Chapter 6

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Contents


```
# install.packages("asaur")  # this must be done once
#install.packages("forestplot")  # must do this once
library(forestplot)
```

```
## Warning: package 'forestplot' was built under R version 3.5.1
```

```
## Loading required package: grid
```

```
## Loading required package: magrittr
```

```
## Loading required package: checkmate
```

```
## Warning: package 'checkmate' was built under R version 3.5.1
```

```
library(survival)
library(asaur)
```

Section 6.1 - Covariate Adjustment

Simulated dataset from Chapter 4.2, Example 4.3

```
lambda.mutant.0 <- 0.03       # control
lambda.mutant.1 <- 0.03*0.55  # treated, smaller rate
lambda.wt.0 <- 0.03*0.2       # control, wt has smaller rate than mutant
lambda.wt.1 <- 0.03*0.2*0.55  # treated

set.seed(4321)

tt.control.mutant <- rexp(25, rate=lambda.mutant.0)
tt.treat.mutant <- rexp(125, rate=lambda.mutant.1)
tt.control.wt <- rexp(125, rate=lambda.wt.0)
tt.treat.wt <- rexp(25, rate=lambda.wt.1)
ttAll <- c(tt.control.mutant, tt.treat.mutant, tt.control.wt,
    tt.treat.wt)

status <- rep(1, length(ttAll))   # all events

genotype <- c(rep("mutant", 150), rep("wt", 150))
trt <- c(rep(0, 25), rep(1, 125), rep(0, 125), rep(1, 25))
geneConfounder <- data.frame(ttAll, status, trt, genotype)
head(geneConfounder)
```

```
##       ttAll status trt genotype
## 1 34.408642      1   0   mutant
## 2  1.012941      1   0   mutant
## 3 17.566674      1   0   mutant
## 4 16.695926      1   0   mutant
## 5 19.996723      1   0   mutant
## 6 10.372558      1   0   mutant
```

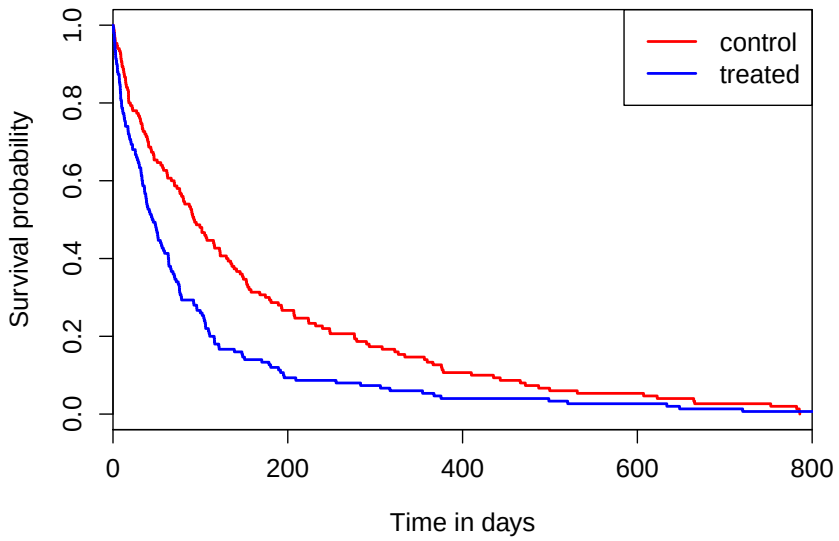
```
summary(geneConfounder)
```

```
##      ttAll              status       trt        genotype
##  Min.   :  0.3091   Min.   :1   Min.   :0.0   mutant:150
##  1st Qu.: 20.2061   1st Qu.:1   1st Qu.:0.0   wt    :150
##  Median : 63.7620   Median :1   Median :0.5
##  Mean   :125.4019   Mean   :1   Mean   :0.5
##  3rd Qu.:148.4976   3rd Qu.:1   3rd Qu.:1.0
##  Max.   :934.5510   Max.   :1   Max.   :1.0
```

```
table(genotype,trt)
```

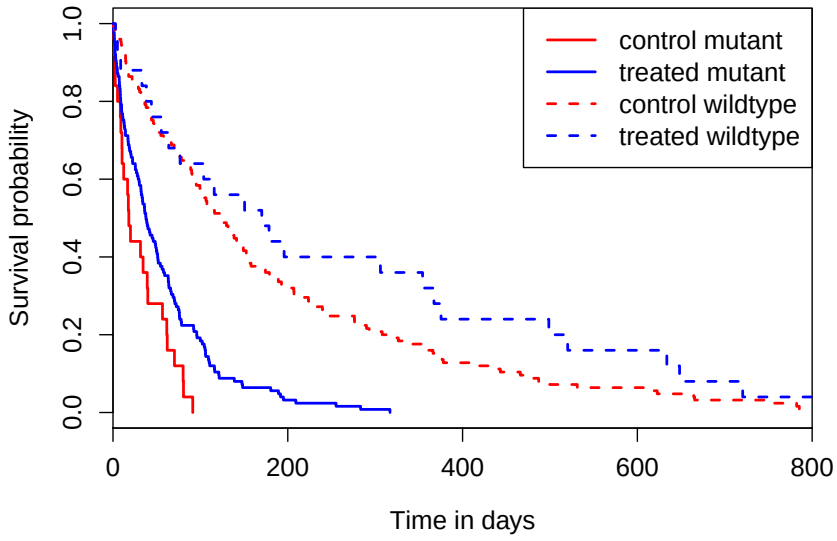
```
##          trt
## genotype   0   1
##   mutant  25 125
##   wt     125  25
```

```
plot(survfit(Surv(ttAll, status) ~ trt, data=geneConfounder),
  col=c("red", "blue"), xlab="Time in days", xlim=c(0,800),
  ylab="Survival probability", lwd=2, cex.axis=1.2, cex.lab=1.2)
legend("topright",
    legend=c("control", "treated"),
    lty=c(1, 1), col=c("red", "blue"), lwd=2, cex=1.2)
```




```
plot(survfit(Surv(ttAll, status) ~ trt, data=geneConfounder,
  subset={genotype == "mutant"}), xlim=c(0,800),
  col=c("red", "blue"), xlab="Time in days",
  ylab="Survival probability", lwd=2, cex.axis=1.2, cex.lab=1.2)

lines(survfit(Surv(ttAll, status) ~ trt, data=geneConfounder,
   subset={genotype == "wt"}),
```

```
   lty=2,  lwd=2, col=c("red", "blue"))

legend("topright",
    legend=c("control mutant", "treated mutant", "control wildtype", "treated wildtype"),
    lty=c(1, 1, 2, 2), col=c("red", "blue", "red", "blue"), lwd=2, cex=1.2)
```



Illustrate the importance of covariate adjustment

```
coxph(Surv(ttAll, status) ~ trt)
```

```
## Call:
## coxph(formula = Surv(ttAll, status) ~ trt)
##
##       coef exp(coef) se(coef)     z       p
## trt 0.464     1.590    0.117 3.96 7.6e-05
##
## Likelihood ratio test=15.5  on 1 df, p=8.2e-05
## n= 300, number of events= 300
```

```
coxph(Surv(ttAll, status) ~ trt + strata(genotype))
```

```
## Call:
```

```
## coxph(formula = Surv(ttAll, status) ~ trt + strata(genotype))
##
##       coef exp(coef) se(coef)     z      p
## trt -0.453     0.636    0.164 -2.76 0.0058
##
## Likelihood ratio test=7.66  on 1 df, p=0.00566
## n= 300, number of events= 300
```

```
coxph(Surv(ttAll, status) ~ trt + genotype)
```

```
## Call:
## coxph(formula = Surv(ttAll, status) ~ trt + genotype)
##
##               coef exp(coef) se(coef)     z      p
## trt        -0.452     0.636    0.163 -2.77 0.0056
## genotypewt -1.568     0.209    0.183 -8.59 <2e-16
##
## Likelihood ratio test=93.4  on 2 df, p=0
## n= 300, number of events= 300
```

Section 6.2 Categorical and continuous covariates

```
# Simulate data with categorical and continuous covariates
#set.seed(4321)  ## you SHOULD set your seed.  I do not know what text used
race <- factor(c("black", "black", "white", "white", "other",
          "other"))
age <- c(48, 52, 87, 82, 67, 53)
model.matrix(~ race + age)[,-1]
```

```
##   raceother racewhite age
## 1         0         0  48
## 2         0         0  52
## 3         0         1  87
## 4         0         1  82
## 5         1         0  67
## 6         1         0  53
```

```
race <- relevel(race, ref="white")
model.matrix(~ race + age)[,-1]
```

```
##   raceblack raceother age
## 1         1         0  48
## 2         1         0  52
## 3         0         0  87
## 4         0         0  82
## 5         0         1  67
## 6         0         1  53
```

```
model.matrix(~ race + age + race:age)[,-1]   #what does this mean?
```

```
##   raceblack raceother age raceblack:age raceother:age
## 1         1         0  48            48             0
## 2         1         0  52            52             0
## 3         0         0  87             0             0
## 4         0         0  82             0             0
## 5         0         1  67             0            67
## 6         0         1  53             0            53
```

```
age <- runif(n=60, min=40, max=80)
race <- factor(c(rep("white", 20), rep("black", 20),
          rep("other", 20)))

race <- relevel(race, ref="white")

log.rate.vec <- -4.5 + c(rep(0,20), rep(1,20), rep(2,20)) + age*0.05
tt <- rexp(n=60, rate=exp(log.rate.vec))
status <- rep(1, 60)

result.cox <- coxph(Surv(tt, status) ~ race + age)
summary(result.cox)
```

```
## Call:
## coxph(formula = Surv(tt, status) ~ race + age)
##
##   n= 60, number of events= 60
##
##              coef exp(coef) se(coef)     z Pr(>|z|)
## raceblack 1.03603   2.81799  0.35622 2.908  0.00363 **
## raceother 1.88924   6.61437  0.41042 4.603 4.16e-06 ***
## age       0.05451   1.05603  0.01384 3.939 8.18e-05 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
```

```
##           exp(coef) exp(-coef) lower .95 upper .95
## raceblack     2.818     0.3549     1.402     5.664
## raceother     6.614     0.1512     2.959    14.786
## age           1.056     0.9469     1.028     1.085
##
## Concordance= 0.698  (se = 0.044 )
## Rsquare= 0.399   (max possible= 0.998 )
## Likelihood ratio test= 30.57  on 3 df,   p=1.049e-06
## Wald test            = 25.43  on 3 df,   p=1.254e-05
## Score (logrank) test = 27.48  on 3 df,   p=4.676e-06
```

Section 6.3 hypothesis testing for nested models

```
library(asaur)
library(survival)
#attach(pharmacoSmoking)
levels(pharmacoSmoking$ageGroup4)
```

```
## [1] "21-34" "35-49" "50-64" "65+"
```

```
levels(pharmacoSmoking$employment)
```

```
## [1] "ft"    "other" "pt"
```

```
modelA.coxph <- coxph(Surv(ttr, relapse) ~ ageGroup4, data=pharmacoSmoking)
modelA.coxph
```

```
## Call:
## coxph(formula = Surv(ttr, relapse) ~ ageGroup4, data = pharmacoSmoking)
##
##                   coef exp(coef) se(coef)     z     p
## ageGroup435-49  0.0293    1.0297   0.3093  0.09 0.925
## ageGroup450-64 -0.7914    0.4532   0.3361 -2.36 0.019
## ageGroup465+   -0.3173    0.7281   0.4435 -0.72 0.474
##
## Likelihood ratio test=12.2  on 3 df, p=0.00666
## n= 125, number of events= 89
```

```
modelB.coxph <- coxph(Surv(ttr, relapse) ~ employment, data=pharmacoSmoking)
modelB.coxph
```

```
## Call:
## coxph(formula = Surv(ttr, relapse) ~ employment, data = pharmacoSmoking)
##
##                   coef exp(coef) se(coef)    z    p
## employmentother 0.198     1.219    0.237 0.84 0.40
## employmentpt    0.450     1.568    0.323 1.39 0.16
##
## Likelihood ratio test=2.06  on 2 df, p=0.357
## n= 125, number of events= 89
```

```
modelC.coxph <- coxph(Surv(ttr, relapse) ~ ageGroup4 + employment, data=pharmacoSmoking)
modelC.coxph
```

```
## Call:
## coxph(formula = Surv(ttr, relapse) ~ ageGroup4 + employment,
##     data = pharmacoSmoking)
##
##                     coef exp(coef) se(coef)     z      p
## ageGroup435-49  -0.130     0.878    0.321 -0.40 0.6859
## ageGroup450-64  -1.024     0.359    0.359 -2.86 0.0043
## ageGroup465+    -0.782     0.457    0.505 -1.55 0.1210
## employmentother  0.526     1.692    0.275  1.91 0.0558
## employmentpt     0.500     1.649    0.332  1.51 0.1314
##
## Likelihood ratio test=16.8  on 5 df, p=0.00492
## n= 125, number of events= 89
```

```
LA <- logLik(modelA.coxph)
LB <- logLik(modelB.coxph)
LC <- logLik(modelC.coxph)

LA; LB; LC
```

```
## 'log Lik.' -380.043 (df=3)
```

```
## 'log Lik.' -385.1232 (df=2)
```

```
## 'log Lik.' -377.7597 (df=5)
```

```
pchisq(as.numeric(2*(LC-LA)), df=2, lower.tail=F)
```

```
## [1] 0.1019462
```

```
pchisq(as.numeric(2*(LC-LB)), df=3, lower.tail=F)
```

```
## [1] 0.002065407
```

```
model.null.coxph <- coxph(Surv(ttr, relapse) ~ 1, data=pharmacoSmoking)
model.null.coxph  #gives the null model log Lik
```

```
## Call:  coxph(formula = Surv(ttr, relapse) ~ 1, data = pharmacoSmoking)
##
## Null model
##   log likelihood= -386.1533
##   n= 125
```

```
#logLik(model.null.coxph)  # this no longer works

anova(modelA.coxph, modelC.coxph)
```

```
## Analysis of Deviance Table
##  Cox model: response is  Surv(ttr, relapse)
##  Model 1: ~ ageGroup4
##  Model 2: ~ ageGroup4 + employment
##    loglik  Chisq Df P(>|Chi|)
## 1 -380.04
## 2 -377.76 4.5666  2    0.1019
```

Section 6.4 Akaike Information Criterion for non-nested models

```
AIC(modelA.coxph)
```

```
## [1] 766.086
```

```
AIC(modelB.coxph)
```

```
## [1] 774.2464
```

```
AIC(modelC.coxph)
```

```
## [1] 765.5194
```

```
summary(pharmacoSmoking)
```

```
##        id              ttr            relapse               grp
##  Min.   :  1.00   Min.   :  0.00   Min.   :0.000   combination:61
##  1st Qu.: 33.00   1st Qu.:  8.00   1st Qu.:0.000   patchOnly  :64
##  Median : 67.00   Median : 49.00   Median :1.000
```

```
##  Mean   : 66.15   Mean   : 77.44   Mean   :0.712
##  3rd Qu.: 99.00   3rd Qu.:182.00   3rd Qu.:1.000
##  Max.   :130.00   Max.   :182.00   Max.   :1.000
##       age           gender         race    employment  yearsSmoking
##  Min.   :22.00   Female:81   black   :38   ft   :72   Min.   : 9.00
##  1st Qu.:41.00   Male  :44   hispanic: 8   other:39   1st Qu.:22.00
##  Median :49.00               other   : 2   pt   :14   Median :30.00
##  Mean   :48.84               white   :77              Mean   :30.88
##  3rd Qu.:56.00                                       3rd Qu.:39.00
##  Max.   :86.00                                       Max.   :56.00
##  levelSmoking ageGroup2  ageGroup4  priorAttempts     longestNoSmoke
##  heavy:89     21-49:66   21-34:16   Min.   :   0.00   Min.   :   0.0
##  light:36     50+  :59   35-49:50   1st Qu.:   1.00   1st Qu.:   7.0
##                          50-64:48   Median :   2.00   Median :  90.0
##                          65+  :11   Mean   :  12.68   Mean   : 539.7
##                                     3rd Qu.:   5.00   3rd Qu.: 365.0
##                                     Max.   :1000.00   Max.   :6205.0
```

```
modelAll.coxph <- coxph(Surv(ttr, relapse) ~ grp + gender + race +
            employment + yearsSmoking + levelSmoking + ageGroup4 +
            priorAttempts + longestNoSmoke, data=pharmacoSmoking)

modelAll.coxph
```

```
## Call:
## coxph(formula = Surv(ttr, relapse) ~ grp + gender + race + employment +
##     yearsSmoking + levelSmoking + ageGroup4 + priorAttempts +
##     longestNoSmoke, data = pharmacoSmoking)
##
##                        coef exp(coef)  se(coef)     z      p
## grppatchOnly       0.643377  1.902896  0.221848  2.90 0.0037
## genderMale         0.019907  1.020107  0.250385  0.08 0.9366
## racehispanic      -0.399617  0.670577  0.518777 -0.77 0.4411
## raceother         -1.254273  0.285283  1.050638 -1.19 0.2325
## racewhite         -0.312569  0.731565  0.261614 -1.19 0.2322
## employmentother    0.654594  1.924361  0.282791  2.31 0.0206
## employmentpt       0.567443  1.763751  0.346384  1.64 0.1014
## yearsSmoking      -0.001123  0.998877  0.015985 -0.07 0.9440
## levelSmokinglight -0.141269  0.868255  0.272866 -0.52 0.6047
## ageGroup435-49    -0.169592  0.844009  0.382501 -0.44 0.6575
## ageGroup450-64    -1.070020  0.343002  0.505834 -2.12 0.0344
## ageGroup465+      -0.736091  0.478983  0.768563 -0.96 0.3382
## priorAttempts      0.000233  1.000233  0.001121  0.21 0.8353
```

```
## longestNoSmoke    -0.000111  0.999889  0.000126 -0.88 0.3804
##
## Likelihood ratio test=30.1  on 14 df, p=0.00737
## n= 125, number of events= 89
```

```
result.step <- step(modelAll.coxph, scope=list(upper=~ grp +
            gender + race + employment + yearsSmoking +
            levelSmoking + ageGroup4 + priorAttempts +
            longestNoSmoke, lower=~grp) )
```

```
## Start:  AIC=770.2
## Surv(ttr, relapse) ~ grp + gender + race + employment + yearsSmoking +
##     levelSmoking + ageGroup4 + priorAttempts + longestNoSmoke
##
##                   Df    AIC
## - race             3 766.98
## - yearsSmoking     1 768.20
## - gender           1 768.20
## - priorAttempts    1 768.24
## - levelSmoking     1 768.47
## - longestNoSmoke   1 769.04
## <none>               770.20
## - employment       2 772.45
## - ageGroup4        3 774.11
##
## Step:  AIC=766.98
## Surv(ttr, relapse) ~ grp + gender + employment + yearsSmoking +
##     levelSmoking + ageGroup4 + priorAttempts + longestNoSmoke
##
##                   Df    AIC
## - levelSmoking     1 764.98
## - gender           1 765.00
## - priorAttempts    1 765.01
## - yearsSmoking     1 765.04
## - longestNoSmoke   1 766.29
## <none>               766.98
## - employment       2 768.37
## - ageGroup4        3 770.16
## + race             3 770.20
##
## Step:  AIC=764.98
## Surv(ttr, relapse) ~ grp + gender + employment + yearsSmoking +
##     ageGroup4 + priorAttempts + longestNoSmoke
```

```
##
##                   Df    AIC
## - gender           1 763.00
## - priorAttempts    1 763.01
## - yearsSmoking     1 763.06
## - longestNoSmoke   1 764.29
## <none>               764.98
## - employment       2 766.37
## + levelSmoking     1 766.98
## - ageGroup4        3 768.18
## + race             3 768.47
##
## Step:  AIC=763
## Surv(ttr, relapse) ~ grp + employment + yearsSmoking + ageGroup4 +
##     priorAttempts + longestNoSmoke
##
##                   Df    AIC
## - priorAttempts    1 761.02
## - yearsSmoking     1 761.08
## - longestNoSmoke   1 762.31
## <none>               763.00
## - employment       2 764.42
## + gender           1 764.98
## + levelSmoking     1 765.00
## - ageGroup4        3 766.32
## + race             3 766.48
##
## Step:  AIC=761.02
## Surv(ttr, relapse) ~ grp + employment + yearsSmoking + ageGroup4 +
##     longestNoSmoke
##
##                   Df    AIC
## - yearsSmoking     1 759.10
## - longestNoSmoke   1 760.34
## <none>               761.02
## - employment       2 762.42
## + priorAttempts    1 763.00
## + gender           1 763.01
## + levelSmoking     1 763.02
## - ageGroup4        3 764.50
## + race             3 764.52
##
```

```
## Step:  AIC=759.1
## Surv(ttr, relapse) ~ grp + employment + ageGroup4 + longestNoSmoke
##
##                   Df    AIC
## - longestNoSmoke   1 758.42
## <none>               759.10
## - employment       2 760.42
## + yearsSmoking     1 761.02
## + gender           1 761.08
## + levelSmoking     1 761.08
## + priorAttempts    1 761.08
## + race             3 762.52
## - ageGroup4        3 766.90
##
## Step:  AIC=758.42
## Surv(ttr, relapse) ~ grp + employment + ageGroup4
##
##                   Df    AIC
## <none>               758.42
## + longestNoSmoke   1 759.10
## - employment       2 760.31
## + yearsSmoking     1 760.34
## + gender           1 760.39
## + priorAttempts    1 760.40
## + levelSmoking     1 760.41
## + race             3 761.53
## - ageGroup4        3 767.24
```

```
result.step
```

```
## Call:
## coxph(formula = Surv(ttr, relapse) ~ grp + employment + ageGroup4,
##     data = pharmacoSmoking)
##
##                    coef exp(coef) se(coef)     z      p
## grppatchOnly      0.656     1.928    0.220  2.99 0.0028
## employmentother   0.623     1.865    0.276  2.25 0.0242
## employmentpt      0.521     1.684    0.332  1.57 0.1163
## ageGroup435-49   -0.112     0.894    0.322 -0.35 0.7279
## ageGroup450-64   -1.023     0.359    0.360 -2.85 0.0044
## ageGroup465+     -0.707     0.493    0.502 -1.41 0.1587
##
## Likelihood ratio test=25.9  on 6 df, p=0.000233
```

```
## n= 125, number of events= 89
```

```
result.stepB<- step(modelAll.coxph, scope=list(upper=~ grp +
            gender + race + employment + yearsSmoking +
            levelSmoking + ageGroup4 + priorAttempts +
            longestNoSmoke, lower=~grp), direction="backward")
```

```
## Start:  AIC=770.2
## Surv(ttr, relapse) ~ grp + gender + race + employment + yearsSmoking +
##     levelSmoking + ageGroup4 + priorAttempts + longestNoSmoke
##
##                   Df    AIC
## - race             3 766.98
## - yearsSmoking     1 768.20
## - gender           1 768.20
## - priorAttempts    1 768.24
## - levelSmoking     1 768.47
## - longestNoSmoke   1 769.04
## <none>               770.20
## - employment       2 772.45
## - ageGroup4        3 774.11
##
## Step:  AIC=766.98
## Surv(ttr, relapse) ~ grp + gender + employment + yearsSmoking +
##     levelSmoking + ageGroup4 + priorAttempts + longestNoSmoke
##
##                   Df    AIC
## - levelSmoking     1 764.98
## - gender           1 765.00
## - priorAttempts    1 765.01
## - yearsSmoking     1 765.04
## - longestNoSmoke   1 766.29
## <none>               766.98
## - employment       2 768.37
## - ageGroup4        3 770.16
##
## Step:  AIC=764.98
## Surv(ttr, relapse) ~ grp + gender + employment + yearsSmoking +
##     ageGroup4 + priorAttempts + longestNoSmoke
##
##                   Df    AIC
## - gender           1 763.00
## - priorAttempts    1 763.01
```

```
## - yearsSmoking    1 763.06
## - longestNoSmoke  1 764.29
## <none>              764.98
## - employment      2 766.37
## - ageGroup4       3 768.18
##
## Step:  AIC=763
## Surv(ttr, relapse) ~ grp + employment + yearsSmoking + ageGroup4 +
##     priorAttempts + longestNoSmoke
##
##                   Df    AIC
## - priorAttempts   1 761.02
## - yearsSmoking    1 761.08
## - longestNoSmoke  1 762.31
## <none>              763.00
## - employment      2 764.42
## - ageGroup4       3 766.32
##
## Step:  AIC=761.02
## Surv(ttr, relapse) ~ grp + employment + yearsSmoking + ageGroup4 +
##     longestNoSmoke
##
##                   Df    AIC
## - yearsSmoking    1 759.10
## - longestNoSmoke  1 760.34
## <none>              761.02
## - employment      2 762.42
## - ageGroup4       3 764.50
##
## Step:  AIC=759.1
## Surv(ttr, relapse) ~ grp + employment + ageGroup4 + longestNoSmoke
##
##                   Df    AIC
## - longestNoSmoke  1 758.42
## <none>              759.10
## - employment      2 760.42
## - ageGroup4       3 766.90
##
## Step:  AIC=758.42
## Surv(ttr, relapse) ~ grp + employment + ageGroup4
##
##              Df    AIC
```

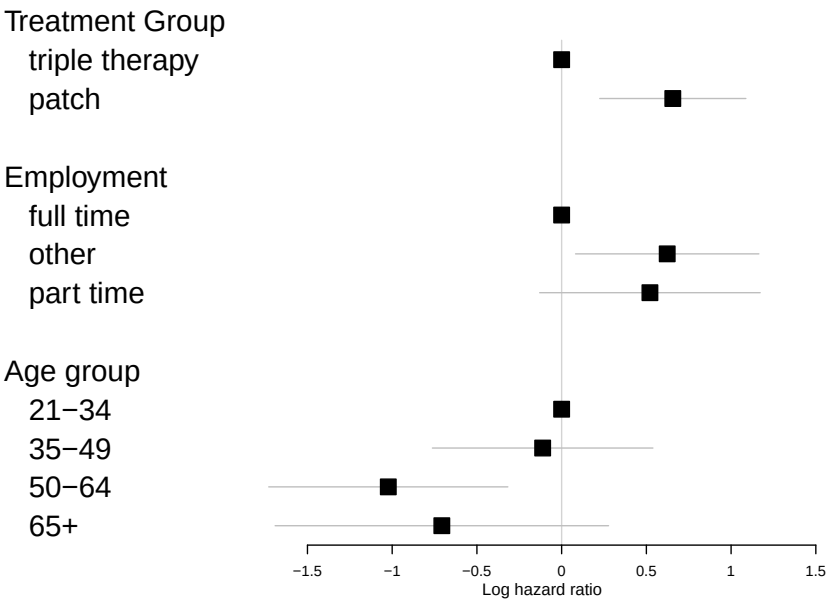
```
## <none>          758.42
## - employment  2 760.31
## - ageGroup4   3 767.24
```

```
result.stepB
```

```
## Call:
## coxph(formula = Surv(ttr, relapse) ~ grp + employment + ageGroup4,
##     data = pharmacoSmoking)
##
##                    coef exp(coef) se(coef)     z      p
## grppatchOnly      0.656     1.928    0.220  2.99 0.0028
## employmentother   0.623     1.865    0.276  2.25 0.0242
## employmentpt      0.521     1.684    0.332  1.57 0.1163
## ageGroup435-49   -0.112     0.894    0.322 -0.35 0.7279
## ageGroup450-64   -1.023     0.359    0.360 -2.85 0.0044
## ageGroup465+     -0.707     0.493    0.502 -1.41 0.1587
##
## Likelihood ratio test=25.9  on 6 df, p=0.000233
## n= 125, number of events= 89
```

```
# forest plots, Fig 6.1

coef.est <- c(NA, 0, 0.656, NA, NA, 0, 0.623, 0.521,
           NA, NA, 0, -0.112, -1.023, -0.707)
se.est <- c(NA, 0, 0.220, NA, NA, 0, 0.276, 0.332,
           NA, NA, 0, 0.332, 0.360, 0.502)
lower <- coef.est - 1.96*se.est
upper <- coef.est + 1.96*se.est


label.factors <- c("Treatment Group", "   triple therapy", "   patch", "",
   "Employment", "   full time", "   other", "   part time",
   "", "Age group", "   21-34", "   35-49", "   50-64", "   65+")

#install.packages("forestplot")  # must do this once
library(forestplot)

forestplot(label.factors,
  coef.est,
  lower,
  upper,
  zero = 0,
```

```
  cex = 1.0,
  lineheight = "auto",
  xlab = "Log hazard ratio",
  boxsize=0.4,
  xticks=c(-1.5, -1.0, -0.5,0,0.5, 1, 1.5),
  txt_gp=fpTxtGp(label=gpar(cex=1.3)),
  new_page=T)
```



Section 6.5, Smooth estimates of continuous covariates

```
modelS4.coxph <- coxph(Surv(ttr, relapse) ~ grp + employment + pspline(age, df=4), data=ph
modelS4.coxph
```

```
## Call:
## coxph(formula = Surv(ttr, relapse) ~ grp + employment + pspline(age,
##     df = 4), data = pharmacoSmoking)
```

```
##
##                                coef se(coef)     se2   Chisq   DF       p
## grppatchOnly                 0.6507   0.2210  0.2194  8.6738 1.00 0.00323
## employmentother              0.6330   0.2774  0.2750  5.2068 1.00 0.02250
## employmentpt                 0.5700   0.3403  0.3332  2.8051 1.00 0.09396
## pspline(age, df = 4), lin -0.0339   0.0102  0.0102 11.0668 1.00 0.00088
## pspline(age, df = 4), non                            4.2026 3.08 0.25164
##
## Iterations: 3 outer, 9 Newton-Raphson
##      Theta= 0.709
## Degrees of freedom for terms= 1.0 2.0 4.1
## Likelihood ratio test=27.3  on 7.02 df, p=0.000297  n= 125
```

```
termplot(modelS4.coxph, se=T, terms=3, ylabs="Log hazard")  #plot the 3rd variable
title('Penalized spline fit of age')
```