NSWPCN Predictor Training

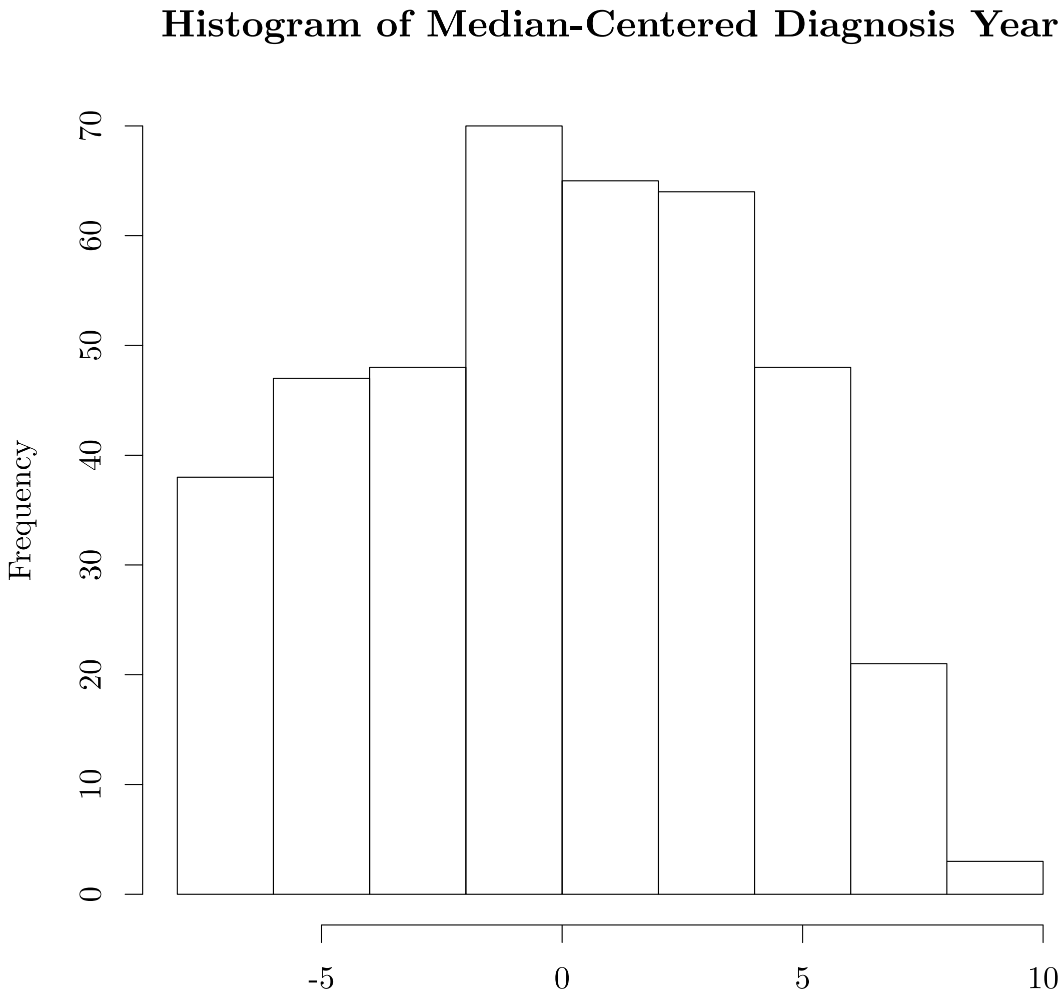
February 18, 2015

1 Preparation

```
library(survival)

## Loading required package:  splines

library(glmulti)

## Loading required package:  rJava
## Loading required package:  methods

library(flexsurv)
library(randomForestSRC)

## Loading required package:  parallel
##
##  randomForestSRC 1.5.5
##
##  Type rfsrc.news() to see new features, changes, and bug fixes.
##

library(reshape2)
library(plyr)
library(ggplot2)

library(MASS)
library(boot)

##
## Attaching package:  ’boot’
##
## The following object is masked from ’package:survival’:
##
##    aml

library(timeROC)

## Loading required package:  pec
## Loading required package:  mvtnorm
## Loading required package:  timereg

load("03_NSWPCN_subset.rda")

library(RColorBrewer)
pal = brewer.pal(4, "Dark2")
names(pal) = c("GG", "CPH", "RSF", "KMO")
```

2 Cohort selection and transformation

```
data$SexM = data$Patient.Sex == "M"
data$Ca199 = data$Path.Ca199.Preop > 100
data$DiagYearCent = as.numeric((data$History.Diagnosis.Date - median(data$History.Diagnosis.Date)) / 365
data$Time = as.numeric(data$History.Death.Date - data$History.Diagnosis.Date)
data$DSD = data$History.DSDeath.Event == 1
data$AgeCent = data$History.Diagnosis.AgeAt.Cent
data$LocBody = data$Path.LocationBody
data$SizeCent = data$Path.Size.Cent
data$A2 = data$Molec.S100A2.DCThresh
data$A4 = data$Molec.S100A4.DCThresh

median(data$DiagYearCent)

## [1] 0

hist(data$DiagYearCent, main = "Histogram of Median-Centered Diagnosis Year", xlab = "")
```



```
temp = NA
temp = ls()
rm(list = temp[!(temp %in% c("pal", "data"))])
```

```
nrow(data)

## [1] 404

data = data[!is.na(data$Time) & !is.na(data$DSD) & !is.na(data$A2) & !is.na(data$A4) & !is.na(data$LocBo
nrow(data)

## [1] 256

data = data[data$Time < 3000,]          # Remove long-term survivors, which are very likely to be data
nrow(data)

## [1] 249

data.all = data
nrow(data.all)

## [1] 249

summary(data.all)

##    Patient.ID   Patient.Sex Cohort.ICGC     History.PreviousMalignancy
##  Min.   :   4   F:126       Mode :logical   Mode :logical
##  1st Qu.: 305   M:123       FALSE:249       FALSE:227
##  Median : 638               NA's :0         TRUE :22
##  Mean   : 621                               NA's :0
##  3rd Qu.:1031
##  Max.   :1453
##
##  History.FdrWithPancCancer History.FdrWithAnyCancer History.Diagnosis.Date
##  Mode :logical             Mode :logical            Min.   :1994-03-09
##  FALSE:239                 FALSE:210                1st Qu.:1998-06-11
##  TRUE :8                   TRUE :39                 Median :2001-07-28
##  NA's :2                   NA's :0                  Mean   :2000-12-26
##                                                     3rd Qu.:2003-06-26
##                                                     Max.   :2006-08-14
##
##  History.Diagnosis.AgeAt History.AlcoholLevel History.Smoking.Status
##  Min.   :28.0            0:158                Never  :144
##  1st Qu.:62.0            1: 46                Ceased : 51
##  Median :69.0            2: 22                Current: 54
##  Mean   :67.4            3: 23
##  3rd Qu.:75.0
##  Max.   :87.0
##
##  History.Smoking.PackYears History.Comorbid.Diabetes
##  Min.   : 2.0              Mode :logical
##  1st Qu.:20.0              FALSE:186
##  Median :27.5              TRUE :63
##  Mean   :31.6              NA's :0
##  3rd Qu.:46.2
##  Max.   :80.0
##  NA's   :189
##  History.Comorbid.ChronicPancreatitis History.Recurrence.Event
##  Mode :logical                        Min.   :0.00
##  FALSE:238                            1st Qu.:1.00
##  TRUE :11                             Median :1.00
##  NA's :0                              Mean   :0.96
##                                       3rd Qu.:1.00
##                                       Max.   :1.00
##
##  History.Recurrence.Date History.DSDeath.Event History.Death.Date
##  Min.   :1994-07-21      Min.   :0.000         Min.   :1995-01-12
##  1st Qu.:2000-01-08      1st Qu.:1.000         1st Qu.:1999-12-01
##  Median :2002-06-03      Median :1.000         Median :2002-12-18
##  Mean   :2002-03-22      Mean   :0.952         Mean   :2002-09-02
##  3rd Qu.:2005-02-04      3rd Qu.:1.000         3rd Qu.:2005-05-21
##  Max.   :2009-01-29      Max.   :1.000         Max.   :2011-10-03
##  NA's   :85
##  History.Followup.Date History.Death.EventTimeDays Treat.Resected
##  Min.   :2009-10-24    Min.   :  20                Mode:logical
##  1st Qu.:2009-10-24    1st Qu.: 270                TRUE:249
##  Median :2009-10-24    Median : 479                NA's:0
##  Mean   :2009-11-30    Mean   : 617
##  3rd Qu.:2009-10-24    3rd Qu.: 851
##  Max.   :2010-06-03    Max.   :2701
##  NA's   :243
##  Treat.ProcedureWhipple Treat.MarginPositive Treat.Chemo.Any
##  Mode :logical          Mode :logical        Mode :logical
##  FALSE:48               FALSE:145            FALSE:101
##  TRUE :201              TRUE :104            TRUE :121
##  NA's :0                NA's :0              NA's :27
##
##
##
##  Treat.Chemo.Adjuvant Treat.Chemo.Adjuvant.GE3Cycles
##  Mode :logical        Mode :logical
##  FALSE:175            FALSE:204
##  TRUE :74             TRUE :45
##  NA's :0              NA's :0
##
##
##
##  Treat.Chemo.Palliative Treat.Chemo.PalliativeDC Treat.Chemo.GEM
##  Mode :logical          Mode :logical            Mode :logical
##  FALSE:1                FALSE:178                FALSE:156
##  TRUE :66               TRUE :71                 TRUE :92
##  NA's :182              NA's :0                  NA's :1
##
##
##
##  Treat.Radio     Path.LocationBody   Path.Size    Path.Bilirubin.Preop
##  Mode :logical   Mode :logical     Min.   : 8.0   Min.   : 0.06
##  FALSE:205       FALSE:201         1st Qu.:25.0   1st Qu.: 0.64
##  TRUE :44        TRUE :48          Median :30.0   Median : 3.45
##  NA's :0         NA's :0           Mean   :33.6   Mean   : 7.10
##                                    3rd Qu.:40.0   3rd Qu.:10.22
##                                    Max.   :90.0   Max.   :45.03
##                                                   NA's   :99
##  Path.Ca199.Preop Path.Bilirubin.Postop Path.Ca199.Postop
##  Min.   :     1   Min.   : 0.12         Min.   :    1
##  1st Qu.:    67   1st Qu.: 0.47         1st Qu.:   15
##  Median :   197   Median : 0.70         Median :   74
##  Mean   :  2701   Mean   : 1.92         Mean   : 1528
##  3rd Qu.:   802   3rd Qu.: 1.26         3rd Qu.:  271
##  Max.   :101075   Max.   :25.38         Max.   :31760
##  NA's   :168      NA's   :106           NA's   :143
##         Path.Subtype Path.Differentiation Path.LN.Involved
##  Adenosquamous: 18   1: 16                Min.   : 0.00
##  Large Cell   :  0   2:162                1st Qu.: 0.00
##  Mucinous     :  5   3: 71                Median : 1.00
##  NotSpecified : 39   4:  0                Mean   : 1.72
##  Papillary    :  2                        3rd Qu.: 2.00
##  Tubular      :185                        Max.   :12.00
##                                           NA's   :4
##  Path.LN.Inspected Path.Invasion.Vascular Path.Invasion.Perineural
##  Min.   : 0.0      Mode :logical          Mode :logical
##  1st Qu.: 5.0      FALSE:133              FALSE:63
##  Median : 8.5      TRUE :116              TRUE :186
##  Mean   : 9.8      NA's :0                NA's :0
##  3rd Qu.:13.0
##  Max.   :52.0
##  NA's   :21
##  Stage.pT  Stage.pN   Stage.pM   Molec.BNIP3.NucInt Molec.BNIP3.CytoInt
##  Tis:  0   N0  : 83   M0  :182   0   :  6           0   :  1
##  T1 : 18   N1  :160   M1  :  9   1   :208           1   :130
##  T2 : 34   NA's:  6   NA's: 58   2   : 21           2   : 76
##  T3 :197                         3   :  2           3   : 30
##  T4 :  0                         NA's: 12           NA's: 12
##
##
##  Molec.CCND1.CytoLo Molec.CCND1.CytoHi Molec.CCND1.MembLo
##  0   :159           0   :75            0   :100
##  1   : 34           1   :90            1   : 71
##  2   :  4           2   :32            2   : 18
##  3   :  1           3   : 1            3   :  9
##  NA's: 51           NA's:51            NA's: 51
##
##
##  Molec.CCND1.MembHi Molec.Grb7.Int Molec.Grb7.Percent Molec.HCNT3PlusHENT1
##  0   :32            0   :51        Min.   :  0.0      Mode :logical
##  1   :89            1   :94        1st Qu.:  3.0      FALSE:96
##  2   :46            2   :42        Median : 18.0      TRUE :98
##  3   :31            3   : 7        Mean   : 31.1      NA's :55
##  NA's:51            NA's:55        3rd Qu.: 55.0
##                                    Max.   :100.0
##                                    NA's   :55
##  Molec.HENT1.Percent Molec.HENT1.Int Molec.HER2      Molec.HOXB2.Percent
##  Min.   :  0.0       0   : 19        Mode :logical   Min.   :  0.0
##  1st Qu.: 11.2       1   :117        FALSE:37        1st Qu.: 35.0
##  Median : 42.5       2   : 53        TRUE :11        Median : 70.0
##  Mean   : 44.4       3   : 13        NA's :201       Mean   : 60.8
##  3rd Qu.: 75.0       NA's: 47                        3rd Qu.: 90.0
##  Max.   :100.0                                       Max.   :100.0
##  NA's   :47                                          NA's   :43
##  Molec.HOXB2.Int Molec.RON.Int Molec.S100A2.Int Molec.S100A2.Percent
##  0   : 14        0   : 20      0:88             Min.   :  0.0
##  1   :141        1   :111      1:63             1st Qu.:  0.0
##  2   : 36        2   : 64      2:57             Median : 10.0
##  3   : 15        3   : 10      3:41             Mean   : 28.7
##  NA's: 43        NA's: 44                       3rd Qu.: 60.0
##                                                 Max.   :100.0
##
##  Molec.S100A2.StromaScore Molec.S100A4.CytoInt Molec.S100A4.CytoPercent
##  Mode :logical            0:72                 Min.   :  0.0
##  FALSE:183                1:93                 1st Qu.:  0.0
##  TRUE :22                 2:43                 Median : 10.0
##  NA's :44                 3:41                 Mean   : 34.6
##                                                3rd Qu.: 75.0
##                                                Max.   :100.0
##
##  Molec.S100A4.NucInt Molec.S100A4.NucPercent Stage.Overall
##  0:80                Min.   :  0.0           IIB    :120
##  1:68                1st Qu.:  0.0           IIA    : 43
##  2:65                Median :  5.0           IB     : 12
##  3:36                Mean   : 26.4           IV     :  9
##                      3rd Qu.: 60.0           IA     :  7
##                      Max.   :100.0           (Other):  0
##                                              NA's   : 58
##  History.Death.Event Molec.S100A4.DCThresh Molec.S100A2.DCThresh
##  Min.   :0.000       Mode :logical         Mode :logical
##  1st Qu.:1.000       FALSE:61              FALSE:209
##  Median :1.000       TRUE :188             TRUE :40
##  Mean   :0.984       NA's :0               NA's :0
##  3rd Qu.:1.000
##  Max.   :1.000
##
##  Stage.pT.Simplified Path.Ca199.Preop.Cent Path.Ca199.Postop.Cent
##  T1 : 18             Min.   :-5.38         Min.   :-3.97
##  T2 : 34             1st Qu.:-1.18         1st Qu.:-1.25
##  T34:197             Median :-0.10         Median : 0.34
##                      Mean   : 0.01         Mean   : 0.57
##                      3rd Qu.: 1.31         3rd Qu.: 1.63
##                      Max.   : 6.14         Max.   : 6.40
##                      NA's   :168           NA's   :143
##  History.Diagnosis.AgeAt.Cent History.Smoking.PackYears.Cent
##  Min.   :-40.00               Min.   :-28.00
##  1st Qu.: -6.00               1st Qu.:-10.00
##  Median :  1.00               Median : -2.50
##  Mean   : -0.57               Mean   :  1.65
##  3rd Qu.:  7.00               3rd Qu.: 16.25
##  Max.   : 19.00               Max.   : 50.00
##                               NA's   :189
##  Path.Size.Cent   Path.Bilirubin.Preop.Cent Path.Bilirubin.Postop.Cent
##  Min.   :-22.00   Min.   :-3.39             Min.   :-0.53
##  1st Qu.: -5.00   1st Qu.:-2.81             1st Qu.:-0.18
##  Median :  0.00   Median : 0.00             Median : 0.06
##  Mean   :  3.57   Mean   : 3.65             Mean   : 1.27
##  3rd Qu.: 10.00   3rd Qu.: 6.77             3rd Qu.: 0.61
##  Max.   : 60.00   Max.   :41.58             Max.   :24.74
##                   NA's   :99                NA's   :106
##  History.Diagnosis.Date.Cent Path.LN.InvolvedFraction Path.LN.Negative
##  Min.   :-2867              Min.   :0.000            Min.   : 0.00
##  1st Qu.:-1312              1st Qu.:0.000            1st Qu.: 4.00
##  Median : -169              Median :0.143            Median : 7.00
##  Mean   : -382              Mean   :0.213            Mean   : 8.01
##  3rd Qu.:  529              3rd Qu.:0.333            3rd Qu.:11.00
##  Max.   : 1674              Max.   :1.000            Max.   :45.00
##                             NA's   :22               NA's   :21
##     SexM          Ca199          DiagYearCent        Time
##  Mode :logical   Mode :logical   Min.   :-7.849   Min.   :  20
##  FALSE:126       FALSE:29        1st Qu.:-3.592   1st Qu.: 270
##  TRUE :123       TRUE :52        Median :-0.463   Median : 478
##  NA's :0         NA's :168       Mean   :-1.047   Mean   : 615
##                                  3rd Qu.: 1.448   3rd Qu.: 804
##                                  Max.   : 4.583   Max.   :2701
##
##     DSD             AgeCent        LocBody          SizeCent
##  Mode :logical   Min.   :-40.00   Mode :logical   Min.   :-22.00
##  FALSE:12        1st Qu.: -6.00   FALSE:201       1st Qu.: -5.00
##  TRUE :237       Median :  1.00   TRUE :48        Median :  0.00
##  NA's :0         Mean   : -0.57   NA's :0         Mean   :  3.57
##                  3rd Qu.:  7.00                   3rd Qu.: 10.00
##                  Max.   : 19.00                   Max.   : 60.00
##
##      A2              A4
##  Mode :logical   Mode :logical
##  FALSE:209       FALSE:61
##  TRUE :40        TRUE :188
##  NA's :0         NA's :0
##
##
##
```

3 Data splitting

There's going to be an awful lot of model manipulation and black magic going on. Create a holdout validation set for final model comparison and selection.

```
set.seed(20150201)
sel.val = sample.int(nrow(data), floor(nrow(data)/5))
sel.val = 1:nrow(data) %in% sel.val
mean(sel.val)
```

```
## [1] 0.1968
```

```
data.val = data[sel.val,,drop = FALSE]
data = data[!sel.val,,drop = FALSE]
nrow(data)
```

```
## [1] 200
```

```
nrow(data.val)

## [1] 49
```

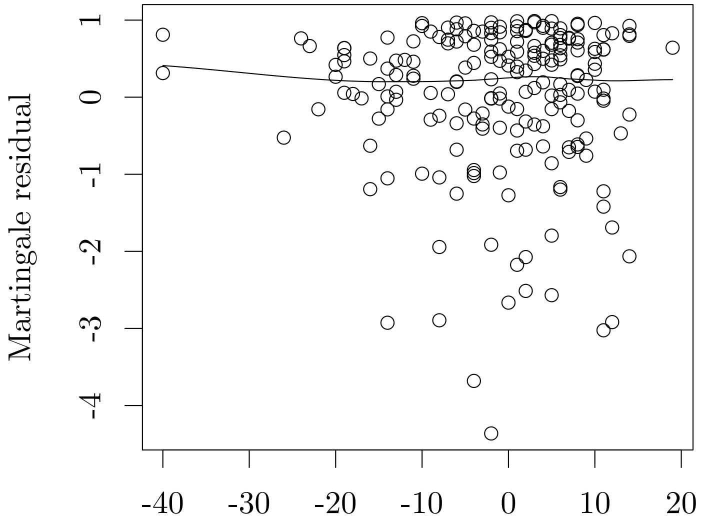
4 EDA

Use the CPH model as a convenient framework for EDA.

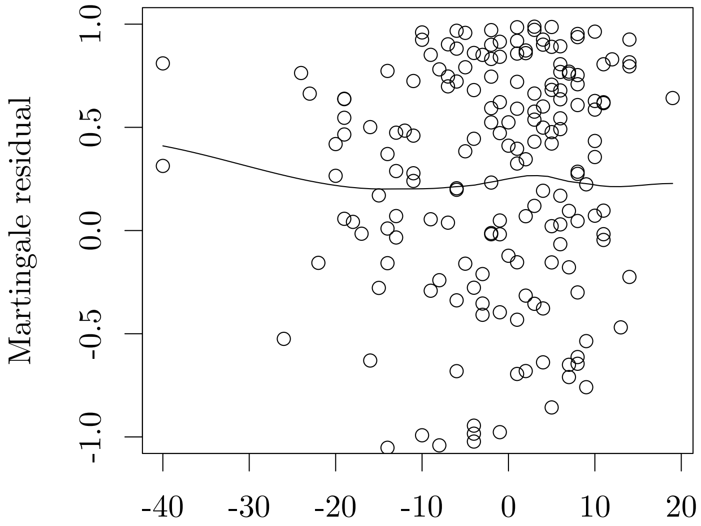
4.1 Functional form

Investigate functional form with martingale residuals.

```
fit.cph.NoAge = coxph(Surv(Time, DSD) ~ DiagYearCent + SexM + LocBody + SizeCent + A2 + A4, data = data
scatter.smooth(data$AgeCent, resid(fit.cph.NoAge, type = "martingale"), xlab = "", ylab = "Martingale re
```

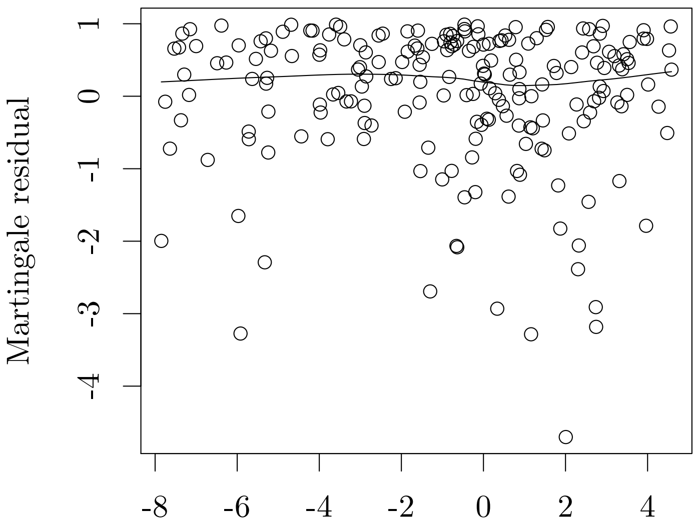


```
scatter.smooth(data$AgeCent, resid(fit.cph.NoAge, type = "martingale"), xlab = "", ylab = "Martingale re
```

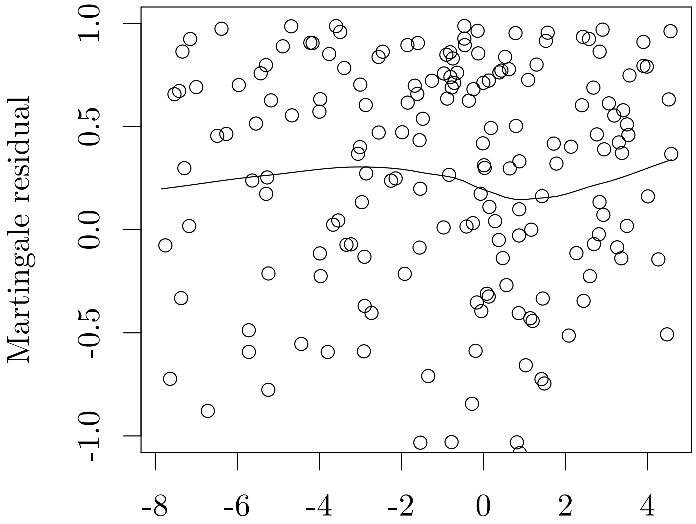


Close enough to linear.

```
fit.cph.NoDate = coxph(Surv(Time, DSD) ~ SexM + AgeCent + LocBody + SizeCent + A2 + A4, data = data)
scatter.smooth(data$DiagYearCent, resid(fit.cph.NoDate, type = "martingale"), xlab = "", ylab = "Marting
```

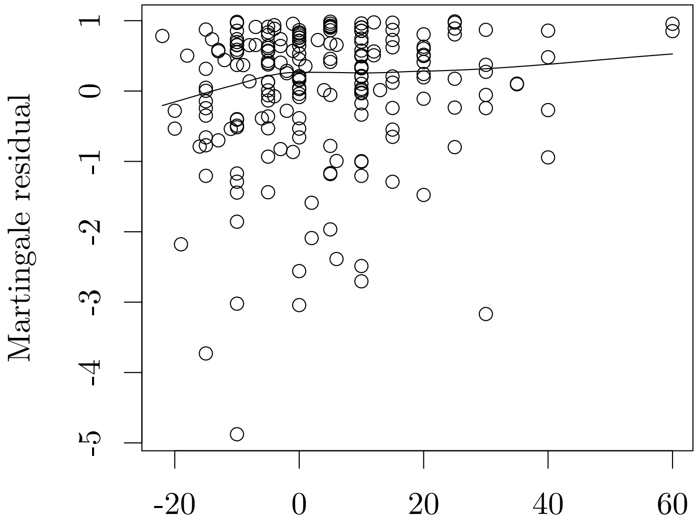


```
scatter.smooth(data$DiagYearCent, resid(fit.cph.NoDate, type = "martingale"), xlab = "", ylab = "Marting
```

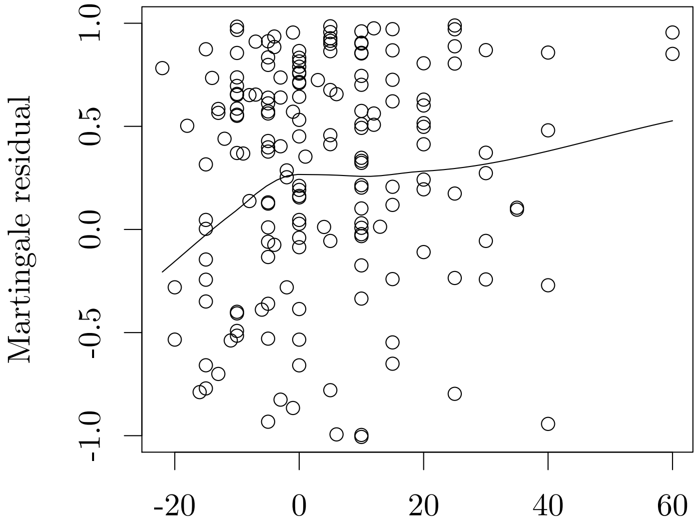


Doesn't appear to have much of an effect.

```
fit.cph.NoSize = coxph(Surv(Time, DSD) ~ DiagYearCent + SexM + AgeCent + LocBody + A2 + A4, data = data)
scatter.smooth(data$SizeCent, resid(fit.cph.NoSize, type = "martingale"), xlab = "", ylab = "Martingale
```



```
scatter.smooth(data$SizeCent, resid(fit.cph.NoSize, type = "martingale"), xlab = "", ylab = "Martingale
```



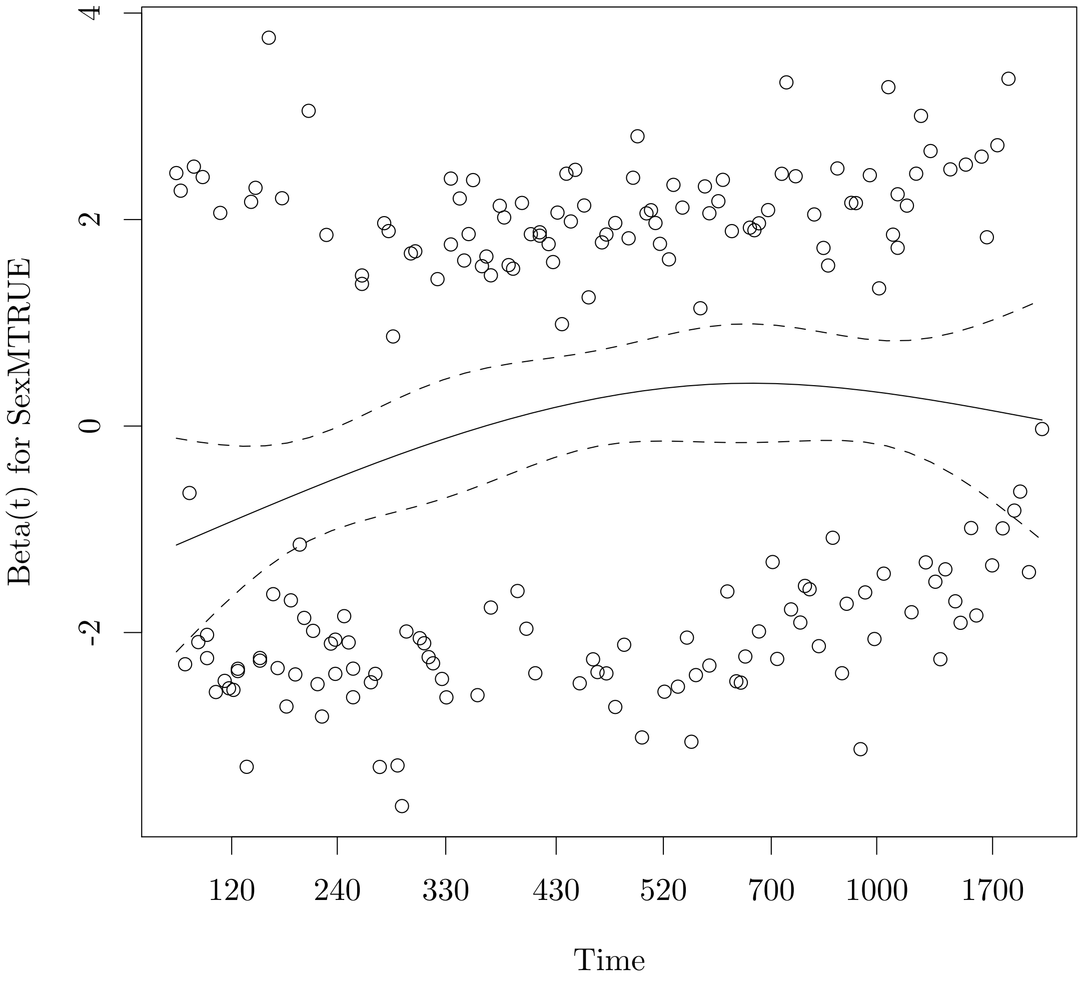
The size relationship appears to have a knee, close to size == 0, around which the relationship is approximately linear.

Model size as: $SizeCent + SizeCent I(SizeCent > 0) \equiv SizeCent + SizeCent_{+}$

```
data$SizePlus = pmax(data$SizeCent, 0)
data.val$SizePlus = pmax(data.val$SizeCent, 0)
data.all$SizePlus = pmax(data.all$SizeCent, 0)
```

4.2 PH assumption: full model

```
fit.cph = coxph(Surv(Time, DSD) ~ SexM + AgeCent + LocBody + SizeCent + SizePlus + A2 + A4, data = data)
cox.zph(fit.cph)

##                    rho    chisq      p
## SexMTRUE     0.17964  6.56115 0.0104
## AgeCent     -0.10574  2.40668 0.1208
## LocBodyTRUE -0.04856  0.37895 0.5382
## SizeCent     0.00231  0.00106 0.9740
## SizePlus    -0.01130  0.02666 0.8703
## A2TRUE      -0.03995  0.29907 0.5845
## A4TRUE      -0.08343  1.33308 0.2483
## GLOBAL            NA 13.17267 0.0680

plot(cox.zph(fit.cph)[1])
```

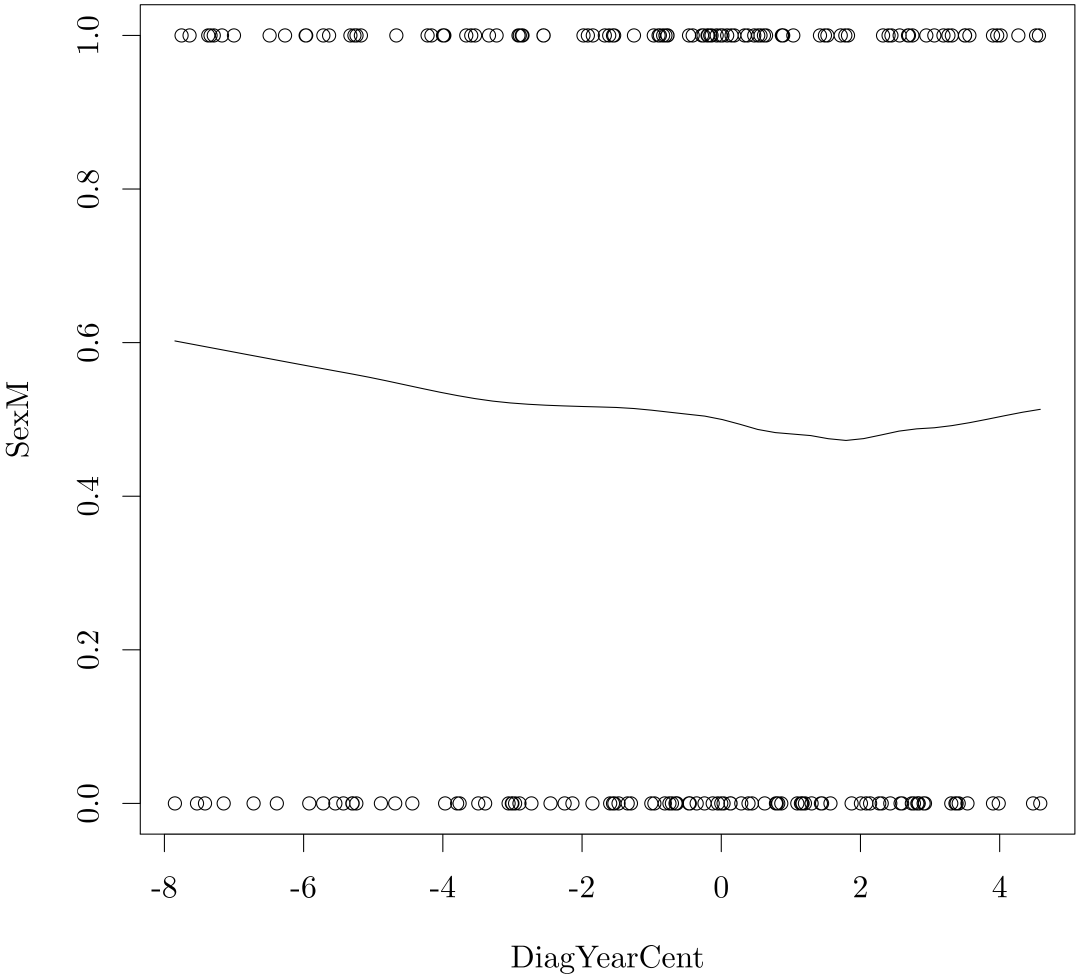


```
fit.cph = coxph(Surv(Time, DSD) ~ strata(SexM) + AgeCent + LocBody + SizeCent + SizePlus + A2 + A4, data
cox.zph(fit.cph)

##                   rho   chisq      p
## AgeCent     -0.11339 2.78186 0.0953
## LocBodyTRUE -0.04618 0.34177 0.5588
## SizeCent     0.00662 0.00857 0.9262
## SizePlus    -0.01329 0.03588 0.8498
## A2TRUE      -0.04361 0.35772 0.5498
## A4TRUE      -0.07985 1.25354 0.2629
## GLOBAL            NA 6.03352 0.4194
```

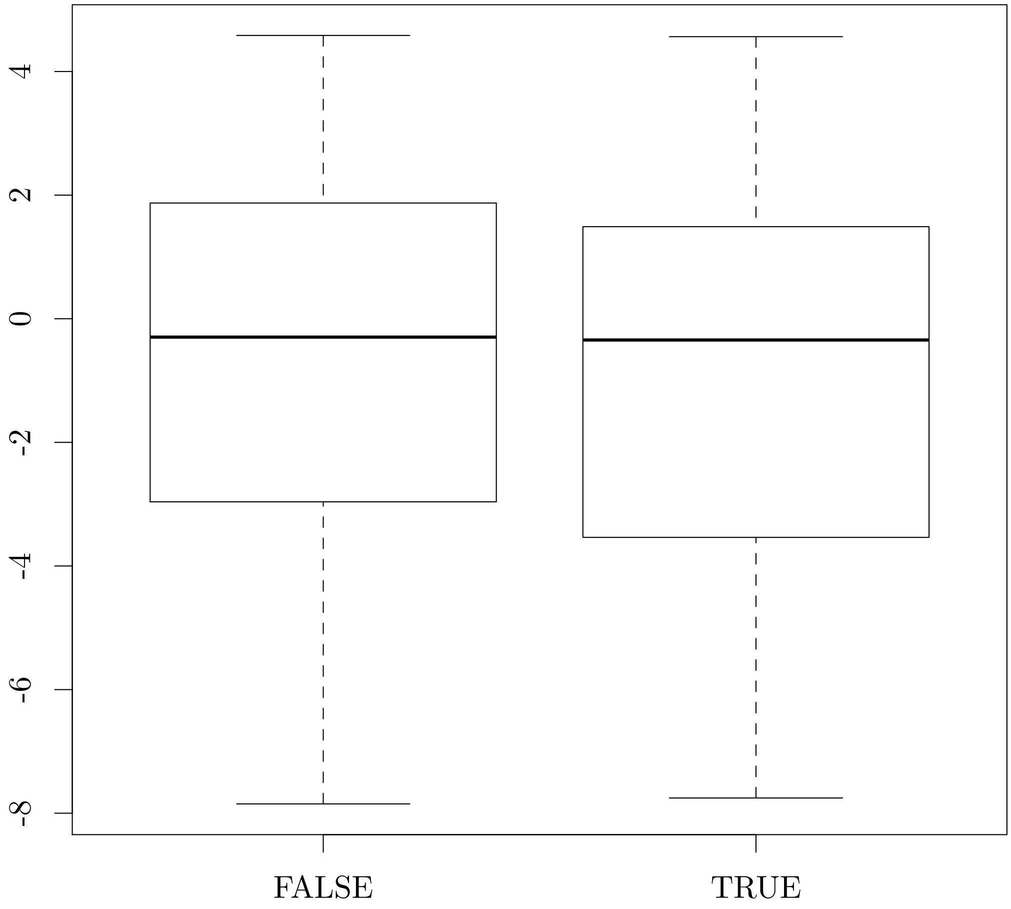
Using a threshold of 0.1 for the CPH tests, sex is stuffing things up. Stratification by sex makes good sense, given known variation in survival between the sexes. It would have been possible to model this with a Sex:Age term in an AFT model, but given this is CPH, a baseline change is needed.

4.3 Date of diagnosis test

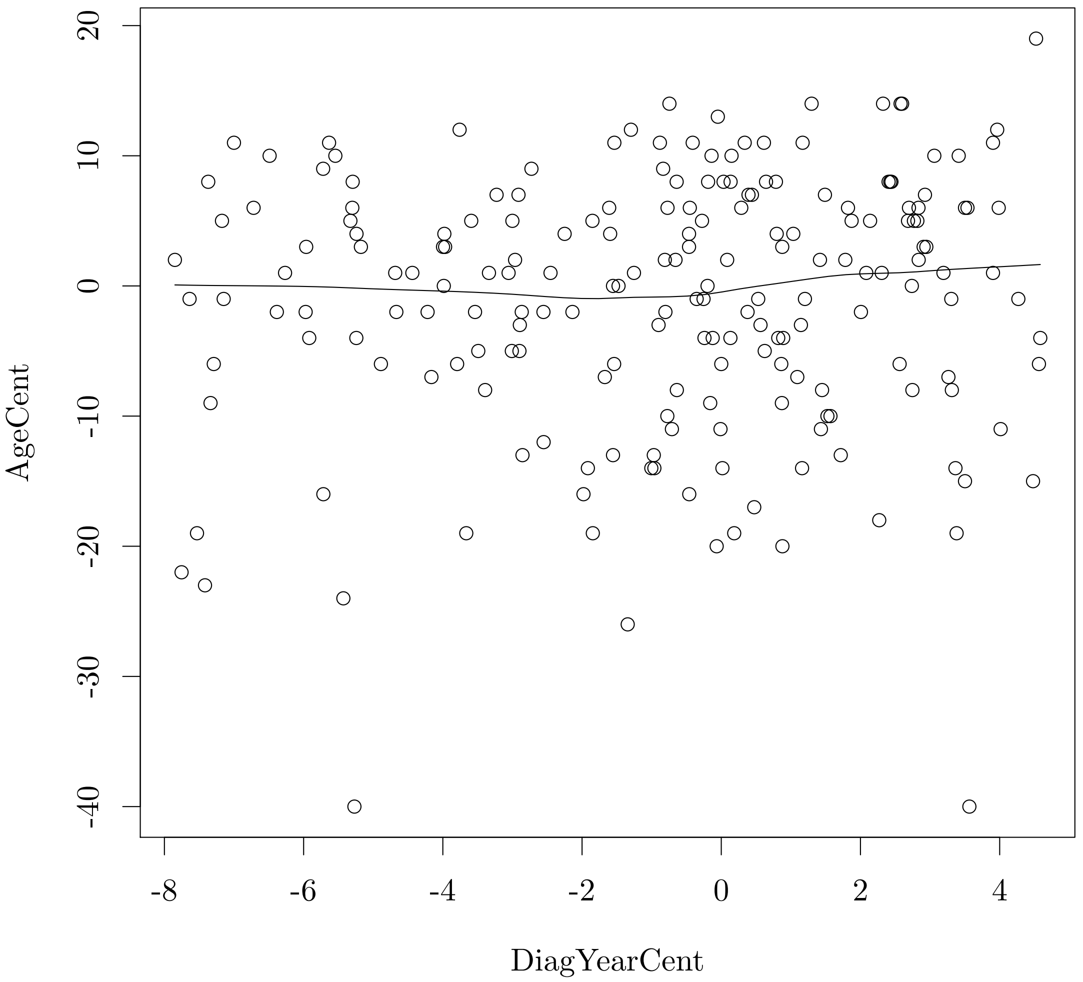
```
temp1 = coxph(Surv(Time, DSD) ~ strata(SexM) + AgeCent + LocBody + SizeCent + SizePlus + A2 + A4, data =
temp2 = coxph(Surv(Time, DSD) ~ strata(SexM) + AgeCent + LocBody + SizeCent + SizePlus + A2 + A4 + DiagY
anova(temp1, temp2)

## Analysis of Deviance Table
##  Cox model: response is  Surv(Time, DSD)
##  Model 1: ~ strata(SexM) + AgeCent + LocBody + SizeCent + SizePlus + A2 + A4
##  Model 2: ~ strata(SexM) + AgeCent + LocBody + SizeCent + SizePlus + A2 + A4 + DiagYearCent
##   loglik Chisq Df P(>|Chi|)
## 1   -682
## 2   -682  0.86  1      0.35

library(energy)

scatter.smooth(data$DiagYearCent, data$SexM, xlab = "DiagYearCent", ylab = "SexM")
```



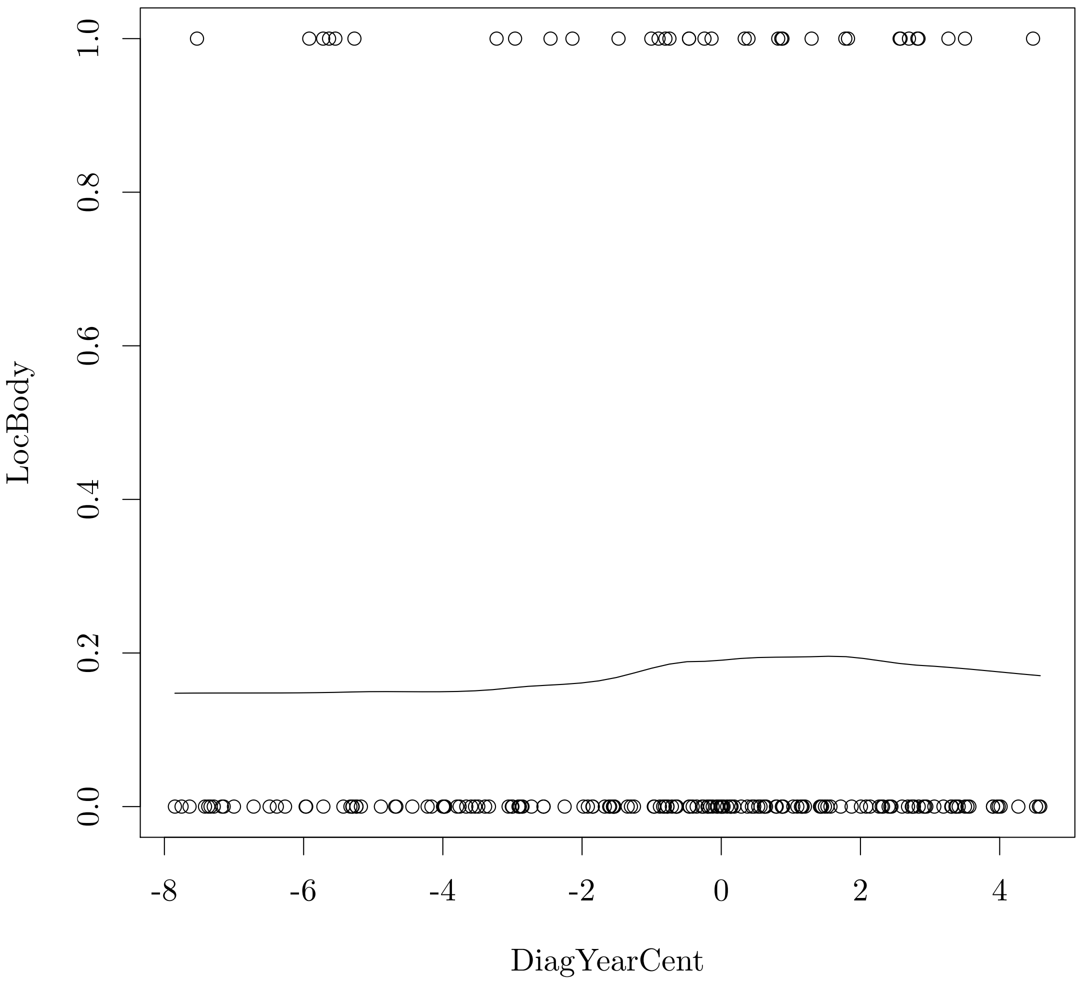
```
boxplot(DiagYearCent ~ SexM, data)
```



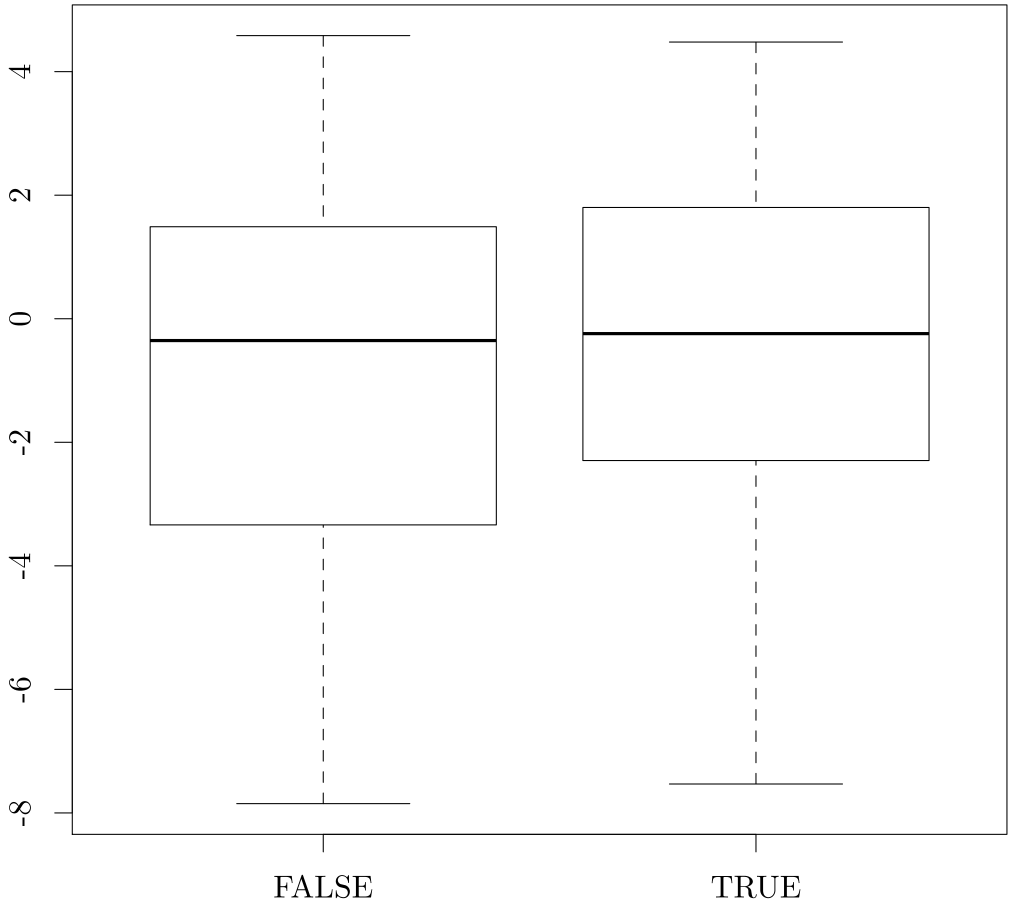
```
kruskal.test(data$DiagYearCent, data$SexM)

##
##  Kruskal-Wallis rank sum test
##
## data:  data$DiagYearCent and data$SexM
## Kruskal-Wallis chi-squared = 0.4306, df = 1, p-value = 0.5117

dcov.test(data$DiagYearCent, data$SexM, R = 499)

##
##  dCov test of independence
##
## data:  index 1, replicates 499
## nV^2 = 0.7729, p-value = 0.784
## sample estimates:
##    dCov
## 0.06217

scatter.smooth(data$DiagYearCent, data$AgeCent, xlab = "DiagYearCent", ylab = "AgeCent")
```



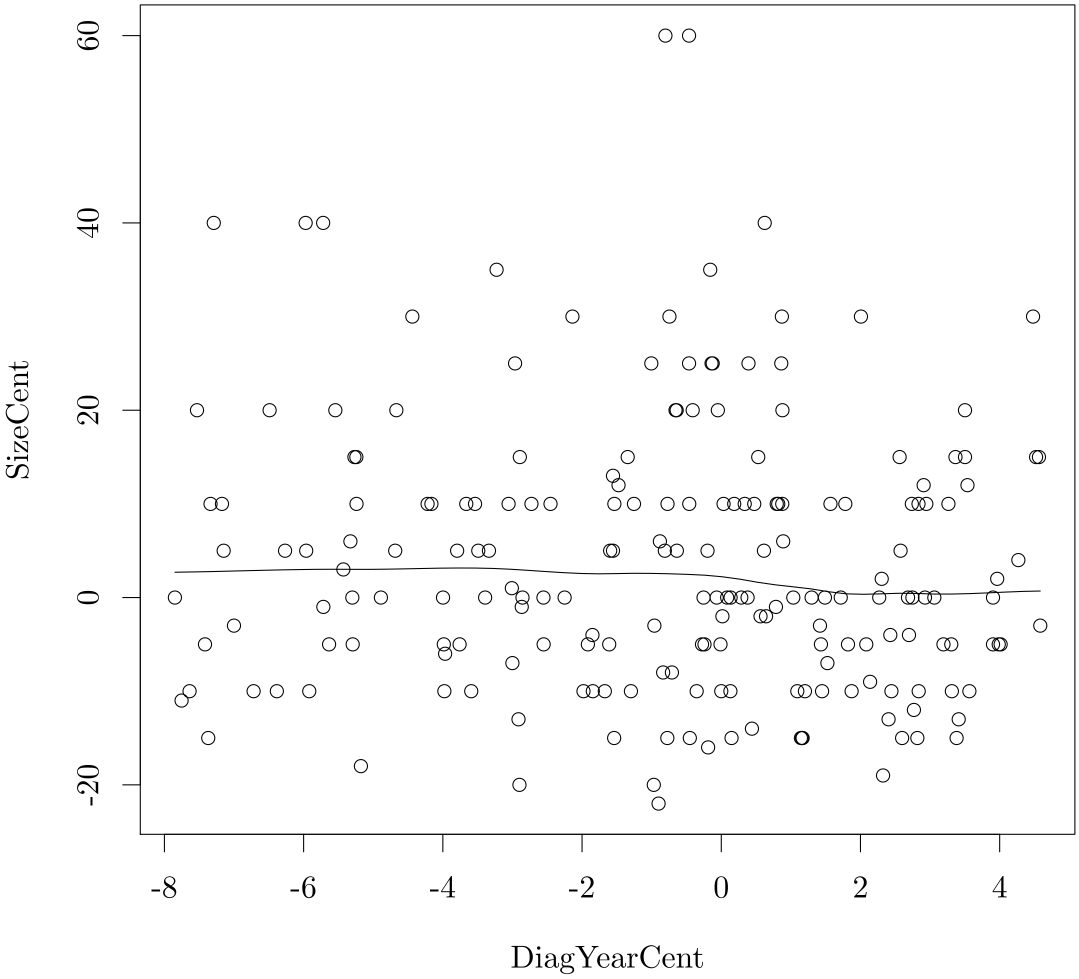
```
cor.test(data$DiagYearCent, data$AgeCent, method = "kendall")

##
##  Kendall's rank correlation tau
##
## data:  data$DiagYearCent and data$AgeCent
## z = 1.026, p-value = 0.3049
## alternative hypothesis: true tau is not equal to 0
## sample estimates:
##     tau
## 0.04952

dcov.test(data$DiagYearCent, data$AgeCent, R = 499)

##
##  dCov test of independence
##
## data:  index 1, replicates 499
## nV^2 = 36.72, p-value = 0.448
## sample estimates:
##   dCov
## 0.4285

scatter.smooth(data$DiagYearCent, data$LocBody, xlab = "DiagYearCent", ylab = "LocBody")
```



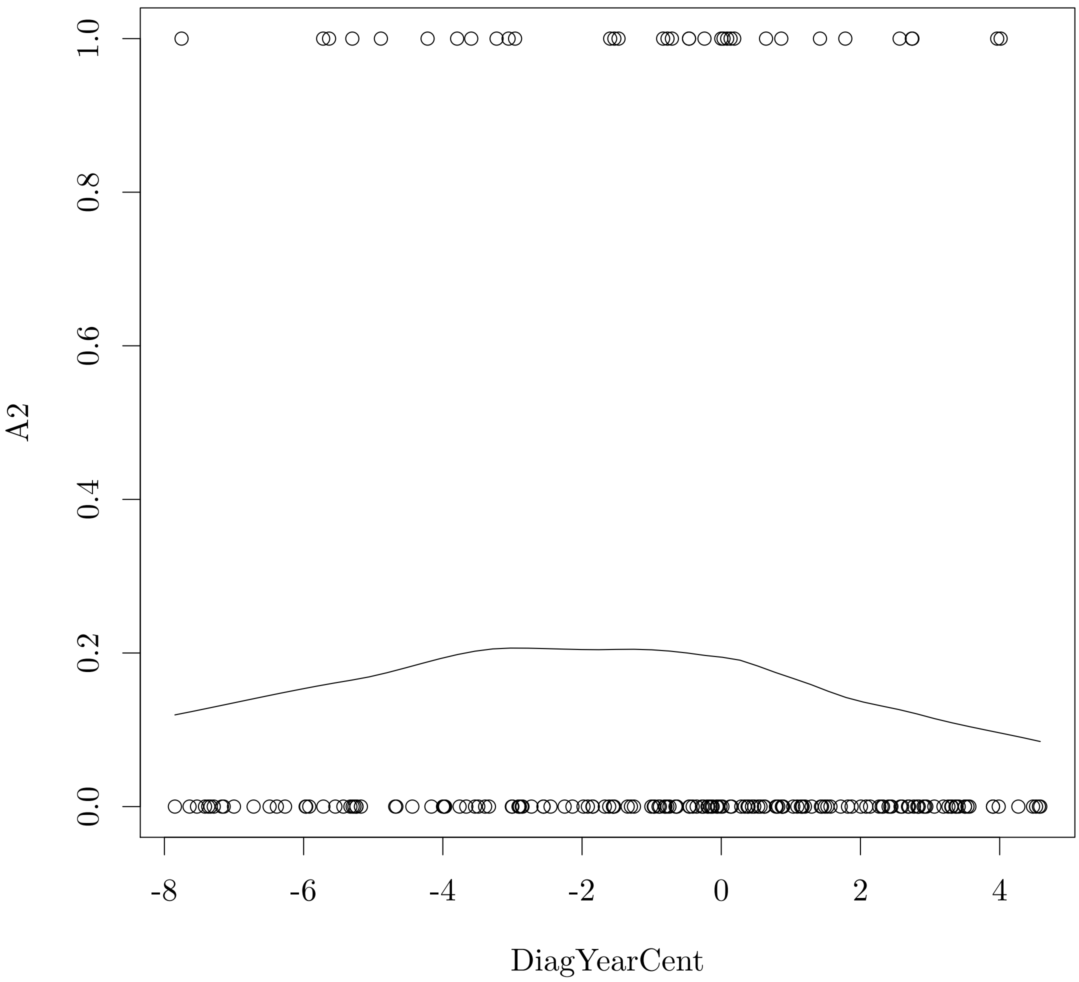
```
boxplot(DiagYearCent ~ LocBody, data)
```



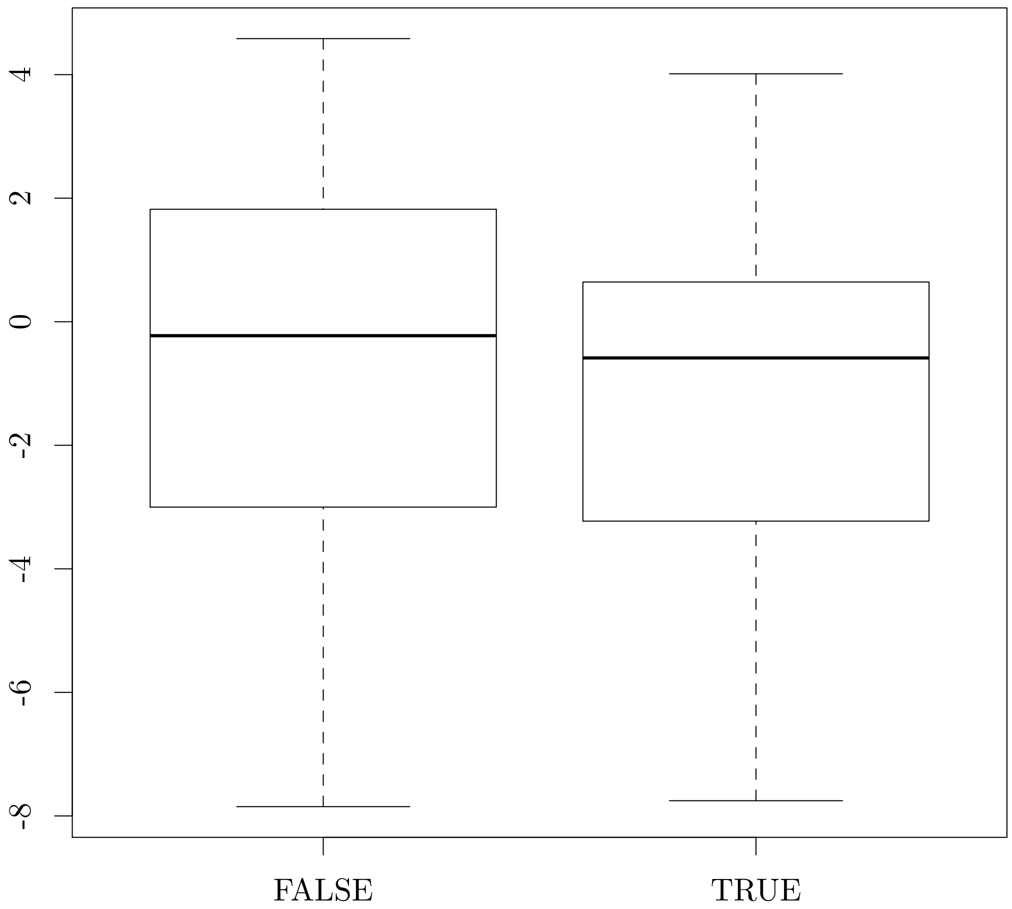
```
kruskal.test(data$DiagYearCent, data$LocBody)

##
##  Kruskal-Wallis rank sum test
##
## data:  data$DiagYearCent and data$LocBody
## Kruskal-Wallis chi-squared = 0.2357, df = 1, p-value = 0.6273

dcov.test(data$DiagYearCent, data$LocBody, R = 499)

##
##  dCov test of independence
##
## data:  index 1, replicates 499
## nV^2 = 0.4203, p-value = 0.812
## sample estimates:
##    dCov
## 0.04584

scatter.smooth(data$DiagYearCent, data$SizeCent, xlab = "DiagYearCent", ylab = "SizeCent")
```



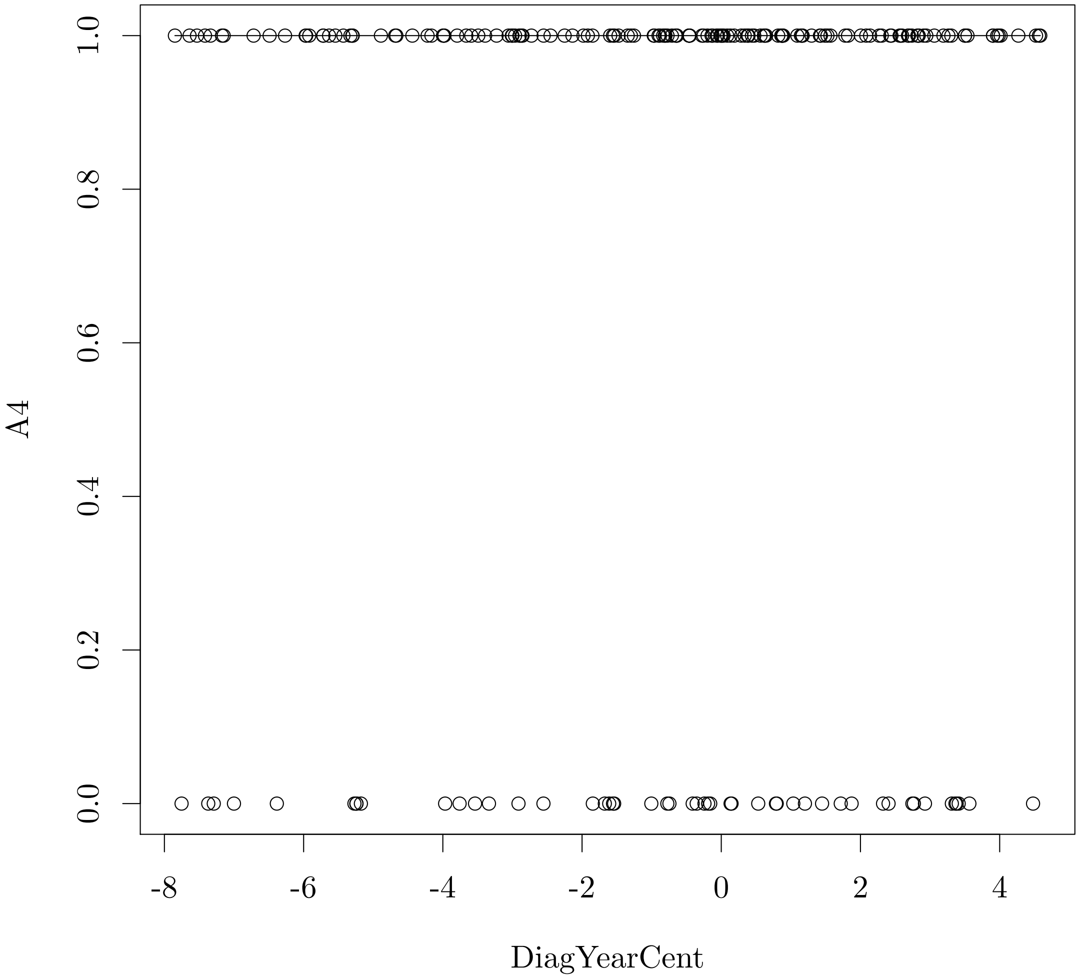
```
cor.test(data$DiagYearCent, data$SizeCent, method = "kendall")

##
##  Kendall's rank correlation tau
##
## data:  data$DiagYearCent and data$SizeCent
## z = -1.095, p-value = 0.2737
## alternative hypothesis: true tau is not equal to 0
## sample estimates:
##      tau
## -0.05367

dcov.test(data$DiagYearCent, data$SizeCent, R = 499)

##
##  dCov test of independence
##
## data:  index 1, replicates 499
## nV^2 = 59.67, p-value = 0.372
## sample estimates:
##   dCov
## 0.5462

scatter.smooth(data$DiagYearCent, data$A2, xlab = "DiagYearCent", ylab = "A2")
```



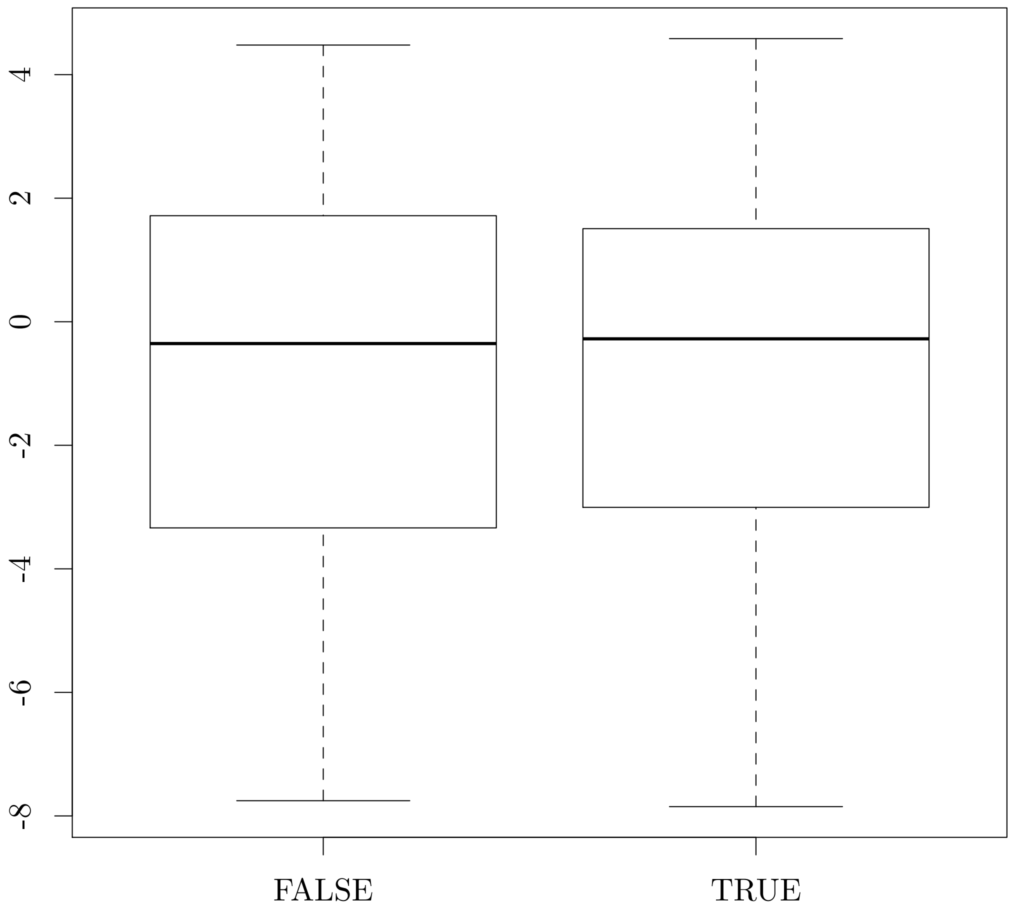
```r
boxplot(DiagYearCent ~ A2, data)
```



```
kruskal.test(data$DiagYearCent, data$A2)

##
##  Kruskal-Wallis rank sum test
##
## data:  data$DiagYearCent and data$A2
## Kruskal-Wallis chi-squared = 0.5693, df = 1, p-value = 0.4505

dcov.test(data$DiagYearCent, data$A2, R = 499)

##
##  dCov test of independence
##
## data:  index 1, replicates 499
## nV^2 = 0.6903, p-value = 0.558
## sample estimates:
##    dCov
## 0.05875

scatter.smooth(data$DiagYearCent, data$A4, xlab = "DiagYearCent", ylab = "A4")
```



```
boxplot(DiagYearCent ~ A4, data)
```

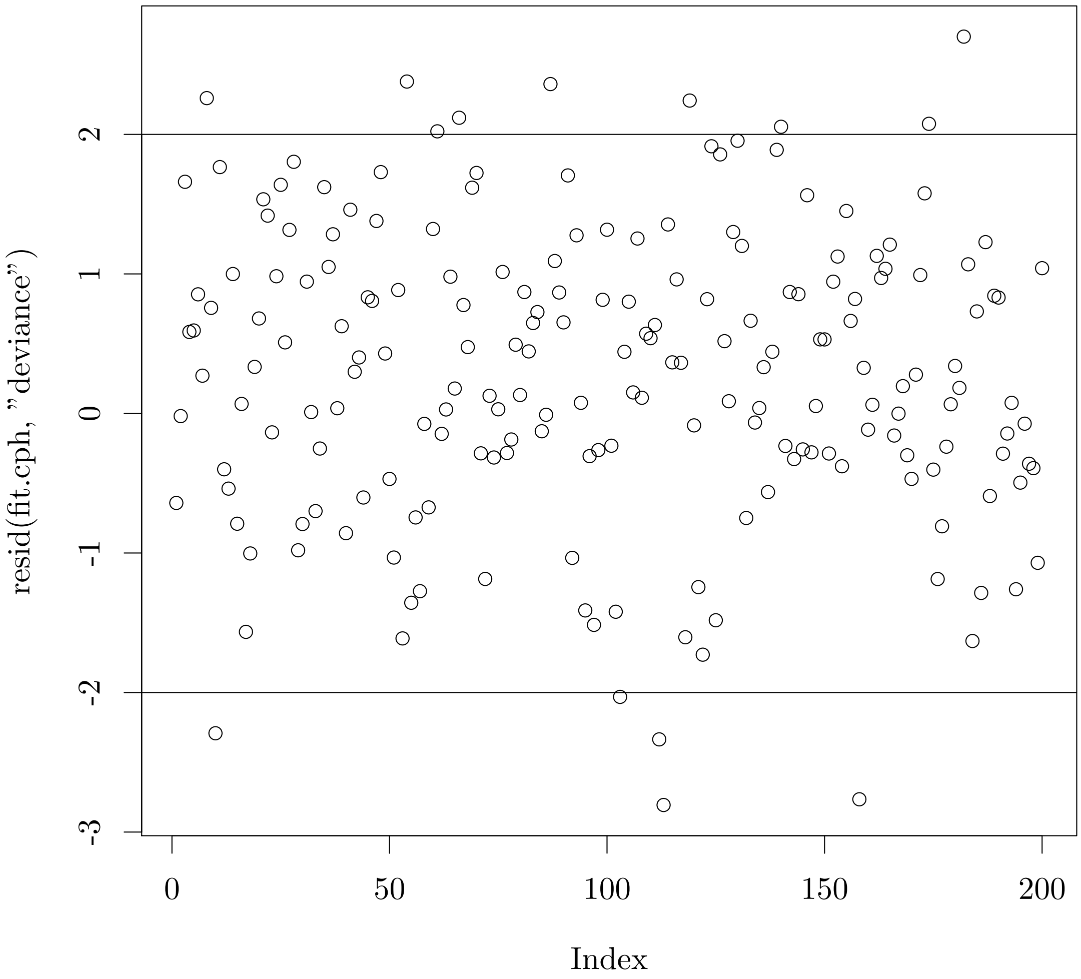


```
kruskal.test(data$DiagYearCent, data$A4)

##
##  Kruskal-Wallis rank sum test
##
## data:  data$DiagYearCent and data$A4
## Kruskal-Wallis chi-squared = 0.0055, df = 1, p-value = 0.9411

dcov.test(data$DiagYearCent, data$A4, R = 499)

##
##  dCov test of independence
##
## data:  index 1, replicates 499
## nV^2 = 0.1731, p-value = 0.998
## sample estimates:
##    dCov
## 0.02942
```

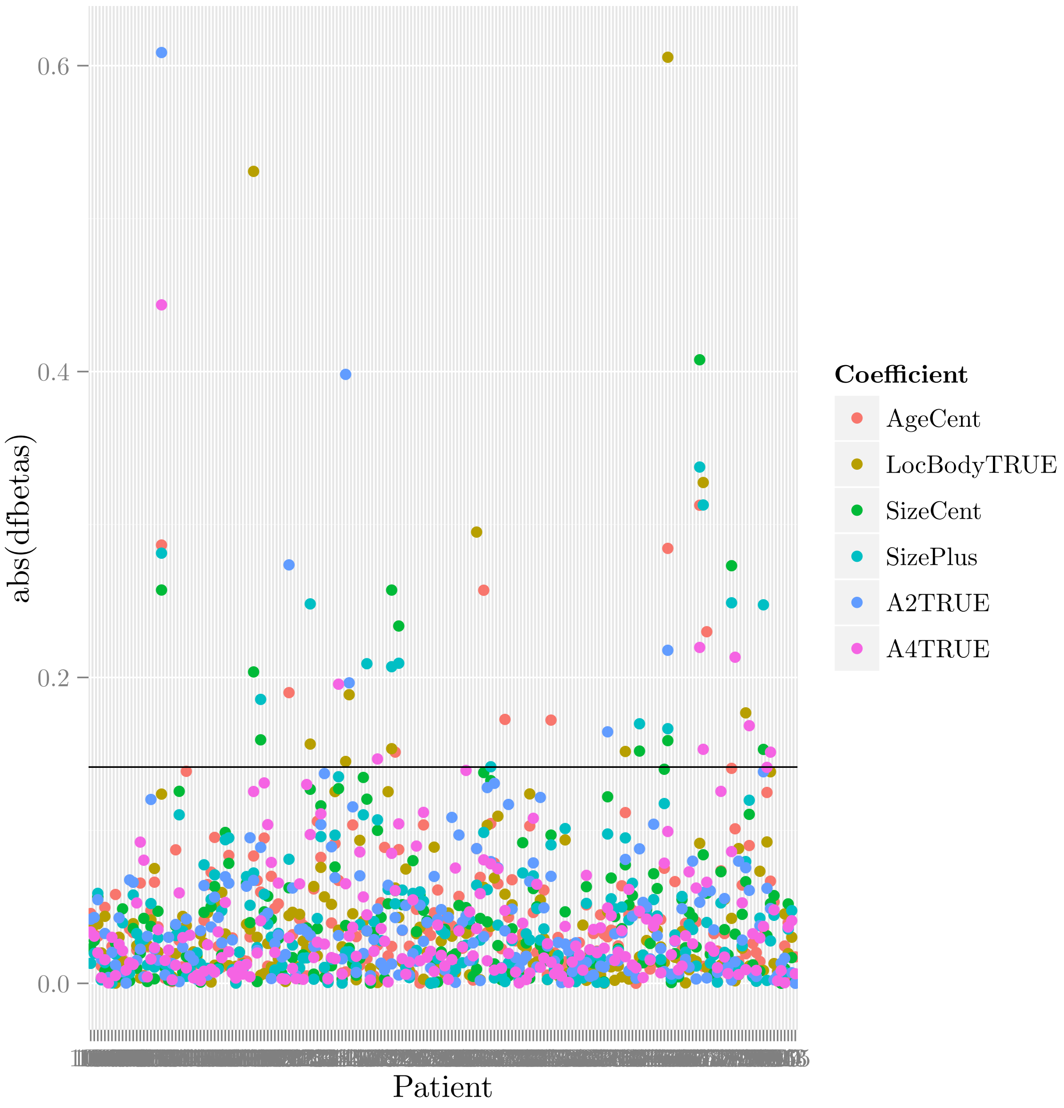
Not significant; good.

4.4 Outliers

```r
plot(resid(fit.cph, "deviance"))
abline(h = c(-2, 2))
```



```r
data$devresid = resid(fit.cph, type = "deviance")
temp = data[abs(data$devresid) >= 2,]
#temp[order(temp£Time),]

temp = resid(fit.cph, type = "dfbetas")
colnames(temp) = names(fit.cph$coefficients)
temp = melt(temp)
colnames(temp) = c("Patient", "Coefficient", "dfbetas")
temp$Patient = gsub("NSWPCN_", "", temp$Patient)
2/sqrt(nrow(data))              # The classic threshold for concern is 2/sqrt(n).

## [1] 0.1414

ggplot(temp, aes(y = abs(dfbetas), x = Patient, col = Coefficient)) + geom_point() + geom_hline(yinterce
```



```
#sort(apply(abs(resid(fit.cph, type = "dfbetas")), 1, max), decreasing = TRUE)
sum(apply(abs(resid(fit.cph, type = "dfbetas")), 1, max) > 2/sqrt(nrow(data)))

## [1] 31

temp = resid(fit.cph, type = "dfbetas")
data$DFBETAS_max = apply(abs(temp), 1, max)
data$DFBETAS_vars = apply(abs(temp), 1, function(x) paste(attr(fit.cph$terms, "term.labels")[x > 2/sqrt(
temp = data[data$DFBETAS_max >= 2/sqrt(nrow(data)) | abs(data$devresid) >= 2,]
#temp[order(temp£DFBETAS_max),]
```

Remove points with deviance residuals ¿ 2.5, or DFBETAS ¿ 0.3.

```
nrow(data)

## [1] 200

data = data[data$DFBETAS_max <= 0.3 & abs(data$devresid) <= 2.5,]
nrow(data)
```

```
## [1] 193

fit.cph = coxph(Surv(Time, DSD) ~ strata(SexM) + AgeCent + LocBody + SizeCent + SizePlus + A2 + A4, data
```

4.5 EDA: Variable selection

```
nobs.coxph <<- function(obj, ...) sum(obj$y[,2])
fit.cph.as.bic1 = glmulti(Surv(Time, DSD) ~ strata(SexM) + AgeCent + LocBody + SizeCent + SizePlus + A2

## Initialization...
## TASK: Exhaustive screening of candidate set.
## Fitting...
##
## After 50 models:
## Best model: Surv(Time,DSD)~1+A2+A4
## Crit= 1569.99720157408
## Mean crit= 1579.04206453807
##
## After 100 models:
## Best model: Surv(Time,DSD)~1+strata(SexM)+SizeCent+A2
## Crit= 1322.28966392719
## Mean crit= 1493.81514417481
##
## After 150 models:
## Best model: Surv(Time,DSD)~1+strata(SexM)+SizeCent+A2+A4
## Crit= 1319.12027767861
## Mean crit= 1416.9645603344
## Completed.

fit.cph.as.aicc1 = glmulti(Surv(Time, DSD) ~ strata(SexM) + AgeCent + LocBody + SizeCent + SizePlus + A2

## Initialization...
## TASK: Exhaustive screening of candidate set.
## Fitting...
##
## After 50 models:
## Best model: Surv(Time,DSD)~1+LocBody+SizeCent+A4
## Crit= 1562.92910743338
## Mean crit= 1570.63396981566
##
## After 100 models:
## Best model: Surv(Time,DSD)~1+strata(SexM)+LocBody+SizeCent+A2
## Crit= 1315.8613218026
## Mean crit= 1484.90325895394
##
## After 150 models:
## Best model: Surv(Time,DSD)~1+strata(SexM)+LocBody+SizeCent+A2+A4
## Crit= 1309.03451494962
## Mean crit= 1406.96604818801
## Completed.

rm(nobs.coxph)
summary(fit.cph.as.bic1)$bestmodel
```

```
## [1] "Surv(Time, DSD) ~ 1 + strata(SexM) + SizeCent + A2 + A4"

summary(fit.cph.as.aicc1)$bestmodel

## [1] "Surv(Time, DSD) ~ 1 + strata(SexM) + LocBody + SizeCent + A2 + "
## [2] "    A4"
```

Also run BIC stepwise, because we can.

```
stepAIC(fit.cph, k = log(nrow(data)))

## Start:  AIC=1330
## Surv(Time, DSD) ~ strata(SexM) + AgeCent + LocBody + SizeCent +
##     SizePlus + A2 + A4
##
##            Df  AIC
## - SizePlus  1 1325
## - SizeCent  1 1326
## - AgeCent   1 1327
## - LocBody   1 1328
## <none>        1330
## - A4        1 1333
## - A2        1 1334
##
## Step:  AIC=1325
## Surv(Time, DSD) ~ strata(SexM) + AgeCent + LocBody + SizeCent +
##     A2 + A4
##
##            Df  AIC
## - AgeCent   1 1322
## - LocBody   1 1322
## - SizeCent  1 1324
## <none>        1325
## - A2        1 1329
## - A4        1 1330
##
## Step:  AIC=1322
## Surv(Time, DSD) ~ strata(SexM) + LocBody + SizeCent + A2 + A4
##
##            Df  AIC
## - LocBody   1 1319
## - SizeCent  1 1321
## <none>        1322
## - A2        1 1325
## - A4        1 1326
##
## Step:  AIC=1319
## Surv(Time, DSD) ~ strata(SexM) + SizeCent + A2 + A4
##
##            Df  AIC
## <none>        1319
## - SizeCent  1 1322
## - A4        1 1322
## - A2        1 1324
## Call:
```

```
## coxph(formula = Surv(Time, DSD) ~ strata(SexM) + SizeCent + A2 +
##     A4, data = data)
##
##
##             coef exp(coef) se(coef)    z      p
## SizeCent 0.0159      1.02  0.00543 2.92 0.0035
## A2TRUE   0.7003      2.01  0.20650 3.39 0.0007
## A4TRUE   0.5154      1.67  0.18497 2.79 0.0053
##
## Likelihood ratio test=34.1  on 3 df, p=1.92e-07  n= 193, number of events= 184
```

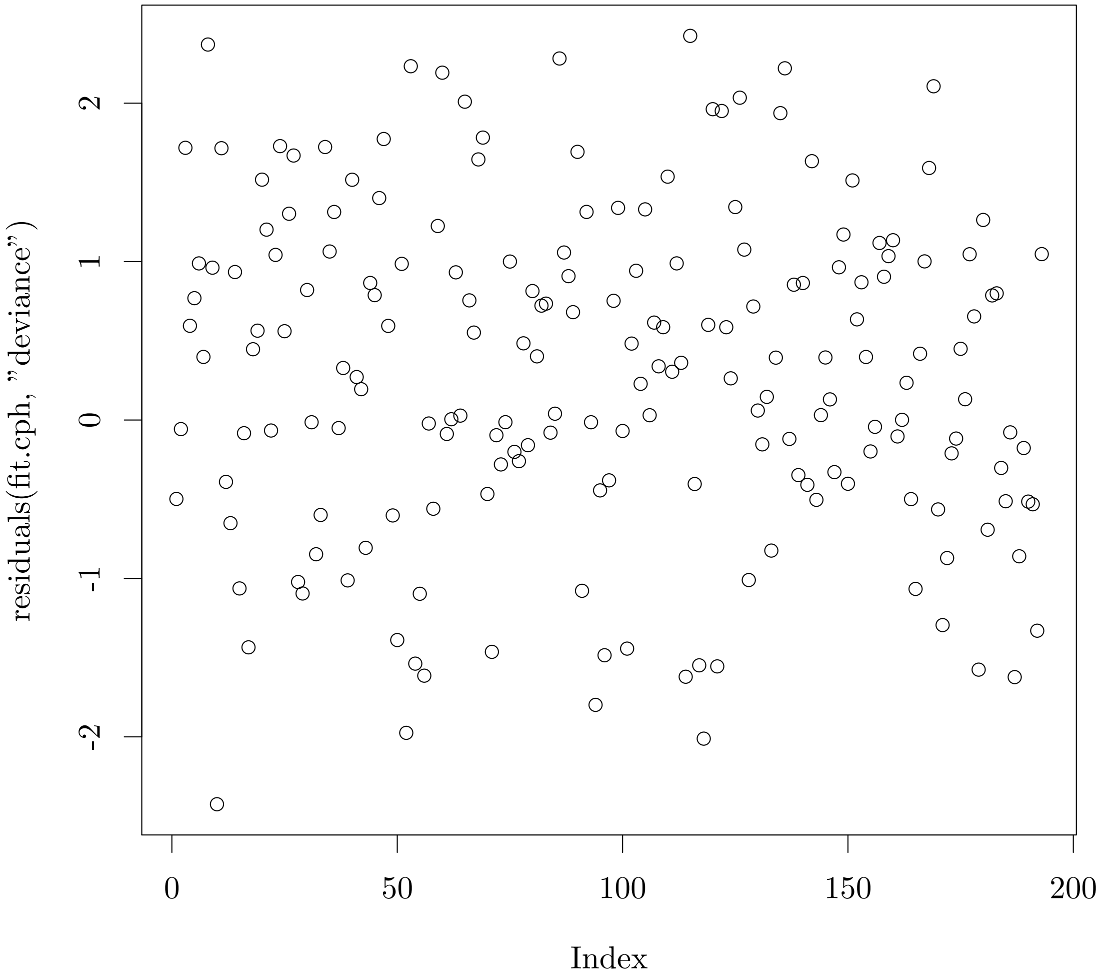
```
stepAIC(fit.cph, k = 2)
```

```
## Start:  AIC=1311
## Surv(Time, DSD) ~ strata(SexM) + AgeCent + LocBody + SizeCent +
##     SizePlus + A2 + A4
##
##            Df  AIC
## - SizePlus  1 1309
## - SizeCent  1 1310
## - AgeCent   1 1311
## <none>        1311
## - LocBody   1 1311
## - A4        1 1317
## - A2        1 1318
##
## Step:  AIC=1309
## Surv(Time, DSD) ~ strata(SexM) + AgeCent + LocBody + SizeCent +
##     A2 + A4
##
##            Df  AIC
## - AgeCent   1 1309
## <none>        1309
## - LocBody   1 1309
## - SizeCent  1 1311
## - A2        1 1316
## - A4        1 1317
##
## Step:  AIC=1309
## Surv(Time, DSD) ~ strata(SexM) + LocBody + SizeCent + A2 + A4
##
##            Df  AIC
## <none>        1309
## - LocBody   1 1309
## - SizeCent  1 1311
## - A2        1 1315
## - A4        1 1316
## Call:
## coxph(formula = Surv(Time, DSD) ~ strata(SexM) + LocBody + SizeCent +
##     A2 + A4, data = data)
##
##
##                coef exp(coef) se(coef)    z      p
## LocBodyTRUE 0.3806      1.46   0.2267 1.68 0.0930
## SizeCent    0.0126      1.01   0.0058 2.18 0.0290
## A2TRUE      0.6301      1.88   0.2120 2.97 0.0030
## A4TRUE      0.5312      1.70   0.1850 2.87 0.0041
##
## Likelihood ratio test=36.7  on 4 df, p=2.04e-07  n= 193, number of events= 184
```

4.6 Final Fits

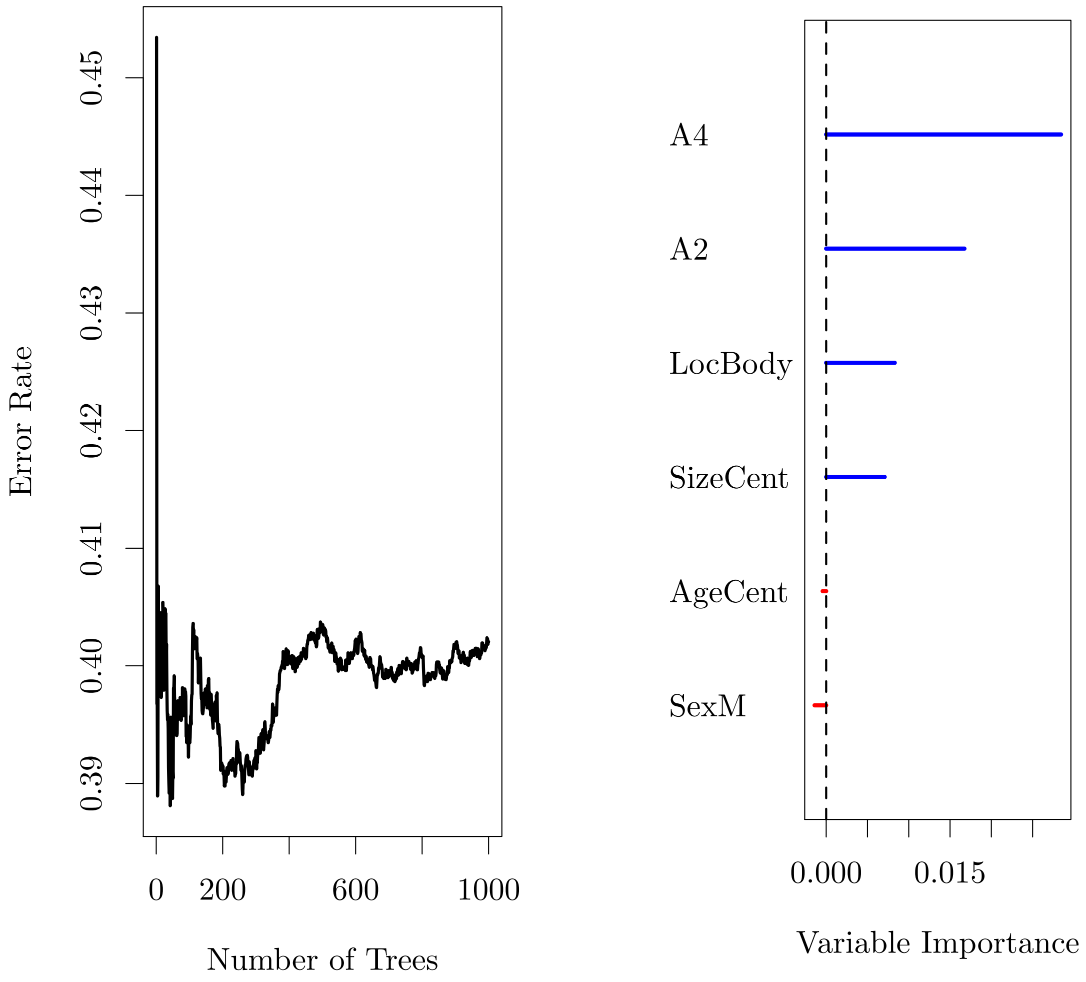
```
fit.cph.as.bic = coxph(Surv(Time, DSD) ~ strata(SexM) + SizePlus + A2 + A4, data = data)
cox.zph(fit.cph.as.bic)

##              rho  chisq     p
## SizePlus  0.0212 0.0876 0.767
## A2TRUE    0.0340 0.2136 0.644
## A4TRUE   -0.0808 1.1972 0.274
## GLOBAL        NA 1.3865 0.709

fit.cph.as.aicc = coxph(Surv(Time, DSD) ~ strata(SexM)+AgeCent+LocBody+SizeCent+A2+A4+SizeCent:AgeCent+s
cox.zph(fit.cph.as.aicc)

##                                    rho   chisq      p
## AgeCent                       -0.16098 5.43356 0.0198
## LocBodyTRUE                    0.03967 0.30863 0.5785
## SizeCent                       0.00379 0.00275 0.9581
## A2TRUE                         0.04060 0.34304 0.5581
## A4TRUE                        -0.06803 0.84941 0.3567
## AgeCent:SizeCent               0.03856 0.28388 0.5942
## strata(SexM)SexM=TRUE:SizeCent  0.00853 0.01322 0.9085
## GLOBAL                              NA 7.49932 0.3788

fit.cph.sw.bic = coxph(Surv(Time, DSD) ~ strata(SexM) + SizeCent + A2 + A4, data = data)
cox.zph(fit.cph.sw.bic)

##              rho  chisq     p
## SizeCent  0.0162 0.0507 0.822
## A2TRUE    0.0312 0.1797 0.672
## A4TRUE   -0.0874 1.4015 0.236
## GLOBAL        NA 1.4878 0.685

fit.cph.sw.aic = coxph(Surv(Time, DSD) ~ strata(SexM) + LocBody + SizeCent + A2 + A4, data = data)
cox.zph(fit.cph.sw.aic)

##                 rho  chisq     p
## LocBodyTRUE  0.0180 0.0592 0.808
## SizeCent     0.0280 0.1465 0.702
## A2TRUE       0.0292 0.1636 0.686
## A4TRUE      -0.0839 1.2904 0.256
## GLOBAL           NA 1.6815 0.794

fit.cph = fit.cph.sw.aic
```

```
plot(residuals(fit.cph, "deviance"))
```



```
residuals(fit.cph, "deviance")[abs(residuals(fit.cph, "deviance")) >= 2]

##  NSWPCN_125  NSWPCN_133  NSWPCN_315  NSWPCN_324  NSWPCN_333  NSWPCN_374
##       2.370      -2.425       2.233       2.193       2.009       2.282
##  NSWPCN_779  NSWPCN_788  NSWPCN_799 NSWPCN_1017 NSWPCN_1165
##       2.425      -2.011       2.035       2.220       2.107

temp = sort(apply(abs(residuals(fit.cph, "dfbetas")), 1, max))
#temp
2/sqrt(nrow(data))

## [1] 0.144

mean(temp > 2/sqrt(nrow(data)))

## [1] 0.1244

temp[temp > 2/sqrt(nrow(data))]

##  NSWPCN_354  NSWPCN_445  NSWPCN_133  NSWPCN_374  NSWPCN_784  NSWPCN_777
##      0.1457      0.1524      0.1566      0.1580      0.1618      0.1637
##  NSWPCN_195  NSWPCN_296  NSWPCN_267 NSWPCN_1155  NSWPCN_154  NSWPCN_794
##      0.1652      0.1674      0.1711      0.1804      0.1895      0.2037
##  NSWPCN_802  NSWPCN_142  NSWPCN_799  NSWPCN_313  NSWPCN_192  NSWPCN_317
##      0.2056      0.2174      0.2178      0.2219      0.2225      0.2541
##  NSWPCN_318  NSWPCN_788  NSWPCN_145 NSWPCN_1253 NSWPCN_1212  NSWPCN_310
##      0.2567      0.2749      0.3006      0.4234      0.4528      0.4926
```

```
set.seed(20150208)
fit.rsf = rfsrc(Surv(Time, DSD) ~ SexM + AgeCent + LocBody + SizeCent + A2 + A4, data = data, mtry = 1,
plot(fit.rsf)
```



```
##
##              Importance   Relative Imp
## A4               0.0284         1.0000
## A2               0.0167         0.5887
## LocBody          0.0083         0.2920
## SizeCent         0.0071         0.2492
## AgeCent         -0.0004        -0.0149
## SexM            -0.0014        -0.0494
```

```
fit.gg = flexsurvreg(Surv(Time, DSD) ~ SexM + LocBody + SizeCent + A2 + A4,
        anc = list(
                sigma = ~ SexM,
                Q = ~ SexM),
        data = data, dist = "gengamma")

fit.gg2 = flexsurvreg(Surv(Time, DSD) ~ SexM+AgeCent+LocBody+SizeCent+A2+A4+SizeCent:AgeCent+SexM:SizeCe
        anc = list(
                sigma = ~ SexM,
                Q = ~ SexM),
        data = data, dist = "gengamma")

fit.gg$loglik

## [1] -1325

fit.gg2$loglik

## [1] -1321

pchisq(2*(fit.gg2$loglik - fit.gg$loglik), 3, lower.tail = FALSE)

## [1] 0.04837

AIC(fit.gg)

## [1] 2669

AIC(fit.gg2)

## [1] 2668

fit.gg

##
## Call:
## flexsurvreg(formula = Surv(Time, DSD) ~ SexM + LocBody + SizeCent +     A2 + A4, anc = list(sigma =
##
## Estimates:
##                  data mean  est       L95%      U95%      se
## mu                     NA    6.53611   6.19247   6.87976   0.17533
## sigma                  NA    0.78047   0.67245   0.90585   0.05932
## Q                      NA    0.11827  -0.49632   0.73287   0.31357
## SexMTRUE          0.51813    0.28181  -0.07256   0.63619   0.18081
## LocBodyTRUE       0.17098   -0.20952  -0.50577   0.08673   0.15115
## SizeCent          3.65285   -0.00879  -0.01600  -0.00158   0.00368
## A2TRUE            0.16580   -0.38962  -0.65941  -0.11983   0.13765
## A4TRUE            0.75130   -0.39725  -0.62687  -0.16763   0.11716
## sigma(SexMTRUE)   0.51813   -0.26267  -0.49374  -0.03159   0.11790
## Q(SexMTRUE)       0.51813    0.48452  -0.32987   1.29891   0.41551
##                  exp(est)  L95%      U95%
## mu                     NA        NA        NA
## sigma                  NA        NA        NA
## Q                      NA        NA        NA
## SexMTRUE          1.32553   0.93001   1.88927
## LocBodyTRUE       0.81097   0.60304   1.09060
## SizeCent          0.99124   0.98412   0.99842
## A2TRUE            0.67731   0.51715   0.88707
## A4TRUE            0.67217   0.53426   0.84567
## sigma(SexMTRUE)   0.76900   0.61034   0.96890
## Q(SexMTRUE)       1.62340   0.71902   3.66531
##
## N = 193,  Events: 184,  Censored: 9
## Total time at risk: 114833
## Log-likelihood = -1325, df = 10
## AIC = 2669
```

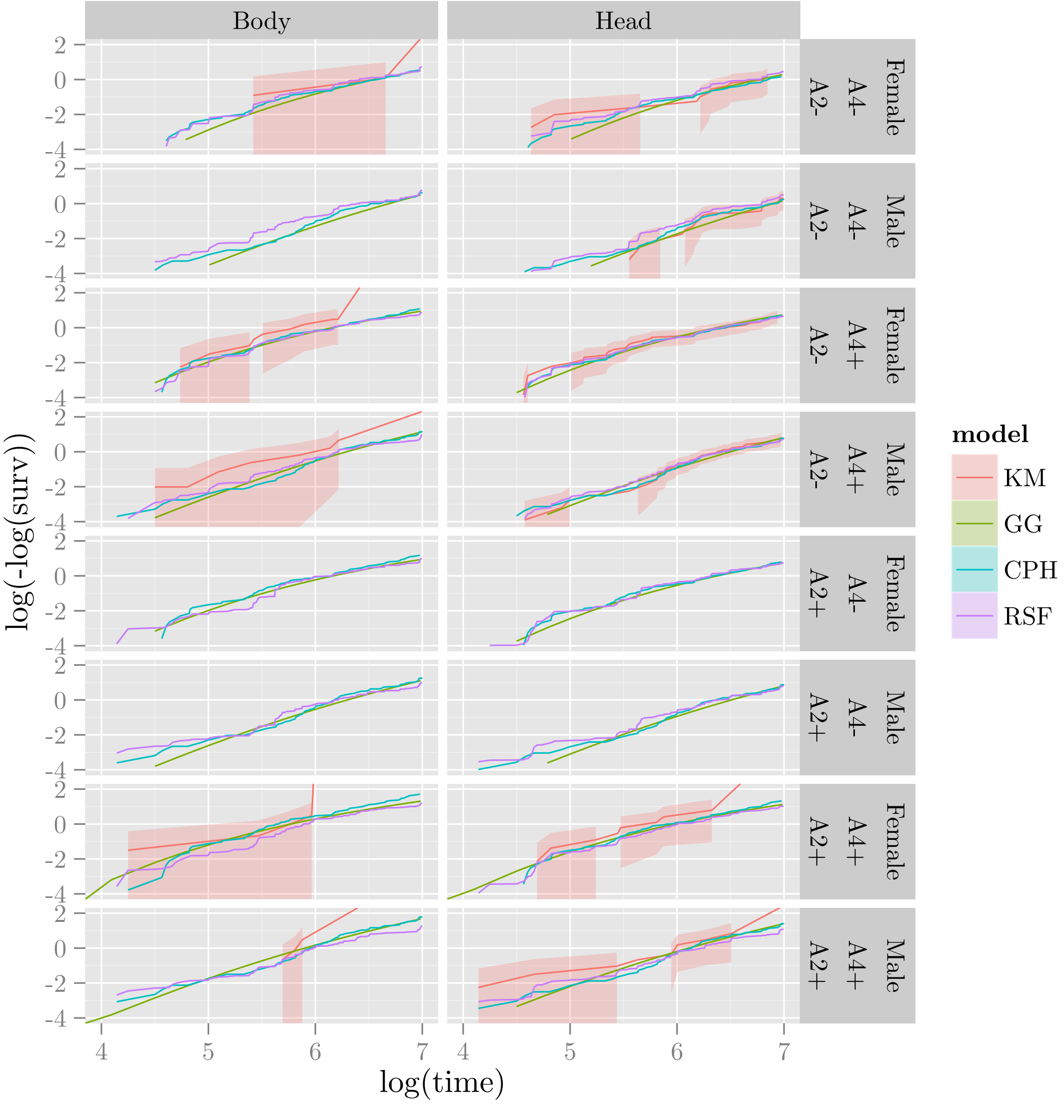
```
fit.gg2
```

```
##
## Call:
## flexsurvreg(formula = Surv(Time, DSD) ~ SexM + AgeCent + LocBody +     SizeCent + A2 + A4 + SizeCent:
##
## Estimates:
##                    data mean  est        L95%       U95%       se
## mu                        NA   6.530218   6.184887   6.875549   0.176192
## sigma                     NA   0.771216   0.660311   0.900749   0.061092
## Q                         NA   0.228786  -0.410815   0.868387   0.326333
## SexMTRUE            0.518135   0.322116  -0.039753   0.683986   0.184631
## AgeCent            -1.067358   0.010352   0.000170   0.020534   0.005195
## LocBodyTRUE         0.170984  -0.271326  -0.558764   0.016113   0.146655
## SizeCent            3.652850  -0.004245  -0.015597   0.007107   0.005792
## A2TRUE              0.165803  -0.358631  -0.618603  -0.098660   0.132641
## A4TRUE              0.751295  -0.354054  -0.574822  -0.133287   0.112639
## AgeCent:SizeCent   -8.896373  -0.000855  -0.001550  -0.000160   0.000354
## SexMTRUE:SizeCent   1.772021  -0.006910  -0.020503   0.006684   0.006936
## sigma(SexMTRUE)     0.518135  -0.334045  -0.602093  -0.065998   0.136762
## Q(SexMTRUE)         0.518135   0.550014  -0.328860   1.428889   0.448414
##                    exp(est)   L95%       U95%
## mu                        NA         NA         NA
## sigma                     NA         NA         NA
## Q                         NA         NA         NA
## SexMTRUE            1.380045   0.961027   1.981761
## AgeCent             1.010406   1.000170   1.020746
## LocBodyTRUE         0.762368   0.571915   1.016243
## SizeCent            0.995764   0.984524   1.007133
## A2TRUE              0.698632   0.538697   0.906051
## A4TRUE              0.701837   0.562805   0.875214
## AgeCent:SizeCent    0.999145   0.998452   0.999840
## SexMTRUE:SizeCent   0.993114   0.979706   1.006706
## sigma(SexMTRUE)     0.716021   0.547664   0.936133
## Q(SexMTRUE)         1.733278   0.719744   4.174059
##
## N = 193,  Events: 184,  Censored: 9
## Total time at risk: 114833
## Log-likelihood = -1321, df = 13
## AIC = 2668
```

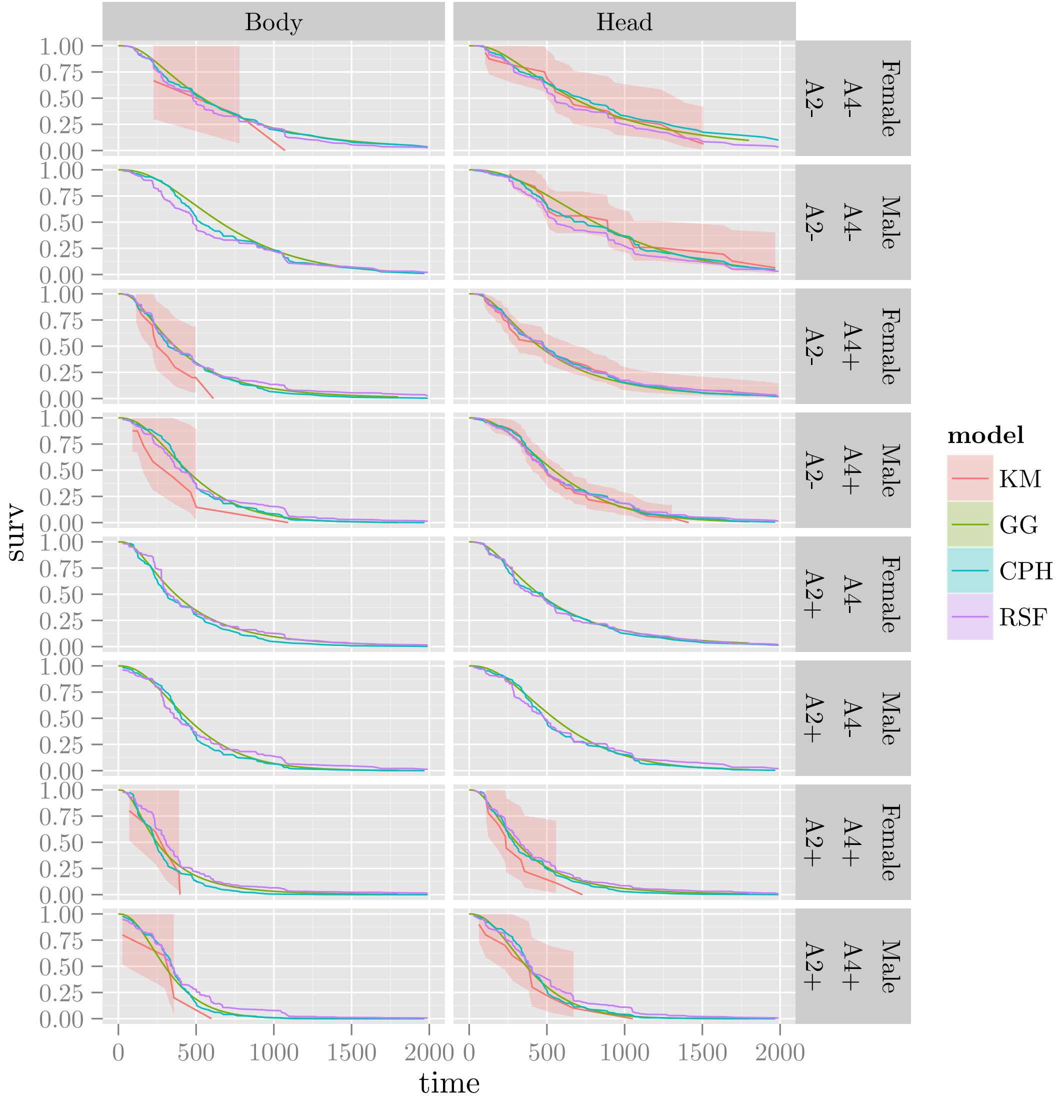
5 Fit assessment

Plot fit stratified by sex, separate curves for A2, A4 status, at median (approx.) Size.

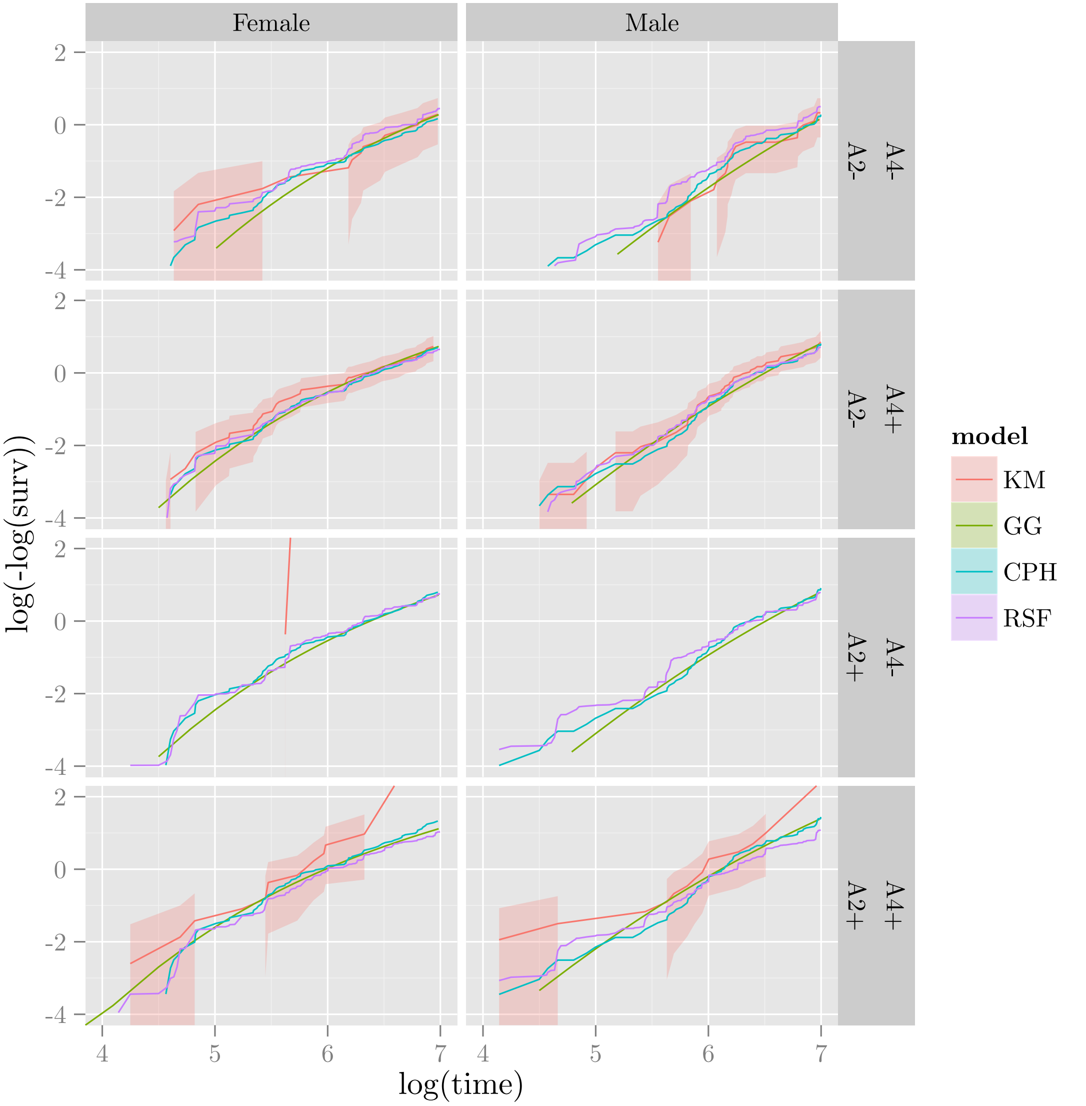
```
temp.grid = expand.grid(A4 = c(FALSE, TRUE), A2 = c(FALSE, TRUE), SexM = c(FALSE, TRUE), SizeCent = 0, A
temp.grid$ID = sprintf("SexM=%s, A2=% -5s, A4=% -5s, LocBody=%s", temp.grid$SexM, temp.grid$A2, temp.gri
temp.preds = summary(fit.gg, newdata = temp.grid, type = "survival", t = seq(0, 365*5, 30))
temp.preds2 = do.call(rbind, temp.preds)
temp.preds2$group = rep(gsub(".*ID=", "", names(temp.preds)), each = nrow(temp.preds[[1]]))
temp.preds.cox = survfit(fit.cph, newdata = temp.grid)
temp.preds.rsf = predict(fit.rsf, newdata = temp.grid)

temp.survfit = survfit(Surv(Time, DSD) ~ SexM + A2 + A4 + LocBody, data)
temp.data = data.frame(time = temp.survfit$time, surv = temp.survfit$surv, upper = temp.survfit$lower, l
temp.data = rbind(temp.data, data.frame(time = temp.preds2$time, surv = temp.preds2$est, upper = temp.pr
temp.data = rbind(temp.data, data.frame(time = temp.preds.cox$time, surv = temp.preds.cox$surv, upper =
temp.data = rbind(temp.data, data.frame(time = rep(temp.preds.rsf$time.interest, each = nrow(temp.preds.

temp.data$Sex = c("Male", "Female")[grepl("SexM=FALSE", temp.data$group)+1]
temp.data$A2 = c("A2-", "A2+")[grepl("A2=TRUE", temp.data$group)+1]
temp.data$A4 = c("A4-", "A4+")[grepl("A4=TRUE", temp.data$group)+1]
temp.data$Location = c("Head", "Body")[grepl("LocBody=TRUE", temp.data$group)+1]

temp.data$lower[temp.data$model != "KM"] = NA
temp.data$upper[temp.data$model != "KM"] = NA
ggplot(temp.data, aes(x = log(time), y = log(-log(surv)), ymin = log(-log(lower)), ymax = log(-log(upper
        geom_ribbon(alpha = 0.25, colour = NA) +
        geom_line() +
        xlim(4, 7) + ylim(-4, 2) +
        facet_grid(A2 ~ A4 ~ Sex ~ Location)

## Warning:  Removed 64 rows containing missing values (geom_path).
## Warning:  Removed 70 rows containing missing values (geom_path).
## Warning:  Removed 59 rows containing missing values (geom_path).
## Warning:  Removed 69 rows containing missing values (geom_path).
## Warning:  Removed 60 rows containing missing values (geom_path).
## Warning:  Removed 70 rows containing missing values (geom_path).
## Warning:  Removed 57 rows containing missing values (geom_path).
## Warning:  Removed 66 rows containing missing values (geom_path).
## Warning:  Removed 58 rows containing missing values (geom_path).
## Warning:  Removed 59 rows containing missing values (geom_path).
## Warning:  Removed 56 rows containing missing values (geom_path).
## Warning:  Removed 56 rows containing missing values (geom_path).
## Warning:  Removed 57 rows containing missing values (geom_path).
## Warning:  Removed 58 rows containing missing values (geom_path).
## Warning:  Removed 57 rows containing missing values (geom_path).
## Warning:  Removed 56 rows containing missing values (geom_path).
```



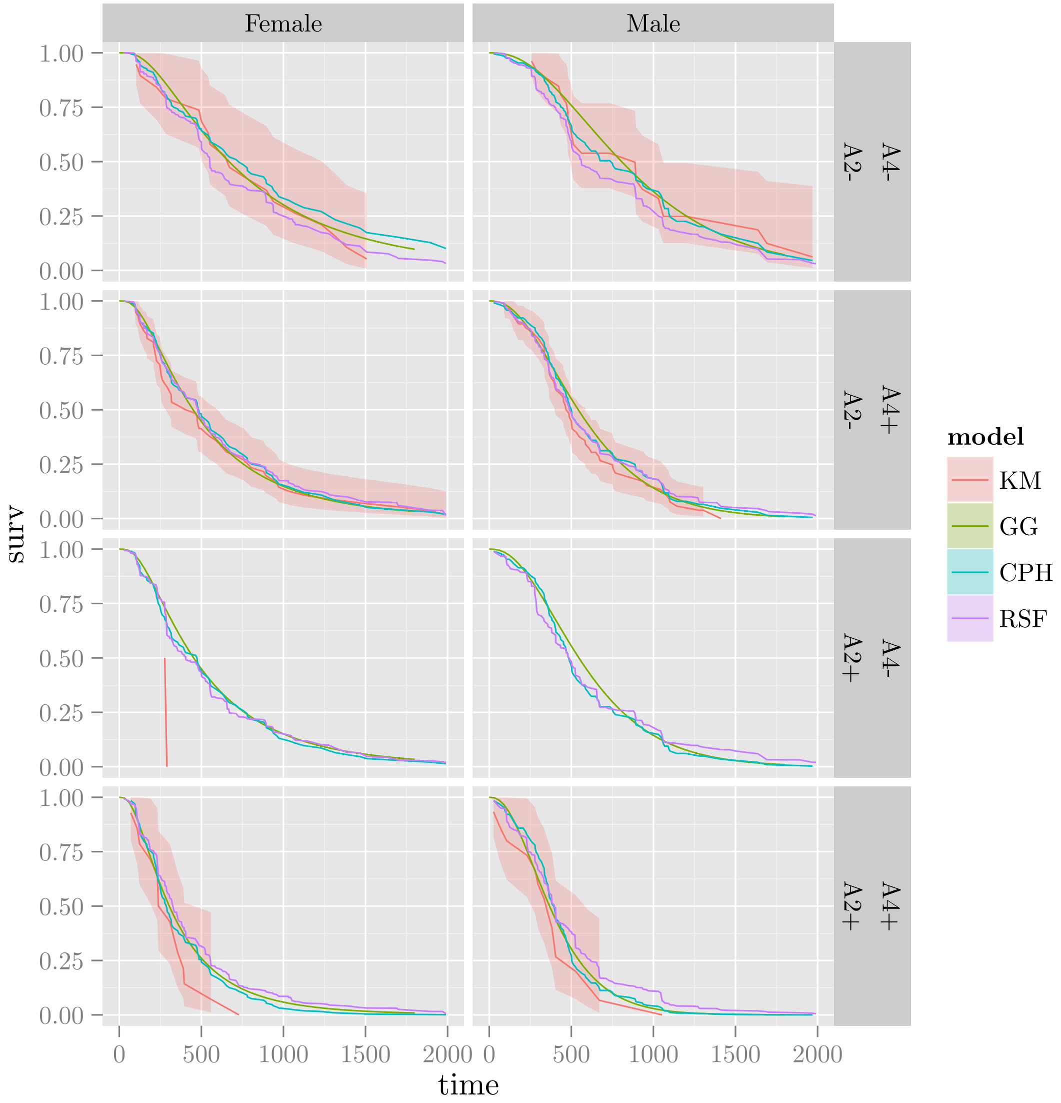
```
ggplot(temp.data, aes(x = time, y = surv, ymin = lower, ymax = upper, colour = model, fill = model)) +
        geom_ribbon(alpha = 0.25, colour = NA) +
        geom_line() + xlim(0, 2000) + ylim(0, 1) +
        facet_grid(A2 ˜ A4 ˜ Sex ˜ Location)

## Warning:  Removed 4 rows containing missing values (geom_path).
## Warning:  Removed 5 rows containing missing values (geom_path).
## Warning:  Removed 3 rows containing missing values (geom_path).
## Warning:  Removed 4 rows containing missing values (geom_path).
## Warning:  Removed 4 rows containing missing values (geom_path).
## Warning:  Removed 5 rows containing missing values (geom_path).
## Warning:  Removed 3 rows containing missing values (geom_path).
## Warning:  Removed 3 rows containing missing values (geom_path).
## Warning:  Removed 4 rows containing missing values (geom_path).
## Warning:  Removed 4 rows containing missing values (geom_path).
## Warning:  Removed 3 rows containing missing values (geom_path).
## Warning:  Removed 3 rows containing missing values (geom_path).
## Warning:  Removed 4 rows containing missing values (geom_path).
## Warning:  Removed 4 rows containing missing values (geom_path).
## Warning:  Removed 3 rows containing missing values (geom_path).
## Warning:  Removed 3 rows containing missing values (geom_path).
```



```
temp.grid = expand.grid(A4 = c(FALSE, TRUE), A2 = c(FALSE, TRUE), SexM = c(FALSE, TRUE), SizeCent = 0, A
temp.grid$ID = sprintf("SexM=%s, A2=% -5s, A4=% -5s, LocBody=%s", temp.grid$SexM, temp.grid$A2, temp.gri
temp.preds = summary(fit.gg, newdata = temp.grid, type = "survival", t = seq(0, 365*5, 30))
temp.preds2 = do.call(rbind, temp.preds)
temp.preds2$group = rep(gsub(".*ID=", "", names(temp.preds)), each = nrow(temp.preds[[1]]))
temp.preds.cox = survfit(fit.cph, newdata = temp.grid)
temp.preds.rsf = predict(fit.rsf, newdata = temp.grid)

temp.survfit = survfit(Surv(Time, DSD) ~ SexM + A2 + A4, data)
temp.data = data.frame(time = temp.survfit$time, surv = temp.survfit$surv, upper = temp.survfit$lower, l
temp.data = rbind(temp.data, data.frame(time = temp.preds2$time, surv = temp.preds2$est, upper = temp.pr
temp.data = rbind(temp.data, data.frame(time = temp.preds.cox$time, surv = temp.preds.cox$surv, upper =
temp.data = rbind(temp.data, data.frame(time = rep(temp.preds.rsf$time.interest, each = nrow(temp.preds.

temp.data$Sex = c("Male", "Female")[grepl("SexM=FALSE", temp.data$group)+1]
temp.data$A2 = c("A2-", "A2+")[grepl("A2=TRUE", temp.data$group)+1]
temp.data$A4 = c("A4-", "A4+")[grepl("A4=TRUE", temp.data$group)+1]

temp.data$lower[temp.data$model != "KM"] = NA
temp.data$upper[temp.data$model != "KM"] = NA
ggplot(temp.data, aes(x = log(time), y = log(-log(surv)), ymin = log(-log(lower)), ymax = log(-log(upper
        geom_ribbon(alpha = 0.25, colour = NA) +
        geom_line() +
        xlim(4, 7) + ylim(-4, 2) +
        facet_grid(A2 ~ A4 ~ Sex)

## Warning:  Removed 70 rows containing missing values (geom_path).
## Warning:  Removed 69 rows containing missing values (geom_path).
## Warning:  Removed 71 rows containing missing values (geom_path).
## Warning:  Removed 67 rows containing missing values (geom_path).
## Warning:  Removed 59 rows containing missing values (geom_path).
## Warning:  Removed 56 rows containing missing values (geom_path).
## Warning:  Removed 58 rows containing missing values (geom_path).
## Warning:  Removed 57 rows containing missing values (geom_path).
```



```
ggplot(temp.data, aes(x = time, y = surv, ymin = lower, ymax = upper, colour = model, fill = model)) +
        geom_ribbon(alpha = 0.25, colour = NA) +
        geom_line() + xlim(0, 2000) + ylim(0, 1) +
        facet_grid(A2 ~ A4 ~ Sex)

## Warning:  Removed 5 rows containing missing values (geom_path).
## Warning:  Removed 4 rows containing missing values (geom_path).
## Warning:  Removed 5 rows containing missing values (geom_path).
## Warning:  Removed 3 rows containing missing values (geom_path).
## Warning:  Removed 4 rows containing missing values (geom_path).
## Warning:  Removed 3 rows containing missing values (geom_path).
## Warning:  Removed 4 rows containing missing values (geom_path).
## Warning:  Removed 3 rows containing missing values (geom_path).
```



6 Model selection

It looks like that's as far as we can go with tweaking the fits. Time to put the different models against each other on the holdout data, and choose a winner.

DIY IBS, wooo.

```
calcIBS = function(surv, pred, pred_times, max_time, min_time = 0)
{
        stopifnot(nrow(surv) == nrow(pred) && length(pred_times) == ncol(pred))

        n = nrow(surv)
        marg_survfit = survfit(surv ~ 1)
        marg_censfit = survfit(Surv(surv[,1], !surv[,2]) ~ 1)
        marg_surv_func = approxfun(marg_survfit$time, marg_survfit$surv, method = "constant", yleft = 1,
        marg_cens_func = approxfun(marg_censfit$time, marg_censfit$surv, method = "constant", yleft = 1,

        pred_funcs = apply(pred, 1, function(pat_preds) approxfun(pred_times, pat_preds, yleft = 1, yrig

        indiv_patient_bsc = function(pat_i, tstars)
        {
                observed_time = surv[pat_i, 1]
                observed_event = surv[pat_i, 2]
                pred_func = pred_funcs[[pat_i]]
                category = 1*(observed_time <= tstars & observed_event) + 2*(observed_time > tstars) + 3
                bsc = rep(NA, length(tstars))
                bsc[category == 1] = pred_func(tstars[category == 1])^2 / marg_cens_func(observed_time)
                bsc[category == 2] = (1 - pred_func(tstars[category == 2]))^2 / marg_cens_func(tstars[ca
                bsc[category == 3] = 0
                bsc
        }

        bsc_func = function(tstars) { rowMeans(sapply(1:n, function(pat_i) indiv_patient_bsc(pat_i, tsta

        weight_func = function(tstars) { (1 - marg_surv_func(tstars)) / (1 - marg_surv_func(max_time)) }

        # Be slack and do trapezoidal int. with a fine grid.  It should be possible
        # to calulate the int. exactly but I cbfed.
        int_grid = seq(min_time, max_time, length.out = 1e3)
        bsc_vals = bsc_func(int_grid)
        weight_vals = weight_func(int_grid)
        int_vals = bsc_vals * weight_vals
        ibsc = (2*sum(int_vals) - int_vals[1] - int_vals[length(int_vals)]) * (diff(range(int_grid))) /

        return(list(bsc = bsc_vals, weights = weight_vals, eval_times = int_grid, ibsc = ibsc))
}
```

Calculate survival probability predictions for each of the models, on the validation data.

```
ibs_times = sort(unique(data.val$Time))
ibs_preds_gg = as.matrix(t(sapply(summary(fit.gg, newdata = data.val, type = "survival", t = ibs_times),
ibs_preds_gg2 = as.matrix(t(sapply(summary(fit.gg2, newdata = data.val, type = "survival", t = ibs_times
temp_cox_preds = survfit(fit.cph, newdata = data.val)
ibs_preds_cph = simplify2array(tapply(1:length(temp_cox_preds$time), rep(names(temp_cox_preds$strata), t
        approx(x = temp_cox_preds$time[strat_i], y = temp_cox_preds$surv[strat_i], xout = ibs_times, met
ibs_preds_cph = t(ibs_preds_cph[,rownames(data.val)])
temp_rsf_preds = predict(fit.rsf, newdata = data.val)
ibs_preds_rsf = t(apply(temp_rsf_preds$survival, 1, function(survs) approx(temp_rsf_preds$time.interest,
# Patients (from data.val) are in rows, times (from ibs_times) in columns.
```

```r
# Add a no-information KM predictor
temp_km0 = survfit(Surv(Time, DSD) ~ 1, data)
ibs_preds_km0 = t(matrix(rep(approx(temp_km0$time, temp_km0$surv, xout = ibs_times, method = "constant",
ibs_preds_all = list(gg = ibs_preds_gg, gg2 = ibs_preds_gg2, cph = ibs_preds_cph, rsf = ibs_preds_rsf,
```

```r
val.prob.times = seq(0, max(data.val$Time), 1)

temp.coefs = coef(fit.gg)
val.linpred.gg = sapply(1:length(temp.coefs), function(coef_i) {
        # if (names(temp.coefs)[coef_i] == "SexMTRUE") {
 #        rep(0, nrow(data.val))
        # } else
        if (names(temp.coefs)[coef_i] %in% colnames(data.val)) {
        temp.coefs[coef_i] * data.val[,names(temp.coefs)[coef_i]]
    } else if (gsub("TRUE$", "", names(temp.coefs)[coef_i]) %in% colnames(data.val)) {
        temp.coefs[coef_i] * data.val[,gsub("TRUE$", "", names(temp.coefs)[coef_i])]
    } else {
        rep(0, nrow(data.val))
    } })
val.linpred.gg = -rowSums(val.linpred.gg)   # Negate to bring into concordance with the direction of Co
temp = summary(fit.gg, newdata = data.val, ci = FALSE)
val.prob.gg = sapply(temp, function(x) approx(x[,1], x[,2], xout = val.prob.times, yleft = 1, yright =
colnames(val.prob.gg) = rownames(data.val)

temp.coefs = coef(fit.gg2)
val.linpred.gg2 = sapply(1:length(temp.coefs), function(coef_i) {
        # if (names(temp.coefs)[coef_i] == "SexMTRUE") {
 #        rep(0, nrow(data.val))
        # } else
        if (names(temp.coefs)[coef_i] %in% colnames(data.val)) {
        temp.coefs[coef_i] * data.val[,names(temp.coefs)[coef_i]]
    } else if (gsub("TRUE$", "", names(temp.coefs)[coef_i]) %in% colnames(data.val)) {
        temp.coefs[coef_i] * data.val[,gsub("TRUE$", "", names(temp.coefs)[coef_i])]
    } else {
        rep(0, nrow(data.val))
    } })
val.linpred.gg2 = -rowSums(val.linpred.gg2)    # Negate to bring into concordance with the direction of
temp = summary(fit.gg2, newdata = data.val, ci = FALSE)
val.prob.gg2 = sapply(temp, function(x) approx(x[,1], x[,2], xout = val.prob.times, yleft = 1, yright =
colnames(val.prob.gg2) = rownames(data.val)

val.linpred.cph = predict(fit.cph, newdata = data.val)
temp = survfit(fit.cph, newdata = data.val)
val.prob.cph = simplify2array(tapply(1:length(temp$surv), rep(names(temp$strata), temp$strata), functio

temp = predict(fit.rsf, newdata = data.val)
# val.linpred.rsf = temp£predicted
# Median survival time:
val.linpred.rsf = apply(temp$survival, 1, function(s1) {
    sfunc = approxfun(temp$time.interest, s1, yleft = 1, yright = 0, rule = 2)
    med = uniroot(function(x) sfunc(x) - 0.5, lower = min(temp$time.interest), upper = max(temp$time.int
    med
```

```
})
val.linpred.rsf = -val.linpred.rsf
val.prob.rsf = apply(temp$survival, 1, function(s1) approx(temp$time.interest, s1, xout = val.prob.times
colnames(val.prob.rsf) = rownames(data.val)

summary(coxph(Surv(Time, DSD) ~ val.linpred.gg, data.val))
```

```
## Call:
## coxph(formula = Surv(Time, DSD) ~ val.linpred.gg, data = data.val)
##
##   n= 49, number of events= 49
##
##                 coef exp(coef) se(coef)    z Pr(>|z|)
## val.linpred.gg 1.54      4.68     0.45 3.43    6e-04
##
##                 exp(coef) exp(-coef) lower .95 upper .95
## val.linpred.gg      4.68      0.214      1.94      11.3
##
## Concordance= 0.673  (se = 0.05 )
## Rsquare= 0.216   (max possible= 0.997 )
## Likelihood ratio test= 11.9  on 1 df,   p=0.000554
## Wald test            = 11.8  on 1 df,   p=0.000599
## Score (logrank) test = 12.2  on 1 df,   p=0.000485
```

```
summary(coxph(Surv(Time, DSD) ~ val.linpred.gg2, data.val))
```

```
## Call:
## coxph(formula = Surv(Time, DSD) ~ val.linpred.gg2, data = data.val)
##
##   n= 49, number of events= 49
##
##                  coef exp(coef) se(coef)    z Pr(>|z|)
## val.linpred.gg2 1.78      5.93     0.51 3.49  0.00048
##
##                  exp(coef) exp(-coef) lower .95 upper .95
## val.linpred.gg2      5.93      0.169      2.18      16.1
##
## Concordance= 0.668  (se = 0.05 )
## Rsquare= 0.216   (max possible= 0.997 )
## Likelihood ratio test= 11.9  on 1 df,   p=0.000563
## Wald test            = 12.2  on 1 df,   p=0.000483
## Score (logrank) test = 12.5  on 1 df,   p=0.00041
```

```
summary(coxph(Surv(Time, DSD) ~ val.linpred.cph, data.val))
```

```
## Call:
## coxph(formula = Surv(Time, DSD) ~ val.linpred.cph, data = data.val)
##
##   n= 49, number of events= 49
##
##                   coef exp(coef) se(coef)    z Pr(>|z|)
## val.linpred.cph 1.139     3.123    0.311 3.66  0.00025
##
##                  exp(coef) exp(-coef) lower .95 upper .95
## val.linpred.cph      3.12       0.32       1.7      5.75
```

```
##
## Concordance= 0.65  (se = 0.05 )
## Rsquare= 0.236   (max possible= 0.997 )
## Likelihood ratio test= 13.2  on 1 df,   p=0.000284
## Wald test            = 13.4  on 1 df,   p=0.000252
## Score (logrank) test = 13.9  on 1 df,   p=0.000192
```

```
summary(coxph(Surv(Time, DSD) ~ val.linpred.rsf, data.val))
```

```
## Call:
## coxph(formula = Surv(Time, DSD) ~ val.linpred.rsf, data = data.val)
##
##   n= 49, number of events= 49
##
##                    coef exp(coef) se(coef)    z Pr(>|z|)
## val.linpred.rsf 0.00811   1.00814  0.00209 3.87  0.00011
##
##                 exp(coef) exp(-coef) lower .95 upper .95
## val.linpred.rsf      1.01      0.992         1      1.01
##
## Concordance= 0.663  (se = 0.05 )
## Rsquare= 0.258   (max possible= 0.997 )
## Likelihood ratio test= 14.6  on 1 df,   p=0.000133
## Wald test            = 15  on 1 df,   p=0.000107
## Score (logrank) test = 15.5  on 1 df,   p=8.4e-05
```

```
anova(coxph(Surv(Time, DSD) ~ offset(val.linpred.gg) + val.linpred.gg, data.val))
```

```
## Analysis of Deviance Table
##  Cox model: response is Surv(Time, DSD)
## Terms added sequentially (first to last)
##
##                 loglik Chisq Df Pr(>|Chi|)
## NULL              -139
## val.linpred.gg    -139  1.47  1       0.23
```

```
anova(coxph(Surv(Time, DSD) ~ offset(val.linpred.gg2) + val.linpred.gg2, data.val))
```

```
## Analysis of Deviance Table
##  Cox model: response is Surv(Time, DSD)
## Terms added sequentially (first to last)
##
##                  loglik Chisq Df Pr(>|Chi|)
## NULL               -140
## val.linpred.gg2    -139  2.32  1       0.13
```

```
anova(coxph(Surv(Time, DSD) ~ offset(val.linpred.cph) + val.linpred.cph, data.val))
```

```
## Analysis of Deviance Table
##  Cox model: response is Surv(Time, DSD)
## Terms added sequentially (first to last)
##
##                  loglik Chisq Df Pr(>|Chi|)
## NULL               -138
## val.linpred.cph    -138   0.2  1       0.66
```

```
anova(coxph(Surv(Time, DSD) ~ offset(val.linpred.rsf) + val.linpred.rsf, data.val))

## Warning in fitter(X, Y, strats, offset, init, control, weights = weights, :  Ran out of
iterations and did not converge
## Error in fitter(X, Y, strats, offset, init, control, weights = weights, :  NA/NaN/Inf in
foreign function call (arg 6)

summary(coxph(Surv(Time, DSD) ~ offset(val.linpred.gg) + SexM + AgeCent + LocBody + SizeCent + A2 + A4,

## Call:
## coxph(formula = Surv(Time, DSD) ~ offset(val.linpred.gg) + SexM +
##     AgeCent + LocBody + SizeCent + A2 + A4, data = data.val)
##
##   n= 49, number of events= 49
##
##                 coef exp(coef) se(coef)     z Pr(>|z|)
## SexMTRUE     0.10665   1.11255  0.37675  0.28     0.78
## AgeCent     -0.00735   0.99268  0.02276 -0.32     0.75
## LocBodyTRUE  0.29902   1.34854  0.37945  0.79     0.43
## SizeCent     0.00391   1.00392  0.01002  0.39     0.70
## A2TRUE       0.30761   1.36017  0.49719  0.62     0.54
## A4TRUE       0.27581   1.31760  0.39889  0.69     0.49
##
##             exp(coef) exp(-coef) lower .95 upper .95
## SexMTRUE        1.113      0.899     0.532      2.33
## AgeCent         0.993      1.007     0.949      1.04
## LocBodyTRUE     1.349      0.742     0.641      2.84
## SizeCent        1.004      0.996     0.984      1.02
## A2TRUE          1.360      0.735     0.513      3.60
## A4TRUE          1.318      0.759     0.603      2.88
##
## Concordance= 0.672  (se = 0.05 )
## Rsquare= 0.064   (max possible= 0.997 )
## Likelihood ratio test= 3.25  on 6 df,   p=0.777
## Wald test            = 3.3  on 6 df,   p=0.77
## Score (logrank) test = 3.36  on 6 df,   p=0.763

summary(coxph(Surv(Time, DSD) ~ offset(val.linpred.gg2) + SexM + AgeCent + LocBody + SizeCent + A2 + A4,

## Call:
## coxph(formula = Surv(Time, DSD) ~ offset(val.linpred.gg2) + SexM +
##     AgeCent + LocBody + SizeCent + A2 + A4, data = data.val)
##
##   n= 49, number of events= 49
##
##                coef exp(coef) se(coef)    z Pr(>|z|)
## SexMTRUE    0.14695   1.15830  0.37675 0.39     0.70
## AgeCent     0.00300   1.00301  0.02276 0.13     0.90
## LocBodyTRUE 0.23722   1.26772  0.37945 0.63     0.53
## SizeCent    0.00846   1.00849  0.01002 0.84     0.40
## A2TRUE      0.33860   1.40298  0.49719 0.68     0.50
## A4TRUE      0.31901   1.37576  0.39889 0.80     0.42
##
##             exp(coef) exp(-coef) lower .95 upper .95
## SexMTRUE         1.16      0.863     0.554      2.42
## AgeCent          1.00      0.997     0.959      1.05
## LocBodyTRUE      1.27      0.789     0.603      2.67
## SizeCent         1.01      0.992     0.989      1.03
## A2TRUE           1.40      0.713     0.529      3.72
## A4TRUE           1.38      0.727     0.630      3.01
##
## Concordance= 0.672  (se = 0.05 )
## Rsquare= 0.081   (max possible= 0.997 )
## Likelihood ratio test= 4.13  on 6 df,   p=0.659
## Wald test            = 4.14  on 6 df,   p=0.658
## Score (logrank) test = 4.23  on 6 df,   p=0.646
```

```
summary(coxph(Surv(Time, DSD) ˜ offset(val.linpred.cph) + SexM + AgeCent + LocBody + SizeCent + A2 + A4,
```

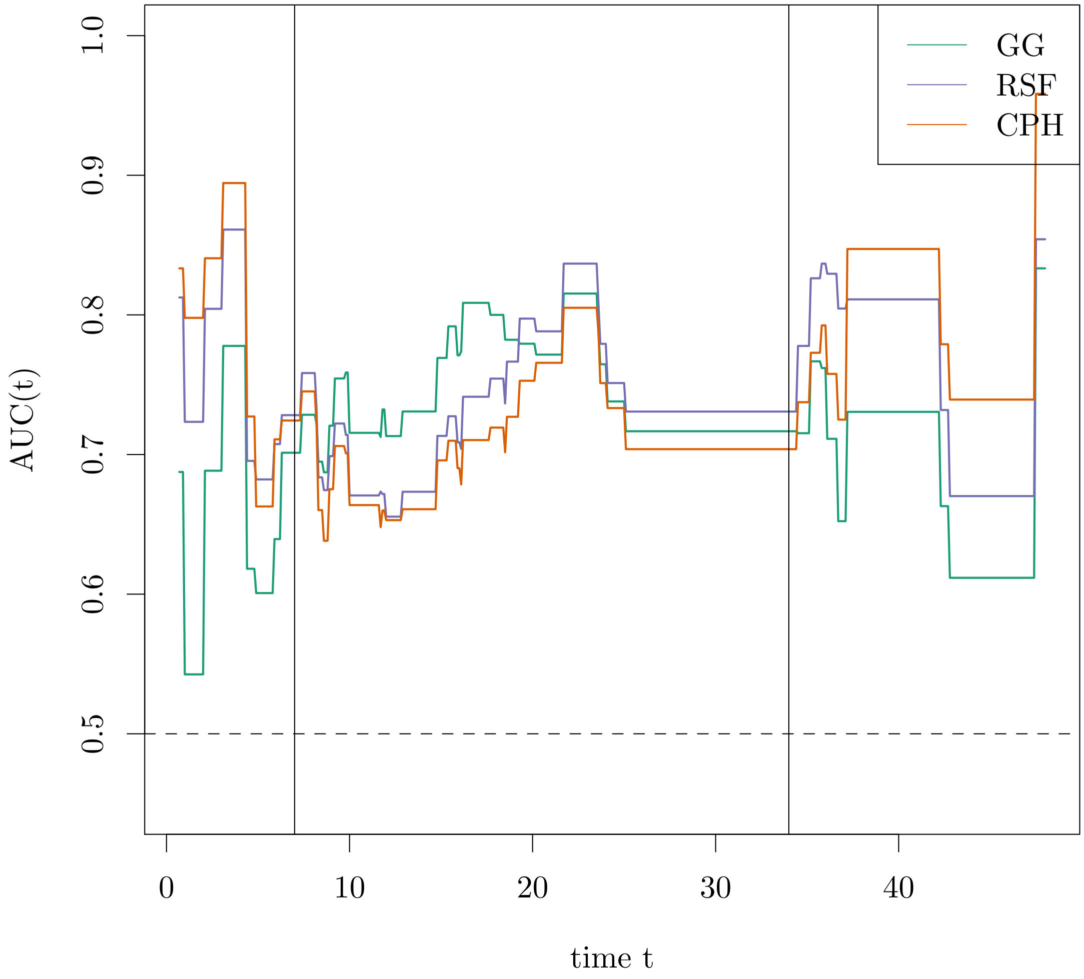
```
## Call:
## coxph(formula = Surv(Time, DSD) ˜ offset(val.linpred.cph) + SexM +
##     AgeCent + LocBody + SizeCent + A2 + A4, data = data.val)
##
##   n= 49, number of events= 49
##
##                   coef exp(coef)  se(coef)     z Pr(>|z|)
## SexMTRUE    -2.37e-01  7.89e-01  3.77e-01 -0.63     0.53
## AgeCent     -7.35e-03  9.93e-01  2.28e-02 -0.32     0.75
## LocBodyTRUE  1.28e-01  1.14e+00  3.79e-01  0.34     0.74
## SizeCent     5.99e-05  1.00e+00  1.00e-02  0.01     1.00
## A2TRUE       6.71e-02  1.07e+00  4.97e-01  0.13     0.89
## A4TRUE       1.42e-01  1.15e+00  3.99e-01  0.36     0.72
##
##             exp(coef) exp(-coef) lower .95 upper .95
## SexMTRUE        0.789      1.267     0.377      1.65
## AgeCent         0.993      1.007     0.949      1.04
## LocBodyTRUE     1.137      0.880     0.540      2.39
## SizeCent        1.000      1.000     0.981      1.02
## A2TRUE          1.069      0.935     0.404      2.83
## A4TRUE          1.152      0.868     0.527      2.52
##
## Concordance= 0.672  (se = 0.05 )
## Rsquare= 0.015   (max possible= 0.996 )
## Likelihood ratio test= 0.73  on 6 df,   p=0.994
## Wald test            = 0.72  on 6 df,   p=0.994
## Score (logrank) test = 0.72  on 6 df,   p=0.994
```

```
summary(coxph(Surv(Time, DSD) ˜ offset(val.linpred.rsf) + SexM + AgeCent + LocBody + SizeCent + A2 + A4,
```

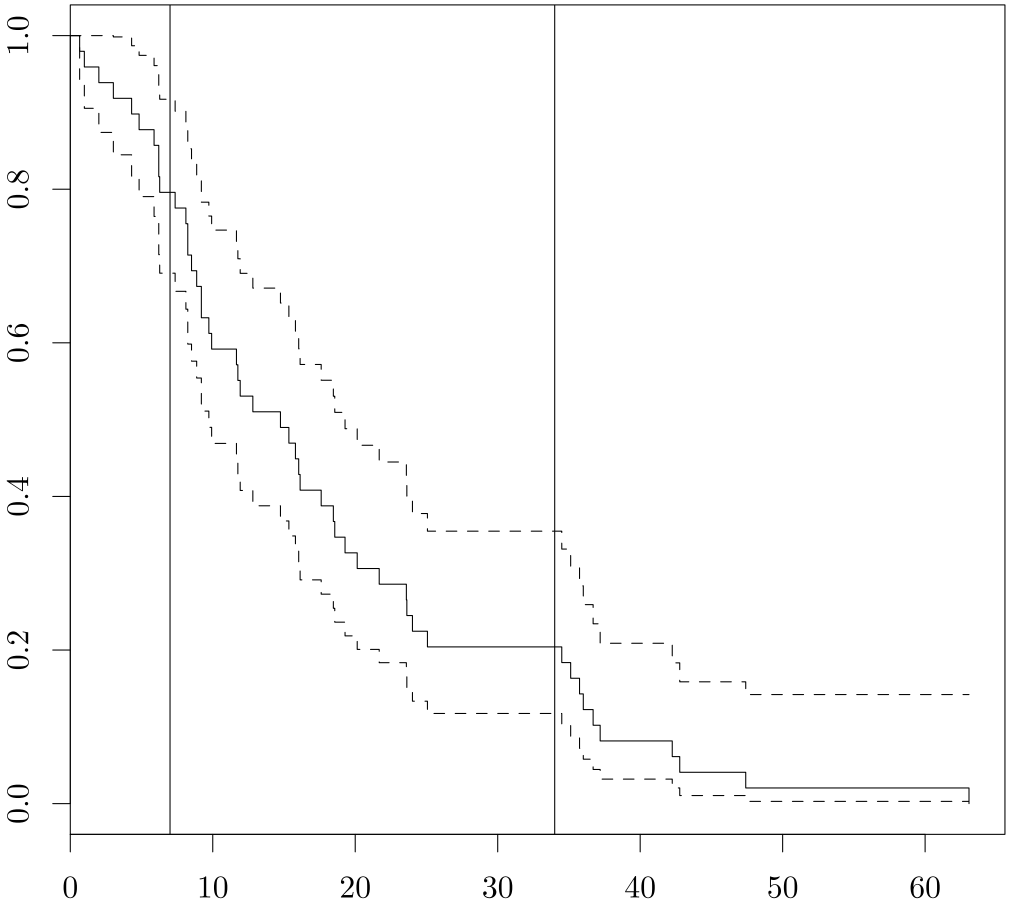
```
## Warning in fitter(X, Y, strats, offset, init, control, weights = weights, :  Ran out of
iterations and did not converge
## Error in fitter(X, Y, strats, offset, init, control, weights = weights, :  NA/NaN/Inf in
foreign function call (arg 6)
```

Cumulative-dynamic:

```
temp.times = seq(0.1, 48, 0.1)
temp.gg = timeROC(T = data.val$Time/365.25*12, delta = data.val$DSD*1, marker = val.linpred.gg, cause =
temp.gg2 = timeROC(T = data.val$Time/365.25*12, delta = data.val$DSD*1, marker = val.linpred.gg2, cause
temp.rsf = timeROC(T = data.val$Time/365.25*12, delta = data.val$DSD*1, marker = val.linpred.rsf, cause
temp.cph = timeROC(T = data.val$Time/365.25*12, delta = data.val$DSD*1, marker = val.linpred.cph, cause
plotAUCcurve(temp.gg, conf.int = FALSE, add = FALSE, col = pal["GG"])
plotAUCcurve(temp.rsf, conf.int = FALSE, add = TRUE, col = pal["RSF"])
plotAUCcurve(temp.cph, conf.int = FALSE, add = TRUE, col = pal["CPH"])
legend("topright", legend = c("GG", "RSF", "CPH"), col = pal[c("GG", "RSF", "CPH")], lty = "solid")
abline(v = c(7, 34))
```

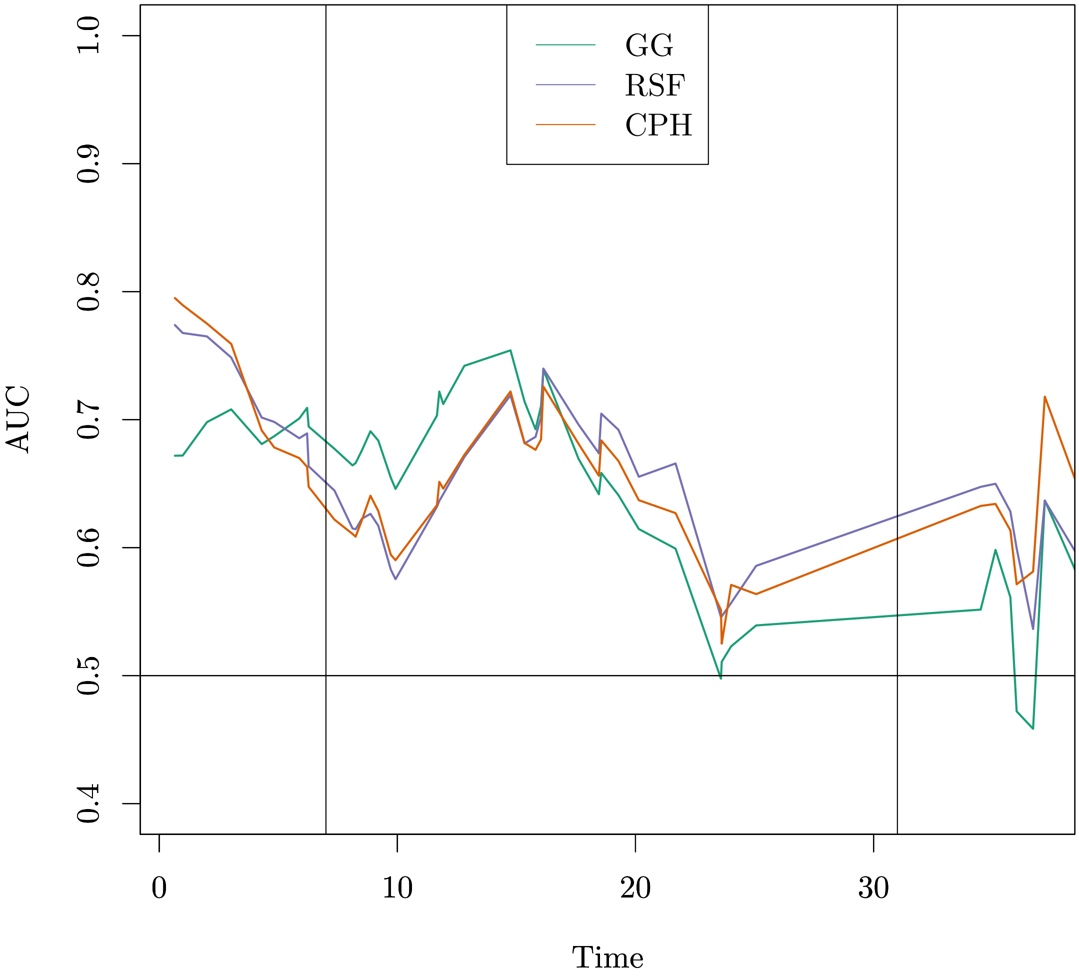


```
plot(survfit(Surv(data.val$Time/365.25*12, data.val$DSD) ~ 1))
abline(v = c(7, 34))
```



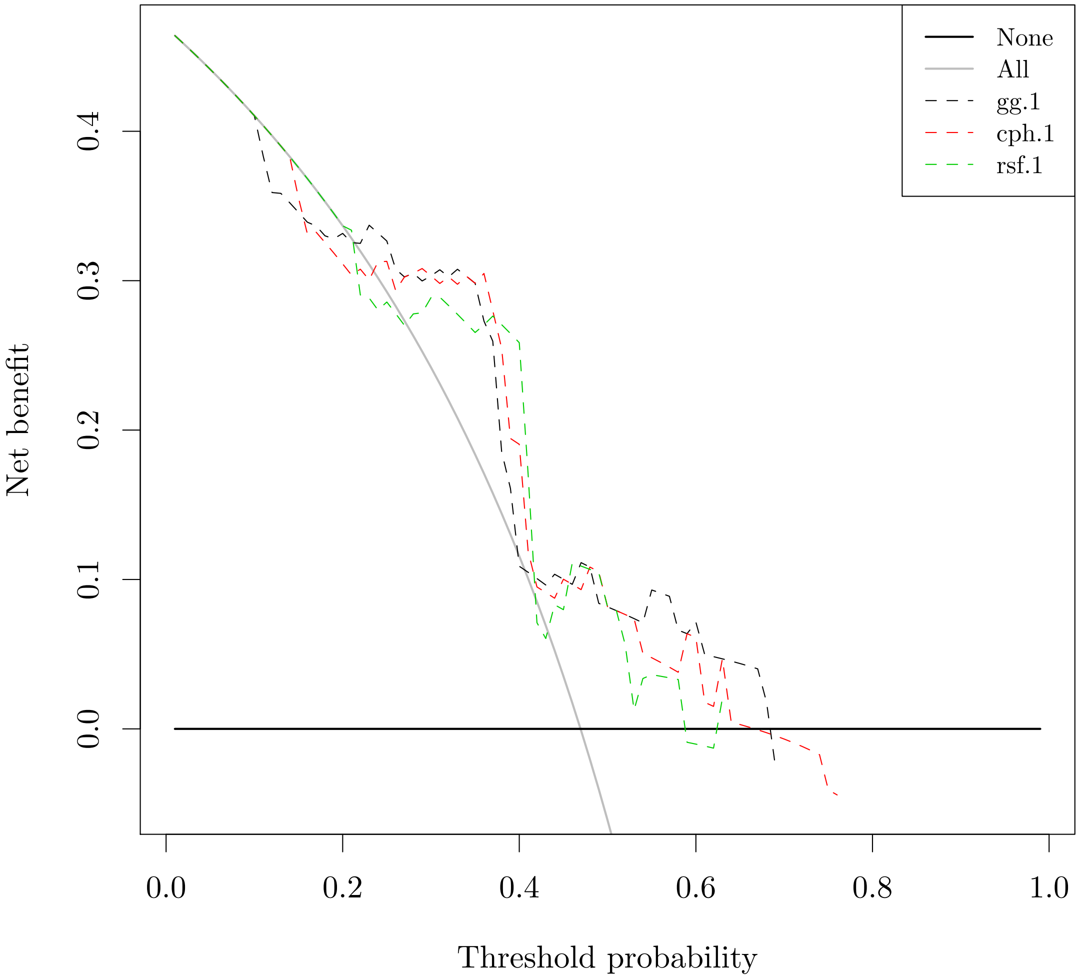
Incident-dynamic:

```
library(risksetROC)
invisible(risksetAUC(data.val$Time/365.25*12, status = data.val$DSD, marker = val.linpred.gg, tmax = 36
par(new = TRUE)
invisible(risksetAUC(data.val$Time/365.25*12, status = data.val$DSD, marker = val.linpred.rsf, tmax = 36
par(new = TRUE)
invisible(risksetAUC(data.val$Time/365.25*12, status = data.val$DSD, marker = val.linpred.cph, tmax = 36
par(new = TRUE)
legend("top", legend = c("GG", "RSF", "CPH"), col = pal[c("GG", "RSF", "CPH")], lty = "solid")
abline(v = c(7, 31))
```

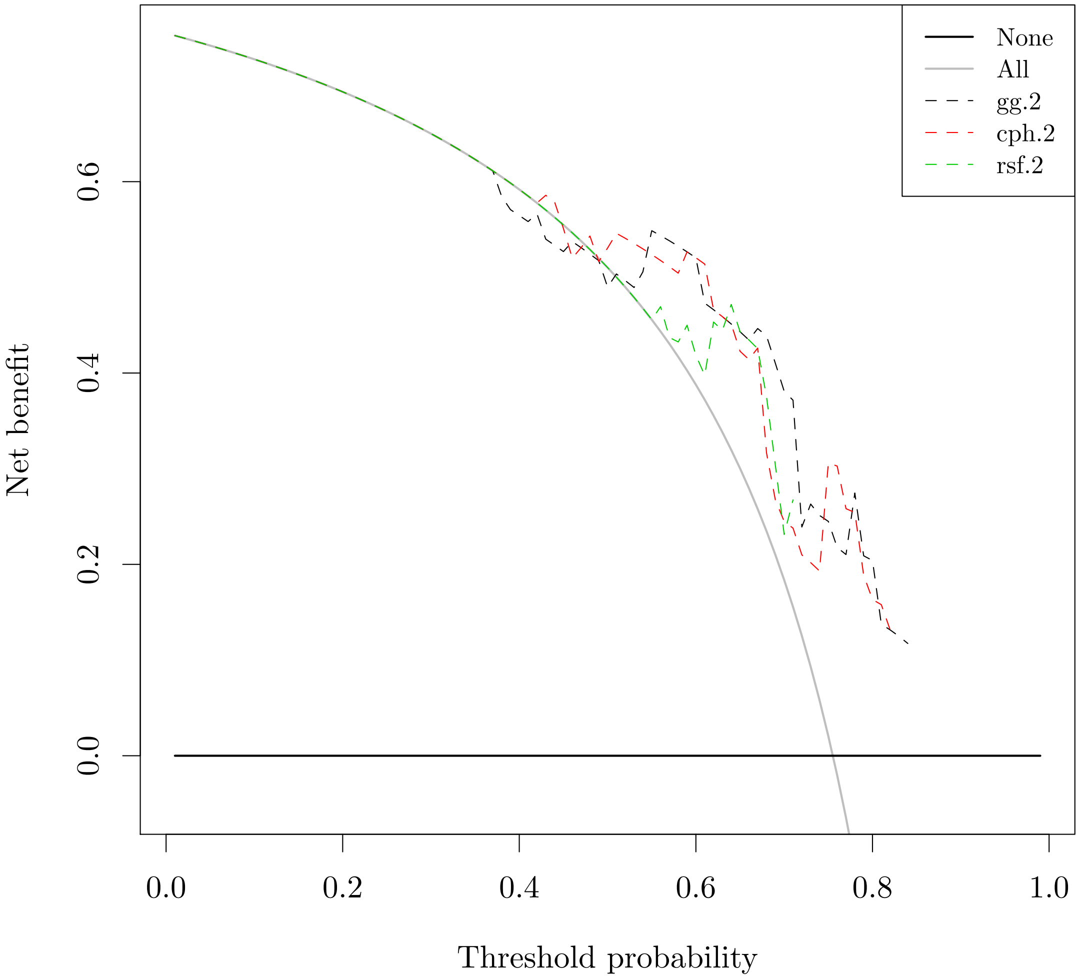


Decision curve analysis.

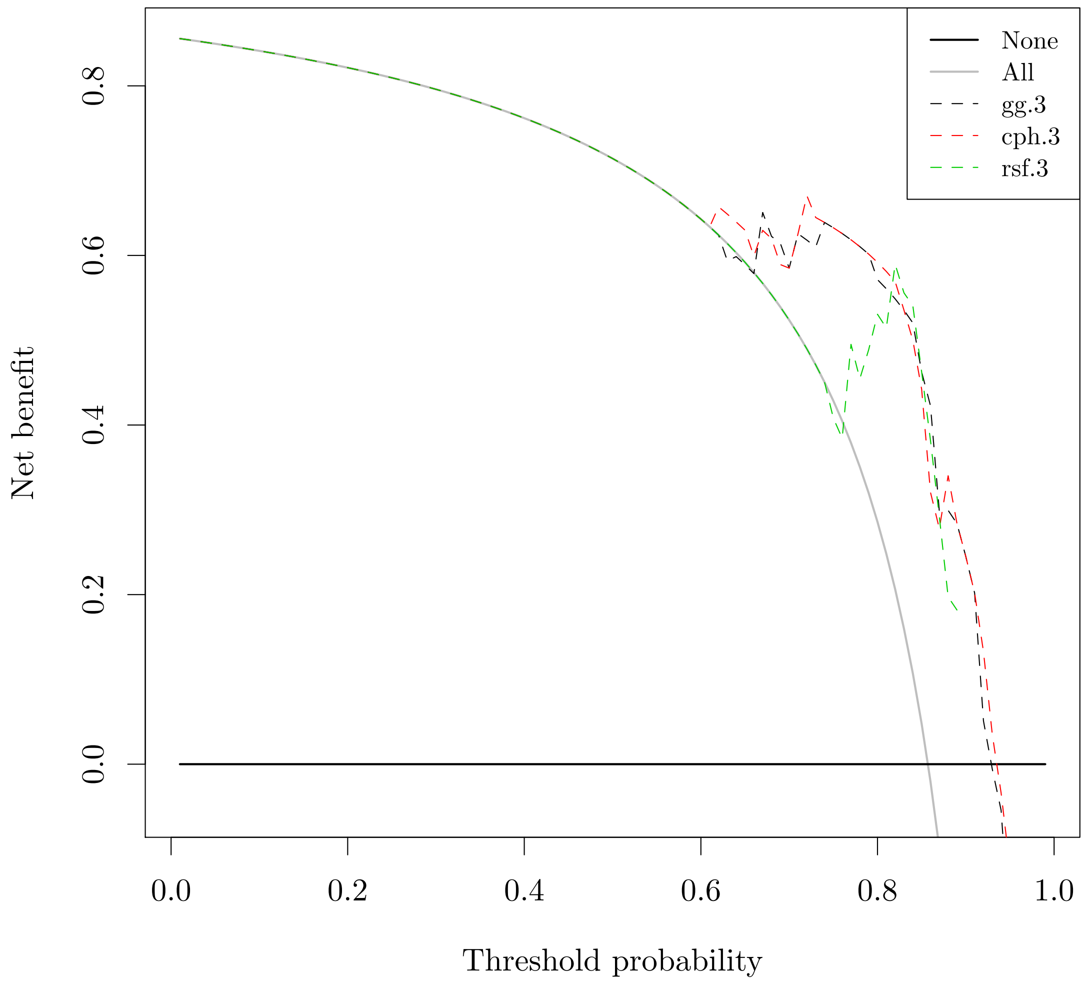
```
source("stdca.R")
temp.data = data.frame(Time = data.val$Time, DSD = data.val$DSD*1,
    gg.1 = 1-val.prob.gg[val.prob.times == 365,], gg.2 = 1-val.prob.gg[val.prob.times == 365*2,], gg.3 =
    cph.1 = 1-val.prob.cph[val.prob.times == 365,], cph.2 = 1-val.prob.cph[val.prob.times == 365*2,], cp
    rsf.1 = 1-val.prob.rsf[val.prob.times == 365,], rsf.2 = 1-val.prob.rsf[val.prob.times == 365*2,], rs
invisible(stdca(data = temp.data, outcome = "DSD", ttoutcome = "Time", predictors = c("gg.1", "cph.1", "

## [1] "gg.1: No observations with risk greater than 70% that have followup through the timepoint select
## [2] "cph.1: No observations with risk greater than 77% that have followup through the timepoint selec
## [3] "rsf.1: No observations with risk greater than 64%, and therefore net benefit not calculable in t
```



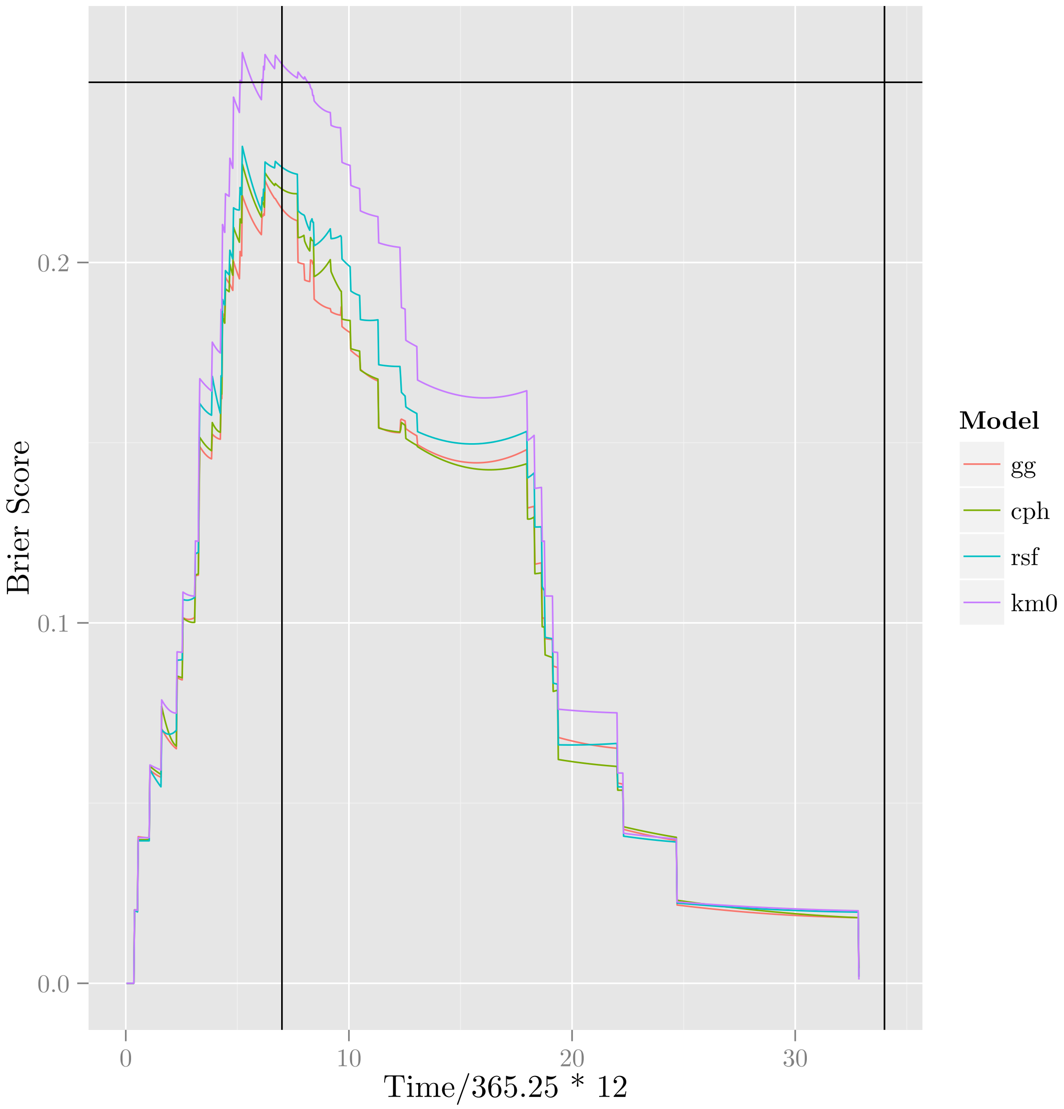
```
invisible(stdca(data = temp.data, outcome = "DSD", ttoutcome = "Time", predictors = c("gg.2", "cph.2", '

## [1] "gg.2: No observations with risk greater than 85% that have followup through the timepoint select
## [2] "cph.2: No observations with risk greater than 83% that have followup through the timepoint selec
## [3] "rsf.2: No observations with risk greater than 72% that have followup through the timepoint selec
```



```
invisible(stdca(data = temp.data, outcome = "DSD", ttoutcome = "Time", predictors = c("gg.3", "cph.3", '

## [1] "gg.3: No observations with risk greater than 97% that have followup through the timepoint select
## [2] "cph.3: No observations with risk greater than 97% that have followup through the timepoint selec
## [3] "rsf.3: No observations with risk greater than 90% that have followup through the timepoint selec
```



```
temp = sapply(list(gg = ibs_preds_gg, cph = ibs_preds_cph, rsf = ibs_preds_rsf, km0 = ibs_preds_km0), fu
temp = melt(temp)
colnames(temp) = c("Time", "Model", "BS")
ggplot(temp, aes(x = Time/365.25*12, y = BS, colour = Model)) + geom_line() + ylab("Brier Score") + geom
```



BCA bootstrapping on the differences.

```
set.seed(20150208)
ibsc_boots2 = boot(data.val, statistic = function(d, i) {
        gg = calcIBS(Surv(d$Time, d$DSD)[i,], ibs_preds_gg[i,], ibs_times, 34*365.25/12, 7*365.25/12)$ib
        cph = calcIBS(Surv(d$Time, d$DSD)[i,], ibs_preds_cph[i,], ibs_times, 34*365.25/12, 7*365.25/12)$
        rsf = calcIBS(Surv(d$Time, d$DSD)[i,], ibs_preds_rsf[i,], ibs_times, 34*365.25/12, 7*365.25/12)$
        km0 = calcIBS(Surv(d$Time, d$DSD)[i,], ibs_preds_km0[i,], ibs_times, 34*365.25/12, 7*365.25/12)$
        c(gg - km0, cph - km0, rsf - km0, gg - rsf, cph - rsf, gg - cph)
}, R = 1000)
ibsc_boots2_ci = t(sapply(1:length(ibsc_boots2$t0), function(i) boot.ci(ibsc_boots2, index = i, type = '
rownames(ibsc_boots2_ci) = c("gg-km0", "cph-km0", "rsf-km0", "gg-rsf", "cph-rsf", "gg-cph")
colnames(ibsc_boots2_ci) = c("level", "orderi1", "orderi2", "lci", "uci")
ibsc_boots2

##
## ORDINARY NONPARAMETRIC BOOTSTRAP
##
##
## Call:
```

```
## boot(data = data.val, statistic = function(d, i) {
##     gg = calcIBS(Surv(d$Time, d$DSD)[i, ], ibs_preds_gg[i, ],
##         ibs_times, 34 * 365.25/12, 7 * 365.25/12)$ibs
##     cph = calcIBS(Surv(d$Time, d$DSD)[i, ], ibs_preds_cph[i,
##         ], ibs_times, 34 * 365.25/12, 7 * 365.25/12)$ibs
##     rsf = calcIBS(Surv(d$Time, d$DSD)[i, ], ibs_preds_rsf[i,
##         ], ibs_times, 34 * 365.25/12, 7 * 365.25/12)$ibs
##     km0 = calcIBS(Surv(d$Time, d$DSD)[i, ], ibs_preds_km0[i,
##         ], ibs_times, 34 * 365.25/12, 7 * 365.25/12)$ibs
##     c(gg - km0, cph - km0, rsf - km0, gg - rsf, cph - rsf, gg -
##         cph)
## }, R = 1000)
##
##
## Bootstrap Statistics :
##     original  bias    std. error
## t1*  -21.062 0.78762       9.856
## t2*  -20.209 0.72053       9.039
## t3*  -14.505 0.34307       4.952
## t4*   -6.557 0.44455       5.798
## t5*   -5.704 0.37746       4.772
## t6*   -0.853 0.06709       2.123
```

```
ibsc_boots2_ci
```

```
##         level orderi1 orderi2     lci    uci
## gg-km0   0.95   19.71   969.3 -39.793 -2.523
## cph-km0  0.95   15.13   961.7 -38.853 -4.508
## rsf-km0  0.95   14.19   960.0 -24.557 -5.655
## gg-rsf   0.95   24.04   974.9 -17.721  5.620
## cph-rsf  0.95   16.32   963.5 -15.865  2.877
## gg-cph   0.95   37.22   985.5  -4.343  4.087
```

All models perform equivalently on the validation set. Select the simplest: gg.

Final model fitting:

```
temp = coxph(Surv(Time, DSD) ~ strata(SexM) + AgeCent + LocBody + SizeCent + SizePlus + A2 + A4, data =
sel = abs(resid(temp, type = "deviance")) <= 2.5 & apply(abs(resid(temp, type = "dfbetas")), 1, max) <=
data.all.polished = data.all[sel,]
nrow(data.all)
```

```
## [1] 249
```

```
nrow(data.all.polished)
```

```
## [1] 240
```

```
fit.final.gg = flexsurvreg(Surv(Time, DSD) ~ SexM + LocBody + SizeCent + A2 + A4,
        anc = list(
                sigma = ~ SexM,
                Q = ~ SexM),
        data = data.all.polished, dist = "gengamma")

fit.final.cph = coxph(Surv(Time, DSD) ~ strata(SexM) + LocBody + SizeCent + A2 + A4, data = data.all.pol
set.seed(20150208)
```

```
fit.final.rsf = rfsrc(Surv(Time, DSD) ~ SexM + AgeCent + LocBody + SizeCent + A2 + A4, data = data.all.p
fit.final.km0 = survfit(Surv(Time, DSD) ~ 1, data.all)
saveRDS(list(gg = fit.final.gg, km0 = fit.final.km0, cph = fit.final.cph, rsf = fit.final.rsf, data.trai

fit.final.gg

##
## Call:
## flexsurvreg(formula = Surv(Time, DSD) ~ SexM + LocBody + SizeCent +     A2 + A4, anc = list(sigma = ~
##
## Estimates:
##                  data mean  est       L95%      U95%      se
## mu                     NA    6.47851   6.18670   6.77032   0.14889
## sigma                  NA    0.75029   0.65968   0.85335   0.04927
## Q                      NA    0.02879  -0.50416   0.56173   0.27192
## SexMTRUE          0.50000    0.37324   0.07777   0.66872   0.15076
## LocBodyTRUE       0.18333   -0.21498  -0.45459   0.02464   0.12226
## SizeCent          3.55833   -0.00887  -0.01480  -0.00295   0.00302
## A2TRUE            0.15417   -0.37292  -0.61497  -0.13088   0.12349
## A4TRUE            0.75000   -0.38434  -0.58916  -0.17952   0.10450
## sigma(SexMTRUE)   0.50000   -0.24520  -0.45420  -0.03621   0.10663
## Q(SexMTRUE)       0.50000    0.76301   0.07052   1.45551   0.35332
##                  exp(est)  L95%      U95%
## mu                     NA        NA        NA
## sigma                  NA        NA        NA
## Q                      NA        NA        NA
## SexMTRUE          1.45244   1.08087   1.95174
## LocBodyTRUE       0.80656   0.63471   1.02495
## SizeCent          0.99117   0.98531   0.99706
## A2TRUE            0.68872   0.54066   0.87732
## A4TRUE            0.68090   0.55479   0.83567
## sigma(SexMTRUE)   0.78255   0.63496   0.96444
## Q(SexMTRUE)       2.14473   1.07306   4.28668
##
## N = 240,  Events: 231,  Censored: 9
## Total time at risk: 141440
## Log-likelihood = -1658, df = 10
## AIC = 3337

fit.final.cph

## Call:
## coxph(formula = Surv(Time, DSD) ~ strata(SexM) + LocBody + SizeCent +
##     A2 + A4, data = data.all.polished, model = TRUE, x = TRUE,
##     y = TRUE)
##
##
##              coef exp(coef) se(coef)    z      p
## LocBodyTRUE 0.402      1.50   0.1884 2.13 0.0330
## SizeCent    0.013      1.01   0.0049 2.64 0.0082
## A2TRUE      0.634      1.89   0.1946 3.26 0.0011
## A4TRUE      0.519      1.68   0.1637 3.17 0.0015
##
## Likelihood ratio test=47.1  on 4 df, p=1.42e-09  n= 240, number of events= 231
```

```
save.image("05_train_NSWPCN_2.rda")
```

7 Session information

```
sessionInfo()

## R version 3.1.1 (2014-07-10)
## Platform: x86_64-unknown-linux-gnu (64-bit)
##
## locale:
##  [1] LC_CTYPE=en_AU.UTF-8          LC_NUMERIC=C
##  [3] LC_TIME=en_AU.UTF-8           LC_COLLATE=en_AU.UTF-8
##  [5] LC_MONETARY=en_AU.UTF-8       LC_MESSAGES=en_AU.UTF-8
##  [7] LC_PAPER=en_AU.UTF-8          LC_NAME=en_AU.UTF-8
##  [9] LC_ADDRESS=en_AU.UTF-8        LC_TELEPHONE=en_AU.UTF-8
## [11] LC_MEASUREMENT=en_AU.UTF-8    LC_IDENTIFICATION=en_AU.UTF-8
##
## attached base packages:
## [1] parallel  methods   splines   stats     graphics  grDevices utils
## [8] datasets  base
##
## other attached packages:
##  [1] risksetROC_1.0.4      energy_1.6.2          RColorBrewer_1.0-5
##  [4] timeROC_0.2           timereg_1.8.6         mvtnorm_1.0-1
##  [7] pec_2.4.4             boot_1.3-13           MASS_7.3-35
## [10] ggplot2_1.0.0         plyr_1.8.1            reshape2_1.4
## [13] randomForestSRC_1.5.5 flexsurv_0.5          glmulti_1.0.7
## [16] rJava_0.9-6           survival_2.37-7       tikzDevice_0.8.1
## [19] knitr_1.8
##
## loaded via a namespace (and not attached):
##  [1] codetools_0.2-9  colorspace_1.2-4 deSolve_1.11     digest_0.6.4
##  [5] evaluate_0.5.5   filehash_2.2-2   foreach_1.4.2    formatR_1.0
##  [9] grid_3.1.1       gtable_0.1.2     highr_0.4        iterators_1.0.7
## [13] labeling_0.3     lava_1.3         muhaz_1.2.6      munsell_0.4.2
## [17] prodlim_1.5.1    proto_0.3-10     Rcpp_0.11.3      scales_0.2.4
## [21] stringr_0.6.2    tools_3.1.1
```