

Phaco meta analysis

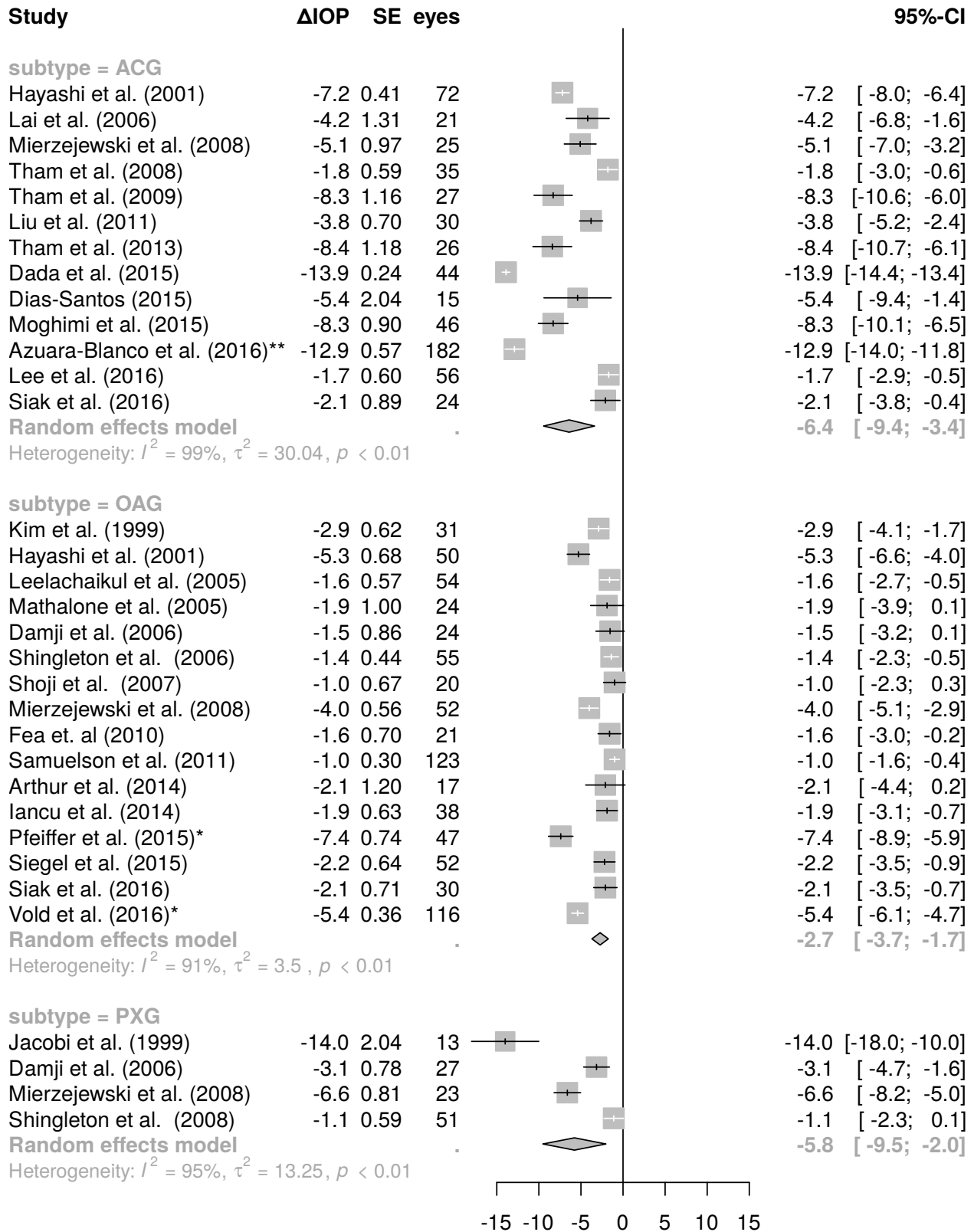
Patrick Mineault

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Analysis of full dataset

Main analysis: ≥ 12 month follow up

```
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"),
       leftlabs=c("Study", "ΔIOP", "SE", "eyes"))
```



Acute

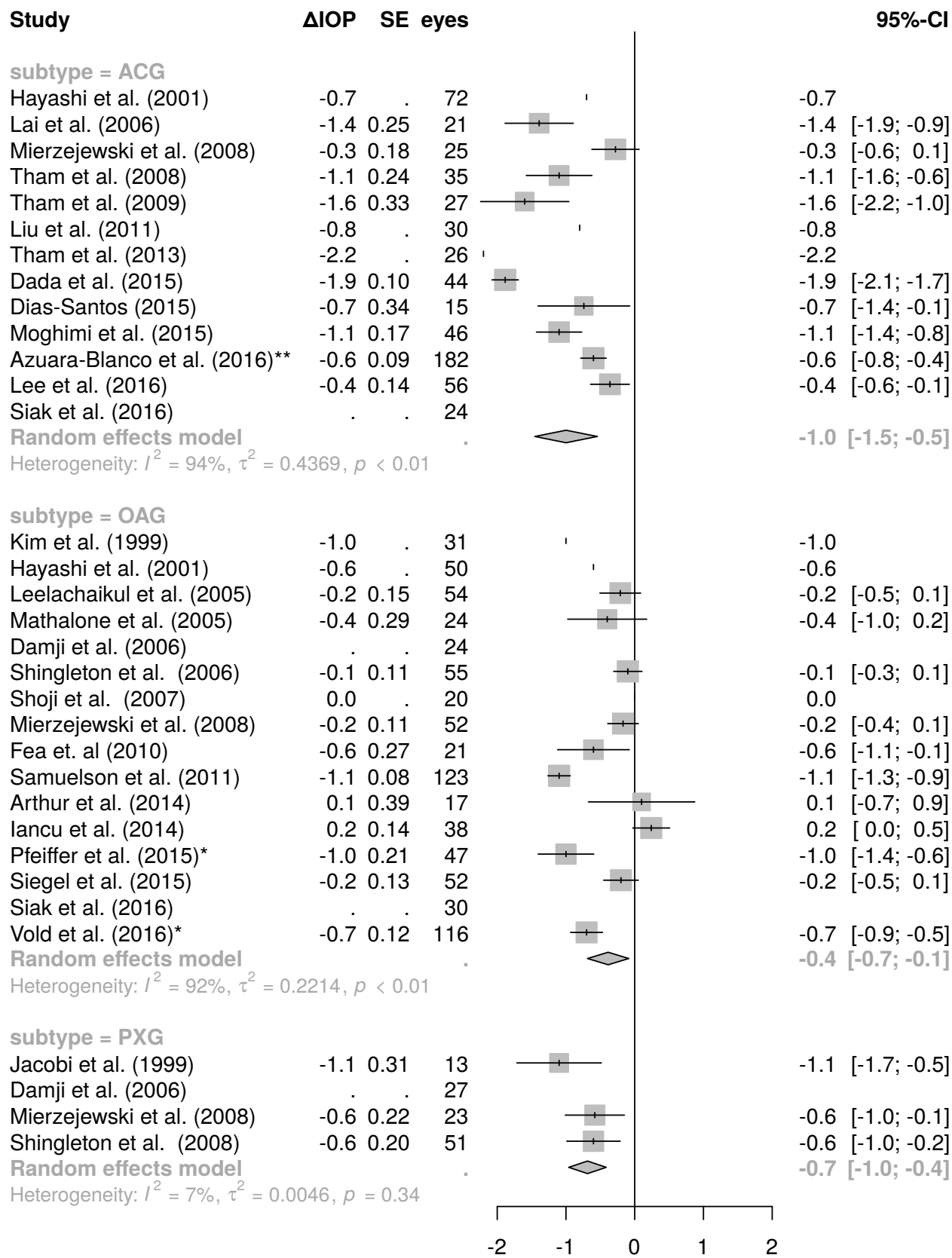
```
df_ <- df %>%
  filter(!is.na(LastPeriodAbsIOPChangeMean), subtype == "acute", MIGsYorN == 'N') %>%
  mutate(subtype=factor(subtype)) %>% dplyr::arrange(Year)
m <- metagen(LastPeriodAbsIOPChangeMean,
             LastPeriodAbsIOPChangeStdDev / sqrt(LastPeriodEyes),
             study.name,
     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

```
##                               95%-CI %W(random)
## Jacobi et al. (2002) -22.7000 [-23.6565; -21.7435]      20.5
## Lam et al. (2008)   -47.1000 [-50.0449; -44.1551]      20.3
## Lee et al. (2010)   -35.8000 [-39.5586; -32.0414]      20.1
## Husain et al. (2012) -44.5000 [-51.8668; -37.1332]     18.9
## Hou et al. (2015)   -35.9600 [-38.9540; -32.9660]      20.3
##
## Number of studies combined: k = 5
##
##                               95%-CI      z  p-value
## Random effects model -37.076 [-48.2779; -25.8742] -6.49 < 0.0001
##
## Quantifying heterogeneity:
## tau^2 = 158.9410; H = 9.13 [7.57; 11.00]; I^2 = 98.8% [98.3%; 99.2%];
## Rb = 97.3% [92.7%; 100.0%]
##
## Test of heterogeneity:
##      Q d.f.  p-value
## 333.21    4 < 0.0001
##
## Details on meta-analytical method:
## - Inverse variance method
## - DerSimonian-Laird estimator for tau^2
```

Meds

```
df_ <- df %>%
  filter(!is.na(LastPeriodAbsIOPChangeMean),
         df$subtype != "acute", MIGsYorN == 'N') %>%
  mutate(subtype=factor(subtype))
m <- metagen(RxChangeMean,
             RxChangeStdDev / 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"),  
leftlabs=c("Study", "ΔIOP", "SE", "eyes"))
```



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

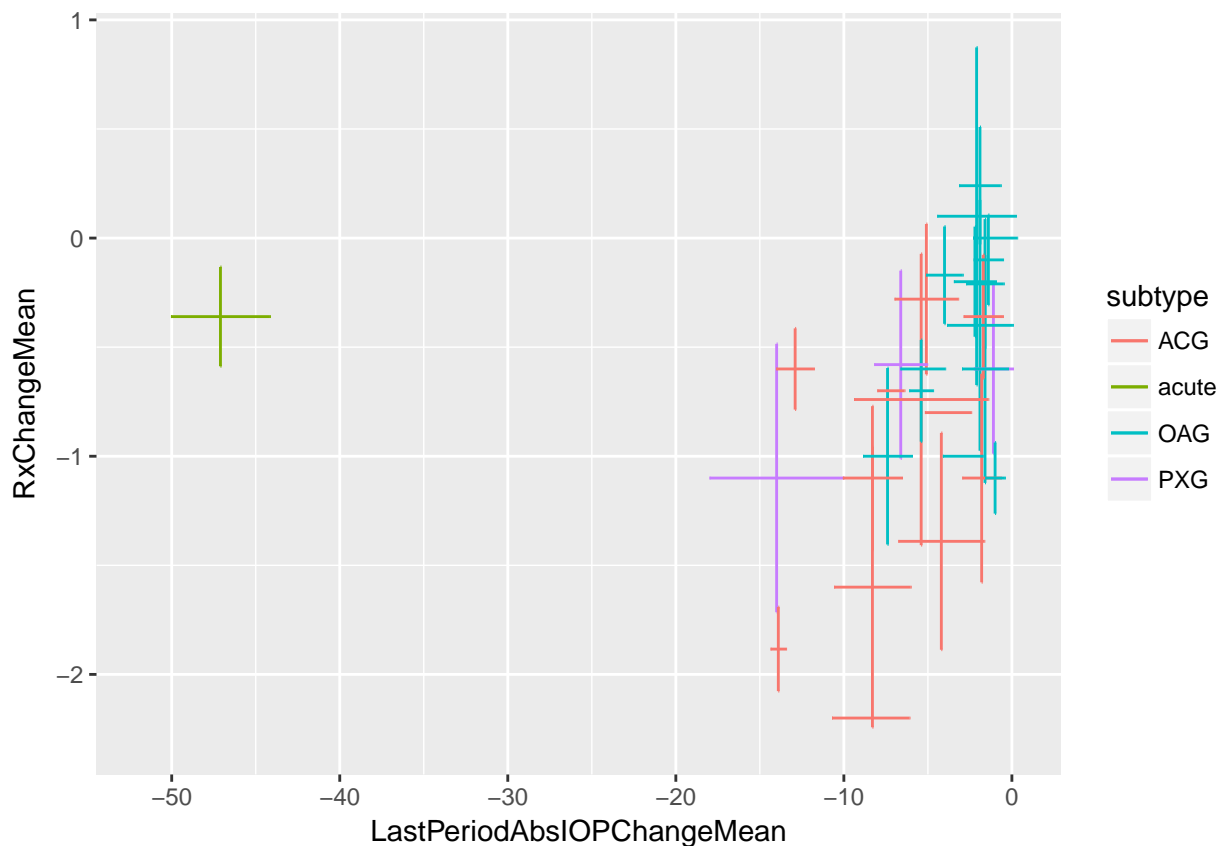
So which is it?

```
df_ <- df %>% mutate(RxChangeSEM = RxChangeStdDev / sqrt>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 21 rows containing missing values (geom_errorbar).

Warning: Removed 15 rows containing missing values (geom_errorbarh).



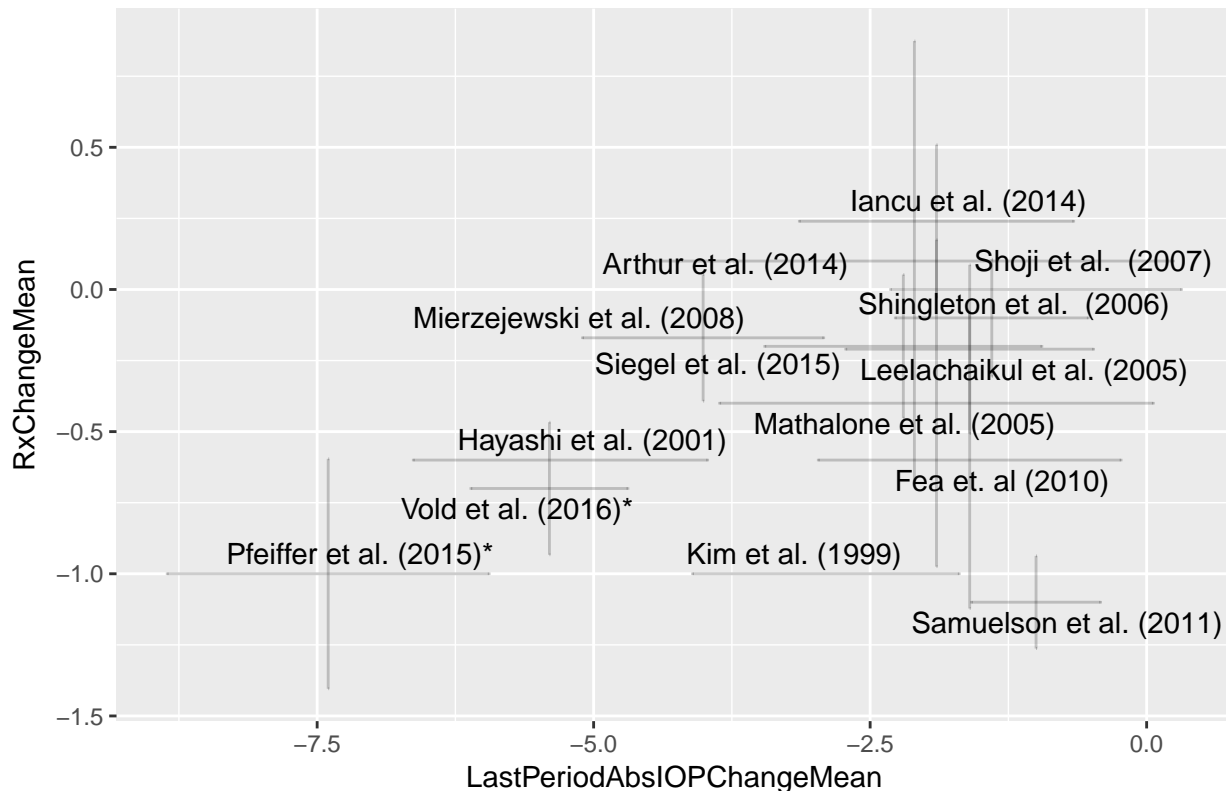
```
ggplot(df_ %>% filter(subtype=='OAG' & MIGsYorN == 'N'),
        aes(x =LastPeriodAbsIOPChangeMean,
```

```

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_rep

```

OAG only



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.

```

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

df_ <- df %>% filter(subtype=='OAG', MIGsYorN == 'N')
drawn.corr <- with(df_, replicate(n = 100,
  draw.corr(LastPeriodAbsIOPChangeMean,
            LastPeriodAbsIOPChangeStdDev / sqrt(LastPeriodEyes),
            RxChangeMean,
            RxChangeStdDev / sqrt(LastPeriodEyes))))
mean(drawn.corr)

```

```
## [1] 0.351358
sd(drawn.corrs)

## [1] 0.1386434
cat("Mean +- SE correlation, no washout\n")

## Mean +- SE correlation, no washout
df_ <- filter.data(df, 'nowashout') %>% filter(subtype=='OAG', MIGsYorN == 'N')
drawn.corrs <- with(df_, replicate(n = 100,
                                draw.corr(LastPeriodAbsIOPChangeMean,
                                           LastPeriodAbsIOPChangeStdDev / sqrt(LastPeriodEyes),
                                           RxChangeMean,
                                           RxChangeStdDev / sqrt(LastPeriodEyes))))
mean(drawn.corrs)

## [1] -0.279246
sd(drawn.corrs)

## [1] 0.2294397
```

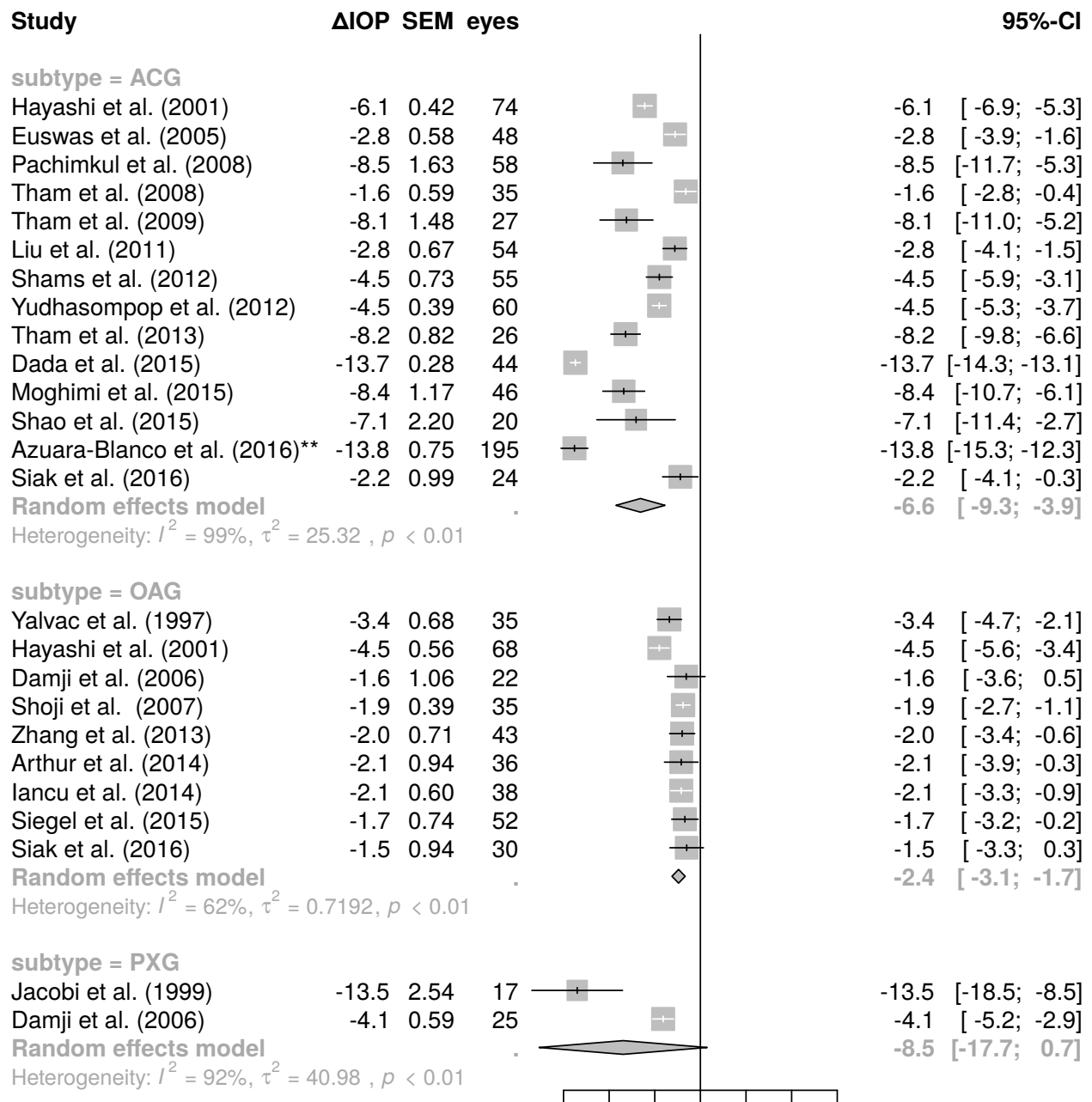
However, this effect goes away when we focus on the studies which don't have washout.

Separate meta-analysis for each time period

```
df <- read.data(fill.last = FALSE)
```

6 month follow-up

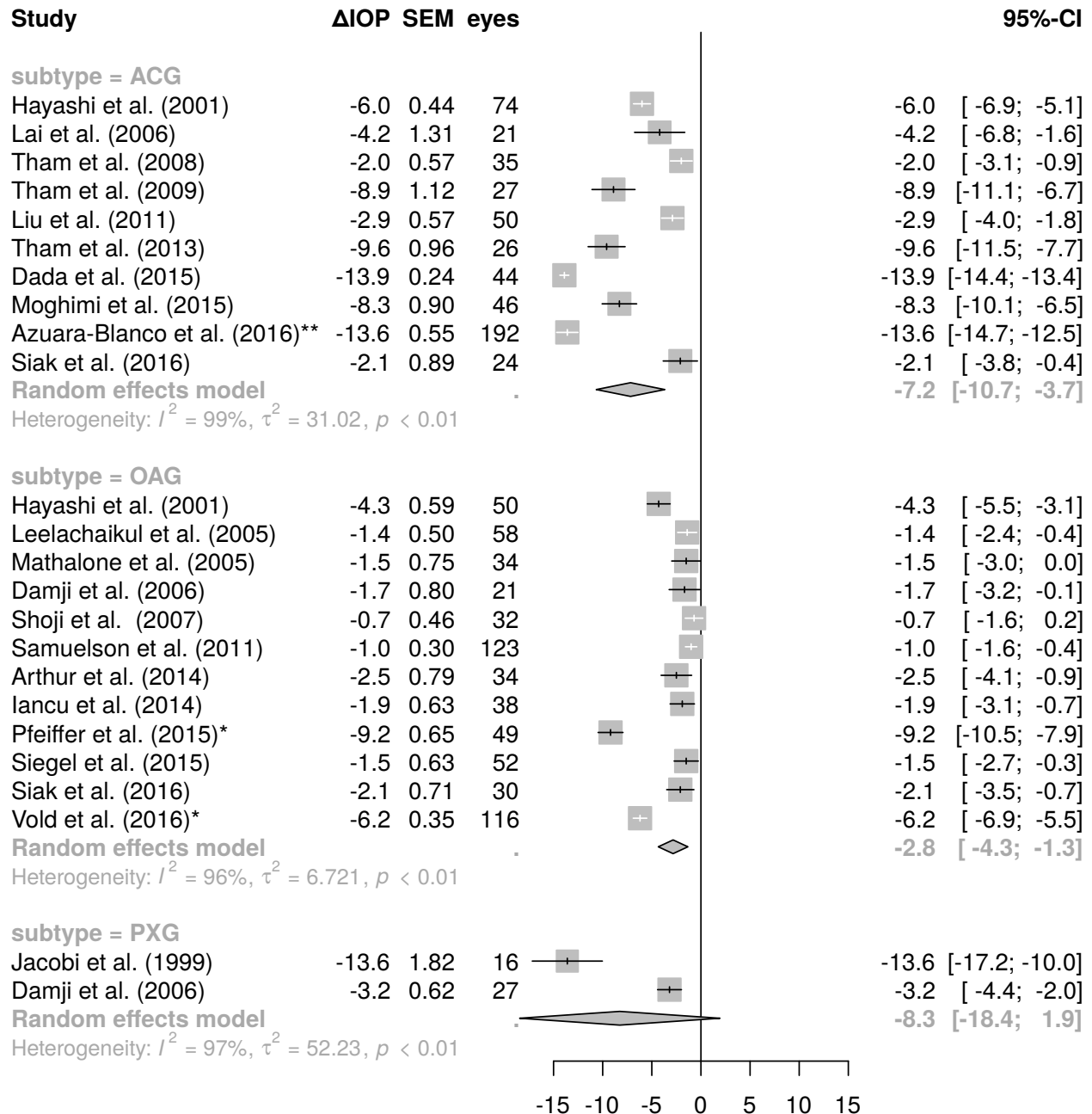
```
df_ <- df %>%
  filter(!is.na(SixMoAbsIOPChangeMean), subtype != "acute") %>%
  mutate(subtype=factor(subtype))
m <- metagen(SixMoAbsIOPChangeMean,
             SixMoAbsIOPChangeStdDev / sqrt(SixMoEyes),
             study.name,
             data=df_,
             byvar=subtype,
             n.e=SixMoEyes)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

12-month follow up

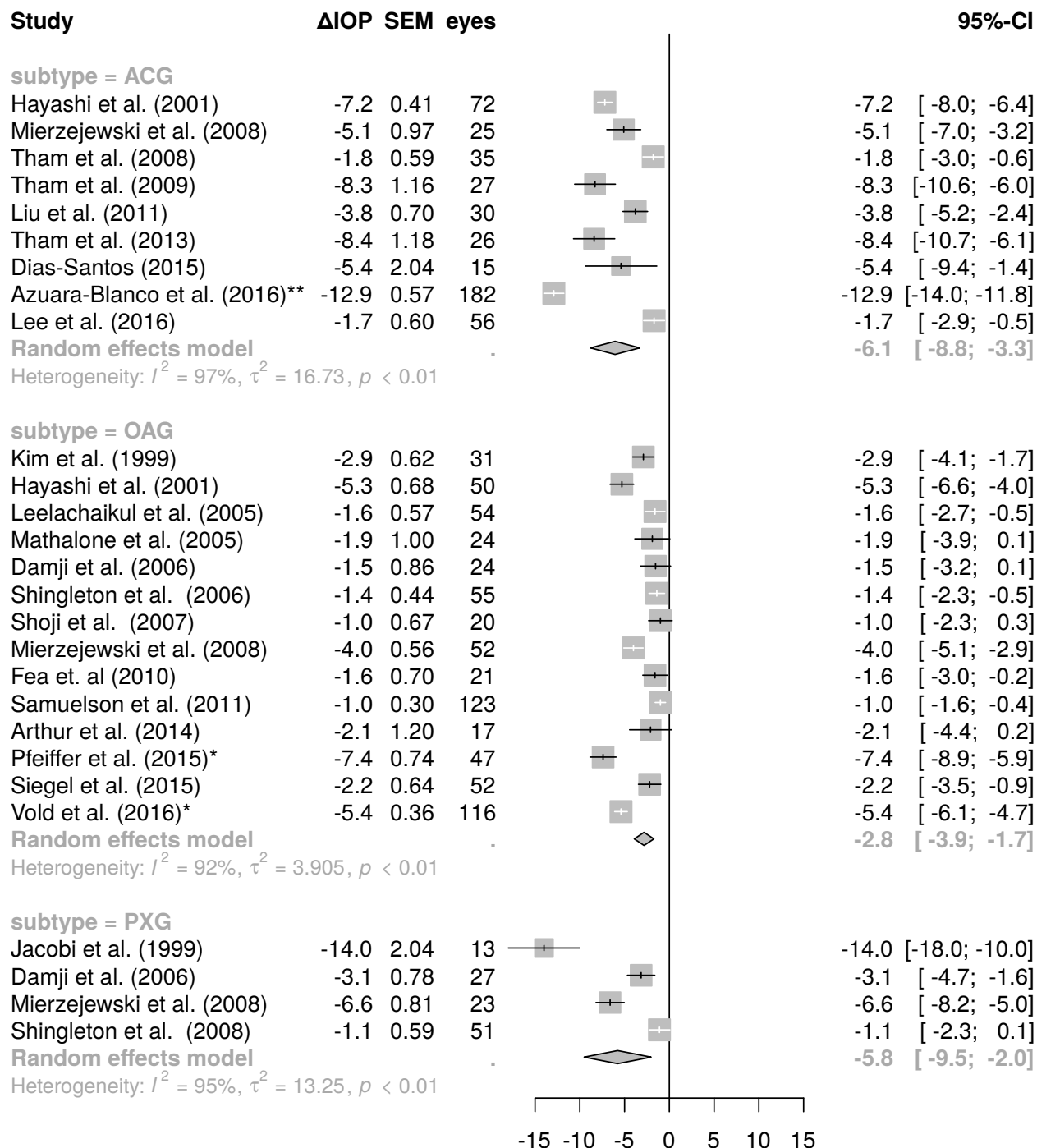
```
df_ <- df %>%
  filter(!is.na(OneYAbsIOPChangeMean), subtype != "acute", MIGsYorN == 'N') %>%
  mutate(subtype=factor(subtype))
m <- metagen(OneYAbsIOPChangeMean,
  OneYAbsIOPChangeStdDev / sqrt(OneYEyes),
  study.name,
  data=df_,
  byvar=subtype,
  n.e=OneYEyes)
```

```
forest(m,
  comb.fixed=FALSE,
  digits=1,
  digits.se = 2,
  overall=FALSE,
  leftcols=c("studlab", "TE", "seTE", "n.e"),
  leftlabs=c("Study", "ΔIOP", "SEM", "eyes"))
```



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"),
       leftlabs=c("Study", "ΔIOP", "SEM", "eyes"))
```



Correlation among time points

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

```
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),
```

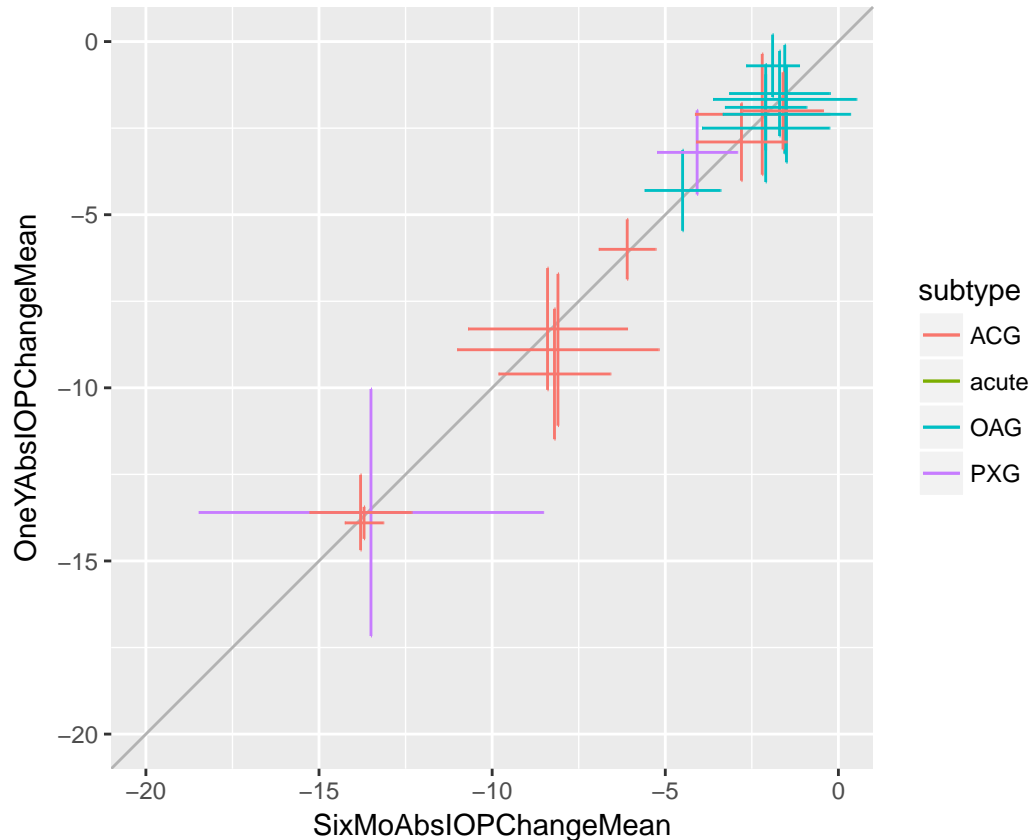
```

    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 25 rows containing missing values (geom_errorbar).

Warning: Removed 25 rows containing missing values (geom_errorbarh).



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

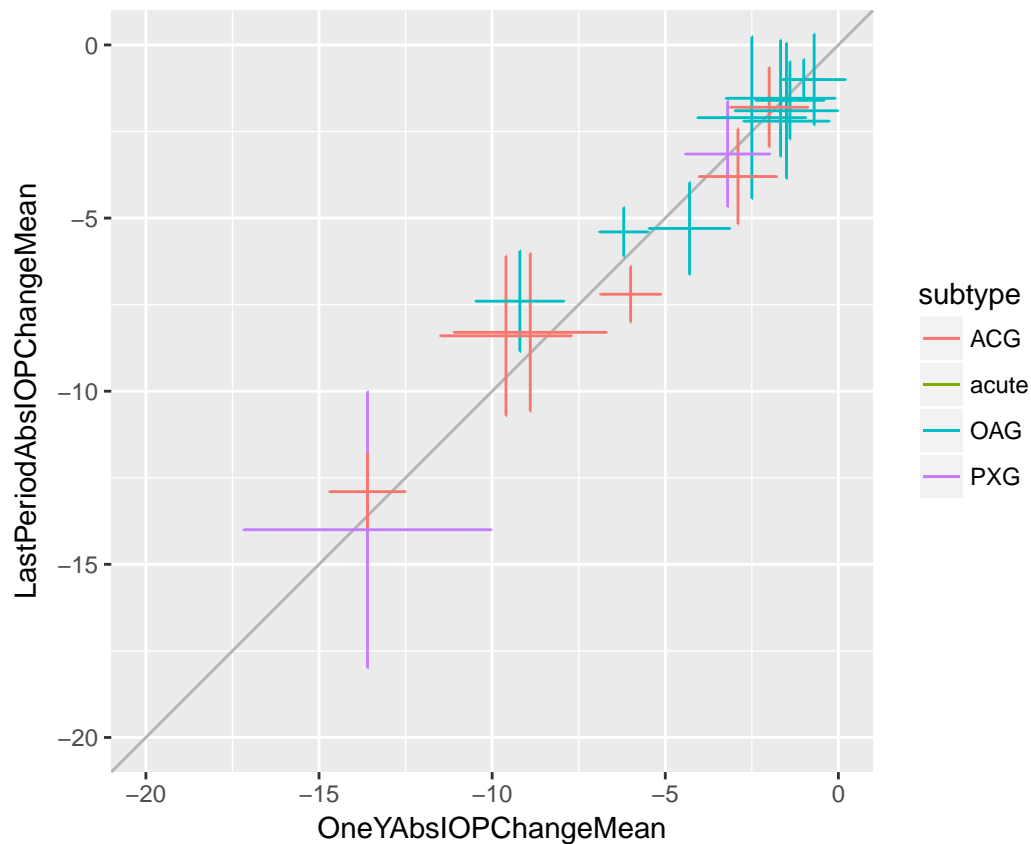
Similarly for one-year vs. last period:

```

ggplot(df, aes(y =LastPeriodAbsIOPChangeMean,
  ymin=LastPeriodAbsIOPChangeMean - 1.96*LastPeriodAbsIOPChangeStdDev / sqrt(LastPeriodEyes),
  ymax=LastPeriodAbsIOPChangeMean + 1.96*LastPeriodAbsIOPChangeStdDev / sqrt(LastPeriodEyes),
  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 26 rows containing missing values (geom_errorbar).
## Warning: Removed 26 rows containing missing values (geom_errorbarh).
```



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

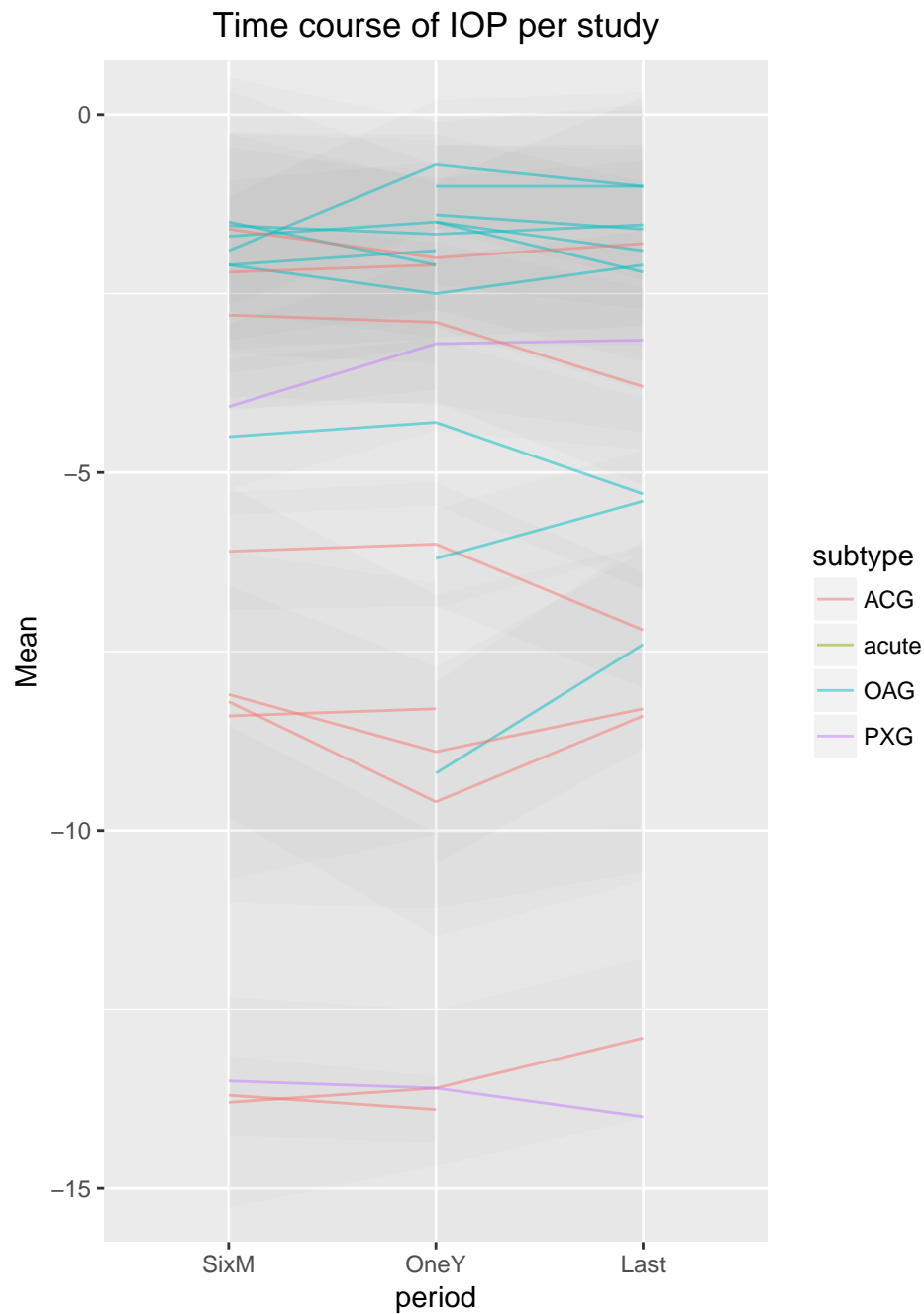
```
library(reshape2)

##
## 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_t

```



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.corr <- 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] 0.6210343
print(sd(drawn.corrs))

## [1] 0.2025096
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] 0.9919608
print(sd(drawn.corrs))

## [1] 0.003583891

```

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 )))))
}

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 ** 2), 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) ~ subtype,
  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_$SixMoAbsIOPChangeStdDev/
##   df_$OneYAbsIOPChangeStdDev/sqrt(df_$OneYEyes), df_$LastPeriodAbsIOPChangeStdDev/sqrt(df_$LastPeriod
##   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)  -5.9077    0.7511 -7.8657  0.0000  -7.3797  -4.4356
## subtypeOAG    2.8997    1.0525  2.7551  0.0059   0.8368   4.9625
##
## (Intercept) ***
## subtypeOAG    **
## OneYAbsIOPChangeMean :
##           Estimate Std. Error      z Pr(>|z|) 95%ci.lb 95%ci.ub
## (Intercept)  -6.0920    0.7607 -8.0089  0.0000  -7.5828  -4.6011
## subtypeOAG    3.3725    1.0576  3.1888  0.0014   1.2996   5.4454
##
## (Intercept) ***
## subtypeOAG    **
## LastPeriodAbsIOPChangeMean :
##           Estimate Std. Error      z Pr(>|z|) 95%ci.lb 95%ci.ub
## (Intercept)  -6.2546    0.6784 -9.2199  0.0000  -7.5842  -4.9250
## subtypeOAG    3.5680    0.9329  3.8246  0.0001   1.7396   5.3965
##
## (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    2.9877 SixMoAbsIOPChangeMean

```

```

## OneYAbsIOPChangeMean      3.0236      0.9981
## LastPeriodAbsIOPChangeMean 2.6030      0.9919
##
## SixMoAbsIOPChangeMean      OneYAbsIOPChangeMean
## OneYAbsIOPChangeMean
## LastPeriodAbsIOPChangeMean      0.9821
##
## Multivariate Cochran Q-test for residual heterogeneity:
## Q = 1625.2906 (df = 62), p-value = 0.0000
## I-square statistic = 96.2%
##
## 36 studies, 68 observations, 6 fixed and 6 random-effects parameters
##      logLik      AIC      BIC
## -118.5856    261.1712    286.6968

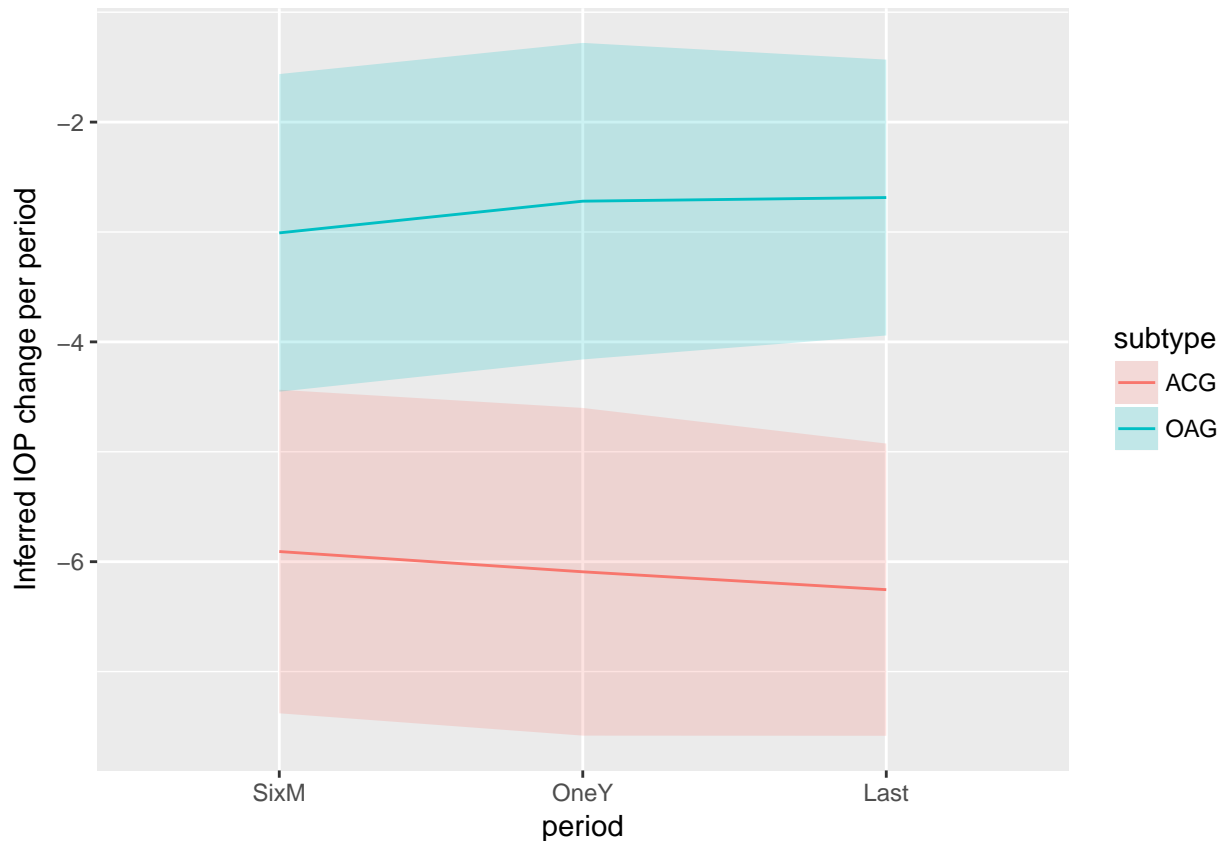
newdata <- data.frame(subtype=c('OAG', 'ACG'))
pred <- predict(thefit, newdata, se=TRUE)
newdata$SixMoAbsIOPChangeMean <- pred$fit[,1]
newdata$OneYAbsIOPChangeMean <- pred$fit[,2]
newdata$LastPeriodAbsIOPChangeMean <- pred$fit[,3]
newdata$SixMoAbsIOPChangeSEM <- pred$se[,1]
newdata$OneYAbsIOPChangeSEM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

library(reshape2)
nd <- melt(newdata)

## Using subtype as id variables

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.

```
df <- read.data()

## These retrospective studies are losing eyes per period - not impossible, but unusual:
## Mathalone et al. (2005)
## Leelachaikul et al. (2005)
## Shoji et al. (2007)
## Liu et al. (2011)
## Arthur et al. (2014)
## Tetz et al. (2015)

## These retrospective studies are gaining eyes as the study goes
## Samuelson et al. (2011)
df_ <- df %>% filter(!is.na>LastPeriodAbsIOPChangeMean), subtype != "acute", MIGsYorN == 'N') %>%
  mutate(subtype=relevel(factor(subtype), ref="OAG"))
m <- metagen>LastPeriodAbsIOPChangeMean,
  LastPeriodAbsIOPChangeStdDev / sqrt>LastPeriodEyes),
  study.name,
  data=df_,
  byvar=subtype,
  n.e=OneYEyes)
```

```

print(metareg(~ LastPeriodEyes, x=m))

##
## Mixed-Effects Model (k = 33; tau^2 estimator: DL)
##
## tau^2 (estimated amount of residual heterogeneity):      26.2513 (SE = 9.6875)
## tau (square root of estimated tau^2 value):             5.1236
## I^2 (residual heterogeneity / unaccounted variability): 98.62%
## H^2 (unaccounted variability / sampling variability):    72.73
## R^2 (amount of heterogeneity accounted for):             0.00%
##
## Test for Residual Heterogeneity:
## QE(df = 31) = 2254.5144, p-val < .0001
##
## Test of Moderators (coefficient(s) 2):
## QM(df = 1) = 0.8360, p-val = 0.3605
##
## Model Results:
##
##              estimate      se      zval      pval      ci.lb      ci.ub
## intrcpt          -3.4752  1.4802  -2.3478  0.0189  -6.3764  -0.5740 *
## LastPeriodEyes   -0.0238  0.0260  -0.9144  0.3605  -0.0747   0.0272
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

print(metareg(~ LastPeriodEyes * subtype, x=m))

##
## Mixed-Effects Model (k = 33; tau^2 estimator: DL)
##
## tau^2 (estimated amount of residual heterogeneity):      15.5304 (SE = 5.8744)
## tau (square root of estimated tau^2 value):             3.9409
## I^2 (residual heterogeneity / unaccounted variability): 97.52%
## H^2 (unaccounted variability / sampling variability):    40.31
## R^2 (amount of heterogeneity accounted for):             36.43%
##
## Test for Residual Heterogeneity:
## QE(df = 27) = 1088.3177, p-val < .0001
##
## Test of Moderators (coefficient(s) 2,3,4,5,6):
## QM(df = 5) = 13.5909, p-val = 0.0184
##
## Model Results:
##
##              estimate      se      zval      pval      ci.lb
## intrcpt          -2.0693  1.8525  -1.1171  0.2640  -5.7002
## LastPeriodEyes   -0.0135  0.0328  -0.4125  0.6800  -0.0778
## subtypeACG        -2.1400  2.5047  -0.8544  0.3929  -7.0492
## subtypePXG       -12.1575  5.1350  -2.3676  0.0179 -22.2219
## LastPeriodEyes:subtypeACG -0.0332  0.0422  -0.7882  0.4306  -0.1159
## LastPeriodEyes:subtypePXG  0.2999  0.1512   1.9839  0.0473   0.0036
##              ci.ub
## intrcpt          1.5615

```

```

## LastPeriodEyes          0.0508
## subtypeACG              2.7691
## subtypePXG             -2.0932 *
## LastPeriodEyes:subtypeACG 0.0494
## LastPeriodEyes:subtypePXG 0.5962 *
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

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

##
## Mixed-Effects Model (k = 33; tau^2 estimator: DL)
##
## tau^2 (estimated amount of residual heterogeneity):    22.3228 (SE = 8.2207)
## tau (square root of estimated tau^2 value):           4.7247
## I^2 (residual heterogeneity / unaccounted variability): 98.40%
## H^2 (unaccounted variability / sampling variability):  62.34
## R^2 (amount of heterogeneity accounted for):           8.63%
##
## Test for Residual Heterogeneity:
## QE(df = 31) = 1932.3895, p-val < .0001
##
## Test of Moderators (coefficient(s) 2):
## QM(df = 1) = 0.0830, p-val = 0.7732
##
## Model Results:
##
##      estimate      se      zval      pval      ci.lb      ci.ub
## intrcpt  89.0966  324.9770   0.2742   0.7840  -547.8466  726.0397
## Year    -0.0466   0.1617  -0.2881   0.7732   -0.3635   0.2703
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

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

##
## Mixed-Effects Model (k = 33; tau^2 estimator: DL)
##
## tau^2 (estimated amount of residual heterogeneity):    13.5115 (SE = 4.9389)
## tau (square root of estimated tau^2 value):           3.6758
## I^2 (residual heterogeneity / unaccounted variability): 97.20%
## H^2 (unaccounted variability / sampling variability):  35.67
## R^2 (amount of heterogeneity accounted for):           44.70%
##
## Test for Residual Heterogeneity:
## QE(df = 27) = 963.1148, p-val < .0001
##
## Test of Moderators (coefficient(s) 2,3,4,5,6):
## QM(df = 5) = 12.4364, p-val = 0.0293
##
## Model Results:
##
##      estimate      se      zval      pval      ci.lb

```

```

## intrcpt          101.1568   356.9373   0.2834   0.7769  -598.4274
## Year             -0.0517    0.1776  -0.2910   0.7710   -0.3999
## subtypeACG       215.3198   581.9158   0.3700   0.7114  -925.2142
## subtypePXG      -2425.5387  1160.3658  -2.0903   0.0366 -4699.8138
## Year:subtypeACG   -0.1088    0.2894  -0.3761   0.7069   -0.6761
## Year:subtypePXG    1.2078    0.5785   2.0879   0.0368    0.0740
##               ci.lb      ci.ub
## intrcpt          800.7410
## Year              0.2965
## subtypeACG       1355.8538
## subtypePXG       -151.2635 *
## Year:subtypeACG    0.4584
## Year:subtypePXG    2.3415 *
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

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

##
## Mixed-Effects Model (k = 33; tau^2 estimator: DL)
##
## tau^2 (estimated amount of residual heterogeneity):      5.0095 (SE = 1.8023)
## tau (square root of estimated tau^2 value):             2.2382
## I^2 (residual heterogeneity / unaccounted variability): 92.99%
## H^2 (unaccounted variability / sampling variability):    14.27
## R^2 (amount of heterogeneity accounted for):             79.50%
##
## Test for Residual Heterogeneity:
## QE(df = 31) = 442.4039, p-val < .0001
##
## Test of Moderators (coefficient(s) 2):
## QM(df = 1) = 57.5862, p-val < .0001
##
## Model Results:
##
##               estimate      se      zval      pval      ci.lb      ci.ub
## intrcpt          11.3336   2.1216   5.3421  <.0001    7.1754   15.4918 ***
## PreOpIOPMean    -0.7859   0.1036  -7.5886  <.0001   -0.9888   -0.5829 ***
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

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

##
## Mixed-Effects Model (k = 33; tau^2 estimator: DL)
##
## tau^2 (estimated amount of residual heterogeneity):      1.3374 (SE = 0.5549)
## tau (square root of estimated tau^2 value):             1.1564
## I^2 (residual heterogeneity / unaccounted variability): 77.18%
## H^2 (unaccounted variability / sampling variability):    4.38
## R^2 (amount of heterogeneity accounted for):             94.53%
##
## Test for Residual Heterogeneity:

```

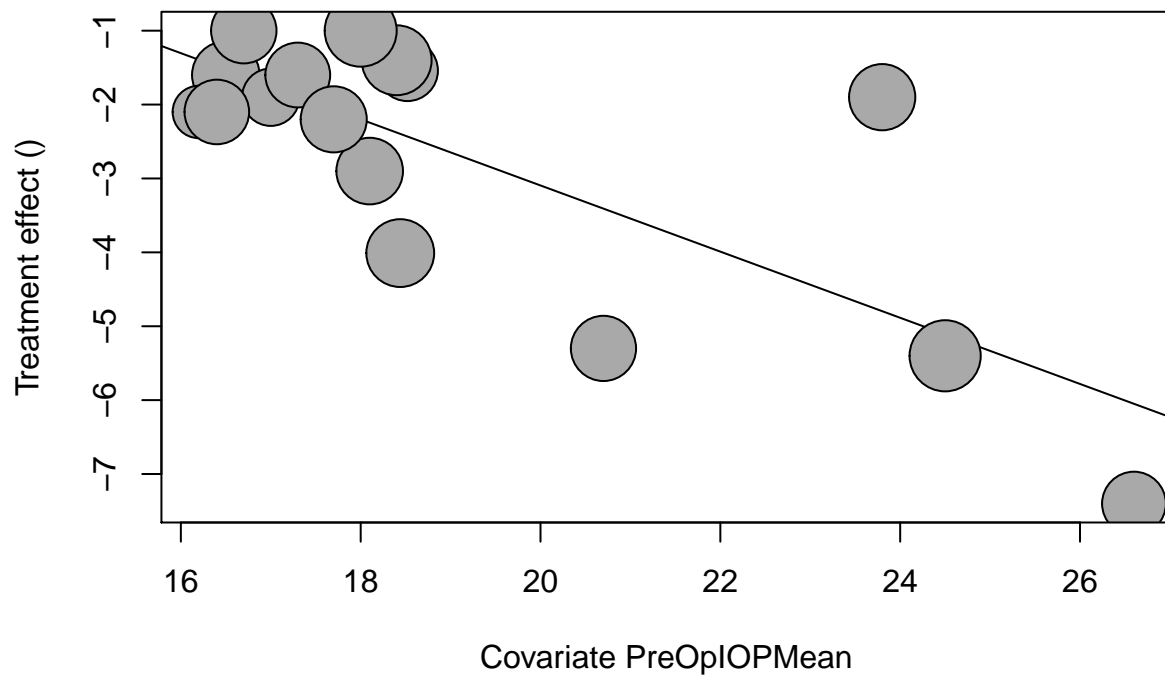
```

## QE(df = 27) = 118.3200, p-val < .0001
##
## Test of Moderators (coefficient(s) 2,3,4,5,6):
## QM(df = 5) = 202.7962, p-val < .0001
##
## Model Results:
##
##               estimate      se      zval      pval      ci.lb
## intrcpt          5.8521  2.1063   2.7784  0.0055   1.7238
## PreOpIOPMean     -0.4475  0.1085  -4.1251 <.0001  -0.6601
## subtypeACG        5.5905  2.7842   2.0079  0.0447   0.1336
## subtypePXG        8.8300  4.5191   1.9539  0.0507  -0.0272
## PreOpIOPMean:subtypeACG -0.4137  0.1375  -3.0091  0.0026  -0.6832
## PreOpIOPMean:subtypePXG -0.4777  0.2179  -2.1928  0.0283  -0.9047
##               ci.ub
## intrcpt          9.9803  **
## PreOpIOPMean     -0.2349  ***
## subtypeACG       11.0475   *
## subtypePXG       17.6873   .
## PreOpIOPMean:subtypeACG -0.1443  **
## PreOpIOPMean:subtypePXG -0.0507   *
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

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

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

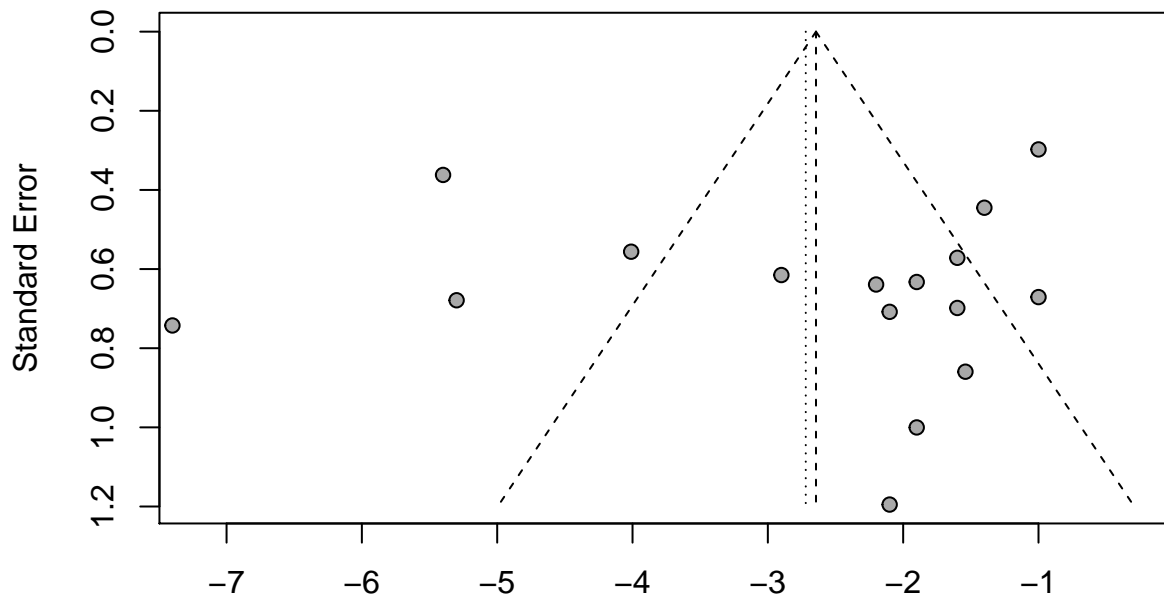
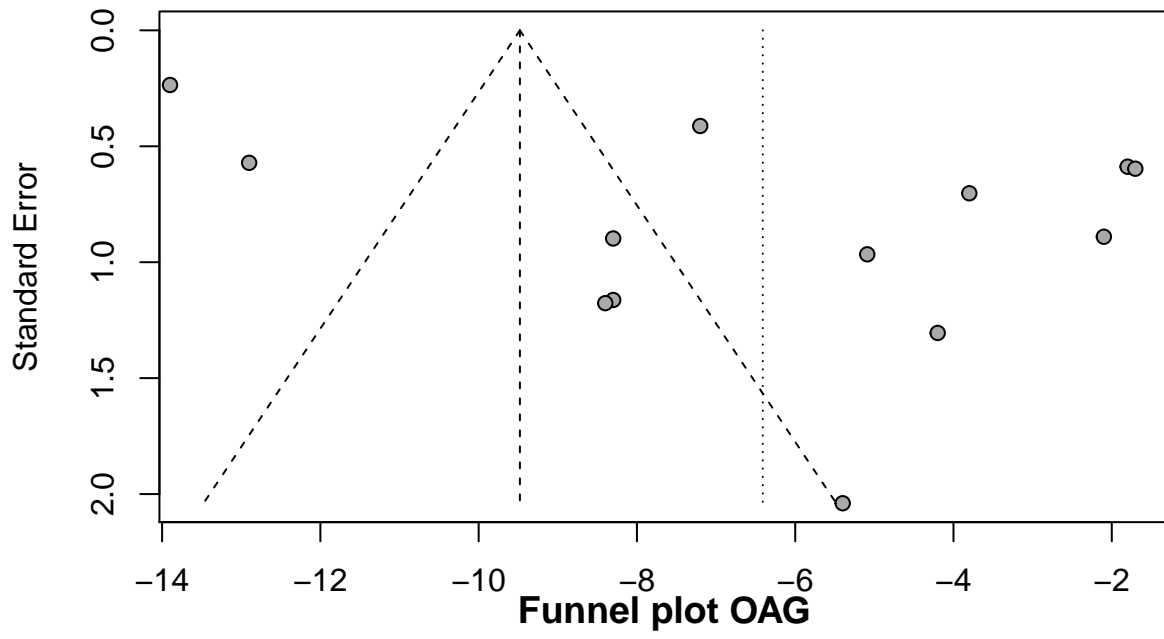
```

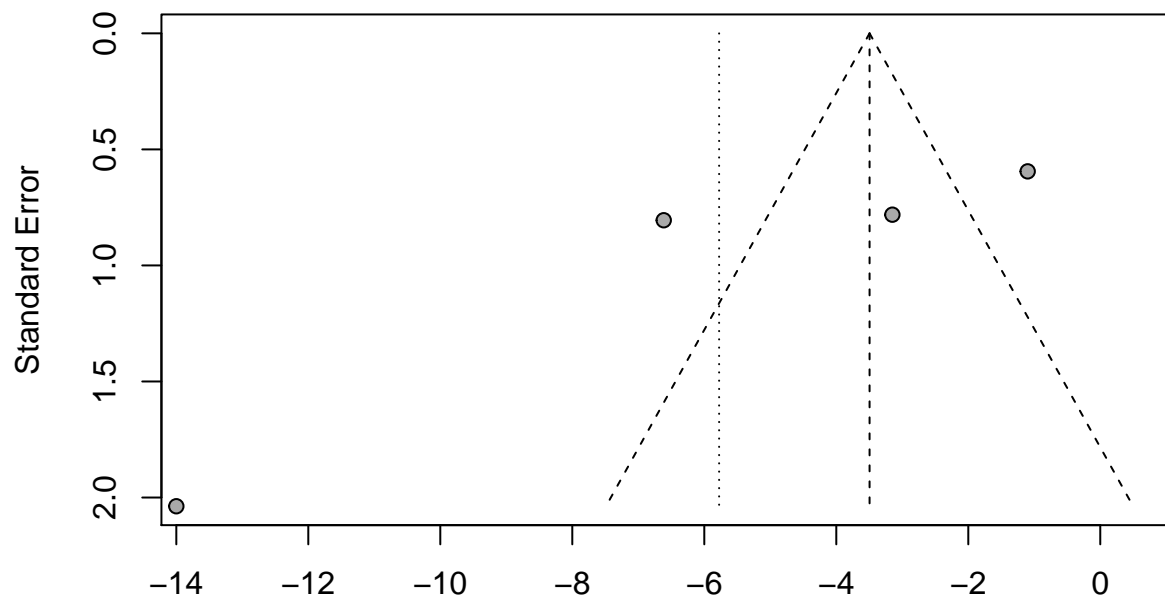
Small study bias

```
df_ <- df %>% filter(!is.na(df$LastPeriodAbsIOPChangeMean),
                     df$subtype != "acute",
                     MIGsYorN == 'N') %>% mutate(subtype=factor(subtype))
for(l in levels(df_$subtype)) {
  m <- metagen(LastPeriodAbsIOPChangeMean,
               LastPeriodAbsIOPChangeStdDev / sqrt(LastPeriodEyes),
               study.name,
               data=df_ %>% filter(subtype == l),
               n.e=LastPeriodEyes)
  funnel(m)
  title(paste('Funnel plot', l))
}
```

Funnel plot ACG

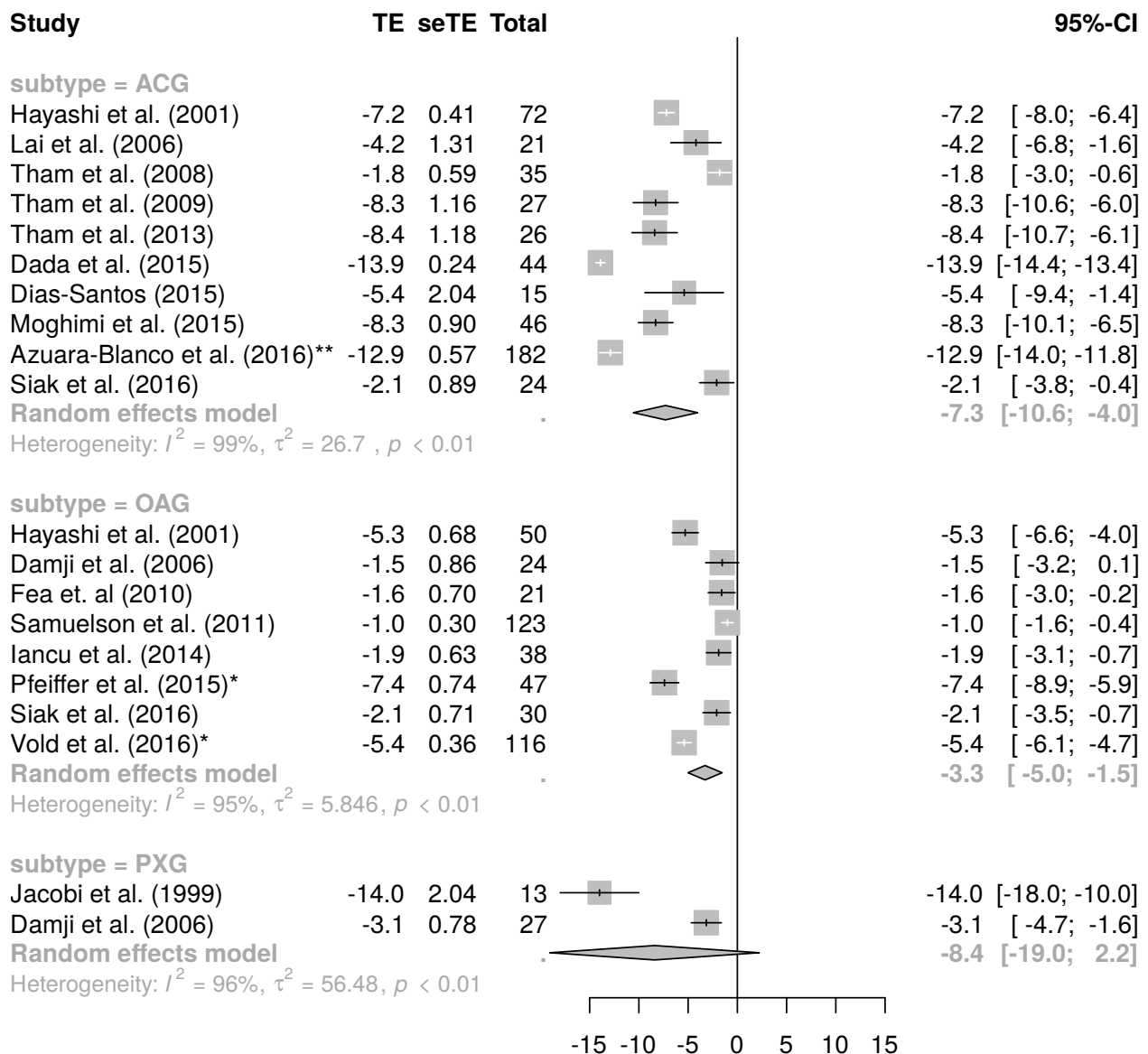


Funnel plot PXG



Alternative filterings of the data

Prospective studies only



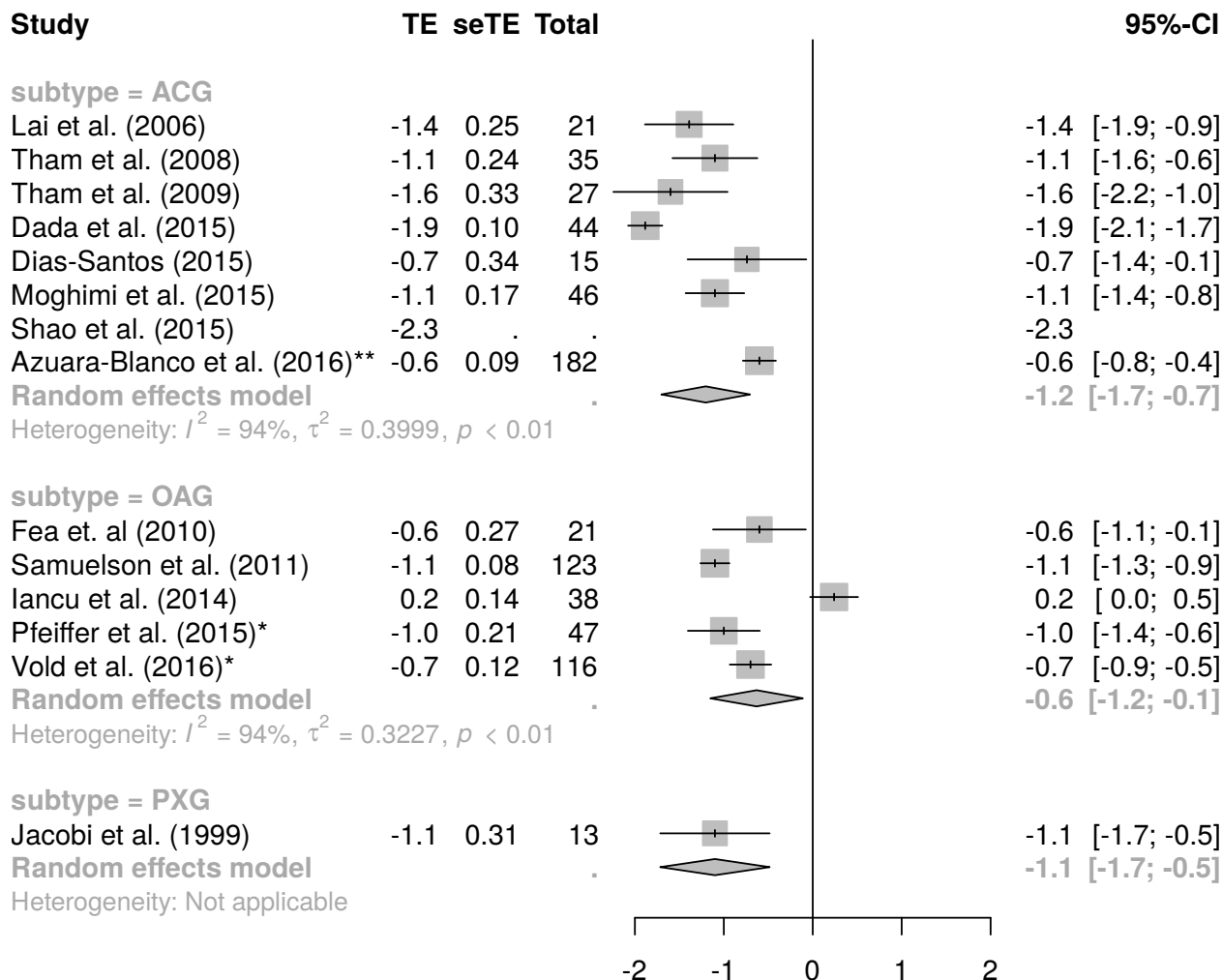
Meds

```
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

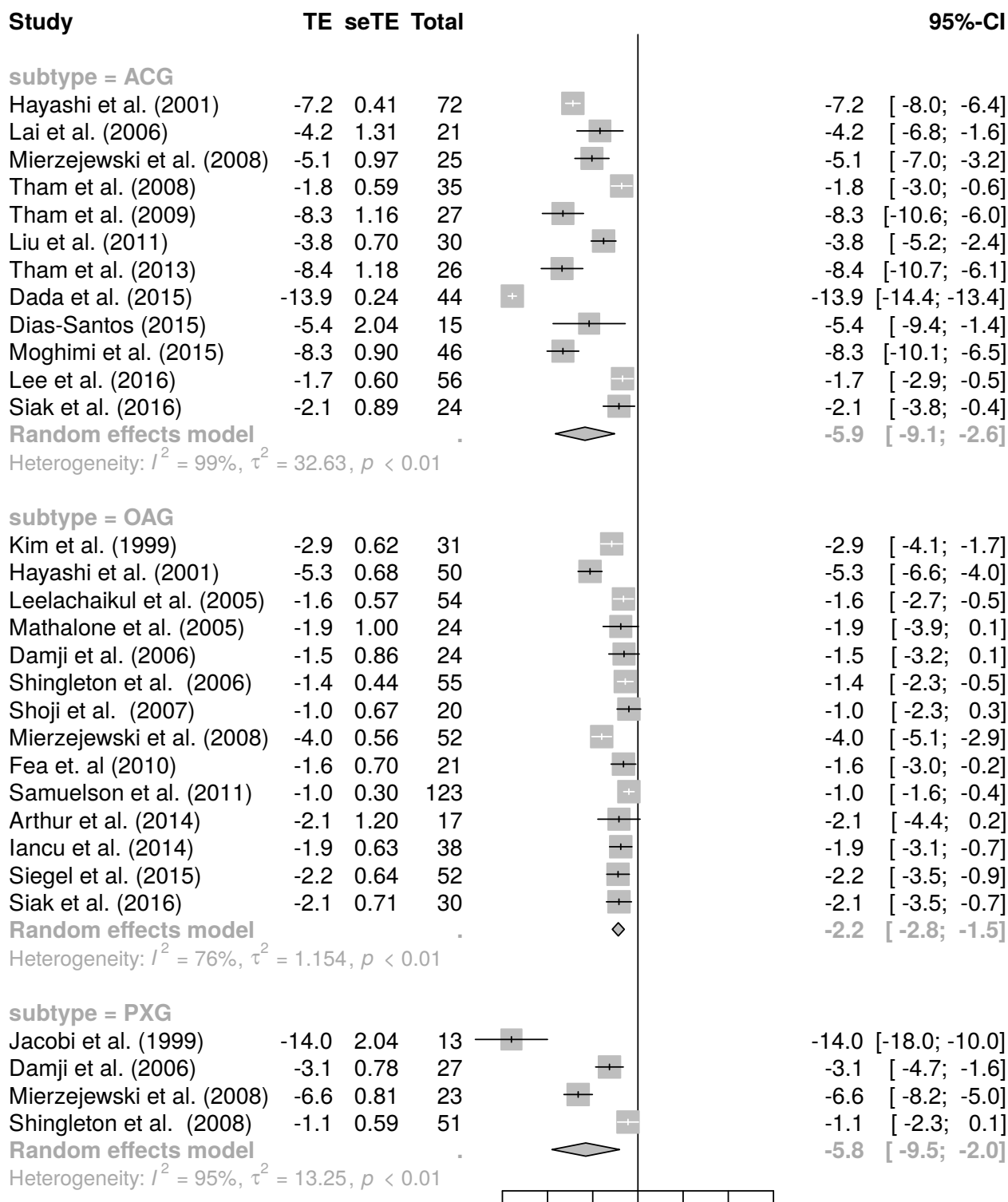
Last period

```

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"))
```



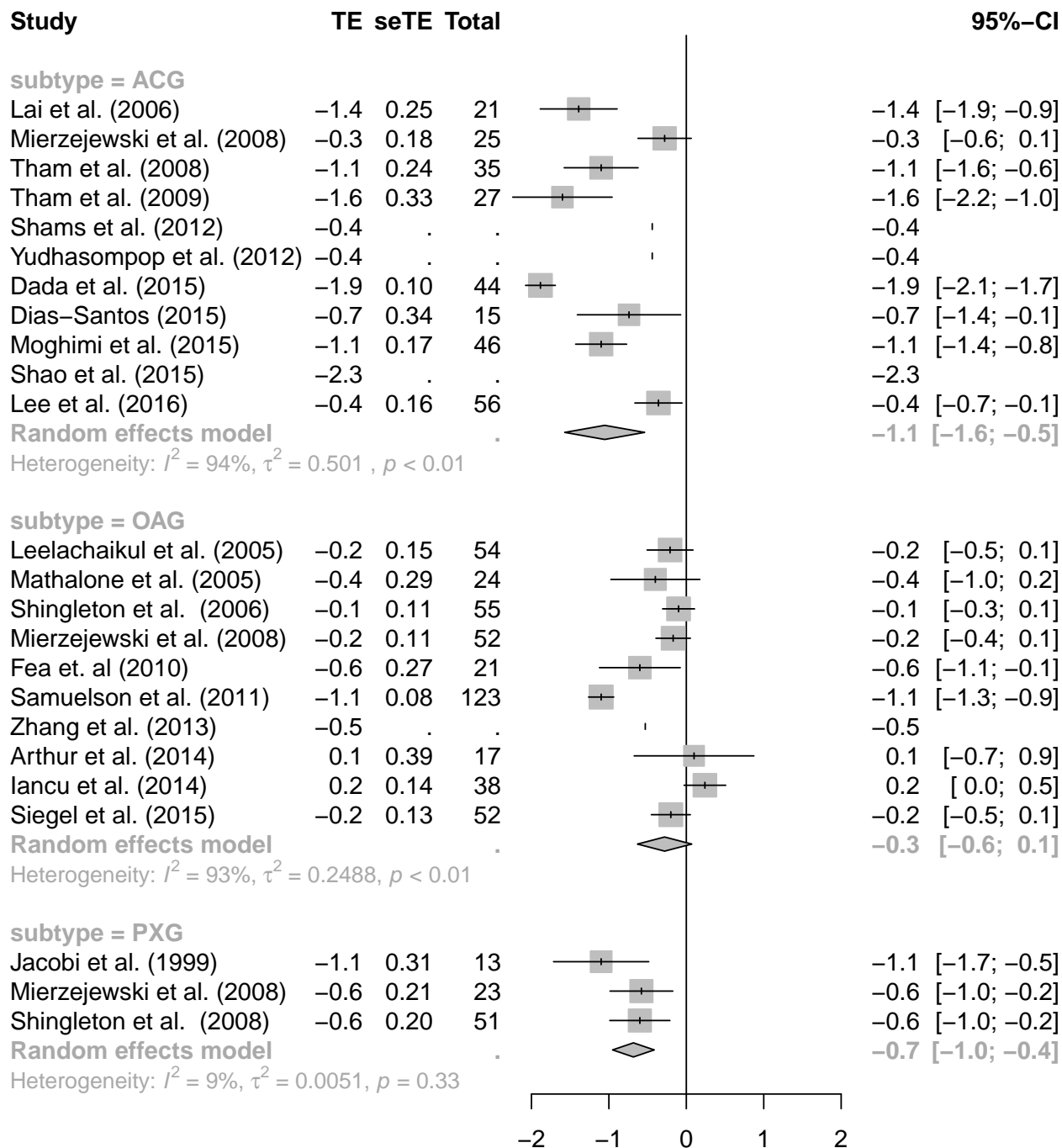
Meds

```
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"))

```

MIGS

We don't report these results because it's a bit misleading – the studies aren't very similar to each other, and we don't use the information in their control arms. We can do a much better job through, for example, network meta-analysis, which we plan to do in a future paper.

```
df <- read.data(drop.migs = FALSE)
```

```
## These retrospective studies are losing eyes per period - not impossible, but unusual:
```

```
## Mathalone et al. (2005)
## Leelachaikul et al. (2005)
## Shoji et al. (2007)
## Liu et al. (2011)
## Arthur et al. (2014)
## Tetz et al. (2015)

## These retrospective studies are gaining eyes as the study goes

## Samuelson et al. (2011)

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"))
```

