Bayesian and frequentist analysis of randomised trial adjusting for covariates

Eamonn O'Brien

01 August, 2016

1 Introduction

Many randomised controlled trials (RCTs) are analysed in a simple manner using only the randomised treatment as the independent variable. We show when the response outcome is continuous that precision of the treatment effect estimate is improved when adjusting for baseline covariates in a randomised controlled trial. We do not expect covariates to be related to the treatment assignment because of randomisation, but they may be related to the outcome, they are therefore not considered to be confounding. However, differences between the outcome which can be attributed to differences in the covariates can be removed, this results in a more precise estimate of treatment effect. This should be considered more often as sample sizes can be reduced. This is not the case for logistic models (principle of the non collapsibility of the odds ratio).

Here, we perform an investigation of adjusted and unadjusted power in the setting of RCT when there is a predictive biomarker; a predictive biomarker is one which potentially provides information that can help to guide treatment decisions. We go on to analysis the simulated trial using frequentist and Bayesian approaches.

2 Prepare for simulations

```
alpha <- 0.05
n.sims <- 500
N <- seq(from=50, to=300, by=20)        # Trial sizes to explore
pow.adj <- pow <- rep(NA, length(N))    # objects to capture power estimates
```

3 Function to investigate power for a RCT including a predictive biomarker contingent on the analyses perfomed (adjusted and unadjusted)

```
for (j in 1:length(N)){

n <- N[j]
significant.experiments.adj  <- significant.experiments.unadj <- rep(NA, n.sims)

for (i in 1: n.sims){

# covariates
effectofbiomarkerC <- -1       # Hypothesize effect of biomarker on outcome in ctrl
effectofbiomarkerT <-  1       # Hypothesize effect of biomarker on outcome in trt
effectofage <- 0               # Hypothesize effect of age on outcome
effectofsex <- 1               # Hypothesize effect of gender on outcome
```

```
effectoftreatment <- 1          # Hypothesize treatment effect on outcome

# covariate effects
baseline <- rnorm(n=n, mean=100, sd=1)          # patient baseline response
treat <- effectoftreatment*(runif(n)<0.5)       # randomised treatment effect
sex <- c(rep("F", n/2), rep("M", n/2))          # Generate "sex" covariate
age <- sample(x=18:65, size=n, replace=TRUE)    # Generate "age" covariate
biomarker <- sample(x=0:1000, size=n, replace=TRUE)/1000   #  generate biomarker score covariate

# hypothesize a treatxbiomarker interaction; diff. treatement effect depending on biomarker score
biomarker.eff <- ifelse(treat==0, effectofbiomarkerC*biomarker, effectofbiomarkerT*biomarker )

# create the outcome, with random error
Y <-  effectofsex*(sex=="M") + effectofage*age + biomarker.eff + baseline + treat + rnorm(n)

# prepare for analysis
d <- data.frame( baseline=baseline , Y=Y , treat=treat ,
                 biomarker=biomarker, sex=sex, age= age  )
dd <- datadist(d, data=d)
options(datadist="dd")

# unadjusted analysis, extract p-value for biomarker treatment interaction
f <- ols( Y ~  biomarker * treat, d)
fa <- anova(f)
p.value <- as.matrix(fa)[5,5]

# Adjusted analysis, extract p-values for biomarker x treatment interaction adjusted for covariat
f <- ols( Y ~ baseline + sex + age + biomarker * treat, d)
fa <- anova(f)
p.value.adj <- as.matrix(fa)[8,5]

# collect p values
significant.experiments.unadj [i] <- (p.value <= alpha)
significant.experiments.adj [i]   <- (p.value.adj <= alpha)

}
    # calculate power
    pow[j]     <- mean(significant.experiments.unadj)
    pow.adj[j] <- mean(significant.experiments.adj)

}
```

4 Plot the results

```
df <-  data.frame(N, pow, pow.adj)
df2 <- melt(data = df, id.vars = "N")      # melt the data to a long format and plot

g <- ggplot(data = df2, aes(x = N,
    y = value,
    color= factor(variable,  labels = c("Unadjusted", "Adjusted")))) +
    geom_line()
g <- g + ylab("Power") + xlab("Sample size") + labs(color = "Analysis")

print(g)
```

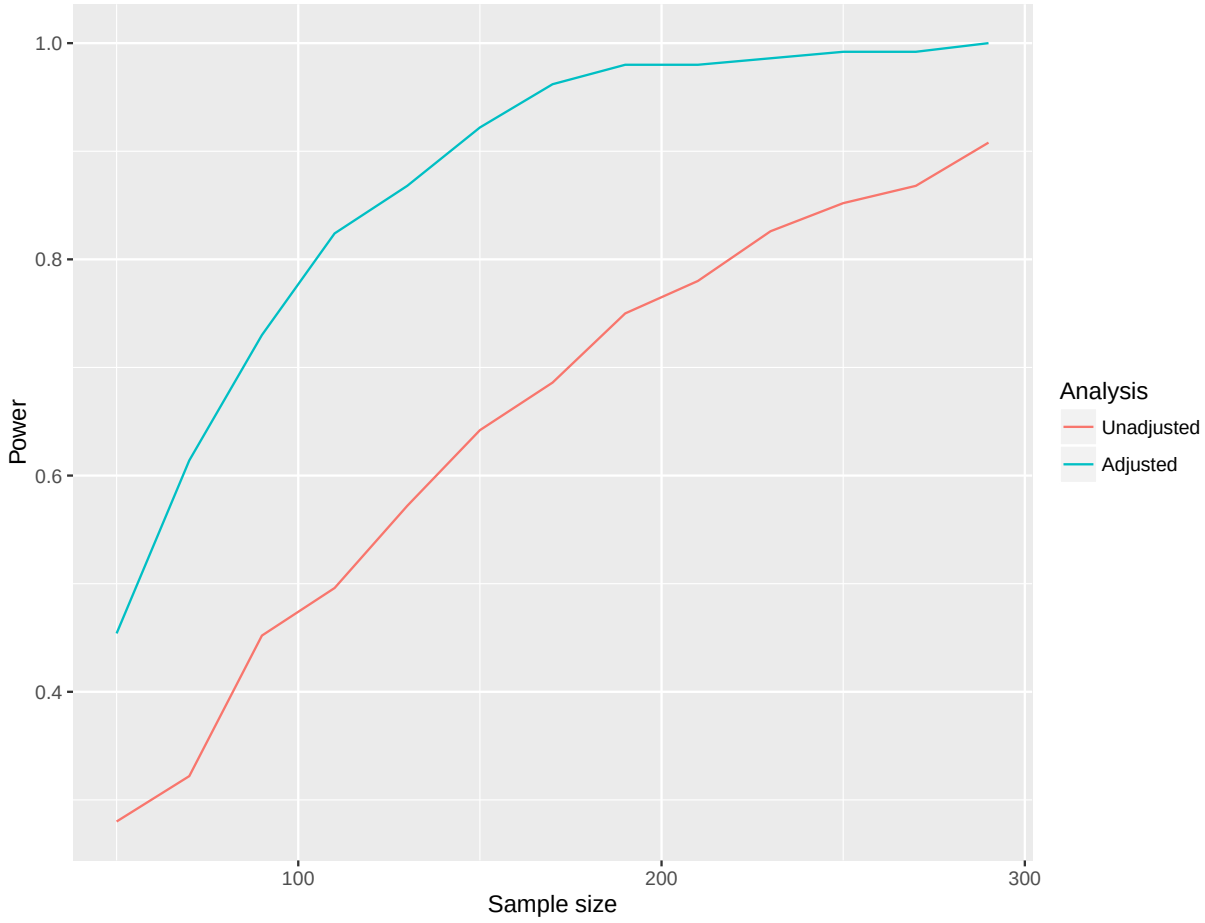


Figure 1: Profiles of power with sample size

5 Based on power estimates of adjusted analyses a trial of 150 patients takes place

```
set.seed(87564)
n <- 150

effectofbiomarkerC <- -1       # Hypothesize the "effect" of biomarker on response in ctrl
effectofbiomarkerT <-  1       # Hypothesize the "effect" of biomarker on response in trt
effectofage <- 0               # Hypothesize the "effect" of age on response
effectofsex <- 1               # Hypothesize the "effect" of gender on response
effectoftreatment <- 1         # Hypothesize the treatment effect on response

baseline <- rnorm(n=n, mean=0, sd=1)            # patient baseline response measurement
treat <- effectoftreatment*(runif(n)<0.5)       # randomised treatment effect
sex <- c(rep("F", n/2), rep("M", n/2))          # Generate "sex" covariate
age <- sample(x=18:65, size=n, replace=TRUE)    # Generate "age" covariate
# hypothesis a treat x biomarker, generate biomarker score covariate
biomarker <- sample(x=0:1000, size=n, replace=TRUE)/1000

# Create the interaction
biomarker.eff <- ifelse(treat==0, effectofbiomarkerC*biomarker, effectofbiomarkerT*biomarker )

# Create the response outcome, with random error
Y <-  effectofsex*(sex=="M") + effectofage*age + biomarker.eff + baseline + treat + rnorm(n)
```

6 Prepare for analysis, create a data frame

```
d <- data.frame( baseline=baseline , Y=Y , treat=treat ,
                 biomarker=biomarker, sex=sex, age= age  )
dd <- datadist(d, data=d) ; options(datadist="dd")
```

7 Analysis, the regression table

```
f<- ols( Y ~ baseline + sex + age + biomarker * treat  , d,  x=TRUE, y=TRUE)
print(f)
```

```
Linear Regression Model

ols(formula = Y ~ baseline + sex + age + biomarker * treat, data = d,
    x = TRUE, y = TRUE)
                Model Likelihood     Discrimination
                   Ratio Test           Indexes
Obs      150    LR chi2    216.47    R2       0.764
sigma 0.9489    d.f.            6    R2 adj   0.754
d.f.     143    Pr(> chi2) 0.0000    g        1.917
```

```
Residuals

    Min      1Q  Median      3Q     Max
-2.1229 -0.6016 -0.1466  0.5352  2.6425

                 Coef    S.E.   t     Pr(>|t|)
Intercept        -0.4744 0.3464 -1.37 0.1730
baseline          0.9801 0.0740 13.25 <0.0001
sex=M             1.1964 0.1563  7.65 <0.0001
age              -0.0002 0.0061 -0.03 0.9750
biomarker        -0.4718 0.3810 -1.24 0.2176
treat             1.6363 0.3317  4.93 <0.0001
biomarker * treat  1.1736 0.5341  2.20 0.0296
```

8 Compute analysis of variance table for the fitted model object with χ^2 statistics. Joint tests of all interaction terms in the model are also performed.

```r
an <- anova(f, main.effect=FALSE, test=c('Chisq')) # try anova(f, test=c('F') ) # F tests
print(an, 'subscripts')
```

```
              Wald Statistics          Response: Y

 Factor                                              d.f. Partial SS   MS           Chi-Square P      Test
 baseline                                              1  1.581096e+02 1.581096e+02 175.61     <.0001 1
 sex                                                   1  5.273128e+01 5.273128e+01  58.57     <.0001 2
 age                                                   1  8.844280e-04 8.844280e-04   0.00     0.9750 3
 biomarker  (Factor+Higher Order Factors)              2  4.556245e+00 2.278122e+00   5.06     0.0796 4,6
  All Interactions                                     1  4.347945e+00 4.347945e+00   4.83     0.0280 6
 treat  (Factor+Higher Order Factors)                  2  1.917280e+02 9.586398e+01 212.95     <.0001 5-6
  All Interactions                                     1  4.347945e+00 4.347945e+00   4.83     0.0280 6
 biomarker * treat  (Factor+Higher Order Factors)      1  4.347945e+00 4.347945e+00   4.83     0.0280 6
 REGRESSION                                            6  4.163693e+02 6.939488e+01 462.45     <.0001 1-6
 ERROR                                               143  1.287503e+02 9.003520e-01

Subscripts correspond to:
[1] baseline          sex=M             age               biomarker         treat             biomarker
```

9 Plot the results, show the effect of the main effect combined with all interactions involving that factor.

```
plot(an,
what=c("proportion chisq"), # also try what='proportion R2' chisqminusdf
xlab=NULL, pch=16,
rm.totals=TRUE, rm.ia=FALSE, rm.other=NULL,
sort=c("descending"), margin=NULL, pl=TRUE,
trans=NULL, ntrans=40 )
```

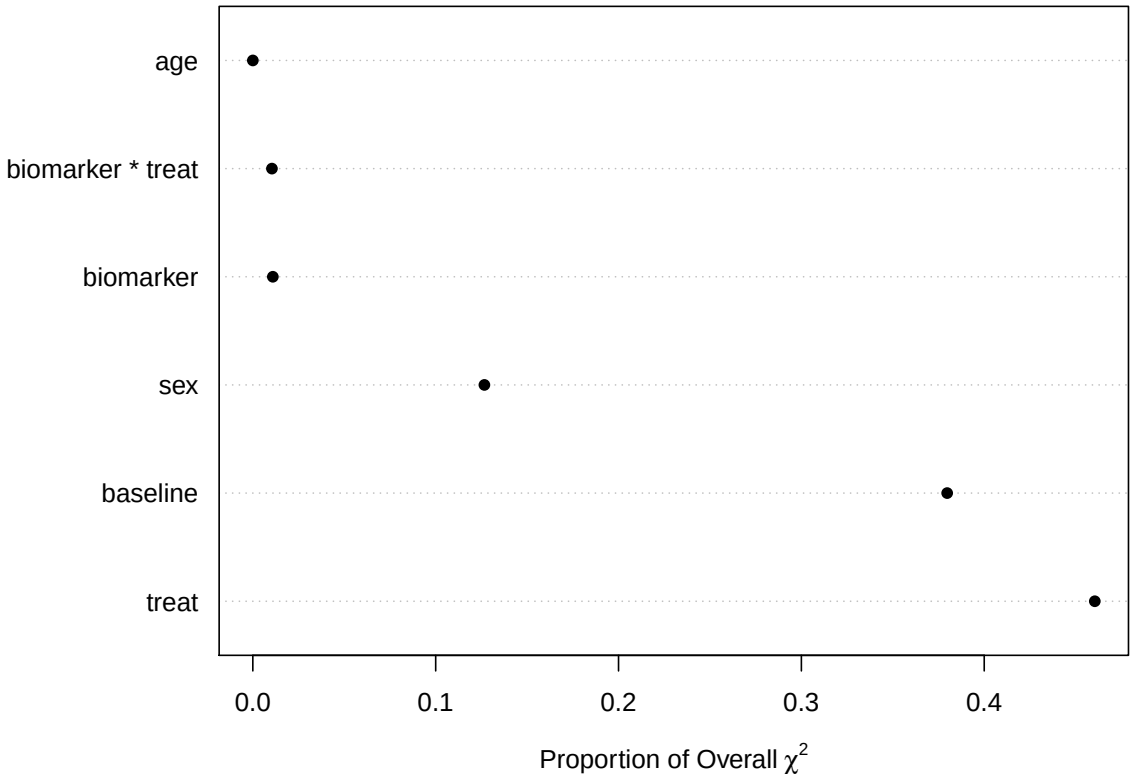


Figure 2: The default for plot(anova()) is to display the Wald Chi2 statistic minus its degrees of freedom for assessing the partial effect of each variable. Even though this is not scaled [0,1] it is probably the best method in general because it penalizes a variable requiring a large number of parameters to achieve the Chi2. If a predictor interacts with any other predictor(s), the Chi2 and partial R2 measures combine the appropriate interaction effects with main effects. For example if the model was y ~ biomarker * treatment the statistic for treatment is the combined effects of treatment as a main effect plus the effect modification that treatment provides for the biomarker effect. This is an assessment of whether there is a difference between the treatment for any biomarker score.

10 Compute predicted values and confidence limits, specify which predictors are to vary

```
plot(Predict(f),   anova=an, pval=TRUE)     # marginal main effects
```

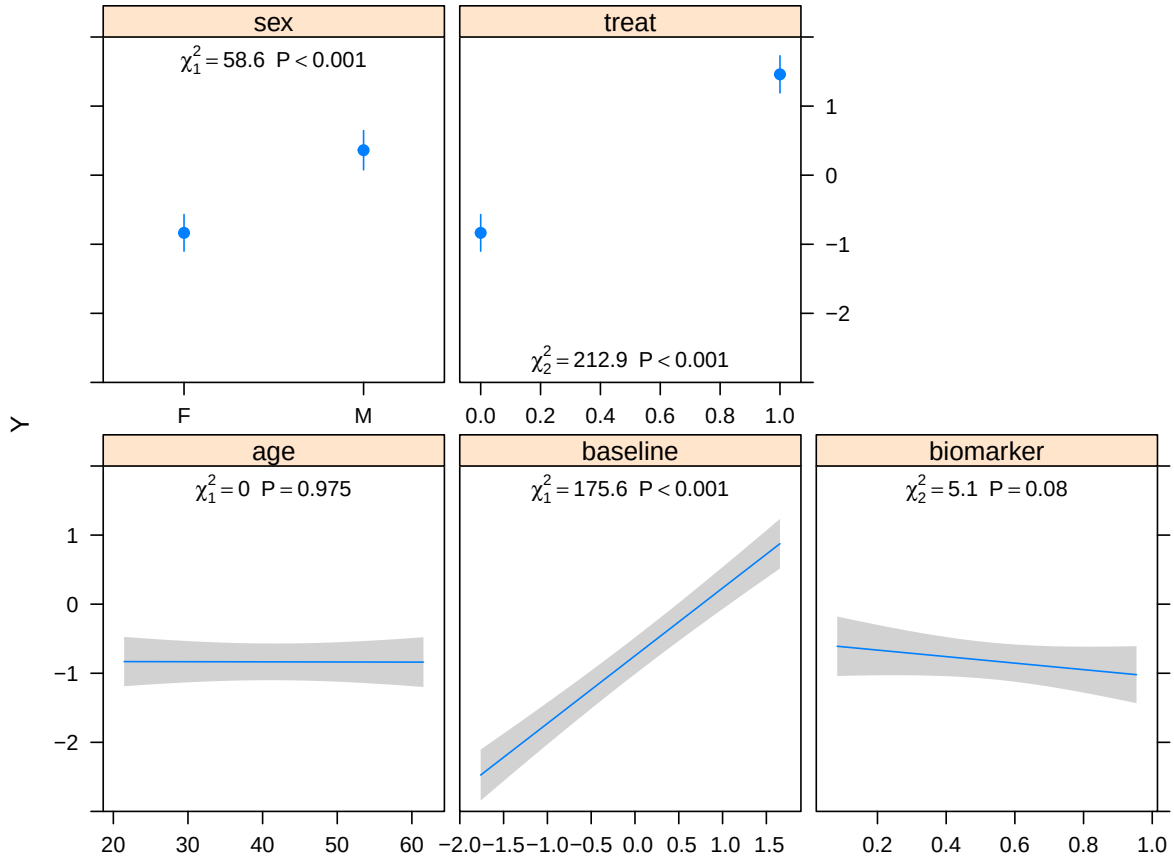


Figure 3: Show predicted values and confidence bands

11 The key result: Compute predicted values and confidence limits, specify which predictors are to vary. The effect of the biomarker in control arm on outcome moving from 0 to 1 signature score and the treatment effect on outcome when biomarker score is fixed at the median biomarker score.

```
summary(f, biomarker=c(0,1), treat=0, est.all=FALSE)
```

```
        Effects              Response : Y
```

```
 Factor    Low High Diff. Effect   S.E.    Lower 0.95 Upper 0.95
 biomarker 0   1    1     -0.47177 0.38098 -1.2248    0.28131
 treat     0   1    1      2.29470 0.15806  1.9823    2.60710

Adjusted to: biomarker=0.561 treat=0
```

12 The key result: the adjusted effect of the biomarker in the treatment arm on outcome moving from 0 to 1 signature score. The treatment effect on outcome is shown when biomarker score is fixed at the median biomarker score.

```
summary(f, biomarker=c(0,1), treat=1, est.all=FALSE)
```

```
            Effects              Response : Y

 Factor    Low High Diff. Effect  S.E.    Lower 0.95 Upper 0.95
 biomarker 0   1    1     0.70188 0.37271 -0.034848  1.4386
 treat     0   1    1     2.29470 0.15806  1.982300  2.6071

Adjusted to: biomarker=0.561 treat=1
```

```
ggplot(Predict(f,  biomarker, treat), anova=an, pval=TRUE)    # interaction
```

13 Plot the other covariate effects for information. Show sex main effect on outcome.

```
summary(f, sex=c("M","F"), est.all=FALSE)
```

```
            Effects              Response : Y

 Factor    Low High Diff. Effect S.E.    Lower 0.95 Upper 0.95
 sex - M:F 1   2    NA    1.1964 0.15633 0.88737    1.5054
```

```
ggplot(Predict(f,   sex), anova=an, pval=TRUE)
```

14 Show age main effect on outcome.

```
summary(f, age=c(18,65), est.all=FALSE)
```

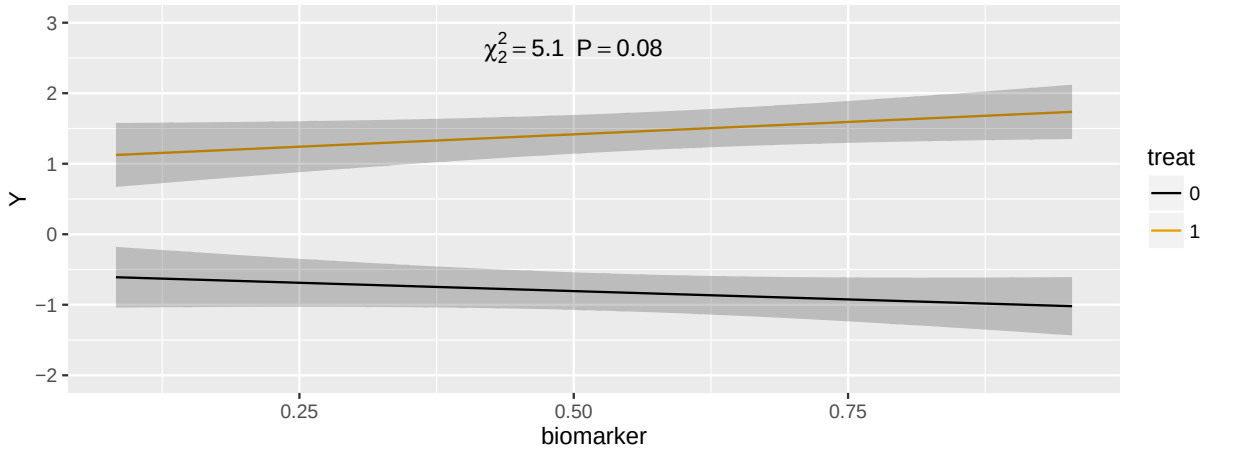


Figure 4: Biomarker effect on outcome in treatment arm

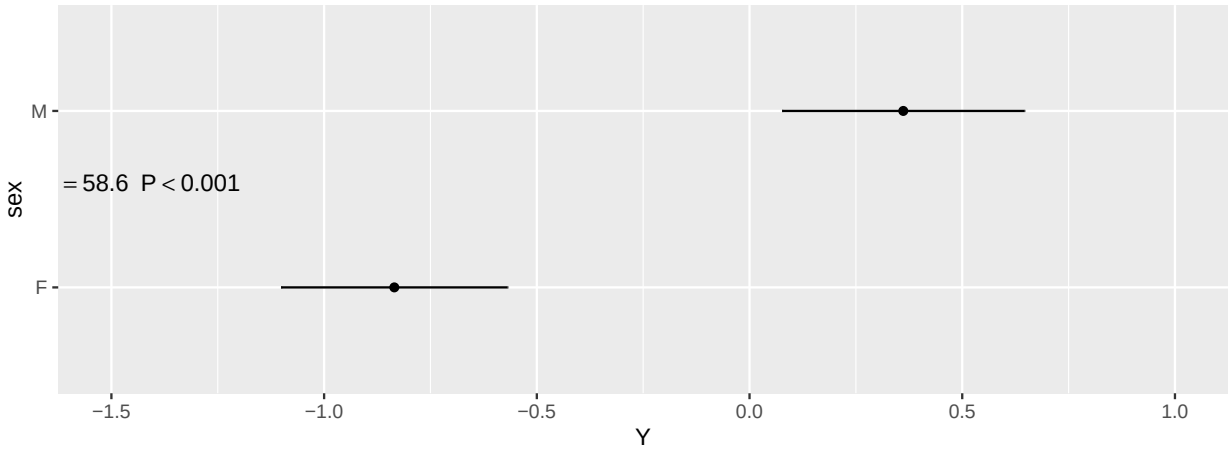
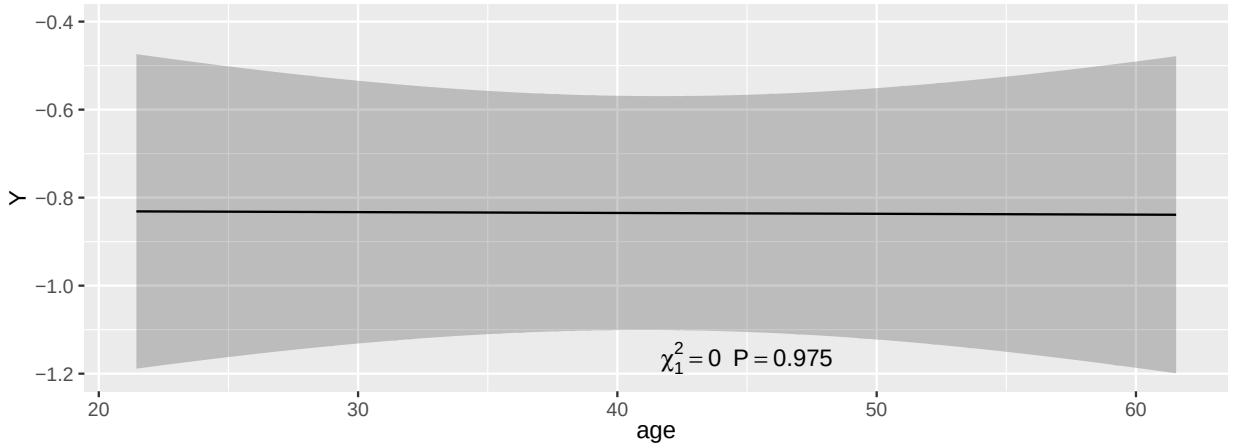


Figure 5: Sex main effect on outcome

```
            Effects              Response : Y

Factor Low High Diff. Effect     S.E.    Lower 0.95 Upper 0.95
age    18  65   47    -0.0089619 0.28594 -0.57418   0.55626
```

```
ggplot(Predict(f,  age), anova=an, pval=TRUE)
```



Adjusted to:baseline=−0.08996 sex=F biomarker=0.561 treat=0

Figure 6: Age main effect on outcome

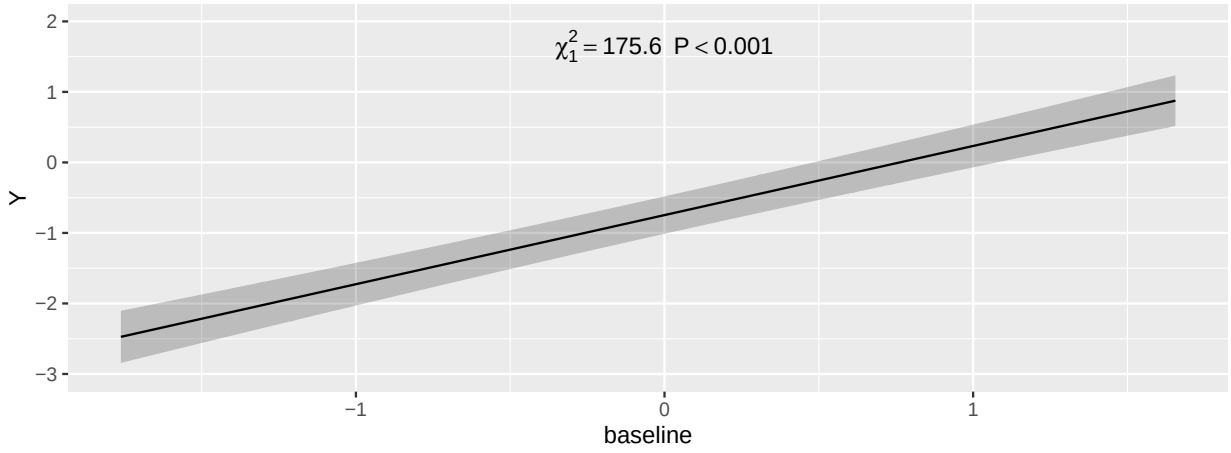
15 Show baseline main effect on outcome. A strong relationship as expected, patients with high values of the response at baseline would be expected to have high values at the outcome of the trial.

```
summary(f, baseline=c(-1,1), est.all=FALSE)
```

```
            Effects              Response : Y
```

```
Factor   Low High Diff. Effect S.E.    Lower 0.95 Upper 0.95
baseline -1  1    2     1.9601 0.14791 1.6677     2.2525
```

```
ggplot(Predict(f,  baseline), anova=an, pval=TRUE)
```



Adjusted to:sex=F age=41 biomarker=0.561 treat=0

Figure 7: Baseline main effect on outcome

16 Reproduce the regression table using the summary function, except showing the effect of the biomarker on outcome in control arm only

```
summary(f, baseline=c(0,1), sex=c("M","F") , age=c(0,1),
           biomarker=c(0,1),  treat=c(0)  )
```

```
           Effects              Response : Y

Factor    Low High Diff. Effect      S.E.      Lower 0.95 Upper 0.95
```

```
 baseline  0   1     1     0.98006000 0.0739570  0.833870  1.126200
 age       0   1     1    -0.00019068 0.0060839 -0.012217  0.011835
 biomarker 0   1     1    -0.47177000 0.3809800 -1.224800  0.281310
 treat     0   1     1     2.29470000 0.1580600  1.982300  2.607100
 sex - M:F 1   2    NA     1.19640000 0.1563300  0.887370  1.505400

Adjusted to: biomarker=0.561 treat=0
```

17 The effect with changing biomarker scores in the treatment arm.

```
summary(f, baseline=c(0,1), sex=c("M","F") , age=c(0,1),
          biomarker=c(0,1),  treat=1 )
```

```
            Effects              Response : Y

 Factor    Low High Diff. Effect      S.E.      Lower 0.95 Upper 0.95
 baseline  0   1     1     0.98006000 0.0739570  0.833870  1.126200
 age       0   1     1    -0.00019068 0.0060839 -0.012217  0.011835
 biomarker 0   1     1     0.70188000 0.3727100 -0.034848  1.438600
 treat     0   1     1     2.29470000 0.1580600  1.982300  2.607100
 sex - M:F 1   2    NA     1.19640000 0.1563300  0.887370  1.505400

Adjusted to: biomarker=0.561 treat=1
```

18 The contrast function, match the regression table for treatment effect

```
contrast(f,list(treat=1, biomarker=0, age=0, baseline=0),
           list(treat=0, biomarker=0, age=0, baseline=0))
```

```
  baseline sex age biomarker Contrast      S.E.     Lower   Upper    t Pr(>|t|)
1        0   F   0         0 1.636266 0.3316772 0.9806421 2.29189 4.93        0

Error d.f.= 143

Confidence intervals are 0.95 individual intervals
```

19 The contrast function, treatment effect when covariates held at median

```
   contrast(f,list(treat=1, biomarker=median(biomarker),
                   age=median(age), baseline=median(baseline), sex="F"),
            list(treat=0, biomarker=median(biomarker),
                 age=median(age), baseline=median(baseline), sex="F"))
```

```
  biomarker age    baseline sex Contrast      S.E.    Lower    Upper     t Pr(>|t|)
1     0.561  41 -0.08995563   F 2.294679 0.1580551 1.982253 2.607106 14.52        0

Error d.f.= 143

Confidence intervals are 0.95 individual intervals
```

```
        contrast(f, list(treat=1),list(treat=0))
```

```
     baseline sex age biomarker Contrast      S.E.    Lower    Upper     t Pr(>|t|)
1 -0.08995563   F  41     0.561 2.294679 0.1580551 1.982253 2.607106 14.52        0

Error d.f.= 143

Confidence intervals are 0.95 individual intervals
```

20 Assumption check

```
    r <- residuals(f)
    plot(r); abline(h=0)
```

```
    qqnorm(r) ; qqline(r)
```

```
   # resid(f, "dfbetas")
   # which.influence(f)
```

21 Bayesian analysis using STAN, the model statement

```
        d$sex2 <- as.numeric(ifelse(d$sex=="M", 1,0)  )

        m1 <- map( alist( Y ~ dnorm(mu, sigma),

                        mu <- b0 + b1*baseline + b2*sex2 + b3*age +
                        b4*biomarker + b5*treat + b6*biomarker*treat,

                        b0 ~ dnorm(0, 100),
                        c(b1, b2, b3, b4, b5, b6) ~ dnorm(0, 10),
                        sigma ~ dunif(0, 10) ),
                    data=d )
```

22 Bayesian analysis using STAN, frequentist and Bayesian results

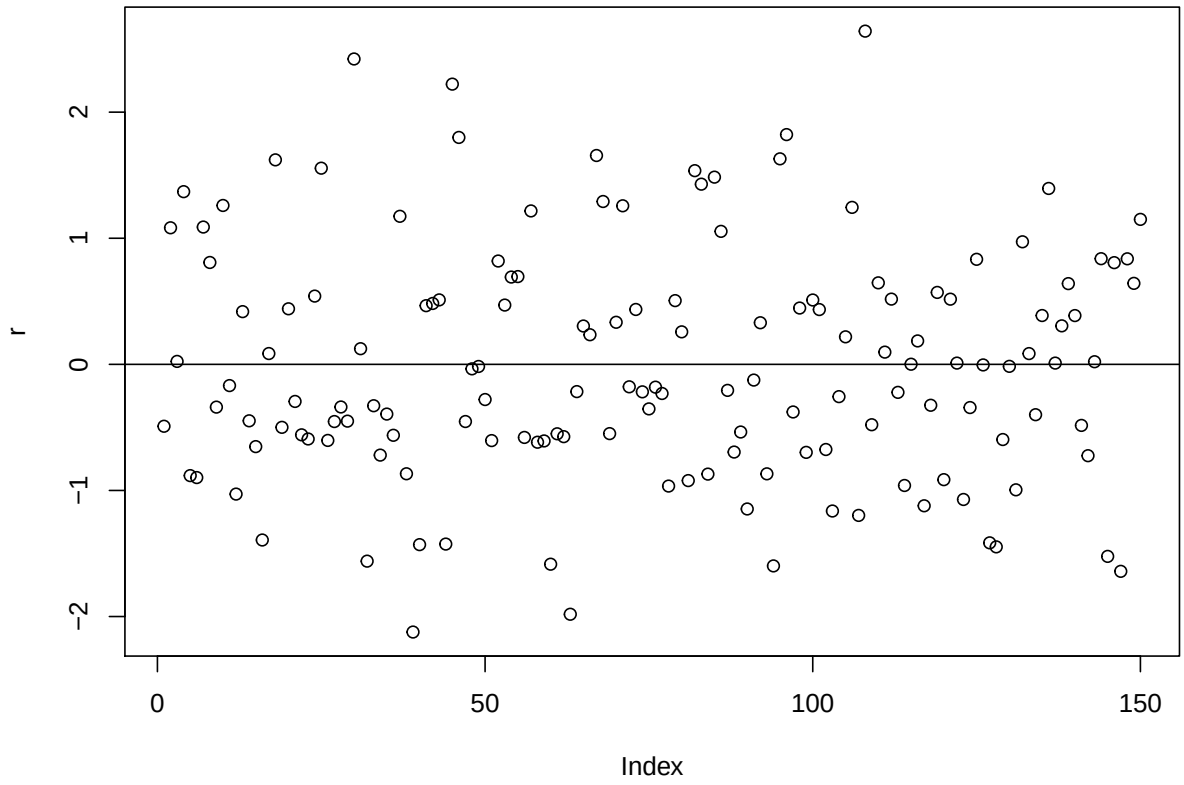


Figure 8: Check OLS assumptions

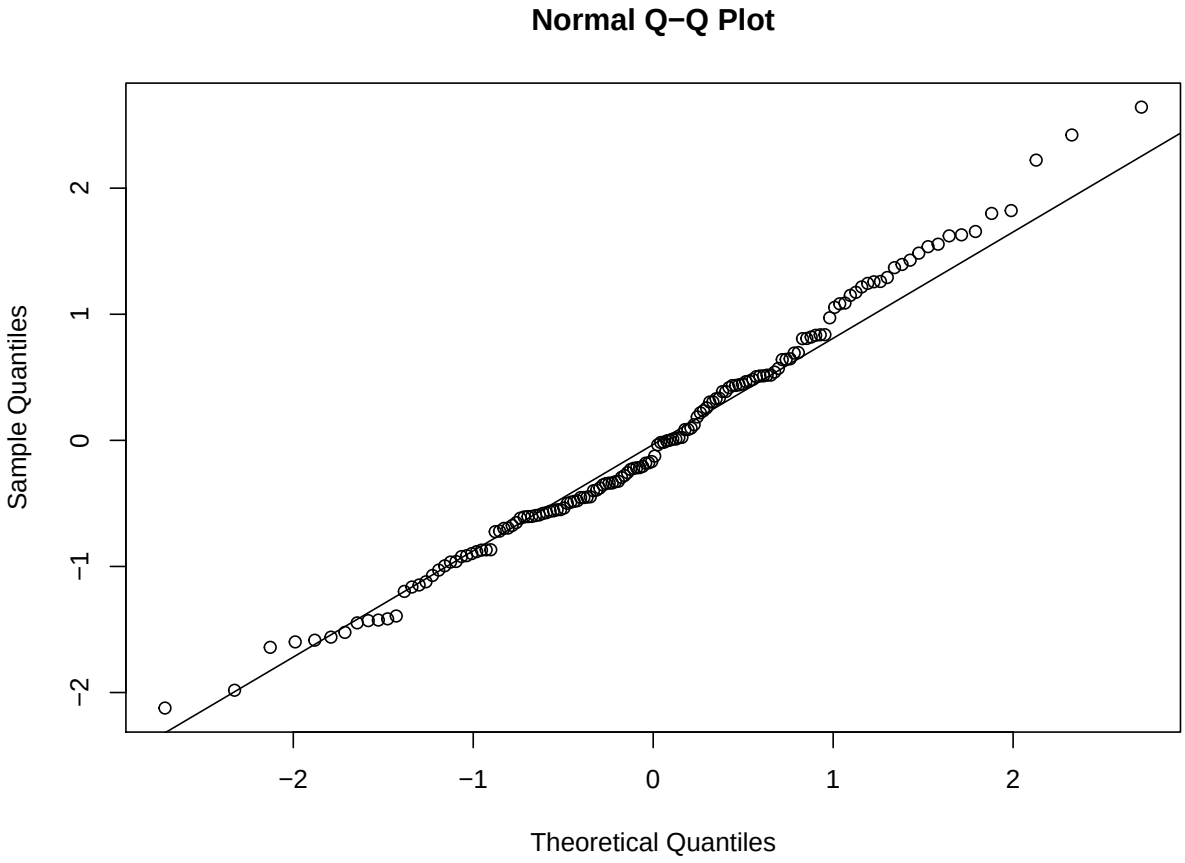


Figure 9: Check OLS assumptions

```
Linear Regression Model

ols(formula = Y ~ baseline + sex + age + biomarker * treat, data = d,
    x = TRUE, y = TRUE)
                 Model Likelihood     Discrimination
                    Ratio Test           Indexes
Obs      150    LR chi2    216.47    R2       0.764
sigma 0.9489    d.f.            6    R2 adj   0.754
d.f.     143    Pr(> chi2) 0.0000    g        1.917

Residuals

    Min      1Q  Median      3Q     Max
-2.1229 -0.6016 -0.1466  0.5352  2.6425

                  Coef    S.E.   t     Pr(>|t|)
Intercept         -0.4744 0.3464 -1.37 0.1730
baseline           0.9801 0.0740 13.25 <0.0001
sex=M              1.1964 0.1563  7.65 <0.0001
age               -0.0002 0.0061 -0.03 0.9750
biomarker         -0.4718 0.3810 -1.24 0.2176
treat              1.6363 0.3317  4.93 <0.0001
biomarker * treat  1.1736 0.5341  2.20 0.0296

       Mean StdDev  5.5% 94.5%
b0    -0.47   0.34 -1.01  0.07
b1     0.98   0.07  0.86  1.10
b2     1.20   0.15  0.95  1.44
b3     0.00   0.01 -0.01  0.01
b4    -0.47   0.37 -1.06  0.12
b5     1.64   0.32  1.12  2.15
b6     1.17   0.52  0.34  2.00
sigma  0.93   0.05  0.84  1.01
```

23 Plot the predicted effects adjusted for a specific covariate pattern. Counterfactual samples of patients are simulated and plotted. To match the frequentist prediction the Bayesian analysis is adjusted to the median values for continuous variables.

```r
par(mfrow=c(1,2))

P.biomarker <- seq( from=0 , to=1, length.out=75 ) # Assess effect across this range
P.baseline <- mean( d$baseline )                   # Hold Baseline at mean
P.sex <- 1                                         # Hold sex at MALE
P.age <- mean(d$age)                               # Hold age at mean

# use these to match the rms prediction output
P.baseline <- median(d$baseline)                   # duplicate rms
```

```r
P.age <- median(d$age)
P.sex <- 0

pred.data1 <- data.frame(                          # Make predictions for this dataset
  biomarker=P.biomarker,
  baseline=P.baseline,
  sex2=P.sex,
  age=P.age,
  treat=0                                          # Treatment 0
)

# compute counterfactual mean response (mu1)
mu1 <- link( m1 , data=pred.data1 )  # default 1000
mu.mean <- apply( mu1 , 2 , mean )
mu.PI <- apply( mu1 , 2 , PI )

# simulate counterfactual response outcomes
R.sim1 <- sim( m1 , data=pred.data1 , n=1e4 )
R.PI <- apply( R.sim1 , 2 , PI )

# display predictions, hiding raw data with type="n"
plot( Y ~ biomarker , data=d , type="n" )
mtext( "treatment 0" )
lines( P.biomarker , mu.mean )
shade( mu.PI , P.biomarker , col= col.alpha("blue", 0.15))
shade( R.PI ,  P.biomarker , col= col.alpha("purple", 0.15))
points(R.sim1[1,] ~ P.biomarker)

# repeat all again but for the treatment arm
pred.data2 <- data.frame(
  biomarker=P.biomarker,
  baseline=P.baseline,
  sex2=P.sex,
  age=P.age,
  treat=1                                          # Treatment 1
)

# compute counterfactual mean response (mu2)
mu2 <- link( m1 , data=pred.data2 )
mu.mean <- apply( mu2 , 2 , mean )
mu.PI <- apply( mu2 , 2, PI )

# simulate counterfactual response outcomes
R.sim2 <- sim( m1 , data=pred.data2 , n=1e4 )
R.PI <- apply( R.sim2 , 2 , PI )

# display predictions, hiding raw data with type="n"
plot( Y ~ biomarker , data=d , type="n" )
mtext( "treatment 1" )
lines( P.biomarker , mu.mean )
shade( mu.PI , P.biomarker , col= col.alpha("blue", 0.15))
shade( R.PI ,  P.biomarker , col= col.alpha("purple", 0.15))
```

```
    points(R.sim2[1,] ~ P.biomarker)
    mtext(paste("Plot of the predicted effects with simulated patients in each treatment group,\n adj
    side = 3, line = -2, outer = TRUE)
```

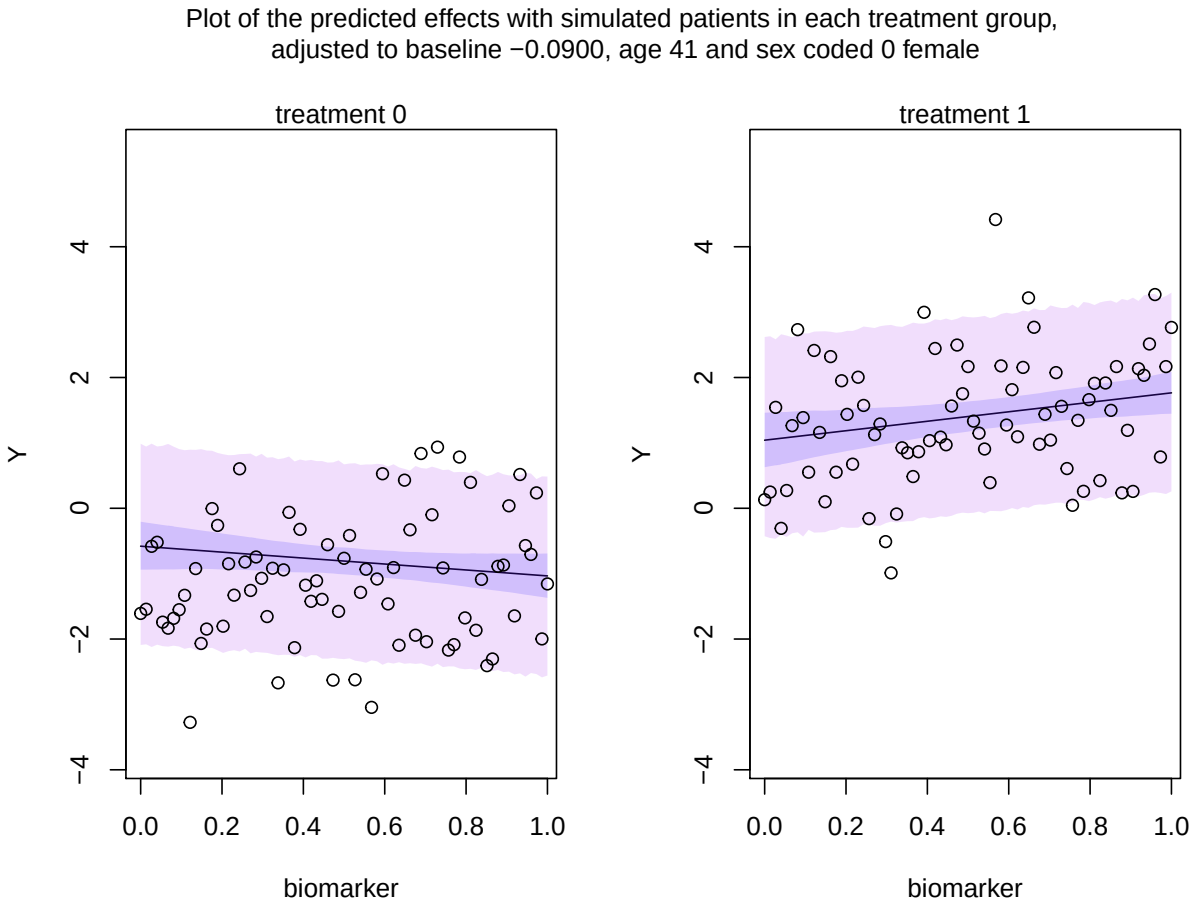


Figure 10: Predicted effects (Statistical Rethinking page 129)

```
    par(mfrow=c(1,1))

# plot(precis(m1))
```

24 Plot the predicted teatment effects, showing treatment effect modification with biomarker. Counterfactual samples of patients are simulated and plotted. Adjusted to baseline -0.0900, age 41 and sex coded 0 female

```
    mu.diff <- mu2 - mu1
    r.diff <- R.sim2 - R.sim1
```

```
mu.mean <- apply( mu.diff,  2 , mean)
mu.PI <-   apply( mu.diff , 2 , PI)
R.PI <-    apply( r.diff , 2 , PI)

plot( Y ~ biomarker , data=d , type="n" , ylab="Treatment difference trt-ctrl" )
text( "Difference in treatment effect with biomarker score" )
lines( P.biomarker , mu.mean )
shade( mu.PI , P.biomarker , col= col.alpha("blue", 0.15))
shade( R.PI ,  P.biomarker ,  col= col.alpha("purple", 0.15))
x <- sample(1:1000,1)
points(r.diff[x,] ~ P.biomarker)
abline(h=0)
```

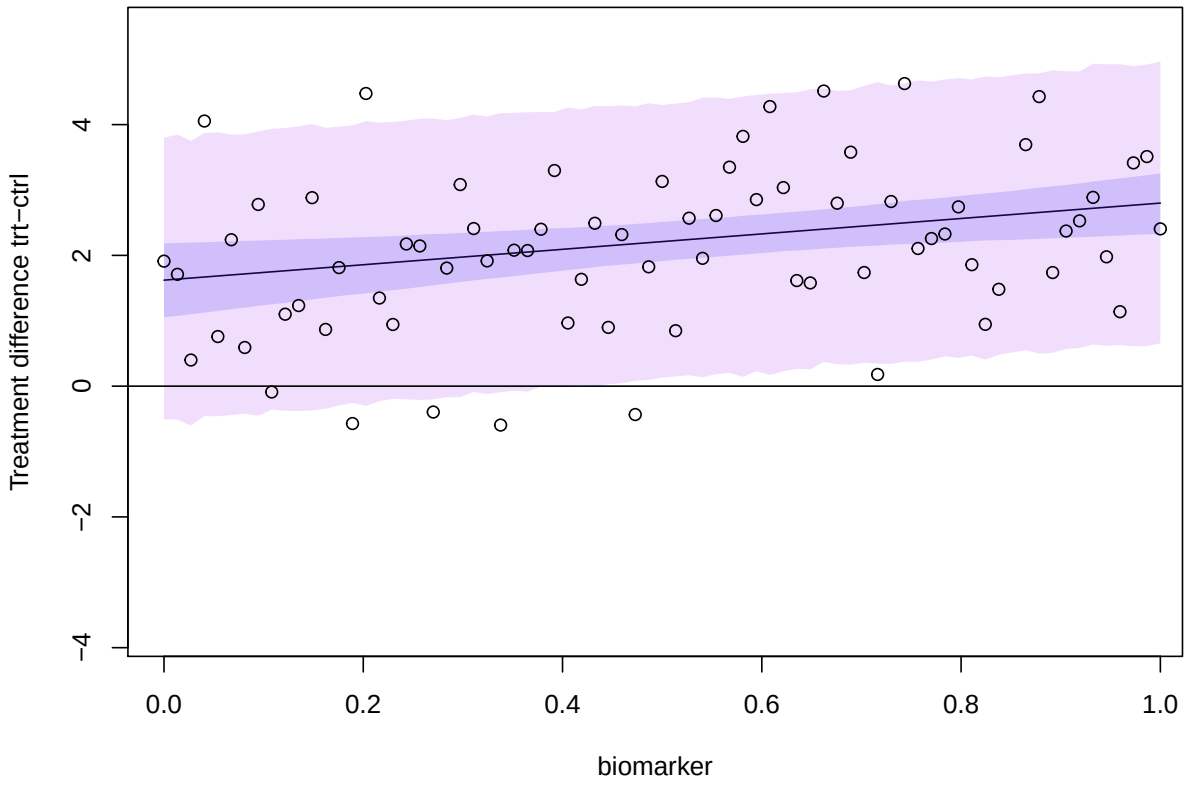
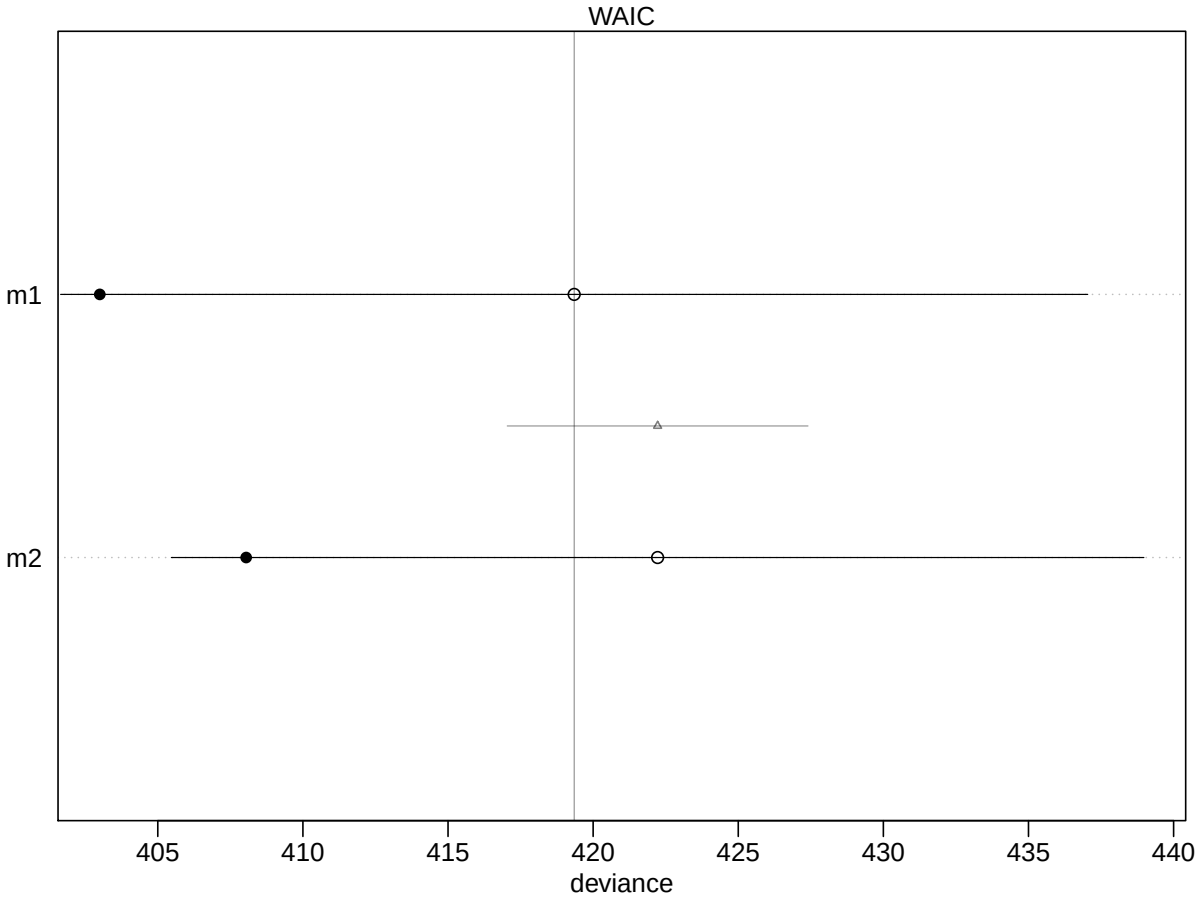


Figure 11: Predicted effects (Statistical Rethinking page 129)

25 Model comparison with main effects model m2. The interaction model's (m1) weight means there is probability of 0.81 that the model will make the best predictions on new data, conditional on the set of models considered.

```
    WAIC pWAIC dWAIC weight    SE  dSE
m1 419.3   8.2   0.0   0.81 17.70   NA
m2 422.2   7.1   2.9   0.19 16.76 5.18
```



26 Assumption check

```
pairs(m1)
```

```
post <-extract.samples(m1)
par(mfrow=c(2,4))
for ( i in 1:8 )  { plot(post[,i] , type='l', main=names(post)[i]) }
```

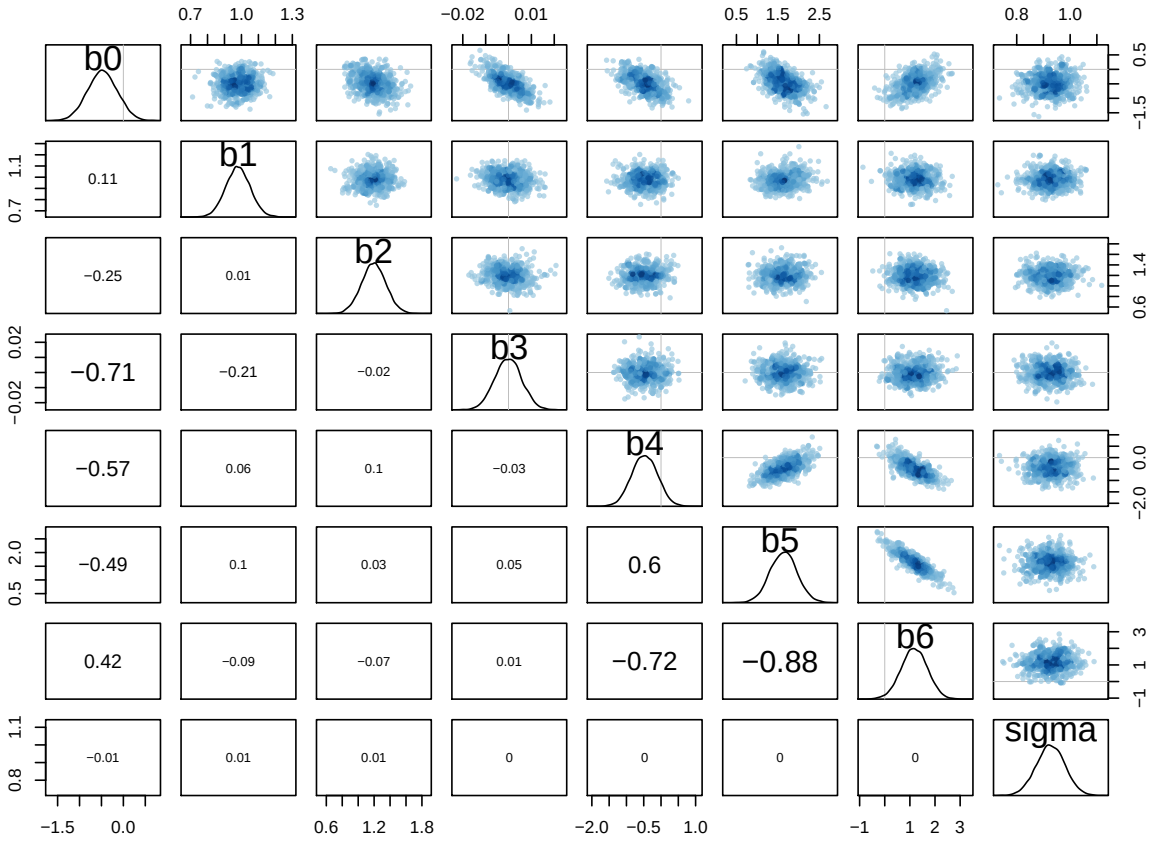


Figure 12: Check chains are mixing

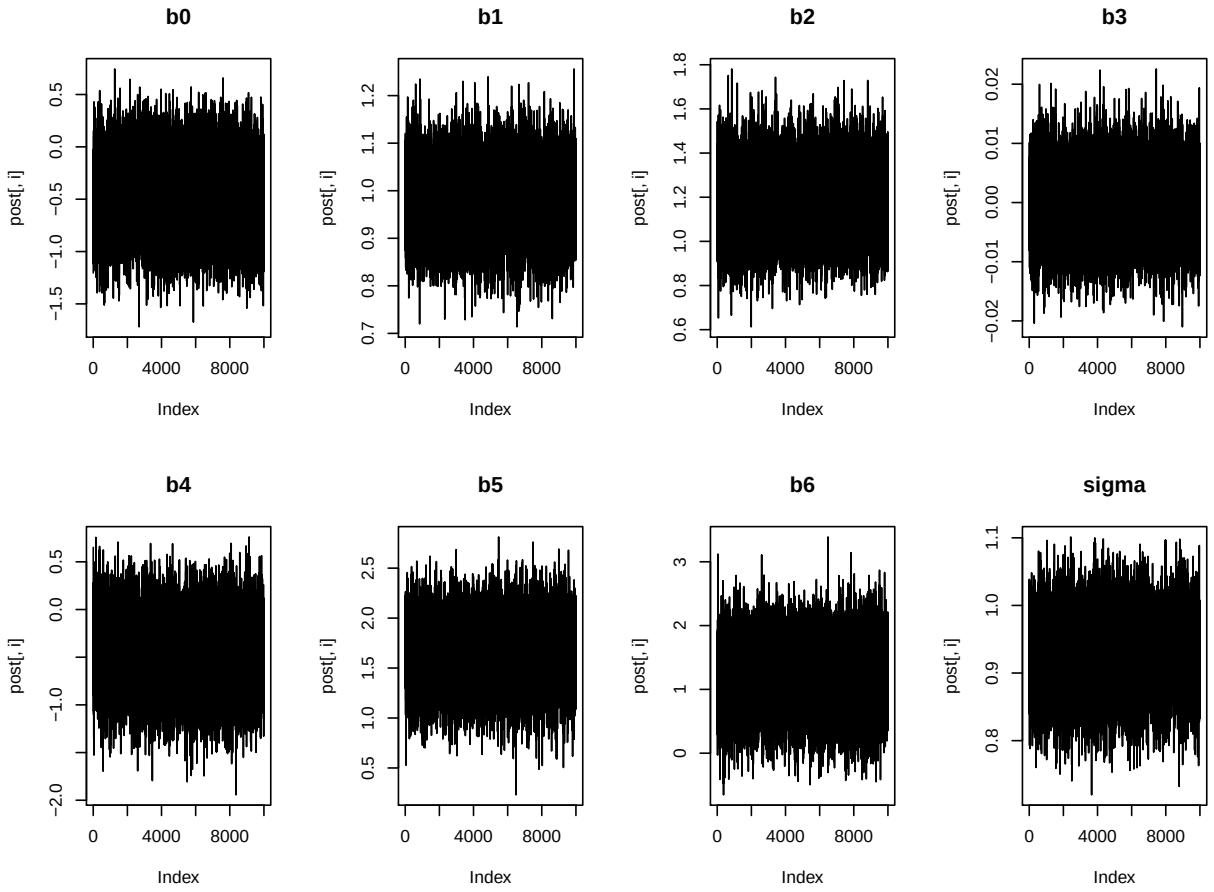
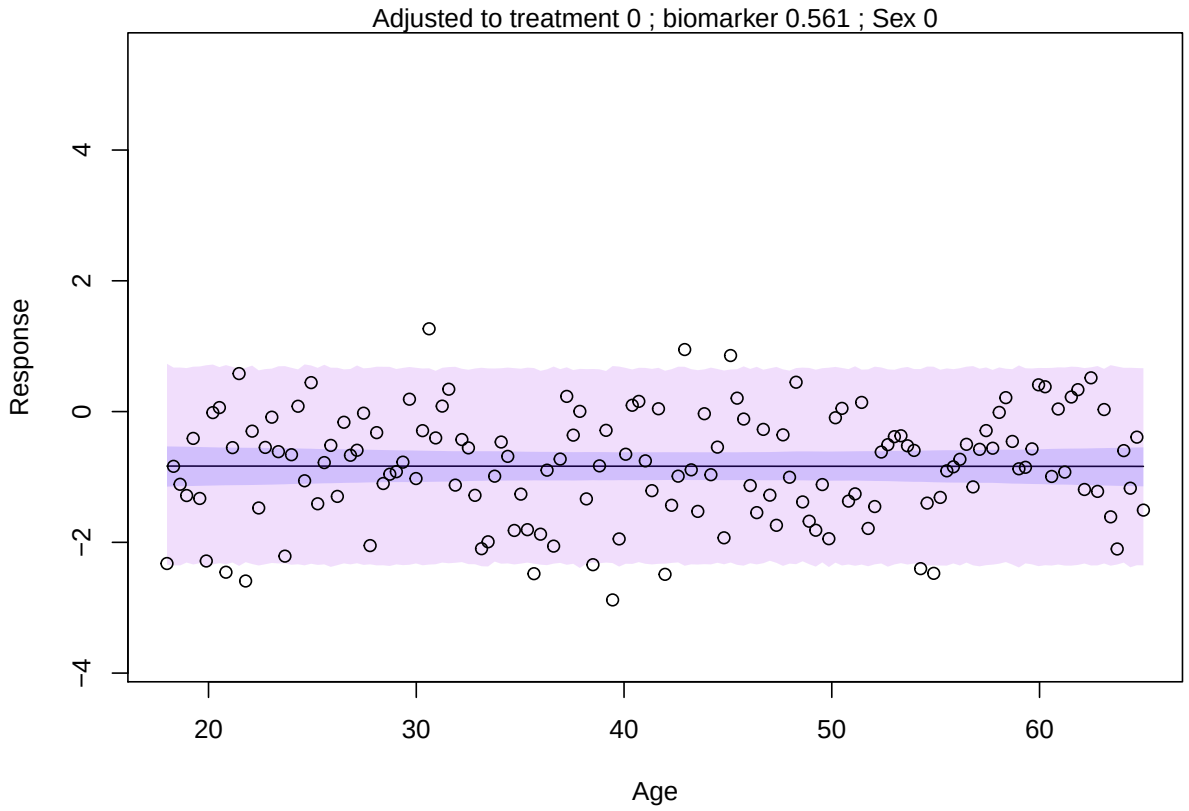
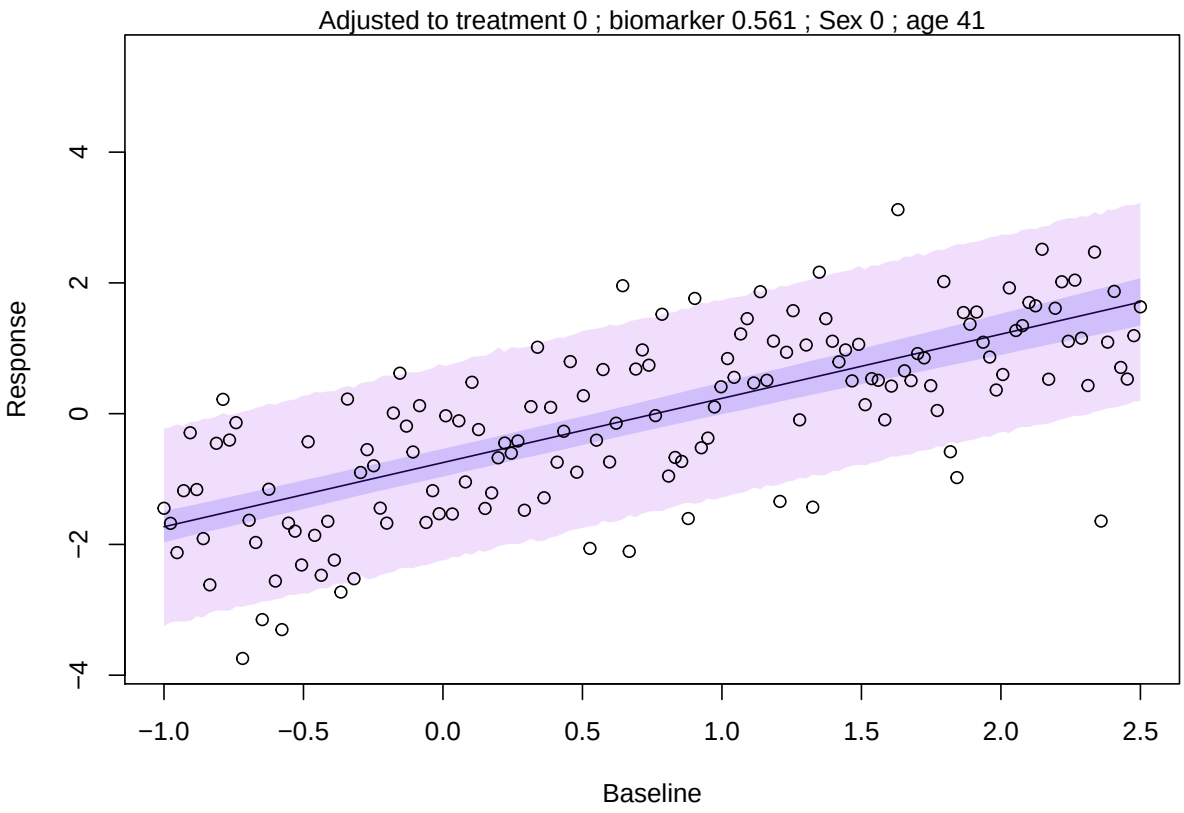


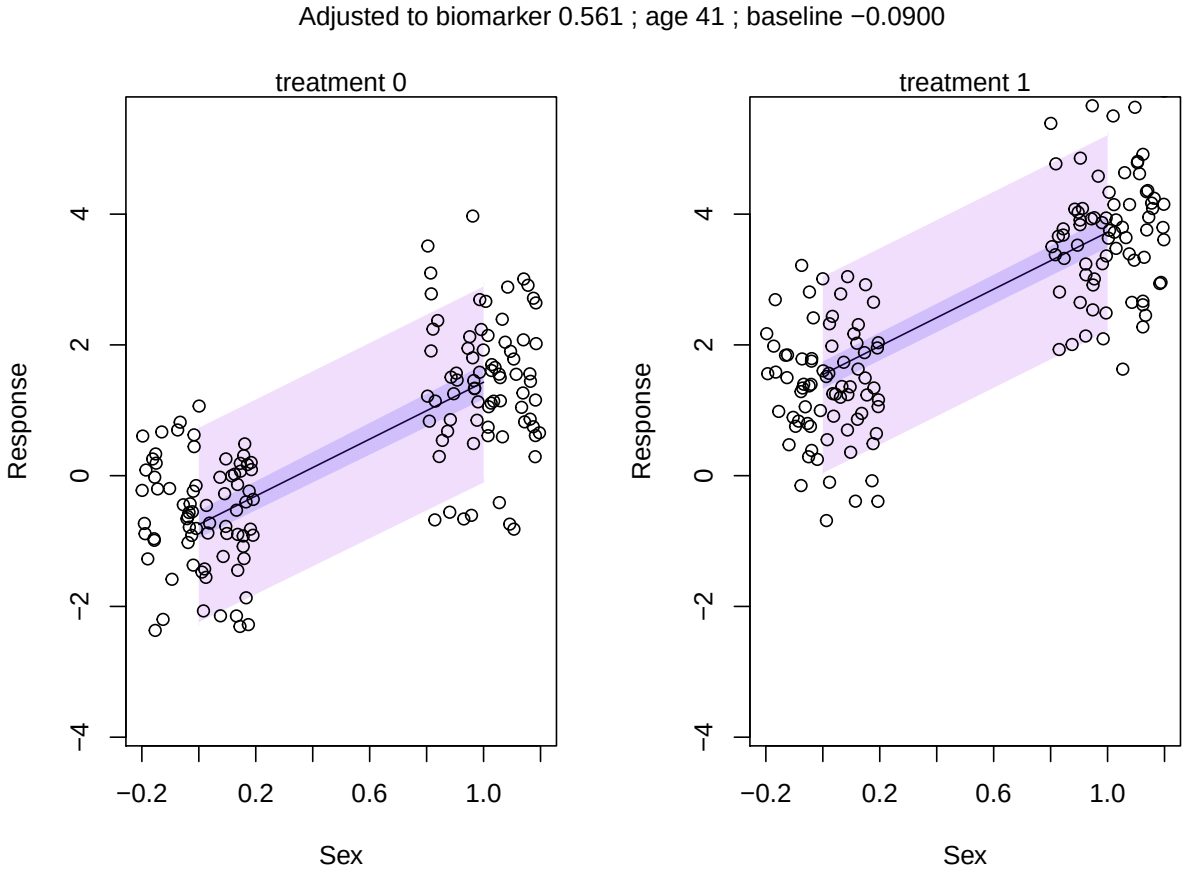
Figure 13: Check chains are mixing

```
par(mfrow=c(1,1))
```

27 For completion the effects of the other covariates




Adjusted to treatment 0 ; biomarker 0.561 ; Sex 0 ; age 41
Response
Baseline
−4
−2
0
2
4
−1.0
−0.5
0.0
0.5
1.0
1.5
2.0
2.5



28 References

Statistical Rethinking, Richard McElearth post treatment bias p151, WAIC p199 and simulate p129

http://thestatsgeek.com/2014/02/01/adjusting-for-baseline-covariates-in-randomized-controlled-trials/
http://egap.org/content/power-analysis-simulations-r

http://stackoverflow.com/questions/14554558/simulate-a-linear-model-100-times

http://stats.stackexchange.com/questions/155246/which-variable-relative-importance-method-to-use

29 Computing Environment

```
R version 3.2.2 (2015-08-14)
Platform: x86_64-w64-mingw32/x64 (64-bit)
Running under: Windows 8 x64 (build 9200)

locale:
[1] LC_COLLATE=English_United Kingdom.1252  LC_CTYPE=English_United Kingdom.1252
[3] LC_MONETARY=English_United Kingdom.1252 LC_NUMERIC=C
[5] LC_TIME=English_United Kingdom.1252

attached base packages:
[1] grid      parallel  stats     graphics  grDevices utils     datasets  methods   base

other attached packages:
 [1] VennDiagram_1.6.17   futile.logger_1.4.3  rethinking_1.58      rstan_2.10.1         StanHeaders_2.
 [6] reshape_0.8.5        rms_4.5-0            SparseM_1.7          Hmisc_3.17-4         ggplot2_2.1.0
[11] Formula_1.2-1        survival_2.39-5      lattice_0.20-33      knitr_1.13

loaded via a namespace (and not attached):
 [1] zoo_1.7-13           splines_3.2.2        colorspace_1.2-6     htmltools_0.3.5      stats4_3.2.2
 [6] loo_0.1.6            yaml_2.1.13          chron_2.3-47         foreign_0.8-66       RColorBrewer_1
[11] lambda.r_1.1.9       matrixStats_0.50.2   multcomp_1.4-6       plyr_1.8.4           stringr_1.0.0
[16] MatrixModels_0.4-1   munsell_0.4.3        gtable_0.2.0         mvtnorm_1.0-5        codetools_0.2-
[21] coda_0.18-1          evaluate_0.9         labeling_0.3         latticeExtra_0.6-28  inline_0.3.14
[26] quantreg_5.26        TH.data_1.0-7        Rcpp_0.12.6          KernSmooth_2.23-15   acepack_1.3-3.
[31] scales_0.4.0         formatR_1.4          gridExtra_2.2.1      digest_0.6.9         stringi_1.1.1
[36] polspline_1.1.12     tools_3.2.2          sandwich_2.3-4       magrittr_1.5         futile.options
[41] cluster_2.0.3        MASS_7.3-45          Matrix_1.2-2         data.table_1.9.6     rmarkdown_1.0
[46] rpart_4.1-10         nnet_7.3-12          nlme_3.1-128

[1] "~/X/"
```

This took 190.32 seconds to execute.