

# Bayesian and frequentist analysis of randomised trial adjusting for covariates

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## 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 performed (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. treatment 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 covariates
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)
```

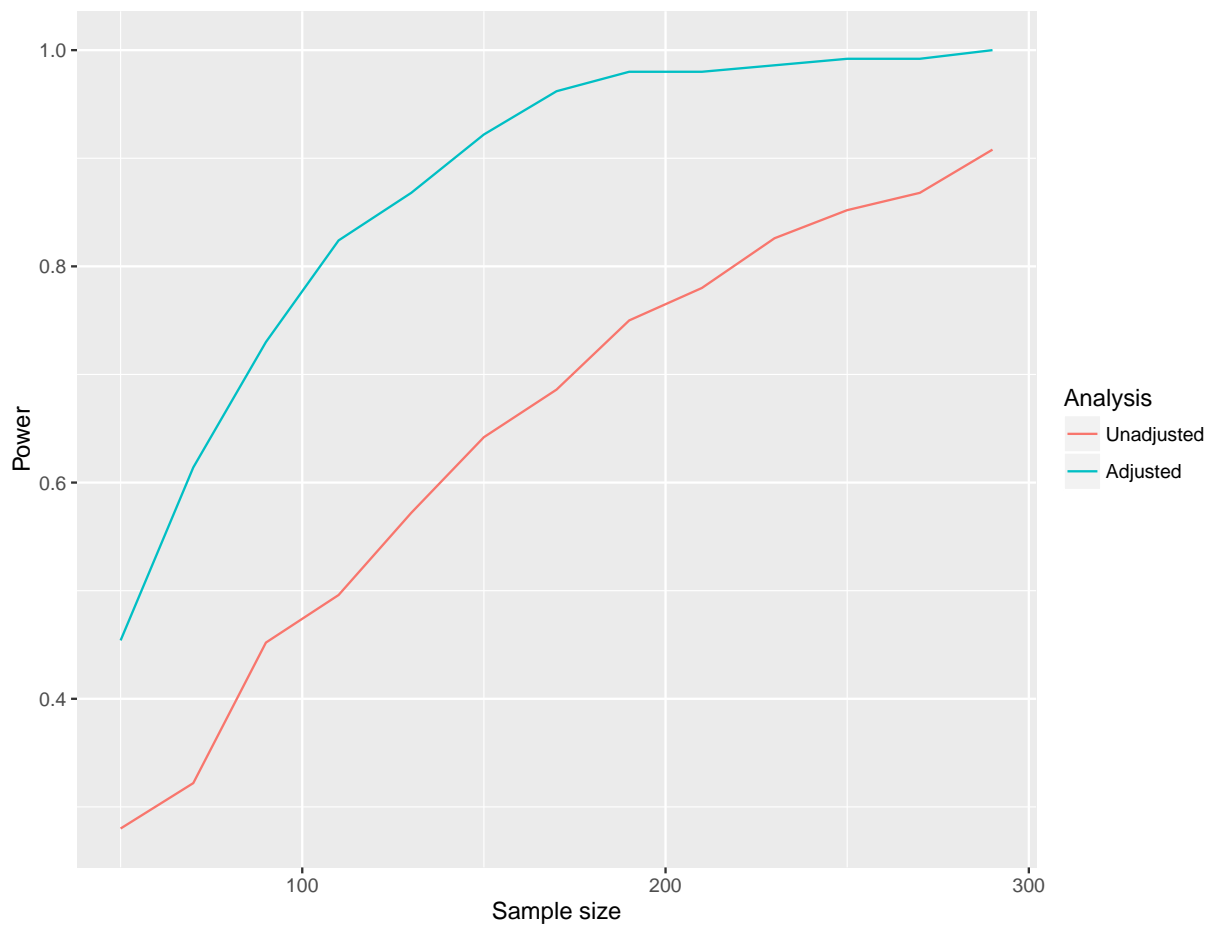


Figure 1: Profiles of power with sample size

## 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  $\chi^2$  statistics. Joint tests of all interaction terms in the model are also performed.

```
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 )
```

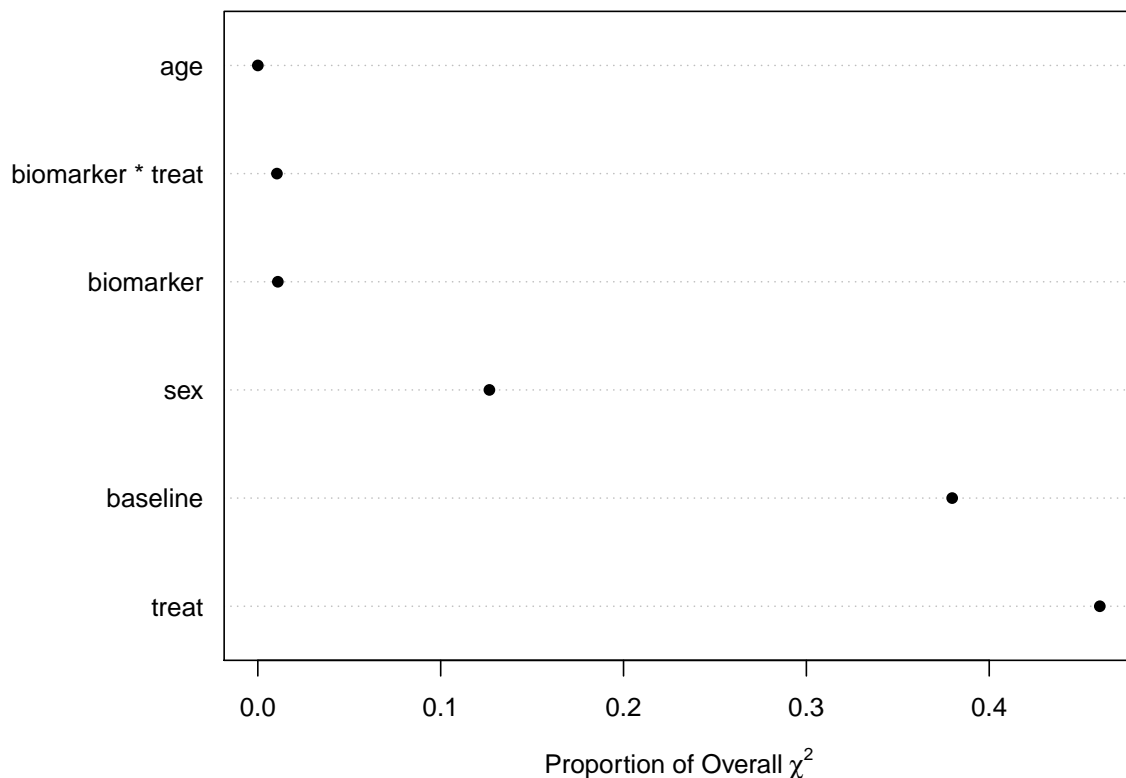


Figure 2: The default for `plot(anova())` is to display the Wald Chi2 statistic minus its degrees of freedom for assessing the partial effect of each variable. Even though this is not scaled  $[0,1]$  it is probably the best method in general because it penalizes a variable requiring a large number of 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  $y \sim \text{biomarker} * \text{treatment}$  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
```

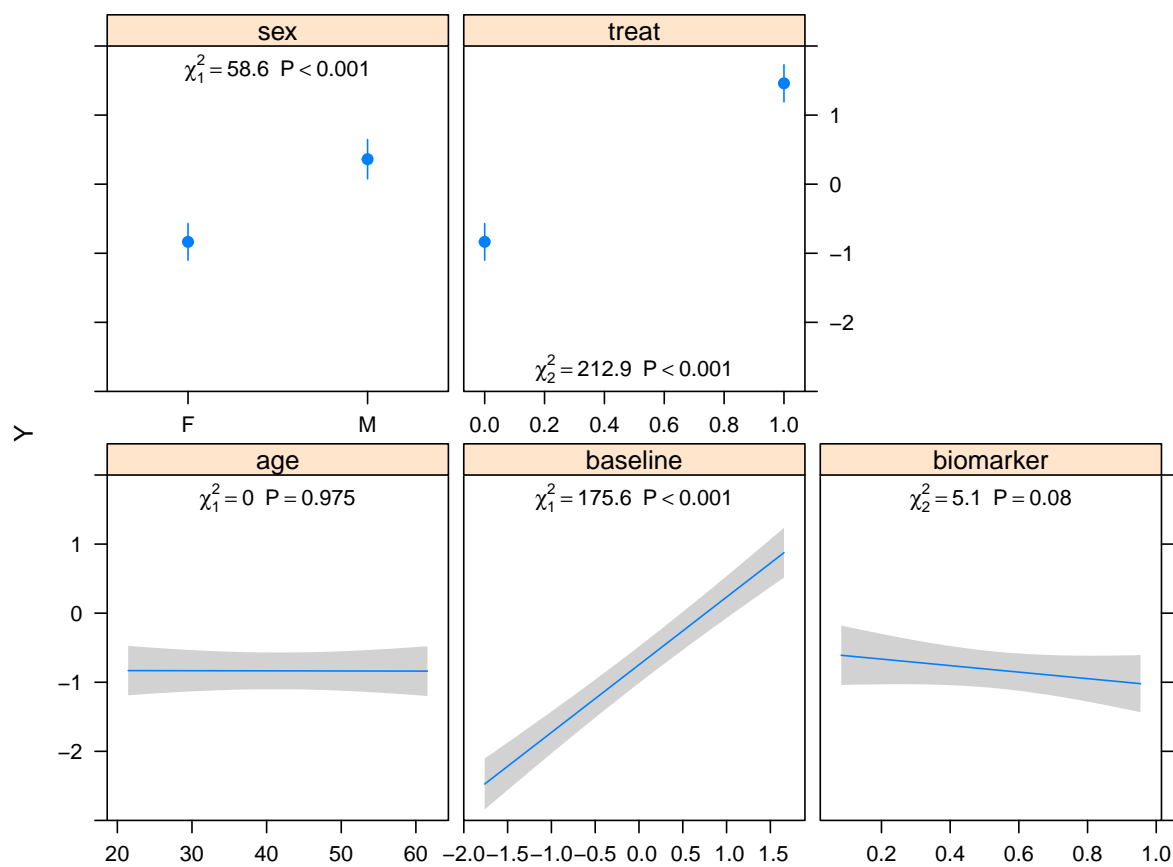


Figure 3: Show predicted values and confidence bands

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)
```



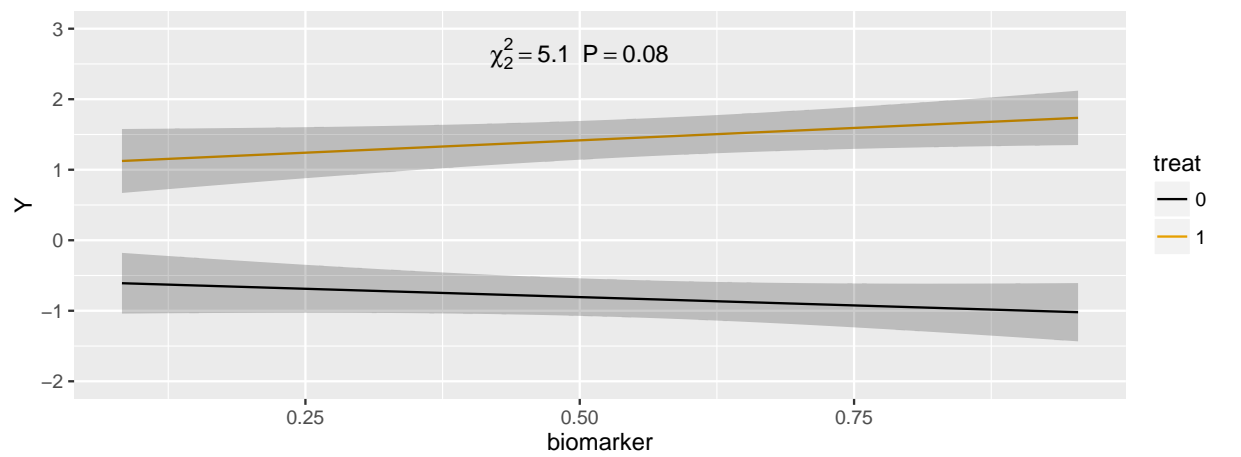
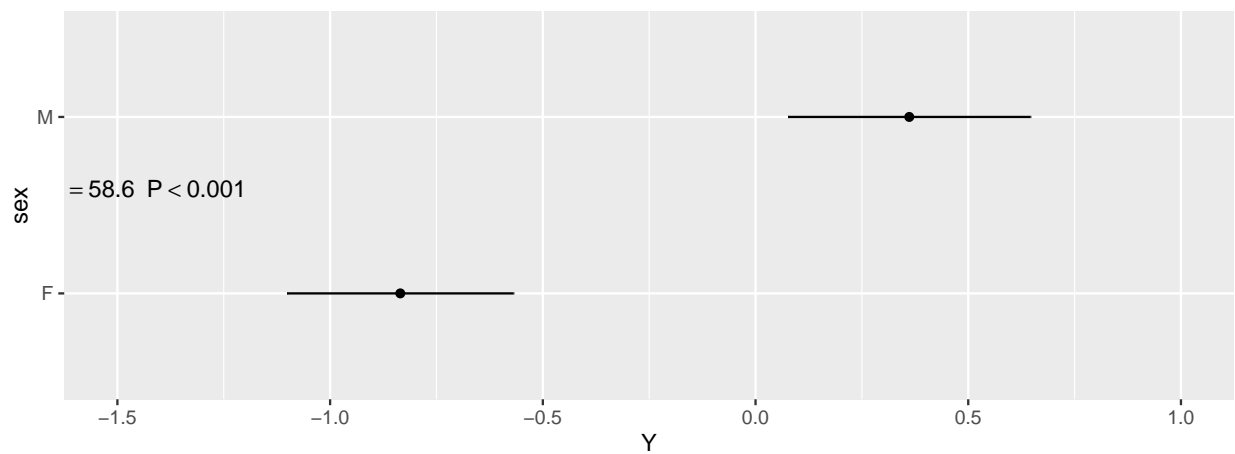


Figure 4: Biomarker effect on outcome in treatment arm

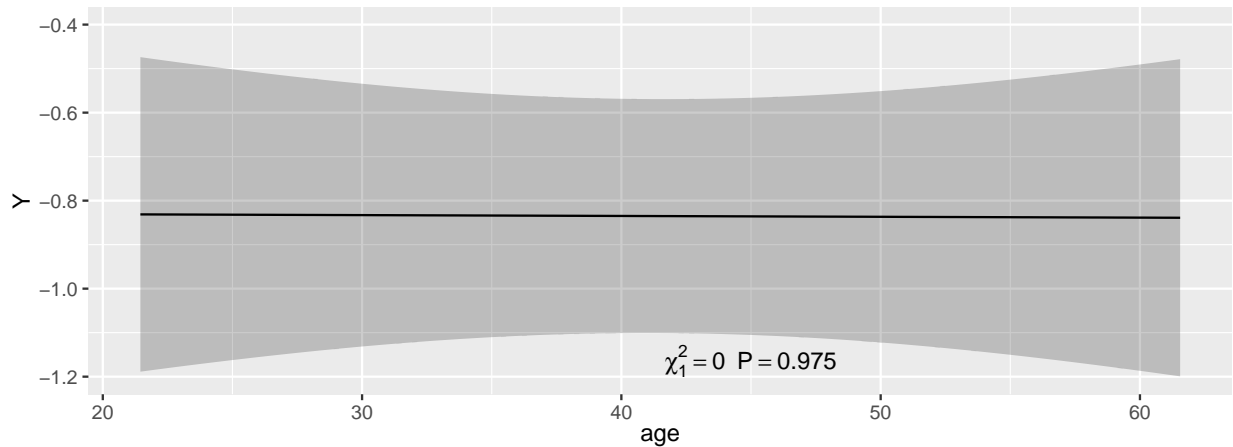


Adjusted to:baseline=-0.08996 age=41 biomarker=0.561 treat=0

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

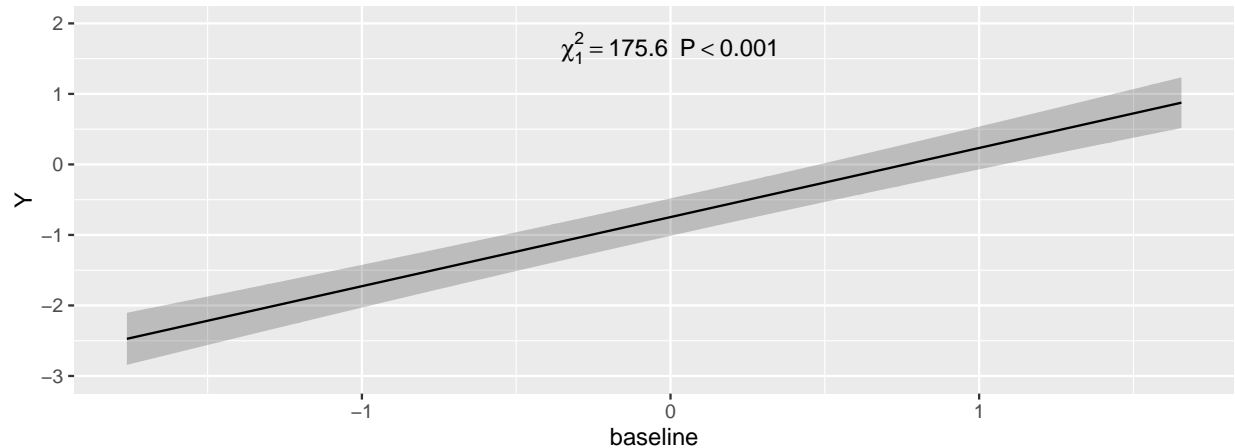
- 15 Show baseline main effect on outcome. A strong relationship as expected, patients with high values of the response at baseline would be expected to have high values at the outcome of the trial.

```
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) )

# was initially using map and not map2stan
# seems to be important that enough iterations are run
# otherwise there is an error and only default 1000
# simulations are generated and the rest NAs

m1 <- map2stan( 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,
                chains=3, iter=5000 , warmup=1000 )
```

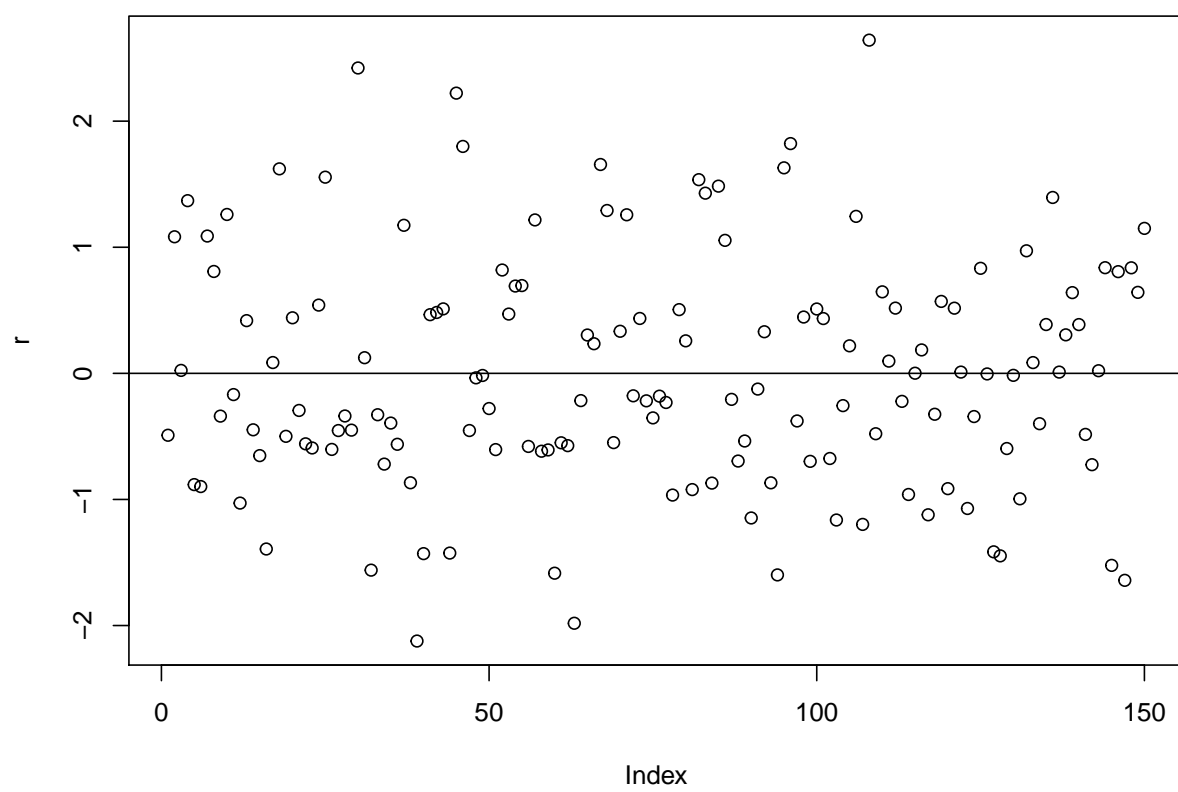


Figure 8: Check OLS assumptions

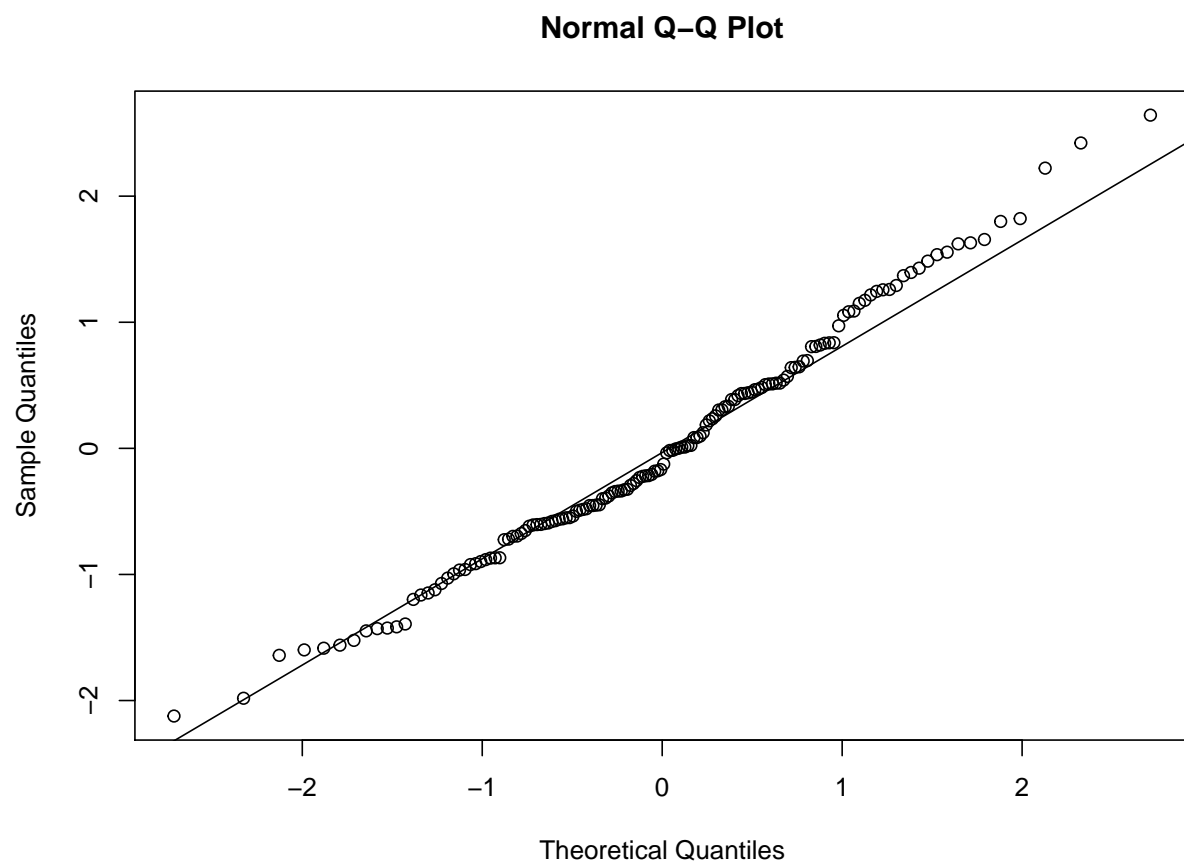


Figure 9: Check OLS assumptions



## 22 Bayesian analysis using STAN, frequentist and Bayesian results

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         |
| sigma | 0.9489 | d.f.             | 6              |
| 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 | lower 0.89 | upper 0.89 | n_eff | Rhat |
|-------|-------|--------|------------|------------|-------|------|
| b0    | -0.48 | 0.34   | -1.03      | 0.06       | 6922  | 1    |
| b1    | 0.98  | 0.07   | 0.87       | 1.10       | 11096 | 1    |
| b2    | 1.19  | 0.15   | 0.95       | 1.45       | 10344 | 1    |
| b3    | 0.00  | 0.01   | -0.01      | 0.01       | 9592  | 1    |
| b4    | -0.47 | 0.38   | -1.07      | 0.15       | 6959  | 1    |
| b5    | 1.64  | 0.33   | 1.11       | 2.18       | 6381  | 1    |
| b6    | 1.16  | 0.53   | 0.29       | 1.98       | 6454  | 1    |
| sigma | 0.96  | 0.06   | 0.87       | 1.05       | 10804 | 1    |

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.

```
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$baseline) # duplicate rms
P.age <- median(d$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 , n=simulations) # default is 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=simulations )
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 , n=simulations)
mu.mean <- apply( mu2 , 2 , mean )
mu.PI <- apply( mu2 , 2 , PI )

# simulate counterfactual response outcomes
R.sim2 <- sim( m1 , data=pred.data2 , n=simulations )
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)

```

Plot of the predicted effects with simulated patients in each treatment group,  
adjusted to baseline -0.0900, age 41 and sex coded 0 female

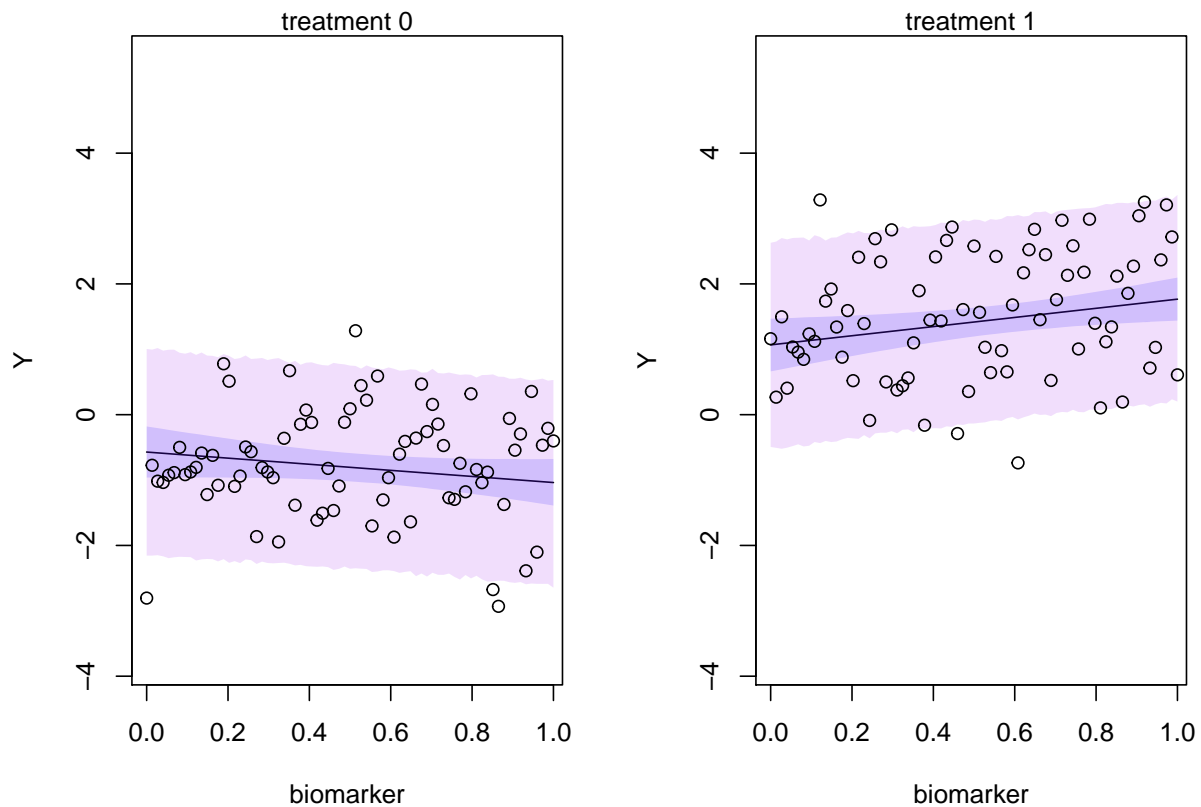


Figure 10: Predicted effects (Statistical Rethinking page 129)

```

par(mfrow=c(1,1))

# plot(precis(m1))

```

- 24 Plot the predicted treatment 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:simulations,1)      # choose one simulated dataset to plot
points(r.diff[x,] ~ P.biomarker)
abline(h=0)
```

- 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.

```
m2 <- map2stan( alist( Y ~ dnorm(mu, sigma),

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

                    b0 ~ dnorm(0, 100),
                    c(b1, b2, b3, b4, b5) ~ dnorm(0, 10),
                    sigma ~ dunif(0, 10) ),
  data=d,
  chains=3, iter=5000 , warmup=1000 )
```

|    | WAIC  | pWAIC | dWAIC | weight | SE    | dSE  |
|----|-------|-------|-------|--------|-------|------|
| m1 | 418.8 | 7.5   | 0.0   | 0.8    | 16.59 | NA   |
| m2 | 421.6 | 6.5   | 2.8   | 0.2    | 15.71 | 4.86 |

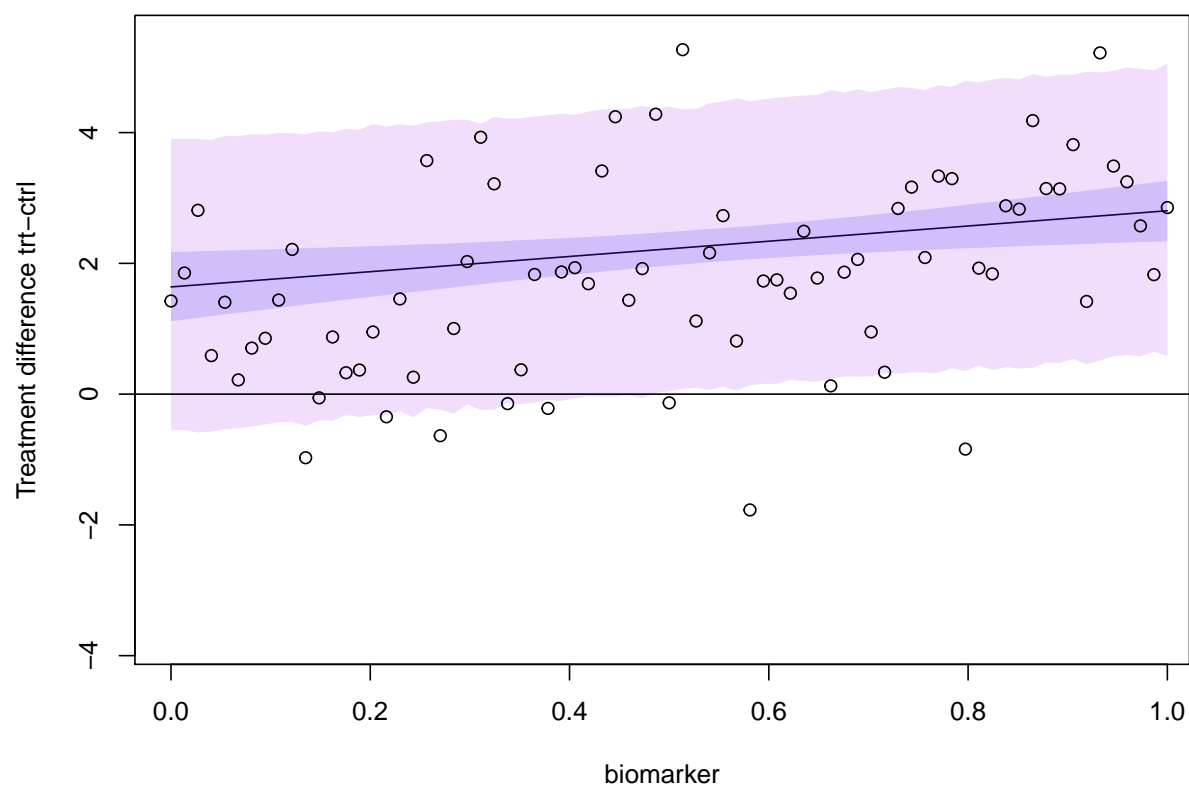
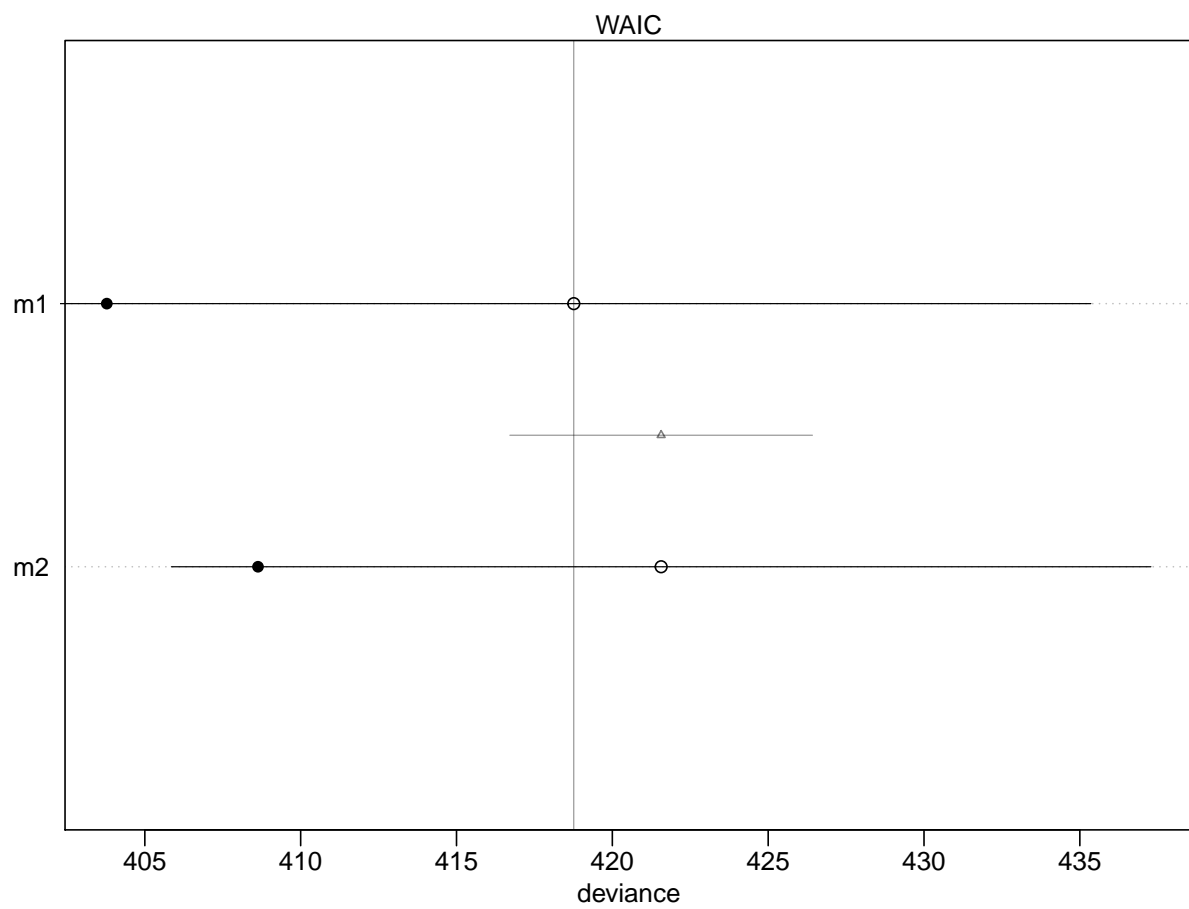


Figure 11: Predicted effects (Statistical Rethinking page 129)



## 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]) } #post[,i]
# par(mfrow=c(1,1))

plot(m1)
```

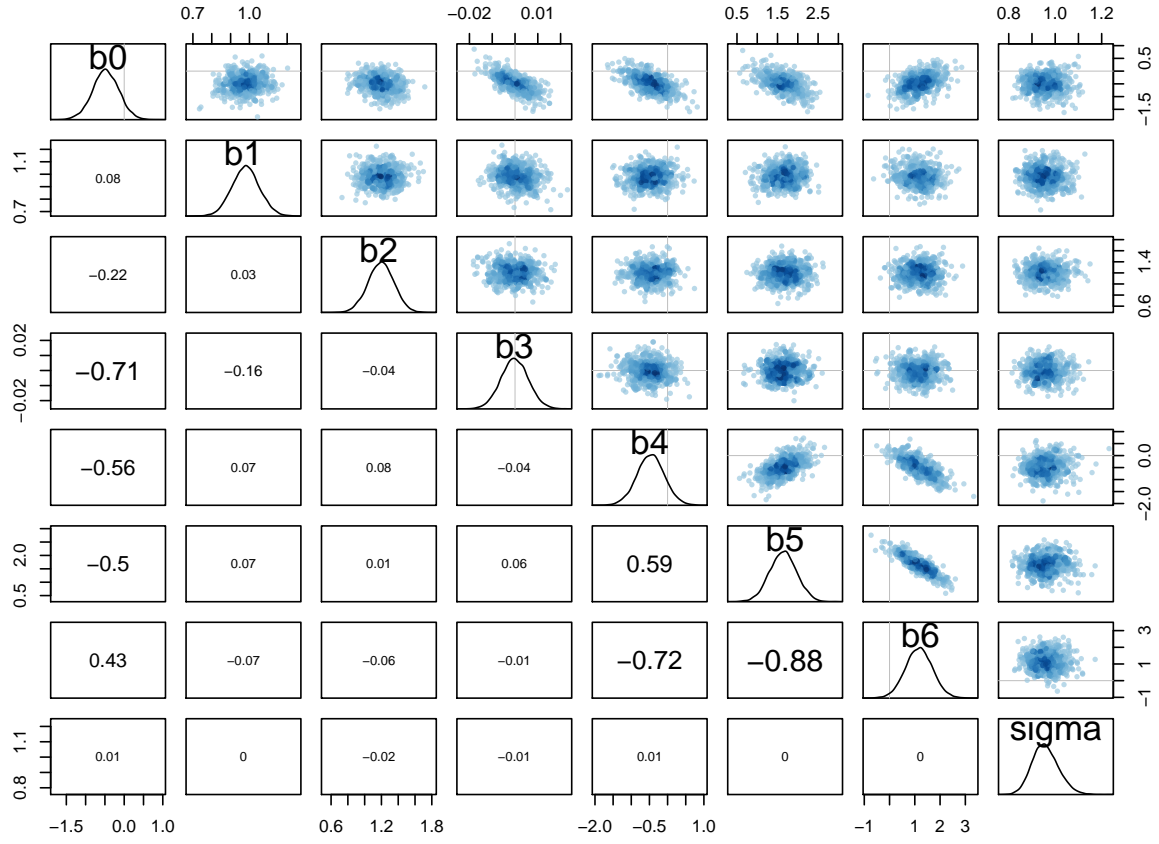


Figure 12: Check chains are mixing

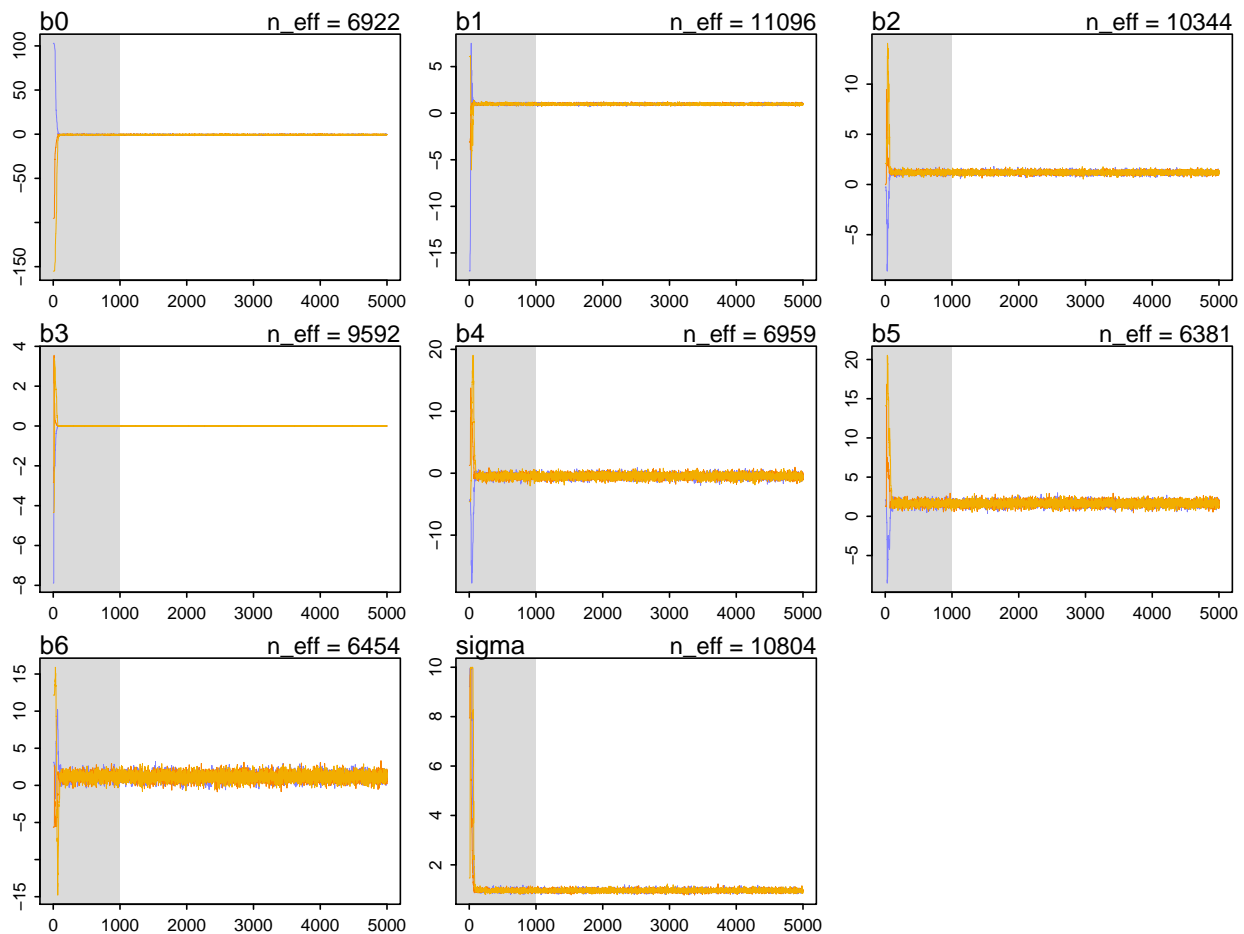
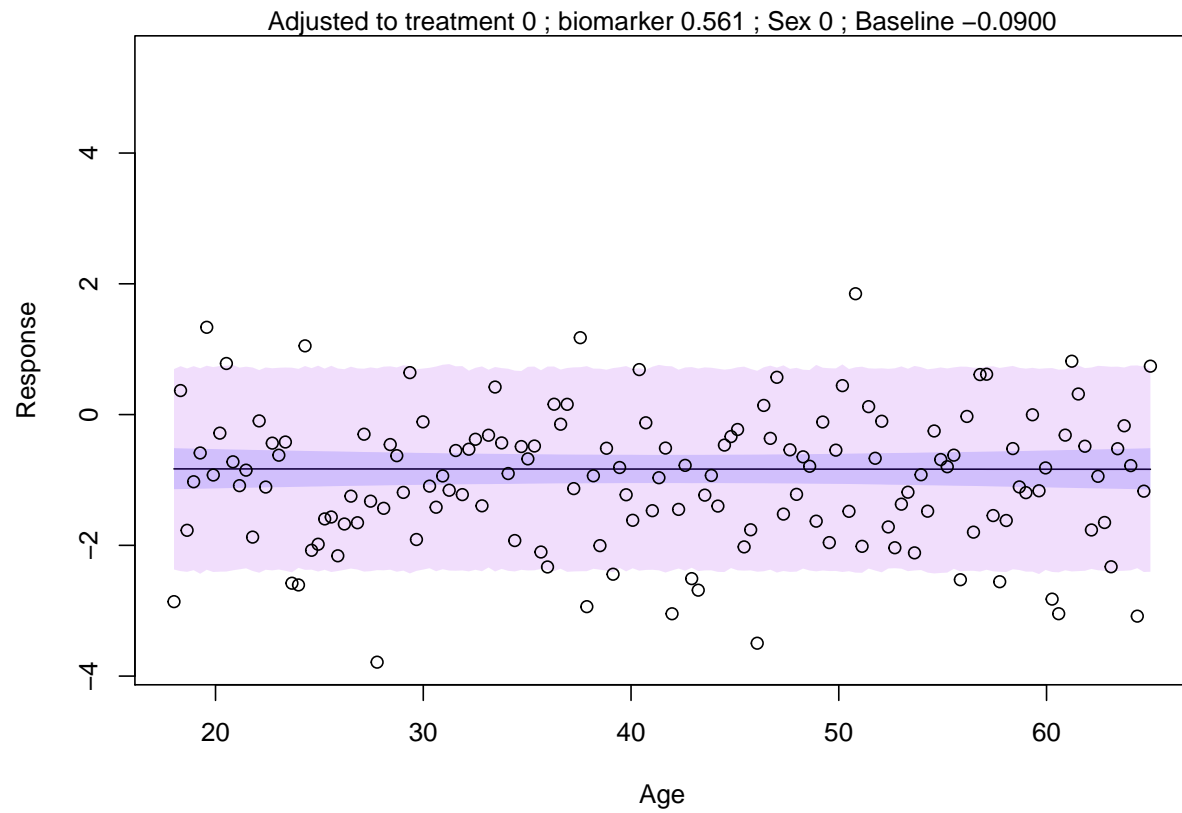
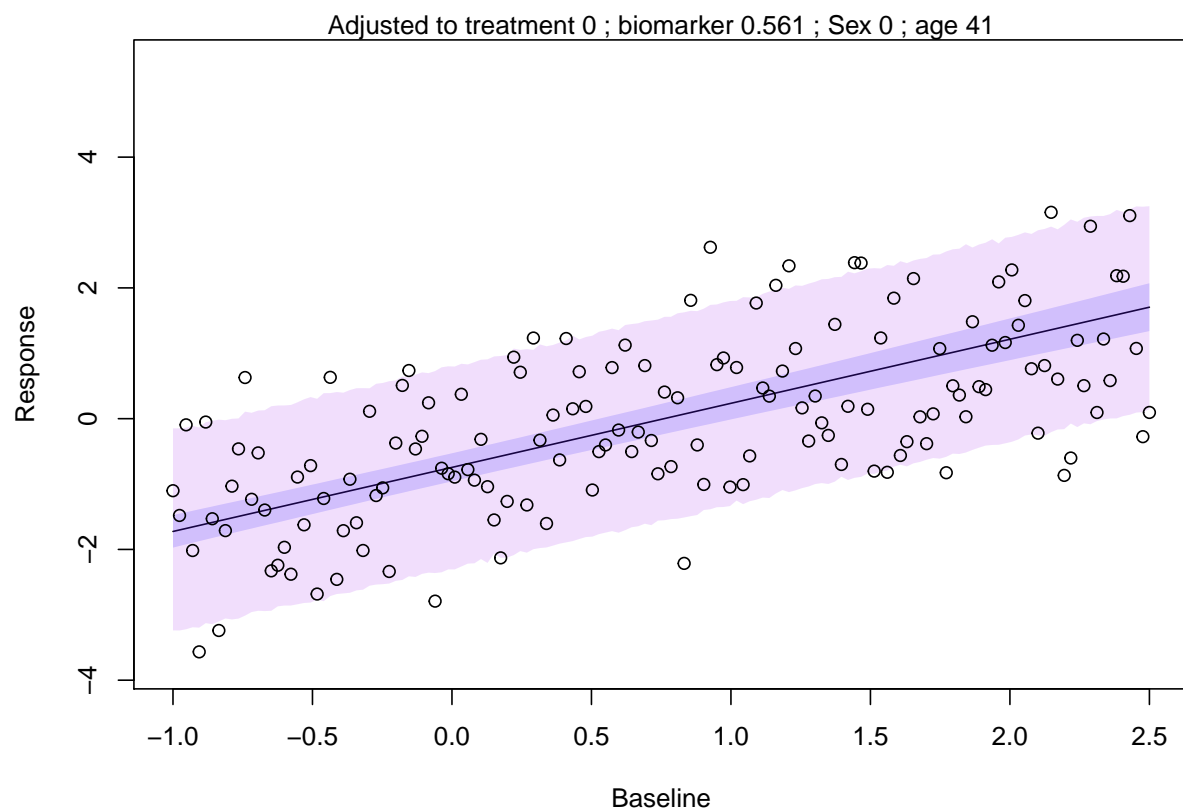


Figure 13: Check chains are mixing

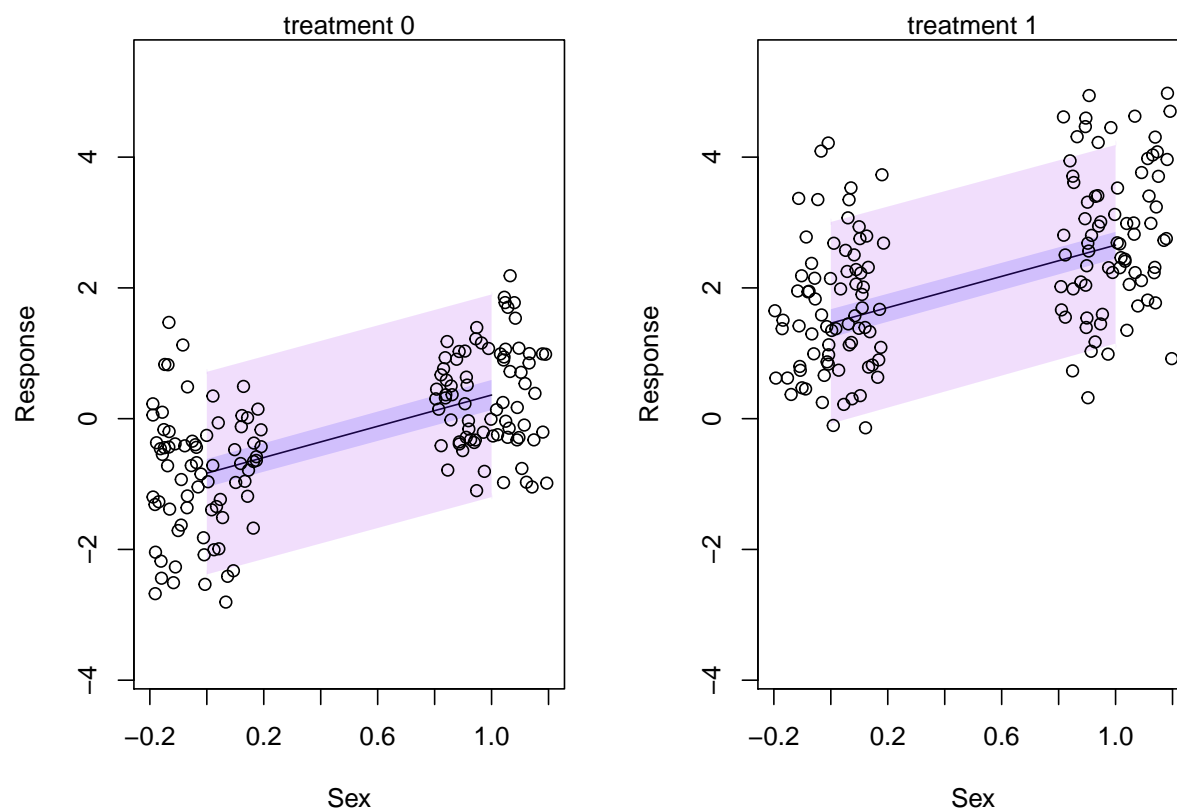


## 27 For completion the effects of the other covariates





Adjusted to biomarker 0.561 ; age 41 ; baseline  $-0.0900$



## 28 References

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

<http://thstatsgeek.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
[2] LC_CTYPE=English_United Kingdom.1252
[3] LC_MONETARY=English_United Kingdom.1252
[4] LC_NUMERIC=C
[5] LC_TIME=English_United Kingdom.1252
```

attached base packages:

```
[1] parallel stats graphics grDevices utils datasets
[7] methods base
```

other attached packages:

```
[1] rethinking_1.58      rstan_2.11.1      StanHeaders_2.11.0
[4] reshape_0.8.5        rms_4.5-0          SparseM_1.7
[7] Hmisc_3.17-4          ggplot2_2.1.0      Formula_1.2-1
[10] survival_2.39-5       lattice_0.20-33    knitr_1.14
```

loaded via a namespace (and not attached):

```
[1] zoo_1.7-13           splines_3.2.2      colorspace_1.2-6
[4] htmltools_0.3.5      stats4_3.2.2       loo_0.1.6
[7] yaml_2.1.13          chron_2.3-47        foreign_0.8-66
[10] RColorBrewer_1.1-2    matrixStats_0.50.2 multcomp_1.4-6
[13] plyr_1.8.4           stringr_1.1.0       MatrixModels_0.4-1
[16] munsell_0.4.3         gtable_0.2.0        mvtnorm_1.0-5
[19] codetools_0.2-14     coda_0.18-1         evaluate_0.9
[22] labeling_0.3          latticeExtra_0.6-28 inline_0.3.14
[25] quantreg_5.26         TH.data_1.0-7       Rcpp_0.12.6
[28] KernSmooth_2.23-15    acepack_1.3-3.3     scales_0.4.0
[31] formatR_1.4           gridExtra_2.2.1     digest_0.6.10
[34] stringi_1.1.1         polyspline_1.1.12    grid_3.2.2
[37] tools_3.2.2           sandwich_2.3-4       magrittr_1.5
[40] cluster_2.0.3         MASS_7.3-45         Matrix_1.2-2
[43] data.table_1.9.6      rmarkdown_1.0       rpart_4.1-10
[46] nnet_7.3-12           nlme_3.1-128
```

```
[1] "~/GIT\\RCT-adjusting-for-covariates"
```

This took 92.42 seconds to execute.