0.47006
                                         0.44148
optimizer (Nelder_Mead) convergence code: 0 (OK); 0 optimizer warnings; 1 lme4 warnings
attr(,"class")
[1] "mitml.result" "list"
R> # testEstimates(as.mitml.result(fit))
```

4. Case study III: HIV data

Data are simulated and included in the GJRM package. We will use the following variables:

- region Cluster variable,
- hiv HIV diagnosis (0=no, 1=yes),
- age Age of the patient,
- marital Marital status,
- condom Condom use during last intercourse,
- smoke Smoker (levels; inclusion restriction variable).

The imputation of these date is based on the toy example from IPDMA Heckman Github repo.



R=region+language+(1|InterviewID) model with interviewer as random effects, because the observations are not independent. Interviews are not allocated randomly. In theory we expect the inclusion-restriction variable to be randomly assigned, that's why we're adding region and language to compensate for non-random allocation. [TODO: Explain exclusion-restriction, refer to paper Johanna].

Load the data:

R> data("obesity", package = "miceheckman")

We obtain here the random effects for each interviewer, this is an approximation of the interviewer's skill which will be used as an exclusion constraint. Here, since the location of the interviewer was not randomly assigned to the subjects, the assignment was corrected for region and language.

Set the Heckman model as imputation method

R> #Set prediction matrix and methods
R> ini <- mice(obesity, maxit = 0)</pre>

5. Discussion

- JOMO in **mice** -> on the side for now
- Additional levels of clustering
- More complex data types: timeseries and polynomial relationship in the clustering.

6. Think about

- Adding evaluations of the imputations such as convergence checks
- Adding some kind of help function to mice that suggests a suitable predictor matrix to the user, given a certain analysis model.
- Adding a multilevel_ampute() wrapper function in mice.
- Exporting mids objects to other packages like lme4 or coxme?
- Adding a ICC=0 dataset to show that even if there is no clustering it doesn't hurt.
- Show use case for deductive imputation for cluster level variables?
- env dump in repo
- I don't know if in your article you cover something about model complexity, for example sometimes I have to switch from 2l. methods to 1l. methods just because the model didn't converge.. this is due to the considered imputation model is very complex regarding the amount of information counted... I know that a solution for an imputation

model with many predictors is to check correlation plots as you did or use quickpred().. (maybe you can add this somewhere after the correlation plots).....But as for cluster specification, I don't know if besides plots of distribution per cluster there is something else can be done to see if i have to use 1l. or 2l. for a given variable, also I have no idea.. how to test which is better between 2l.norm or 2l.2stage.norm.

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References

- Audigier V, White IR, Jolani S, Debray TPA, Quartagno M, Carpenter J, van Buuren S, Resche-Rigon M (2018). "Multiple Imputation for Multilevel Data with Continuous and Binary Variables." <u>Statistical Science</u>, **33**(2), 160–183. ISSN 0883-4237, 2168-8745. doi: 10.1214/18-STS646. 1702.00971.
- de Jong VMT, Moons KGM, Eijkemans MJC, Riley RD, Debray TPA (2021). "Developing More Generalizable Prediction Models from Pooled Studies and Large Clustered Data Sets." Statistics in Medicine, 40(15), 3533–3559. ISSN 1097-0258. doi:10.1002/sim.8981.
- Debray T, de Jong V (2021). "Metamisc: Meta-Analysis of Diagnosis and Prognosis Research Studies."
- Drechsler J (2015). "Multiple Imputation of Multilevel Missing Data—Rigor Versus Simplicity." <u>Journal of Educational and Behavioral Statistics</u>, **40**(1), 69–95. ISSN 1076-9986. doi:10.3102/1076998614563393.
- Enders CK, Mistler SA, Keller BT (2016). "Multilevel Multiple Imputation: A Review and Evaluation of Joint Modeling and Chained Equations Imputation." <u>Psychological Methods</u>, **21**(2), 222–240. ISSN 1939-1463. doi:10.1037/met0000063.
- Gelman A, Hill J (2006). <u>Data Analysis Using Regression and Multilevel/Hierarchical Models</u>. Cambridge University Press. ISBN 978-1-139-46093-4.
- Grund S, Lüdtke O, Robitzsch A (2018). "Multiple Imputation of Missing Data for Multilevel Models: Simulations and Recommendations." <u>Organizational Research Methods</u>, **21**(1), 111–149. ISSN 1094-4281. doi:10.1177/1094428117703686.
- Hox J, van Buuren S, Jolani S (2015). "Incomplete Multilevel Data: Problems and Solutions." In J Harring, L Staplecton, S Beretvas (eds.), <u>Advances in Multilevel Modeling</u> for Educational Research: Addressing Practical Issues Found in Real-World Applications,

- CILVR Series on Latent Variable Methodology, pp. 39–62. Information Age Publishing Inc., Charlotte, NC. ISBN 978-1-68123-328-4.
- Hox JJ, Moerbeek M, van de Schoot R (2017). <u>Multilevel Analysis: Techniques and Applications</u>, Third Edition. Routledge. ISBN 978-1-317-30868-3.
- Jolani S (2018). "Hierarchical Imputation of Systematically and Sporadically Missing Data: An Approximate Bayesian Approach Using Chained Equations." <u>Biometrical Journal</u>. Biometrische Zeitschrift, **60**(2), 333–351. ISSN 1521-4036. doi:10.1002/bimj.201600220.
- Localio AR, Berlin JA, Ten Have TR, Kimmel SE (2001). "Adjustments for Center in Multicenter Studies: An Overview." Annals of Internal Medicine, 135(2), 112–123. ISSN 0003-4819. doi:10.7326/0003-4819-135-2-200107170-00012.
- Meng XL (1994). "Multiple-Imputation Inferences with Uncongenial Sources of Input." <u>Statistical Science</u>, **9**(4), 538–558. ISSN 0883-4237, 2168-8745. doi:10.1214/ss/1177010269.
- Radice GMaR (2021). "GJRM: Generalised Joint Regression Modelling."
- Reiter JP, Raghunathan T, Kinney SK (2006). "The Importance of Modeling the Sampling Design in Multiple Imputation for Missing Data." <u>undefined</u>.
- Resche-Rigon M, White IR, Bartlett JW, Peters SAE, Thompson SG (2013). "Multiple Imputation for Handling Systematically Missing Confounders in Meta-Analysis of Individual Participant Data." Statistics in medicine, **32**(28), 4890–4905. ISSN 1097-0258 0277-6715. doi:10.1002/sim.5894.
- Rubin DB (1976). "Inference and Missing Data." <u>Biometrika</u>, **63**(3), 581–592. doi:10.2307/2335739.
- Van Buuren S (2018). Flexible Imputation of Missing Data. Chapman and Hall/CRC.
- van Buuren S, Groothuis-Oudshoorn K (2021). "Mice: Multivariate Imputation by Chained Equations."
- Yucel RM (2008). "Multiple Imputation Inference for Multivariate Multilevel Continuous Data with Ignorable Non-Response." Philosophical Transactions of the Royal Society A: Mathematical, Physical and Engineering Sciences, 366(1874), 2389–2403. doi:10.1098/rsta.2008.0038.

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