Imputing missing data

MEVM04

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November 23, 2015

1 Introduction

Missing values are common in clinical research and can occur for many reasons. Crudely, they can be separated into missing values on the predictor(s) (x, also known as independent variables) and on the outcome(s) (y, also known as dependent variables).

In the first case, missing data might occur because a participant did not wish to disclose information on their weight (here, a predictor); in the second case, observations might be missing because the blood pressure gauge had malfunctioned when the participant's blood pressure was measured. Whether a value is missing on x or y affect our ability to 1) do something about it, and 2) the consequences for our results. In this text, we will deal with each instance of missing values in turn.

A common choice when data is missing is *case deletion*: deleting each observation for which a value is missing, which is also known as doing a complete cases analysis. Many common statistical models, analysis of variance for instance, requires complete cases to work properly, whilst some, such as tree-based models, do not [1]; such models, however, are beyond the scope of this text. Whilst it is frequent, case deletion is generally bad practice since it can lead to unpredictable bias [2] and inefficiency [3].

A better alternative to case deletion is *imputation*, which is when you fill in (impute) missing values based on information given by other variables. In its simplest form, missing data on a person's weight might be substituted with the mean weight of the entire group (though as we shall see there are much better options available).

This text is an assignment for a class in my master's programme: *MEVMo4*, wherein I have attempted to outline the basics of missing data with a focus on how to handle missing valued on predictor variables using imputation. The text is based heavily on books by Steyerberg [4] and Harrell [5]; as a final step, I have provided a worked-through example given in the latter book.

As a secondary objective, this text is an attempt of reproducible research using *knitR* for *R* (R Core Team). All of the files used to produce this text (including plots and statistical analyses) will therefore be provided publicly on Github at https://github.com/Hjalt/mevmo4imput.

2 Types of missing data

Apart from whether predictor or outcome variables are missing, there are three types of missing data:

MCAR Missing Completely At Random

MAR Missing At Random

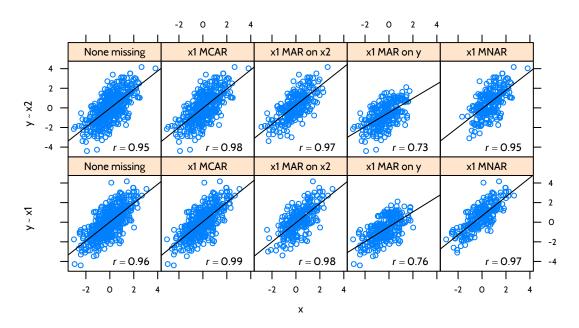


Figure 1: Different types of missing data and their effects on the correlation coefficient. x1 and x2 are normally distributed. The true correlation coefficients (r) are 1. Only when data is MAR on y is the correlation coefficient noticeably erroneous. This example has been adapted from Steyerberg [4]

MNAR Missing Not At Random

MCAR means that there is no pattern to why the data is missing; perhaps the scale had malfunctioned and weight data had to be discarded. When data is MAR there is conversely a pattern to its absence, although that pattern is apparent from the data – younger people might for example have refused to be weighed more frequently (and we recorded age). Lastly, when data is MNAR there is a pattern that cannot be deciphered from the available data. Perhaps people of lower income did not want to step up on the scale but we did not measure income. MNAR is a particularly problematic form since it is by definition impossible to understand if and how it might be affecting the results.

3 Missing data on independent variables

The situation where data is missing on predictors deserves most attention as it is both common and manageable, whilst being detrimental to our results (if not taken care of).

In Figure 1 various scenarios of missing predictor values have been simulated from a simple linear model

$$y = x1 + x2 + error$$

Here, x1, x2, and the error term are generated from a normal distribution with a mean of 0, and a standard deviation of 1, 1, and 0.1 respectively. Thus, the true slope of the relationship is r = 1, which can be seen from the first panel. This example has been adapted and revised from the code excerpts from Steyerberg [4].

When data is MCAR on x1, the foremost consequence is that we lose statistical power. If for instance every other participant had one variable missing out of 5, this would mean that half of the sample was dropped from the analysis, even though only 10% of the data was missing. As we see on the slope, however, data that is MCAR does not actually affect the estimate, simply because it is random and not systematic missingness.

In the third panel, x1 is missing for lower levels of x2, which is a case of MAR. Here, too, is the slope unbiased (but would not be if the relationship was different for lower, compared with higher, values of x2.

In the fourth panel, x1 is missing for higher levels of y – also a case of MAR. We can see here that the slope estimate is biased low (r = 0.73 for x1 and r = 0.76 for x2).

Finally, in the fifth panel, x1 is missing for higher values of x1 – a pattern that cannot be deduced from the data. This is an instance of MNAR. The slope is unbiased in this instance, which is related to missingness of x1 being related to x1 itself. If there was a third variable in the mix, to which x1 owed its missingness, the results would be different.

4 Single imputation

4.1 Simple mean imputation

A simple, but flawed, option is to replace missing values with the mean of the variable, which is suboptimal because it fails to take advantage of patterns in the data, i.e., correlations between variables that otherwise can improve the accuracy of imputations. Moreover, it underestimates the variance (the randomness) of the estimates, which leads to overconfidence in the estimates.

Better options exist in conditional mean imputation, stochastic regression imputation, and multiple imputation.

4.2 Conditional mean imputation

In conditional mean imputation (or regression imputation), missing data on a variable are imputed using the patters of how the variable correlates with other variables. As with simple mean imputation, however, conditional mean imputation underestimates the variance of the imputations; if, for example, we were to impute missing values in Figure 1 with conditional mean imputation, all those values would lie along the imputation slope and this would not reflect the true nature of variance.

4.3 Stochastic regression imputation

Stochastic regression imputation alleviates the issue of underestimated variance by randomly sampling from the distribution of predicted values, that is, the distribution that in conditional mean imputation would have been used to compute the mean, whereby it simulates the random error that is inherent to all real measurements.

5 Multiple imputation

Though single imputation techniques are efficient and sometimes adequate, they present one drawback in that the randomness inherent to the imputation step itself is not explicitly covered in the analysis. The simplest way of looking at this is to consider that only after we are done imputing do we conduct

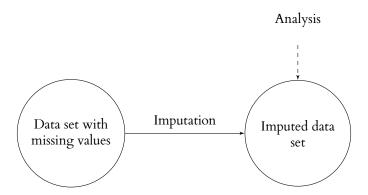


Figure 2: Flow chart of single imputation models.

our analysis 2, which means that any bias we introduce with our imputation model is disregarded – this poses a serious problem for the external validity of our model.

This issue is solved with *multiple imputation*, a statistical technique that was designed by Rubin [6] as a flexible method for dealing with missing data. In multiple imputation, several data sets are produced by random sampling from the original data set. In each of these sets an imputation model is fit (as in conditional mean imputation) and a estimate is established as an aggregate of all of these data sets. Because we are then including the variance of imputation in the aggregate, we directly take bias from the imputation step into account.

5.1 Chained equations

If data is missing on several variables, it might be necessary to impute in steps, which is known as chained equations multiple imputation. It works by first imputing data on one variable, then creating a new sample from the original data plus the imputations, and thereafter repeating the imputation step. This iterative process can proceed for as long as desired, but most software use a stopping-rule to drop out of the loop at some preestablished point.

6 Missing data on dependent variable

Observations with missing data on the dependent variable (outcome) are commonly excluded from the analysis. And if they are MCAR, there is an argument to do so since no additional information can be gathered from the remaining data if the variable of interest is missing [5].

Yet, when data on Y is MAR, bias might occur. Harrell recommends that researchers should as a minimum characterize any patterns of missingness, and simulation studies show that there are benefits to imputation also on y [7].

7 Issues with imputation

In imputation we assume that data is MAR, i.e. we are able to figure out from the rest of the variables why data is missing. However, this assumption is by definition not testable [8] (but becomes increasingly tenable as more variables are measured).

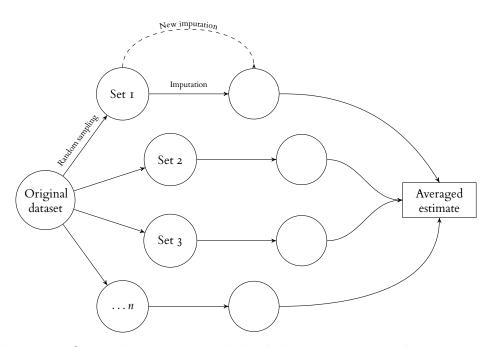


Figure 3: Flow chart of multiple imputation model with chained equations. The entire situation is only visualized for *Set 1*.

If the assumption does not hold and data is instead MNAR then imputation can only lead to increased bias, and it would be advisable to stick to case deletion. However, as many empirical as well as simulation experiments have shown, imputation generally leads to less bias and more efficiency with relatively little bias.

8 A worked-through example

- 8.1 Explore the variables and patterns of missing data in the SUPPORT dataset.
- 8.1.1 Print univariate summaries of all variables. Make a plot (showing all variables on one page) that describes especially the continuous variables.

We start with some descriptive variables

```
library(Hmisc)

# Load the SUPPORT data set.
getHdata(support)

# Total proportion of missing values
sum(sapply(support, is.na))/length(sapply(support, is.na))

## [1] 0.1375429

# Print some summary statistics of every variable
describe(support)
```

```
## support
##
## 35 Variables 1000 Observations
## age : Age
 n missing unique Info Mean .05 .10
## 1000 0 970 1 62.47 33.76 38.91 51.81
## .50 .75 .90 .95
## 64.90 74.50 81.87 86.00
##
## lowest : 18.04 18.41 19.76 20.30 20.31
## highest: 95.51 96.02 96.71 100.13 101.85
## -----
## death : Death at any time up to NDI date:31DEC94
## n missing unique Info Sum Mean
## 1000 0 2 0.67 668 0.668
## -----
## n missing unique
## 1000 0 2
## female (438, 44%), male (562, 56%)
## -----
## hospdead : Death in Hospital
## n missing unique Info Sum Mean
## 1000 0 2 0.57 253 0.253
## slos : Days from Study Entry to Discharge
  n missing unique Info Mean .05 .10 .25
  1000 0 88 1 17.86
.50 .75 .90 .95
11 20 37 53
##
                              4
                                   4
##
              37
##
##
## lowest : 3 4 5 6 7, highest: 145 164 202 236 241
## -----
## d.time : Days of Follow-Up
## n missing unique Info Mean .05 .10 .25
## 1000 0 582 1 475.7 5.0 8.0 27.0
            .90
  .50 .75
##
                   .95
## 256.5 725.0 1464.3 1757.1
##
## lowest: 3 4 5 6 7
## highest: 2006 2011 2022 2024 2029
## -----
## dzgroup
## n missing unique
```

```
## 1000 0 8
##
##
    ARF/MOSF w/Sepsis COPD CHF Cirrhosis Coma Colon Cancer
## Frequency
                  391 116 143 55 60 49
## %
                   39 12 14
                                 6 6
                                              5
     Lung Cancer MOSF w/Malig
## Frequency 100 86
## %
              10
                        9
## -----
## dzclass
## n missing unique
    1000 0 4
##
##
## ARF/MOSF (477, 48%)
## COPD/CHF/Cirrhosis (314, 31%)
## Coma (60, 6%), Cancer (149, 15%)
## -----
## num.co : number of comorbidities
  n missing unique Info Mean
## 1000 0 8 0.94 1.886
##
     0 1 2 3 4 5 6 7
## Frequency 120 337 269 151 76 29 17 1
       12 34 27 15 8 3 2 0
## -----
## edu : Years of Education
  n missing unique Info Mean .05 .10 .25
##
    798 202 25 0.97 11.78 6 8
                                             10
    .50
         .75
##
                .90 .95
    12
##
          14
                16
                      18
## lowest : 0 1 2 3 4, highest: 20 21 22 24 30
## income
## n missing unique
   651 349 4
##
##
## under $11k (309, 47%), $11-$25k (161, 25%)
## $25-$50k (106, 16%), >$50k (75, 12%)
## -----
## scoma : SUPPORT Coma Score based on Glasgow D3
## n missing unique Info Mean .05 .10 .25
## 1000 0 11 0.65 11.74 0.0 0.0 0.0
## .50 .75 .90 .95
##
   0.0 9.0 44.0 62.4
##
```

```
## 0 9 26 37 41 44 55 61 89 94 100
## Frequency 704 83 58 24 19 45 11 6 8 7 35
## % 70 8 6 2 2 4 1 1 1 1 4
## -----
## charges : Hospital Charges
  n missing unique Info Mean .05 .10
                                            .25
    975 25 967 1 56271 3757 4688 10029
.50 .75 .90 .95
##
##
## 26499 63622 147109 223582
##
## lowest: 1636 1680 1830 2045 2082
## highest: 504660 538323 543761 706577 740010
## -----
## totcst : Total RCC cost
  n missing unique Info Mean .05 .10 .25
   895 105 895 1 30490 2484 3081 5899
.50 .75 .90 .95
## 15110 37598 72906 114932
##
## lowest : 0 1162 1201 1285 1396
## highest: 269131 299966 338955 357919 390461
## totmcst : Total micro-cost
    n missing unique Info Mean .05 .10
   628 372 617 1 26168 1653 2548 5297
##
    .50
          .75
               .90
                      .95
##
  13828 33691 66229 96753
##
##
## lowest: 0.0 829.6 834.6 914.4 1016.4
## highest: 154709.0 198047.0 234875.9 246904.0 271467.2
## -----
## avtisst : Average TISS, Days 3-25
## n missing unique Info Mean .05 .10 .25
    994 6 241 1 22.64 6.00 8.00 12.00
.50 .75 .90 .95
    .50
  19.00 31.75 43.33 48.00
##
##
## lowest : 1.667 2.500 3.000 3.500 4.000
## highest: 58.500 59.000 60.000 61.000 64.000
## race
## n missing unique
## 995 5 5
##
     white black asian other hispanic
## Frequency 781 157 9 12 36
```

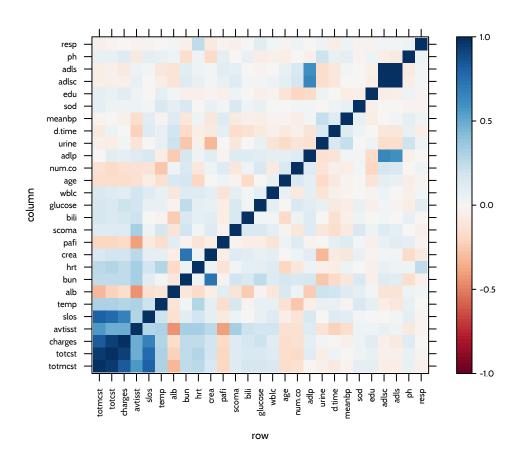
```
## % 78 16 1 1 4
## -----
## meanbp : Mean Arterial Blood Pressure Day 3
## n missing unique Info Mean .05 .10 .25
   1000 0 122 1 84.98 47.00 55.00 64.75
.50 .75 .90 .95
##
   .50
##
   78.00 107.00 120.00 128.05
##
##
## lowest : 0 20 27 30 32, highest: 155 158 161 162 180
## -----
## wblc : White Blood Cell Count Day 3
  n missing unique Info Mean .05 .10 .25
                  1 12.4 2.475 4.800 6.899
   976 24 282
##
  .50 .75 .90 .95
##
## 10.449 15.500 22.248 27.524
## lowest: 0.05000 0.06999 0.09999 0.14999 0.19998
## highest: 60.00000 61.19531 67.09375 79.39062 100.00000
## -----
## hrt : Heart Rate Day 3
  n missing unique Info Mean .05 .10
                                        .25
   1000 0 124 1 97.87 54.0 60.0 72.0
##
   .50 .75 .90 .95
##
   100.0 120.0 135.0 146.1
##
## lowest : 0 11 30 35 36, highest: 189 193 199 232 300
## -----
## resp : Respiration Rate Day 3
  n missing unique Info Mean .05 .10
                                       .25
  1000 0 45 0.99 23.49
##
                             9
                                  10
                                        18
   .50
        .75
             .90 .95
##
         29
    24
##
              36
                    40
##
## lowest : 0 4 6 7 8, highest: 48 49 52 60 64
## -----
## temp : Temperature (celcius) Day 3
  n missing unique Info Mean .05 .10 .25
  1000 0 64 1 37.08 35.50 35.80 36.20
##
             .90 .95
   .50 .75
##
  36.70 38.09 38.80 39.20
##
## lowest : 32.50 33.70 34.00 34.09 34.40
## highest: 40.20 40.59 40.90 41.00 41.20
## -----
## pafi : PaO2/(.01*FiO2) Day 3
## n missing unique Info Mean .05 .10 .25
```

```
## 747 253 463 1 244.2 92.61 115.00 156.33
  .50 .75 .90 .95
##
## 226.66 310.00 400.00 442.81
## lowest : 34.00 39.00 45.00 48.00 53.33
## highest: 600.00 623.75 640.00 680.00 869.38
## -----
## alb : Serum Albumin Day 3
    n missing unique Info Mean .05 .10 .25
    622 378 38 1 2.917 1.800 2.000 2.400
##
    .50
         .75
               .90
                     .95
  2.800 3.400 4.000 4.199
##
##
## lowest : 1.100 1.200 1.300 1.400 1.500
## highest: 4.500 4.600 4.699 4.800 4.899
## -----
## bili : Bilirubin Day 3
## n missing unique Info Mean .05 .10 .25
    703 297 115 1 2.527 0.3000 0.3000 0.5000
.50 .75 .90 .95
   .50
## 0.7999 1.7998 5.8594 12.5896
## lowest : 0.09999 0.19998 0.29999 0.39996 0.50000
## highest: 32.39844 33.00000 35.00000 39.29688 50.09375
## -----
## crea : Serum creatinine Day 3
  n missing unique Info Mean .05 .10
   997 3 87 1 1.808 0.6000 0.7000 0.8999
.50 .75 .90 .95
##
          .75
##
## 1.2000 1.8999 3.6396 5.5996
## lowest: 0.3 0.4 0.5 0.6 0.7
## highest: 10.4 10.6 11.2 11.6 11.8
## -----
## sod : Serum sodium Day 3
  n missing unique Info Mean .05 .10 .25
                                129 131
##
  1000 0 42 1 137.7
                                            134
##
   .50
          .75
               .90
                     .95
         141 145
    137
##
                     148
## lowest : 118 120 121 122 123, highest: 156 157 158 168 175
## -----
## ph : Serum pH (arterial) Day 3
    n missing unique Info Mean .05 .10
##
                                           .25
    750 250 53 1 7.416 7.289 7.319 7.380
.50 .75 .90 .95
##
##
```

```
## 7.420 7.470 7.500 7.520
##
## lowest : 6.960 6.989 7.069 7.119 7.130
## highest: 7.590 7.600 7.609 7.659 7.670
## -----
## glucose : Glucose Day 3
  n missing unique Info Mean .05 .10 .25
   530 470 226 1 156.4 74.0 82.0 100.0
   .50 .75 .90 .95
##
  128.0 185.0 269.3 327.5
##
## lowest : 11 25 30 42 51, highest: 492 512 528 576 598
## -----
## bun : BUN Day 3
  n missing unique Info Mean .05 .10 .25
545 455 106 1 32.61 7.0 9.0 14.0
.50 .75 .90 .95
##
  23.0 43.0 68.6 88.8
##
##
## lowest : 1 2 3 4 5, highest: 124 125 127 128 146
## -----
## urine : Urine Output Day 3
## n missing unique Info Mean .05 .10 .25
   483 517 359 1 2194 141.7 600.0 1208.5
.50 .75 .90 .95
## 1925.0 2900.0 4087.6 4822.5
## lowest: 0 1 5 8 15
## highest: 7275 7360 7455 7560 7750
## -----
## adlp : ADL Patient Day 3
## n missing unique Info Mean
## 366 634 8 0.84 1.246
##
        0 1 2 3 4 5 6 7
## Frequency 194 73 28 20 12 19 16 4
    53 20 8 5 3 5 4 1
## -----
## adls : ADL Surrogate Day 3
## n missing unique Info Mean
   690 310 8 0.9 1.755
##
##
    0 1 2 3 4 5 6 7
## Frequency 313 126 54 39 42 34 52 30
## % 45 18 8 6 6 5 8 4
```

```
## sfdm2
## n missing unique
##
    841 159 5
##
## no(M2 and SIP pres) (326, 39%)
## adl>=4 (>=5 if sur) (111, 13%)
## SIP>=30 (59, 7%), Coma or Intub (7, 1%)
## <2 mo. follow-up (338, 40%)
## adlsc : Imputed ADL Calibrated to Surrogate
  n missing unique Info Mean .05 .10 .25
## 1000 0 251 0.97 1.98 0.000 0.000 0.000
## .50 .75 .90 .95
## 1.670 3.042 5.000 6.000
##
## lowest : 0.0000 0.4948 0.4948 1.0000 1.1667
## highest: 5.9932 6.0000 6.3398 6.4658 7.0000
```

To make a plot, we first drop the categorical variables from the data set, then we compute a correlation matrix, reorganize it with a factor analysis and then plot it using the facilities of levelplot in lattice.

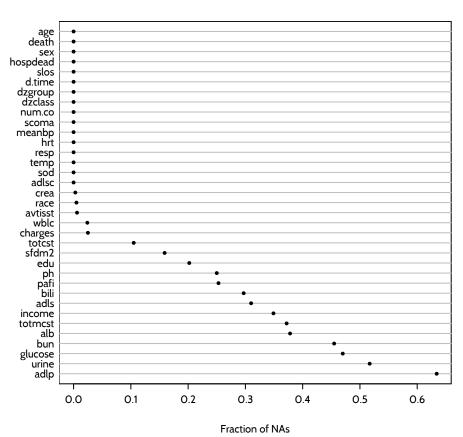


8.2 Make a plot showing the extent of missing data and tendencies for some variables to be missing on the same patients.

We use Harrel's Hmisc package to plot the relationships of missingness between variables.

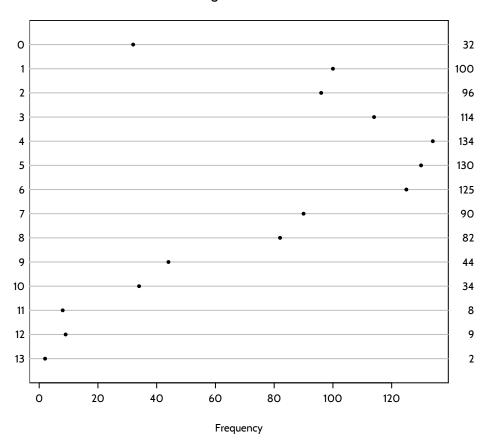
```
library(Hmisc)
naplot(naclus(support), which = "all")
```

Fraction of NAs in each Variable

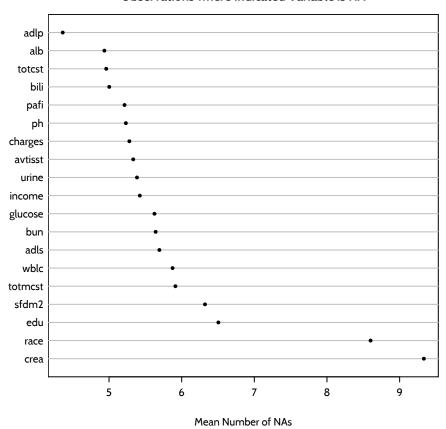


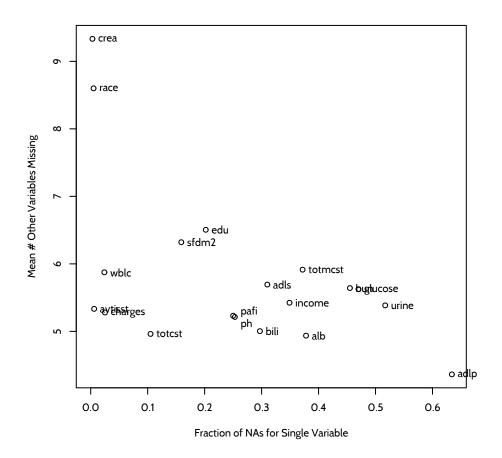
14

Number of Missing Variables Per Observation



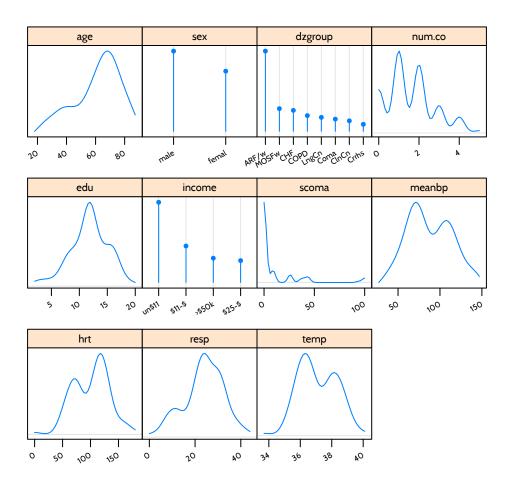
Mean Number of Other Variables Missing for Observations where Indicated Variable is NA





8.3 Total hospital costs (variable totcst) were estimated from hospitalspecific Medicare cost-to-charge ratios. Characterize what kind of patients have missing totcst. For this characterization use the following patient descriptors: age, sex, dzgroup, num.co, edu, income, scoma, meanbp, hrt, resp, temp.

We can solve this by plotting distributions of the various variables involved.



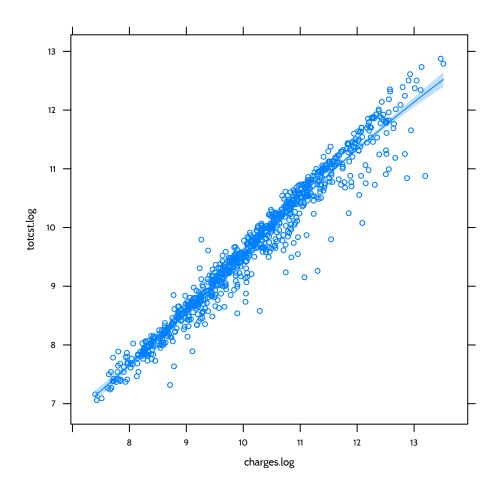
8.4 Prepare for later development of a model to predict costs by developing reliable imputations for missing costs. Remove the observation having zero totcst.

We start by removing values for which the outcome (totcst) is missing or zero.

```
support.complete <- subset(support, !is.na(totcst) & totcst > 0)
```

8.4.1 The cost estimates are not available on 105 patients. Total hospital charges (bills) are available on all but 25 patients. Relate these two variables to each other with an eye toward using charges to predict totost when totost is missing. Make graphs that will tell whether linear regression or linear regression after taking logs of both variables is better.

```
panel.xyplot(...)
panel.smoother(..., span = 0.9)
})
```



8.4.2 Impute missing total hospital costs in SUPPORT based on a regression model relating charges to costs, when charges are available.

We need to specify an imputation model, which means we need to find the slope and intercept of the regression model

8.4.3 Compute the likely error in approximating total cost using charges by computing the median absolute difference between predicted and observed total costs in the patients having both variables available. If you used a log transformation, also compute the median absolute percent error in imputing total costs by anti-logging the absolute difference in predicted logs.

We start in reverse with the mmedian absolute percent error:

Next, the median absolute deviation:

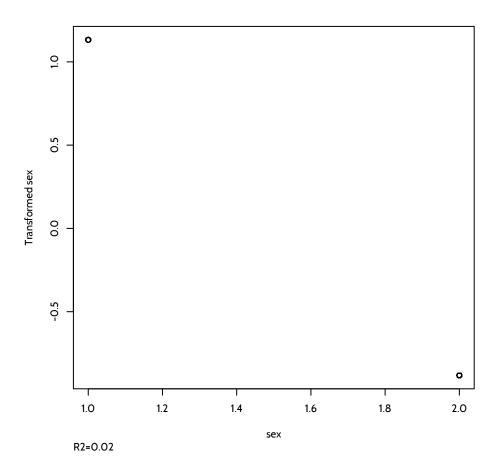
8.5 State briefly why single conditional median imputation is OK here.

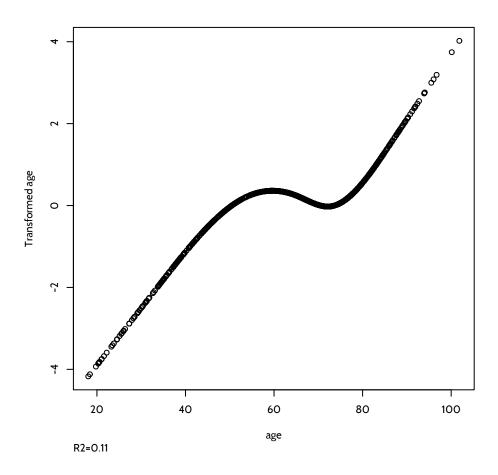
```
lm.cc <- lm(totcst ~ charges, support.complete)
lm.im <- lm(totcst ~ charges, support.tf)</pre>
```

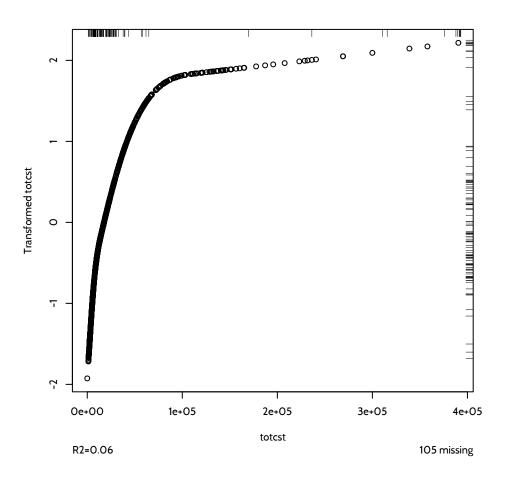
Although we have quite a large proportion of missing values (14%), we are introducing very little bias since our median absolute percent error is only 1.18%. Simply put: because all observed outcomes lie close to the predicted ones, the bias we get from assuming that our missing values are on the slope is neglible.

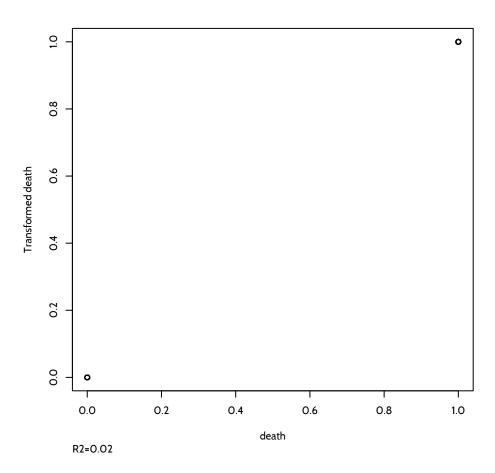
8.6 Use transcan to develop single imputations for total cost, commenting on the strength of the model fitted by transcan as well as how strongly each variable can be predicted from all the others.

I decided to pick only some of the variables.









```
summary(support.trans)
## transcan(x = \sim sex + age + totcst + death, imputed = T, transformed = TRUE,
##
      data = support)
##
## Iterations: 5
##
## R-squared achieved in predicting each variable:
##
##
             age totcst death
      sex
    0.019 0.113 0.058 0.022
##
## Adjusted R-squared:
##
##
             age totcst death
      sex
##
   0.014 0.106 0.050 0.017
## Coefficients of canonical variates for predicting each (row) variable
##
```

```
sex age totcst death
        0.70 0.83 -0.95
## sex
## age 0.26 -0.87 0.84
## totcst 0.37 -1.04 0.35
## death -0.03 0.07 0.02
## Summary of imputed values
##
## totcst
                                                   .25
##
     n missing unique Info Mean .05 .10
     105 0 99 1 55123
                                      5853 7291
                                                   8965
           .75
                  .90
##
     .50
                         .95
##
   14743 28658 210999 390460
##
## lowest : 1528 1719 2213 4376
                                  4595
## highest: 238595 313517 313661 375291 390460
## Starting estimates for imputed values:
##
##
        sex
                 age
                        totcst
                                 death
##
     2.0000 64.8965 15110.1000
                               1.0000
```

totcst can be imputed beneficially by sex and age but not by death.

8.7 Use predictive mean matching to multiply impute cost 10 times per missing observation. Describe graphically the distributions of imputed values and briefly compare these to distributions of non-imputed values. State in a simple way what the sample variance of multiple imputations for a single observation of a continuous predictor is approximating.

We use the aregImpute function here.

```
Iteration 11
Iteration 12
Iteration 13
support.aregImp
##
## Multiple Imputation using Bootstrap and PMM
##
## aregImpute(formula = ~age + sex + slos + num.co + totcst + charges,
      data = support, n.impute = 10, type = "pmm")
##
##
## n: 1000 p: 6 Imputations: 10
                                  nk: 3
##
## Number of NAs:
      age sex slos num.co totcst charges
                     0
              0
       0
                               0
                                     105
                                             2.5
##
##
          type d.f.
##
## age
             S
## sex
             С
## slos
                  2
                  2
## num.co
## totcst
           s 2
## charges
          S
##
## Transformation of Target Variables Forced to be Linear
## R-squares for Predicting Non-Missing Values for Each Variable
## Using Last Imputations of Predictors
   totcst charges
   0.908 0.910
```

The sample variance of multiple imputations is approximating the measurement error that comes from the imputation itself. Since we are fitting an imputation model to the data, our imputed values are also following the random error of those fits; with multiple imputations, we can estimate that bias, which in turn will yield estimates that are less biased that those from single imputations.

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