Exploration of power and treatment effect precision using an adjusted analysis for a randomised controlled trial (Bayesian & frequentist)

Eamonn O'Brien

04 September, 2016

1 Introduction

Many randomised controlled trials (RCTs) are analysed in a simple manner using only the randomised treatment as the independent variable. But when the response outcome is continuous, 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 a RCT. We then choose a sample size and simulate a single RCT. The RCT is then analysed using a frequentist approach and a Bayesian approach.

2 Prepare for stochastic simulations

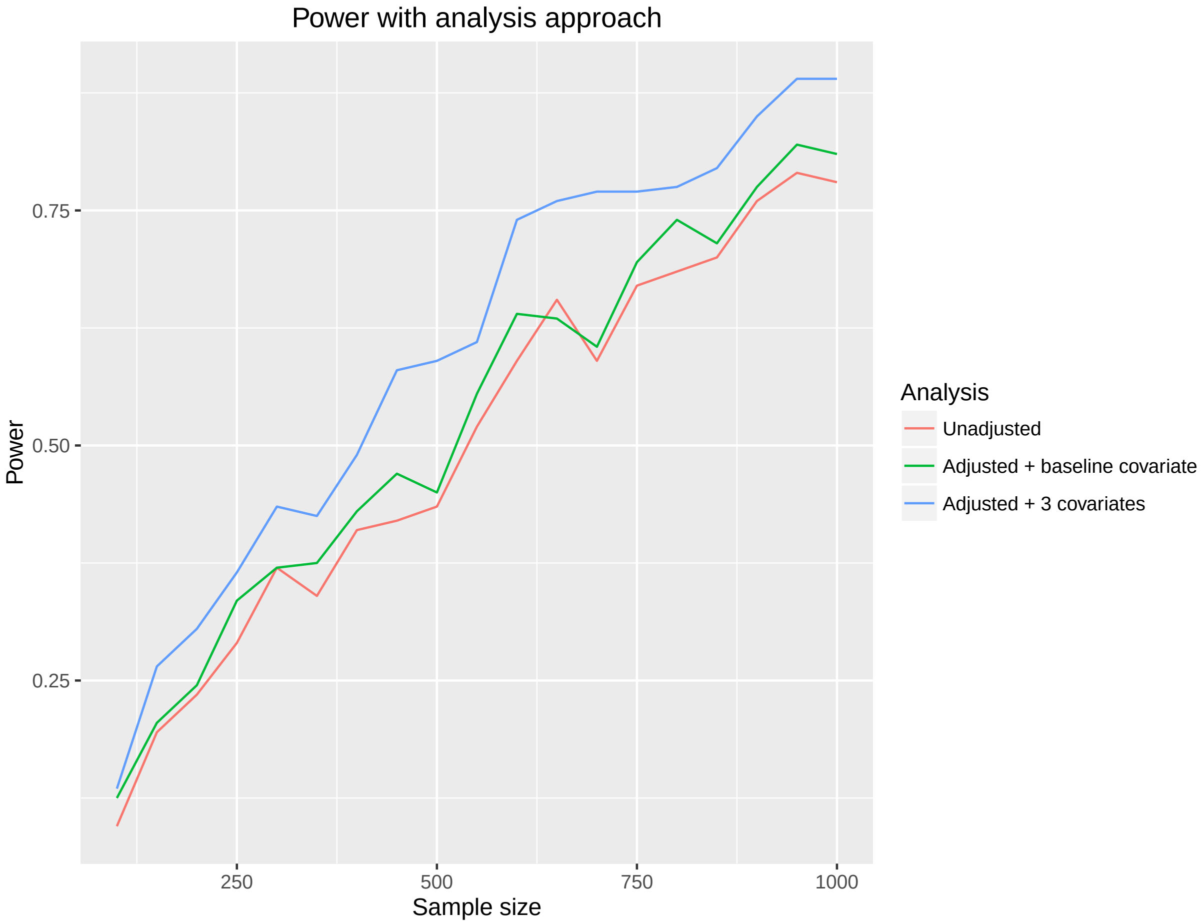
```
alpha <- 0.05
n.sims <- 200                                      # simulations
N <- seq(from=100, to=1000, by=50)                 # trial sizes to explore
pow.adj1 <- pow.adj2 <- pow <- rep(NA, length(N)) # object to capture summary power estimates
bias <-  array(NA, dim=c(length(N),6))             # object to capture summary coeff estimates
```

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

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

  n <- N[j]

  #objects to collect simulations for each sample size before summary stats are calculated
  significant.unadjusted <- significant.adj1 <- significant.adj2 <- rep(NA, n.sims)
  est <- array(NA, dim=c(n.sims,6))

  for (i in 1: n.sims){

       # Hyp the effect of age on outcome, a unit change in outcome over the whole age range,
       # so ~0.02 effect on outcome for each increase in age of 1 year
       effect.of.age <- 1/(65-18)
       effect.of.sex <- 5                           # Hypothesize the effect of sex on outcome
       effect.of.treatment <- 1                     # Hypothesize the treatment effect on outcome

       # Hypothesize baseline version of response on outcome,
       # a unit increase results in 0.5 increase in outcome,
       # strong predictor so 5 over the baseline range
       effect.of.baseline <- 1/2
       intercept <- 100
       noise <- 5                                   # random error

       #collect the true parmaeters to see how well we recover them
       covp <- c(intercept,  effect.of.baseline,  effect.of.sex,
                 effect.of.age, effect.of.treatment, effect.of.treatment)

    # covariate effects
    baseline <- runif(n,100,110)                    # baseline effect
    treat <- 1*(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

    # create the outcome, with random error
    Y <- effect.of.sex*(sex=="M") + effect.of.age*age + effect.of.baseline*baseline +
      effect.of.treatment*treat + rnorm(n, intercept, noise)

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

    # Unadjusted analysis, extract p-value treatment effect
    f0 <- ols(Y ~ treat, d)
    fa <- anova(f0)
    p.value <- as.matrix(fa)[1,5]

    # Adjusted analysis, extract p-value treatment effect  adjusted for 1 covariates
    fa <- anova( ols(Y ~ baseline + treat, d))
    p.value.adj1 <- as.matrix(fa)[2,5]
    # Adjusted analysis, extract p-value treatment effect adjusted for 3 covariates
    f <- ols(Y ~ baseline + sex + age + treat, d)
    fa <- anova(f)
    p.value.adj2 <- as.matrix(fa)[4,5]

    # collect p values
    significant.unadjusted[i]  <-  p.value <= alpha
    significant.adj1[i]   <-  p.value.adj1 <= alpha
    significant.adj2[i]   <-  p.value.adj2 <= alpha

    #get the simulations coefficient estimates for sample size
    est[i,]<- c(f$coefficients , f0$coefficients[2][[1]])

  }

  # summarise the simulations, calculate power
  pow[j]      <- mean(significant.unadjusted)
  pow.adj1[j] <- mean(significant.adj1)
  pow.adj2[j] <- mean(significant.adj2)

  # mean the simulations  for the parameter estimates
  x <- apply(est, 2, mean)

  # calculate relative bias and store
  bias[j,] <- 100*(x-covp)/covp

}
```

4 Plot the power with sample size relationships

```
df <-  data.frame(N, pow, pow.adj1, pow.adj2)
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 + baseline covariate" , "Adjusted + 3 covariates")))) +
geom_line()
g <- g + ylab("Power") + xlab("Sample size") + labs(color = "Analysis") +
    ggtitle("Power with analysis approach")

print(g)
```



5 Plot the percent relative bias with sample size relationships

```
namez <-  c("intercept","effect.of.baseline","effect.of.sex","effect.of.age",
            "effect.of.treatment", "unadj.effect.of.treatment")
bias <- data.frame(bias)
names(bias) <- namez

df <-  data.frame(cbind(N=N, bias))
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 = namez))) +
geom_line()
g <- g + ylab("% Relative bias") + xlab("Sample size") + labs(color = "Parameter") +
  ggtitle("% Relative Bias in coefficients") +
  geom_hline(aes(yintercept=0) , color="black", linetype="dashed")
g <- g + facet_grid(. ~ variable) + guides(colour=FALSE)

print(g)
```

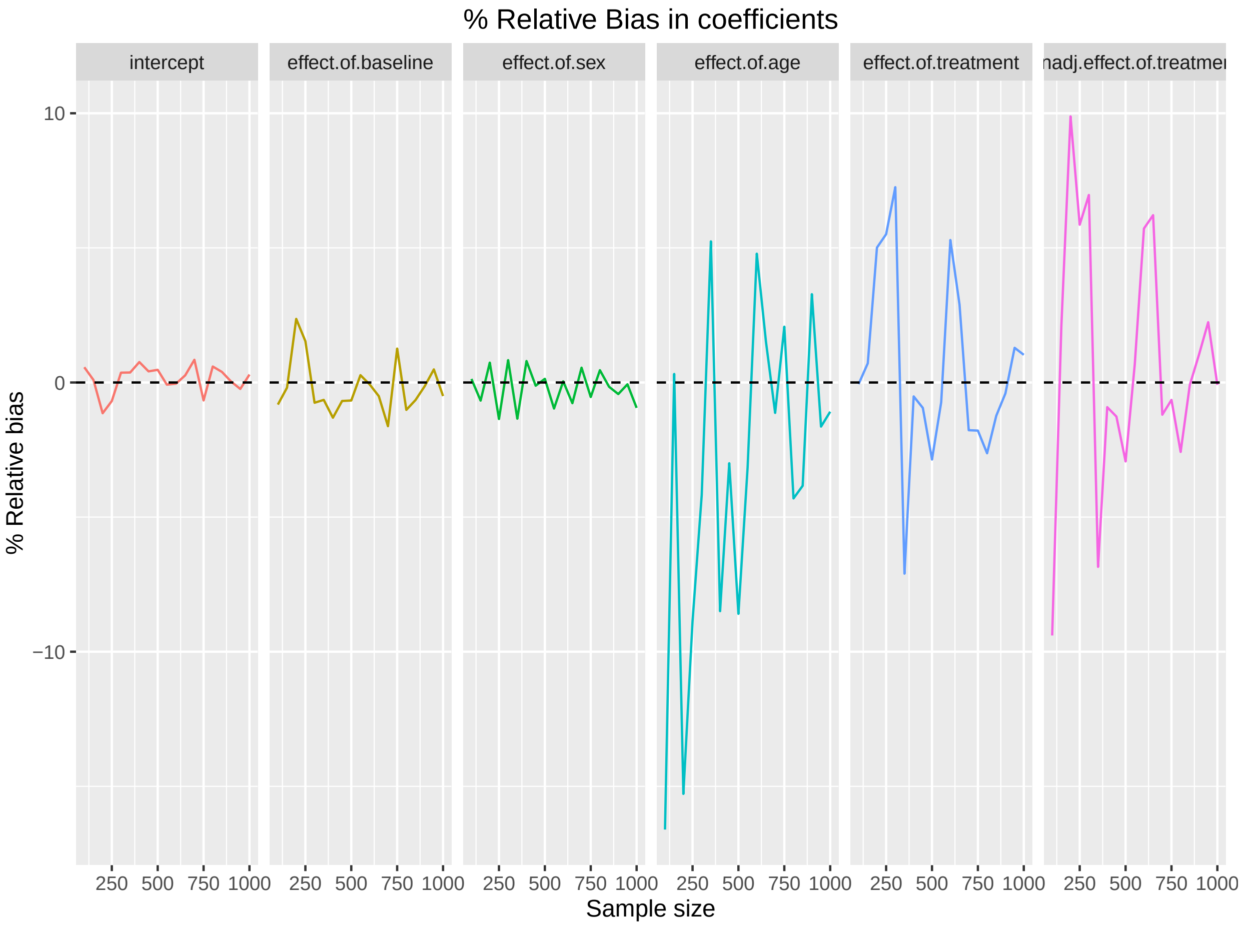


Figure 1: Profiles of percentage relative bias with sample size

6 Show the % relative bias with sample size relationships

```
x.c <- bias  # format all numerical variables
x.c[] <- lapply(x.c, function(.col){
       if (is.numeric(.col)) return(sprintf("%.1f", .col))
       else return(.col)
   })

print(x.c)
```

```
   intercept effect.of.baseline effect.of.sex effect.of.age effect.of.treatment unadj.effect.of.treatmen
1        0.6               -0.8           0.1         -16.6                -0.1                       -9
2        0.1               -0.2          -0.7           0.3                 0.7                        2
3       -1.1                2.4           0.7         -15.3                 5.0                        9
4       -0.7                1.5          -1.4          -8.9                 5.5                        5
5        0.4               -0.8           0.8          -4.2                 7.3                        7
6        0.4               -0.6          -1.3           5.2                -7.1                       -6
7        0.8               -1.3           0.8          -8.5                -0.5                       -0
8        0.4               -0.7          -0.1          -3.0                -0.9                       -1
9        0.5               -0.7           0.1          -8.6                -2.9                       -2
10      -0.1                0.3          -1.0          -3.2                -0.7                        0
11      -0.0               -0.1           0.0           4.8                 5.3                        5
12       0.3               -0.5          -0.8           1.5                 2.9                        6
13       0.8               -1.6           0.5          -1.1                -1.8                       -1
14      -0.7                1.3          -0.5           2.1                -1.8                       -0
15       0.6               -1.0           0.5          -4.3                -2.6                       -2
16       0.4               -0.7          -0.2          -3.8                -1.2                       -0
17       0.0               -0.1          -0.4           3.3                -0.4                        1
18      -0.2                0.5          -0.1          -1.6                 1.3                        2
19       0.3               -0.5          -0.9          -1.1                 1.0                       -0
```

7 Based on power estimates of adjusted analyses a trial of 800 patients takes place

```
set.seed(87564)
n <- 800                          # sample size

effect.of.age <- 1/(65-18)        # Hypothesize the effect of age on outcome
effect.of.sex <- 5                # Hypothesize the effect of sex on outcome
effect.of.treatment <- 1          # Hypothesize the treatment effect on outcome
effect.of.baseline <- 1/2         # Hypothesize the baseline effect on outcome
intercept <- 100
noise <- 5                        # the standard deviation for the simulated data

baseline <- runif(n,100,110)                    # Generate baseline covariate
treat <- 1*(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
```

```r
    # Create the response outcome, with random error
    Y <- effect.of.sex*(sex=="M") + effect.of.age*age + effect.of.baseline*baseline +
    effect.of.treatment*treat + rnorm(n, intercept, noise)

    # alternative data creation
    dat <- data.frame( baseline=baseline, treat=treat, sex=sex, age=age)

    X <- model.matrix(~baseline + treat + sex + age, dat)

    #the regression slopes
    betas <-c(intercept, effect.of.baseline, effect.of.treatment, effect.of.sex, effect.of.age)

    # the simulated data
    y_norm <- rnorm(800, X%*%betas, noise)

    lm( Y ~      baseline + sex + age + treat)
```

```
Call:
lm(formula = Y ~ baseline + sex + age + treat)

Coefficients:
(Intercept)     baseline         sexM          age        treat
  96.326964     0.535192     5.183220     0.009781     1.706045
```

```r
    lm( y_norm ~ baseline + sex + age + treat)
```

```
Call:
lm(formula = y_norm ~ baseline + sex + age + treat)

Coefficients:
(Intercept)     baseline         sexM          age        treat
    94.1915       0.5508       5.8003       0.0232       1.1279
```

8 Create a data frame

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

9 Bayesian analysis using STAN, the model statement

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


 m0 <- map( alist( Y ~ dnorm(mu, sigma),

                  mu <- b0 + b4*treat,

                  b0 ~ dnorm(0, 100),
                  b4 ~ dnorm(0, 10),
                  sigma ~ dunif(0, 10) ),
           data=d )

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

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

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

# construct centered predictors
# d$baseline <- d$baseline - mean(d$baseline)
# d$age <- d$age - mean(d$age)

     m1 <- map2stan( alist( Y ~ dnorm(mu, sigma),

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

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

10 Bayesian analysis using STAN, frequentist and Bayesian results together

```
        Mean StdDev   2.5%  97.5%
b0    155.57   0.29 155.00 156.14
b4      1.61   0.42   0.80   2.42
sigma   5.88   0.15   5.59   6.17
```

```
       Mean StdDev lower 0.95 upper 0.95 n_eff Rhat
b0    95.98   6.47      83.21     108.78  5361    1
b1     0.54   0.06       0.42       0.66  5372    1
b2     5.18   0.35       4.49       5.85  8782    1
```

```
b3      0.01    0.01      -0.02       0.04  8617     1
b4      1.70    0.36       1.01       2.40  7708     1
sigma   5.05    0.13       4.81       5.30  8220     1
```

11 Model assumption check

```
    pairs(m1)
```

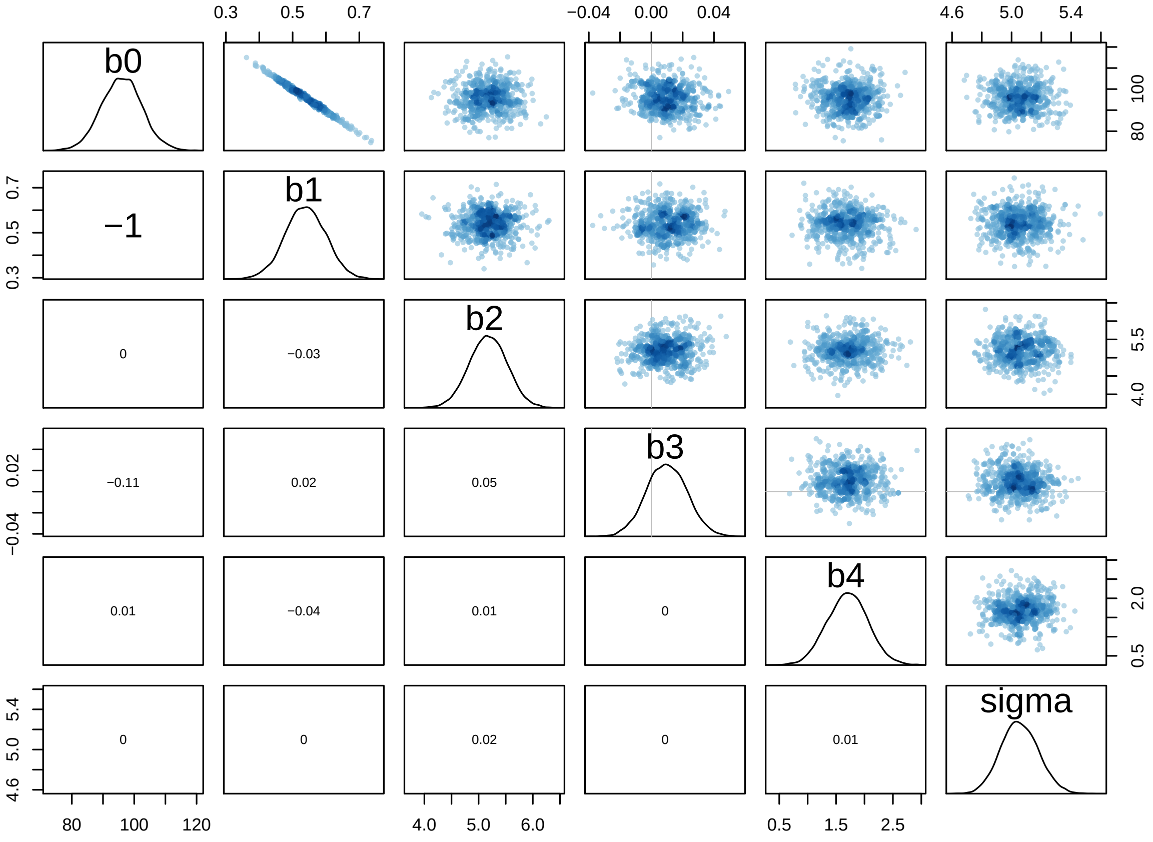
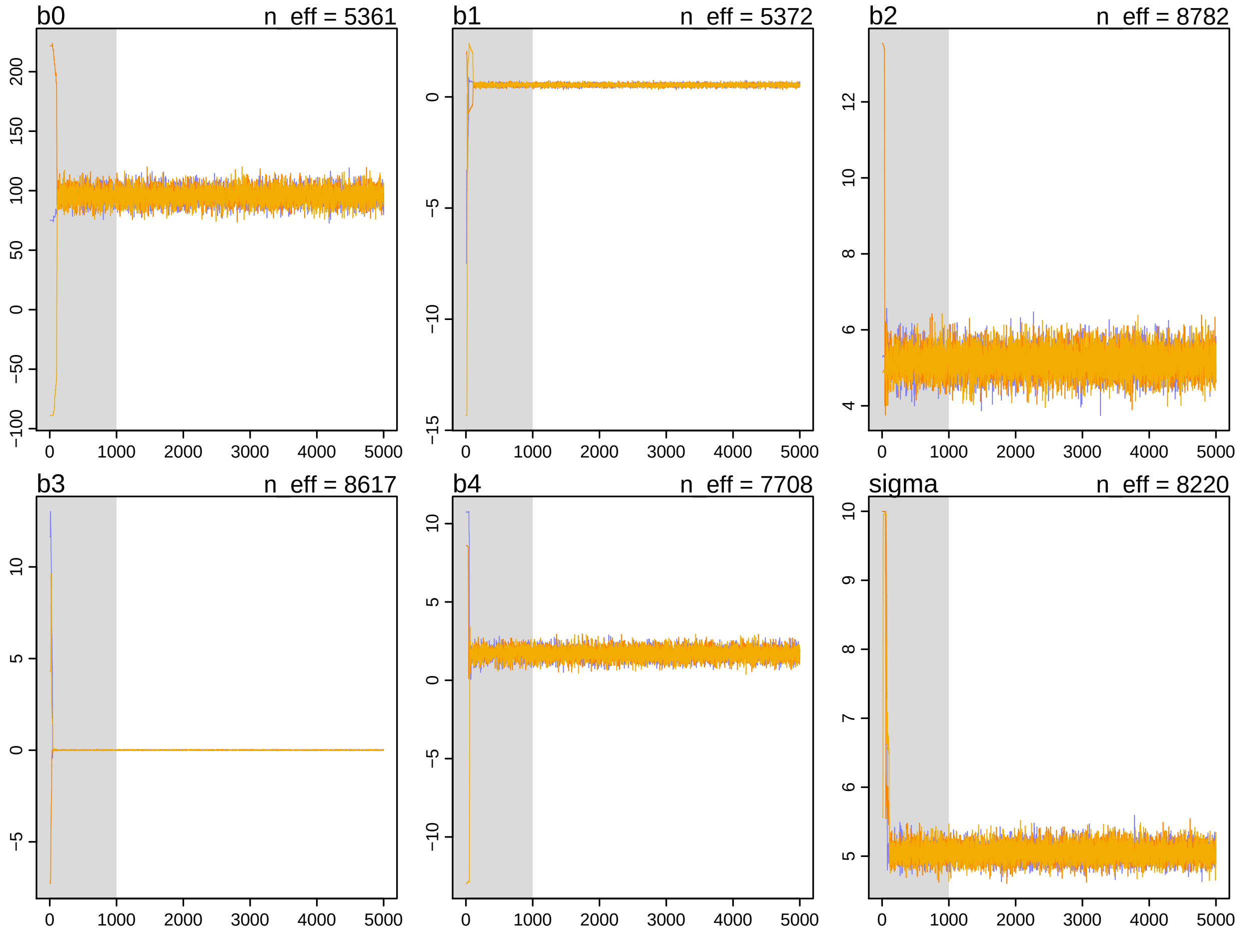


Figure 2: Check chains are mixing

```
    post <- extract.samples(m1)
   # lapply(post, densityplot)
#     par(mfrow=c(3,3))
#     for ( i in 1:6 )  { plot(post[i] , type='l', main=names(post)[i]) }
#     par(mfrow=c(1,1))

    plot(m1)
```


b0
n_eff = 5361
200
150
100
50
0
−50
−100
b1
n_eff = 5372
0
−5
−10
−15
b2
n_eff = 8782
12
10
8
6
4
b3
n_eff = 8617
10
5
0
−5
b4
n_eff = 7708
10
5
0
−5
−10
sigma
n_eff = 8220
10
9
8
7
6
5
0
1000
2000
3000
4000
5000

12 Plot the predicted effects, counterfactual samples of 100 patients are also simulated and plotted.

13 Treatment effect

```
nn <- 100 # just plot this number of patient rather than 800
post0 <- extract.samples(m0)

namez <- "Treatment"
x <- c(rep(0,nn/2) , rep(1, nn/2))

pred.data1 <- data.frame(    # Make predictions for this dataset
     treat= x
)

# compute counterfactual mean response (mu1)
mu1 <- link( m0 , data=pred.data1 )
mu.mean <- apply( mu1 , 2 , mean )
mu.PI <- apply( mu1 , 2 , PI )

# simulate counterfactual response outcomes
R.sim1 <- sim( m0 , data=pred.data1 , n=1e4 ) # n < posterior samples or error?
R.PI <- apply( R.sim1 , 2 , PI )

# Need Y to be the same length as x, these values are not plotted
Y <- seq(from=min( R.sim1, na.rm=T), max(R.sim1, na.rm=T), length.out=nn )

par(mfrow=c(1,2))

# mean and response outcome plot
plot( Y ~ x  , type="n", xlab=paste(namez), ylab="Response", xlim=c(-0.2,1.2 ),
# get appropriate y range
ylim=c(min( R.sim1,na.rm=T)*1, max( R.sim1, na.rm=T)*1), xaxt = "n")
axis(side = 1,   at = c(0,1), labels = c(0,1),     tck=-.05) # better ticks on x axis
# plot this info
lines( x , mu.mean )                                         # plot this info
shade( mu.PI , x , col= col.alpha("blue",   0.15))
shade( R.PI ,  x , col= col.alpha("purple", 0.15))
points(R.sim1[1,] ~ jitter(x))   # pick one of the many simulations to plot

# mean effect
plot(Y ~ x, type="n", xlab=paste(namez), ylab="Response" , ylim=c(155,158), xaxt = "n")
axis(side = 1, at = c(0,1), labels = c(0,1),  tck=-.05) # better axes
lines( x , mu.mean )
shade( mu.PI , x , col= col.alpha("blue", 0.15))
grid(nx = NULL, ny = NULL)

# title
mtext(line=-3, text= "Unadjusted treatment effect estimate", outer=T, cex=.7)

# title
```

```
foo<-post0$b4                        # collect the appropriate mcmc samples
mtext( line= -2,
text=paste(namez ," mean effect ", p2(mean(foo)),", SD=", p3(sd(foo)) ,", 95% CI (",
p2(quantile(foo, c(.025))), ", ", p2(quantile(foo, c(0.975))),"), p>0 = ",
mean(foo>0), sep="") ,outer = TRUE, cex = 1)
```

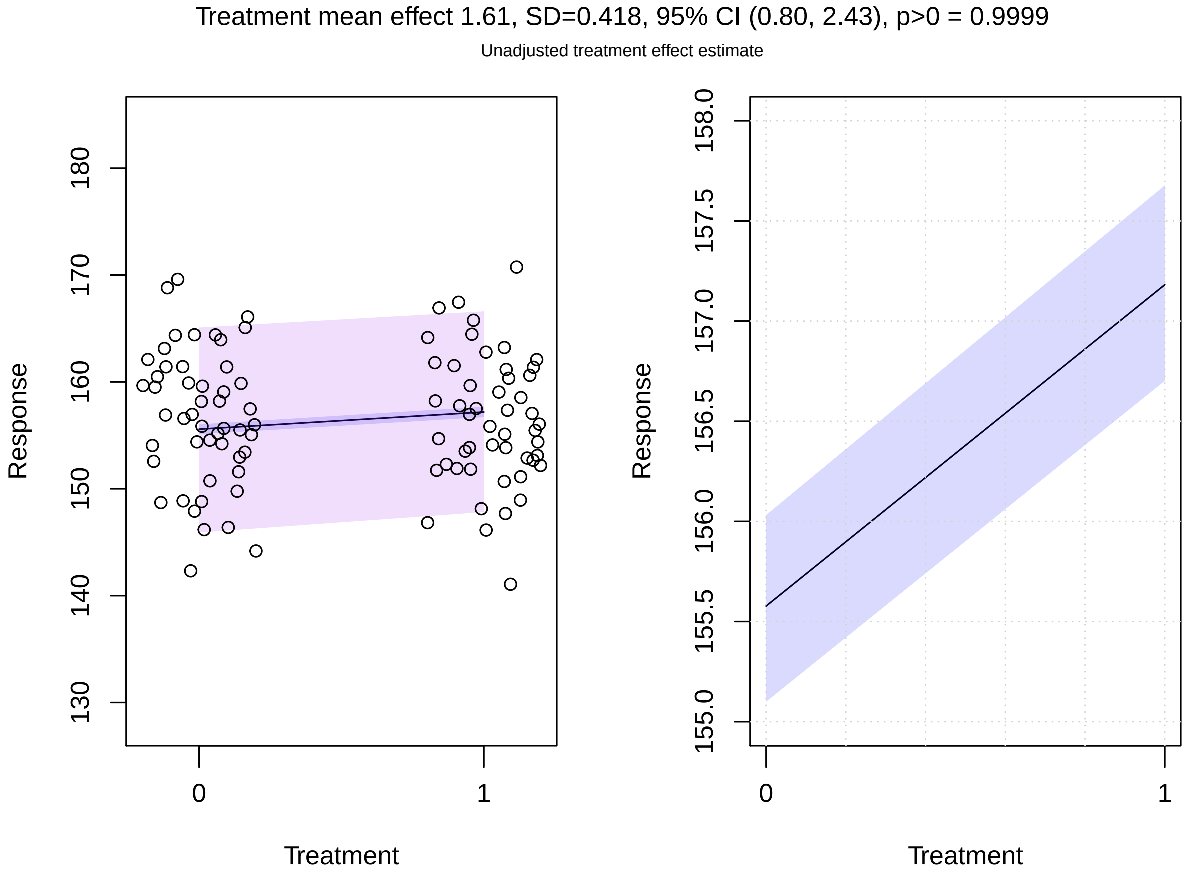


Figure 3: Effects of treatment on outcome, simulated response outcomes left panel, mean response right panel

14 Adjusted analysis

```
nn<-100 # just plot this number of patient rather than 800

par(mfrow=c(1,1))
P.baseline <- median(d$baseline)                    # Hold baseline
P.treat <- c(rep(0,nn/2) , rep(1, nn/2))            # vary
P.age <- median(d$age)                              # Hold age at median
P.sex <- 0                                          # Hold sex at female 0

namez <- "Treatment"
```

```
x <- P.treat    # define the variable here, so less typing later perhaps

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

# compute counterfactual mean response (mu1)
mu1 <- link( m1 , data=pred.data1 )
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 )

# Need Y to be the same length as x, these values are not plotted
Y <- seq(from=min( R.sim1, na.rm=T), max(R.sim1, na.rm=T), length.out=nn )

par(mfrow=c(1,2))

# mean and response outcome plot
plot( Y ~ x  , type="n", xlab=paste(namez), ylab="Response" , xlim=c(-0.2,1.2 ),
ylim=c(min( R.sim1, na.rm=T)*1, max( R.sim1, na.rm=T)*1), xaxt = "n")          # get appropriat
axis(side = 1,   at = c(0,1), labels = c(0,1),     tck=-.05) # better ticks on x axis
# plot this info
lines( x , mu.mean )                                         # plot this info
shade( mu.PI , x , col= col.alpha("blue",   0.15))
shade( R.PI ,  x , col= col.alpha("purple", 0.15))
points(R.sim1[1,] ~ jitter(x))   # pick one of the many simulations to plot

# mean effect
plot(Y ~ x, type="n", xlab=paste(namez), ylab="Response" , ylim=c(152,156), xaxt = "n")
axis(side = 1, at = c(0,1), labels = c(0,1),  tck=-.05) # better axes
lines( x , mu.mean )
shade( mu.PI , x , col= col.alpha("blue", 0.15))
grid(nx = NULL, ny = NULL)

# title
mtext( line=-3, text=paste(namez ,"effect adjusted to age",
P.age ,"; baseline", p2(P.baseline),"; sex coded", P.sex, sep=" "),  outer=T, cex=.7)

# title
foo<-post$b4                    # collect the appropriate mcmc samples

mtext( line= -2,
text=paste(namez ," mean effect ", p2(mean(foo , na.rm=T)),", SD=", p3(sd(foo,na.rm=T)) ,", 95%
p2(quantile(foo, c(.025), na.rm=T)), ", ", p2(quantile(foo, c(0.975), na.rm=T)),"), p>0 = ",
mean(foo>0), sep="")
,outer = TRUE, cex = 1)
```

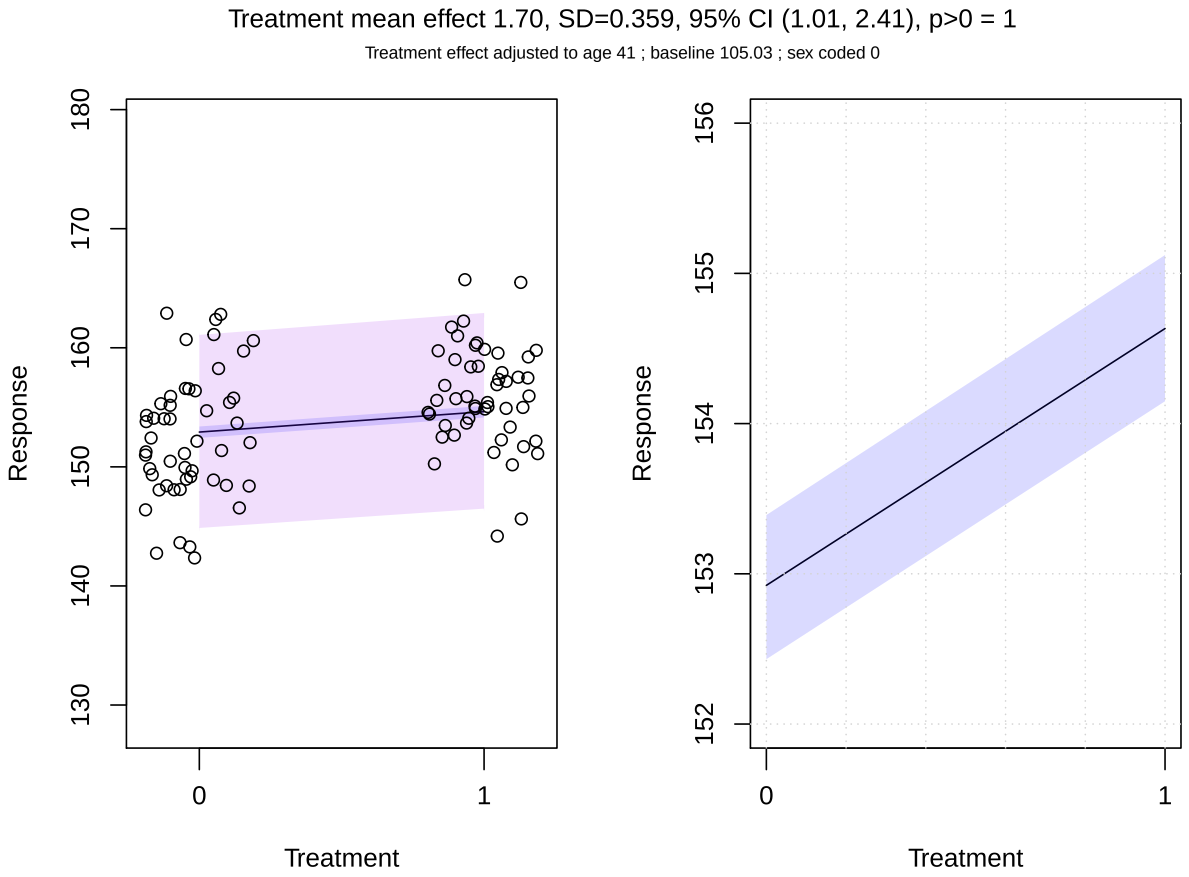


Figure 4: Effects of treatment on outcome, simulated response outcomes left panel, mean response right panel

15 For completion the effects of the other covariates on outcome; age

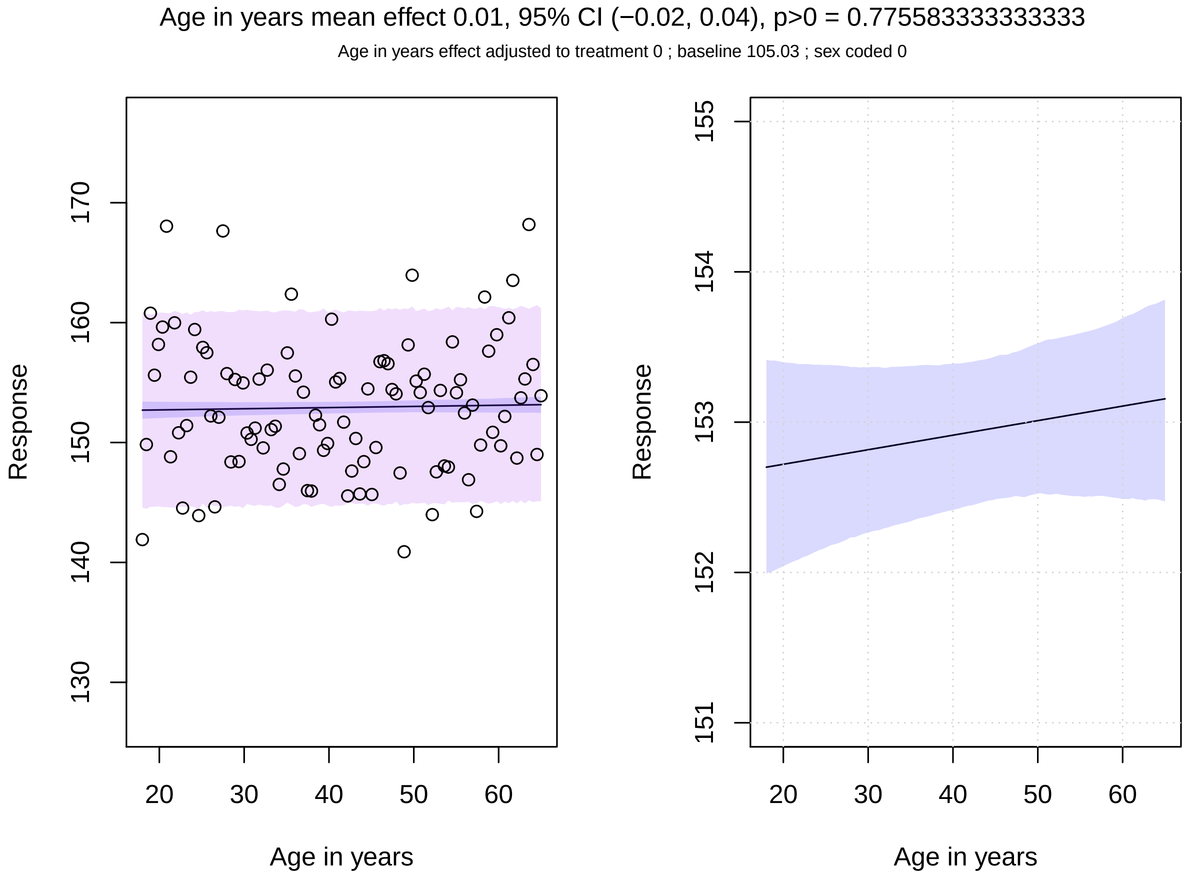


Figure 5: Effects of age on outcome, simulated response outcomes left panel, mean response right panel

16 Baseline effect on outcome

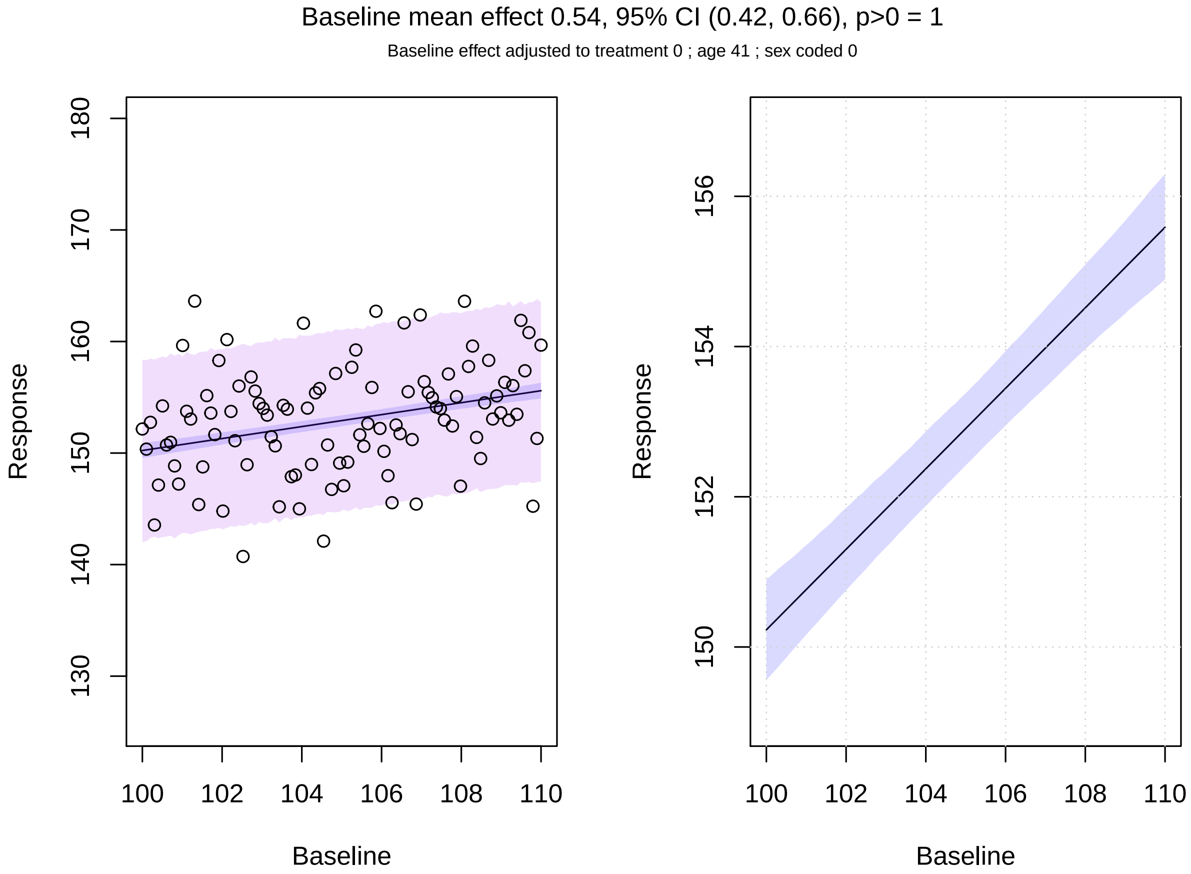
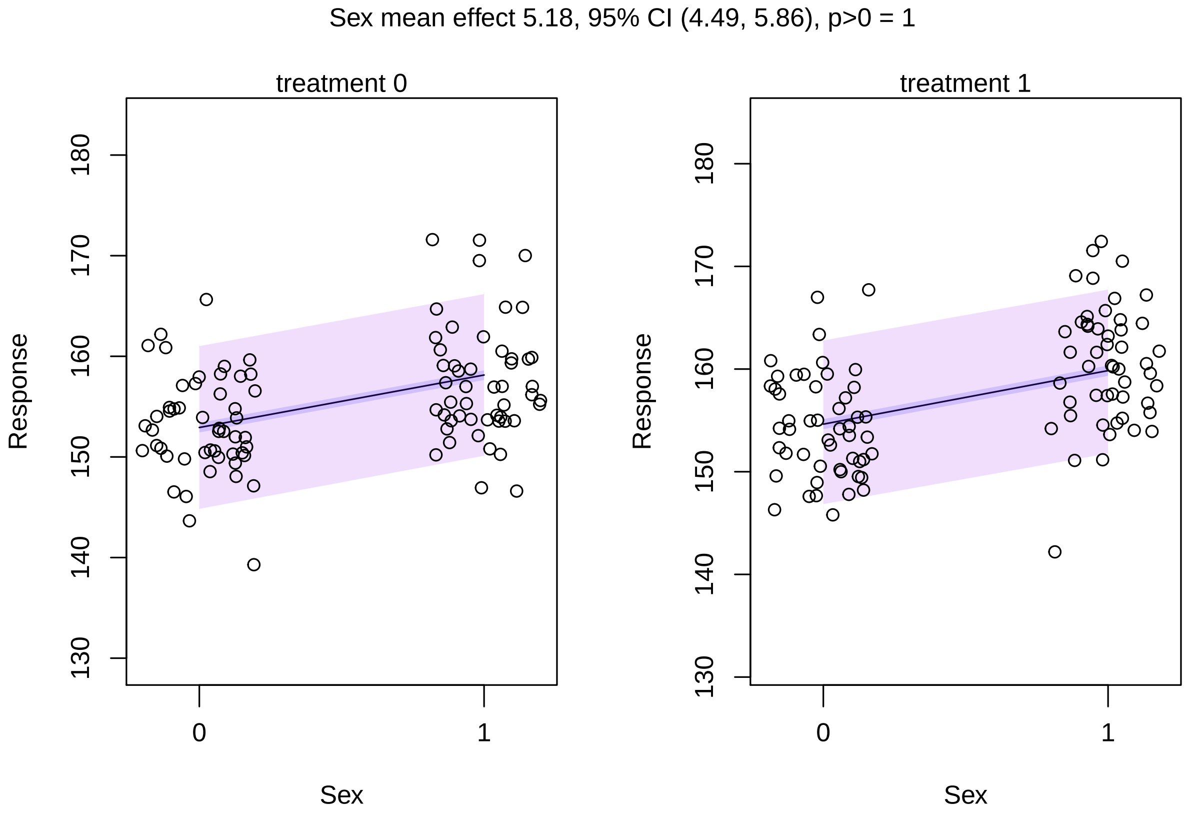
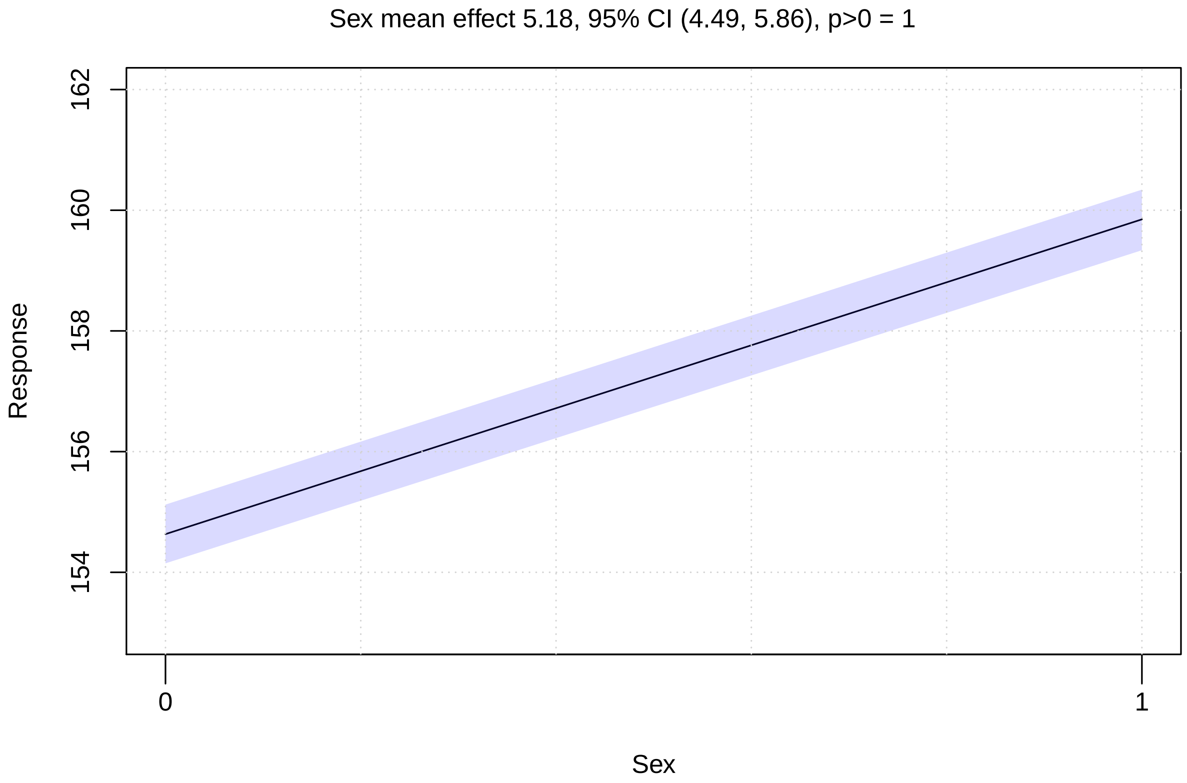


Figure 6: Effects of baseline on outcome, simulated response outcomes left panel, mean response right panel

17 Effect on outcome; sex. There is no real need to show treatment as well, as no interaction was modelled.



Sex effect adjusted to age 41 ; baseline 105.0275



Sex effect adjusted to age 41 ; baseline 105.0275

18 Frequentist analysis, print the regression table (also print Bayesian)

```
precis(m1)
```

```
       Mean StdDev lower 0.89 upper 0.89 n_eff Rhat
b0    95.98   6.47      85.52     106.13  5361    1
b1     0.54   0.06       0.45       0.64  5372    1
b2     5.18   0.35       4.63       5.74  8782    1
b3     0.01   0.01      -0.01       0.03  8617    1
b4     1.70   0.36       1.14       2.28  7708    1
sigma  5.05   0.13       4.86       5.26  8220    1
```

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

```
Linear Regression Model

ols(formula = Y ~ baseline + sex + age + treat, data = d, x = TRUE,
    y = TRUE)
                Model Likelihood     Discrimination
                   Ratio Test           Indexes
Obs       800    LR chi2    263.60    R2       0.281
sigma 5.0481    d.f.            4    R2 adj   0.277
d.f.      795    Pr(> chi2) 0.0000    g        3.626

Residuals

     Min       1Q   Median       3Q      Max
-15.8808  -3.3450  -0.1489   3.4544  15.8508

          Coef    S.E.   t     Pr(>|t|)
Intercept 96.3270 6.5606 14.68 <0.0001
baseline   0.5352 0.0621  8.62 <0.0001
sex=M      5.1832 0.3576 14.49 <0.0001
age        0.0098 0.0128  0.76 0.4458
treat      1.7060 0.3572  4.78 <0.0001
```

19 Compute analysis of variance table for the fitted model object with χ^2 statistics.

```
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      Tested
 baseline     1   1891.44228 1891.44228  74.22     <.0001 1
 sex          1   5353.62495 5353.62495 210.08     <.0001 2
 age          1     14.83008   14.83008   0.58     0.4455 3
 treat        1    581.34701  581.34701  22.81     <.0001 4
 REGRESSION   4   7906.66760 1976.66690 310.27     <.0001 1-4
 ERROR      795  20259.11554   25.48316

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

20 Plot the partial effect of each variable.

```
par(mfrow=c(3,1))
plot(an,
what=c("proportion chisq"),
xlab=NULL, pch=16,
rm.totals=TRUE, rm.ia=FALSE, rm.other=NULL,
sort=c("descending"), margin=NULL, pl=TRUE,
trans=NULL, ntrans=40 )

 plot(an,
what=c("chisqminusdf"))

  plot(an,
what=c('proportion R2'))
```

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

21 Compute predicted values and confidence limits

```
plot(Predict(f),   anova=an, pval=TRUE)
```

22 The key result, computed predicted values and confidence limits for the treatment effect on outcome. Notice the larger SE for the unadjusted analysis.

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

```
            Effects              Response : Y

Factor Low High Diff. Effect S.E.    Lower 0.95 Upper 0.95
treat  0   1    1     1.706  0.35719 1.0049     2.4072
```

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

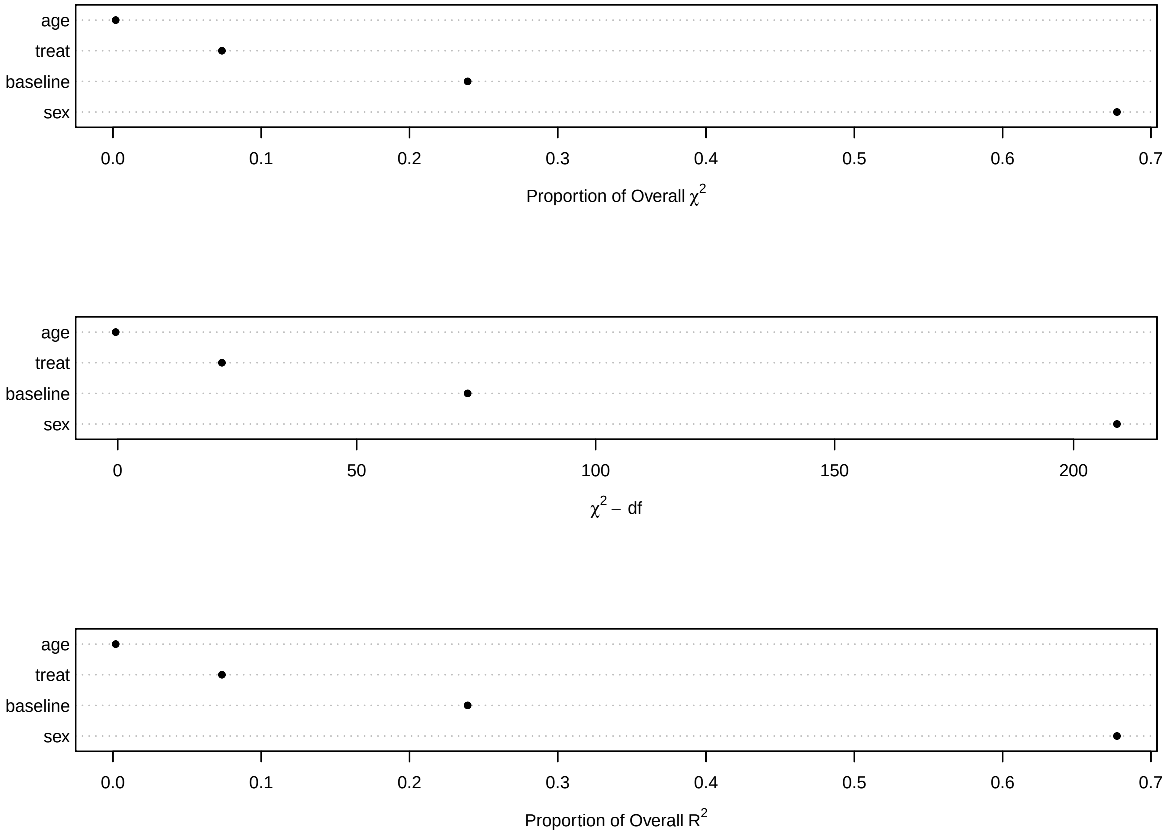


Figure 7: The default for plot(anova()) is to display the Wald Chi2 statistic minus its degrees of freedom for assessing the partial effect of each variable. Even though this is not scaled [0,1] it is probably the best method in general because it penalizes a variable requiring a large number of parameters 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.

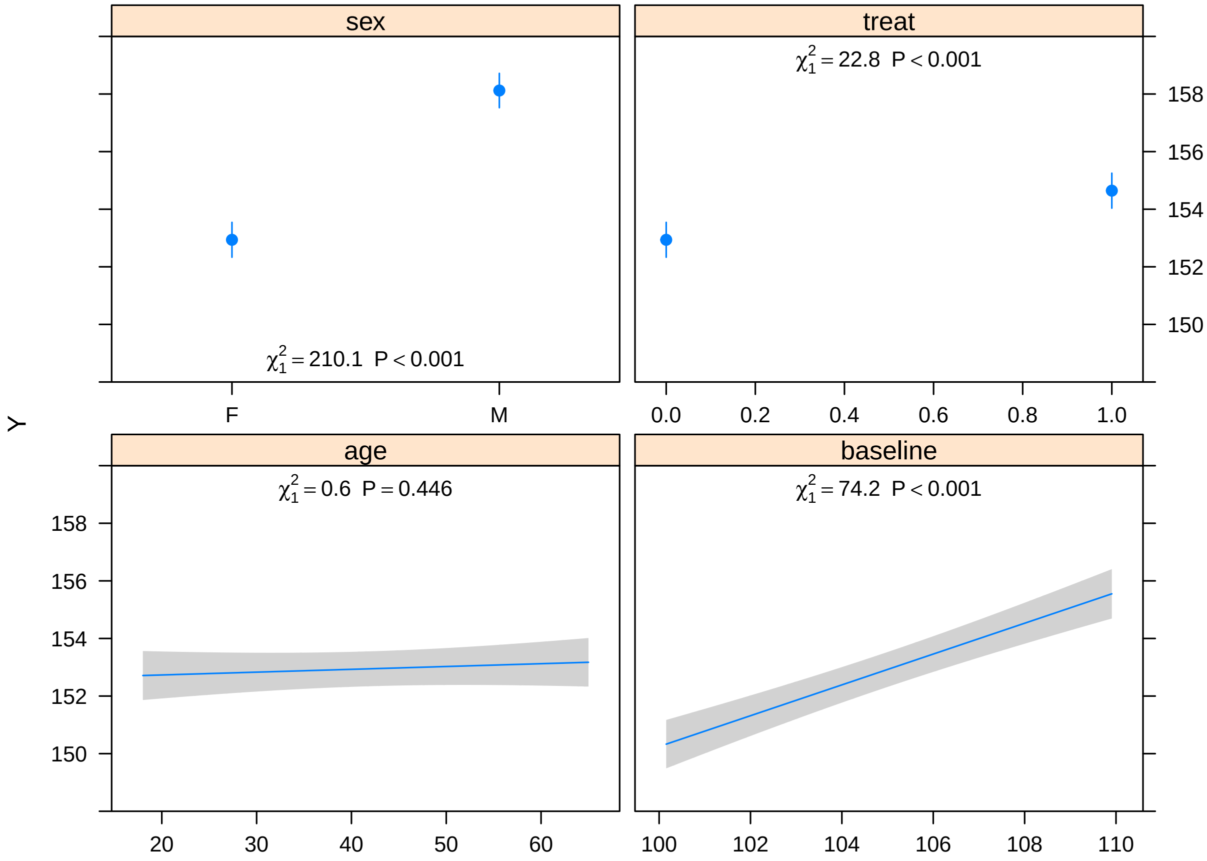
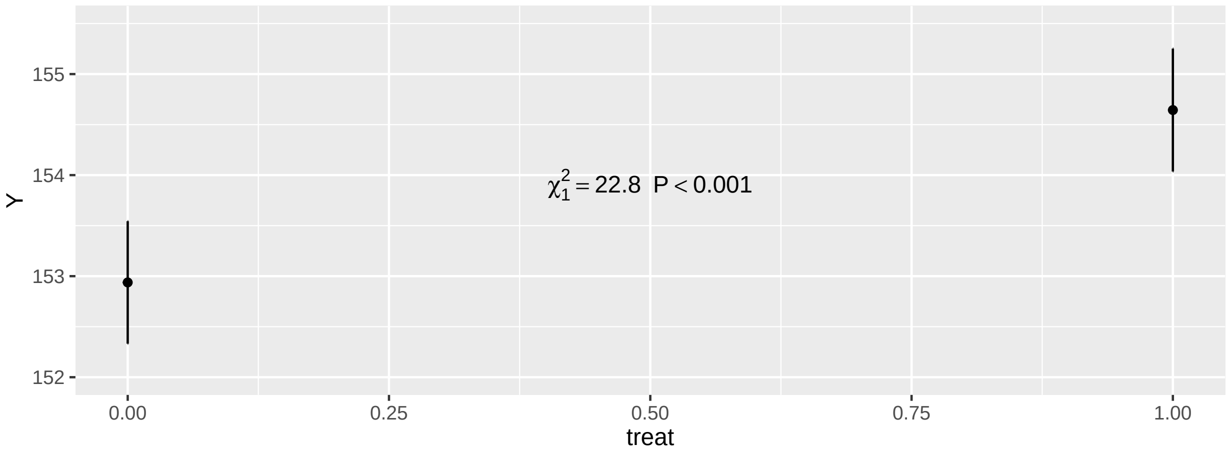


Figure 8: Show predicted values and confidence bands

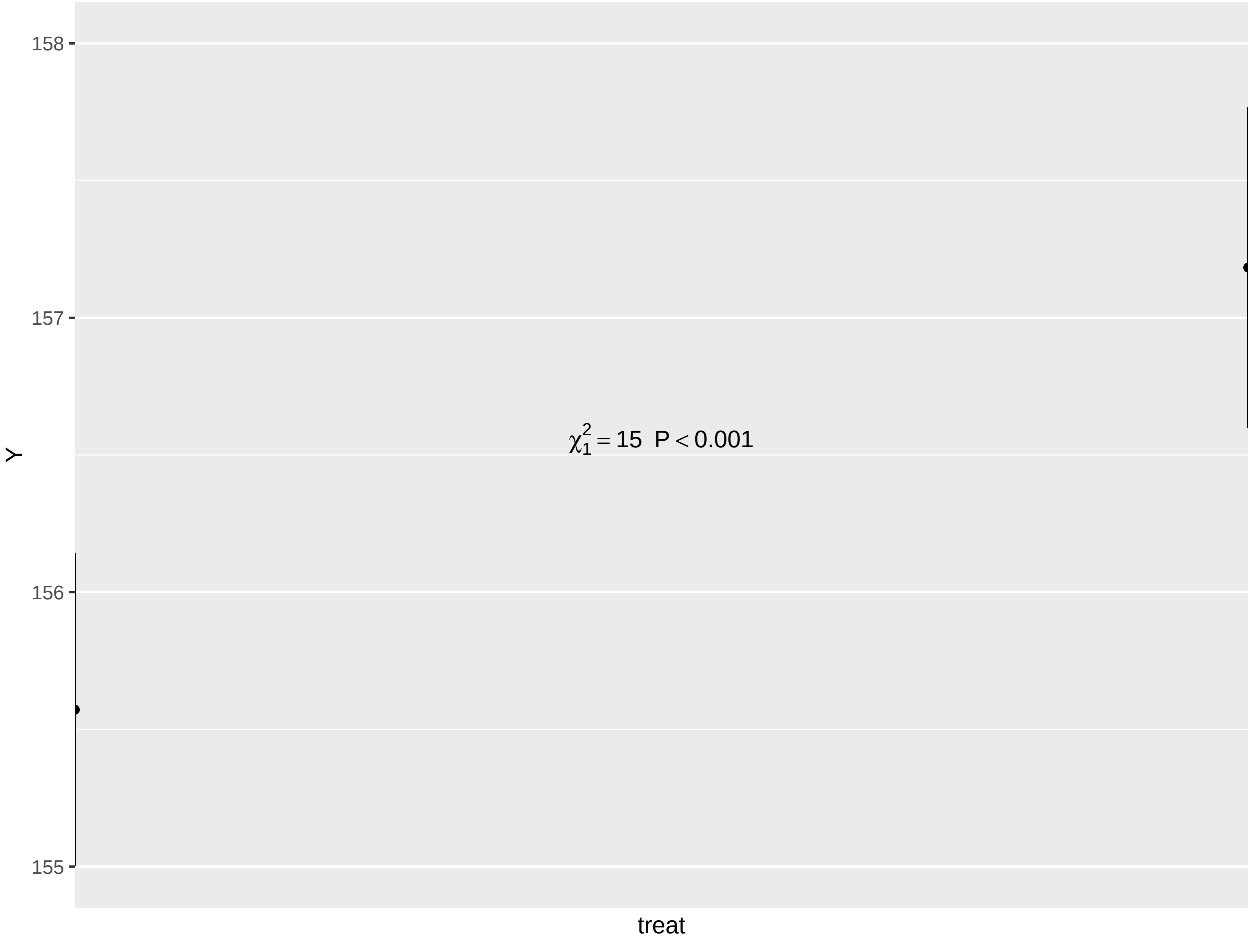


Adjusted to:baseline=105 sex=F age=41

```
#univariate
f0 <- ols( Y ~ treat   , d,  x=TRUE, y=TRUE)
summary(f0, treat=c(0,1))
```

```
             Effects              Response : Y

 Factor Low High Diff. Effect S.E.    Lower 0.95 Upper 0.95
 treat  0   1    1     1.6114 0.41636 0.79413    2.4287
```

```
an0 <- anova(f0, main.effect=FALSE, test=c('Chisq'))
ggplot(Predict(f0), anova=an0, pval=TRUE)
```



23 Plot the other covariate effects for information. Sex main effect on outcome.

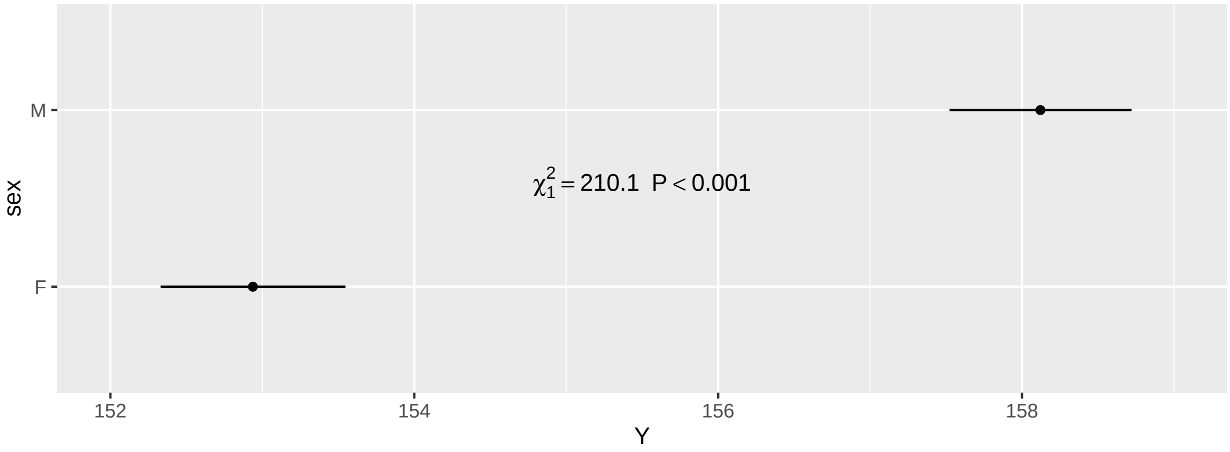
```r
summary(f, sex=c("M","F"), est.all=FALSE)
```

```
             Effects              Response : Y 

 Factor     Low High Diff. Effect S.E.   Lower 0.95 Upper 0.95
 sex - M:F 1    2    NA    5.1832 0.3576 4.4813     5.8852    
```

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

24 Show age main effect on outcome.

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

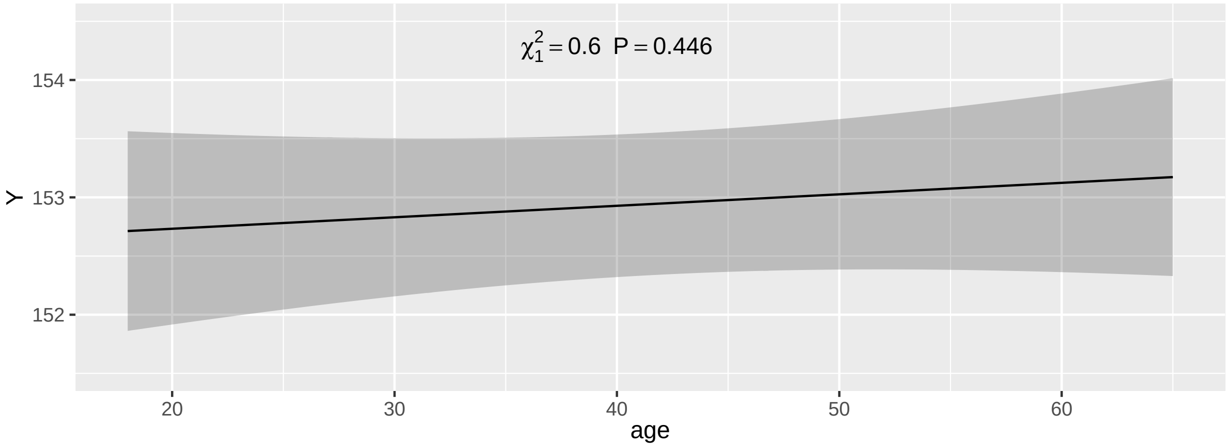


Adjusted to:baseline=105 age=41 treat=0

Figure 9: 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    0.45971 0.60262 -0.7232    1.6426
```

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



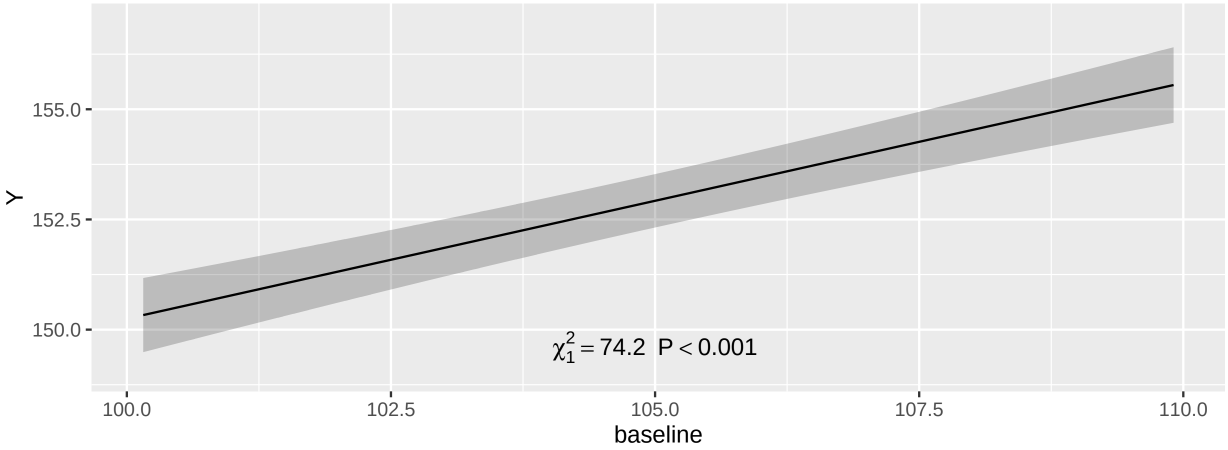
Adjusted to:baseline=105 sex=F treat=0

25 Show baseline main effect on outcome.

```
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     1.0704 0.12424 0.8265     1.3143    
```

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



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

Figure 10: Baseline main effect on outcome

26 Reproduce the regression table using the summary function

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

```
             Effects              Response : Y

 Factor     Low High Diff. Effect    S.E.     Lower 0.95 Upper 0.95
 baseline   0   1     1    0.5351900 0.062121  0.413250  0.65713
 age        0   1     1    0.0097812 0.012822 -0.015387  0.03495
 treat      0   1     1    1.7060000 0.357190  1.004900  2.40720
 sex - M:F  1   2    NA    5.1832000 0.357600  4.481300  5.88520
```

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

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

```
  age baseline sex Contrast    S.E.    Lower    Upper    t Pr(>|t|)
1   0        0   F 1.706045 0.35719 1.004898 2.407192 4.78        0

Error d.f.= 795

Confidence intervals are 0.95 individual intervals
```

28 The contrast function, treatment effect when covariates held at median, however this does not matter as there is no interaction in the model

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

```
  age baseline sex Contrast    S.E.    Lower    Upper    t Pr(>|t|)
1  41 105.0275   F 1.706045 0.35719 1.004898 2.407192 4.78        0

Error d.f.= 795

Confidence intervals are 0.95 individual intervals
```

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

```
  baseline sex age Contrast    S.E.    Lower    Upper    t Pr(>|t|)
1 105.0275   F  41 1.706045 0.35719 1.004898 2.407192 4.78        0

Error d.f.= 795

Confidence intervals are 0.95 individual intervals
```

29 Assumption check

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

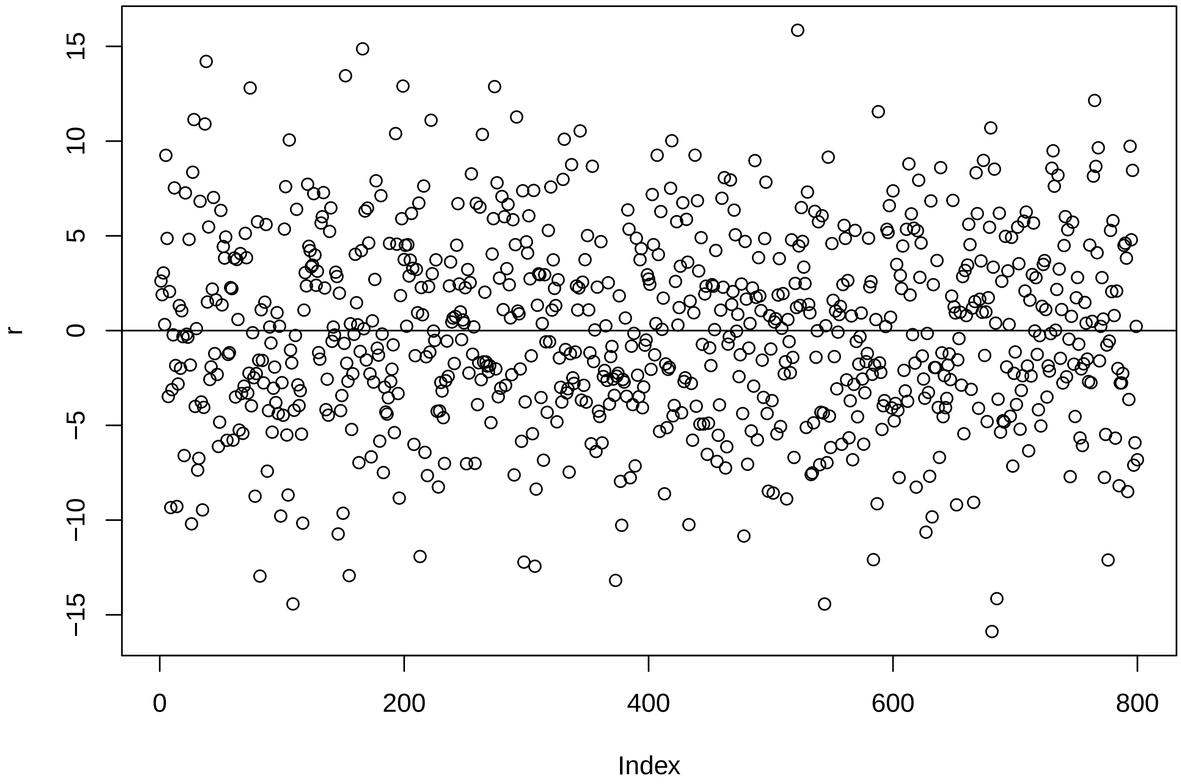


Figure 11: Check OLS assumptions

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

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

30 References

Statistical Rethinking 1st Edition, 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

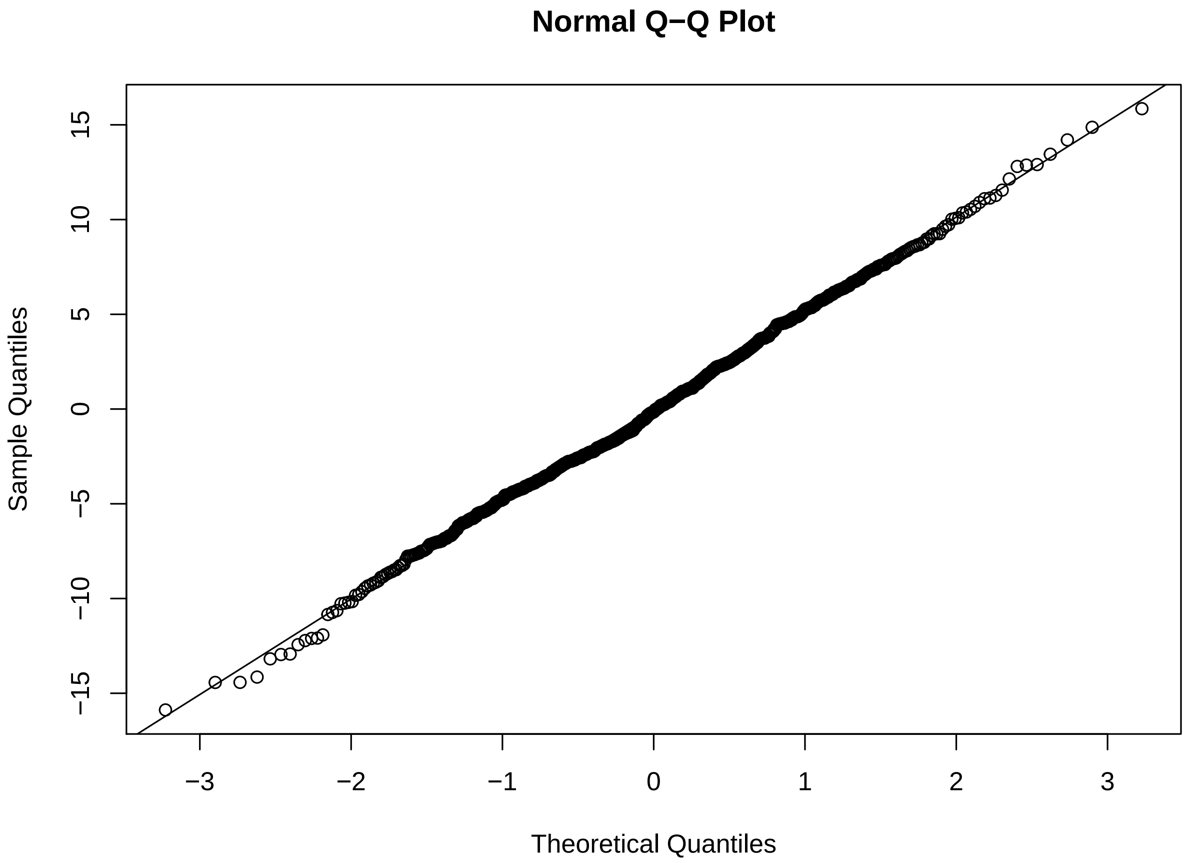


Figure 12: Check OLS assumptions

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

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

31 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          reshape2_1.4.1      splines_3.2.2
 [4] colorspace_1.2-6    htmltools_0.3.5     stats4_3.2.2
 [7] loo_0.1.6           yaml_2.1.13         chron_2.3-47
[10] foreign_0.8-66      RColorBrewer_1.1-2  matrixStats_0.50.2
[13] multcomp_1.4-6      plyr_1.8.4          stringr_1.1.0
[16] MatrixModels_0.4-1  munsell_0.4.3       gtable_0.2.0
[19] mvtnorm_1.0-5       codetools_0.2-14    coda_0.18-1
[22] evaluate_0.9        labeling_0.3        latticeExtra_0.6-28
[25] inline_0.3.14       quantreg_5.26       TH.data_1.0-7
[28] Rcpp_0.12.6         KernSmooth_2.23-15  acepack_1.3-3.3
[31] scales_0.4.0        formatR_1.4         gridExtra_2.2.1
[34] digest_0.6.10       stringi_1.1.1       polspline_1.1.12
[37] grid_3.2.2          tools_3.2.2         sandwich_2.3-4
[40] magrittr_1.5        cluster_2.0.3       MASS_7.3-45
[43] 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
```

This took 398.19 seconds to execute.