SRM analysis

Makayla

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Introduction

This document provides all the code and output for the analysis that has been previously discussed. These are split into data cleaning steps, summary of the cleaned data, and statistical analysis of the cleaned data. Naturally, each step builds on the earlier steps, so it is important to verify that the earlier steps make sense, before going much further.

The coding is done entirely in the R software, using (where possible) well-known functions, that most R users would understand. More idiosynctratic use of R is noted, when it arises.

Please feel free to ask questions, and to correct anything I've done that doesn't match the intended analysis.

Data cleaning

First we read in the data and note how the column letters (in Excel) match up to the variable names we use in this analysis:

```
library("readxl")
data <- read_excel("Copy of 2013 2014 for data entry (2).xlsx", sheet=1)
#names(srm)
dLETTERS <- sapply(1:26, function(i){paste(LETTERS[i], LETTERS[i], sep="")})
cbind(c(LETTERS, dLETTERS)[1:38], names(data))
```

```
## Warning in cbind(c(LETTERS, dLETTERS)[1:38], names(data)): number of rows of
## result is not a multiple of vector length (arg 1)
```

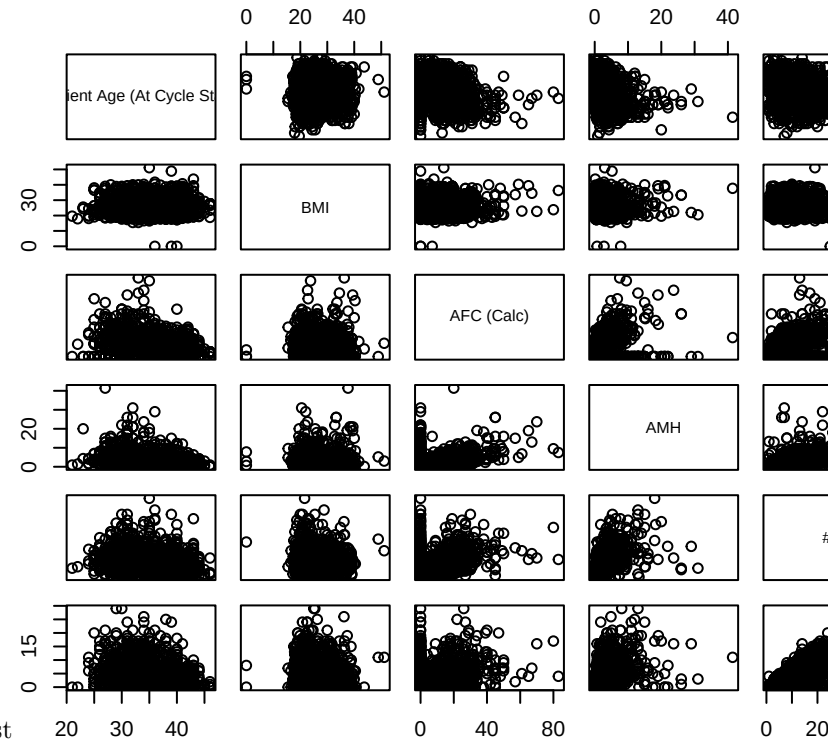
```
##       [,1] [,2]
##  [1,] "A"  "MPI"
##  [2,] "B"  "Patient Age (At Cycle Start)"
##  [3,] "C"  "Treatment #"
##  [4,] "D"  "BMI"
##  [5,] "E"  "AFC (Calc)"
##  [6,] "F"  "AMH"
##  [7,] "G"  "Lupron Protocol"
##  [8,] "H"  "E2 Day 3"
##  [9,] "I"  "FSH Dose Day 3"
## [10,] "J"  "E2 Day 4"
## [11,] "K"  "FSH Dose Day 4"
## [12,] "L"  "E2 Day 5"
## [13,] "M"  "FSH Dose Day 5"
## [14,] "N"  "E2 Day 6"
## [15,] "O"  "FSH Dose Day 6"
## [16,] "P"  "E2 Day 7"
## [17,] "Q"  "FSH Dose Day 7"
## [18,] "R"  "E2 Day 8"
```

```
## [19,] "S"  "FSH Dose Day 8"
## [20,] "T"  "E2 Day 9"
## [21,] "U"  "FSH Dose Day 9"
## [22,] "V"  "E2 Day 10"
## [23,] "W"  "FSH Dose Day 10"
## [24,] "X"  "E2 Day 11"
## [25,] "Y"  "FSH Dose Day 11"
## [26,] "Z"  "E2 Day 12"
## [27,] "AA" "FSH Dose Day 12"
## [28,] "BB" "FD US #1"
## [29,] "CC" "FD US #2"
## [30,] "DD" "FD US #3"
## [31,] "EE" "FD US #4"
## [32,] "FF" "E2 Day 13"
## [33,] "GG" "FSH Dose Day 13"
## [34,] "HH" "E2 Day 14"
## [35,] "II" "FSH Dose Day 14"
## [36,] "JJ" "FD US #5"
## [37,] "KK" "E2 Day 15"
## [38,] "LL" "FSH Dose Day 15"
## [39,] "A"  "#MII"
## [40,] "B"  "Number Fertilized (ICSI)"
## [41,] "C"  "Number Fertilized (IVF)"
## [42,] "D"  "Blast Conversion"
## [43,] "E"  "Total Blast Conversion"
## [44,] "F"  "PGD"
## [45,] "G"  "No. of embryos biopsied"
## [46,] "H"  "No. of embryos diagnosed"
```

Some simple numeric summaries of some variables of interest

```
# variables of interest
summary(data[, c(2,4,5, 6, 39, 43)])
```

```
##  Patient Age (At Cycle Start)      BMI          AFC (Calc)          AMH
##  Min.   :21.00                Min.   : 0.00   Min.   : 0.000   Min.   : 0.017
##  1st Qu.:32.00                1st Qu.:21.40   1st Qu.: 0.000   1st Qu.: 0.790
##  Median :35.00                Median :23.90   Median : 7.000   Median : 2.000
##  Mean   :35.46                Mean   :25.07   Mean   : 9.571   Mean   : 2.971
##  3rd Qu.:39.00                3rd Qu.:27.60   3rd Qu.:15.250   3rd Qu.: 3.900
##  Max.   :46.00                Max.   :51.10   Max.   :83.000   Max.   :41.410
##                                                                NA's   :46
##       #MII      Total Blast Conversion
##  Min.   : 1.0   Min.   : 0.000
##  1st Qu.: 6.0   1st Qu.: 0.000
##  Median :10.0   Median : 2.000
##  Mean   :11.3   Mean   : 3.631
##  3rd Qu.:15.0   3rd Qu.: 5.000
##  Max.   :55.0   Max.   :29.000
##  NA's   :660    NA's   :46
```



Simple pairwise scatterplots of some variables of interest

Examining protocol

```
## Lupron Protocol
##       Antagonist          LPL 10/5           Lupron Lupron Microdose
##              901               622                 1               322
##      Not entered     Unstimulated
##                2                 4
```

Examining FSH dose: there are some strange values, which we need to omit and then convert the stored data to be numeric, not character strings:

```
# FSH dose
summary(data[,c(9,11,13)])  # what does PM, QD mean? Also blank? (Skip for now)
```

```
##  FSH Dose Day 3     FSH Dose Day 4     FSH Dose Day 5
##  Length:1852        Length:1852        Length:1852
##  Class :character   Class :character   Class :character
##  Mode  :character   Mode  :character   Mode  :character
```

```
table(data[,9])   # 6 QD
```

```
## FSH Dose Day 3
##      100   100 PM      112    112.5 112.5 PM      125   125 PM      150
##       20        2        1         4        2       14        1      170
##   150 pm   150 PM    162.5       175   175 PM    187.5      200   200 PM
##        1       18        1        14        3        5       72        5
##      225   225 PM      250   250 PM    262.5      275   275 PM      300
##      224       23       40        12        5        9        2      269
##   300 [M   300 PM   300 QD    337.5       350      375   375 PM   375 QD
##        1       39        2         1        2      188       21        5
##  3775 QD   400 PM      425   425 PM      450   450 PM   450 QD      475
##        1        1        2         1      115       10        1        1
##     5 QD      525   525 PM      600   600 PM   600 QD       75    75 PM
```

```
##        2       19        1        2        1        1       10        2
```

```
table(data[,11])  # 2 QD
```

```
## FSH Dose Day 4
##                125                 15                150             150 PM
##                  1                  1                  6                  1
##                175                200             200 PM                225
##                  2                  1                  1                  2
##                250                300             300 QD                375
##                  2                  7                  1                  2
##             375 QD                400                450                525
##                  1                  1                  4                  2
## 69.599999999999994
##                  1
```

```
table(data[,13])  # 4 QD
```

```
## FSH Dose Day 5
##      100   100 PM      112    112.5 112.5 PM      125   125 PM      150
##       26        1        1        5        1       16        2      177
##   150 pm   150 PM      175   175 PM    187.5      200   200 PM      225
##        1       19       16        4        3       68        5      199
##   225 PM   225 QD      250   250 PM      255    262.5      275   275 PM
##       19        1       46        8        1        5        8        2
##      300   300 PM   300 QD      350   350 PM      375   375 PM   375 QD
##      288       43        5        4        1      223       27       11
##      400      414      425   425 PM      450   450 pm   450 PM   450 QD
##        5        1        2        1      327        1       34       32
##      475       50      525   525 PM   525 QD      575      600   600 PM
##        3        1       52        8        7        1        1        1
##       75    75 PM
##       19        6
```

```
# convert to numbers
data$fsh3 <- as.numeric(apply(data[,9], 1, function(x){strsplit(x, " ", fixed=TRUE)[[1]][1]}))
data$fsh4 <- as.numeric(apply(data[,11], 1, function(x){strsplit(x, " ", fixed=TRUE)[[1]][1]}))
data$fsh5 <- as.numeric(apply(data[,13], 1, function(x){strsplit(x, " ", fixed=TRUE)[[1]][1]}))
summary(data[,c("fsh3","fsh4","fsh5")])
```

```
##       fsh3             fsh4            fsh5
##  Min.   :   5.0   Min.   : 15.0   Min.   : 50.0
##  1st Qu.: 200.0   1st Qu.:150.0   1st Qu.:225.0
##  Median : 300.0   Median :275.0   Median :300.0
##  Mean   : 279.8   Mean   :270.4   Mean   :312.3
##  3rd Qu.: 375.0   3rd Qu.:375.0   3rd Qu.:450.0
##  Max.   :3775.0   Max.   :525.0   Max.   :600.0
##  NA's   :506      NA's   :1816    NA's   :114
```

Filling in the missing FSH3 values with those from later in the study, where these are available:

```
# fill in missing FSH3 values with later, if available
table(is.na(data$fsh3))
```

```
##
## FALSE  TRUE
##  1346   506
```

```
data$fsh3[is.na(data$fsh3)] <- data$fsh4[is.na(data$fsh3)]
table(is.na(data$fsh3))
```

```
##
## FALSE  TRUE
##  1375   477
```

```
data$fsh3[is.na(data$fsh3)] <- data$fsh5[is.na(data$fsh3)]
table(is.na(data$fsh3))
```

```
##
## FALSE  TRUE
##  1791    61
```

Examining estradiol:

```
# Estradiol
names(data)[c(20,22,24,26)]
```

```
## [1] "E2 Day 9"  "E2 Day 10" "E2 Day 11" "E2 Day 12"
```

```
summary(data[,c(20,22,24,26)])
```

```
##    E2 Day 9           E2 Day 10       E2 Day 11      E2 Day 12
##  Length:1852        Min.   :   60   Min.   :  103   Length:1852
##  Class :character   1st Qu.: 1120   1st Qu.: 1053   Class :character
##  Mode  :character   Median : 1834   Median : 1720   Mode  :character
##                     Mean   : 2208   Mean   : 2228
##                     3rd Qu.: 2859   3rd Qu.: 2818
##                     Max.   :14998   Max.   :18712
##                     NA's   :952     NA's   :1209
```

There's a single ">3000" value in E2 Day 9. Change it to NA.

```
data[which(data[,20]=="> 3000"),20]
```

```
## # A tibble: 1 x 1
##   `E2 Day 9`
##   <chr>
## 1 > 3000
```

```
# [1666,20]
data[1666,c(20,22,24,26)]
```

```
## # A tibble: 1 x 4
##   `E2 Day 9` `E2 Day 10` `E2 Day 11` `E2 Day 12`
##   <chr>            <dbl>       <dbl> <chr>
## 1 > 3000              NA          NA <NA>
```

```
data[1666,20] <- NA
data[,20] <- as.numeric(unlist(data[,20]))
```

```
## Warning: NAs introduced by coercion
```

Construct last value recorded for E2 – after first omitting 339 (!) observations with no E2 at all

```
# first omit 338 (!) observations with no E2 at all
table(apply(data[,c(20,22,24,26)], 1, function(x){sum(is.na(x))}))
```

```
##
##   0   1   2   3   4
```

```
##   3  99 634 778 338
```

```
na.counts <- apply(data[,c(20,22,24,26)], 1, function(x){sum(is.na(x))})
data <- data[na.counts != 4,]
## dim(data)
data <- as.data.frame(data)
data$lastE2 <- data[,20]
table(is.na(data$lastE2))
```

```
##
## FALSE  TRUE
##   489  1025
```

```
data$lastE2 <- ifelse(!is.na(data[,22]), data[,22], data$lastE2)
table(is.na(data$lastE2))
```

```
##
## FALSE  TRUE
##  1225   289
```

```
data$lastE2 <- ifelse(!is.na(data[,24]), data[,24], data$lastE2)
table(is.na(data$lastE2))
```

```
##
## FALSE  TRUE
##  1510     4
```

```
data$lastE2 <- ifelse(!is.na(data[,26]), data[,26], data$lastE2)
table(is.na(data$lastE2))
```

```
##
## FALSE
##  1514
```

```
data$lastE2 <- as.numeric(unlist(data$lastE2))
```

```
## Warning: NAs introduced by coercion
```

Removing 2 BMIs of zero:

```
data <- data[data$BMI>0,]
#dim(data)
```

Remove a single "Lupron" only lupron protocol also single "Unstimulated"

```
data <- subset(data, data[,7]!="Lupron")
data <- subset(data, data[,7]!="Unstimulated")
dim(data)
```

```
## [1] 1510   50
```

Remove a single FSH3 value in excess of 3000

```
data <- subset(data, fsh3 < 3000)
```

Fill in missing #MII values with Total Blast Conversion, if available

```
data$`#MII`[is.na(data$`#MII`)] <- data$`Total Blast Conversion`[is.na(data$`#MII`)]
```

Removing Total Blast Conversion is NA

```
data <- subset(data, !is.na(data[,43]))
```

#MII should be >= Total Blast Conversion

```
table(data$`#MII` >= data$`Total Blast Conversion`)      # There are 2
```

```
##
## FALSE  TRUE
##     2  1451
```

Remove #MII < Total Blast Conversion

```
data <- subset(data, (data$`#MII` >= data$`Total Blast Conversion`)==TRUE)
```

Remove lastE2 is NA

```
data <- subset(data, !is.na(lastE2))
dim(data)       # Final data after data cleaning
```

```
## [1] 1450   50
```

Our parameters of interest are: age, BMI; antral follicle count (AFC), and AMH, listed in columns B, D, E, and F respectively

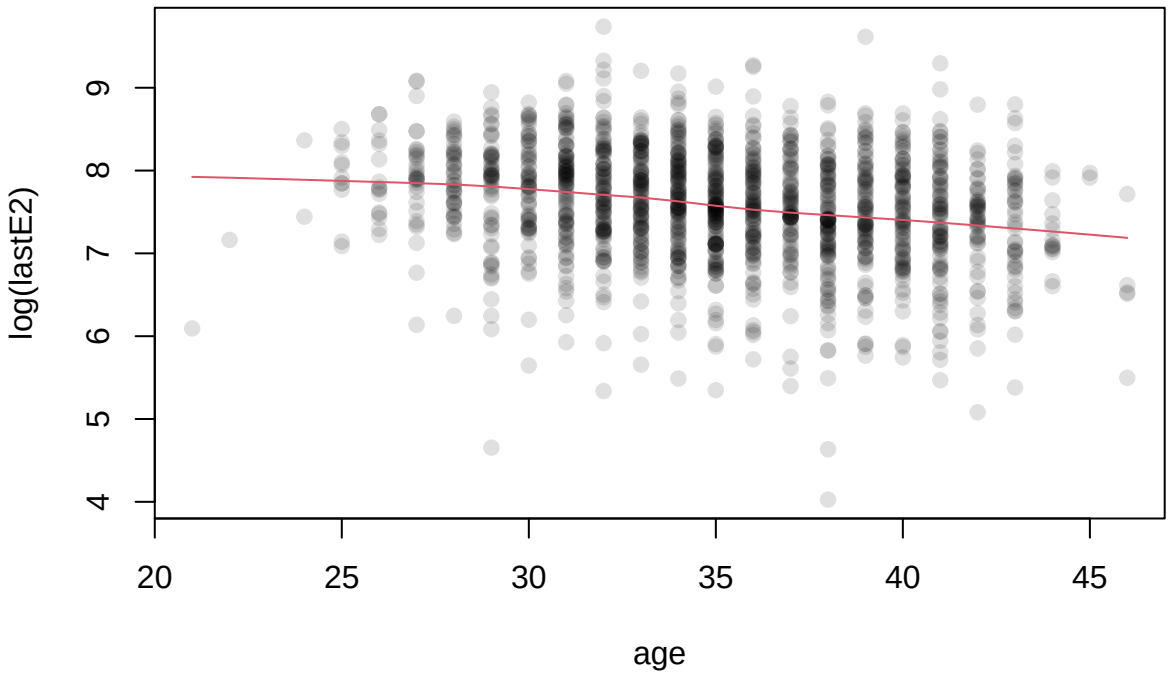
Three "protocols" are used. microdose Lupron or MDL; long lupron or LL and antagonist.

Setting up variable with names that match these, which will make subsequent code easier to read

```
data$age <- data[,2]
data$bmi <- data$BMI
data$lupprot <- data[,7]
data$amh <- data$AMH
data$afc <- data[,5]
data$mii <- data[,39]
data$Total_bc <- data[,43]
```

Data summary

```
plot(log(lastE2)~age , data=data, pch=19, col="#00000020")
lines(lowess(x=data$age, y=log(data$lastE2), iter=0), col=2)
```



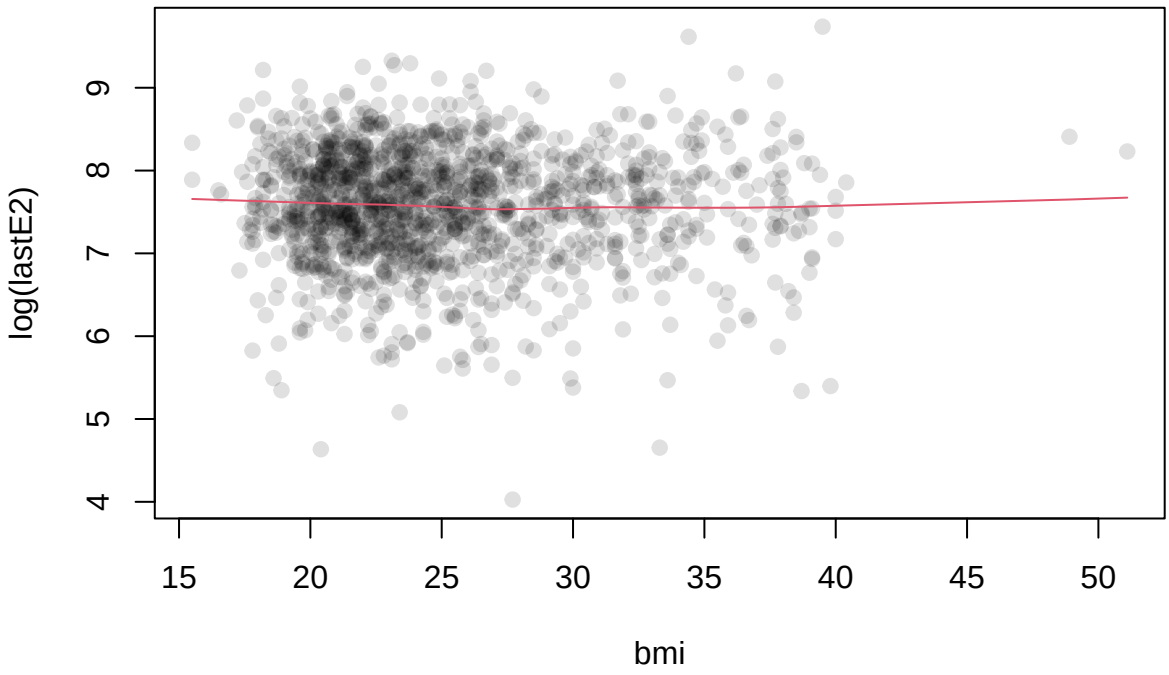

```
plot(log(lastE2)~bmi, data=data, pch=19, col="#00000020")
lines(lowess(x=data$bmi, y=log(data$lastE2), iter=0), col=2)

#table(data$lupprot)
library(tidyverse)
```

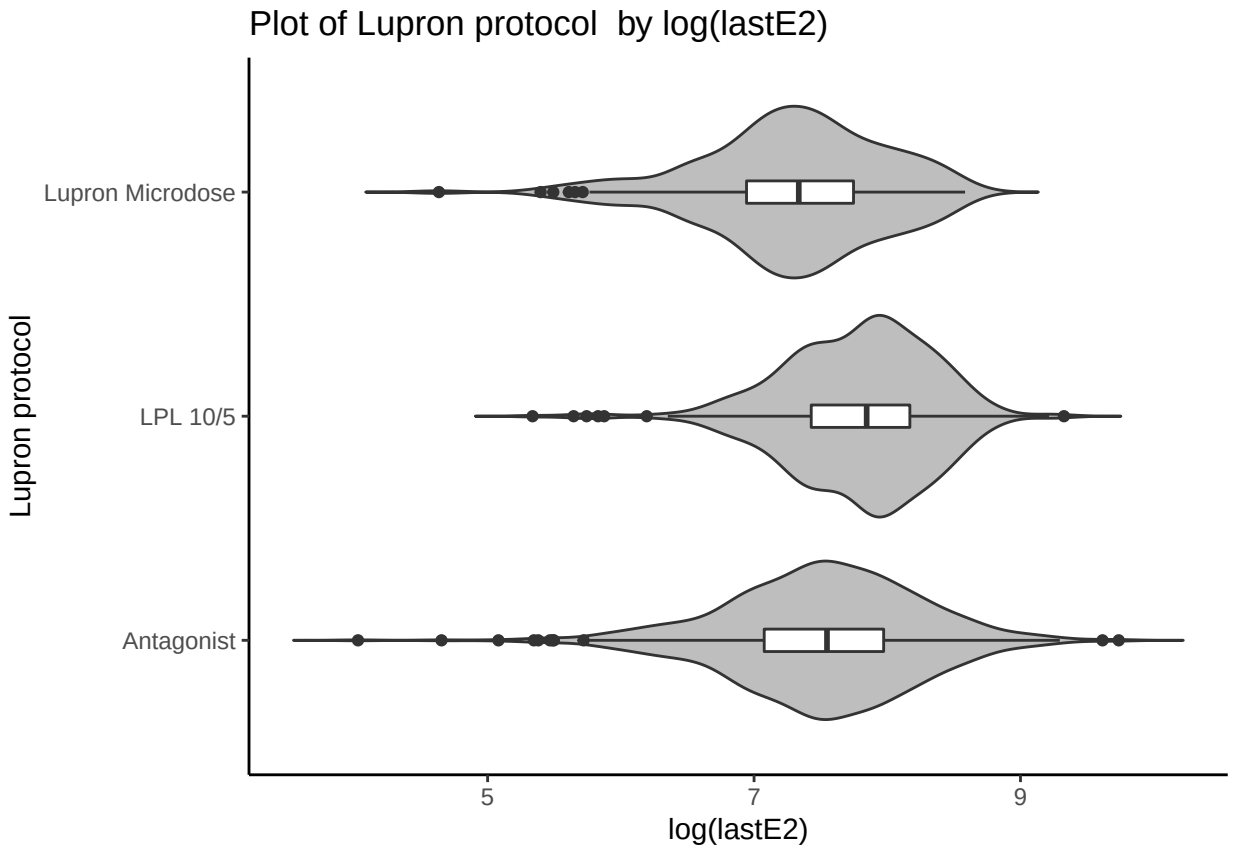
```
## -- Attaching packages --------------------------------------- tidyverse 1.3.1 --
```

```
## v ggplot2 3.3.6     v purrr   0.3.4
## v tibble  3.1.7     v dplyr   1.0.9
## v tidyr   1.2.0     v stringr 1.4.0
## v readr   2.1.2     v forcats 0.5.1
```

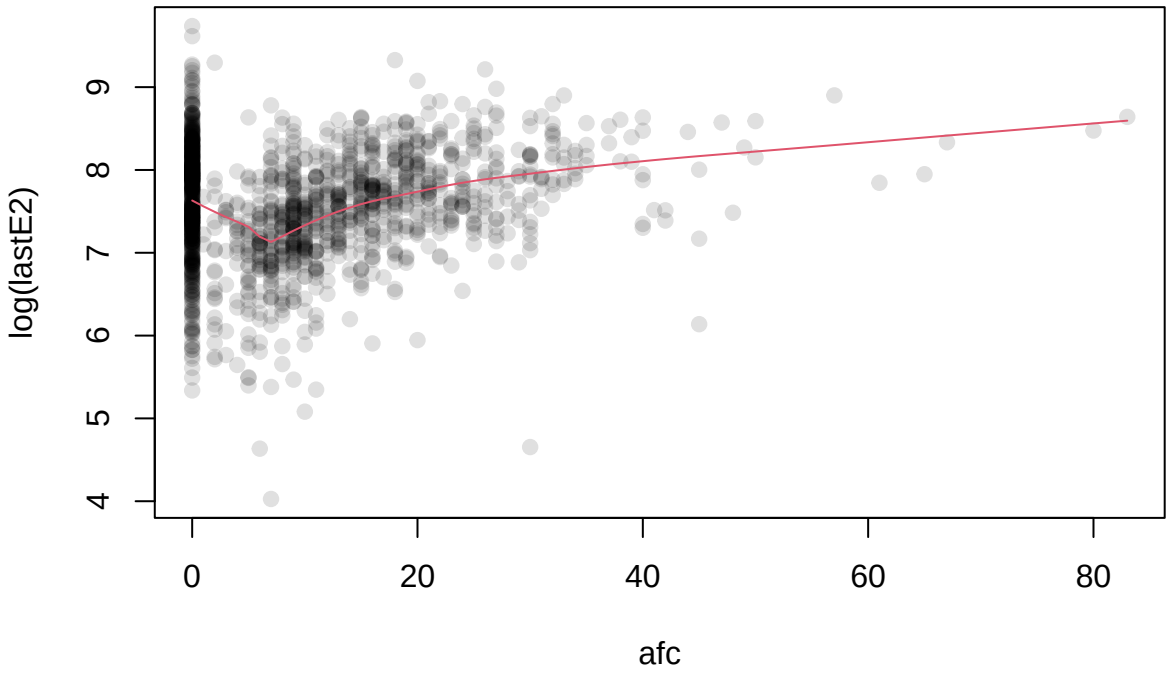
```
## -- Conflicts ------------------------------------------ tidyverse_conflicts() --
## x dplyr::filter() masks stats::filter()
## x dplyr::lag()    masks stats::lag()
```



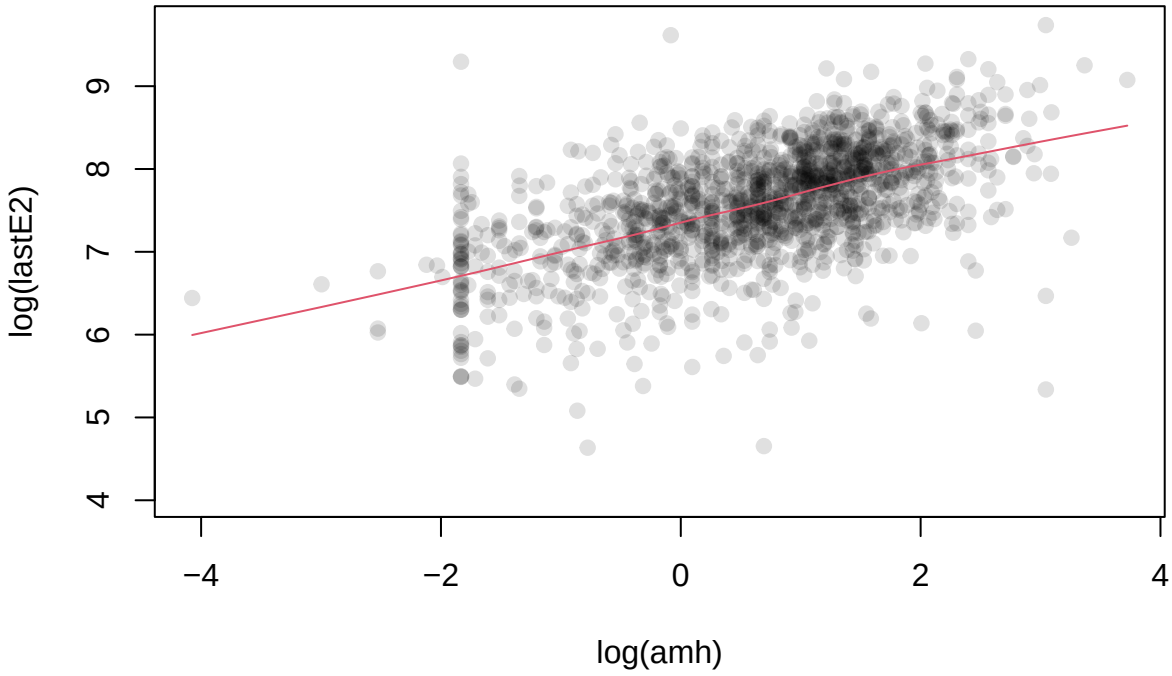

```
ggplot(data, aes(x=log(lastE2), y=lupprot)) +
        geom_violin(trim=FALSE, fill="gray")+
        labs(title="Plot of Lupron protocol  by log(lastE2)",x="log(lastE2)", y = "Lupron protocol")+
        geom_boxplot(width=0.1)+
        theme_classic()
```



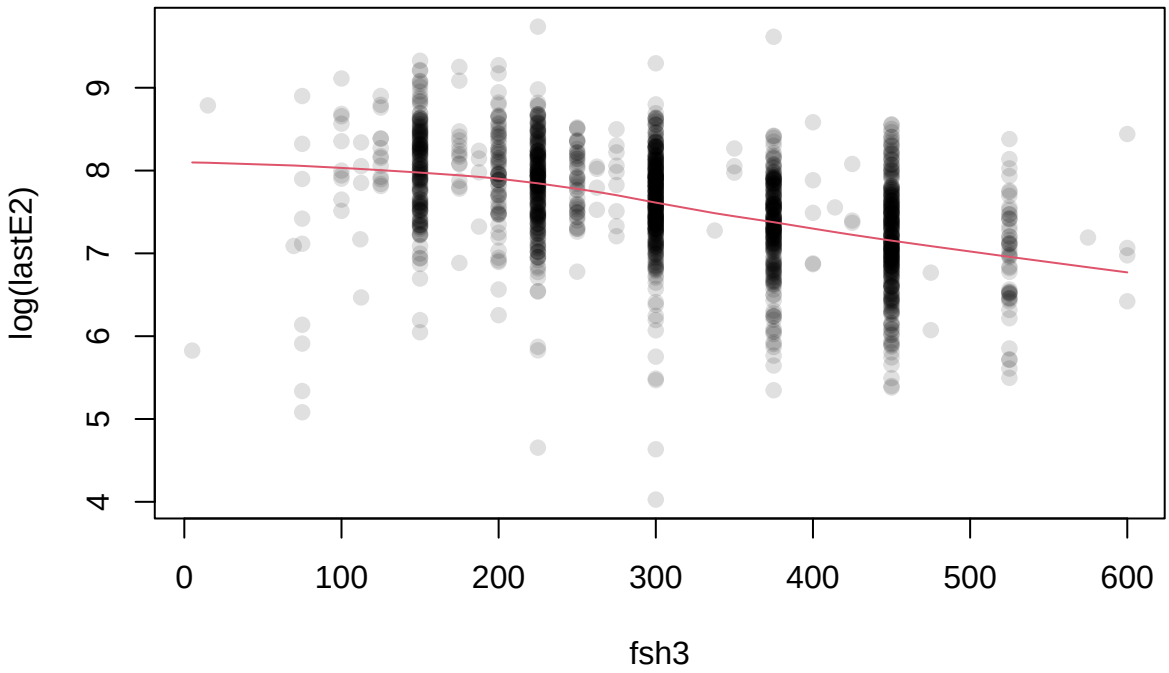
```
plot(log(lastE2)~afc, data=data, pch=19, col="#00000020")
with(subset(data), lines(lowess(x=afc, y=log(lastE2), iter=0), col=2))
```



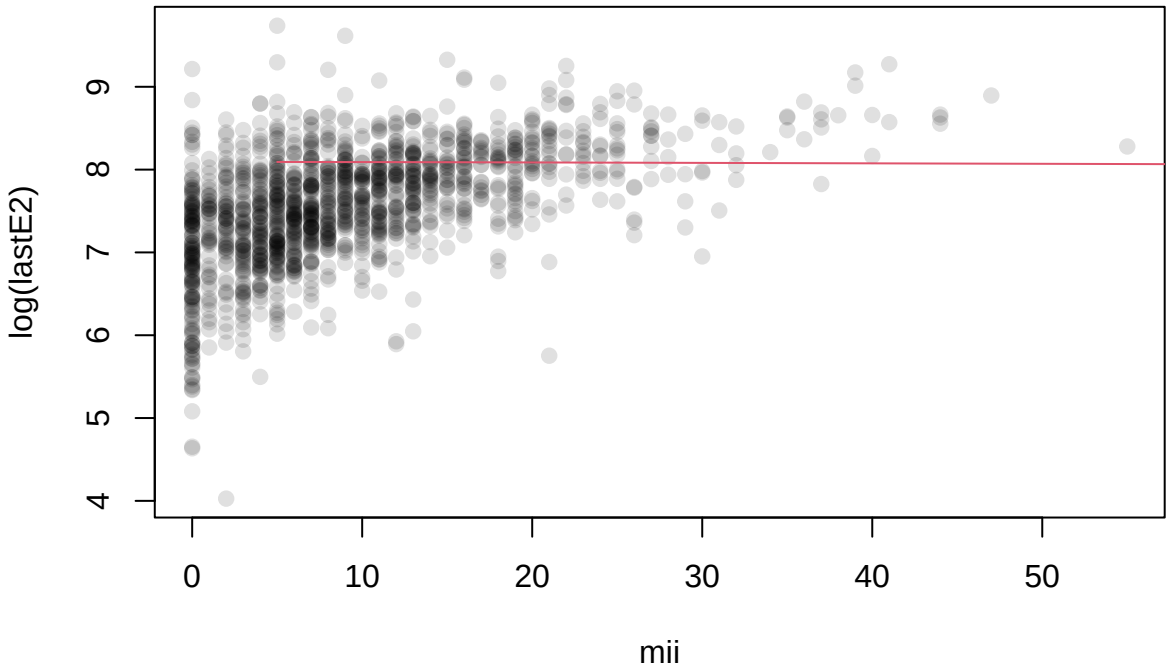

```
plot(log(lastE2)~log(amh), data=data, pch=19, col="#00000020")
with(subset(data, !is.na(amh)), lines(lowess(x=log(amh), y=log(lastE2), iter=0), col=2))
```



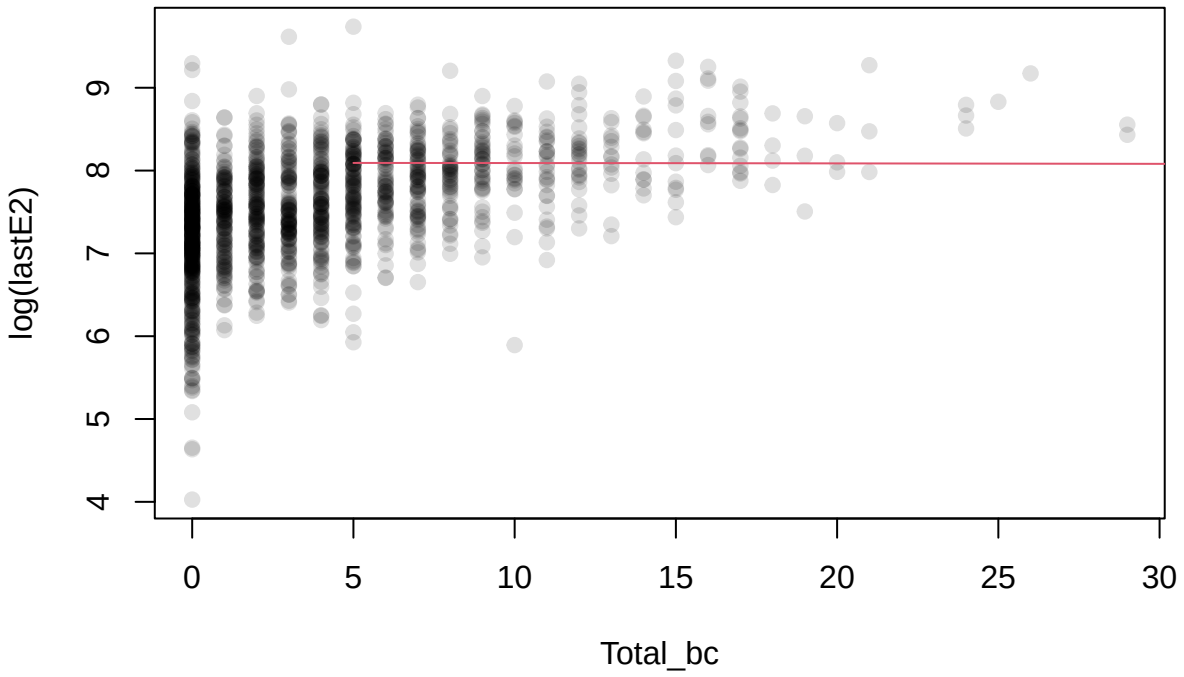

```
plot(log(lastE2)~fsh3, data=data, pch=19, col="#00000020")
with(subset(data, !is.na(amh)), lines(lowess(x=fsh3, y=log(lastE2), iter=0), col=2))
```




```
plot(log(lastE2)~mii, data=data, pch=19, col="#00000020")
with(subset(data, !is.na(mii)), lines(lowess(x=fsh3, y=log(lastE2), iter=0), col=2))
```




```
plot(log(lastE2)~Total_bc, data=data, pch=19, col="#00000020")
with(subset(data, !is.na(Total_bc)), lines(lowess(x=fsh3, y=log(lastE2), iter=0), col=2))
```



Correlations between pairs of variables

```
data$logamh <- log(data$amh)
data$loglastE2 <- log(data$lastE2)
round(cor(data[,c("age","bmi","afc","logamh", "lastE2","fsh3", "mii","Total_bc")], use="pairwise.comple
```

```
##             age   bmi    afc logamh lastE2   fsh3    mii Total_bc
## age       1.000 0.028 -0.191 -0.354 -0.211  0.461 -0.245   -0.280
## bmi       0.028 1.000  0.036  0.038  0.009  0.011  0.007    0.005
## afc      -0.191 0.036  1.000  0.246  0.124 -0.282  0.197    0.079
## logamh   -0.354 0.038  0.246  1.000  0.508 -0.668  0.519    0.460
## lastE2   -0.211 0.009  0.124  0.508  1.000 -0.439  0.505    0.504
## fsh3      0.461 0.011 -0.282 -0.668 -0.439  1.000 -0.438   -0.415
## mii      -0.245 0.007  0.197  0.519  0.505 -0.438  1.000    0.702
## Total_bc -0.280 0.005  0.079  0.460  0.504 -0.415  0.702    1.000
```

Statistical analysis

For convenience, construct variables indicating whether AFC=0, and "dummy variables" encoding Lupron protocols;

```
data$afc0 <- ifelse(data$afc==0, 1, 0)
table(data$lupprot)
```

```
##
##       Antagonist         LPL 10/5 Lupron Microdose
##              722              508              220
```

```
data$lup.lpl05<- ifelse(data$lupprot=="LPL 10/5", 1, 0)
data$lup.lpmic<- ifelse(data$lupprot=="Lupron Microdose", 1, 0)
```

A first analysis: linear regression of log-last E2 value on FSH adjusting for age, BMI, lupron protocol, AFC and whether AFC=0, and log AMH. Those with missing AMH values are omitted:

```
#srm$cutafc <- cut(srm$afc, c(-1,0,5,10,15,20,30,100))
#table(srm$cutafc)
clean.data <- subset(data, !is.na(amh))
m1 <- lm(log(lastE2)~age + bmi + afc + afc0 + log(amh) + factor(lupprot) +fsh3, data=clean.data)
cmat <- coef(summary(m1))
#library("rigr")
#m1.r <- regress("mean", loglastE2~age + bmi + cutafc +logamh + factor(lupprot) + fsh3, data=clean.srm)
#print(m1.r)
signif(cbind(est=cmat[,1], confint(m1), p.value=cmat[,4]),3)
```

```
##                                       est    2.5 %    97.5 %   p.value
## (Intercept)                      7.370000  7.06000  7.670000 2.46e-292
## age                              0.004290 -0.00289  0.011500  2.41e-01
## bmi                             -0.006520 -0.01200 -0.001010  2.05e-02
## afc                              0.007600  0.00342  0.011800  3.77e-04
## afc0                             0.198000  0.10800  0.289000  1.85e-05
## log(amh)                         0.297000  0.26100  0.334000  1.60e-53
## factor(lupprot)LPL 10/5          0.229000  0.16500  0.292000  2.67e-12
## factor(lupprot)Lupron Microdose  0.269000  0.17900  0.360000  6.03e-09
## fsh3                            -0.000748 -0.00112 -0.000379  7.34e-05
```

Turn this into a nomogram:

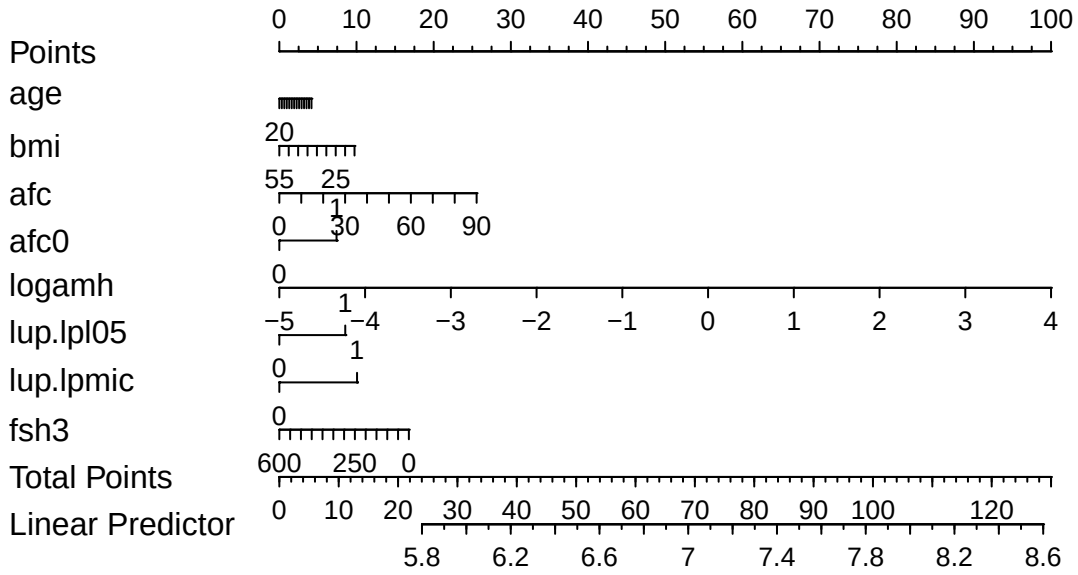
```
##
## Attaching package: 'Hmisc'

## The following objects are masked from 'package:dplyr':
##
##     src, summarize

## The following objects are masked from 'package:base':
##
##     format.pval, units

##
## Attaching package: 'SparseM'

## The following object is masked from 'package:base':
##
##     backsolve
```



Interpretation: this plot shows that AMH is doing the bulk of the work when the model determines a value for (mean) E2 among those with particular covariate values. For all the other variables, comparing individuals at opposite ends of the plotted axis, the difference in log E2 value is not impressive. But for those with even minor AMH differences, we see greater differentiation between their mean log E2 values.

Residual confounding might be a concern here, so a version that adjusts more flexibly for age, AMH, and then evaluates what FSH3 contributes after that:

```
library("splines")
m3a <- lm(loglastE2~bs(age) + bmi + afc + afc0 + bs(logamh) + factor(lupprot), data=clean.data)
m3b <- lm(loglastE2~bs(age) + bmi + afc + afc0 + bs(logamh) + factor(lupprot) + fsh3, data=clean.data)
summary(m3b)
```

```
##
## Call:
## lm(formula = loglastE2 ~ bs(age) + bmi + afc + afc0 + bs(logamh) +
##     factor(lupprot) + fsh3, data = clean.data)
##
## Residuals:
##      Min       1Q   Median       3Q      Max
## -3.13203 -0.29452  0.04933  0.34407  2.66486
##
## Coefficients:
##                                Estimate Std. Error t value Pr(>|t|)
## (Intercept)                   6.4586239  0.4321844  14.944  < 2e-16 ***
## bs(age)1                      0.3429520  0.4604570   0.745 0.456513
## bs(age)2                      0.1020228  0.1697126   0.601 0.547837
## bs(age)3                      0.2960844  0.3044791   0.972 0.331005
## bmi                          -0.0062486  0.0028369  -2.203 0.027785 *
## afc                           0.0076014  0.0021376   3.556 0.000389 ***
## afc0                          0.1993294  0.0462933   4.306 1.78e-05 ***
## bs(logamh)1                  -0.0059009  0.6956270  -0.008 0.993233
## bs(logamh)2                   1.4758718  0.2506378   5.888 4.87e-09 ***
## bs(logamh)3                   1.7884856  0.4760884   3.757 0.000179 ***
## factor(lupprot)LPL 10/5       0.2258600  0.0337382   6.694 3.12e-11 ***
```

```
## factor(lupprot)Lupron Microdose  0.2747260  0.0463061   5.933 3.75e-09 ***
## fsh3                            -0.0007304  0.0001943  -3.758 0.000178 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 0.5372 on 1401 degrees of freedom
## Multiple R-squared:  0.375,  Adjusted R-squared:  0.3697
## F-statistic: 70.06 on 12 and 1401 DF,  p-value: < 2.2e-16
```

```
anova(m3a,m3b)
```

```
## Analysis of Variance Table
##
## Model 1: loglastE2 ~ bs(age) + bmi + afc + afc0 + bs(logamh) + factor(lupprot)
## Model 2: loglastE2 ~ bs(age) + bmi + afc + afc0 + bs(logamh) + factor(lupprot) +
##     fsh3
##   Res.Df    RSS Df Sum of Sq      F   Pr(>F)
## 1   1402 408.36
## 2   1401 404.29  1    4.0763 14.126 0.000178 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

Interpretation: FSH3 appears to contribute, after accounting for AMH and other variables, but the contribution is *much* smaller than for AMH. We can tell this because the coefficient is essentially identical to the less-flexible fit, illustrated by the nomogram.

Interaction analyses - Linear Regression

It's of interest to see whether FSH3 modifies the E2:AMH relationship. No modification does not mean no effect, just that the effect of FSH appears similar regardless of the value of AMH.

```
data$fsh3cat <- cut(data$fsh3, c(0,150,250,350,600))
data$lupprot.f <- factor(data$lupprot)
data$amh.f <- cut(data$amh, quantile(data$amh, seq(0,1,l=5), na.rm=TRUE))
table( data$amh.f )
```

```
##
## (0.017,0.92]  (0.92,2.15]     (2.15,4]     (4,41.4]
##          355          352          353          353
```

```
m3 <- lm(loglastE2~age + bmi + afc + afc0 + logamh*fsh3cat + lupprot.f, data=subset(data, !is.na(amh)))
summary(m3)
```

```
##
## Call:
## lm(formula = loglastE2 ~ age + bmi + afc + afc0 + logamh * fsh3cat +
##     lupprot.f, data = subset(data, !is.na(amh)))
##
## Residuals:
##      Min       1Q   Median       3Q      Max
## -3.14755 -0.29680  0.04248  0.34734  2.56025
##
## Coefficients:
##                            Estimate Std. Error t value Pr(>|t|)
## (Intercept)                7.154043   0.170369  41.991  < 2e-16 ***
## age                        0.003956   0.003648   1.084 0.278346
## bmi                       -0.007468   0.002817  -2.651 0.008116 **
```

```
## afc                         0.007648   0.002126   3.597 0.000333 ***
## afc0                        0.195833   0.045994   4.258 2.20e-05 ***
## logamh                      0.347124   0.048819   7.110 1.84e-12 ***
## fsh3cat(150,250]           -0.027256   0.108758  -0.251 0.802152
## fsh3cat(250,350]            0.091714   0.097375   0.942 0.346427
## fsh3cat(350,600]           -0.111060   0.094347  -1.177 0.239337
## lupprot.fLPL 10/5           0.240819   0.032967   7.305 4.64e-13 ***
## lupprot.fLupron Microdose   0.273252   0.045876   5.956 3.26e-09 ***
## logamh:fsh3cat(150,250]     0.044834   0.064445   0.696 0.486737
## logamh:fsh3cat(250,350]    -0.068549   0.060497  -1.133 0.257363
## logamh:fsh3cat(350,600]    -0.084239   0.054290  -1.552 0.120973
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 0.5343 on 1400 degrees of freedom
## Multiple R-squared:  0.3823, Adjusted R-squared:  0.3765
## F-statistic: 66.65 on 13 and 1400 DF,  p-value: < 2.2e-16
```

```
anova(m3)
```

```
## Analysis of Variance Table
##
## Response: loglastE2
##                   Df Sum Sq Mean Sq  F value    Pr(>F)
## age                1  35.33  35.334 123.7943 < 2.2e-16 ***
## bmi                1   0.23   0.227   0.7936   0.37316
## afc                1  10.34  10.342  36.2327 2.233e-09 ***
## afc0               1  49.82  49.823 174.5591 < 2.2e-16 ***
## logamh             1 121.79 121.791 426.7043 < 2.2e-16 ***
## fsh3cat            3   8.07   2.689   9.4219 3.642e-06 ***
## lupprot.f          2  19.52   9.762  34.2028 3.143e-15 ***
## logamh:fsh3cat     3   2.18   0.728   2.5496   0.05429 .
## Residuals       1400 399.59   0.285
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
m4 <- lm(loglastE2~age + bmi + afc + afc0 + bs(logamh)*fsh3cat + lupprot.f, data=subset(data, !is.na(aml
summary(m4)
```

```
##
## Call:
## lm(formula = loglastE2 ~ age + bmi + afc + afc0 + bs(logamh) *
##     fsh3cat + lupprot.f, data = subset(data, !is.na(amh)))
##
## Residuals:
##      Min       1Q   Median       3Q      Max
## -2.90186 -0.29417  0.04245  0.34270  2.57680
##
## Coefficients:
##                               Estimate Std. Error t value Pr(>|t|)
## (Intercept)                   5.395956   2.041065   2.644 0.008293 **
## age                           0.004393   0.003656   1.202 0.229685
## bmi                          -0.006851   0.002834  -2.418 0.015753 *
## afc                           0.007581   0.002127   3.564 0.000378 ***
## afc0                          0.198355   0.046041   4.308 1.76e-05 ***
```

```
## bs(logamh)1                   -0.050602   3.639390  -0.014 0.988909
## bs(logamh)2                    3.327238   1.425955   2.333 0.019772 *
## bs(logamh)3                    2.391679   2.262717   1.057 0.290697
## fsh3cat(150,250]              -1.460252   2.992351  -0.488 0.625630
## fsh3cat(250,350]              -0.105330   2.727391  -0.039 0.969199
## fsh3cat(350,600]               0.907774   2.088705   0.435 0.663912
## lupprot.fLPL 10/5              0.226578   0.033571   6.749 2.18e-11 ***
## lupprot.fLupron Microdose      0.273836   0.046138   5.935 3.70e-09 ***
## bs(logamh)1:fsh3cat(150,250]  3.385471   5.132199   0.660 0.509586
## bs(logamh)2:fsh3cat(150,250]  0.053818   2.151782   0.025 0.980050
## bs(logamh)3:fsh3cat(150,250]  2.248333   3.351308   0.671 0.502407
## bs(logamh)1:fsh3cat(250,350]  2.443518   5.037385   0.485 0.627698
## bs(logamh)2:fsh3cat(250,350] -1.826586   1.670233  -1.094 0.274315
## bs(logamh)3:fsh3cat(250,350]  1.088598   3.425294   0.318 0.750676
## bs(logamh)1:fsh3cat(350,600] -0.315495   3.800094  -0.083 0.933845
## bs(logamh)2:fsh3cat(350,600] -1.380538   1.534707  -0.900 0.368518
## bs(logamh)3:fsh3cat(350,600] -1.704504   2.571826  -0.663 0.507594
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 0.5338 on 1392 degrees of freedom
## Multiple R-squared:  0.3869, Adjusted R-squared:  0.3776
## F-statistic: 41.82 on 21 and 1392 DF,  p-value: < 2.2e-16
```

```
anova(m4)
```

```
## Analysis of Variance Table
##
## Response: loglastE2
##                       Df Sum Sq Mean Sq  F value    Pr(>F)
## age                    1  35.33  35.334 124.0058 < 2.2e-16 ***
## bmi                    1   0.23   0.227   0.7950   0.37275
## afc                    1  10.34  10.342  36.2946 2.168e-09 ***
## afc0                   1  49.82  49.823 174.8573 < 2.2e-16 ***
## bs(logamh)             3 122.64  40.882 143.4761 < 2.2e-16 ***
## fsh3cat                3   7.65   2.550   8.9501 7.126e-06 ***
## lupprot.f              2  19.32   9.660  33.9024 4.205e-15 ***
## bs(logamh):fsh3cat     9   4.91   0.546   1.9155   0.04601 *
## Residuals           1392 396.63   0.285
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
m5 <- lm(loglastE2~age + bmi + afc + afc0 + fsh3*amh.f + lupprot.f, data=subset(data,!is.na(amh)))
summary(m5)
```

```
##
## Call:
## lm(formula = loglastE2 ~ age + bmi + afc + afc0 + fsh3 * amh.f +
##     lupprot.f, data = subset(data, !is.na(amh)))
##
## Residuals:
##      Min       1Q   Median       3Q      Max
## -2.89403 -0.29585  0.04869  0.33712  2.61077
##
## Coefficients:
```

```
##                              Estimate Std. Error t value Pr(>|t|)
## (Intercept)                 7.0370910  0.2118514  33.217  < 2e-16 ***
## age                         0.0019488  0.0037733   0.516  0.60560
## bmi                        -0.0048453  0.0028925  -1.675  0.09413 .
## afc                         0.0101473  0.0021767   4.662 3.44e-06 ***
## afc0                        0.2510238  0.0471010   5.329 1.15e-07 ***
## fsh3                       -0.0005134  0.0003640  -1.411  0.15860
## amh.f(0.92,2.15]            0.5358877  0.1915609   2.797  0.00522 **
## amh.f(2.15,4]               0.8648299  0.1755972   4.925 9.44e-07 ***
## amh.f(4,41.4]               0.8931342  0.1775813   5.029 5.56e-07 ***
## lupprot.fLPL 10/5           0.2050757  0.0340388   6.025 2.16e-09 ***
## lupprot.fLupron Microdose   0.2449580  0.0475173   5.155 2.90e-07 ***
## fsh3:amh.f(0.92,2.15]      -0.0004847  0.0004915  -0.986  0.32424
## fsh3:amh.f(2.15,4]         -0.0008742  0.0004814  -1.816  0.06961 .
## fsh3:amh.f(4,41.4]         -0.0004098  0.0005548  -0.739  0.46018
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 0.5512 on 1399 degrees of freedom
##   (1 observation deleted due to missingness)
## Multiple R-squared:  0.3415, Adjusted R-squared:  0.3354
## F-statistic: 55.82 on 13 and 1399 DF,  p-value: < 2.2e-16
```

```
anova(m5)
```

```
## Analysis of Variance Table
##
## Response: loglastE2
##              Df Sum Sq Mean Sq  F value    Pr(>F)
## age           1  35.27  35.268 116.0678 < 2.2e-16 ***
## bmi           1   0.22   0.220   0.7240    0.3950
## afc           1  10.21  10.213  33.6107 8.309e-09 ***
## afc0          1  49.23  49.234 162.0300 < 2.2e-16 ***
## fsh3          1  60.71  60.709 199.7936 < 2.2e-16 ***
## amh.f         3  47.56  15.854  52.1747 < 2.2e-16 ***
## lupprot.f     2  16.29   8.143  26.8000 3.787e-12 ***
## fsh3:amh.f    3   1.01   0.337   1.1084    0.3445
## Residuals  1399 425.10   0.304
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
m6 <- lm(loglastE2~age + bmi + afc + afc0 + bs(fsh3)*amh.f + lupprot.f, data=subset(data, !is.na(amh)))
summary(m6)
```

```
##
## Call:
## lm(formula = loglastE2 ~ age + bmi + afc + afc0 + bs(fsh3) *
##     amh.f + lupprot.f, data = subset(data, !is.na(amh)))
##
## Residuals:
##      Min       1Q   Median       3Q      Max
## -2.91021 -0.29733  0.03667  0.33304  2.52274
##
## Coefficients:
##                              Estimate Std. Error t value Pr(>|t|)
```

```
## (Intercept)                 5.118777   0.424747  12.051  < 2e-16 ***
## age                         0.003909   0.003778   1.035 0.300985
## bmi                        -0.005463   0.002873  -1.901 0.057446 .
## afc                         0.009681   0.002167   4.467 8.59e-06 ***
## afc0                        0.245000   0.046835   5.231 1.94e-07 ***
## bs(fsh3)1                   2.949543   0.769130   3.835 0.000131 ***
## bs(fsh3)2                   1.511968   0.412751   3.663 0.000258 ***
## bs(fsh3)3                   1.307875   0.487380   2.683 0.007372 **
## amh.f(0.92,2.15]            1.539051   0.980245   1.570 0.116627
## amh.f(2.15,4]               2.576004   0.700701   3.676 0.000246 ***
## amh.f(4,41.4]               2.121921   0.552007   3.844 0.000127 ***
## lupprot.fLPL 10/5           0.196806   0.033802   5.822 7.20e-09 ***
## lupprot.fLupron Microdose   0.260038   0.047563   5.467 5.41e-08 ***
## bs(fsh3)1:amh.f(0.92,2.15] -1.252039   1.817502  -0.689 0.491014
## bs(fsh3)2:amh.f(0.92,2.15] -1.899026   0.710808  -2.672 0.007636 **
## bs(fsh3)3:amh.f(0.92,2.15] -0.584407   1.202737  -0.486 0.627116
## bs(fsh3)1:amh.f(2.15,4]    -2.800570   1.530203  -1.830 0.067435 .
## bs(fsh3)2:amh.f(2.15,4]    -2.201166   0.603356  -3.648 0.000274 ***
## bs(fsh3)3:amh.f(2.15,4]    -1.776764   1.212976  -1.465 0.143202
## bs(fsh3)1:amh.f(4,41.4]    -1.636239   1.306611  -1.252 0.210679
## bs(fsh3)2:amh.f(4,41.4]    -1.770377   0.864404  -2.048 0.040739 *
## bs(fsh3)3:amh.f(4,41.4]    -1.629766   1.558258  -1.046 0.295794
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 0.5452 on 1391 degrees of freedom
##   (1 observation deleted due to missingness)
## Multiple R-squared:  0.3595, Adjusted R-squared:  0.3499
## F-statistic: 37.18 on 21 and 1391 DF,  p-value: < 2.2e-16
```

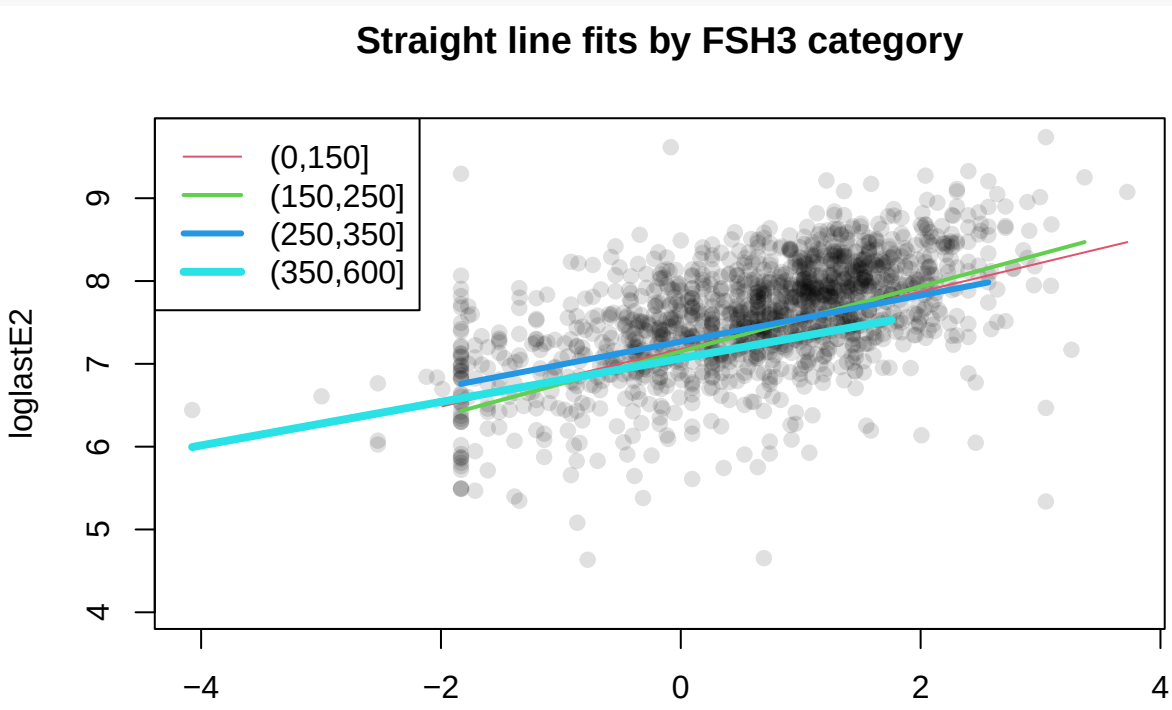
```
anova(m6)
```

```
## Analysis of Variance Table
##
## Response: loglastE2
##                   Df Sum Sq Mean Sq  F value    Pr(>F)
## age                1  35.27  35.268 118.6431 < 2.2e-16 ***
## bmi                1   0.22   0.220   0.7401    0.3898
## afc                1  10.21  10.213  34.3564 5.722e-09 ***
## afc0               1  49.23  49.234 165.6250 < 2.2e-16 ***
## bs(fsh3)           3  71.55  23.850  80.2314 < 2.2e-16 ***
## amh.f              3  40.86  13.621  45.8214 < 2.2e-16 ***
## lupprot.f          2  17.07   8.537  28.7175 6.008e-13 ***
## bs(fsh3):amh.f     9   7.69   0.854   2.8732    0.0023 **
## Residuals       1391 413.49   0.297
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

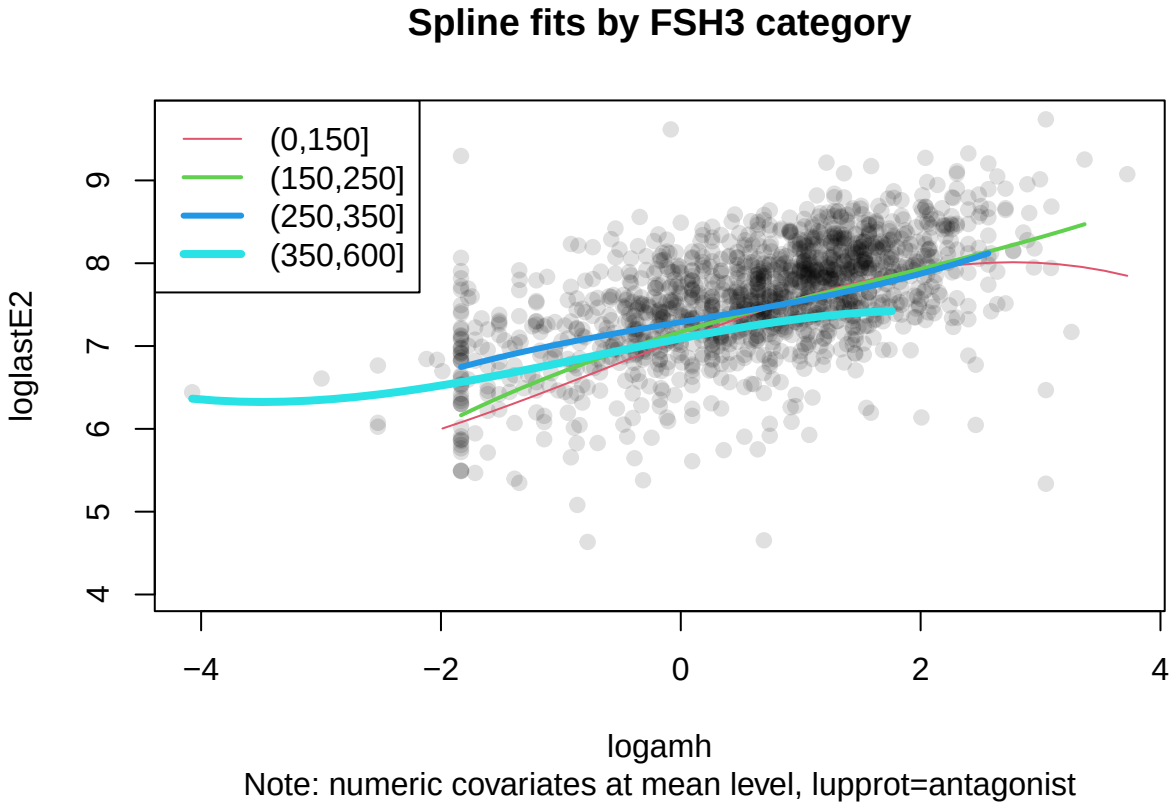
```
myranges <- sapply(1:4, function(i){ range( subset(data, fsh3cat==levels(data$fsh3cat)[i])$logamh, na.r
myranges2 <- sapply(1:4, function(i){ range( subset(data, amh.f==levels(data$amh.f)[i])$fsh3, na.rm=TRU
```

```
with(data, plot(loglastE2~ logamh, pch=19, col="#00000020"))
for(i in 1:4){
    mynewdata <- data.frame(age=mean(data$age), bmi=mean(data$age), afc=mean(data$afc),
```

```
afc0=mean(data$afc0), fsh3cat=levels(data$fsh3cat)[i], lupprot.f="Antagonist",
    logamh=seq(myranges[1,i], myranges[2,i], l=31) )
    myfit <- predict(m3, newdata= mynewdata)
    lines(x=mynewdata$logamh, y=myfit, lwd=i, col=i+1)
}
legend("topleft", col=2:5, lwd=1:4, levels(data$fsh3cat))
title(main="Straight line fits by FSH3 category", sub="Note: numeric covariates at mean level, lupprot=a
```




```
with(data, plot(loglastE2~ logamh, pch=19, col="#00000020"))
for(i in 1:4){
    mynewdata <- data.frame(age=mean(data$age), bmi=mean(data$age), afc=mean(data$afc),
afc0=mean(data$afc0), fsh3cat=levels(data$fsh3cat)[i], lupprot.f="Antagonist",
    logamh=seq(myranges[1,i], myranges[2,i], l=31) )
    myfit <- predict(m4, newdata= mynewdata)
    lines(x=mynewdata$logamh, y=myfit, lwd=i, col=i+1)
}
legend("topleft", col=2:5, lwd=1:4, levels(data$fsh3cat))
title(main="Spline fits by FSH3 category", sub="Note: numeric covariates at mean level, lupprot=antagoni
```



Note: numeric covariates at mean level, lupprot=antagonist

Statistical learning approaches

```
#install.packages("glmnet")
library("glmnet")
```

```
## Loading required package: Matrix
```

```
##
## Attaching package: 'Matrix'
```

```
## The following objects are masked from 'package:tidyr':
##
##     expand, pack, unpack
```

```
## Loaded glmnet 4.1-4
```

```
# comparison of main effects-only model with CV lasso
par(mfrow=c(1,2))
coef(summary(m1))
```

```
##                                     Estimate   Std. Error   t value
## (Intercept)                    7.3651363633 0.1559526653 47.226742
## age                            0.0042864597 0.0036573807  1.172003
## bmi                           -0.0065152109 0.0028082777 -2.320002
## afc                            0.0075997866 0.0021323218  3.564090
## afc0                           0.1983474269 0.0461550992  4.297411
## log(amh)                       0.2972937902 0.0184904865 16.078203
## factor(lupprot)LPL 10/5        0.2285524498 0.0323891389  7.056453
## factor(lupprot)Lupron Microdose 0.2694409936 0.0460402640  5.852290
## fsh3                          -0.0007484203 0.0001882011 -3.976706
```

```
##                                      Pr(>|t|)
## (Intercept)                       2.463381e-292
## age                                2.413947e-01
## bmi                                2.048343e-02
## afc                                3.773456e-04
## afc0                               1.846991e-05
## log(amh)                           1.596457e-53
## factor(lupprot)LPL 10/5            2.674165e-12
## factor(lupprot)Lupron Microdose    6.025233e-09
## fsh3                               7.343337e-05
```

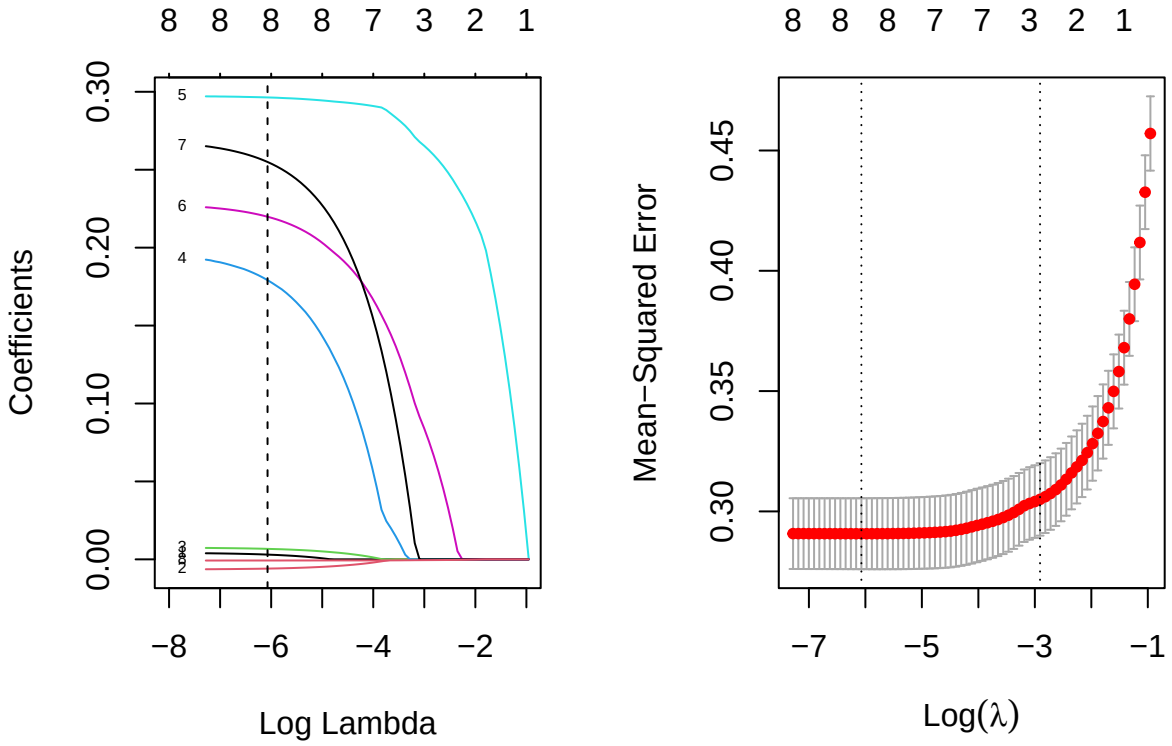
```
plot(glmnet(x=model.matrix(m1)[,-1], y=m1$model[,1]),
xvar="lambda", label=TRUE, xlim=c(-8,-1))
set.seed(4)
cv.glmnet1 <- cv.glmnet(x=model.matrix(m1)[,-1], y=m1$model[,1])
print(cv.glmnet1 )
```

```
##
## Call:  cv.glmnet(x = model.matrix(m1)[, -1], y = m1$model[, 1])
##
## Measure: Mean-Squared Error
##
##      Lambda Index Measure      SE Nonzero
## min 0.00231    56  0.2907 0.01475       8
## 1se 0.05459    22  0.3050 0.01507       3
```

```
tail( anova(m1)[,"Mean Sq"], 1)
```

```
## [1] 0.2881211
```

```
abline(v=log(cv.glmnet1$lambda.min), lty=2)
plot(cv.glmnet1 )
```



```
cv.glmnet1$lambda.min
```

```
## [1] 0.002308725
```

```
log(cv.glmnet1$lambda.min)
```

```
## [1] -6.07106
```

```
cbind( coef(m1), coef(cv.glmnet1, s = "lambda.min"))
```

```
## 9 x 2 sparse Matrix of class "dgCMatrix"
##                                                    s1
## (Intercept)                          7.3651363633  7.4096973184
## age                                  0.0042864597  0.0030546837
## bmi                                 -0.0065152109 -0.0059294936
## afc                                  0.0075997866  0.0067282097
## afc0                                 0.1983474269  0.1791451556
## log(amh)                             0.2972937902  0.2963774450
## factor(lupprot)LPL 10/5              0.2285524498  0.2198354296
## factor(lupprot)Lupron Microdose      0.2694409936  0.2549748141
## fsh3                                -0.0007484203 -0.0007308659
```

Interpretation: the lasso approach can potentially achieve better prediction of logE2 values, by shrinking the "classical" estimates towards zero in a way suggested by the patterns in the data. This makes them more stable, albeit at the cost of some bias. Cross-validation is used to choose the apparently-best degree of shrinkage, i.e. the best tradeoff. But for this large dataset with clear signals, it seems we do best not shrinking at all.

Also note how, if we were to shrink the coefficients anyway, AMH is the last one to be shrunk, emphasizing what we saw in the other analyses.

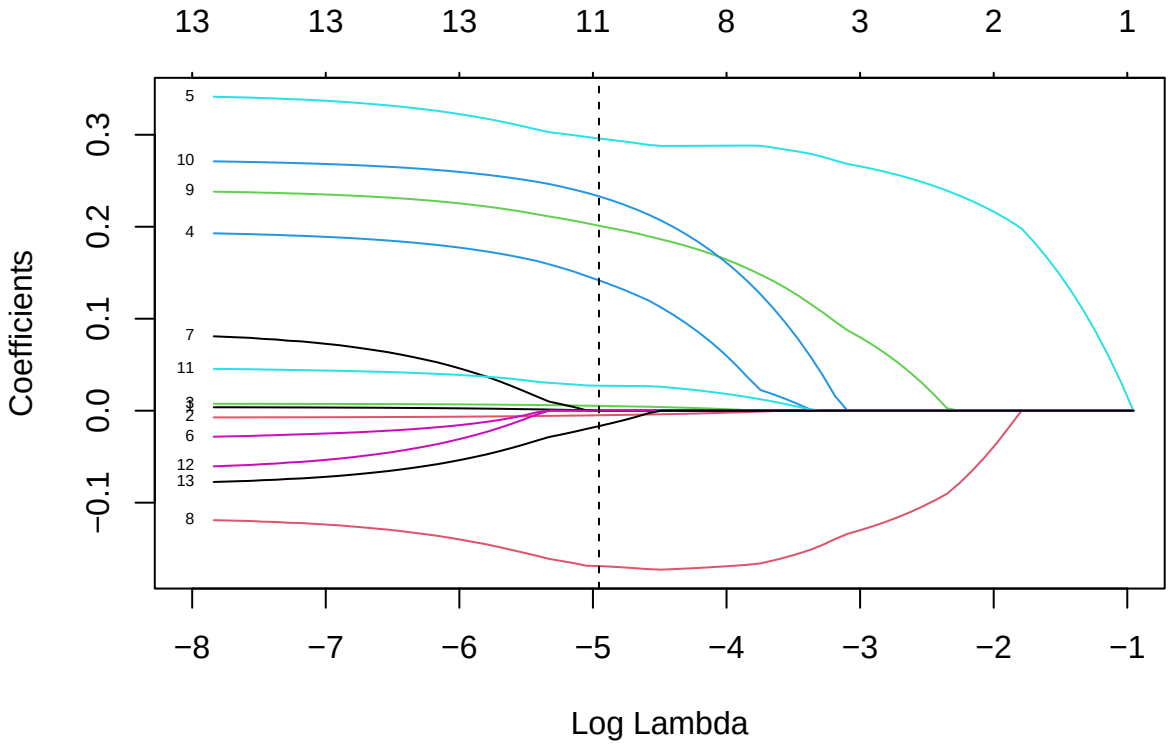
Trying the same approach for the more flexible representation of FSH3, and its interaction with AMH, we again see that all the AMH terms persist best under shrinkage. Also, lasso's degree of improvement in prediction (proportion of variance explained, known as R^2) is very minor, when optimized via cross-validation.

```
# comparison of main effects-only model with CV lasso
coef(summary(m3))
```

```
##                                Estimate  Std. Error    t value      Pr(>|t|)
## (Intercept)                 7.154042882 0.170369051 41.9914464 4.452362e-250
## age                         0.003955658 0.003647568  1.0844642  2.783457e-01
## bmi                        -0.007468188 0.002817130 -2.6509912  8.116114e-03
## afc                         0.007647908 0.002126158  3.5970550  3.330390e-04
## afc0                        0.195832542 0.045994078  4.2577773  2.202247e-05
## logamh                      0.347124332 0.048818683  7.1104813  1.837952e-12
## fsh3cat(150,250]           -0.027255807 0.108757709 -0.2506103  8.021522e-01
## fsh3cat(250,350]            0.091713905 0.097375400  0.9418591  3.464273e-01
## fsh3cat(350,600]           -0.111060203 0.094346943 -1.1771468  2.393370e-01
## lupprot.fLPL 10/5           0.240818652 0.032966690  7.3049084  4.641112e-13
## lupprot.fLupron Microdose   0.273252469 0.045876022  5.9563243  3.257934e-09
## logamh:fsh3cat(150,250]     0.044834024 0.064445214  0.6956921  4.867372e-01
## logamh:fsh3cat(250,350]    -0.068549482 0.060496937 -1.1331066  2.573635e-01
## logamh:fsh3cat(350,600]    -0.084239459 0.054290440 -1.5516444  1.209733e-01
```

```
#plot(glmnet(x=model.matrix(m3)[,-1], y=m3$model[,1]))
plot(glmnet(x=model.matrix(m3)[,-1], y=m3$model[,1]),
xvar="lambda", label=TRUE, xlim=c(-8,-1))
set.seed(4)
```

```
cv.glmnet3 <- cv.glmnet(x=model.matrix(m3)[,-1], y=m3$model[,1])
abline(v=log(cv.glmnet3$lambda.min), lty=2)
```



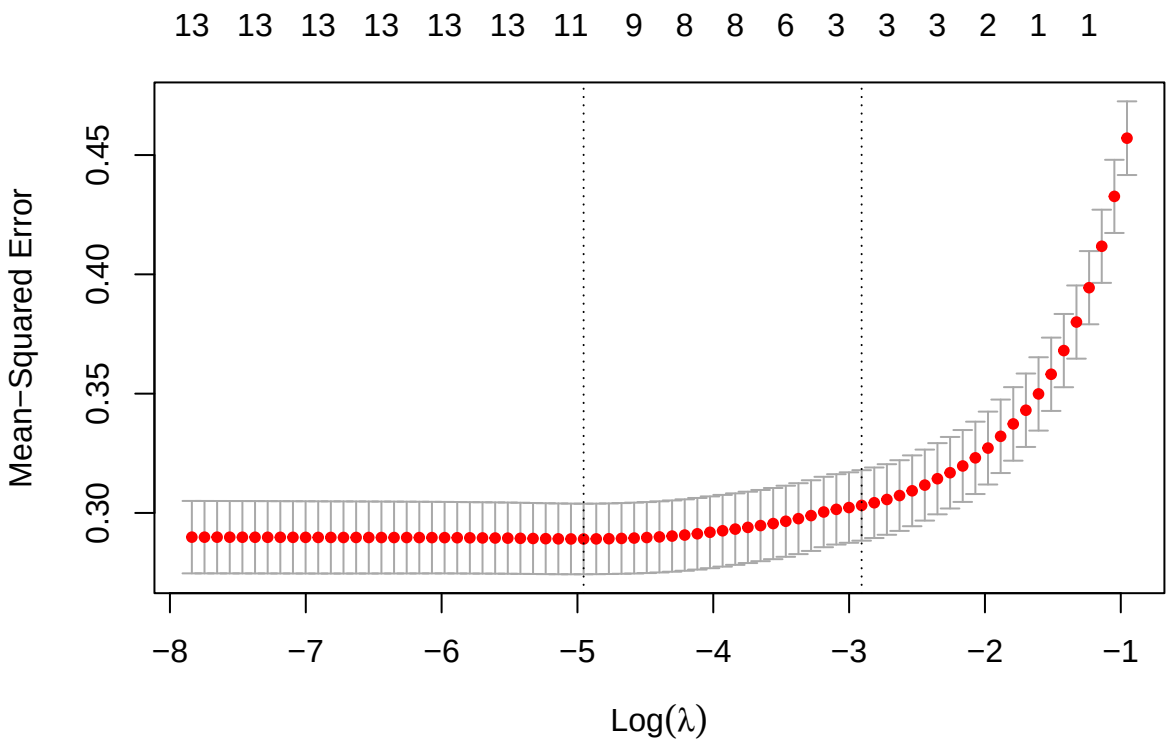

```
print(cv.glmnet3 )
```

```
##
## Call:  cv.glmnet(x = model.matrix(m3)[, -1], y = m3$model[, 1])
##
## Measure: Mean-Squared Error
##
##      Lambda Index Measure      SE Nonzero
## min 0.00705    44  0.2891 0.01478      10
## 1se 0.05459    22  0.3031 0.01477       3
```

```
tail( anova(m3)[,"Mean Sq"], 1)
```

```
## [1] 0.2854232
```

```
plot(cv.glmnet3 )
```




```
cv.glmnet3$lambda.min
```

```
## [1] 0.007050512
```

```
log(cv.glmnet3$lambda.min)
```

```
## [1] -4.954655
```

```
cbind( coef(m3), coef(cv.glmnet3, s = "lambda.min"))
```

```
## 14 x 2 sparse Matrix of class "dgCMatrix"
##                                                s1
## (Intercept)                 7.154042882  7.360019e+00
## age                         0.003955658  9.132309e-05
## bmi                        -0.007468188 -4.984006e-03
## afc                         0.007647908  5.226483e-03
## afc0                        0.195832542  1.417112e-01
## logamh                      0.347124332  2.959619e-01
## fsh3cat(150,250]           -0.027255807  .
## fsh3cat(250,350]            0.091713905  .
## fsh3cat(350,600]           -0.111060203 -1.688898e-01
## lupprot.fLPL 10/5           0.240818652  2.010569e-01
## lupprot.fLupron Microdose   0.273252469  2.331045e-01
## logamh:fsh3cat(150,250]     0.044834024  2.713846e-02
## logamh:fsh3cat(250,350]    -0.068549482  .
## logamh:fsh3cat(350,600]    -0.084239459 -1.680133e-02
```

Poisson regression

```
# mii
m7 <- glm(mii ~ age + bmi + afc + afc0 + log(amh) + factor(lupprot) + fsh3,
```

```
          data=clean.data,
          family = poisson(link="log"))
summary(m7)
```

analysis for the number of mature oocytes

```
##
## Call:
## glm(formula = mii ~ age + bmi + afc + afc0 + log(amh) + factor(lupprot) +
##     fsh3, family = poisson(link = "log"), data = clean.data)
##
## Deviance Residuals:
##     Min       1Q   Median       3Q      Max
## -6.6527  -1.7119  -0.2744   1.0750   6.7755
##
## Coefficients:
##                                   Estimate Std. Error z value Pr(>|z|)
## (Intercept)                      2.2872869  0.0940037  24.332  < 2e-16 ***
## age                             -0.0038307  0.0022211  -1.725  0.08458 .
## bmi                             -0.0055309  0.0016924  -3.268  0.00108 **
## afc                              0.0097027  0.0010537   9.208  < 2e-16 ***
## afc0                             0.2183277  0.0280148   7.793 6.53e-15 ***
## log(amh)                         0.3342061  0.0129332  25.841  < 2e-16 ***
## factor(lupprot)LPL 10/5         -0.0537967  0.0192955  -2.788  0.00530 **
## factor(lupprot)Lupron Microdose -0.1001255  0.0360370  -2.778  0.00546 **
## fsh3                            -0.0008112  0.0001230  -6.595 4.26e-11 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## (Dispersion parameter for poisson family taken to be 1)
##
##     Null deviance: 9327.9  on 1413  degrees of freedom
## Residual deviance: 6367.8  on 1405  degrees of freedom
## AIC: 11361
##
## Number of Fisher Scoring iterations: 5
```

```
# offset = log(lastE2)?
```

log(amh) and afc contribute a lot to determine the number of mature oocytes

analysis for the total number of blast conversion

```
## Total_bc
m8 <- glm(Total_bc ~ age + bmi + afc + afc0 + log(amh) + factor(lupprot) + fsh3,
          data=clean.data,
          family = poisson(link="log"))
summary(m8)
```

```
##
## Call:
## glm(formula = Total_bc ~ age + bmi + afc + afc0 + log(amh) +
##     factor(lupprot) + fsh3, family = poisson(link = "log"), data = clean.data)
##
## Deviance Residuals:
```

```
##     Min       1Q   Median       3Q      Max
## -5.1448  -1.7639  -0.5323   0.9650   6.9080
##
## Coefficients:
##                                    Estimate Std. Error z value Pr(>|z|)
## (Intercept)                       1.8524713  0.1432374  12.933  < 2e-16 ***
## age                              -0.0189733  0.0033827  -5.609 2.04e-08 ***
## bmi                              -0.0068763  0.0025598  -2.686  0.00723 **
## afc                               0.0116037  0.0016201   7.162 7.94e-13 ***
## afc0                              0.5401892  0.0434131  12.443  < 2e-16 ***
## log(amh)                          0.3506871  0.0200623  17.480  < 2e-16 ***
## factor(lupprot)LPL 10/5           0.0778032  0.0288083   2.701  0.00692 **
## factor(lupprot)Lupron Microdose -0.1830569  0.0609744  -3.002  0.00268 **
## fsh3                             -0.0010939  0.0001895  -5.772 7.84e-09 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## (Dispersion parameter for poisson family taken to be 1)
##
##     Null deviance: 6869.7  on 1413  degrees of freedom
## Residual deviance: 4861.0  on 1405  degrees of freedom
## AIC: 8263.2
##
## Number of Fisher Scoring iterations: 5
```

afc0 and log(amh) contribute a lot to determine the total number of blast conversion.

```
anova(m8)
```

```
## Analysis of Deviance Table
##
## Model: poisson, link: log
##
## Response: Total_bc
##
## Terms added sequentially (first to last)
##
##
##                 Df Deviance Resid. Df Resid. Dev
## NULL                             1413     6869.7
## age              1   536.32      1412     6333.4
## bmi              1     0.49      1411     6332.9
## afc              1     4.45      1410     6328.4
## afc0             1   599.97      1409     5728.5
## log(amh)         1   794.61      1408     4933.9
## factor(lupprot)  2    39.39      1406     4894.5
## fsh3             1    33.49      1405     4861.0
```

```
# Create fert contains either ICSI or IVF
clean.data$fert <- clean.data$`Number Fertilized (ICSI)`
clean.data$fert[clean.data$fert == 0] <- clean.data$`Number Fertilized (IVF)`[clean.data$fert == 0]
m9 <- glm(fert ~ age + bmi + afc + afc0 + log(amh) + factor(lupprot) + fsh3,
          data=clean.data,
          family = poisson(link="log"))
```

```
summary(m9)
```

analysis for the number of fertilized

```
##
## Call:
## glm(formula = fert ~ age + bmi + afc + afc0 + log(amh) + factor(lupprot) +
##     fsh3, family = poisson(link = "log"), data = clean.data)
##
## Deviance Residuals:
##     Min       1Q   Median       3Q      Max
## -6.2450  -1.4088  -0.2037   0.8836   7.2662
##
## Coefficients:
##                                   Estimate Std. Error z value Pr(>|z|)
## (Intercept)                      2.2616128  0.1010589  22.379  < 2e-16 ***
## age                             -0.0062585  0.0023791  -2.631 0.008522 **
## bmi                             -0.0076541  0.0018232  -4.198 2.69e-05 ***
## afc                              0.0093975  0.0011652   8.065 7.32e-16 ***
## afc0                             0.3343847  0.0302547  11.052  < 2e-16 ***
## log(amh)                         0.3055909  0.0137721  22.189  < 2e-16 ***
## factor(lupprot)LPL 10/5          0.0030812  0.0205071   0.150 0.880566
## factor(lupprot)Lupron Microdose -0.1428927  0.0391868  -3.646 0.000266 ***
## fsh3                            -0.0008339  0.0001312  -6.356 2.07e-10 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## (Dispersion parameter for poisson family taken to be 1)
##
##     Null deviance: 7149.4  on 1413  degrees of freedom
## Residual deviance: 4628.6  on 1405  degrees of freedom
## AIC: 9618.1
##
## Number of Fisher Scoring iterations: 5
```

Also, afc0 and log(amh) contribute a lot to determine the total number of fertilized.

```
anova(m9)
```

```
## Analysis of Deviance Table
##
## Model: poisson, link: log
##
## Response: fert
##
## Terms added sequentially (first to last)
##
##
##                 Df Deviance Resid. Df Resid. Dev
## NULL                             1413     7149.4
## age              1   520.64      1412     6628.8
## bmi              1     0.25      1411     6628.6
## afc              1    53.48      1410     6575.1
## afc0             1   679.83      1409     5895.2
## log(amh)         1  1197.21      1408     4698.0
```

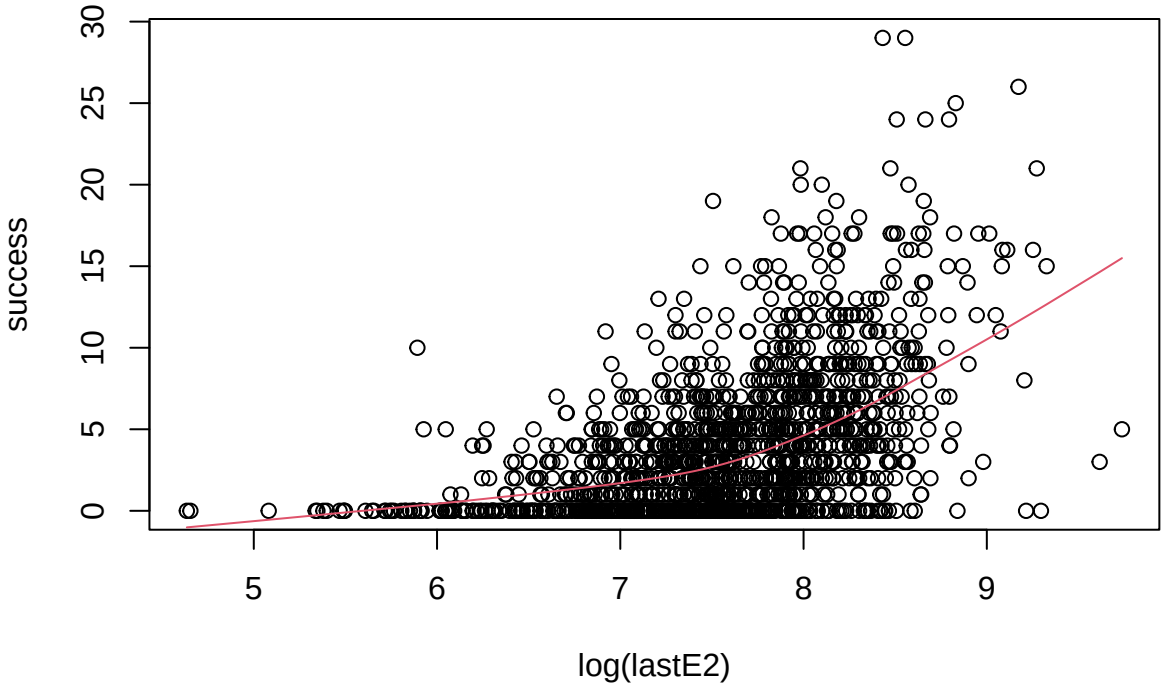
```
## factor(lupprot)  2    28.94      1406     4669.1
## fsh3             1    40.50      1405     4628.6
```

Logistic Regression

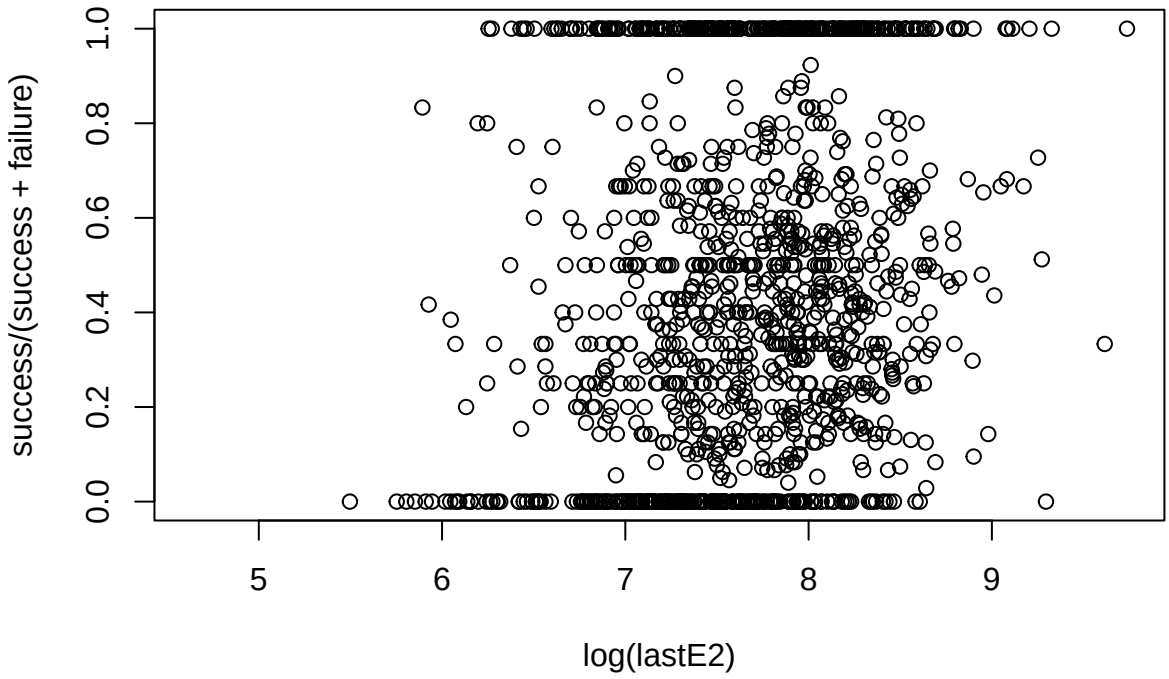
Create counts of success (conversion or not) and counts of failure

```
clean.data$success <- clean.data$Total_bc
clean.data$failure <- clean.data$mii - clean.data$Total_bc
```

```
plot(success ~ log(lastE2), clean.data)
with(clean.data, lines(lowess(success ~ log(lastE2)),col=2))
```




```
# scatterplot standardized for trial size
plot(success/(success + failure) ~ log(lastE2), clean.data, ylim = c(0,1))
```




```
m10 <- glm(cbind(success, failure) ~ age + bmi + afc + afc0 + log(amh) + factor(lupprot) + fsh3,
           data = clean.data,
           family = "binomial")
summary(m10)
```

```
##
## Call:
## glm(formula = cbind(success, failure) ~ age + bmi + afc + afc0 +
##     log(amh) + factor(lupprot) + fsh3, family = "binomial", data = clean.data)
##
## Deviance Residuals:
##    Min      1Q  Median      3Q     Max
## -6.613  -1.400   0.000   1.418   7.063
##
## Coefficients:
##                                   Estimate Std. Error z value Pr(>|z|)
## (Intercept)                      0.4578877  0.1902784   2.406   0.0161 *
## age                             -0.0277408  0.0044734  -6.201 5.60e-10 ***
## bmi                             -0.0012794  0.0034513  -0.371   0.7109
## afc                              0.0041372  0.0023295   1.776   0.0757 .
## afc0                             0.5910620  0.0607876   9.723  < 2e-16 ***
## log(amh)                         0.0364132  0.0276691   1.316   0.1882
## factor(lupprot)LPL 10/5          0.2494872  0.0395665   6.306 2.87e-10 ***
## factor(lupprot)Lupron Microdose -0.0512981  0.0770136  -0.666   0.5054
## fsh3                            -0.0005963  0.0002650  -2.250   0.0244 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## (Dispersion parameter for binomial family taken to be 1)
##
##     Null deviance: 6168.6  on 1263  degrees of freedom
## Residual deviance: 5782.5  on 1255  degrees of freedom
## AIC: 7822.7
```

```
##
## Number of Fisher Scoring iterations: 4
```

afc0 contributes a lot to determine the success of blast conversion.

Analysis for the fertilized rate

```
# Create fertilized rate and remove NA
clean.data$fert.rate <- clean.data$fert / clean.data$mii
table(is.na(clean.data$fert.rate))
```

```
##
## FALSE  TRUE
##  1349    65
```

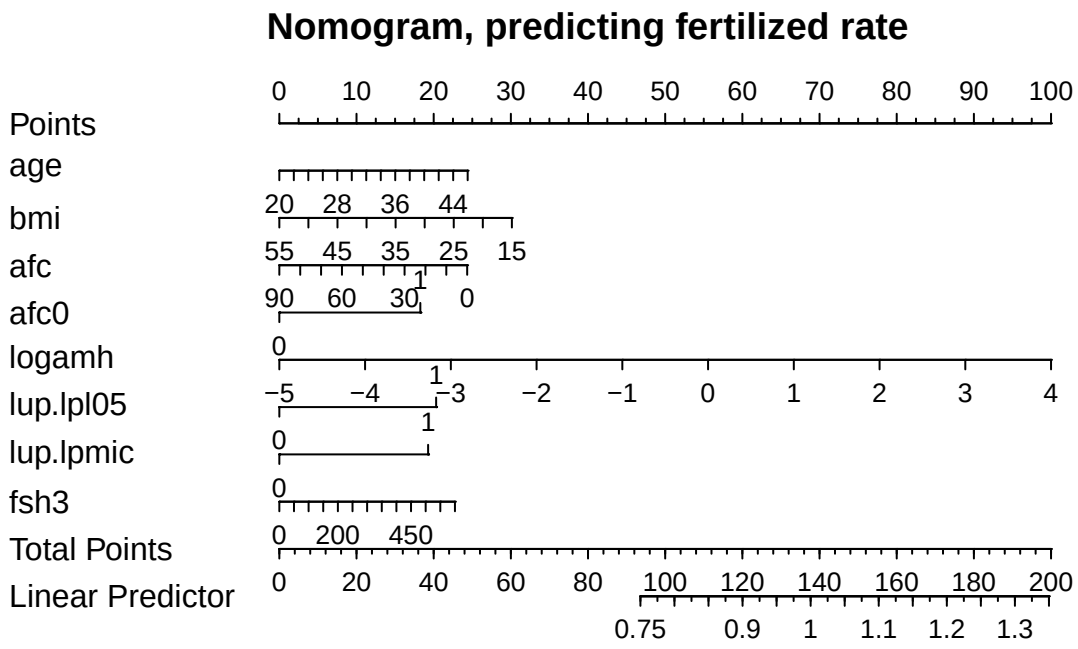
```
clean.data <- subset(clean.data, !is.na(clean.data$fert.rate))
clean.data <- subset(clean.data, !is.infinite(clean.data$fert.rate))
```

```
# Linear model for fertilized rate
m11 <- lm(fert.rate~age + bmi + afc + afc0 + log(amh) + factor(lupprot) +fsh3, data=clean.data)
summary(m11)
```

```
##
## Call:
## lm(formula = fert.rate ~ age + bmi + afc + afc0 + log(amh) +
##     factor(lupprot) + fsh3, data = clean.data)
##
## Residuals:
##     Min      1Q  Median      3Q     Max
## -1.1876 -0.4556 -0.2437  0.0198 12.9964
##
## Coefficients:
##                                   Estimate Std. Error t value Pr(>|t|)
## (Intercept)                      0.8009138  0.3392456   2.361   0.0184 *
## age                              0.0053187  0.0079041   0.673   0.5011
## bmi                             -0.0042690  0.0061994  -0.689   0.4912
## afc                             -0.0015326  0.0046081  -0.333   0.7395
## afc0                             0.1035367  0.1029138   1.006   0.3146
## log(amh)                         0.0629628  0.0437099   1.440   0.1500
## factor(lupprot)LPL 10/5          0.1151412  0.0705617   1.632   0.1030
## factor(lupprot)Lupron Microdose  0.1092518  0.1061149   1.030   0.3034
## fsh3                             0.0002149  0.0004275   0.503   0.6152
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 1.117 on 1255 degrees of freedom
## Multiple R-squared:  0.007291,   Adjusted R-squared:  0.0009629
## F-statistic: 1.152 on 8 and 1255 DF,  p-value: 0.3253
```

Nomogram predicting fertilized rate

```
m12 <- ols(fert.rate~age + bmi + afc + afc0 + logamh + lup.lpl05 + lup.lpmic + fsh3, data=clean.data)
dd <- datadist(clean.data[,c("age","bmi","afc","afc0","logamh","lupprot", "lup.lpl05","lup.lpmic", "fsh3
plot(nomogram(m12))
title("Nomogram, predicting fertilized rate")
```



This plot shows that AMH highly affect the model determining a value for fertilized rate among those with particular covariate values.

conversion rate

```
clean.data$conv.rate <- clean.data$Total_bc / clean.data$mii
table(is.na(clean.data$conv.rate))
```

```
##
## FALSE
##  1264
```

```
clean.data <- subset(clean.data, !is.na(clean.data$conv.rate))
table(is.na(clean.data$conv.rate))
```

```
##
## FALSE
##  1264
```

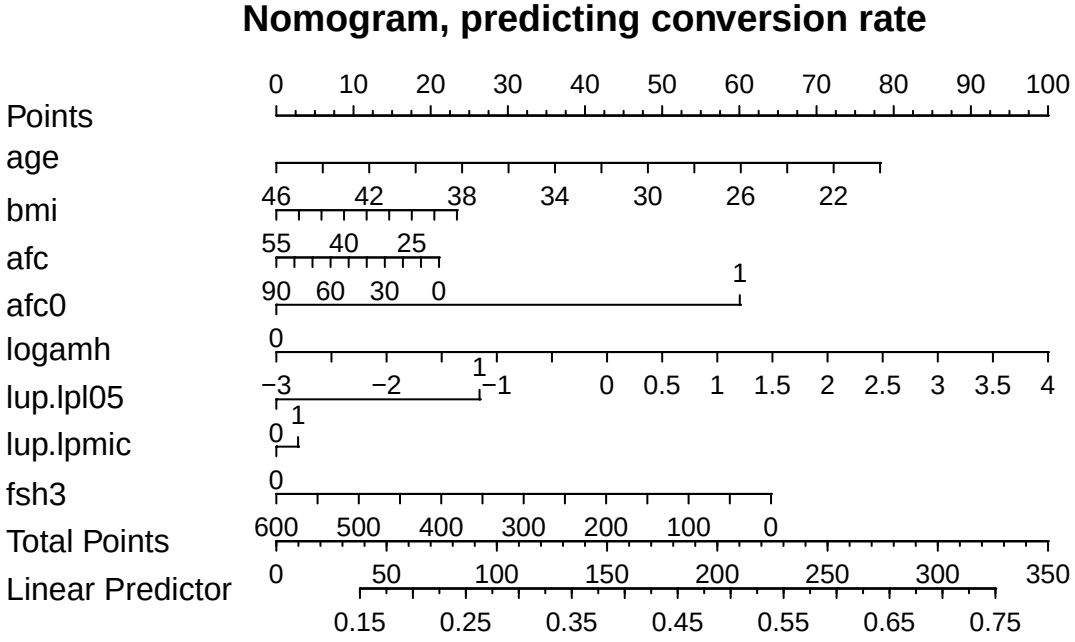
```
# Linear model for conversion rate
m13 <- lm(fert.rate~age + bmi + afc + afc0 + log(amh) + factor(lupprot) +fsh3, data=clean.data)
summary(m13)
```

```
##
## Call:
## lm(formula = fert.rate ~ age + bmi + afc + afc0 + log(amh) +
##     factor(lupprot) + fsh3, data = clean.data)
##
## Residuals:
##     Min      1Q  Median      3Q     Max
## -1.1876 -0.4556 -0.2437  0.0198 12.9964
##
## Coefficients:
##                                Estimate Std. Error t value Pr(>|t|)
## (Intercept)                   0.8009138  0.3392456   2.361   0.0184 *
## age                           0.0053187  0.0079041   0.673   0.5011
## bmi                          -0.0042690  0.0061994  -0.689   0.4912
```

```
## afc                               -0.0015326  0.0046081  -0.333   0.7395
## afc0                               0.1035367  0.1029138   1.006   0.3146
## log(amh)                           0.0629628  0.0437099   1.440   0.1500
## factor(lupprot)LPL 10/5            0.1151412  0.0705617   1.632   0.1030
## factor(lupprot)Lupron Microdose    0.1092518  0.1061149   1.030   0.3034
## fsh3                               0.0002149  0.0004275   0.503   0.6152
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 1.117 on 1255 degrees of freedom
## Multiple R-squared:  0.007291,   Adjusted R-squared:  0.0009629
## F-statistic: 1.152 on 8 and 1255 DF,  p-value: 0.3253
```

Nomogram predicting conversion rate

```
m14 <- ols(conv.rate~age + bmi + afc + afc0 + logamh + lup.lpl05 + lup.lpmic + fsh3, data=clean.data)
dd <- datadist(clean.data[,c("age","bmi","afc","afc0","logamh","lupprot", "lup.lpl05","lup.lpmic", "fsh3
plot(nomogram(m14))
title("Nomogram, predicting conversion rate")
```



This plot shows that AMH is doing the most bulk of the work when the model determining a value for conversion rate among those with particular covariate values. In addition, age, afc0 and fsh3 also highly affect the model.