432 Class 10 Slides

github.com/THOMASELOVE/2020-432

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Setup

```
library(magrittr); library(janitor); library(here)

library(skimr)
library(naniar)
library(simputation)
library(broom)
library(rms) # note: also loads Hmisc
library(tidyverse)
```

Today's Data

Heart and Estrogen/Progestin Study (HERS)

- Clinical trial of hormone therapy for the prevention of recurrent heart attacks and deaths among 2763 post-menopausal women with existing coronary heart disease (see Hulley et al 1998 and many subsequent references, including Vittinghoff, Chapter 4.)
- We're exluding the women in the trial with a diabetes diagnosis.

The Codebook (n = 2032)

Variable	Description
-	subject code
subject	3
HT	factor: hormone therapy or placebo
diabetes	yes or no (all are no in our sample)
ldl	LDL cholesterol in mg/dl
age	age in years
${\tt smoking}$	yes or no
drinkany	yes or no
sbp	systolic BP in mm Hg
physact	5-level factor, details next slide
bmi	body-mass index in kg/m ²

Goal Predict 1dl using age, smoking, drinkany, sbp, physact and bmi, across both HT levels but restricted to women without diabetes.

The physact variable

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

```
# A tibble: 5 x 2
physact n
<chr> chr> cint>
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
```

Comparison is to activity levels for these women just before menopause.

Any missing data?

miss_var_summary(hers1)

```
# A tibble: 10 x 3
  variable n_miss pct_miss
  <chr> <int> <dbl>
 1 ldl
                7 0.344
                2 0.0984
 2 drinkany
                2 0.0984
3 bmi
4 subject
 5 ht
 6 age
7 smoking
8 sbp
 9 physact
                    0
10 diabetes
                    0
```

Single Imputation for drinkany, bmi and ldl

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

```
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...

miss_var_summary(hers2)

```
A tibble: 11 x 3
  variable n_miss pct_miss
  <chr> <int>
                       <dbl>
1 subject
2 ldl
3 ht
4 age
5 smoking
6 drinkany
7 sbp
8 physact
9 bmi
10 diabetes
11 drinkany_n
```

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:

- 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.
- It then uses this fitted flexible model to predict the target variable in all of the original observations.
- 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

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 4)

```
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
```

fit3 Imputation Results (2 of 4)

```
R-squares for Predicting Non-Missing Values for Each
Variable Using Last Imputations of Predictors
ldl drinkany bmi
0.041 0.014 0.109
```

fit3 Imputation Results (3 of 4)

Resampling results for determining the complexity of imputation models

Variable being imputed: Idl

Bootstrap bias-corrrected summaries:

Statistic	nk = 0	nk = 3	nk = 4	nk = 5
R^2	0.0139	0.0149	0.00776	0.0124
mean absolute error	28.3594	42.9139	44.09937	39.8266
median abs. error	22.8301	35.5441	38.85302	32.6386

10-fold cross-validated:

Statistic	nk = 0	nk = 3	nk = 4	nk = 5
R^2	0.0214	0.0180	0.01517	0.0191
mean absolute error	145.7176	43.5007	45.02428	44.2456
median abs. error	141.4238	36.4102	38.88053	37.3141

fit3 Imputation Results (4 of 4)

Variable being imputed: drinkany

```
    nk=0
    nk=3
    nk=4
    nk=5

    Bootstrap
    R^2
    0.0163
    0.0113
    0.0102
    0.00986

    10-fold cv R^2
    0.0205
    0.0249
    0.0163
    0.01358

    Bootstrap
    mean |error|
    0.4470
    0.4568
    0.4558
    0.46624

    10-fold cv mean |error|
    0.0000
    0.0000
    0.0000
    0.0000

    10-fold cv median |error|
    0.0000
    0.0500
    0.1000
    0.0000
```

Variable being imputed: bmi

```
    nk=0
    nk=3
    nk=4
    nk=5

    Bootstrap
    R^2
    0.0845
    0.0932
    0.0946
    0.0847

    10-fold cv
    R^2
    0.0864
    0.0903
    0.0968
    0.0899

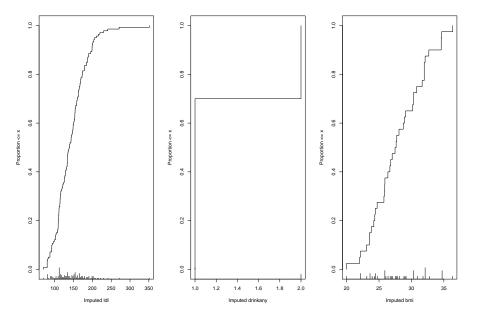
    Bootstrap
    mean |error|
    3.7829
    4.8119
    4.9226
    5.1775

    10-fold cv
    mean |error|
    27.6776
    4.8359
    4.9390
    5.1136

    Bootstrap
    median |error|
    2.9955
    3.9704
    3.9371
    4.2634

    10-fold cv
    median |error|
    27.0143
    3.9894
    3.9431
    4.1876
```

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 1d1, 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.

Kitchen Sink Model (Main Effects only)

Analysis of Variance

```
Factor d.f. Partial SS MS F
                9330.911 9330.911 6.93 0.0085
            1
age
       1 8199.755 8199.755 6.09 0.0137
smoking
drinkany 1 6444.424 6444.424 4.79 0.0288
sbp
          1 9274.287 9274.287 6.89 0.0087
       4 10874.528 2718.632 2.02 0.0891
physact
            1 15876.957 15876.957 11.80 0.0006
bmi
REGRESSION
            9
               60077.708 6675.301 4.96 < .0001
ERROR
         2022 2721037.890 1345.716
```

Response: 1d1

Spearman ρ^2 **Plot**

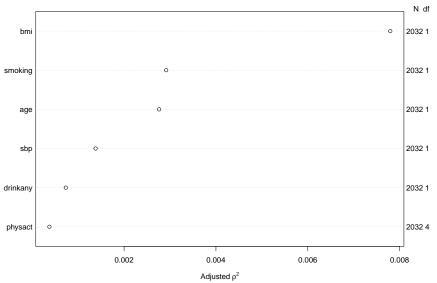
How should we prioritize the degrees of freedom we spend on non-linearity?

Plot's on the next page.

• Note the use of the simple imputation hers2 data here. Why?

Spearman ρ^2 **Plot** Result





Spending Degrees of Freedom

We're spending 9 degrees of freedom in our kitchen sink model. (We can verify this with anova or the plot.)

- Each quantitative main effect costs 1 df to estimate
- Each binary categorical variable also costs 1 df
- Multi-categorical variables with L levels cost L-1 df to estimate

Suppose we're willing to spend up to a total of ${\bf 14}$ degrees of freedom (i.e. a combined 5 more on interaction terms and other ways to capture non-linearity.)

What should we choose?

What did we see in the Spearman ρ^2 Plot?

Group 1 (largest adjusted ρ^2)

• bmi, a quantitative predictor, is furthest to the right

Group 2 (next largest)

- smoking, a binary predictor, is next, followed closely by
- age, a quantitative predictor

Other predictors (rest of the group)

- sbp, quantitative
- drinkany, binary
- physact, multi-categorical (5 levels)

Impact of Adding Non-Linearity on Degrees of Freedom Spent

What happens when we add a non-linear term?

- Adding a polynomial of degree D costs D degrees of freedom.
 - So a polynomial of degree 2 (quadratic) costs 2 df, or 1 more than the main effect alone.
- Adding a restricted cubic spline with K knots costs K-1 df.
 - So adding a rcs with 4 knots uses 3 df, or 2 more than the main effect alone.
 - We restrict ourselves to considering splines with 3, 4, or 5 knots.
- Adding an interaction (product term) depends on the main effects of the predictors we are interacting
 - If the product term's predictors have df1 and df2 degrees of freedom, the product term adds df1 \times df2 degrees of freedom to the main effects model.
 - An interaction of a binary and quantitative variable adds $1 \times 1 = 1$ additional degree of freedom to the main effects model.
 - When we use a quantitative variable in a spline and interaction, we'll do the interaction on the main effect, not the spline.

Model we'll fit with ols

Fitting a model to predict 1d1 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 the main effect of bmi

We can fit this to the data

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

Fitting the model to the complete cases

where %ia% identifies the linear interaction alone.

m1 results (slide 1 of 3)

> m1

```
Frequencies of Missing Values Due to Each Variable

1dl bmi age sbp drinkany physact smoking
7 2 0 0 2 0 0
```

Linear Regression Model

		Model Likelihood		Discrimi	nation
		Ratio Te	est	Index	es
Obs	2021	LR chi2	52.61	R2	0.026
sigma36	.7430	d.f.	14	R2 adj	0.019
d.f.	2006	Pr(> chi2)	0.0000	g	6.629

m1 results (slide 2 of 3)

	Coef	S.E.	t F	r(> t)
Intercept	121.6057	68.2000	1.78	0.0747
bmi	1.5687	1.0107	1.55	0.1208
bmi'	-8.6685	9.1577	-0.95	0.3440
bmi''	40.5712	37.4468	1.08	0.2787
bmi'''	-55.8872	44.5946	-1.25	0.2103
age	-0.5791	1.9657	-0.29	0.7683
age^2	0.0018	0.0149	0.12	0.9024
sbp	0.1221	0.0453	2.69	0.0072
drinkany=yes	-3.7427	1.6629	-2.25	0.0245
physact=much less active	-4.5660	3.8904	-1.17	0.2407
physact=much more active	-0.3291	2.7521	-0.12	0.9048
physact=somewhat less active	-0.0160	2.5270	-0.01	0.9950
physact=somewhat more active	3.7731	2.0293	1.86	0.0631
smoking=yes	-7.0832	12.0586	-0.59	0.5570
<pre>smoking=yes * bmi</pre>	0.4961	0.4391	1.13	0.2587

m1 results (slide 3 of 3)

Residuals

```
Min 1Q Median 3Q Max -113.440 -24.519 -3.778 20.940 197.087
```

Fitting the model after simple imputation

where, again, %ia% identifies the linear interaction alone.

m2 results (slide 1 of 2)

```
> m2
Linear Regression Model
 ols(formula = ldl \sim 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
    2032 LR chi2 53.14 R2
                                       0.026
Obs
 sigma36.6503 d.f.
                           14
                                R2 adi 0.019
 d.f. 2017 Pr(> chi2) 0.0000
                                        6.631
                                q
 Residuals
     Min 10 Median 30
                                   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

anova(m2) results

> anova(m2)	
Analysis of Variance	Response: ldl
Facebook	d 6 Postdol co wo
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

Validation of summary statistics

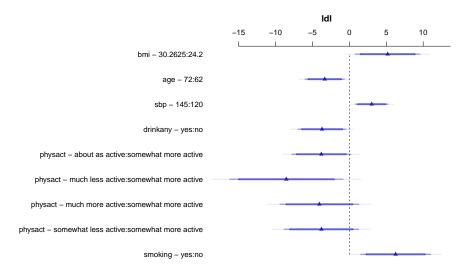
validate(m2)

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

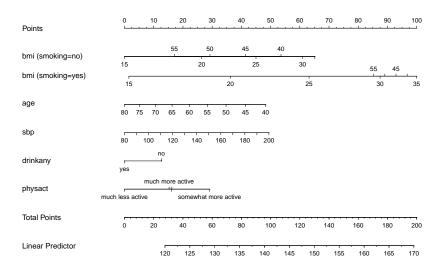
summary(m2) results

```
summary(m2)
            Effects
                                 Response : 1d1
Factor
                                                           High
                                                                           Effect S.E.
                                                                                          Lower 0.95 Upper 0.95
bmi
                                                      24.2 30.263 6.0625
                                                                           5.1862 2.2217
                                                                                            0.82921
                                                                                                      9.54330
                                                      62.0 72.000 10.0000 -3.3412 1.3450
                                                                                           -5.97890
                                                                                                     -0.70357
age
                                                     120.0 145.000 25.0000
                                                                           3.0218 1.1270
                                                                                            0.81165
                                                                                                      5.23190
sbp
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
                                                             2.000
                                                                        NA -8.5439 3.9035 -16.19900
                                                                                                     -0.88862
                                                       5.0
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
                                                             2.000
smoking - yes:no
                                                       1.0
                                                                           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.

```
$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.

```
$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 using Multiple Imputation

What do we have now?

• An imputation model fit3

A prediction model

Now we put them together with the fit.mult.impute function...

Linear Regression & Imputation Model

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 \sim 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 10 Median 30
                               Max
-113.10 -24.46 -3.81 20.92 197.42
```

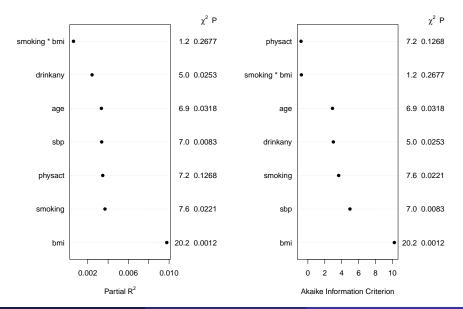
m3imp results (2 of 2)

	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: 1d1
                                              d.f. Partial SS
Factor
     (Factor+Higher Order Factors)
                                                     27514.6406 5502.9281 4.08 0.0011
All Interactions
                                                      1692.6044 1692.6044 1.26 0.2626
Nonlinear
                                                      9741 6194 3247 2065 2 41 0 0653
                                                      9078 9851 4539 4926 3 37 0 0347
age
Nonlinear
                                                        16.5032
                                                                  16.5032 0.01 0.9119
sbp
                                                      9721.1667 9721.1667 7.21 0.0073
drinkany
                                                      6822.3861 6822.3861 5.06 0.0246
physact
                                                      9690.3632 2422.5908 1.80 0.1267
smoking (Factor+Higher Order Factors)
                                                     10845.6127 5422.8063 4.02 0.0180
All Interactions
                                                      1692.6044 1692.6044 1.26 0.2626
smoking * bmi (Factor+Higher Order Factors)
                                                      1692,6044 1692,6044 1,26 0,2626
                                                      9747.0966 2436.7741 1.81 0.1246
TOTAL NONLINEAR
                                                     11717.3715 2343.4743 1.74 0.1225
TOTAL NONLINEAR + INTERACTION
REGRESSION
                                                     71571 1297 5112 2236 3 79 < 0001
                                              2017 2718570.0412 1347.8285
ERROR
```

Evaluation via Partial R² and AIC (result)



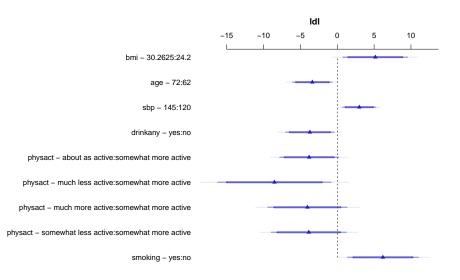
Evaluation via Partial R² and AIC (code)

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

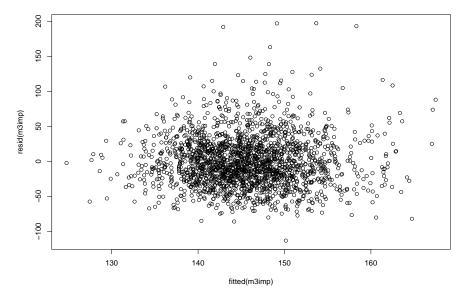
summary(m3imp)

```
summary(m3imp)
             Effects
                                  Response : 1d1
                                                                             Effect S.E.
 Factor
                                                      Low
                                                            High
                                                                                            Lower 0.95 Upper 0.95
                                                       24.2
                                                             30.263 6.0625
                                                                              5.2108 2.2283
                                                                                              0.84072
                                                                                                         9.58080
 bmi
 age
                                                       62.0 72.000 10.0000 -3.3219 1.3498
                                                                                             -5.96910
                                                                                                        -0.67463
                                                      120.0 145.000 25.0000
                                                                                              0.81989
                                                                                                        5.25880
 sbp
                                                                              3.0394 1.1317
 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
                                                              2.000
 smoking - yes:no
                                                        1.0
                                                                          NA 6.3067 2.4196
                                                                                              1.56150
                                                                                                       11.05200
Adjusted to: bmi=26.9 smoking=no
```

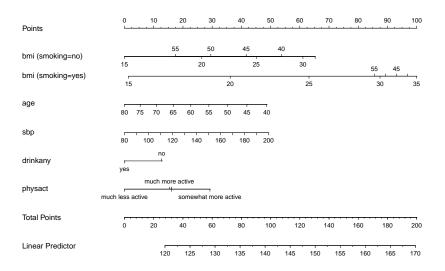
plot(summary(m3imp))



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



plot(nomogram(m3imp))



Next Step

Can we do all of this for a logistic regression model?