432 Class 10 Slides

github.com/THOMASELOVE/2020-432

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Setup

```r
library(skimr); library(janitor)
library(simputation); library(broom)
library(rms) # note: also loads Hmisc
library(tidyverse)
```

Today's Materials

- Hormone Therapy and Baseline Cholesterol Levels in the `HERS` clinical trial

The HERS trial is described in Vittinghoff et al., especially Chapter 4.

Hormone Therapy and Baseline ldl in the HERS Trial

HERS clinical trial of hormone therapy (`ht`). We're excluding the women with diabetes here.

```
hers <- read_csv("data/hersdata.csv") %>% clean_names()

hers1 <- hers %>%
    filter(diabetes == "no") %>%
    select(subject, ldl, ht, age, smoking, drinkany, sbp,
           physact, bmi, diabetes)
```

Data describe 2032 women without diabetes

```r
head(hers1)
```

```
# A tibble: 6 x 10
  subject   ldl ht      age smoking drinkany   sbp physact
    <dbl> <dbl> <chr> <dbl> <chr>   <chr>    <dbl> <chr>
1       1  122. plac~    70 no      no         138 much m~
2       2  242. plac~    62 no      no         118 much l~
3       4  116. plac~    64 yes     yes        152 much l~
4       5  151. plac~    65 no      no         175 somewh~
5       6  138. horm~    68 no      yes        174 about ~
6       8  121. horm~    69 no      no         178 much m~
# ... with 2 more variables: bmi <dbl>, diabetes <chr>
```

The Codebook (n = 2032)

Variable	Description	Missing?
`subject`	subject code	0
`ldl`	LDL cholesterol in mg/dl	7
`HT`	factor: hormone therapy or placebo	0
`age`	age in years	0
`smoking`	yes or no	0
`drinkany`	yes or no	2
`sbp`	systolic BP in mm Hg	0
`physact`	5-level factor	0
`bmi`	body-mass index in kg/m^2	2
`diabetes`	yes or no (all of these are no)	0

Our Modeling Goal

Predict `ldl` using

- `age`
- `smoking`
- `drinkany`
- `sbp`
- `physact`
- `bmi`
- the interaction of `smoking` and `bmi`

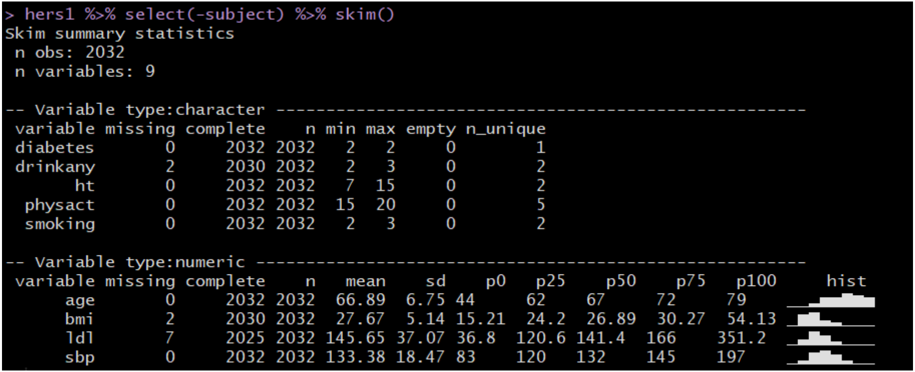
Details on physact variable

```
hers1 %>% count(physact)
```

```
# A tibble: 5 x 2
  physact                   n
  <chr>                 <int>
1 about as active         674
2 much less active        107
3 much more active        252
4 somewhat less active    322
5 somewhat more active    677
```

Skim?

```r
hers1 %>% select(-subject) %>% skim()
```



```
> hers1 %>% select(-subject) %>% skim()
Skim summary statistics
 n obs: 2032
 n variables: 9

-- Variable type:character ---------------------------------------------------------
 variable missing complete    n min max empty n_unique
 diabetes       0     2032 2032   2   2     0        1
 drinkany       2     2030 2032   2   3     0        2
       ht       0     2032 2032   7  15     0        2
  physact       0     2032 2032  15  20     0        5
  smoking       0     2032 2032   2   3     0        2

-- Variable type:numeric -----------------------------------------------------------
 variable missing complete    n   mean    sd    p0   p25    p50   p75  p100     hist
      age       0     2032 2032  66.89  6.75 44     62    67     72    79
      bmi       2     2030 2032  27.67  5.14 15.21  24.2  26.89  30.27 54.13
      ldl       7     2025 2032 145.65 37.07 36.8  120.6 141.4  166   351.2
      sbp       0     2032 2032 133.38 18.47 83    120   132    145   197
```

Missingness pattern?

```
na.pattern(hers1) # from Hmisc
```

```
pattern
0000000000 0000000010 0000010000 0100000000 
      2021          2          2          7 
```

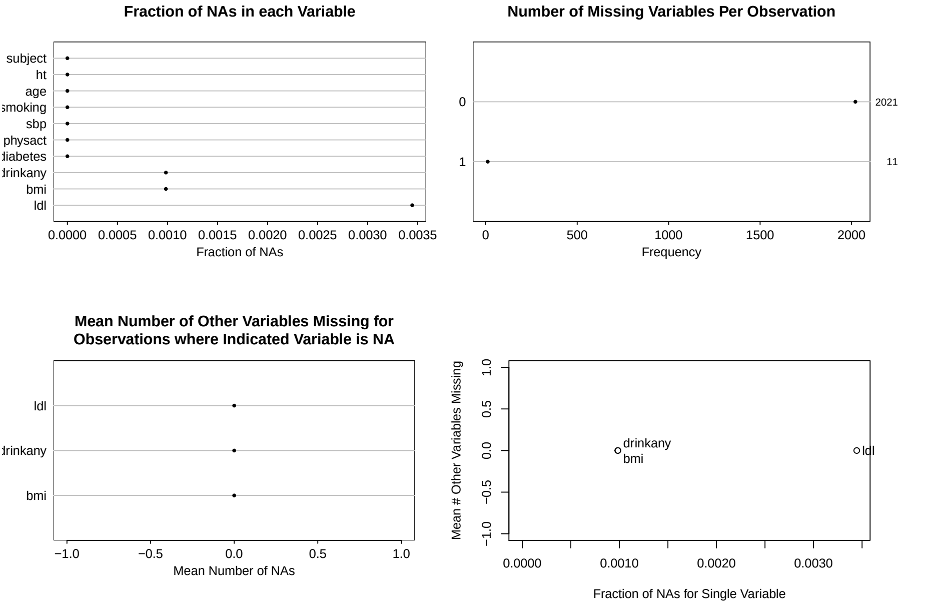
```
names(hers1)
```

```
 [1] "subject"  "ldl"      "ht"       "age"      "smoking" 
 [6] "drinkany" "sbp"      "physact"  "bmi"      "diabetes"
```

Next slide

```
par(mfrow = c(2,2))
naplot(naclus(hers1))
par(mfrow = c(1,1))
```

naplot(naclus(hers1))



Simple Imputation into `hers2`

Simple Imputation for drinkany, bmi and ldl

Since drinkany is a factor, we have to do some extra work to impute.

```r
set.seed(432092)

hers2 <- hers1 %>%
    mutate(drinkany_n =
               ifelse(drinkany == "yes", 1, 0)) %>%
    impute_pmm(drinkany_n ~ age + smoking) %>%
    mutate(drinkany =
               ifelse(drinkany_n == 1, "yes", "no")) %>%
    impute_rlm(bmi ~ age + smoking + sbp) %>%
    impute_rlm(ldl ~ age + smoking + sbp + bmi)
```

Now, check missingness. . .

```r
na.pattern(hers2)
```

```
pattern
00000000000
       2032
```

```r
names(hers2)
```

```
 [1] "subject"    "ldl"        "ht"         "age"
 [5] "smoking"    "drinkany"   "sbp"        "physact"
 [9] "bmi"        "diabetes"   "drinkany_n"
```

Multiple Imputation with `aregImpute`

Multiple Imputation using `aregImpute` from `Hmisc`

Model to predict all missing values of any variables, using additive regression bootstrapping and predictive mean matching.

Steps are:

1. `aregImpute` draws a sample with replacement from the observations where the target variable is observed, not missing.
2. It then fits a flexible additive model to predict this target variable while finding the optimum transformation of it.
3. It then uses this fitted flexible model to predict the target variable in all of the original observations.
4. Finally, it imputes each missing value of the target variable with the observed value whose predicted transformed value is closest to the predicted transformed value of the missing value.

Fitting a Multiple Imputation Model

```
set.seed(4320132)
dd <- datadist(hers1)
options(datadist = "dd")
fit3 <- aregImpute(~ ldl + age + smoking + drinkany +
                        sbp + physact + bmi,
                     nk = c(0, 3:5), tlinear = FALSE,
                     data = hers1, B = 10, n.impute = 20)
```

```
Iteration 1 Iteration 2 Iteration 3 Iteration 4 Iteration 5 It
```

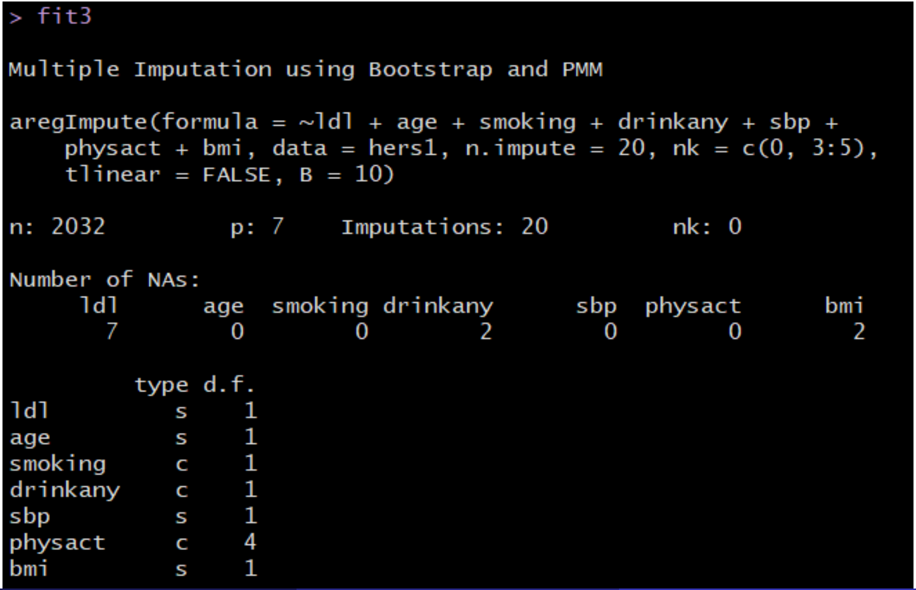
Multiple Imputation using `aregImpute` from `Hmisc`

`aregImpute` requires specifications of all variables, and several other details:

- `n.impute` = number of imputations, we'll run 20
- `nk` = number of knots to describe level of complexity, with our choice `nk = c(0, 3:5)` we'll fit both linear models and models with restricted cubic splines with 3, 4, and 5 knots
- `tlinear = FALSE` allows the target variable to have a non-linear transformation when `nk` is 3 or more
- `B = 10` specifies 10 bootstrap samples will be used
- `data` specifies the source of the variables

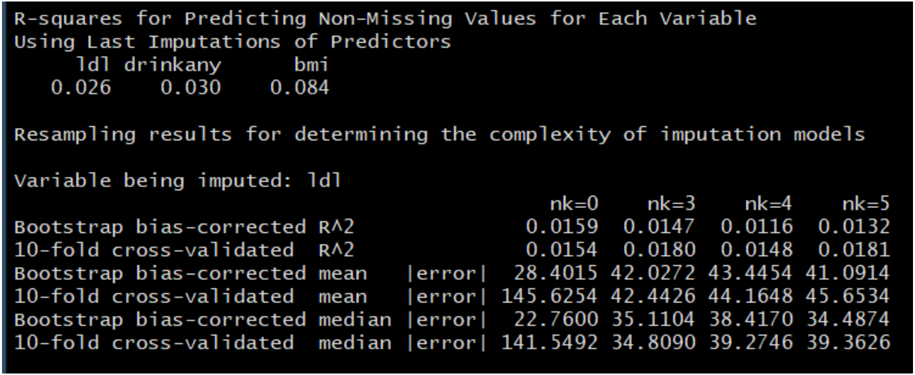
aregImpute Imputation Results (1 of 3)

```
fit3
```



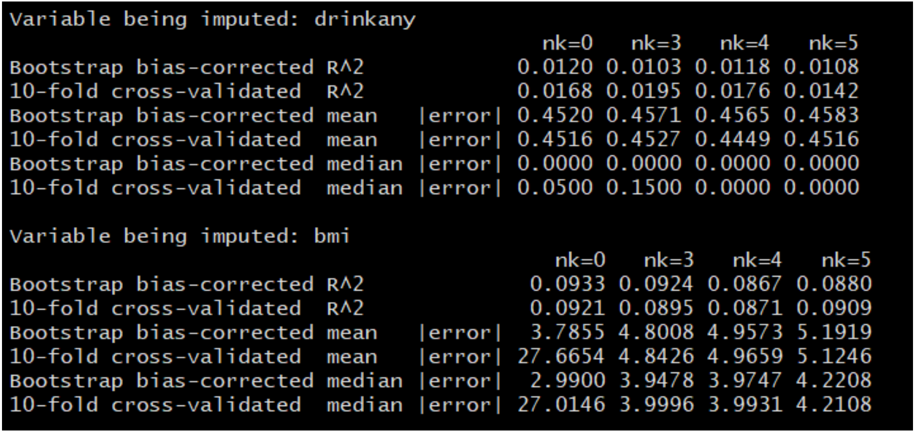
```
> fit3

Multiple Imputation using Bootstrap and PMM

aregImpute(formula = ~ldl + age + smoking + drinkany + sbp +
    physact + bmi, data = hers1, n.impute = 20, nk = c(0, 3:5),
    tlinear = FALSE, B = 10)

n: 2032        p: 7    Imputations: 20         nk: 0

Number of NAs:
     ldl      age  smoking drinkany      sbp  physact      bmi
       7        0        0        2        0        0        2

        type d.f.
ldl        s    1
age        s    1
smoking    c    1
drinkany   c    1
sbp        s    1
physact    c    4
bmi        s    1
```

aregImpute Imputation Results (2 of 3)



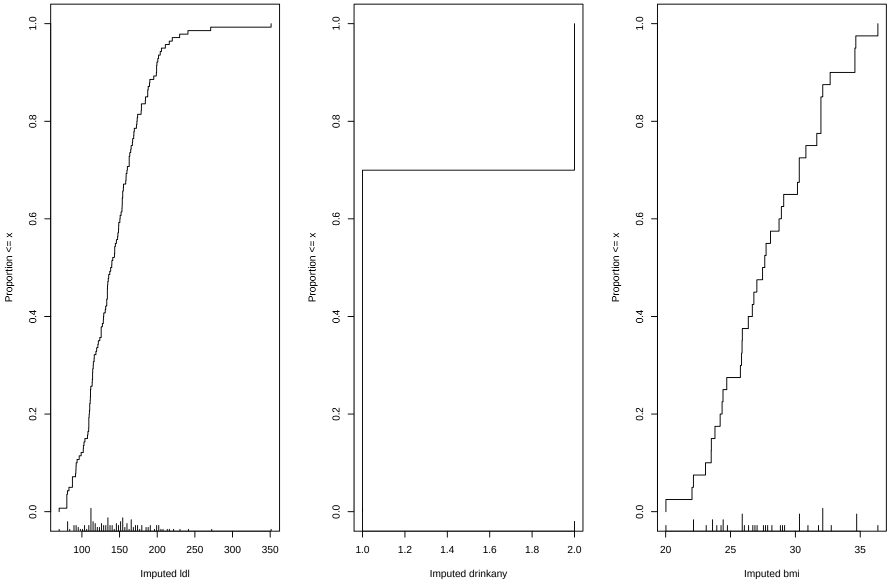
```
R-squares for Predicting Non-Missing Values for Each Variable
Using Last Imputations of Predictors
     ldl drinkany      bmi
   0.026    0.030    0.084

Resampling results for determining the complexity of imputation models

Variable being imputed: ldl
                                            nk=0    nk=3    nk=4    nk=5
Bootstrap bias-corrected R^2              0.0159  0.0147  0.0116  0.0132
10-fold cross-validated  R^2              0.0154  0.0180  0.0148  0.0181
Bootstrap bias-corrected mean   |error|  28.4015 42.0272 43.4454 41.0914
10-fold cross-validated  mean   |error| 145.6254 42.4426 44.1648 45.6534
Bootstrap bias-corrected median |error|  22.7600 35.1104 38.4170 34.4874
10-fold cross-validated  median |error| 141.5492 34.8090 39.2746 39.3626
```

aregImpute Imputation Results (3 of 3)



```
Variable being imputed: drinkany
                                          nk=0   nk=3   nk=4   nk=5
Bootstrap bias-corrected R^2            0.0120 0.0103 0.0118 0.0108
10-fold cross-validated  R^2            0.0168 0.0195 0.0176 0.0142
Bootstrap bias-corrected mean   |error| 0.4520 0.4571 0.4565 0.4583
10-fold cross-validated  mean   |error| 0.4516 0.4527 0.4449 0.4516
Bootstrap bias-corrected median |error| 0.0000 0.0000 0.0000 0.0000
10-fold cross-validated  median |error| 0.0500 0.1500 0.0000 0.0000

Variable being imputed: bmi
                                           nk=0   nk=3   nk=4   nk=5
Bootstrap bias-corrected R^2             0.0933 0.0924 0.0867 0.0880
10-fold cross-validated  R^2             0.0921 0.0895 0.0871 0.0909
Bootstrap bias-corrected mean   |error|  3.7855 4.8008 4.9573 5.1919
10-fold cross-validated  mean   |error| 27.6654 4.8426 4.9659 5.1246
Bootstrap bias-corrected median |error|  2.9900 3.9478 3.9747 4.2208
10-fold cross-validated  median |error| 27.0146 3.9996 3.9931 4.2108
```

A plot of the imputed values. . . (results)



A plot of the imputed values... (code)

```
par(mfrow = c(1,3))
plot(fit3)
par(mfrow = c(1,1))
```

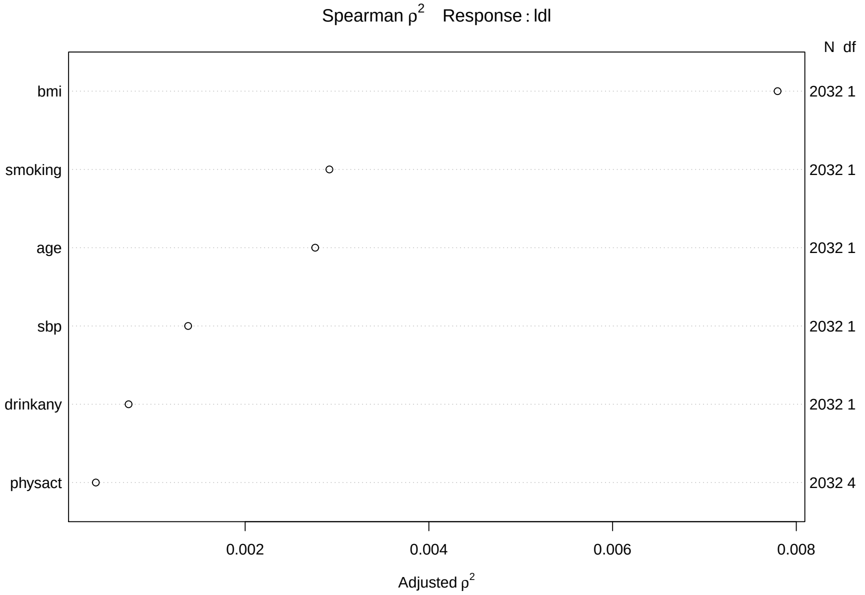
- For `ldl`, we imputed most of the 7 missing subjects in most of the 20 imputation runs to values within a range of around 120 through 200, but occasionally, we imputed values that were substantially lower than 100.
- For `drinkany` we imputed about 70% no and 30% yes.
- For `bmi`, we imputed values ranging from about 23 to 27 in many cases, and up near 40 in other cases.
- This method never imputes a value for a variable that doesn't already exist in the data.

Spearman ρ^2 Plot

We've already decided to include a bmi*smoking product term, but how should we prioritize the degrees of freedom we spend on non-linearity otherwise?

```
plot(spearman2(ldl ~ age + smoking + drinkany + sbp +
                         physact + bmi, data = hers2))
```

Spearman ρ^2 Plot Result



Fitting a Linear Regression with `ols`

Model we'll fit

Fitting a model to predict `ldl` using

- `bmi` with a restricted cubic spline, 5 knots
- `age` with a quadratic polynomial
- `sbp` as a linear term
- `drinkany` indicator
- `physact` factor
- `smoking` indicator and its interaction with `bmi`

We could fit this to the data

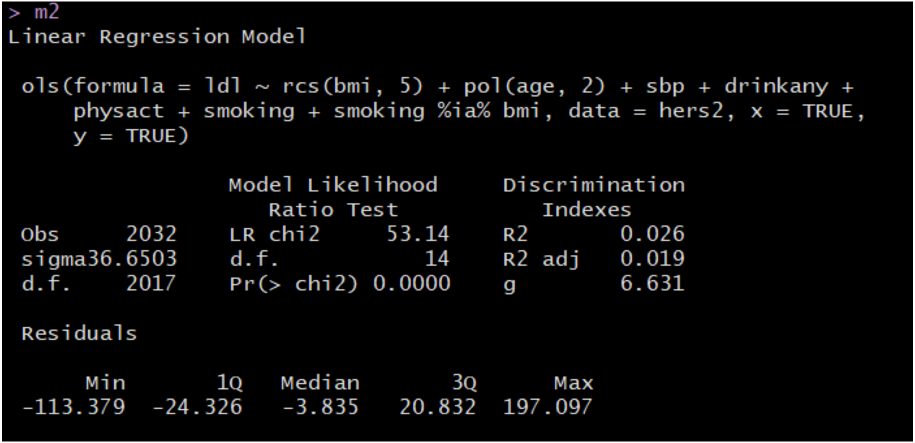
- restricted to complete cases (hers1, effectively)
- after simple imputation (hers2)
- after our multiple imputation (fit3)

Fitting the model after simple imputation

```r
dd <- datadist(hers2)
options(datadist = "dd")

m2 <- ols(ldl ~ rcs(bmi, 5) + pol(age, 2) + sbp +
              drinkany + physact + smoking +
              smoking %ia% bmi, data = hers2,
          x = TRUE, y = TRUE)
```

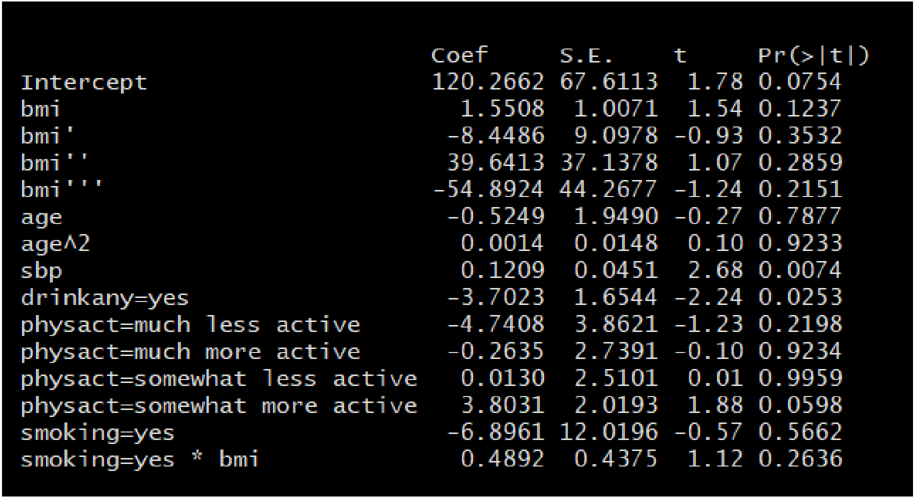
where %ia% identifies the linear interaction alone.

m2 results (slide 1 of 2)



```
> m2
Linear Regression Model

 ols(formula = ldl ~ rcs(bmi, 5) + pol(age, 2) + sbp + drinkany +
     physact + smoking + smoking %ia% bmi, data = hers2, x = TRUE,
     y = TRUE)

                Model Likelihood     Discrimination
                   Ratio Test           Indexes
 Obs      2032    LR chi2      53.14    R2        0.026
 sigma36.6503    d.f.            14    R2 adj    0.019
 d.f.     2017    Pr(> chi2) 0.0000    g         6.631

 Residuals

      Min        1Q    Median        3Q       Max
 -113.379  -24.326   -3.835    20.832  197.097
```

m2 results (slide 2 of 2)



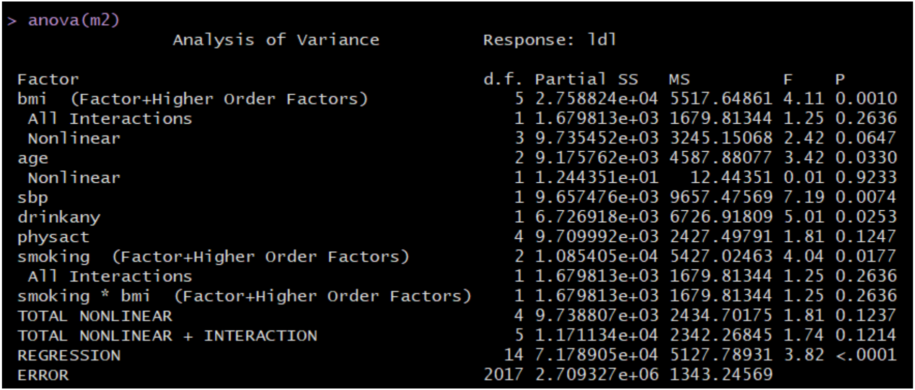
```
                                  Coef     S.E.    t     Pr(>|t|)
Intercept                         120.2662 67.6113  1.78 0.0754
bmi                                 1.5508  1.0071  1.54 0.1237
bmi'                               -8.4486  9.0978 -0.93 0.3532
bmi''                              39.6413 37.1378  1.07 0.2859
bmi'''                            -54.8924 44.2677 -1.24 0.2151
age                                -0.5249  1.9490 -0.27 0.7877
age^2                               0.0014  0.0148  0.10 0.9233
sbp                                 0.1209  0.0451  2.68 0.0074
drinkany=yes                       -3.7023  1.6544 -2.24 0.0253
physact=much less active           -4.7408  3.8621 -1.23 0.2198
physact=much more active           -0.2635  2.7391 -0.10 0.9234
physact=somewhat less active        0.0130  2.5101  0.01 0.9959
physact=somewhat more active        3.8031  2.0193  1.88 0.0598
smoking=yes                        -6.8961 12.0196 -0.57 0.5662
smoking=yes * bmi                   0.4892  0.4375  1.12 0.2636
```

Validation of summary statistics

```r
validate(m2)
```

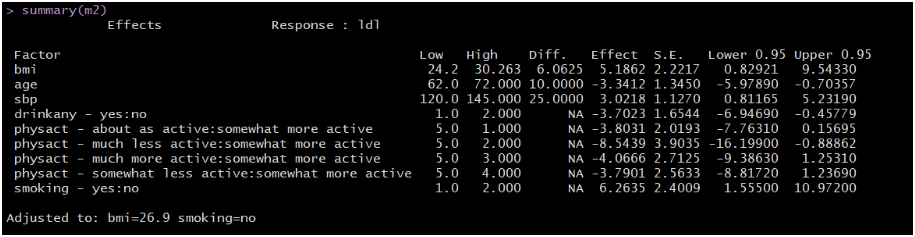
```
          index.orig  training      test optimism
R-square      0.0258    0.0322    0.0193   0.0129
MSE        1333.3300 1331.2658 1342.2160 -10.9502
g             6.6306    7.3074    5.9494   1.3581
Intercept     0.0000    0.0000   25.8305 -25.8305
Slope         1.0000    1.0000    0.8225   0.1775
          index.corrected  n
R-square           0.0129 40
MSE             1344.2801 40
g                  5.2726 40
Intercept         25.8305 40
Slope              0.8225 40
```

anova(m2) results



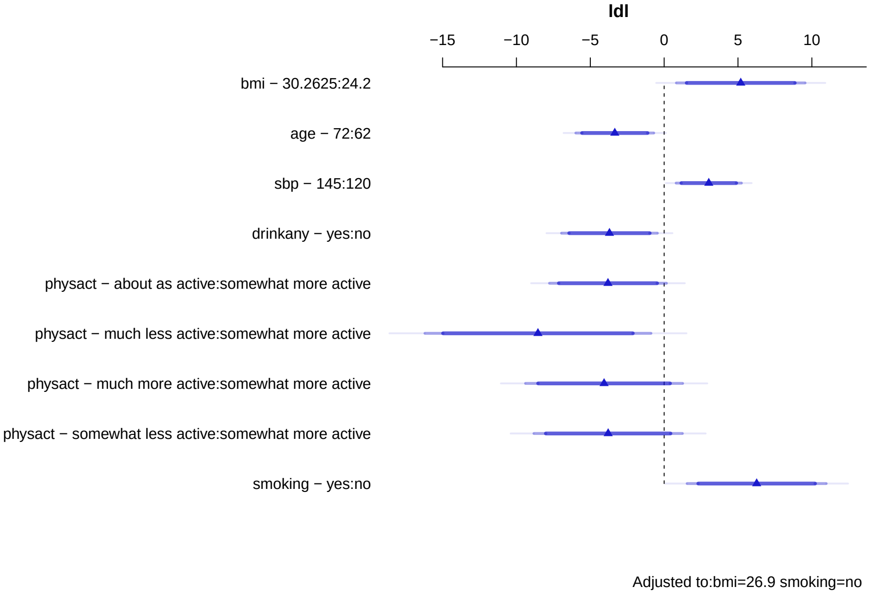
```
> anova(m2)
                Analysis of Variance          Response: ldl

 Factor                                          d.f. Partial SS   MS          F    P
 bmi  (Factor+Higher Order Factors)                 5 2.758824e+04 5517.64861 4.11 0.0010
  All Interactions                                  1 1.679813e+03 1679.81344 1.25 0.2636
  Nonlinear                                         3 9.735452e+03 3245.15068 2.42 0.0647
 age                                                2 9.175762e+03 4587.88077 3.42 0.0330
  Nonlinear                                         1 1.244351e+01   12.44351 0.01 0.9233
 sbp                                                1 9.657476e+03 9657.47569 7.19 0.0074
 drinkany                                           1 6.726918e+03 6726.91809 5.01 0.0253
 physact                                            4 9.709992e+03 2427.49791 1.81 0.1247
 smoking  (Factor+Higher Order Factors)             2 1.085405e+04 5427.02463 4.04 0.0177
  All Interactions                                  1 1.679813e+03 1679.81344 1.25 0.2636
 smoking * bmi  (Factor+Higher Order Factors)       1 1.679813e+03 1679.81344 1.25 0.2636
 TOTAL NONLINEAR                                    4 9.738807e+03 2434.70175 1.81 0.1237
 TOTAL NONLINEAR + INTERACTION                      5 1.171134e+04 2342.26845 1.74 0.1214
 REGRESSION                                        14 7.178905e+04 5127.78931 3.82 <.0001
 ERROR                                           2017 2.709327e+06 1343.24569
```

summary(m2) results

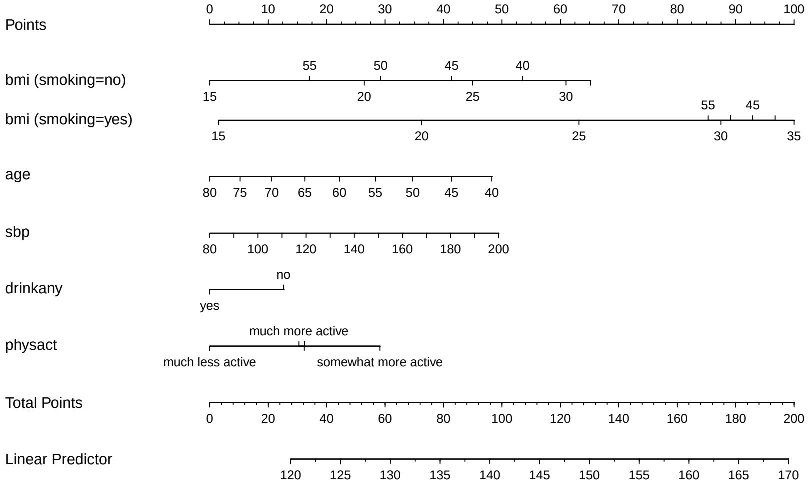


```
> summary(m2)
             Effects              Response : ldl

 Factor                                              Low   High    Diff.   Effect  S.E.   Lower 0.95 Upper 0.95
 bmi                                                  24.2  30.263  6.0625  5.1862 2.2217   0.82921    9.54330
 age                                                  62.0  72.000 10.0000 -3.3412 1.3450  -5.97890   -0.70357
 sbp                                                 120.0 145.000 25.0000  3.0218 1.1270   0.81165    5.23190
 drinkany - yes:no                                     1.0   2.000      NA -3.7023 1.6544  -6.94690   -0.45779
 physact - about as active:somewhat more active        5.0   1.000      NA -3.8031 2.0193  -7.76310    0.15695
 physact - much less active:somewhat more active       5.0   2.000      NA -8.5439 3.9035 -16.19900   -0.88862
 physact - much more active:somewhat more active       5.0   3.000      NA -4.0666 2.7125  -9.38630    1.25310
 physact - somewhat less active:somewhat more active   5.0   4.000      NA -3.7901 2.5633  -8.81720    1.23690
 smoking - yes:no                                      1.0   2.000      NA  6.2635 2.4009   1.55500   10.97200

Adjusted to: bmi=26.9 smoking=no
```

plot(summary(m2)) results



plot(nomogram(m2))



Making Predictions for an Individual

Suppose now that we want to use R to get a prediction for a new individual subject with `bmi` = 30, `age` = 50, `smoking` = yes and `physact` = about as active, `drinkany`= yes and `sbp` of 150.

```
predict(m2, expand.grid(bmi = 30, age = 50, smoking = "yes",
                        physact = "about as active",
                        drinkany = "yes", sbp = 150),
        conf.int = 0.95, conf.type = "individual")
```

```
$linear.predictors        $lower      $upper
          160.9399      88.48615    233.3936
```

Making Predictions for a Long-Run Mean

The other kind of prediction we might wish to make is for the mean of a series of subjects whose `bmi` = 30, `age` = 50, `smoking` = yes and `physact` = about as active, `drinkany`= yes and `sbp` of 150.

```
predict(m2, expand.grid(bmi = 30, age = 50, smoking = "yes",
                        physact = "about as active",
                        drinkany = "yes", sbp = 150),
        conf.int = 0.95, conf.type = "mean")
```

```
$linear.predictors          $lower     $upper
          160.9399        151.8119   170.0679
```

Of course, the confidence interval will always be narrower than the prediction interval given the same predictor values.

Influential Points?

```
which.influence(m2, cutoff = 0.4)
```

```
$Intercept
[1] 1135

$age
[1] 1135

$smoking
[1] 132

$`smoking * bmi`
[1] 132
```

Fitting the model to the complete cases

```
d <- datadist(hers1)
options(datadist = "d")

m1 <- ols(ldl ~ rcs(bmi, 5) + pol(age, 2) + sbp +
              drinkany + physact + smoking +
              smoking %ia% bmi, data = hers1,
          x = TRUE, y = TRUE)
```

where %ia% identifies the linear interaction alone.

Putting it Together

What have we got?

- An imputation model `fit3`

```
fit3 <- aregImpute(~ ldl + age + smoking + drinkany + sbp +
           physact + bmi, nk = c(0, 3:5), tlinear = FALSE,
           data = hers1, B = 10, n.impute = 20, x = TRUE)
```

- A prediction model

```
m1 <- ols(ldl ~ rcs(bmi, 5) + pol(age, 2) + sbp +
            drinkany + physact + smoking + smoking %ia% bmi,
            x = TRUE, y = TRUE)
```

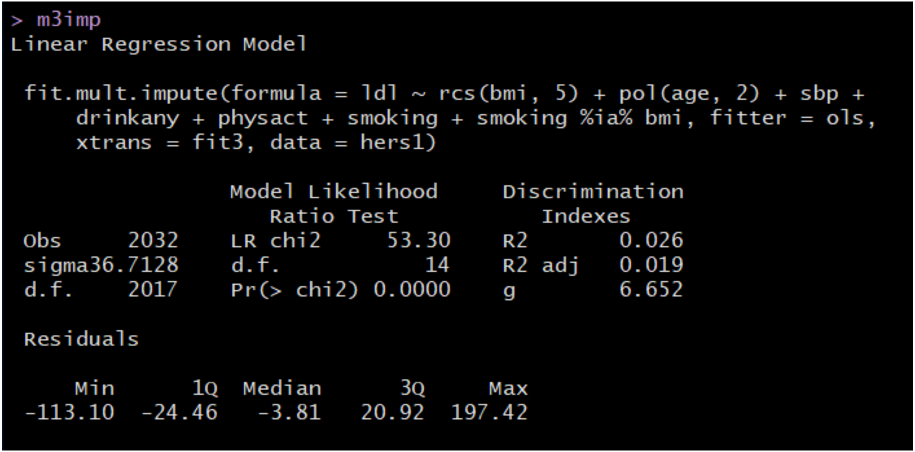
Now we put them together

Linear Regression & Imputation Model

```r
m3imp <-
    fit.mult.impute(ldl ~ rcs(bmi, 5) + pol(age, 2) + sbp +
                        drinkany + physact + smoking +
                        smoking %ia% bmi,
                    fitter = ols, xtrans = fit3,
                    data = hers1)
```

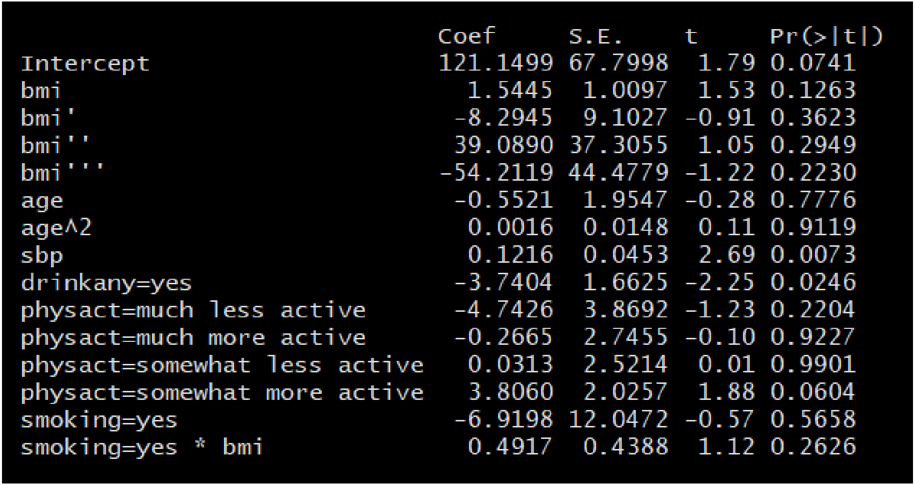
```

Variance Inflation Factors Due to Imputation:

                   Intercept                          bmi 
                        1.00                         1.00 
                        bmi'                        bmi'' 
                        1.00                         1.01 
                      bmi'''                          age 
                        1.01                         1.00 
                       age^2                          sbp 
                        1.00                         1.01 
```

m3imp results (1 of 2)



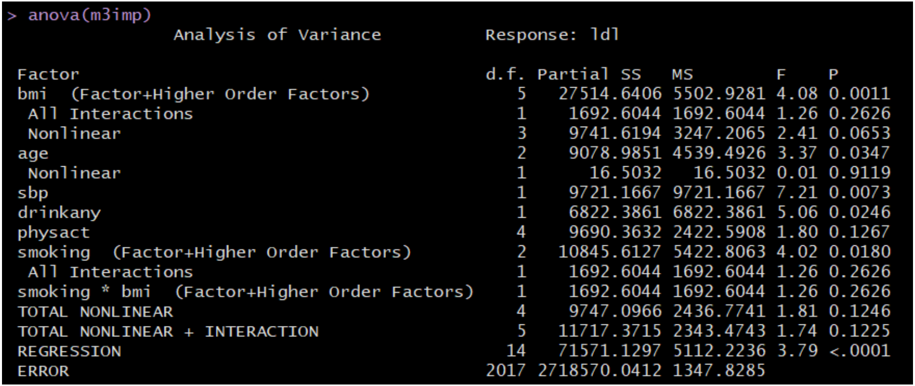
```
> m3imp
Linear Regression Model

 fit.mult.impute(formula = ldl ~ rcs(bmi, 5) + pol(age, 2) + sbp +
     drinkany + physact + smoking + smoking %ia% bmi, fitter = ols,
     xtrans = fit3, data = hers1)

                Model Likelihood     Discrimination
                   Ratio Test           Indexes
 Obs       2032    LR chi2      53.30    R2         0.026
 sigma36.7128    d.f.            14    R2 adj     0.019
 d.f.      2017    Pr(> chi2) 0.0000    g          6.652

 Residuals

     Min       1Q  Median       3Q     Max
 -113.10  -24.46   -3.81   20.92  197.42
```

m3imp results (2 of 2)



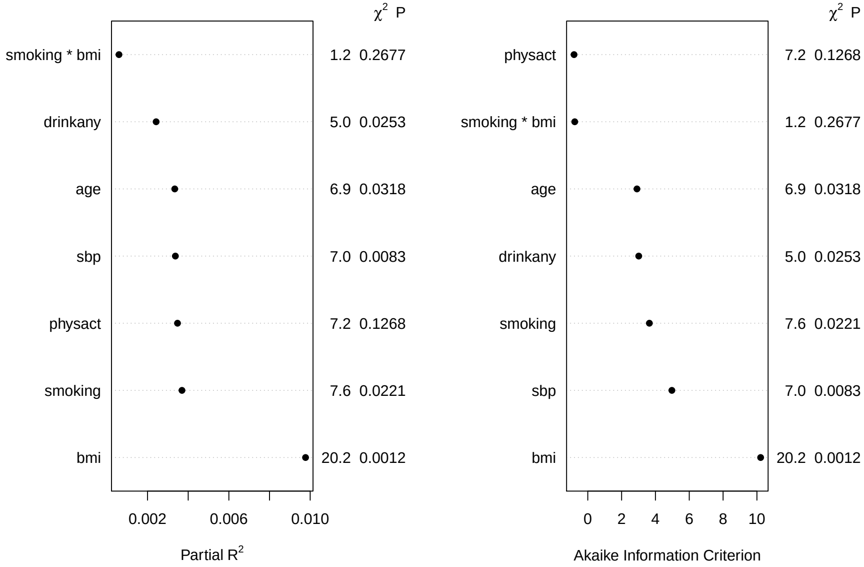
```
                             Coef     S.E.    t     Pr(>|t|)
Intercept                    121.1499 67.7998  1.79 0.0741
bmi                            1.5445  1.0097  1.53 0.1263
bmi'                          -8.2945  9.1027 -0.91 0.3623
bmi''                         39.0890 37.3055  1.05 0.2949
bmi'''                       -54.2119 44.4779 -1.22 0.2230
age                           -0.5521  1.9547 -0.28 0.7776
age^2                          0.0016  0.0148  0.11 0.9119
sbp                            0.1216  0.0453  2.69 0.0073
drinkany=yes                  -3.7404  1.6625 -2.25 0.0246
physact=much less active      -4.7426  3.8692 -1.23 0.2204
physact=much more active      -0.2665  2.7455 -0.10 0.9227
physact=somewhat less active   0.0313  2.5214  0.01 0.9901
physact=somewhat more active   3.8060  2.0257  1.88 0.0604
smoking=yes                   -6.9198 12.0472 -0.57 0.5658
smoking=yes * bmi              0.4917  0.4388  1.12 0.2626
```

anova(m3imp)



```
> anova(m3imp)
                Analysis of Variance          Response: ldl

 Factor                                          d.f. Partial SS   MS        F    P
 bmi  (Factor+Higher Order Factors)                5    27514.6406 5502.9281 4.08 0.0011
  All Interactions                                 1     1692.6044 1692.6044 1.26 0.2626
  Nonlinear                                        3     9741.6194 3247.2065 2.41 0.0653
 age                                               2     9078.9851 4539.4926 3.37 0.0347
  Nonlinear                                        1       16.5032   16.5032 0.01 0.9119
 sbp                                               1     9721.1667 9721.1667 7.21 0.0073
 drinkany                                          1     6822.3861 6822.3861 5.06 0.0246
 physact                                           4     9690.3632 2422.5908 1.80 0.1267
 smoking  (Factor+Higher Order Factors)            2    10845.6127 5422.8063 4.02 0.0180
  All Interactions                                 1     1692.6044 1692.6044 1.26 0.2626
 smoking * bmi  (Factor+Higher Order Factors)      1     1692.6044 1692.6044 1.26 0.2626
 TOTAL NONLINEAR                                   4     9747.0966 2436.7741 1.81 0.1246
 TOTAL NONLINEAR + INTERACTION                     5    11717.3715 2343.4743 1.74 0.1225
 REGRESSION                                       14    71571.1297 5112.2236 3.79 <.0001
 ERROR                                          2017  2718570.0412 1347.8285
```

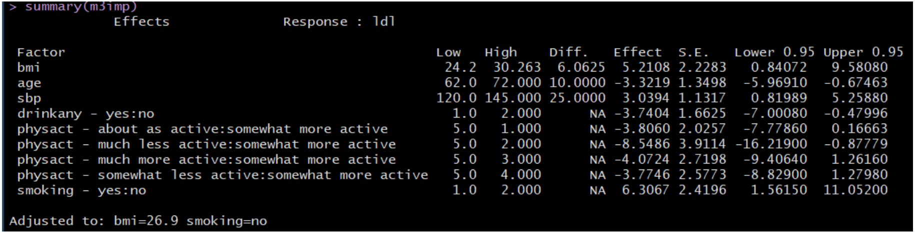
Evaluation via Partial R^2 and AIC (result)



Evaluation via Partial R^2 and AIC (code)

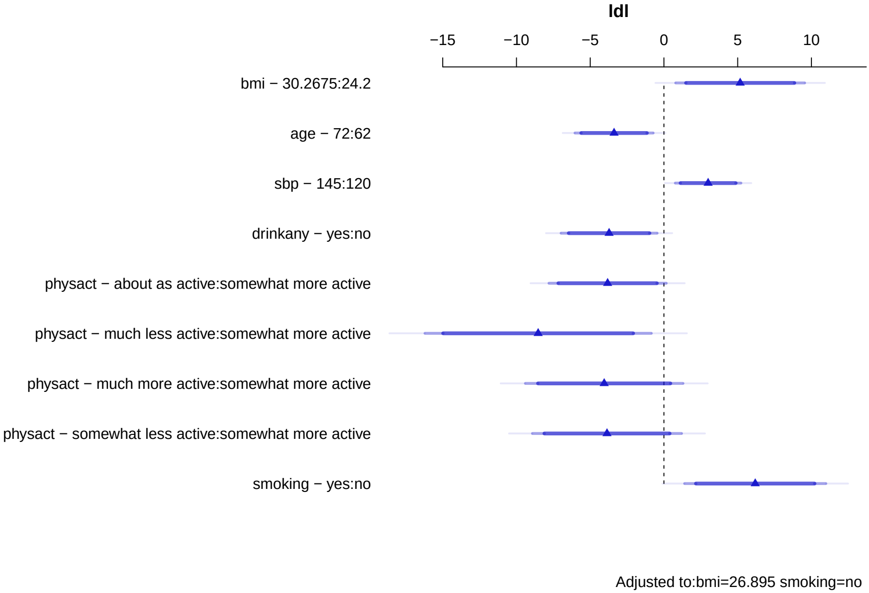
```r
par(mfrow = c(1,2))
plot(anova(m3imp), what="partial R2")
plot(anova(m3imp), what="aic")
par(mfrow = c(1,1))
```

summary(m3imp)

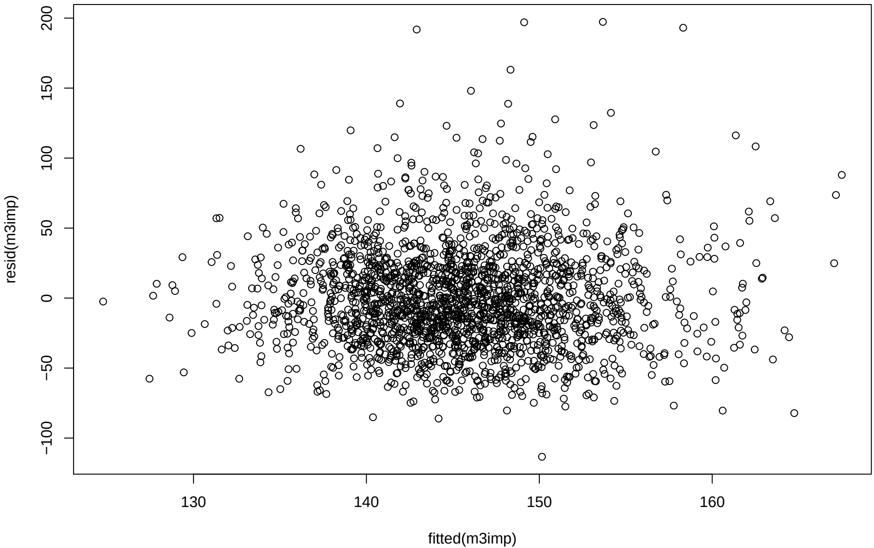


```
> summary(m3imp)
             Effects              Response : ldl

 Factor                                          Low   High    Diff.   Effect  S.E.   Lower 0.95 Upper 0.95
 bmi                                              24.2  30.263  6.0625  5.2108 2.2283   0.84072    9.58080
 age                                              62.0  72.000 10.0000 -3.3219 1.3498  -5.96910   -0.67463
 sbp                                             120.0 145.000 25.0000  3.0394 1.1317   0.81989    5.25880
 drinkany - yes:no                                 1.0   2.000      NA -3.7404 1.6625  -7.00080   -0.47996
 physact - about as active:somewhat more active    5.0   1.000      NA -3.8060 2.0257  -7.77860    0.16663
 physact - much less active:somewhat more active   5.0   2.000      NA -8.5486 3.9114 -16.21900   -0.87779
 physact - much more active:somewhat more active   5.0   3.000      NA -4.0724 2.7198  -9.40640    1.26160
 physact - somewhat less active:somewhat more active  5.0   4.000      NA -3.7746 2.5773  -8.82900    1.27980
 smoking - yes:no                                  1.0   2.000      NA  6.3067 2.4196   1.56150   11.05200

Adjusted to: bmi=26.9 smoking=no
```

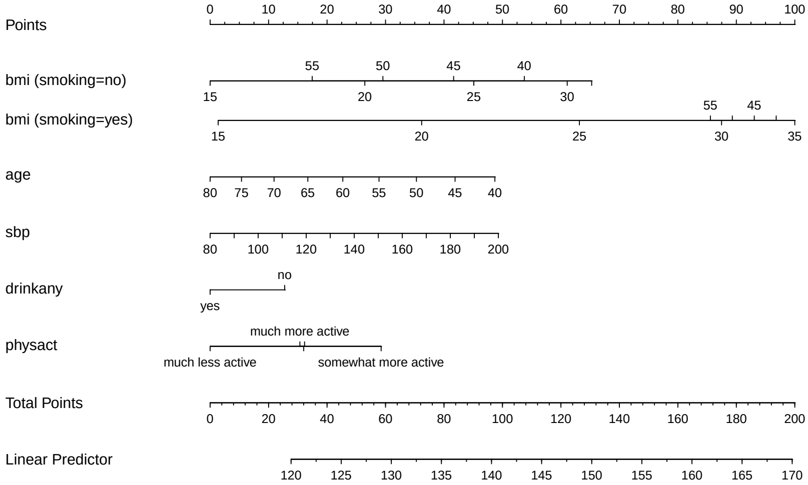
plot(summary(m3imp))



plot(resid(m3imp) ~ fitted(m3imp))



plot(nomogram(m3imp))


Points
bmi (smoking=no)
bmi (smoking=yes)
age
sbp
drinkany
no
yes
physact
much more active
much less active
somewhat more active
Total Points
Linear Predictor