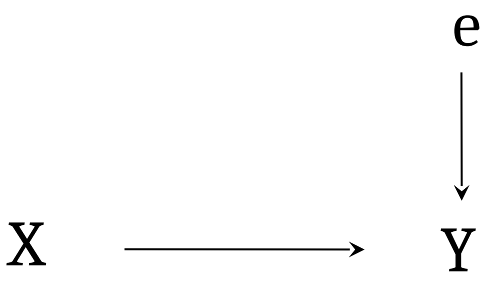
Practical exercises Missing data

Part A: study missingness mechanisms through simulations

We generate datasets with different types of missing mechanisms (using R). We will explore if we are able to estimate the true parameter values back from the simulated data with different analysis approaches.

Try to construct a DAG for each data generating mechanism. The basic DAG (without any missing observations) is presented below. X is the exposure, Y is the outcome, e is a (residual) error term acting on Y. You can add the missingness mechanism into the DAG by adding a ‘selection’ node S that is conditioned on when restricting the analysis to only cases with fully observed data.



1. **Data generation.**

   Generate a dataframe (named ‘dat’) with 1000 cases (rows), each with a value for variable X and variable Y belonging to the following ‘true’ model:

   $Y = 2 + 5X + e$,

   With

   X a sequence of 1000 equally spaced numbers between 0 and 1: 0.001, 0.002, …, 1
   e a normally distributed random variable with mean 0 and standard deviation σ=1

   Save the dataframe in such a way that you can easily re-use it in questions 2-7 below.

2. **No missings**

   Estimate a linear model relating X to Y. Are the parameters estimated accurately?

   (hint: lm(Y~X, data=dat)).

3. Y missing completely at random

a. Make half of the Y values missing using a completely at random mechanism and draw the DAG for this situation.

   (hint: add a random ‘missing indicator’ to the dataframe and put Y-values to NA for those cases with missing indicator value 1).

b. Estimate the same linear model as in (2) but now using only the cases with observed Y value. Are the parameters accurate (look both at point estimates and standard error and compare to 2)?

c. Use multiple imputation to 5 times impute the missing Y values and estimate the linear model on the imputed datasets. Are the parameters estimated correctly now (again look both at point estimates and standard errors)?

   (hint:

```
imp1 <- mice(dat,method="norm", m=5)

# Inspect the multiple imputed information

imp1

# Explore imputed values

imp1$imp

# Perform linear regression on all imputed datasets

fitmi <- with(imp1, lm(Y ~ X))

summary(fitmi)

# pooled results

summary(pool(fitmi))

# make a combined dataframe

dat_imp <- complete(imp1, "long", inc = TRUE)

view(dat_imp)
```

)

4. Y Missing dependent on X

a. Start anew from the complete data frame generated in part 1. Set all Y values to NA for cases where X>0.5.

b. How would you classify this missing mechanism?

c. Draw the DAG matching this mechanism

d. Estimate the same linear model using the cases with complete observations for X and Y. Are the parameter estimates accurate? Look both at point estimates and standard errors

e. Now use multiple imputation like in 3. Again look whether estimated coefficients are accurate.

5. Y Missing dependent on Y

a. Introduce missing values similar to 4a. But now put the Y values to NA if Y>0.5.

b. How would you classify this missing mechanism?

c. Draw the DAG matching this mechanism

d. Estimate the same linear model using the cases with complete observations for X and Y. Are the parameter estimates accurate? Look both at point estimates and standard errors

e. Now use multiple imputation like in 3. Again look whether estimated coefficients are accurate.

6. Y missing dependent on X and Z

a. Generate a new version of Y using the following model:

$$Y = 2 + 5X + Z + e ,$$

with

X a sequence of numbers 0.001, 0.002, …, 1

e a normally distributed random variable with mean 0 and standard deviation σ=1

Z a second standard normal variable

b. Set Y values to NA for cases with X>0.5 and Z>0 and draw the DAG for this situation.

c. Pretend that Z was not measured/available. Fit a linear model relating X to Y and check the estimates of the parameters.

d. Use multiple imputation (again using only X), fit a linear model relating X to Y and check the estimates of the parameters

e. Now include Z during the multiple imputation and again fit a linear model relating X to Y and check the parameter estimates.

f. How would you classify the missing mechanism if Z was measured?
And if it was not measured?

7. Should the outcome be included in the imputation model for missing covariate values?

a. Start from the dataset generated under 1. Introduce missing X values according to a missing completely at random mechanism. Fit a linear model on the complete observations.

b. Use multiple imputation to generate 5 imputed datasets. Instruct R not to use Y when imputing X.

   Hint:

```
(
setup <- mice(dataframe)
predMat <- setup$predictorMatrix
predMat["X","Y"] <- 0
imp7 <- mice(dat,method="norm",predictorMatrix=predMat)
)
```

c. Fit again a linear model relating X to Y on the imputed dataset. Are the estimates accurate?
d. Now use multiple imputation using default settings in which X is imputed based on Y. Fit the linear model relating X to Y. Are the estimates accurate?

Part B: Imputation in a real data application

In this exercise we study specification of the imputation model using a (modified version of a) real data set. The Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD) study was a prospective multicenter cohort study in which patients with end stage renal disease were included at dialysis initiation if they were 18 years or older and had no previous kidney transplantation and no previous dialysis. Patients were followed for several outcomes. Here we focus on the outcome death (yes/no). The research question of interest is whether the type of dialysis - peritoneal dialysis (PD) versus hemodialysis (HD) - is related to the risk of dying.

(Some background: With HD, blood is pumped out of the patient’s body and filtered by an artificial kidney machine. With PD, cleansing fluid is pumped into the patient’s abdominal cavity and the lining of the abdomen acts as a natural filter to wash out waste and toxins.)

1. **Data import and exploration**
   a. Import the data file ‘necosad_death_miss.csv’ into your R session and store it in a dataframe named ‘dat’.
   b. Explore the data set and missing data patterns using e.g. the functions ‘str’, ‘summary’ and ‘md.pattern’.

2. **Complete case analysis**
   a. Relate death to therapy type (peritoneal versus hemodialysis) using logistic regression. Perform first a univariable ‘unadjusted’ regression including only ‘therapy’ and then perform a model additionally including all 7 other covariates as they are potential confounders for the relation between therapy and death.
   b. Look at the difference in estimated odds ratio for therapy between the two models: does adding the potential confounders change the estimate of the therapy effect?
   c. How many patients are used in each of the analyses? How does that impact your answer to question b?

3. **Multiple imputation based on linear regression for gfr**

a. Use multiple imputation (with m=5). The default setting of mice is to use predictive mean matching for numeric data. We here change that setting for the variable ‘gfr’. In particular, specify that you would like to use ‘Bayesian linear model’ for imputing ‘gfr’. You can do this by setting the ‘method’ argument to “norm” for ‘gfr’.

   (Hint:

   ```
   #extract default methods settings
   ini <- mice(dat, maxit = 0)
   meth <- ini$meth
   meth
   #change the method for “gfr”
   meth["gfr"] <- "norm"
   meth
   #use the new ‘meth’ settings during imputation
   imp1 <- mice(dat,method=meth, m=5))
   ```

b. Run the multivariable logistic regression now using the imputed data and compare the odds ratios for gfr and for therapy with those from the complete case analysis in 2b.

c. Explore the imputed values especially for ‘gfr’ and compare these to the distribution of the original gfr values. Did the imputation give plausible values for ‘gfr’?

4. Multiple imputation based on linear regression for log(gfr)

a. Transform the gfr variable using a log(x+1) transformation. Explore distribution of this transformed variable.

   (hint:

   ```
   dat$loggfr <- log(dat$gfr+1))
   ```

b. Redo the imputation after log-transforming the ‘gfr’ variable. You have to additionally tell mice not to use the original ‘gfr’ variable during imputation

   (Hint:

   ```
   ini <- mice(dat, maxit = 0)
   # define methods for imputation
   meth["loggfr"] <- "norm"
   meth["gfr"] <- "~I(exp(loggfr)-1)"
   # and do not use gfr in the imputation models
   predMat <- ini$predictorMatrix
   predMat[,"gfr"] <- 0
   imp2 <- mice(dat,method=meth,predictorMatrix = predMat, m=5))
   ```

c. Check the distribution of the imputed ‘gfr’ variable. Are the values plausible now?

d. Run the multivariable logistic regression now using the data imputed after log transformation and compare the odds ratios for gfr and for therapy with those from the analysis in b. Did the improvement of the imputation method change the odds ratios for therapy and gfr?