Phaco meta analysis

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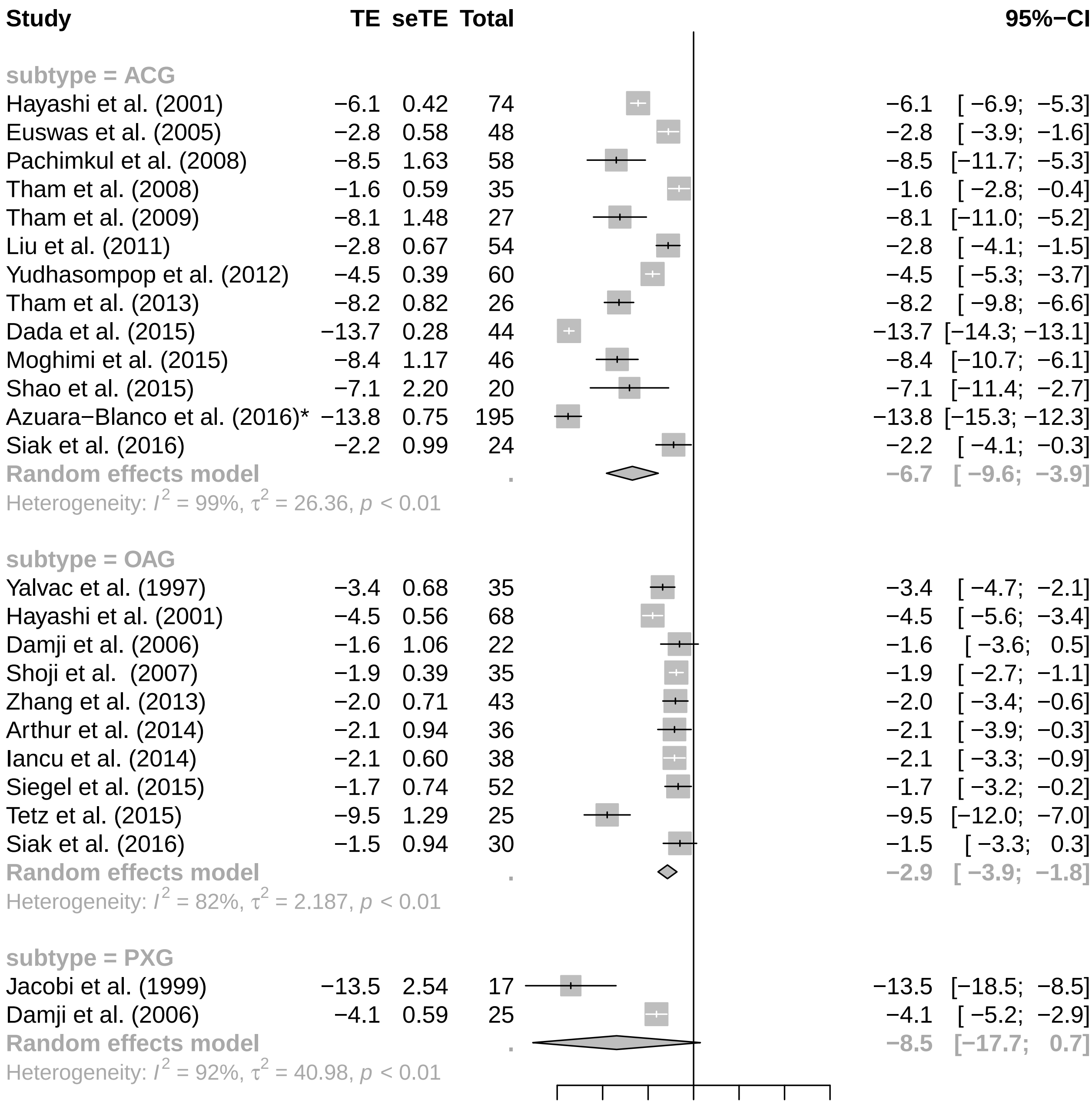
TODO

- Find a better way to deal with wash out - in some cases, the readings may refer to pre-meds or post-meds and some studies have pre- or post-op washout and it's all very annoying.

Analysis of full dataset

6 month follow-up

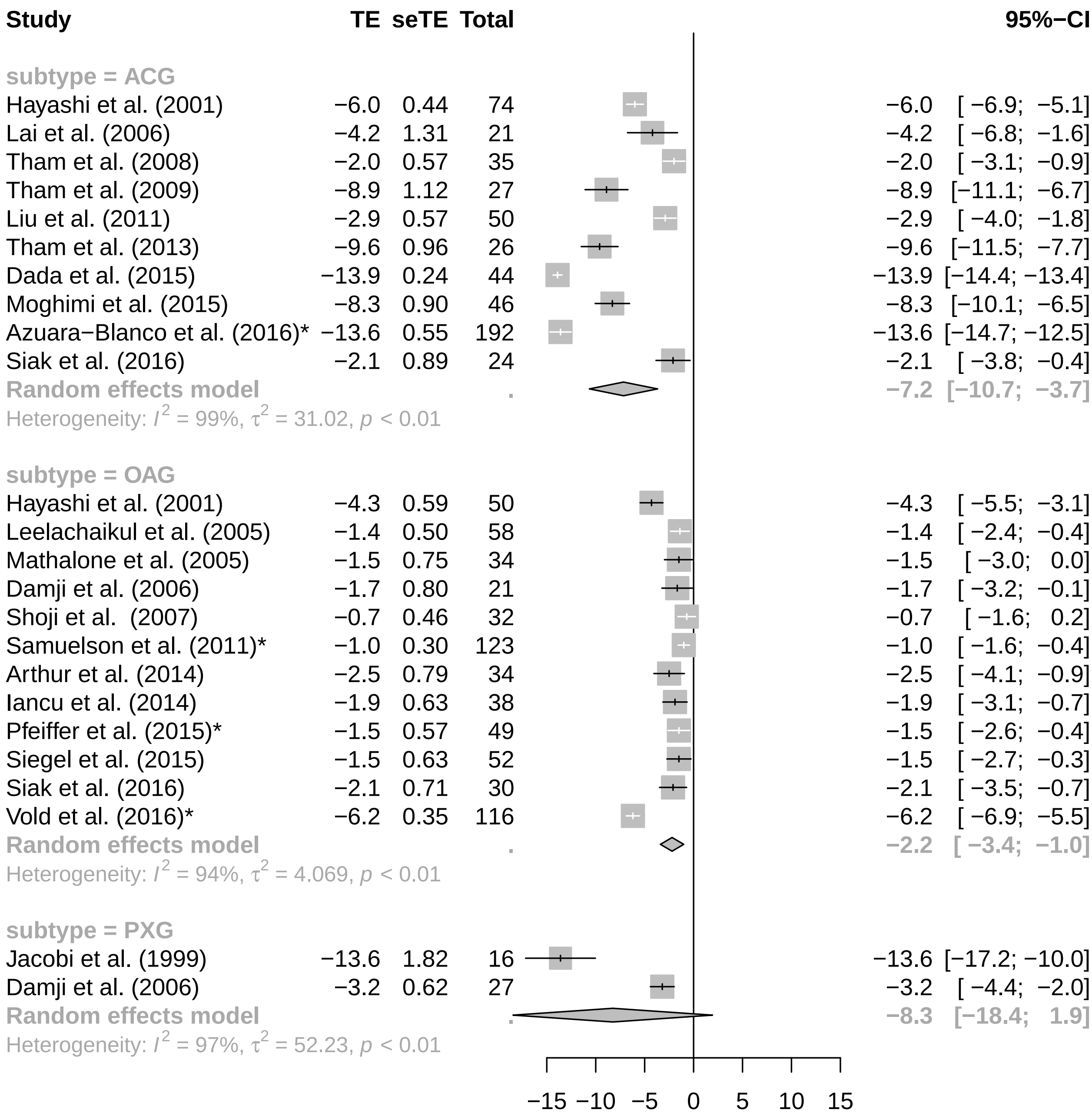
```
df_ <- df %>%
  filter(!is.na(SixMoAbsIOPChangeMean), subtype != "acute") %>%
  mutate(subtype=factor(subtype))
m <- metagen(SixMoAbsIOPChangeMean,
             SixMoAbsIOPChangeStdDev / sqrt(SixMoEyes),
             study.name,
             data=df_,
             byvar=subtype,
             n.e=SixMoEyes)
forest(m,
       comb.fixed=FALSE,
       digits=1,
       digits.se = 2,
       overall=FALSE,
       leftcols=c("studlab", "TE", "seTE", "n.e"))
```



12-month follow up

```
df_ <- df %>%
  filter(!is.na(OneYAbsIOPChangeMean), subtype != "acute", MIGsYorN == 'N') %>%
  mutate(subtype=factor(subtype))
m <- metagen(OneYAbsIOPChangeMean,
             OneYAbsIOPChangeStdDev / sqrt(OneYEyes),
             study.name,
             data=df_,
             byvar=subtype,
             n.e=OneYEyes)
forest(m,
```

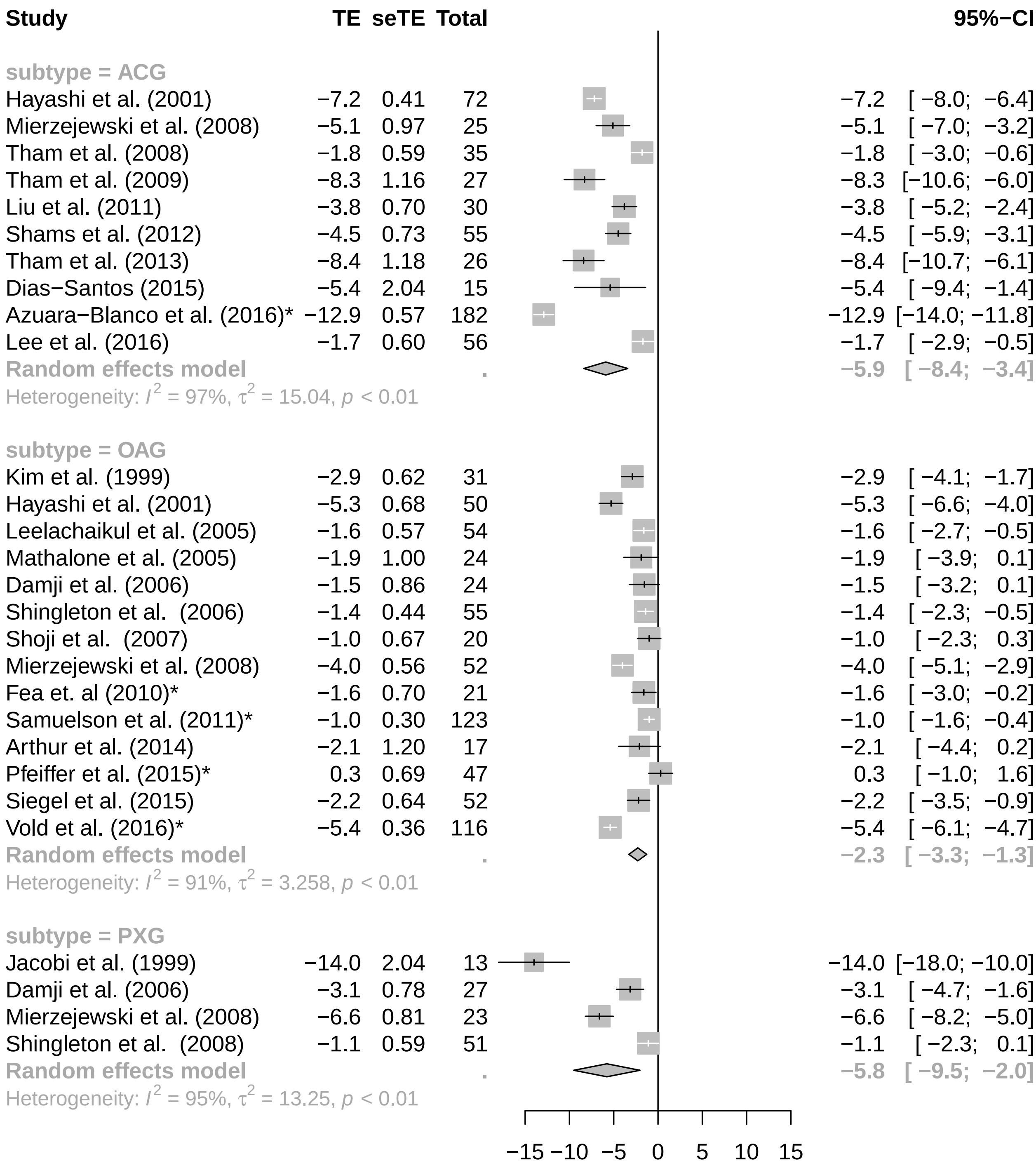
```
       comb.fixed=FALSE,
       digits=1,
       digits.se = 2,
       overall=FALSE,
       leftcols=c("studlab", "TE", "seTE", "n.e"))
```



Last period

```
df_ <- df %>%
  filter(!is.na(LastPeriodAbsIOPChangeMean), subtype != "acute", MIGsYorN == 'N') %>%
  mutate(subtype=factor(subtype))
m <- metagen(LastPeriodAbsIOPChangeMean,
```

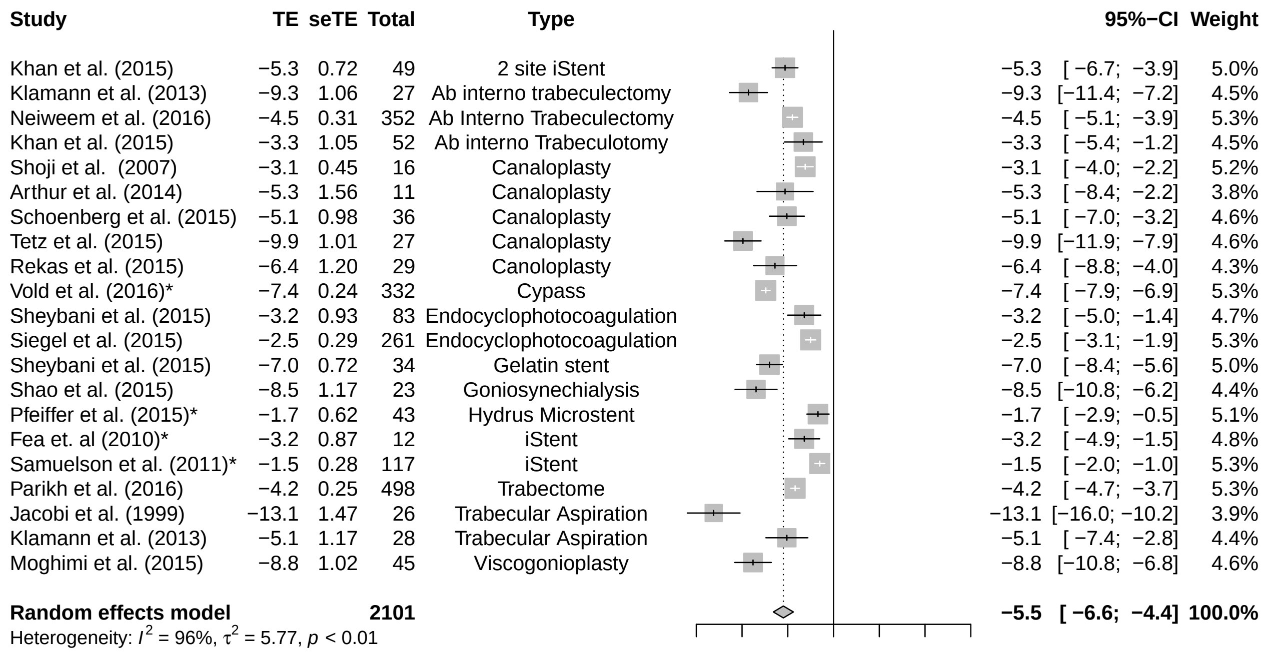
```
              LastPeriodAbsIOPChangeStdDev / sqrt(LastPeriodEyes),
              study.name,
              data=df_,
              byvar=subtype,
              n.e=LastPeriodEyes)
forest(m,
       comb.fixed=FALSE,
       digits=1,
       digits.se = 2,
       overall=FALSE,
       leftcols=c("studlab", "TE", "seTE", "n.e"))
```



MIGS

```
df_ <- df %>%
  filter(!is.na(LastPeriodAbsIOPChangeMean), subtype != "acute", MIGsYorN == 'Y') %>%
  mutate(subtype=factor(subtype)) %>% dplyr::arrange(TypesofMIGSifany, Year)
m <- metagen(LastPeriodAbsIOPChangeMean,
             LastPeriodAbsIOPChangeStdDev / sqrt(LastPeriodEyes),
```

```
             study.name,
             data=df_,
             n.e=LastPeriodEyes)
forest(m,
       comb.fixed=FALSE,
       digits=1,
       digits.se = 2,
       overall=TRUE,
       leftcols=c("studlab", "TE", "seTE", "n.e", "TypesofMIGSifany"),
       leftlabs=c("Study", "TE", "seTE", "Total", "Type"))
```



Acute

```
cat("===================================================================\n")
cat("Six months: \n")
cat("===================================================================\n")
df_ <- df %>%
  filter(!is.na(SixMoAbsIOPChangeMean), subtype == "acute", MIGsYorN == 'N') %>%
  mutate(subtype=factor(subtype)) %>% dplyr::arrange(Year)
m <- metagen(SixMoAbsIOPChangeMean,
             SixMoAbsIOPChangeStdDev / sqrt(SixMoEyes),
             study.name,
             data=df_,
             n.e=SixMoEyes, comb.fixed = FALSE)
print(m)

cat("===================================================================\n")
cat("One year: \n")
cat("===================================================================\n")
df_ <- df %>%
  filter(!is.na(OneYAbsIOPChangeMean), subtype == "acute", MIGsYorN == 'N') %>%
```

```r
  mutate(subtype=factor(subtype)) %>% dplyr::arrange(Year)
m <- metagen(OneYAbsIOPChangeMean,
             OneYAbsIOPChangeStdDev / sqrt(OneYEyes),
             study.name,
             data=df_,
             n.e=OneYEyes, comb.fixed = FALSE)
print(m)

cat("==========================================================================\n")
cat("Last period: \n")
cat("==========================================================================\n")
df_ <- df %>%
  filter(!is.na(LastPeriodAbsIOPChangeMean), subtype == "acute", MIGsYorN == 'N') %>%
  mutate(subtype=factor(subtype)) %>% dplyr::arrange(Year)
m <- metagen(LastPeriodAbsIOPChangeMean,
             LastPeriodAbsIOPChangeStdDev / sqrt(LastPeriodEyes),
             study.name,
             data=df_,
             n.e=LastPeriodEyes, comb.fixed = FALSE)
print(m)
```

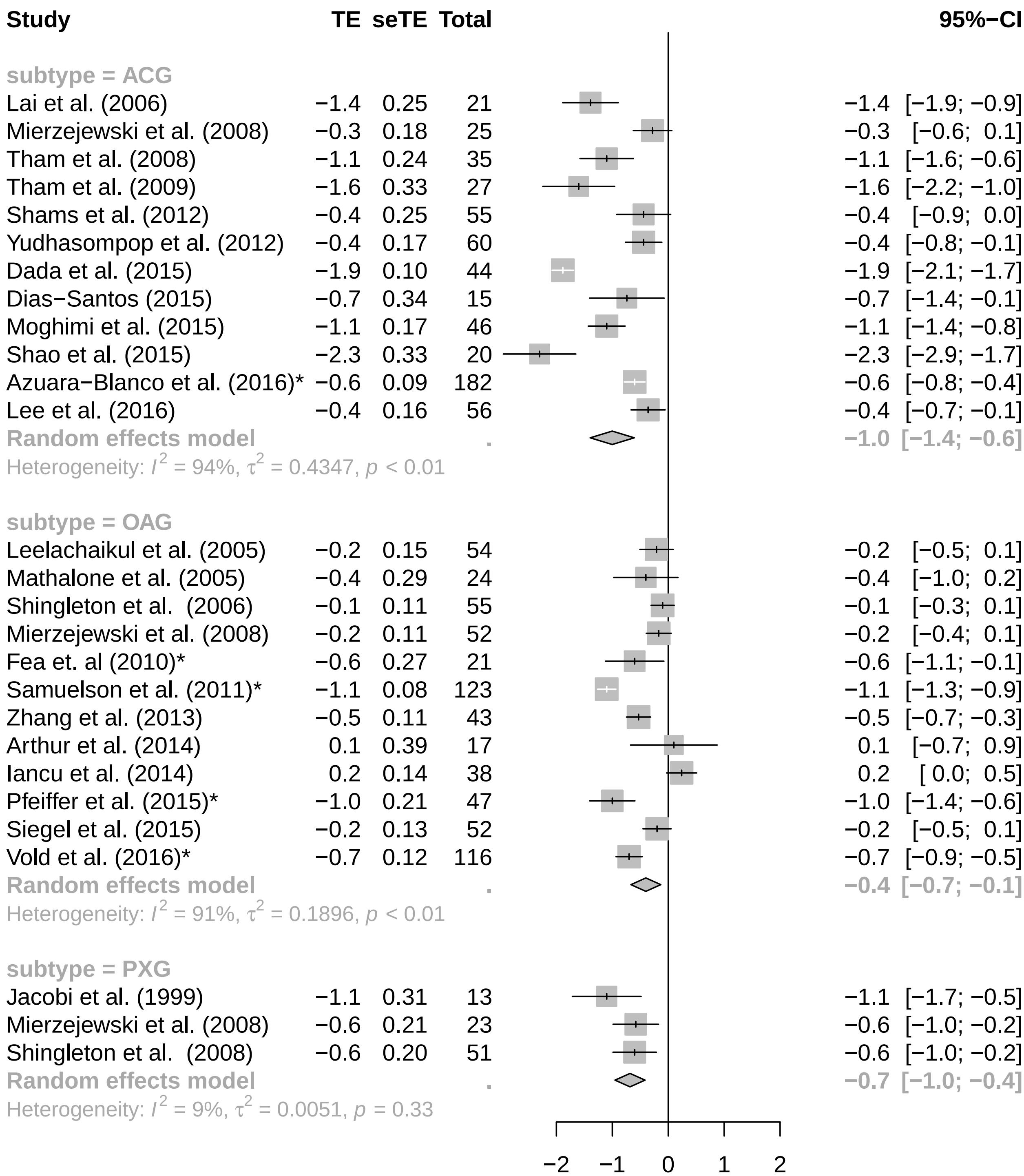
```
## ==========================================================================
## Six months:
## ==========================================================================
##                                          95%-CI %W(random)
## Lam et al. (2008) -47.0000 [-51.0521; -42.9479]       50.2
## Hou et al. (2015) -38.2000 [-42.4159; -33.9841]       49.8
##
## Number of studies combined: k = 2
##
##                                           95%-CI     z  p-value
## Random effects model -42.62 [-51.2438; -33.9963] -9.69 < 0.0001
##
## Quantifying heterogeneity:
##  tau^2 = 34.2694; H = 2.95; I^2 = 88.5%;
##  Rb = 88.5%
##
## Test of heterogeneity:
##     Q d.f.  p-value
##  8.70    1   0.0032
##
## Details on meta-analytical method:
## - Inverse variance method
## - DerSimonian-Laird estimator for tau^2
## ==========================================================================
## One year:
## ==========================================================================
##                                          95%-CI %W(random)
## Lam et al. (2008) -47.6000 [-50.4731; -44.7269]       50.1
## Hou et al. (2015) -35.9600 [-38.9540; -32.9660]       49.9
##
## Number of studies combined: k = 2
##
##                                             95%-CI     z  p-value
```

```
## Random effects model -41.7879 [-53.1949; -30.3809] -7.18 < 0.0001
##
## Quantifying heterogeneity:
##  tau^2 = 65.5036; H = 5.50; I^2 = 96.7%;
##  Rb = 96.7%
##
## Test of heterogeneity:
##      Q d.f.  p-value
##  30.23    1 < 0.0001
##
## Details on meta-analytical method:
## - Inverse variance method
## - DerSimonian-Laird estimator for tau^2
## ========================================================================
## Last period:
## ========================================================================
##                                             95%-CI %W(random)
## Jacobi et al. (2002) -22.7000 [-23.6565; -21.7435]       25.6
## Lam et al. (2008)    -47.1000 [-50.0449; -44.1551]       25.3
## Lee et al. (2010)    -35.8000 [-39.5586; -32.0414]       25.1
## Husain et al. (2012) -44.5000 [-51.8668; -37.1332]       24.0
##
## Number of studies combined: k = 4
##
##                                             95%-CI     z  p-value
## Random effects model -37.3974 [-51.7129; -23.0820] -5.12 < 0.0001
##
## Quantifying heterogeneity:
##  tau^2 = 208.4467; H = 9.89 [8.06; 12.13]; I^2 = 99.0% [98.5%; 99.3%];
##  Rb = 97.7% [93.1%; 100.0%]
##
## Test of heterogeneity:
##       Q d.f.  p-value
##  293.22    3 < 0.0001
##
## Details on meta-analytical method:
## - Inverse variance method
## - DerSimonian-Laird estimator for tau^2
```

Meds

```
df_ <- df %>%
  filter(!is.na(RxChangeMean), !is.na(RxChangeStdDev),
         df$subtype != "acute", MIGsYorN == 'N') %>%
  mutate(subtype=factor(subtype))
m <- metagen(RxChangeMean,
             sqrt(RxPostOpStdDev** 2 + RxPreOpStdDev ** 2) / sqrt(LastPeriodEyes),
             study.name,
             data=df_,
             byvar=subtype,
             n.e=LastPeriodEyes)
forest(m,
```

```
comb.fixed=FALSE,
digits=1,
digits.se = 2,
overall=FALSE,
leftcols=c("studlab", "TE", "seTE", "n.e"))
```



Correlation between meds and drop in IOP

How is IOP drop related to change in meds? Two hypotheses:

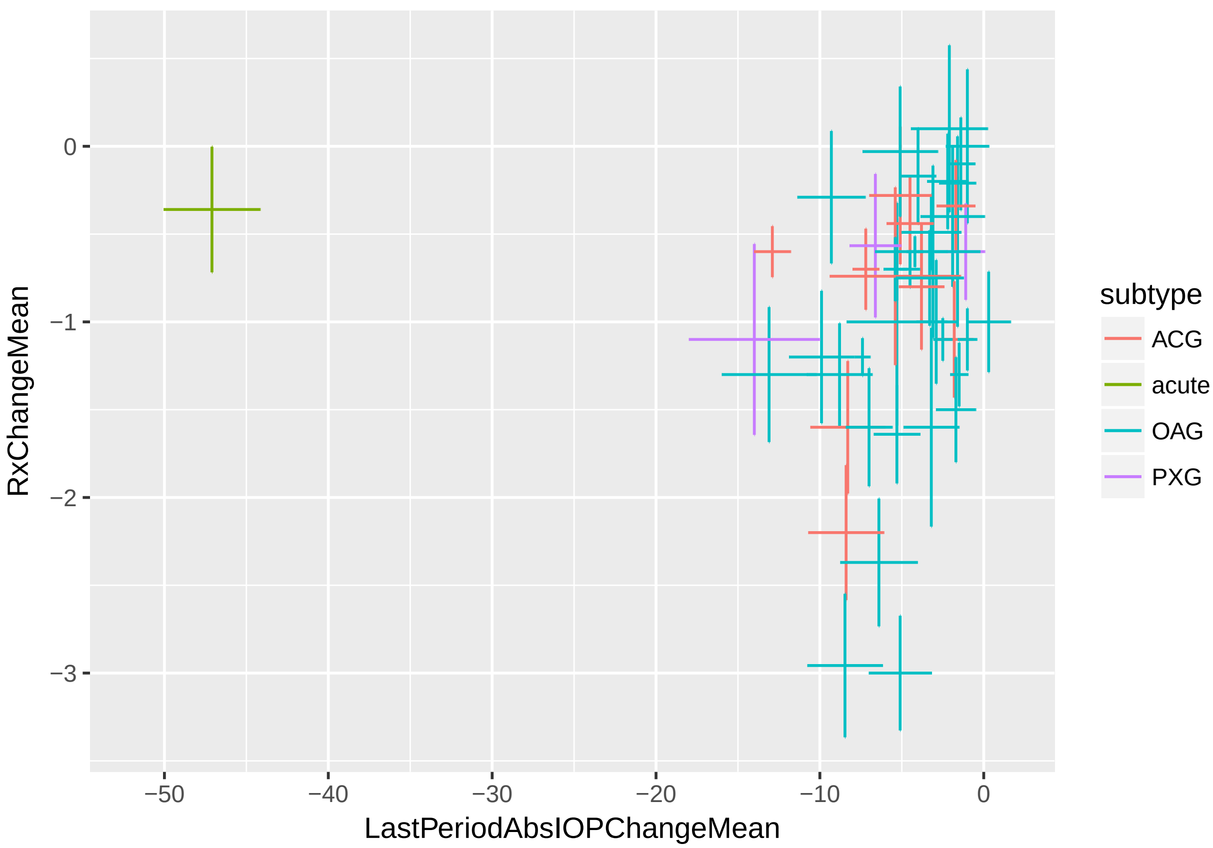
- Those studies that see the largest IOP drops also have drop in meds, as doctors see that can use the newfound *slack* to decrease the number of meds people take
- The studies that see the largest IOP drops are those that don't change meds, because dropping meds would also increase IOP

So which is it?

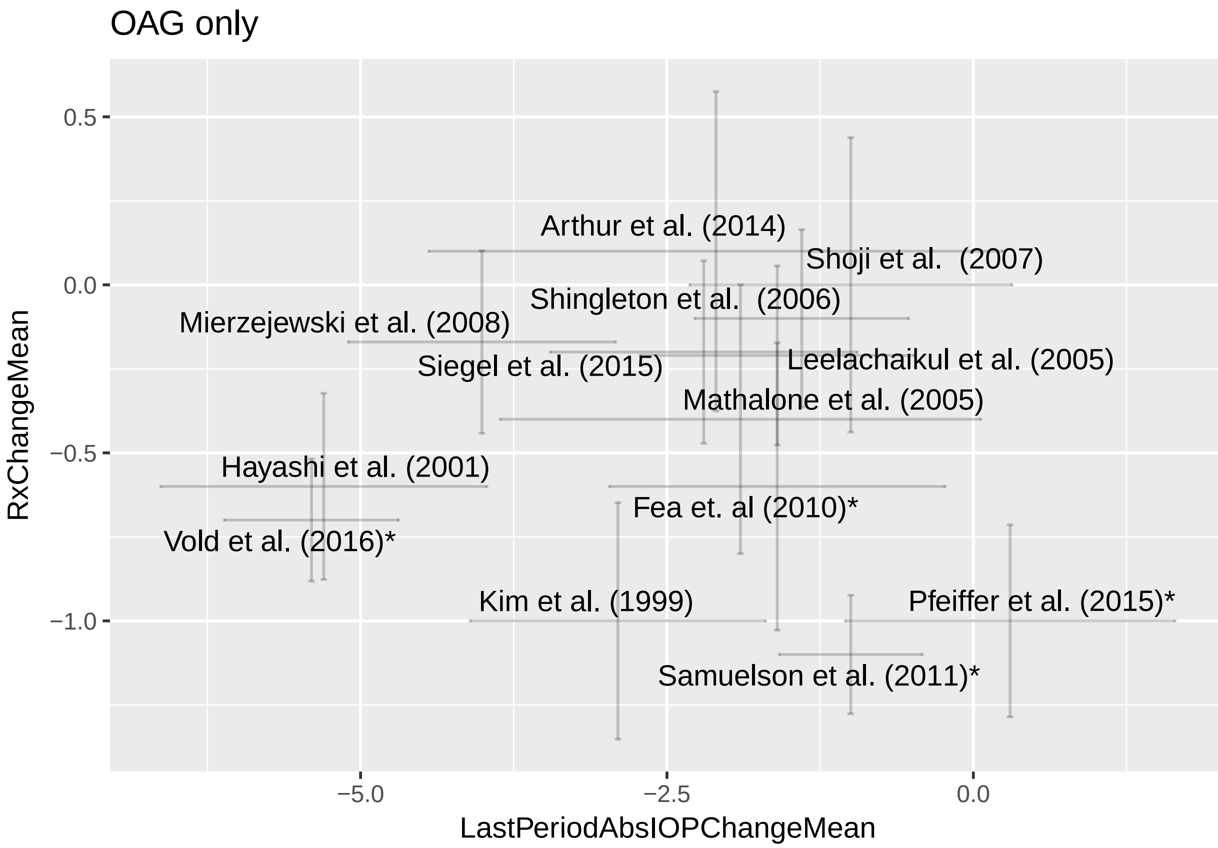
```
df_ <- df %>% mutate(RxChangeMean = RxPostOpMean - RxPreOpMean,
                     RxChangeSEM  = sqrt(1 / ifelse(is.na(LastPeriodEyes), OneYEyes, LastPeriodEyes)),
                     LastPeriodAbsIOPChangeSEM = LastPeriodAbsIOPChangeStdDev / sqrt(LastPeriodEyes))

ggplot(df_, aes(x  =LastPeriodAbsIOPChangeMean,
                xmin=LastPeriodAbsIOPChangeMean - 1.96*LastPeriodAbsIOPChangeSEM,
                xmax=LastPeriodAbsIOPChangeMean + 1.96*LastPeriodAbsIOPChangeSEM,
                y   =RxChangeMean,
                ymin=RxChangeMean - 1.96*RxChangeSEM,
                ymax=RxChangeMean + 1.96*RxChangeSEM,
                color=subtype
                )) + geom_errorbar() + geom_errorbarh()
```

```
## Warning: Removed 18 rows containing missing values (geom_errorbar).
```

```
## Warning: Removed 18 rows containing missing values (geom_errorbarh).
```



```r
ggplot(df_ %>% filter(subtype=='OAG' & MIGsYorN == 'N'),
        aes(x   =LastPeriodAbsIOPChangeMean,
            xmin=LastPeriodAbsIOPChangeMean - 1.96*LastPeriodAbsIOPChangeSEM,
            xmax=LastPeriodAbsIOPChangeMean + 1.96*LastPeriodAbsIOPChangeSEM,
            y    =RxChangeMean,
            ymin=RxChangeMean - 1.96*RxChangeSEM,
            ymax=RxChangeMean + 1.96*RxChangeSEM,
            label=study.name
           )) + geom_errorbar(alpha=.2) + geom_errorbarh(alpha=.2) + ggtitle('OAG only') + geom_text_re
```



There is an apparent positive correlation between the two effect sizes: studies with larger drops in IOP also tend to see larger drops in Rx. This is clearer when we reject the studies with washout.

```r
draw.corr <- function(x.mean, x.sem, y.mean, y.sem) {
  d_ <- data.frame(x = rnorm(n = length(x.mean), mean=x.mean, sd = x.sem),
                   y = rnorm(n = length(x.mean), mean=y.mean, sd = y.sem))
  with(d_ %>% filter(!is.na(x) & !is.na(y)), cor(x, y))
}

cat("Mean +- SE correlation, all studies\n")
```

```
## Mean +- SE correlation, all studies
```

```r
df_ <- df %>% filter(subtype=='OAG', MIGsYorN == 'N')
drawn.corrs <- with(df_, replicate(n = 100,
                                   draw.corr(LastPeriodAbsIOPChangeMean,
                                             LastPeriodAbsIOPChangeStdDev / sqrt(LastPeriodEyes),
                                             RxPostOpMean - RxPreOpMean,
```

```r
                                              1 / sqrt(LastPeriodEyes))))
mean(drawn.corrs)
```

```
## [1] -0.001909355
```

```r
sd(drawn.corrs)
```

```
## [1] 0.1418261
```

```r
cat("Mean +- SE correlation, no washout\n")
```

```
## Mean +- SE correlation, no washout
```

```r
df_ <- filter.data(df, 'nowashout') %>% filter(subtype=='OAG', MIGsYorN == 'N')
drawn.corrs <- with(df_, replicate(n = 100,
                                  draw.corr(LastPeriodAbsIOPChangeMean,
                                            LastPeriodAbsIOPChangeStdDev / sqrt(LastPeriodEyes),
                                            RxPostOpMean - RxPreOpMean,
                                            1 / sqrt(LastPeriodEyes))))
mean(drawn.corrs)
```

```
## [1] 0.3853104
```

```r
sd(drawn.corrs)
```

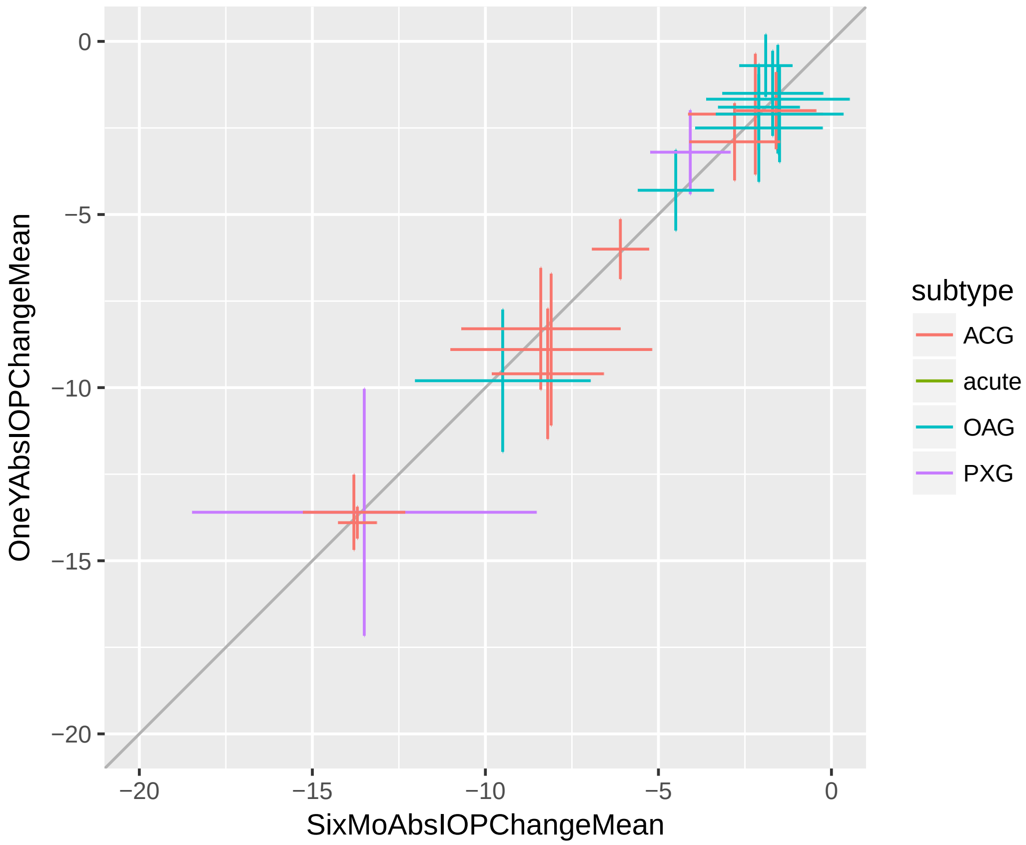
```
## [1] 0.2079009
```

Correlation among time points

Measure the correlation between different outcomes (IOP at 6 months vs. 12 months).

```r
ggplot(df, aes(x    =SixMoAbsIOPChangeMean,
               xmin=SixMoAbsIOPChangeMean - 1.96*SixMoAbsIOPChangeStdDev / sqrt(SixMoEyes),
               xmax=SixMoAbsIOPChangeMean + 1.96*SixMoAbsIOPChangeStdDev / sqrt(SixMoEyes),
               y    = OneYAbsIOPChangeMean,
               ymin= OneYAbsIOPChangeMean - 1.96*OneYAbsIOPChangeStdDev / sqrt(OneYEyes),
               ymax= OneYAbsIOPChangeMean + 1.96*OneYAbsIOPChangeStdDev / sqrt(OneYEyes),
               label=study.name,
               color=subtype
               )) +
  geom_abline(slope = 1, color="gray70") +
  geom_errorbar() + geom_errorbarh() +
  coord_fixed(xlim=c(-20, 0), ylim=c(-20,0))
```

```
## Warning: Removed 45 rows containing missing values (geom_errorbar).

## Warning: Removed 45 rows containing missing values (geom_errorbarh).
```



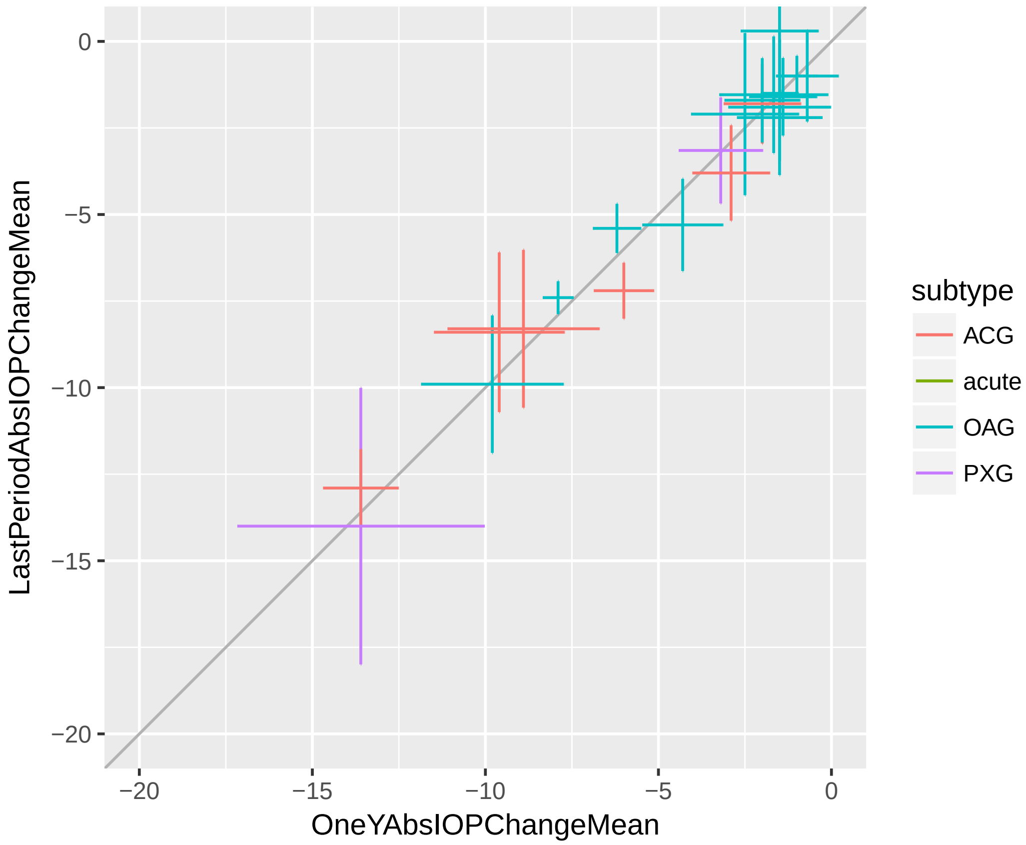
It's very clear that six months and 12 months IOP are highly correlated.

Similarly for one-year vs. last period:

```
ggplot(df, aes(y   =LastPeriodAbsIOPChangeMean,
               ymin=LastPeriodAbsIOPChangeMean - 1.96*LastPeriodAbsIOPChangeStdDev / sqrt(LastPeriodEye
               ymax=LastPeriodAbsIOPChangeMean + 1.96*LastPeriodAbsIOPChangeStdDev / sqrt(LastPeriodEye
               x   = OneYAbsIOPChangeMean,
               xmin= OneYAbsIOPChangeMean - 1.96*OneYAbsIOPChangeStdDev / sqrt(OneYEyes),
               xmax= OneYAbsIOPChangeMean + 1.96*OneYAbsIOPChangeStdDev / sqrt(OneYEyes),
               label=study.name,
               color=subtype
               )) +
  geom_abline(slope = 1, color="gray70") +
  geom_errorbar() + geom_errorbarh() +
  coord_fixed(xlim=c(-20, 0), ylim=c(-20,0))
```

```
## Warning: Removed 43 rows containing missing values (geom_errorbar).
```

```
## Warning: Removed 43 rows containing missing values (geom_errorbarh).
```



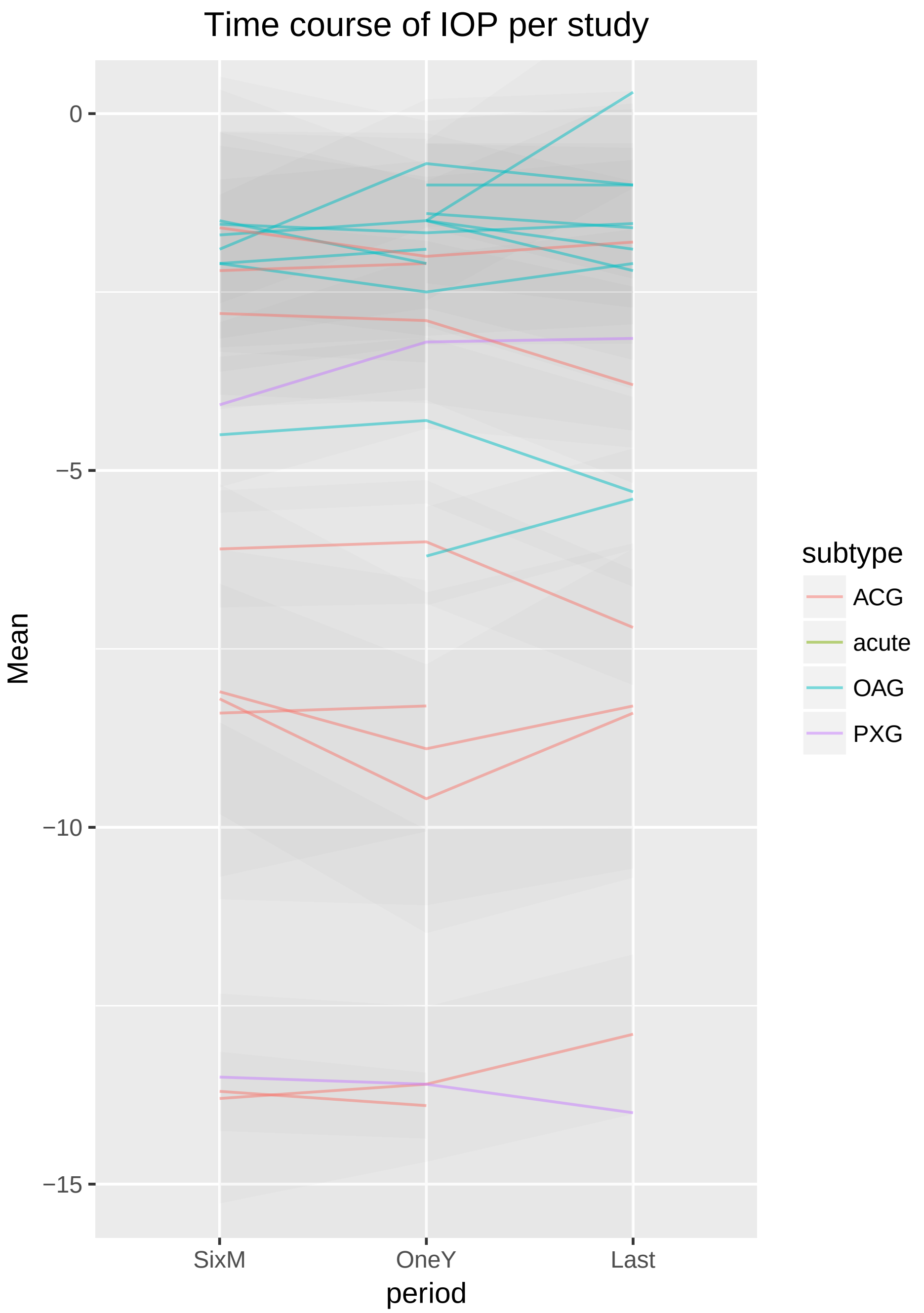
Again, correlations are very high. Present this in another way.

```
library(reshape2)
```

```
##
## Attaching package: 'reshape2'

## The following object is masked from 'package:tidyr':
##
##     smiths
```

```
nd <- melt(df %>%
             filter(MIGsYorN == 'N',
                    1*is.na(SixMoAbsIOPChangeMean) +
                    1*is.na(OneYAbsIOPChangeMean) +
                    1*is.na(LastPeriodAbsIOPChangeMean) < 2) %>%
             mutate(SixMoChangeSEM = SixMoAbsIOPChangeStdDev / sqrt(SixMoEyes),
                    OneYChangeSEM = OneYAbsIOPChangeStdDev / sqrt(OneYEyes),
                    LastPeriodChangeSEM = LastPeriodAbsIOPChangeStdDev / sqrt(LastPeriodEyes)) %>%
             select(study.name, subtype,
                    SixMoAbsIOPChangeMean,
                    OneYAbsIOPChangeMean,
                    LastPeriodAbsIOPChangeMean,
                    SixMoChangeSEM,
                    OneYChangeSEM,
                    LastPeriodChangeSEM), id.vars=c("study.name", "subtype"))
nd$metric <- substr(nd$variable, nchar(as.character(nd$variable)) - 3, nchar(as.character(nd$variable))
nd$period <- substr(nd$variable, 0, 4)
df_ <- dcast(nd, formula = study.name + subtype + period ~ metric)
```

```
df_ <- df_ %>% mutate(period = factor(period, c('SixM', 'OneY', 'Last')),
                      g = paste(study.name, as.character(subtype))) %>% filter(!is.na(Mean))
ggplot(df_, aes(y    =Mean,
               ymin=Mean - 1.96*eSEM,
               ymax=Mean + 1.96*eSEM,
               x    = period,
               label=study.name,
               group=g)) +
  geom_ribbon(alpha=.02) +
  geom_line(alpha=.5, aes(color=subtype)) +
  coord_cartesian(y=c(-15, 0)) + ggtitle('Time course of IOP per study') + theme(plot.title = element_te
```



It's remarkable how consistent measurements are between time periods. At most, we find a change of +- 2.5 mm Hg between the first and last period.

```
df_ <- df %>% filter(subtype=='OAG')
drawn.corrs <- with(df_, replicate(n = 100,
                                   draw.corr(SixMoAbsIOPChangeMean,
                                             SixMoAbsIOPChangeStdDev / sqrt(SixMoEyes),
                                             OneYAbsIOPChangeMean,
                                             OneYAbsIOPChangeStdDev / sqrt(OneYEyes))))
cat("Mean +- SE correlation, OAG only\n")
```

```
## Mean +- SE correlation, OAG only
```

```
print(mean(drawn.corrs))
```

```
## [1] 0.9274425
```

```
print(sd(drawn.corrs))
```

```
## [1] 0.04314969
```

```
df_ <- df
drawn.corrs <- with(df_, replicate(n = 100,
                                   draw.corr(SixMoAbsIOPChangeMean,
                                             SixMoAbsIOPChangeStdDev / sqrt(SixMoEyes),
                                             OneYAbsIOPChangeMean,
                                             OneYAbsIOPChangeStdDev / sqrt(OneYEyes))))
cat("Mean +- SE correlation, All subtypes\n")
```

```
## Mean +- SE correlation, All subtypes
```

```
print(mean(drawn.corrs))
```

```
## [1] 0.9910226
```

```
print(sd(drawn.corrs))
```

```
## [1] 0.004169846
```

This is also reflected in the correlations - even accounting for noise, the correlations are > .9 between month 6 and month 12.

Multivariate inference

Let's use `mvmeta` to infer the effect size for all periods together.

```
library(mvmeta)
```

```
## This is mvmeta 0.4.7. For an overview type: help('mvmeta-package').
```

```
fill.na <- function(x, y, z) {
  return(ifelse(!is.na(x),
                   x,
                   ifelse(is.na(y),
                          z,
                          ifelse(is.na(z),
                            y,
                            sqrt((y**2 + z**2) / 2 )))))
```

```r
}

get.correlation.matrices.tri <- function(x, y, z, assumed.rho) {
  S <- list()
  for(i in 1:length(x)) {
    xx <- fill.na(x[i], y[i], z[i])
    yy <- fill.na(y[i], x[i], z[i])
    zz <- fill.na(z[i], x[i], y[i])
    S[[i]] <- matrix(c(xx ** 2, xx * yy * assumed.rho, xx * zz * assumed.rho ** 2,
                       xx * yy * assumed.rho, yy ** 2, zz * yy* assumed.rho,
                       xx * zz * assumed.rho ** 2, zz * yy * assumed.rho, zz * zz), ncol=3)
  }
  S
}

df_ <- df %>% filter(!is.na(LastPeriodAbsIOPChangeStdDev) |
                     !is.na(SixMoAbsIOPChangeStdDev) |
                     !is.na(OneYAbsIOPChangeStdDev), subtype %in% c('OAG', 'ACG'), MIGsYorN == 'N')

thefit <- mvmeta(cbind(SixMoAbsIOPChangeMean, OneYAbsIOPChangeMean, LastPeriodAbsIOPChangeMean) ~ subtyp
       S=get.correlation.matrices.tri(df_$SixMoAbsIOPChangeStdDev / sqrt(df_$SixMoEyes),
                                      df_$OneYAbsIOPChangeStdDev / sqrt(df_$OneYEyes),
                                      df_$LastPeriodAbsIOPChangeStdDev / sqrt(df_$LastPeriodEyes), .7),
       data=df_,
       method="reml")

summary(thefit)
```

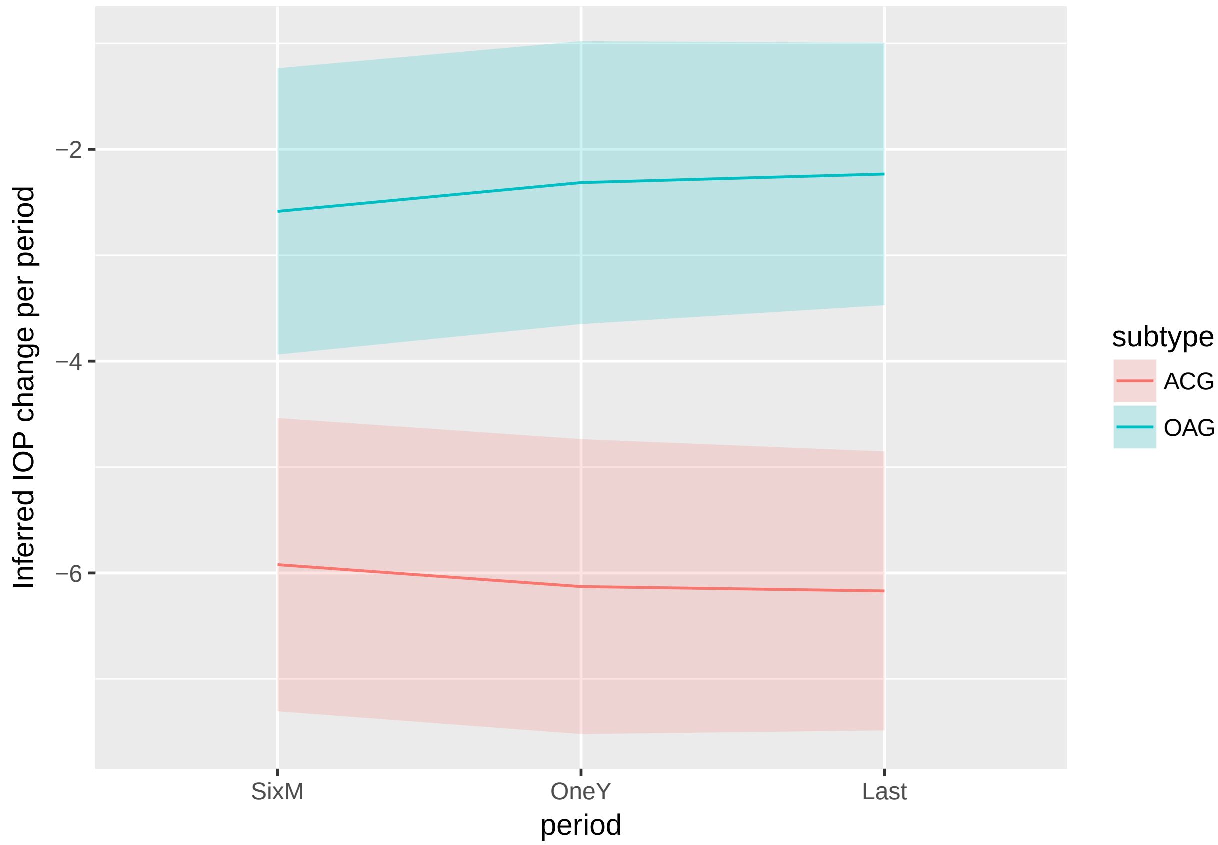
```
## Call:  mvmeta(formula = cbind(SixMoAbsIOPChangeMean, OneYAbsIOPChangeMean,
##     LastPeriodAbsIOPChangeMean) ~ subtype, S = get.correlation.matrices.tri(df_$SixMoAbsIOPChangeStdI
##     df_$OneYAbsIOPChangeStdDev/sqrt(df_$OneYEyes), df_$LastPeriodAbsIOPChangeStdDev/sqrt(df_$LastPer:
##     0.7), data = df_, method = "reml")
##
## Multivariate random-effects meta-regression
## Dimension: 3
## Estimation method: REML
##
## Fixed-effects coefficients
## SixMoAbsIOPChangeMean :
##              Estimate  Std. Error        z  Pr(>|z|)  95%ci.lb  95%ci.ub
## (Intercept)   -5.9217      0.7061  -8.3865    0.0000   -7.3057   -4.5378
## subtypeOAG     3.3355      0.9870   3.3795    0.0007    1.4011    5.2699
##
## (Intercept)  ***
## subtypeOAG   ***
## OneYAbsIOPChangeMean :
##              Estimate  Std. Error        z  Pr(>|z|)  95%ci.lb  95%ci.ub
## (Intercept)   -6.1285      0.7102  -8.6292    0.0000   -7.5205   -4.7365
## subtypeOAG     3.8138      0.9841   3.8754    0.0001    1.8850    5.7425
##
## (Intercept)  ***
## subtypeOAG   ***
## LastPeriodAbsIOPChangeMean :
##              Estimate  Std. Error        z  Pr(>|z|)  95%ci.lb  95%ci.ub
```

```
## (Intercept)   -6.1695      0.6717  -9.1853    0.0000   -7.4860   -4.8531
## subtypeOAG     3.9360      0.9221   4.2683    0.0000    2.1286    5.7433
##
## (Intercept)  ***
## subtypeOAG   ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Between-study random-effects (co)variance components
##  Structure: General positive-definite
##                            Std. Dev                 Corr
## SixMoAbsIOPChangeMean         2.7657  SixMoAbsIOPChangeMean
## OneYAbsIOPChangeMean          2.7806                 0.9963
## LastPeriodAbsIOPChangeMean    2.5526                 0.9813
##
## SixMoAbsIOPChangeMean       OneYAbsIOPChangeMean
## OneYAbsIOPChangeMean
## LastPeriodAbsIOPChangeMean                0.9677
##
## Multivariate Cochran Q-test for residual heterogeneity:
## Q = 1537.5043 (df = 62), p-value = 0.0000
## I-square statistic = 96.0%
##
## 36 studies, 68 observations, 6 fixed and 6 random-effects parameters
##    logLik        AIC        BIC
## -118.6183   261.2367   286.7623
```

```r
newdata <- data.frame(subtype=c('OAG', 'ACG'))
pred <- predict(thefit, newdata, se=TRUE)
newdata$SixMoAbsIOPChangeMean <- pred$fit[,1]
newdata$OneYAbsIOPChangeMean <- pred$fit[,2]
newdata$LastPeriodAbsIOPChangeMean <- pred$fit[,3]
newdata$SixMoAbsIOPChangeSEM <- pred$se[,1]
newdata$OneYAbsIOPChangeSEM <- pred$se[,2]
newdata$LastPeriodAbsIOPChangeSEM <- pred$se[,3]

library(reshape2)
nd <- melt(newdata)
```

```
## Using subtype as id variables
```

```r
nd$period <- substr(nd$variable, 0, 4)
nd$metric <- substr(nd$variable, nchar(as.character(nd$variable)) - 3, nchar(as.character(nd$variable))
df_ <- dcast(nd, formula = subtype + period ~ metric)
df_$period <- factor(df_$period, c('SixM', 'OneY', 'Last'))
ggplot(df_, aes(x=period,
                y=Mean,
                ymin=Mean - 1.96*eSEM,
                ymax=Mean + 1.96*eSEM,
                group=subtype,
                fill=subtype)) + geom_ribbon(alpha=.2) + geom_line(aes(color=subtype)) + ylab("Inferred
```



Meta-regression

Consider relationships between different covariates and outcomes. Focus on the IOP drop at one year and its correlation with different factors.

```r
df_ <- df %>% filter(!is.na(OneYAbsIOPChangeMean), subtype != "acute", MIGsYorN == 'N') %>%
  mutate(subtype=relevel(factor(subtype), ref="OAG"))
m <- metagen(OneYAbsIOPChangeMean,
             OneYAbsIOPChangeStdDev / sqrt(OneYEyes),
             study.name,
             data=df_,
             byvar=subtype,
             n.e=OneYEyes)

print(metareg(~ OneYEyes, x=m))
```

```
##
## Mixed-Effects Model (k = 24; tau^2 estimator: DL)
##
## tau^2 (estimated amount of residual heterogeneity):     30.8712 (SE = 12.8681)
## tau (square root of estimated tau^2 value):             5.5562
## I^2 (residual heterogeneity / unaccounted variability): 99.02%
## H^2 (unaccounted variability / sampling variability):   102.25
## R^2 (amount of heterogeneity accounted for):            0.00%
##
## Test for Residual Heterogeneity:
```

```
## QE(df = 22) = 2249.5296, p-val < .0001
##
## Test of Moderators (coefficient(s) 2):
## QM(df = 1) = 0.9026, p-val = 0.3421
##
## Model Results:
##
##          estimate      se     zval    pval    ci.lb   ci.ub
## intrcpt   -3.3325  1.8721  -1.7801  0.0751  -7.0019  0.3368  .
## OneYEyes  -0.0275  0.0290  -0.9500  0.3421  -0.0843  0.0293
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
print(metareg(~ OneYEyes * subtype, x=m))
```

```
##
## Mixed-Effects Model (k = 24; tau^2 estimator: DL)
##
## tau^2 (estimated amount of residual heterogeneity):     17.0380 (SE = 7.3921)
## tau (square root of estimated tau^2 value):             4.1277
## I^2 (residual heterogeneity / unaccounted variability): 98.16%
## H^2 (unaccounted variability / sampling variability):   54.33
## R^2 (amount of heterogeneity accounted for):            39.83%
##
## Test for Residual Heterogeneity:
## QE(df = 18) = 977.8565, p-val < .0001
##
## Test of Moderators (coefficient(s) 2,3,4,5,6):
## QM(df = 5) = 14.6923, p-val = 0.0118
##
## Model Results:
##
##                     estimate       se     zval    pval     ci.lb    ci.ub
## intrcpt              -1.1839   2.3639  -0.5008  0.6165   -5.8170   3.4491
## OneYEyes             -0.0189   0.0381  -0.4956  0.6202   -0.0936   0.0558
## subtypeACG           -3.5831   3.0929  -1.1585  0.2467   -9.6452   2.4789
## subtypePXG          -27.5433  12.8476  -2.1438  0.0320  -52.7243  -2.3624
## OneYEyes:subtypeACG  -0.0253   0.0469  -0.5397  0.5894   -0.1172   0.0666
## OneYEyes:subtypePXG   0.9644   0.5600   1.7220  0.0851   -0.1333   2.0620
##
## intrcpt
## OneYEyes
## subtypeACG
## subtypePXG           *
## OneYEyes:subtypeACG
## OneYEyes:subtypePXG  .
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
print(metareg(~ Year, x=m))
```

```
##
## Mixed-Effects Model (k = 24; tau^2 estimator: DL)
```

```
##
## tau^2 (estimated amount of residual heterogeneity):     25.2200 (SE = 10.5747)
## tau (square root of estimated tau^2 value):             5.0219
## I^2 (residual heterogeneity / unaccounted variability): 98.82%
## H^2 (unaccounted variability / sampling variability):   84.52
## R^2 (amount of heterogeneity accounted for):            10.94%
##
## Test for Residual Heterogeneity:
## QE(df = 22) = 1859.3429, p-val < .0001
##
## Test of Moderators (coefficient(s) 2):
## QM(df = 1) = 0.0302, p-val = 0.8621
##
## Model Results:
##
##          estimate        se     zval    pval      ci.lb     ci.ub
## intrcpt   63.5684  393.3358   0.1616  0.8716  -707.3556  834.4924
## Year      -0.0340    0.1957  -0.1736  0.8621    -0.4175    0.3496
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```r
print(metareg(~ Year * subtype, x=m))
```

```
##
## Mixed-Effects Model (k = 24; tau^2 estimator: DL)
##
## tau^2 (estimated amount of residual heterogeneity):     11.2606 (SE = 4.8038)
## tau (square root of estimated tau^2 value):             3.3557
## I^2 (residual heterogeneity / unaccounted variability): 97.24%
## H^2 (unaccounted variability / sampling variability):   36.21
## R^2 (amount of heterogeneity accounted for):            60.23%
##
## Test for Residual Heterogeneity:
## QE(df = 18) = 651.7540, p-val < .0001
##
## Test of Moderators (coefficient(s) 2,3,4,5,6):
## QM(df = 5) = 19.9554, p-val = 0.0013
##
## Model Results:
##
##                    estimate         se     zval    pval       ci.lb
## intrcpt             68.7364   390.2739   0.1761  0.8602   -696.1864
## Year                -0.0353     0.1941  -0.1817  0.8558     -0.4158
## subtypeACG         668.7765   603.7615   1.1077  0.2680   -514.5744
## subtypePXG       -3052.2792  1516.1880  -2.0131  0.0441  -6023.9531
## Year:subtypeACG     -0.3350     0.3003  -1.1158  0.2645     -0.9235
## Year:subtypePXG      1.5210     0.7568   2.0097  0.0445      0.0377
##                    ci.ub
## intrcpt         833.6592
## Year              0.3452
## subtypeACG     1852.1273
## subtypePXG      -80.6053  *
## Year:subtypeACG   0.2535
## Year:subtypePXG   3.0043  *
```

```
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```r
print(metareg(~ PreOpIOPMean, x=m))
```

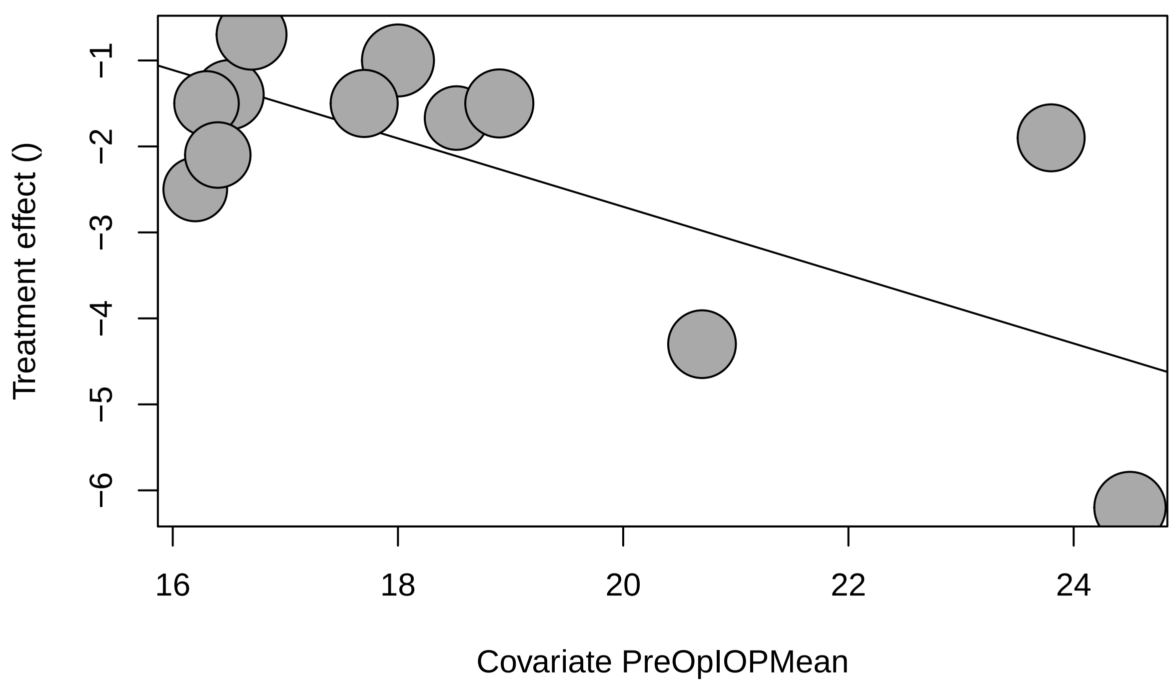
```
##
## Mixed-Effects Model (k = 24; tau^2 estimator: DL)
##
## tau^2 (estimated amount of residual heterogeneity):     4.4783 (SE = 1.8384)
## tau (square root of estimated tau^2 value):             2.1162
## I^2 (residual heterogeneity / unaccounted variability): 93.40%
## H^2 (unaccounted variability / sampling variability):   15.14
## R^2 (amount of heterogeneity accounted for):            84.19%
##
## Test for Residual Heterogeneity:
## QE(df = 22) = 333.0958, p-val < .0001
##
## Test of Moderators (coefficient(s) 2):
## QM(df = 1) = 65.1891, p-val < .0001
##
## Model Results:
##
##               estimate      se     zval    pval    ci.lb    ci.ub
## intrcpt        13.0744  2.2388   5.8399  <.0001   8.6864  17.4624  ***
## PreOpIOPMean   -0.8673  0.1074  -8.0740  <.0001  -1.0779  -0.6568  ***
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```r
print(metareg(~ PreOpIOPMean * subtype, x=m))
```

```
##
## Mixed-Effects Model (k = 24; tau^2 estimator: DL)
##
## tau^2 (estimated amount of residual heterogeneity):     1.2655 (SE = 0.6125)
## tau (square root of estimated tau^2 value):             1.1249
## I^2 (residual heterogeneity / unaccounted variability): 79.37%
## H^2 (unaccounted variability / sampling variability):   4.85
## R^2 (amount of heterogeneity accounted for):            95.53%
##
## Test for Residual Heterogeneity:
## QE(df = 18) = 87.2305, p-val < .0001
##
## Test of Moderators (coefficient(s) 2,3,4,5,6):
## QM(df = 5) = 218.5070, p-val < .0001
##
## Model Results:
##
##                         estimate      se     zval    pval    ci.lb
## intrcpt                   5.2227  2.4821   2.1041  0.0354   0.3578
## PreOpIOPMean             -0.3961  0.1307  -3.0318  0.0024  -0.6522
## subtypeACG                8.2042  3.2360   2.5353  0.0112   1.8617
## subtypePXG                8.4784  5.4425   1.5578  0.1193  -2.1888
## PreOpIOPMean:subtypeACG  -0.5532  0.1601  -3.4547  0.0006  -0.8671
```

```
## PreOpIOPMean:subtypePXG   -0.4570  0.2429  -1.8817  0.0599  -0.9330
##                             ci.ub
## intrcpt                   10.0876    *
## PreOpIOPMean              -0.1400   **
## subtypeACG                14.5467    *
## subtypePXG                19.1455
## PreOpIOPMean:subtypeACG   -0.2394  ***
## PreOpIOPMean:subtypePXG    0.0190    .
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

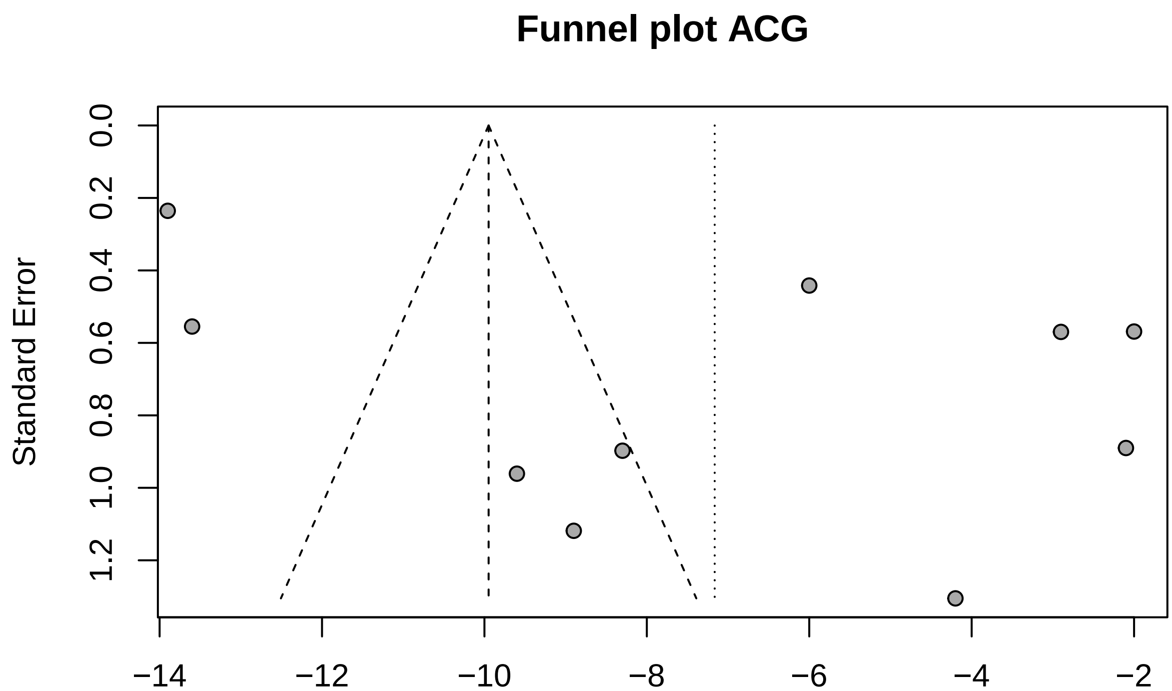
```r
# Same, restricted to OAG only
df_ <- df %>% filter(!is.na(OneYAbsIOPChangeMean), subtype == "OAG", MIGsYorN == 'N') %>%
  mutate(subtype=relevel(factor(subtype), ref="OAG"))
m <- metagen(OneYAbsIOPChangeMean,
             OneYAbsIOPChangeStdDev / sqrt(OneYEyes),
             study.name,
             data=df_,
             byvar=subtype,
             n.e=OneYEyes)

bubble(metareg(~ PreOpIOPMean, x=m))
```

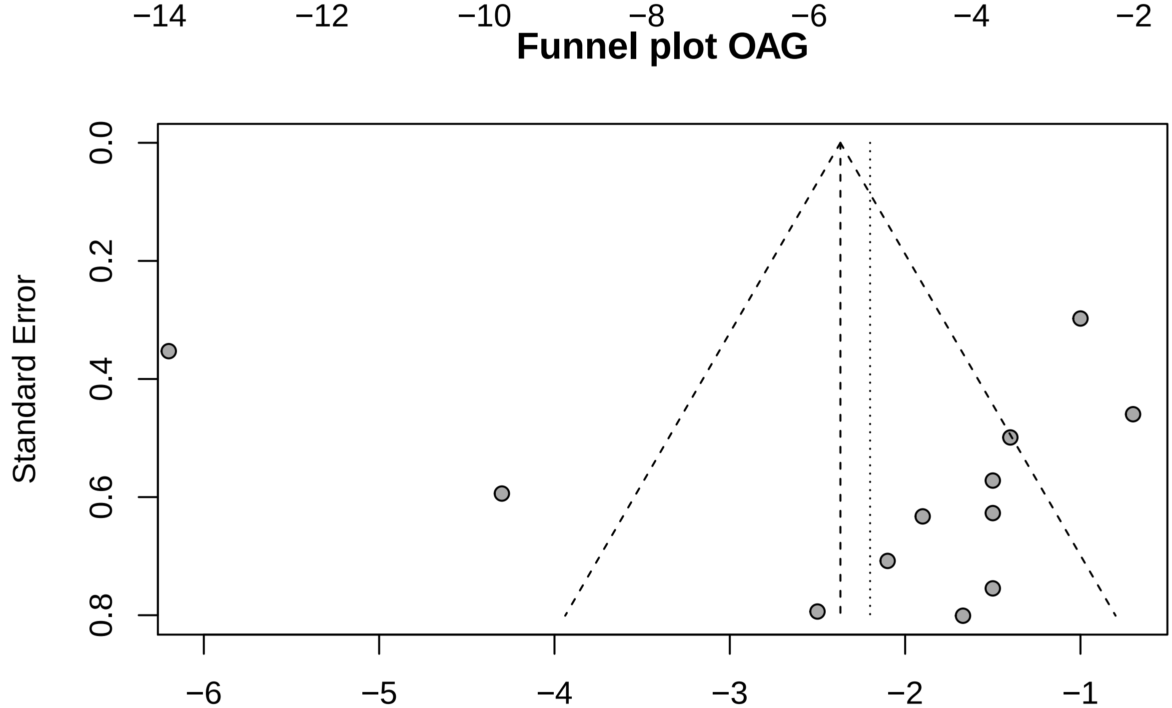


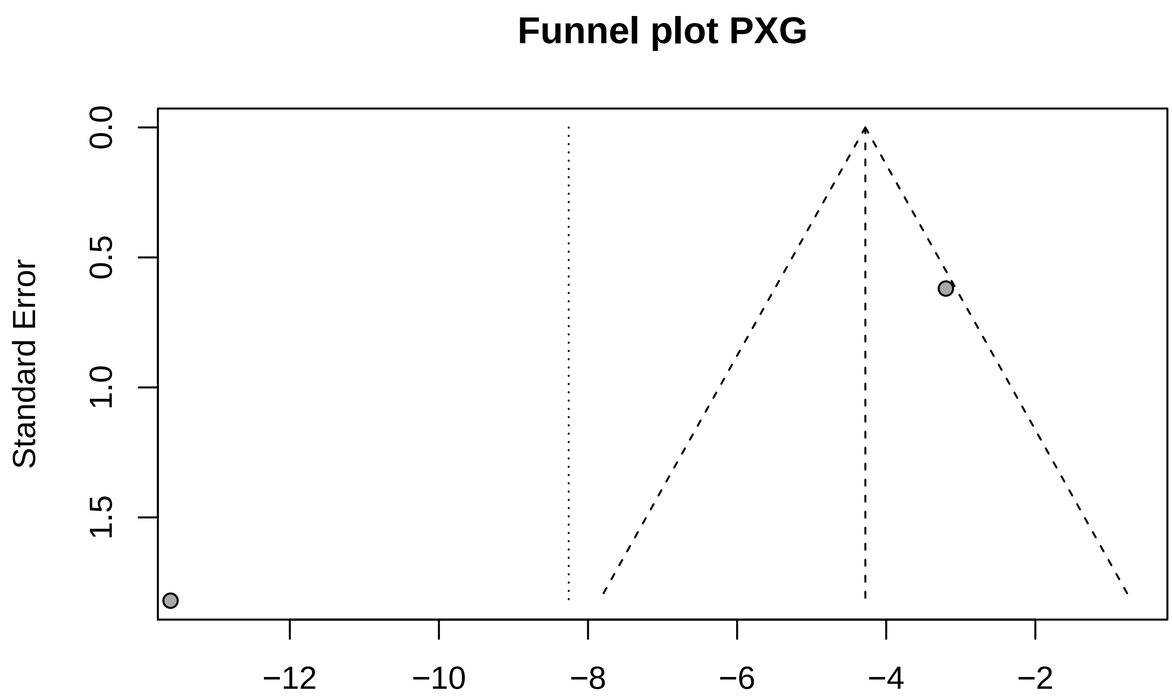
Small study bias

```r
df_ <- df %>% filter(!is.na(df$OneYAbsIOPChangeMean),
                     df$subtype != "acute",
                     MIGsYorN == 'N') %>% mutate(subtype=factor(subtype))
for(l in levels(df_$subtype)) {
  m <- metagen(OneYAbsIOPChangeMean,
```

```
                OneYAbsIOPChangeStdDev / sqrt(OneYEyes),
                study.name,
                data=df_ %>% filter(subtype == l),
                n.e=OneYEyes)
  funnel(m)
  title(paste('Funnel plot', l))
}
```





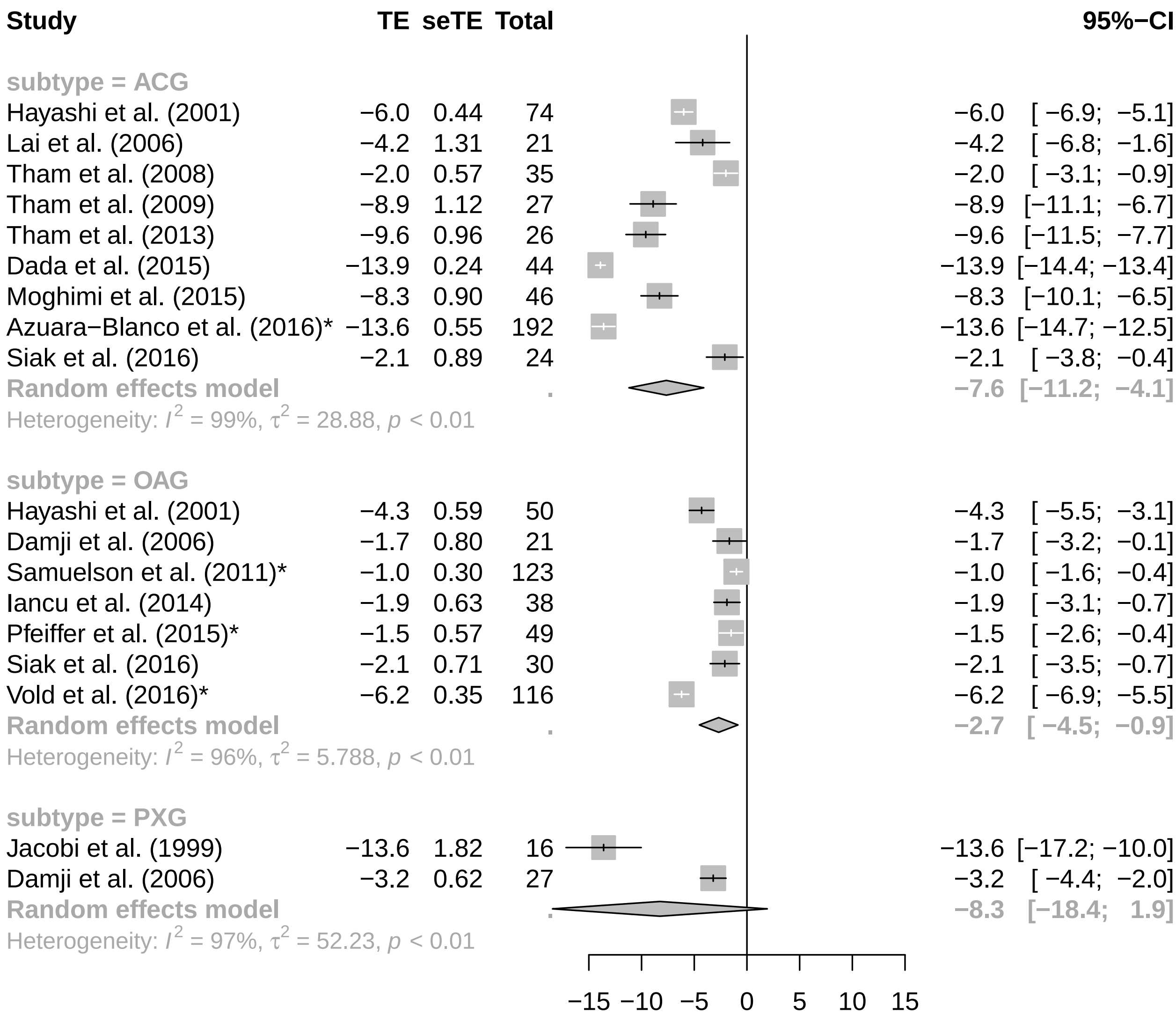


Alternative filterings of the data

Prospective studies only

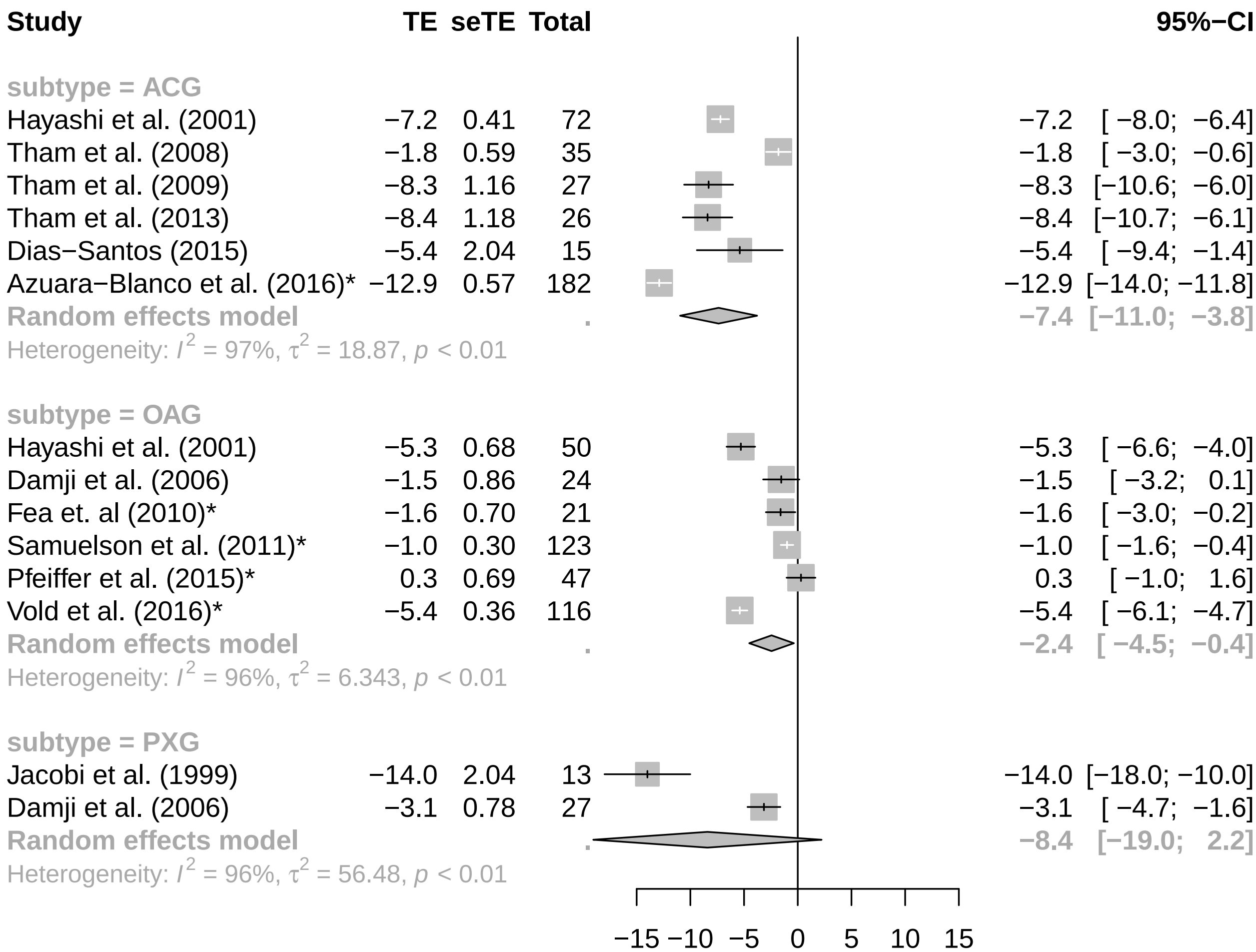
One year

```
df_ <- df %>%
  filter(!is.na(OneYAbsIOPChangeMean), subtype != "acute", MIGsYorN == 'N') %>%
  mutate(subtype=factor(subtype))
m <- metagen(OneYAbsIOPChangeMean,
             OneYAbsIOPChangeStdDev / sqrt(OneYEyes),
             study.name,
             data=df_,
             byvar=subtype,
             n.e=OneYEyes)
forest(m,
       comb.fixed=FALSE,
       digits=1,
       digits.se = 2,
       overall=FALSE,
       leftcols=c("studlab", "TE", "seTE", "n.e"))
```



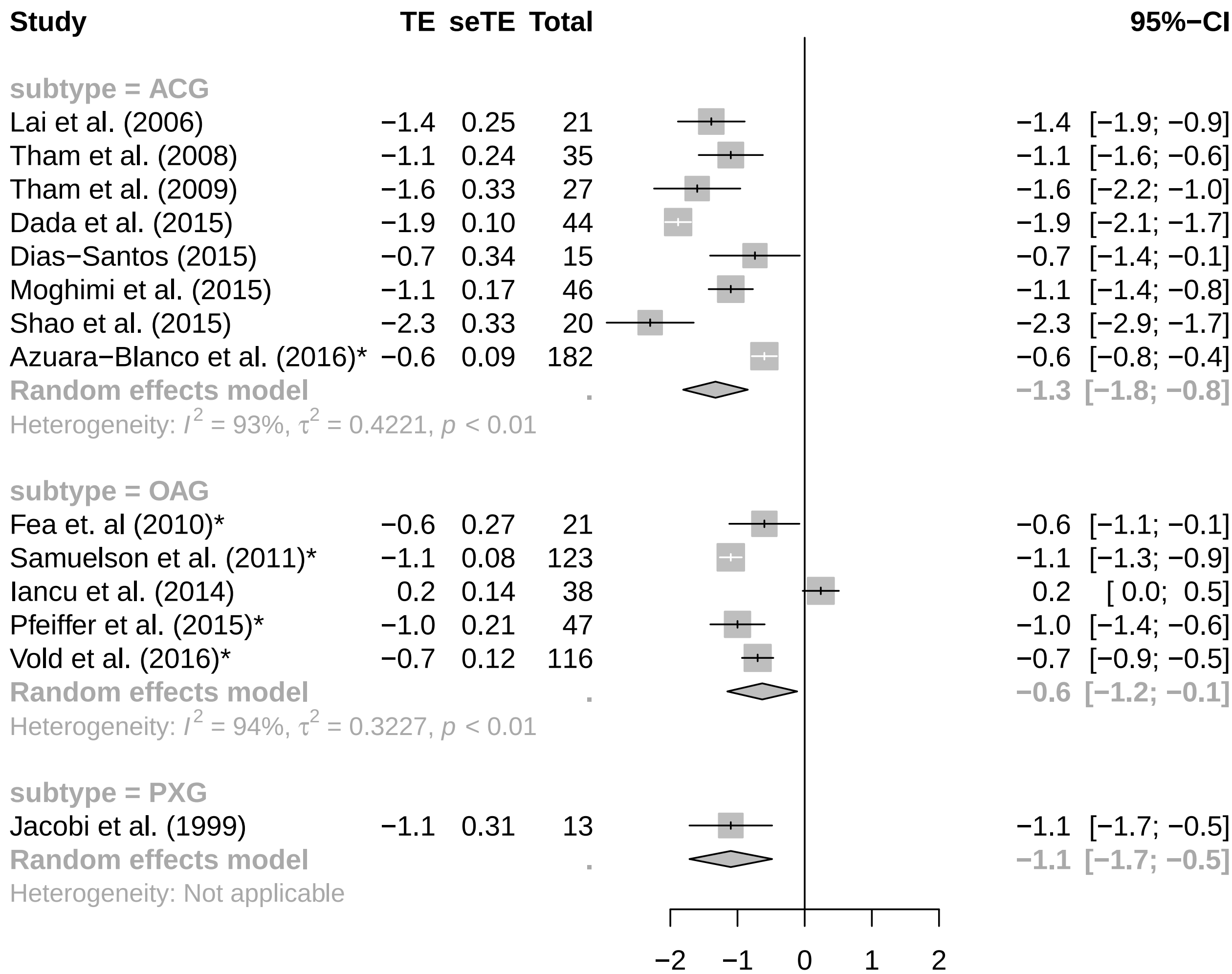
Last period

```
df_ <- df %>%
  filter(!is.na(LastPeriodAbsIOPChangeMean), subtype != "acute", MIGsYorN == 'N') %>%
  mutate(subtype=factor(subtype))
m <- metagen(LastPeriodAbsIOPChangeMean,
             LastPeriodAbsIOPChangeStdDev / sqrt(LastPeriodEyes),
             study.name,
             data=df_,
             byvar=subtype,
             n.e=LastPeriodEyes)
forest(m,
       comb.fixed=FALSE,
       digits=1,
       digits.se = 2,
       overall=FALSE,
       leftcols=c("studlab", "TE", "seTE", "n.e"))
```



Meds

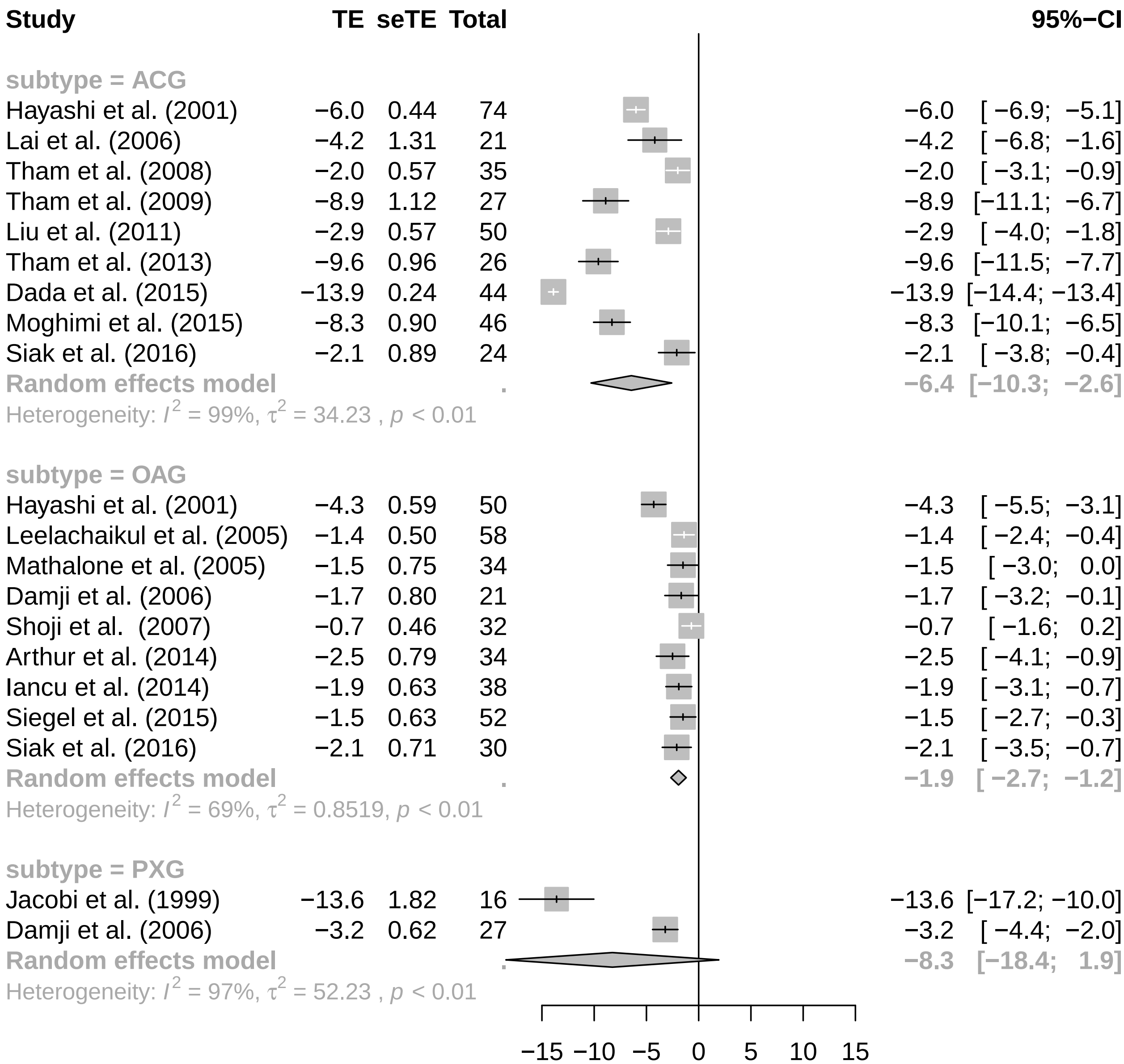
```
df_ <- df %>%
  filter(!is.na(RxChangeMean), !is.na(RxChangeStdDev),
         df$subtype != "acute", MIGsYorN == 'N') %>%
  mutate(subtype=factor(subtype))
m <- metagen(RxChangeMean,
             sqrt(RxPostOpStdDev** 2 + RxPreOpStdDev ** 2) / sqrt(LastPeriodEyes),
             study.name,
             data=df_,
             byvar=subtype,
             n.e=LastPeriodEyes)
forest(m,
       comb.fixed=FALSE,
       digits=1,
       digits.se = 2,
       overall=FALSE,
       leftcols=c("studlab", "TE", "seTE", "n.e"))
```



Excluding washout studies

One year

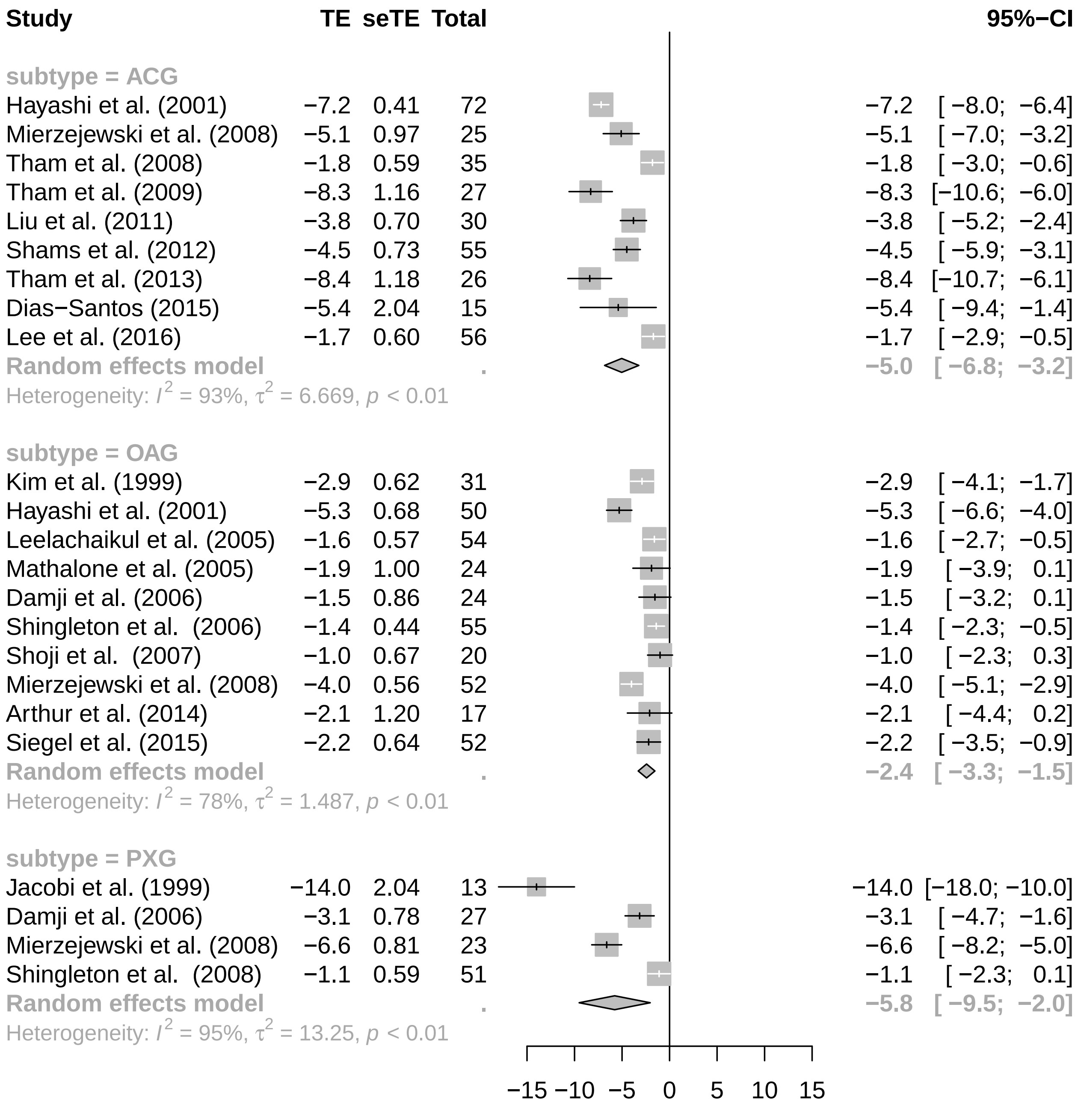
```
df_ <- df %>%
  filter(!is.na(OneYAbsIOPChangeMean), subtype != "acute", MIGsYorN == 'N') %>%
  mutate(subtype=factor(subtype))
m <- metagen(OneYAbsIOPChangeMean,
             OneYAbsIOPChangeStdDev / sqrt(OneYEyes),
             study.name,
             data=df_,
             byvar=subtype,
             n.e=OneYEyes)
forest(m,
       comb.fixed=FALSE,
       digits=1,
       digits.se = 2,
       overall=FALSE,
       leftcols=c("studlab", "TE", "seTE", "n.e"))
```



Last period

```
df_ <- df %>%
  filter(!is.na(LastPeriodAbsIOPChangeMean), subtype != "acute", MIGsYorN == 'N') %>%
  mutate(subtype=factor(subtype))
m <- metagen(LastPeriodAbsIOPChangeMean,
             LastPeriodAbsIOPChangeStdDev / sqrt(LastPeriodEyes),
             study.name,
             data=df_,
             byvar=subtype,
             n.e=LastPeriodEyes)
forest(m,
       comb.fixed=FALSE,
       digits=1,
```

```
        digits.se = 2,
        overall=FALSE,
        leftcols=c("studlab", "TE", "seTE", "n.e"))
```



Meds

```
df_ <- df %>%
  filter(!is.na(RxChangeMean), !is.na(RxChangeStdDev),
         df$subtype != "acute", MIGsYorN == 'N') %>%
  mutate(subtype=factor(subtype))
m <- metagen(RxChangeMean,
```

```
                 sqrt(RxPostOpStdDev** 2 + RxPreOpStdDev ** 2) / sqrt(LastPeriodEyes),
                 study.name,
                 data=df_,
                 byvar=subtype,
                 n.e=LastPeriodEyes)
forest(m,
       comb.fixed=FALSE,
       digits=1,
       digits.se = 2,
       overall=FALSE,
       leftcols=c("studlab", "TE", "seTE", "n.e"))
```