Phaco meta analysis

Patrick Mineault

14/02/2017

Contents

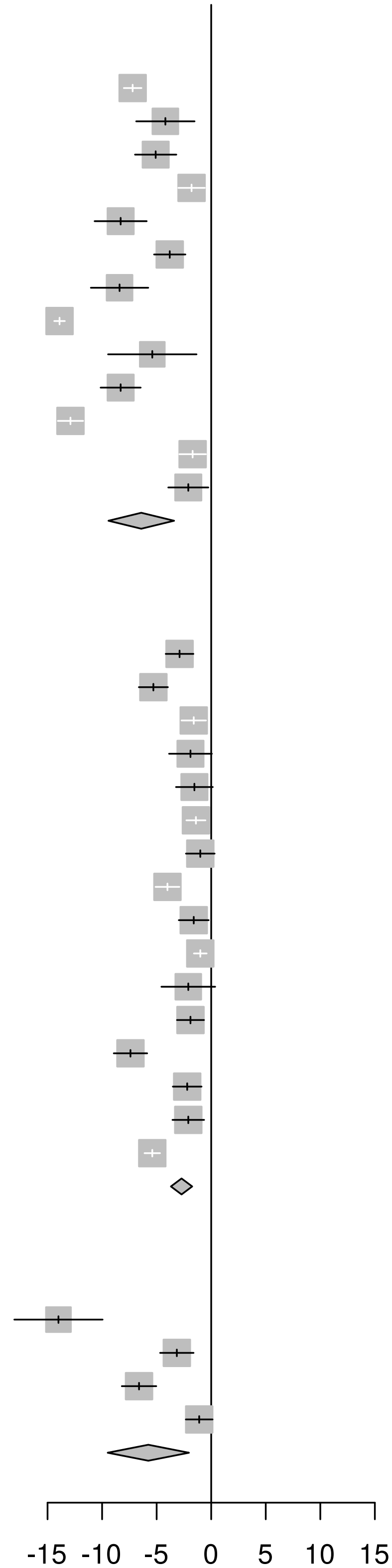
Analysis of full dataset

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"))
```

Study	ΔIOP	SE	eyes		95%-CI
subtype = ACG					
Hayashi et al. (2001)†	-7.2	0.41	72	-7.2	[-8.0; -6.4]
Lai et al. (2006)	-4.2	1.36	21	-4.2	[-6.9; -1.5]
Mierzejewski et al. (2008)	-5.1	0.97	25	-5.1	[-7.0; -3.2]
Tham et al. (2008)	-1.8	0.62	35	-1.8	[-3.0; -0.6]
Tham et al. (2009)	-8.3	1.22	27	-8.3	[-10.7; -5.9]
Liu et al. (2011)	-3.8	0.73	30	-3.8	[-5.2; -2.4]
Tham et al. (2013)	-8.4	1.34	20	-8.4	[-11.0; -5.8]
Dada et al. (2015)	-13.9	0.25	44	-13.9	[-14.4; -13.4]
Dias-Santos (2015)	-5.4	2.07	15	-5.4	[-9.5; -1.3]
Moghimi et al. (2015)	-8.3	0.94	46	-8.3	[-10.1; -6.5]
Azuara-Blanco et al. (2016)**	-12.9	0.59	182	-12.9	[-14.1; -11.7]
Lee et al. (2016)	-1.7	0.62	56	-1.7	[-2.9; -0.5]
Siak et al. (2016)	-2.1	0.94	24	-2.1	[-3.9; -0.3]
Random effects model			.	**-6.4**	**[-9.4; -3.4]**
Heterogeneity: $I^2 = 99\%$, $\tau^2 = 29.57$, $p < 0.01$					
subtype = OAG					
Kim et al. (1999)	-2.9	0.65	31	-2.9	[-4.2; -1.6]
Hayashi et al. (2001)†	-5.3	0.68	50	-5.3	[-6.6; -4.0]
Leelachaikul et al. (2005)	-1.6	0.57	54	-1.6	[-2.7; -0.5]
Mathalone et al. (2005)	-1.9	1.00	24	-1.9	[-3.9; 0.1]
Damji et al. (2006)	-1.5	0.86	24	-1.5	[-3.2; 0.1]
Shingleton et al. (2006)	-1.4	0.44	55	-1.4	[-2.3; -0.5]
Shoji et al. (2007)	-1.0	0.67	20	-1.0	[-2.3; 0.3]
Mierzejewski et al. (2008)	-4.0	0.56	52	-4.0	[-5.1; -2.9]
Fea et. al (2010)	-1.6	0.70	21	-1.6	[-3.0; -0.2]
Samuelson et al. (2011)	-1.0	0.30	123	-1.0	[-1.6; -0.4]
Arthur et al. (2014)	-2.1	1.26	17	-2.1	[-4.6; 0.4]
Iancu et al. (2014)	-1.9	0.63	38	-1.9	[-3.1; -0.7]
Pfeiffer et al. (2015)*	-7.4	0.78	47	-7.4	[-8.9; -5.9]
Siegel et al. (2015)	-2.2	0.67	52	-2.2	[-3.5; -0.9]
Siak et al. (2016)	-2.1	0.74	30	-2.1	[-3.5; -0.7]
Vold et al. (2016)*	-5.4	0.36	116	-5.4	[-6.1; -4.7]
Random effects model			.	**-2.7**	**[-3.7; -1.7]**
Heterogeneity: $I^2 = 91\%$, $\tau^2 = 3.48$, $p < 0.01$					
subtype = PXG					
Jacobi et al. (1999)	-14.0	2.06	13	-14.0	[-18.0; -10.0]
Damji et al. (2006)	-3.1	0.78	27	-3.1	[-4.7; -1.6]
Mierzejewski et al. (2008)	-6.6	0.81	23	-6.6	[-8.2; -5.0]
Shingleton et al. (2008)	-1.1	0.63	51	-1.1	[-2.3; 0.1]
Random effects model			.	**-5.8**	**[-9.5; -2.0]**
Heterogeneity: $I^2 = 95\%$, $\tau^2 = 13.11$, $p < 0.01$					



Acute

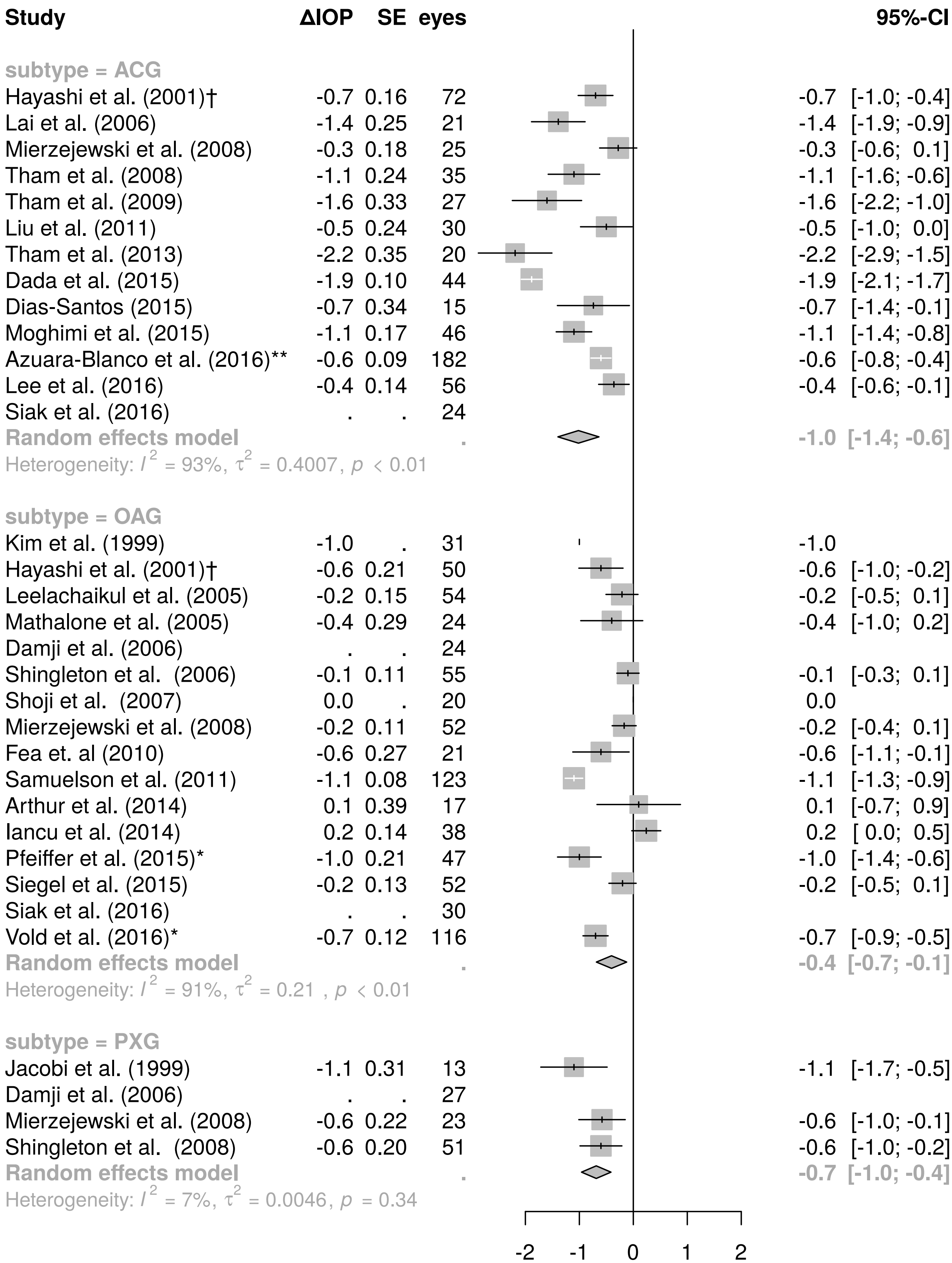
```
df_ <- df %>%
  filter(!is.na(LastPeriodAbsIOPChangeMean), subtype == "acute", MIGsYorN == 'N') %>%
  mutate(subtype=factor(subtype)) %>% dplyr::arrange(Year)
m <- metagen(LastPeriodAbsIOPChangeMean,
             LastPeriodAbsIOPChangeStdDev / sqrt(LastPeriodEyes),
             study.name,
     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

```
##                                               95%-CI %W(random)
## Lam et al. (2008)    -47.1000 [-50.0948; -44.1052]       26.8
## Lee et al. (2010)    -35.8000 [-39.6379; -31.9621]       25.9
## Husain et al. (2012) -44.5000 [-52.0026; -36.9974]       20.6
## Hou et al. (2015)    -35.9600 [-39.0429; -32.8771]       26.7
##
## Number of studies combined: k = 4
##
##                                              95%-CI      z  p-value
## Random effects model -40.665 [-47.1528; -34.1772] -12.28 < 0.0001
##
## Quantifying heterogeneity:
##  tau^2 = 38.5307; H = 3.36 [2.26; 4.99]; I^2 = 91.1% [80.4%; 96.0%];
##  Rb = 87.9% [68.9%; 100.0%]
##
## Test of heterogeneity:
##      Q d.f.  p-value
##  33.84    3 < 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"))
```


Study ΔIOP SE eyes 95%-CI
subtype = ACG
Hayashi et al. (2001)† -0.7 0.16 72 -0.7 [-1.0; -0.4]
Lai et al. (2006) -1.4 0.25 21 -1.4 [-1.9; -0.9]
Mierzejewski et al. (2008) -0.3 0.18 25 -0.3 [-0.6; 0.1]
Tham et al. (2008) -1.1 0.24 35 -1.1 [-1.6; -0.6]
Tham et al. (2009) -1.6 0.33 27 -1.6 [-2.2; -1.0]
Liu et al. (2011) -0.5 0.24 30 -0.5 [-1.0; 0.0]
Tham et al. (2013) -2.2 0.35 20 -2.2 [-2.9; -1.5]
Dada et al. (2015) -1.9 0.10 44 -1.9 [-2.1; -1.7]
Dias-Santos (2015) -0.7 0.34 15 -0.7 [-1.4; -0.1]
Moghimi et al. (2015) -1.1 0.17 46 -1.1 [-1.4; -0.8]
Azuara-Blanco et al. (2016)** -0.6 0.09 182 -0.6 [-0.8; -0.4]
Lee et al. (2016) -0.4 0.14 56 -0.4 [-0.6; -0.1]
Siak et al. (2016) . . 24
Random effects model . -1.0 [-1.4; -0.6]
Heterogeneity: I^2 = 93%, τ^2 = 0.4007, p < 0.01
subtype = OAG
Kim et al. (1999) -1.0 . 31 -1.0
Hayashi et al. (2001)† -0.6 0.21 50 -0.6 [-1.0; -0.2]
Leelachaikul et al. (2005) -0.2 0.15 54 -0.2 [-0.5; 0.1]
Mathalone et al. (2005) -0.4 0.29 24 -0.4 [-1.0; 0.2]
Damji et al. (2006) . . 24
Shingleton et al. (2006) -0.1 0.11 55 -0.1 [-0.3; 0.1]
Shoji et al. (2007) 0.0 . 20 0.0
Mierzejewski et al. (2008) -0.2 0.11 52 -0.2 [-0.4; 0.1]
Fea et. al (2010) -0.6 0.27 21 -0.6 [-1.1; -0.1]
Samuelson et al. (2011) -1.1 0.08 123 -1.1 [-1.3; -0.9]
Arthur et al. (2014) 0.1 0.39 17 0.1 [-0.7; 0.9]
Iancu et al. (2014) 0.2 0.14 38 0.2 [0.0; 0.5]
Pfeiffer et al. (2015)* -1.0 0.21 47 -1.0 [-1.4; -0.6]
Siegel et al. (2015) -0.2 0.13 52 -0.2 [-0.5; 0.1]
Siak et al. (2016) . . 30
Vold et al. (2016)* -0.7 0.12 116 -0.7 [-0.9; -0.5]
Random effects model . -0.4 [-0.7; -0.1]
Heterogeneity: I^2 = 91%, τ^2 = 0.21 , p < 0.01
subtype = PXG
Jacobi et al. (1999) -1.1 0.31 13 -1.1 [-1.7; -0.5]
Damji et al. (2006) . . 27
Mierzejewski et al. (2008) -0.6 0.22 23 -0.6 [-1.0; -0.1]
Shingleton et al. (2008) -0.6 0.20 51 -0.6 [-1.0; -0.2]
Random effects model . -0.7 [-1.0; -0.4]
Heterogeneity: I^2 = 7%, τ^2 = 0.0046, p = 0.34
-2 -1 0 1 2

Correlation between meds and drop in IOP

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

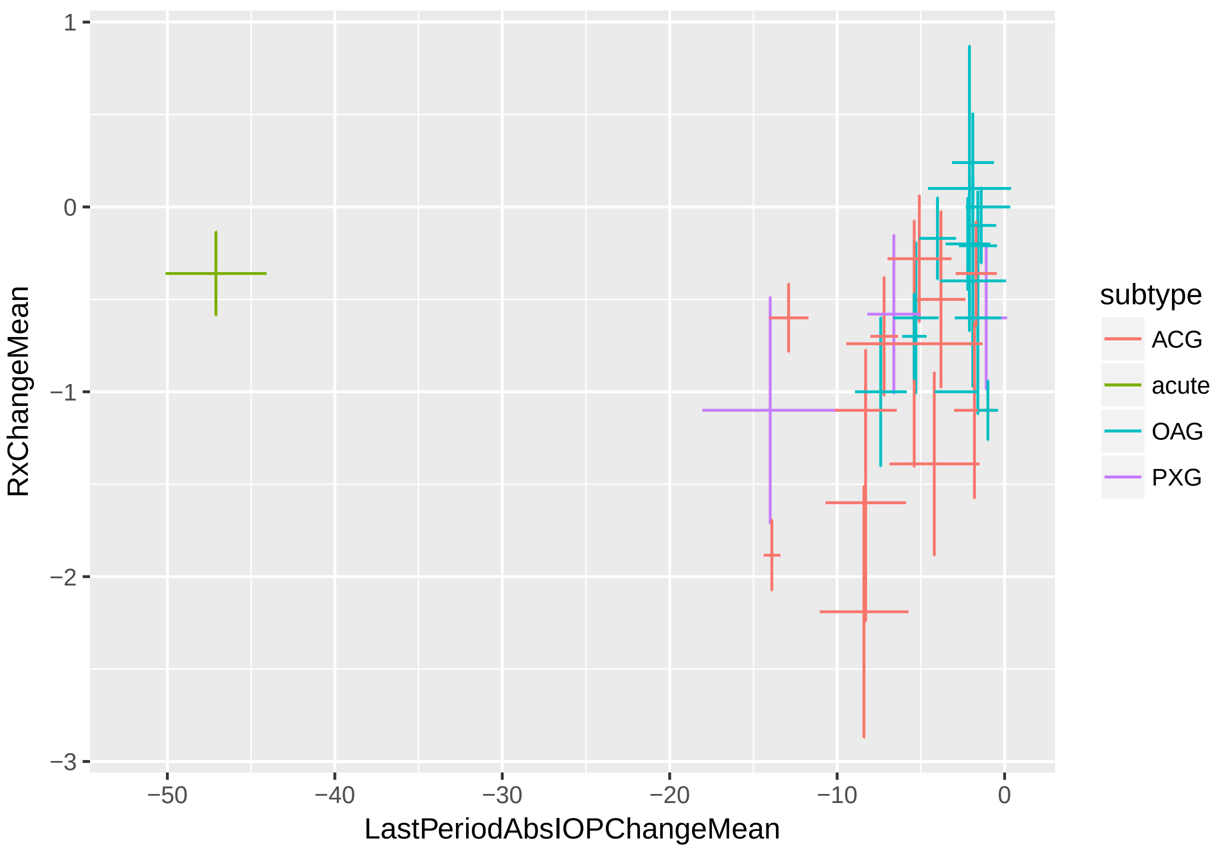
- Those studies that see the largest IOP drops also have drop in meds, as doctors see that can use the newfound *slack* to decrease the number of meds people take
- The studies that see the largest IOP drops are those that don't change meds, because dropping meds would also increase IOP

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()
```

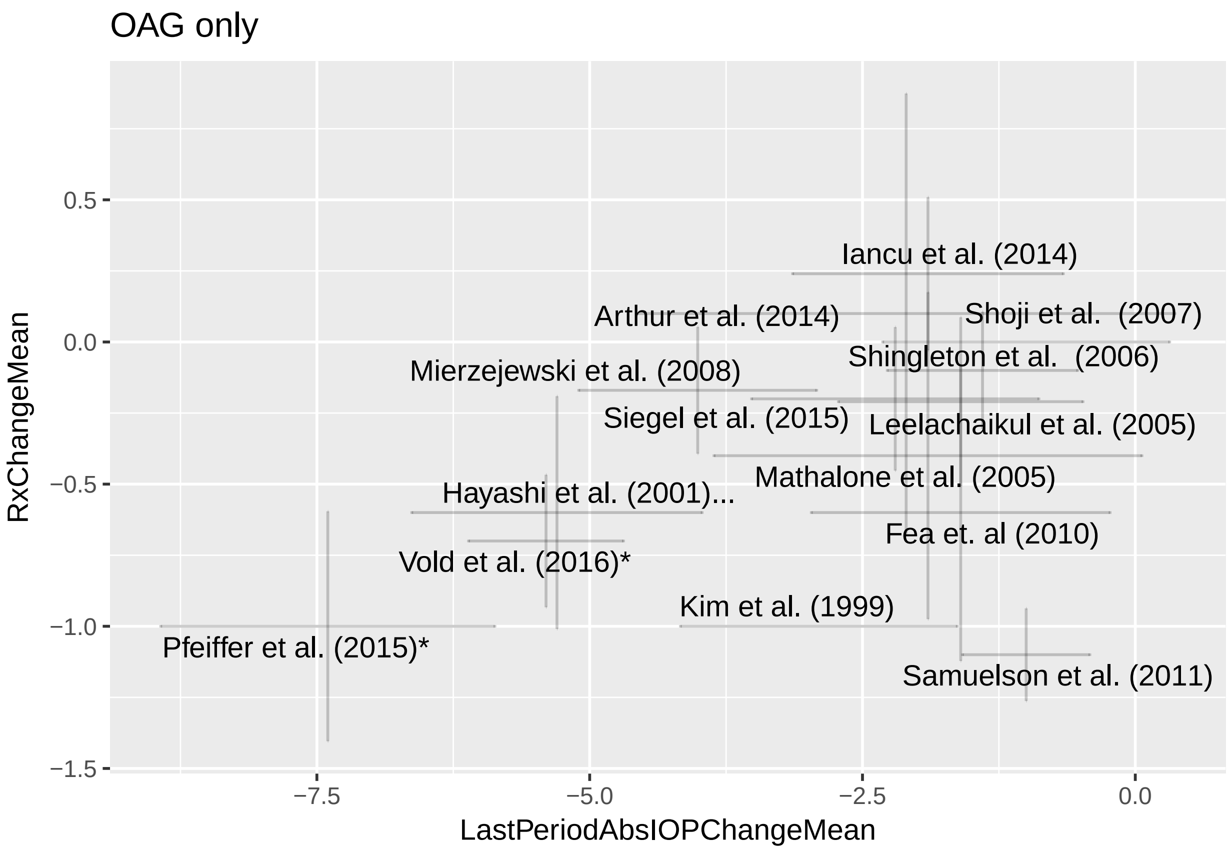
```
## Warning: Removed 17 rows containing missing values (geom_errorbar).
```

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




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

```r
        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.

```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),
                                             RxChangeMean,
                                             RxChangeStdDev / sqrt(LastPeriodEyes))))
mean(drawn.corrs)
```

```
## [1] 0.3812048
```

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

```
## [1] 0.1348602
```

```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),
                                            RxChangeMean,
                                            RxChangeStdDev / sqrt(LastPeriodEyes))))
mean(drawn.corrs)
```

```
## [1] -0.02253974
```

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

```
## [1] 0.1941081
```

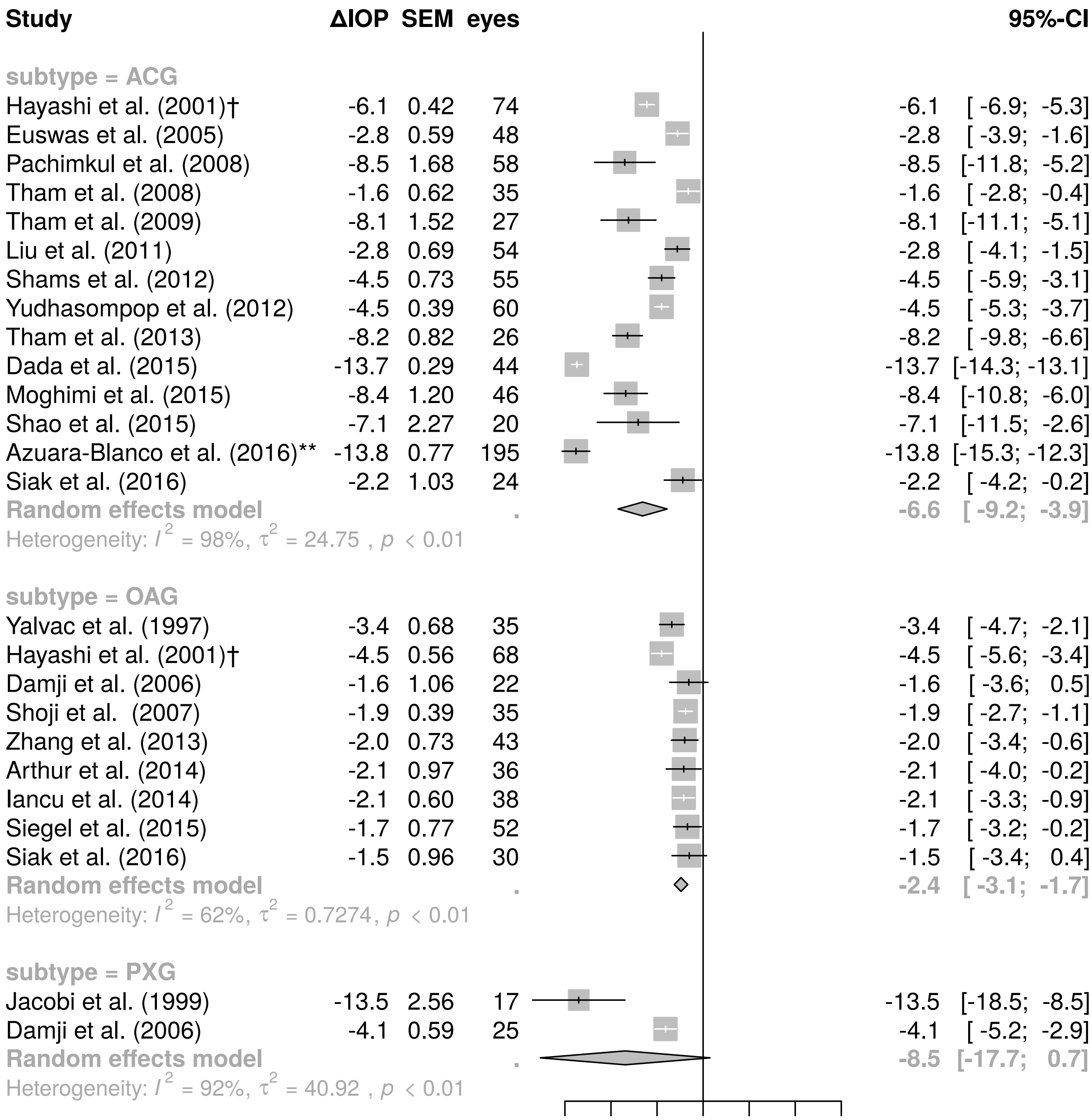
However, this effect goes away when we focus on the studies which don't have washout.

Separate meta-analysis for each time period

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

6 month follow-up

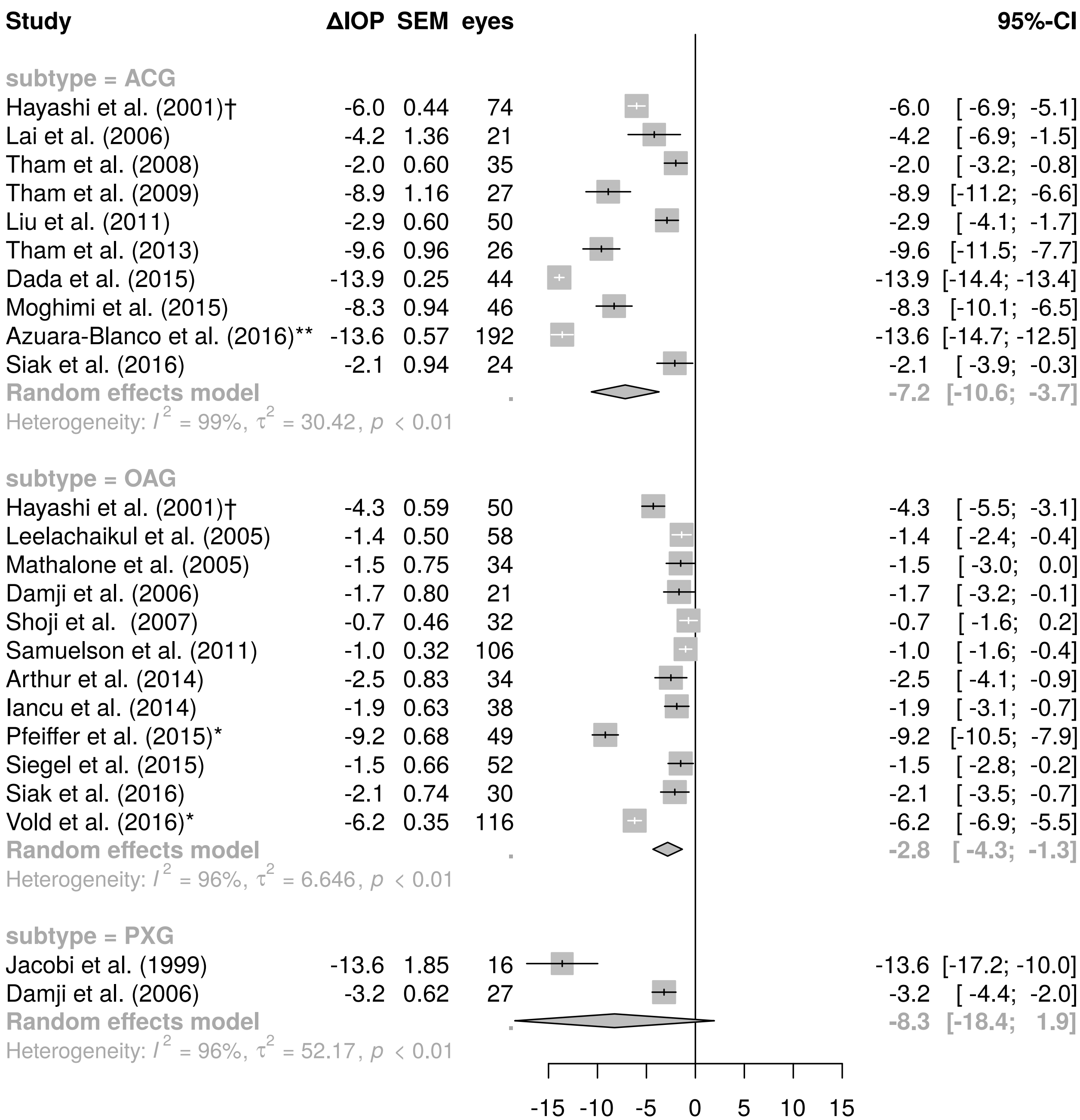
```r
df_ <- df %>%
  filter(!is.na(SixMoAbsIOPChangeMean), subtype != "acute") %>%
  mutate(subtype=factor(subtype))
m <- metagen(SixMoAbsIOPChangeMean,
             SixMoAbsIOPChangeStdDev / sqrt(SixMoEyes),
             study.name,
             data=df_,
             byvar=subtype,
             n.e=SixMoEyes)
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

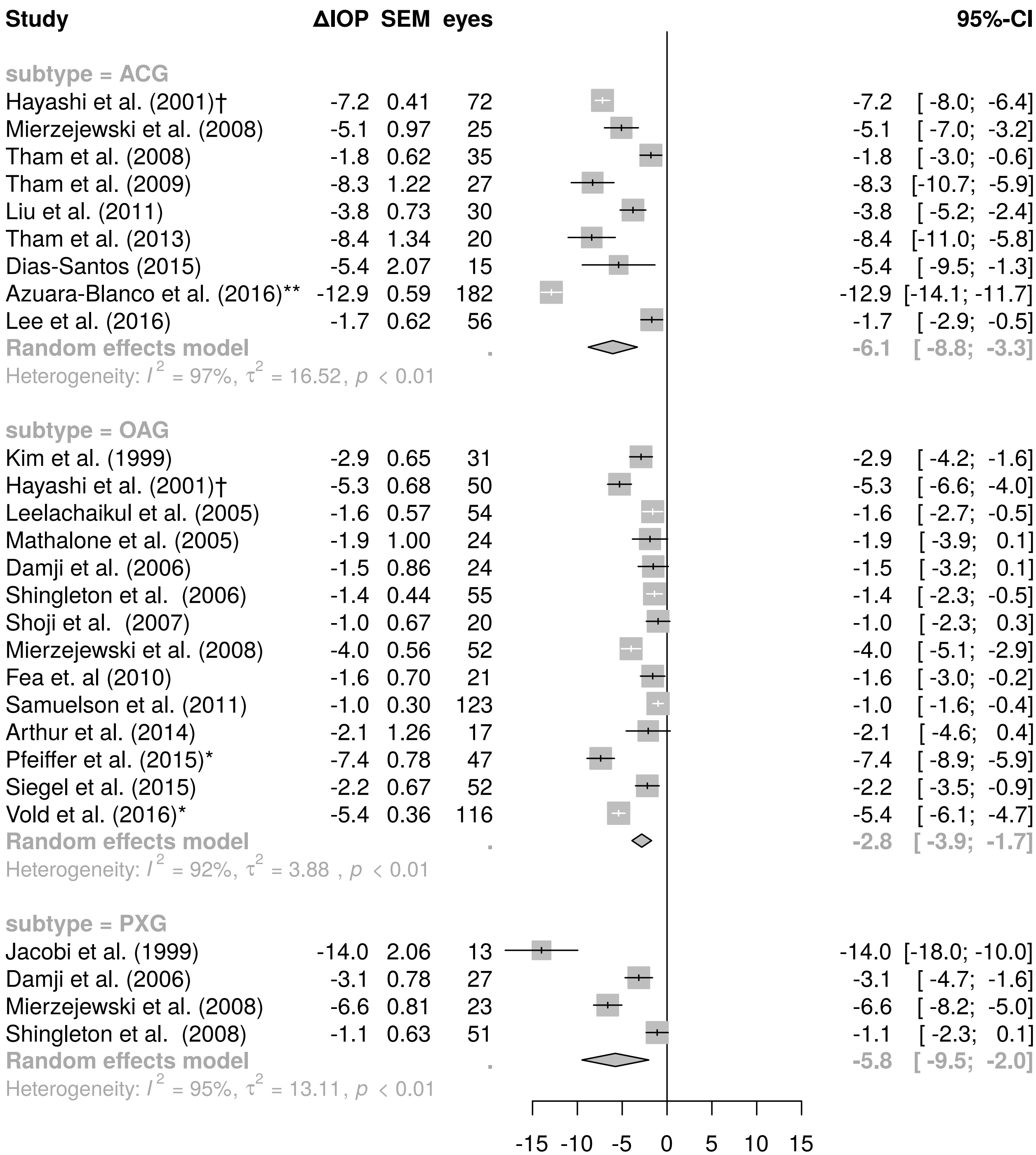
```
df_ <- df %>%
  filter(!is.na(OneYAbsIOPChangeMean), subtype != "acute", MIGsYorN == 'N') %>%
  mutate(subtype=factor(subtype))
m <- metagen(OneYAbsIOPChangeMean,
             OneYAbsIOPChangeStdDev / sqrt(OneYEyes),
             study.name,
             data=df_,
             byvar=subtype,
   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

```r
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).

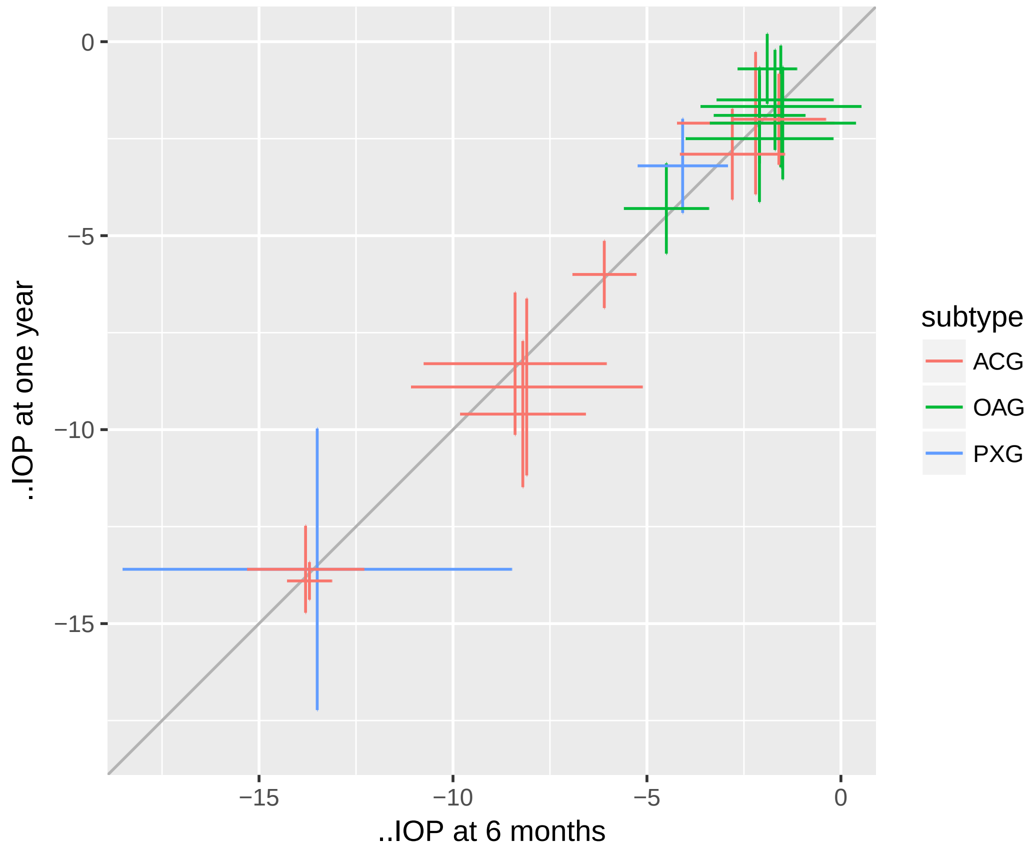
```
ggplot(df %>% filter(subtype != 'acute') %>% mutate(subtype = factor(subtype)),
       aes(x    =SixMoAbsIOPChangeMean,
              xmin=SixMoAbsIOPChangeMean - 1.96*SixMoAbsIOPChangeStdDev / sqrt(SixMoEyes),
              xmax=SixMoAbsIOPChangeMean + 1.96*SixMoAbsIOPChangeStdDev / sqrt(SixMoEyes),
              y    = OneYAbsIOPChangeMean,
```

```r
              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() +
  xlab('ΔIOP at 6 months') +
  ylab('ΔIOP at one year') +
  coord_fixed(xlim=c(-18, 0), ylim=c(-18,0))
```

```
## Warning: Removed 22 rows containing missing values (geom_errorbar).

## Warning: Removed 22 rows containing missing values (geom_errorbarh).

## Warning in grid.Call(L_stringMetric, as.graphicsAnnot(x$label)): conversion
## failure on 'ΔIOP at 6 months' in 'mbcsToSbcs': dot substituted for <ce>

## Warning in grid.Call(L_stringMetric, as.graphicsAnnot(x$label)): conversion
## failure on 'ΔIOP at 6 months' in 'mbcsToSbcs': dot substituted for <94>

## Warning in grid.Call(L_stringMetric, as.graphicsAnnot(x$label)): conversion
## failure on 'ΔIOP at one year' in 'mbcsToSbcs': dot substituted for <ce>

## Warning in grid.Call(L_stringMetric, as.graphicsAnnot(x$label)): conversion
## failure on 'ΔIOP at one year' in 'mbcsToSbcs': dot substituted for <94>

## Warning in grid.Call(L_textBounds, as.graphicsAnnot(x$label), x$x, x$y, :
## conversion failure on 'ΔIOP at one year' in 'mbcsToSbcs': dot substituted
## for <ce>

## Warning in grid.Call(L_textBounds, as.graphicsAnnot(x$label), x$x, x$y, :
## conversion failure on 'ΔIOP at one year' in 'mbcsToSbcs': dot substituted
## for <94>

## Warning in grid.Call(L_textBounds, as.graphicsAnnot(x$label), x$x, x$y, :
## conversion failure on 'ΔIOP at one year' in 'mbcsToSbcs': dot substituted
## for <ce>

## Warning in grid.Call(L_textBounds, as.graphicsAnnot(x$label), x$x, x$y, :
## conversion failure on 'ΔIOP at one year' in 'mbcsToSbcs': dot substituted
## for <94>

## Warning in grid.Call(L_textBounds, as.graphicsAnnot(x$label), x$x, x$y, :
## conversion failure on 'ΔIOP at 6 months' in 'mbcsToSbcs': dot substituted
## for <ce>

## Warning in grid.Call(L_textBounds, as.graphicsAnnot(x$label), x$x, x$y, :
## conversion failure on 'ΔIOP at 6 months' in 'mbcsToSbcs': dot substituted
## for <94>

## Warning in grid.Call(L_textBounds, as.graphicsAnnot(x$label), x$x, x$y, :
## conversion failure on 'ΔIOP at 6 months' in 'mbcsToSbcs': dot substituted
## for <ce>

## Warning in grid.Call(L_textBounds, as.graphicsAnnot(x$label), x$x, x$y, :
## conversion failure on 'ΔIOP at 6 months' in 'mbcsToSbcs': dot substituted
## for <94>
```

```
## Warning in grid.Call(L_textBounds, as.graphicsAnnot(x$label), x$x, x$y, :
## conversion failure on 'ΔIOP at one year' in 'mbcsToSbcs': dot substituted
## for <ce>

## Warning in grid.Call(L_textBounds, as.graphicsAnnot(x$label), x$x, x$y, :
## conversion failure on 'ΔIOP at one year' in 'mbcsToSbcs': dot substituted
## for <94>

## Warning in grid.Call(L_textBounds, as.graphicsAnnot(x$label), x$x, x$y, :
## conversion failure on 'ΔIOP at one year' in 'mbcsToSbcs': dot substituted
## for <ce>

## Warning in grid.Call(L_textBounds, as.graphicsAnnot(x$label), x$x, x$y, :
## conversion failure on 'ΔIOP at one year' in 'mbcsToSbcs': dot substituted
## for <94>

## Warning in grid.Call(L_textBounds, as.graphicsAnnot(x$label), x$x, x$y, :
## conversion failure on 'ΔIOP at one year' in 'mbcsToSbcs': dot substituted
## for <ce>

## Warning in grid.Call(L_textBounds, as.graphicsAnnot(x$label), x$x, x$y, :
## conversion failure on 'ΔIOP at one year' in 'mbcsToSbcs': dot substituted
## for <94>

## Warning in grid.Call(L_textBounds, as.graphicsAnnot(x$label), x$x, x$y, :
## conversion failure on 'ΔIOP at 6 months' in 'mbcsToSbcs': dot substituted
## for <ce>

## Warning in grid.Call(L_textBounds, as.graphicsAnnot(x$label), x$x, x$y, :
## conversion failure on 'ΔIOP at 6 months' in 'mbcsToSbcs': dot substituted
## for <94>

## Warning in grid.Call(L_textBounds, as.graphicsAnnot(x$label), x$x, x$y, :
## conversion failure on 'ΔIOP at 6 months' in 'mbcsToSbcs': dot substituted
## for <ce>

## Warning in grid.Call(L_textBounds, as.graphicsAnnot(x$label), x$x, x$y, :
## conversion failure on 'ΔIOP at 6 months' in 'mbcsToSbcs': dot substituted
## for <94>

## Warning in grid.Call(L_textBounds, as.graphicsAnnot(x$label), x$x, x$y, :
## conversion failure on 'ΔIOP at 6 months' in 'mbcsToSbcs': dot substituted
## for <ce>

## Warning in grid.Call(L_textBounds, as.graphicsAnnot(x$label), x$x, x$y, :
## conversion failure on 'ΔIOP at 6 months' in 'mbcsToSbcs': dot substituted
## for <94>

## Warning in grid.Call(L_textBounds, as.graphicsAnnot(x$label), x$x, x$y, :
## conversion failure on 'ΔIOP at 6 months' in 'mbcsToSbcs': dot substituted
## for <ce>

## Warning in grid.Call(L_textBounds, as.graphicsAnnot(x$label), x$x, x$y, :
## conversion failure on 'ΔIOP at 6 months' in 'mbcsToSbcs': dot substituted
## for <94>

## Warning in grid.Call(L_textBounds, as.graphicsAnnot(x$label), x$x, x$y, :
## conversion failure on 'ΔIOP at 6 months' in 'mbcsToSbcs': dot substituted
## for <ce>

## Warning in grid.Call(L_textBounds, as.graphicsAnnot(x$label), x$x, x$y, :
```

```
## conversion failure on 'ΔIOP at 6 months' in 'mbcsToSbcs': dot substituted
## for <94>

## Warning in grid.Call.graphics(L_text, as.graphicsAnnot(x$label), x$x, x
## $y, : conversion failure on 'ΔIOP at 6 months' in 'mbcsToSbcs': dot
## substituted for <ce>

## Warning in grid.Call.graphics(L_text, as.graphicsAnnot(x$label), x$x, x
## $y, : conversion failure on 'ΔIOP at 6 months' in 'mbcsToSbcs': dot
## substituted for <94>

## Warning in grid.Call(L_textBounds, as.graphicsAnnot(x$label), x$x, x$y, :
## conversion failure on 'ΔIOP at one year' in 'mbcsToSbcs': dot substituted
## for <ce>

## Warning in grid.Call(L_textBounds, as.graphicsAnnot(x$label), x$x, x$y, :
## conversion failure on 'ΔIOP at one year' in 'mbcsToSbcs': dot substituted
## for <94>

## Warning in grid.Call(L_textBounds, as.graphicsAnnot(x$label), x$x, x$y, :
## conversion failure on 'ΔIOP at one year' in 'mbcsToSbcs': dot substituted
## for <ce>

## Warning in grid.Call(L_textBounds, as.graphicsAnnot(x$label), x$x, x$y, :
## conversion failure on 'ΔIOP at one year' in 'mbcsToSbcs': dot substituted
## for <94>

## Warning in grid.Call.graphics(L_text, as.graphicsAnnot(x$label), x$x, x
## $y, : conversion failure on 'ΔIOP at one year' in 'mbcsToSbcs': dot
## substituted for <ce>

## Warning in grid.Call.graphics(L_text, as.graphicsAnnot(x$label), x$x, x
## $y, : conversion failure on 'ΔIOP at one year' in 'mbcsToSbcs': dot
## substituted for <94>
```

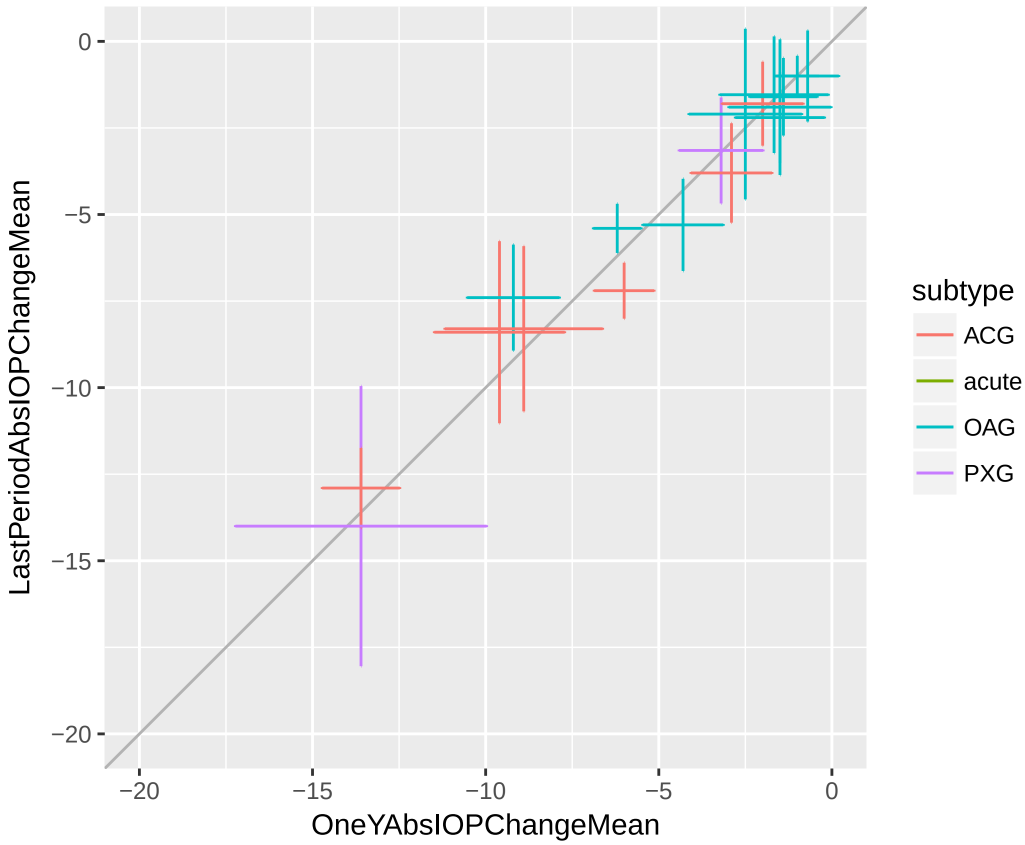


It's very clear that six months and 12 months IOP are highly correlated.

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 26 rows containing missing values (geom_errorbar).

## Warning: Removed 26 rows containing missing values (geom_errorbarh).
```



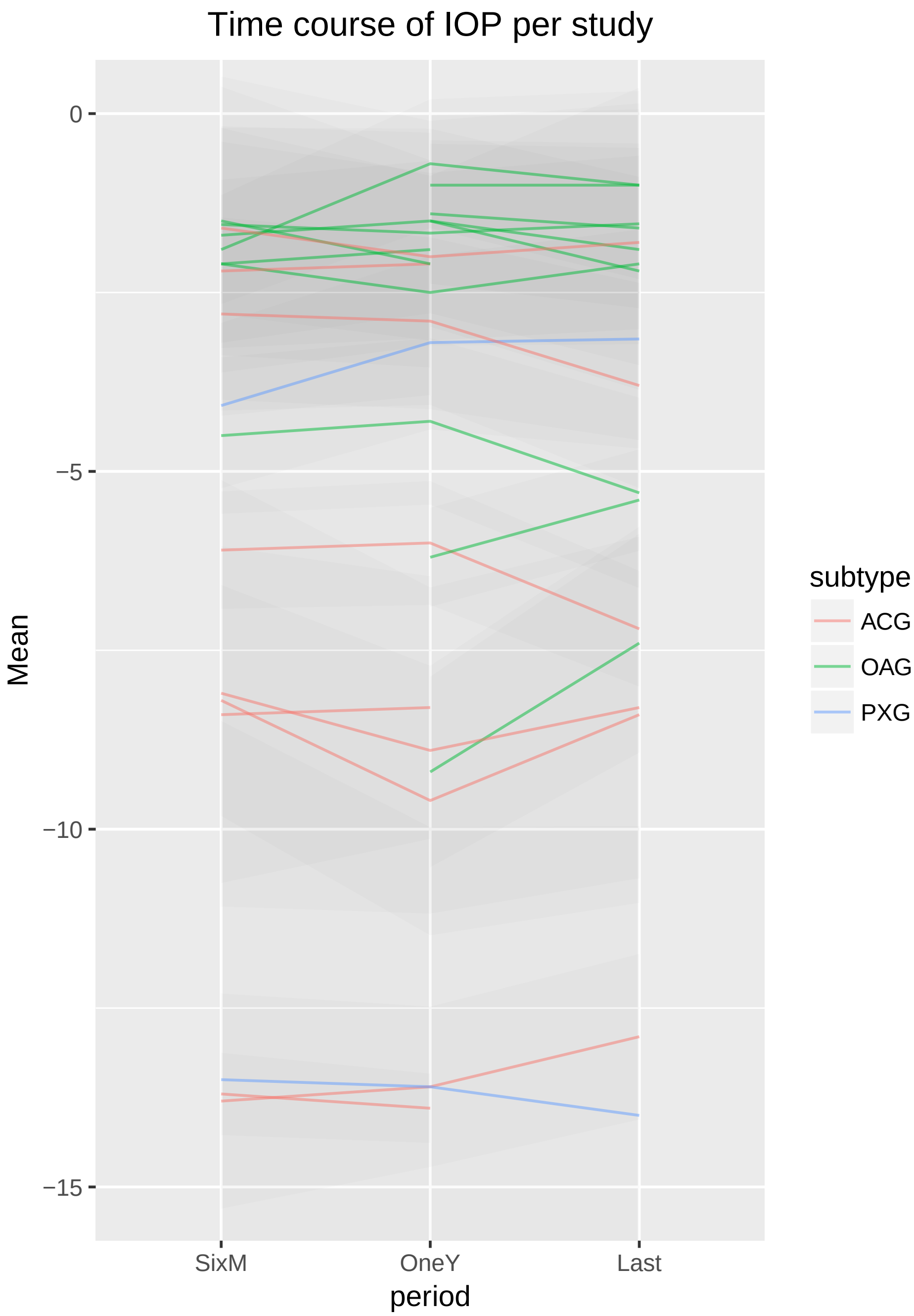
Again, correlations are very high. Present this in another way.

```
library(reshape2)
```

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

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

```
nd <- melt(df %>%
             filter(MIGsYorN == 'N',
                    subtype != 'acute',
                    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
```

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

```
## [1] 0.6287425
```

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

```
## [1] 0.1808015
```

```r
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
```

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

```
## [1] 0.9912487
```

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

```
## [1] 0.003900496
```

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.

```r
library(mvmeta)
```

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

```r
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 * zz), ncol=3)
  }
```

```r
  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)
```

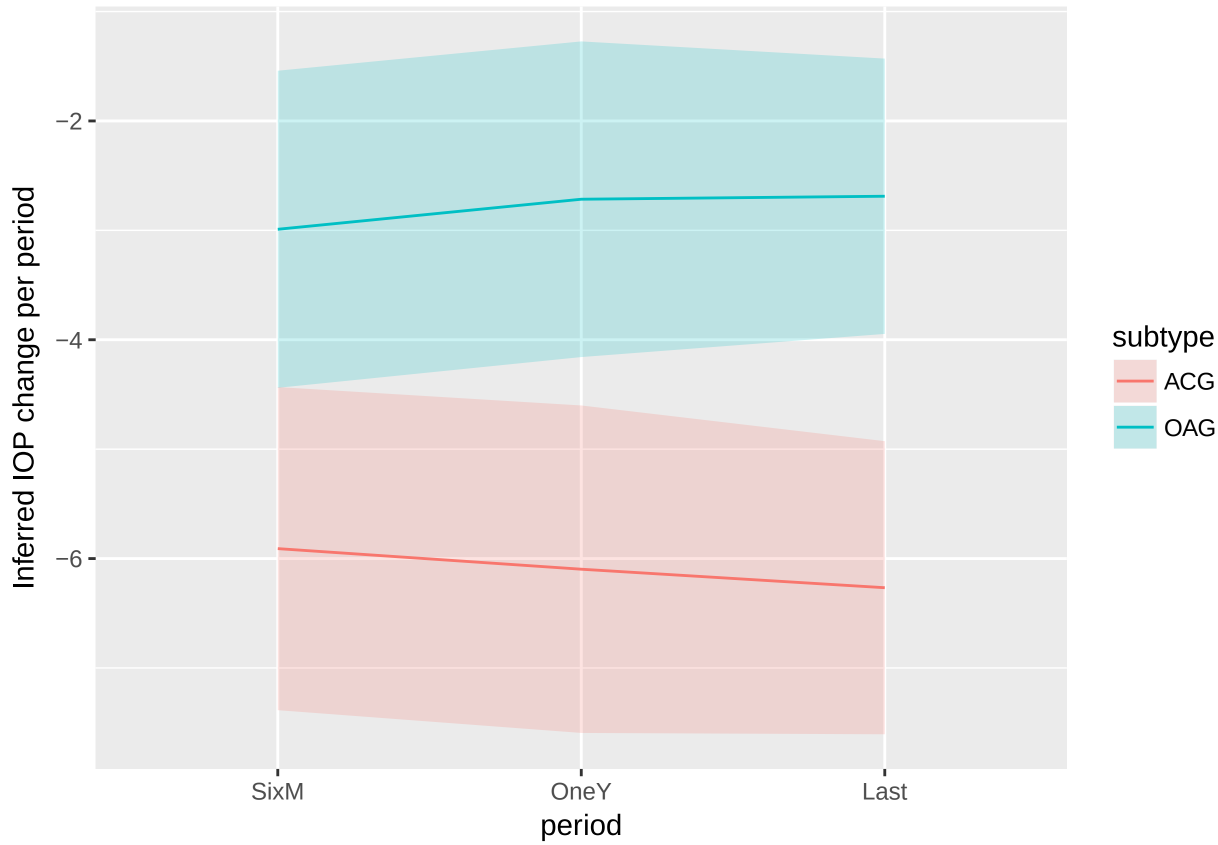
```
## Call:  mvmeta(formula = cbind(SixMoAbsIOPChangeMean, OneYAbsIOPChangeMean,
##   LastPeriodAbsIOPChangeMean) ~ subtype, S = get.correlation.matrices.tri(df_$SixMoAbsIOPChangeStdDev/
##   df_$OneYAbsIOPChangeStdDev/sqrt(df_$OneYEyes), df_$LastPeriodAbsIOPChangeStdDev/sqrt(df_$LastPerio
##     0.7), 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)   -5.9092      0.7536  -7.8415    0.0000   -7.3862   -4.4322
## subtypeOAG     2.9191      1.0558   2.7648    0.0057    0.8497    4.9884
##
## (Intercept)  ***
## subtypeOAG    **
## OneYAbsIOPChangeMean :
##              Estimate  Std. Error        z  Pr(>|z|)  95%ci.lb  95%ci.ub
## (Intercept)   -6.0973      0.7637  -7.9839    0.0000   -7.5941   -4.6004
## subtypeOAG     3.3817      1.0607   3.1882    0.0014    1.3028    5.4606
##
## (Intercept)  ***
## subtypeOAG    **
## LastPeriodAbsIOPChangeMean :
##              Estimate  Std. Error        z  Pr(>|z|)  95%ci.lb  95%ci.ub
## (Intercept)   -6.2665      0.6835  -9.1681    0.0000   -7.6061   -4.9268
## subtypeOAG     3.5782      0.9378   3.8157    0.0001    1.7402    5.4162
##
## (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          2.9873  SixMoAbsIOPChangeMean
```

```
## OneYAbsIOPChangeMean          3.0257                 0.9969
## LastPeriodAbsIOPChangeMean    2.6062                 0.9901
##
## SixMoAbsIOPChangeMean       OneYAbsIOPChangeMean
## OneYAbsIOPChangeMean
## LastPeriodAbsIOPChangeMean                0.9823
##
## Multivariate Cochran Q-test for residual heterogeneity:
## Q = 1520.2986 (df = 62), p-value = 0.0000
## I-square statistic = 95.9%
##
## 36 studies, 68 observations, 6 fixed and 6 random-effects parameters
##    logLik        AIC        BIC
## -118.9294   261.8587   287.3844
```

```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.

```
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)
```

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

```
##
## Mixed-Effects Model (k = 33; tau^2 estimator: DL)
##
## tau^2 (estimated amount of residual heterogeneity):     25.5650 (SE = 9.4030)
## tau (square root of estimated tau^2 value):             5.0562
## I^2 (residual heterogeneity / unaccounted variability): 98.53%
## H^2 (unaccounted variability / sampling variability):   67.85
## R^2 (amount of heterogeneity accounted for):            0.00%
##
## Test for Residual Heterogeneity:
## QE(df = 31) = 2103.4367, p-val < .0001
##
## Test of Moderators (coefficient(s) 2):
## QM(df = 1) = 0.8172, p-val = 0.3660
##
## Model Results:
##
##                 estimate      se     zval    pval    ci.lb    ci.ub
## intrcpt          -3.5035  1.4564  -2.4055  0.0161  -6.3580  -0.6489  *
## LastPeriodEyes   -0.0231  0.0256  -0.9040  0.3660  -0.0733   0.0270
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

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

```
##
## Mixed-Effects Model (k = 33; tau^2 estimator: DL)
##
## tau^2 (estimated amount of residual heterogeneity):     14.9914 (SE = 5.6935)
## tau (square root of estimated tau^2 value):             3.8719
## I^2 (residual heterogeneity / unaccounted variability): 97.33%
## H^2 (unaccounted variability / sampling variability):   37.41
## R^2 (amount of heterogeneity accounted for):            36.88%
##
## Test for Residual Heterogeneity:
## QE(df = 27) = 1010.2000, p-val < .0001
##
## Test of Moderators (coefficient(s) 2,3,4,5,6):
## QM(df = 5) = 13.8935, p-val = 0.0163
##
## Model Results:
##
##                            estimate      se     zval    pval     ci.lb
## intrcpt                     -2.0689  1.8225  -1.1352  0.2563   -5.6409
## LastPeriodEyes              -0.0135  0.0323  -0.4193  0.6750   -0.0767
## subtypeACG                  -2.2014  2.4577  -0.8957  0.3704   -7.0184
## subtypePXG                 -12.1290  5.0623  -2.3959  0.0166  -22.0509
## LastPeriodEyes:subtypeACG   -0.0323  0.0414  -0.7804  0.4352   -0.1134
## LastPeriodEyes:subtypePXG    0.2992  0.1490   2.0089  0.0445    0.0073
##                             ci.ub
## intrcpt                     1.5031
```

```
## LastPeriodEyes              0.0497
## subtypeACG                  2.6156
## subtypePXG                 -2.2071  *
## LastPeriodEyes:subtypeACG   0.0488
## LastPeriodEyes:subtypePXG   0.5912  *
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

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

```
##
## Mixed-Effects Model (k = 33; tau^2 estimator: DL)
##
## tau^2 (estimated amount of residual heterogeneity):     21.8899 (SE = 8.0755)
## tau (square root of estimated tau^2 value):             4.6787
## I^2 (residual heterogeneity / unaccounted variability): 98.30%
## H^2 (unaccounted variability / sampling variability):   58.68
## R^2 (amount of heterogeneity accounted for):            7.84%
##
## Test for Residual Heterogeneity:
## QE(df = 31) = 1818.9826, p-val < .0001
##
## Test of Moderators (coefficient(s) 2):
## QM(df = 1) = 0.0863, p-val = 0.7690
##
## Model Results:
##
##          estimate        se     zval    pval      ci.lb     ci.ub
## intrcpt   90.1158  322.2445   0.2797  0.7797  -541.4717  721.7034
## Year      -0.0471    0.1603  -0.2937  0.7690    -0.3614    0.2672
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

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

```
##
## Mixed-Effects Model (k = 33; tau^2 estimator: DL)
##
## tau^2 (estimated amount of residual heterogeneity):     13.0995 (SE = 4.8228)
## tau (square root of estimated tau^2 value):             3.6193
## I^2 (residual heterogeneity / unaccounted variability): 96.99%
## H^2 (unaccounted variability / sampling variability):   33.20
## R^2 (amount of heterogeneity accounted for):            44.85%
##
## Test for Residual Heterogeneity:
## QE(df = 27) = 896.4438, p-val < .0001
##
## Test of Moderators (coefficient(s) 2,3,4,5,6):
## QM(df = 5) = 12.7238, p-val = 0.0261
##
## Model Results:
##
##                    estimate         se     zval    pval       ci.lb
```

```
## intrcpt            101.1478   352.0056   0.2873  0.7738   -588.7705
## Year                -0.0517     0.1752  -0.2951  0.7680     -0.3951
## subtypeACG         215.6321   574.0691   0.3756  0.7072   -909.5227
## subtypePXG       -2423.4415  1148.3040  -2.1105  0.0348  -4674.0761
## Year:subtypeACG     -0.1090     0.2855  -0.3817  0.7027     -0.6686
## Year:subtypePXG      1.2067     0.5724   2.1080  0.0350      0.0847
##                      ci.ub
## intrcpt            791.0661
## Year                 0.2917
## subtypeACG        1340.7869
## subtypePXG        -172.8070  *
## Year:subtypeACG      0.4506
## Year:subtypePXG      2.3287  *
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

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

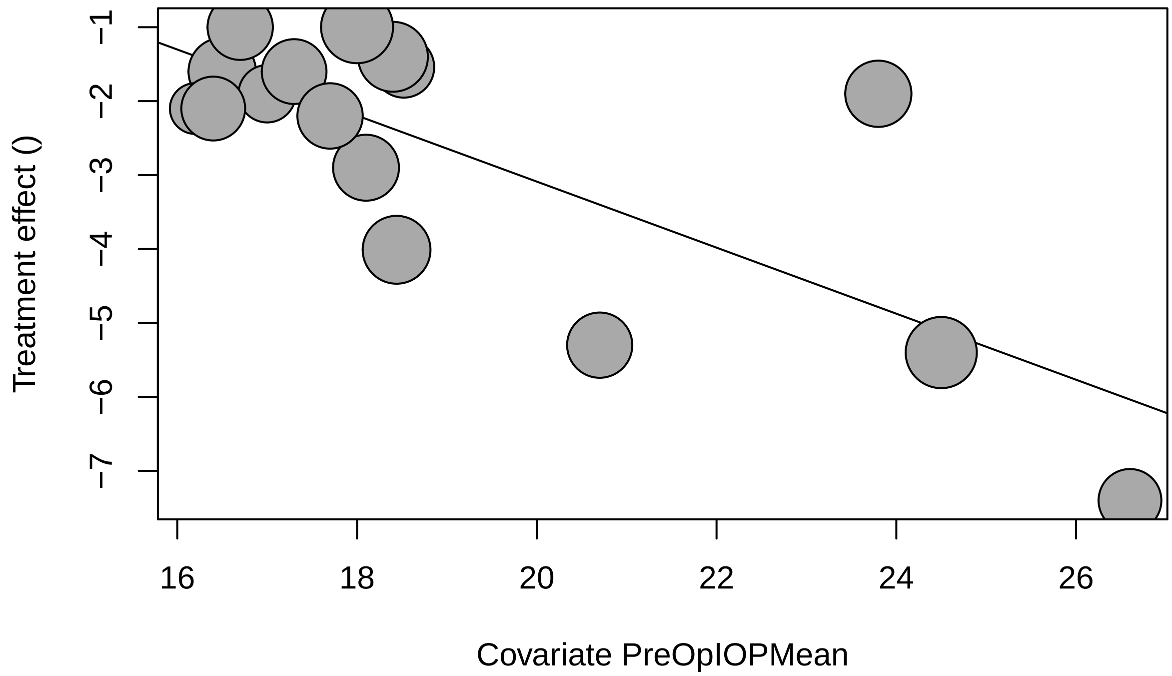
```
##
## Mixed-Effects Model (k = 33; tau^2 estimator: DL)
##
## tau^2 (estimated amount of residual heterogeneity):     4.9949 (SE = 1.8128)
## tau (square root of estimated tau^2 value):             2.2349
## I^2 (residual heterogeneity / unaccounted variability): 92.72%
## H^2 (unaccounted variability / sampling variability):   13.73
## R^2 (amount of heterogeneity accounted for):            78.97%
##
## Test for Residual Heterogeneity:
## QE(df = 31) = 425.7653, p-val < .0001
##
## Test of Moderators (coefficient(s) 2):
## QM(df = 1) = 57.2596, p-val < .0001
##
## Model Results:
##
##               estimate      se     zval    pval    ci.lb    ci.ub
## intrcpt        11.3366  2.1268   5.3304  <.0001   7.1682  15.5051  ***
## PreOpIOPMean   -0.7858  0.1038  -7.5670  <.0001  -0.9894  -0.5823  ***
##
## ---
## 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):     1.3179 (SE = 0.5551)
## tau (square root of estimated tau^2 value):             1.1480
## I^2 (residual heterogeneity / unaccounted variability): 76.22%
## H^2 (unaccounted variability / sampling variability):   4.21
## R^2 (amount of heterogeneity accounted for):            94.45%
##
## Test for Residual Heterogeneity:
```

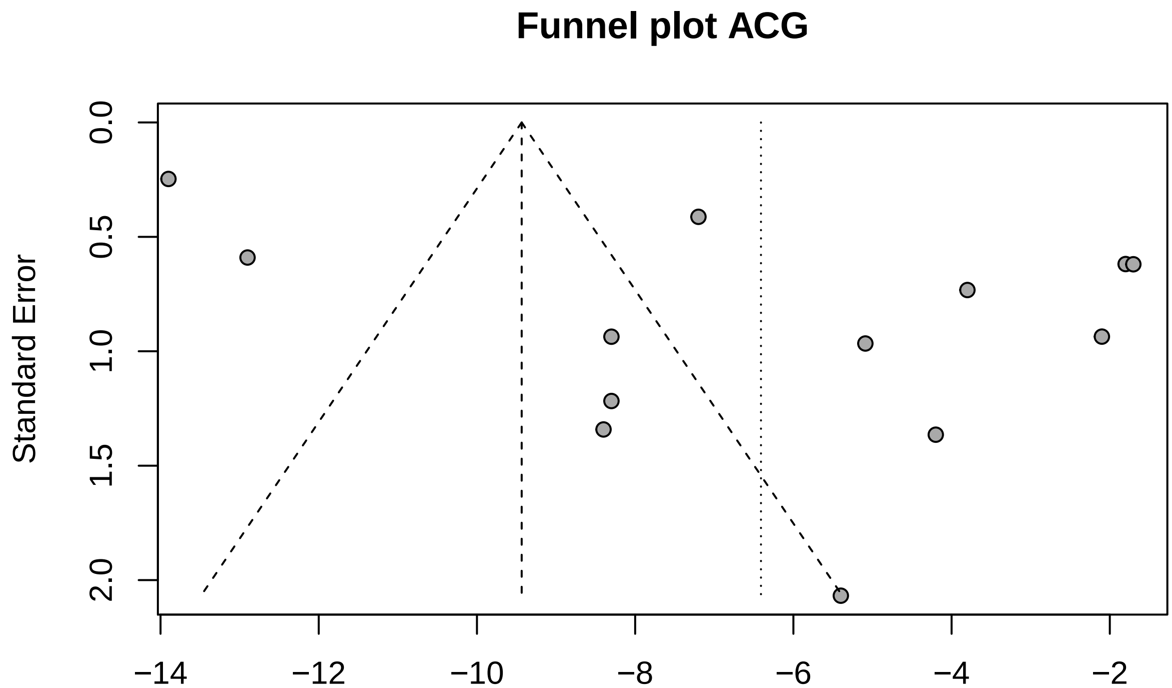
```
## QE(df = 27) = 113.5553, p-val < .0001
##
## Test of Moderators (coefficient(s) 2,3,4,5,6):
## QM(df = 5) = 202.0496, p-val < .0001
##
## Model Results:
##
##                          estimate      se     zval    pval    ci.lb
## intrcpt                    5.8390  2.1095   2.7679  0.0056   1.7044
## PreOpIOPMean              -0.4465  0.1086  -4.1095  <.0001  -0.6594
## subtypeACG                 5.6249  2.7917   2.0149  0.0439   0.1533
## subtypePXG                 8.8496  4.5438   1.9476  0.0515  -0.0560
## PreOpIOPMean:subtypeACG   -0.4165  0.1378  -3.0217  0.0025  -0.6867
## PreOpIOPMean:subtypePXG   -0.4795  0.2191  -2.1878  0.0287  -0.9090
##                            ci.ub
## intrcpt                   9.9736   **
## PreOpIOPMean             -0.2335  ***
## subtypeACG               11.0965    *
## subtypePXG               17.7552    .
## PreOpIOPMean:subtypeACG  -0.1463   **
## PreOpIOPMean:subtypePXG  -0.0499    *
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

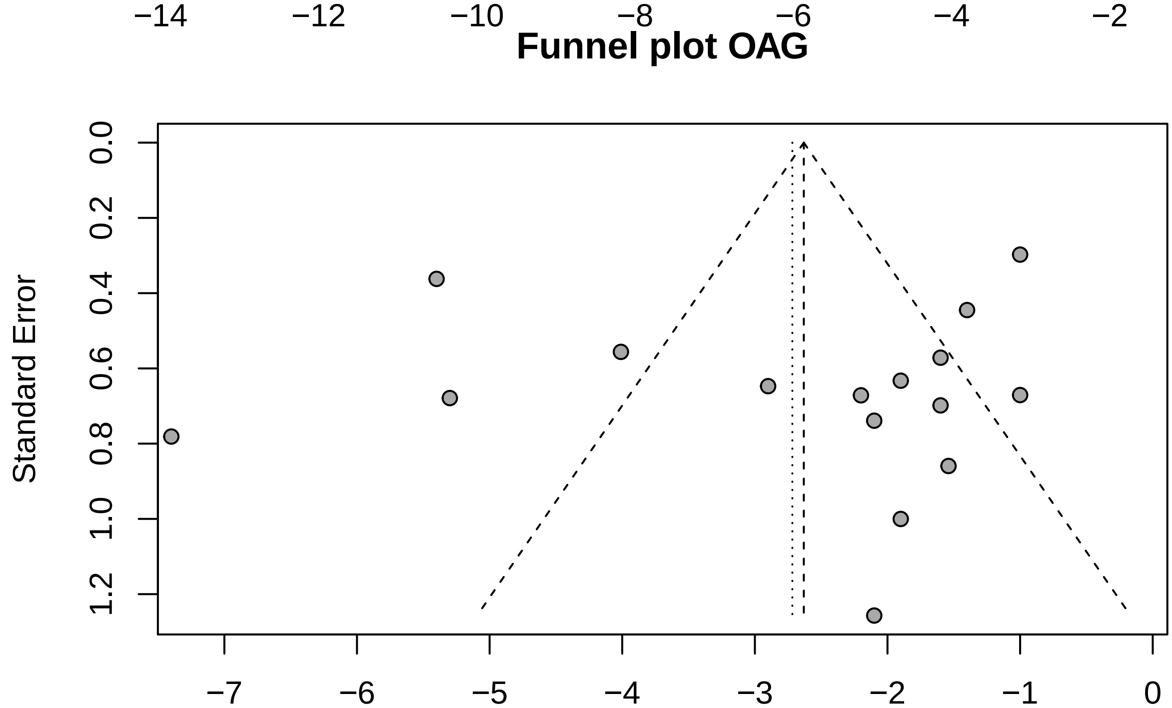
```
# Same, restricted to OAG only
df_ <- df %>% filter(!is.na(LastPeriodAbsIOPChangeMean), subtype == "OAG", MIGsYorN == 'N') %>%
  mutate(subtype=relevel(factor(subtype), ref="OAG"))
m <- metagen(LastPeriodAbsIOPChangeMean,
             LastPeriodAbsIOPChangeStdDev / sqrt(LastPeriodEyes),
        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

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

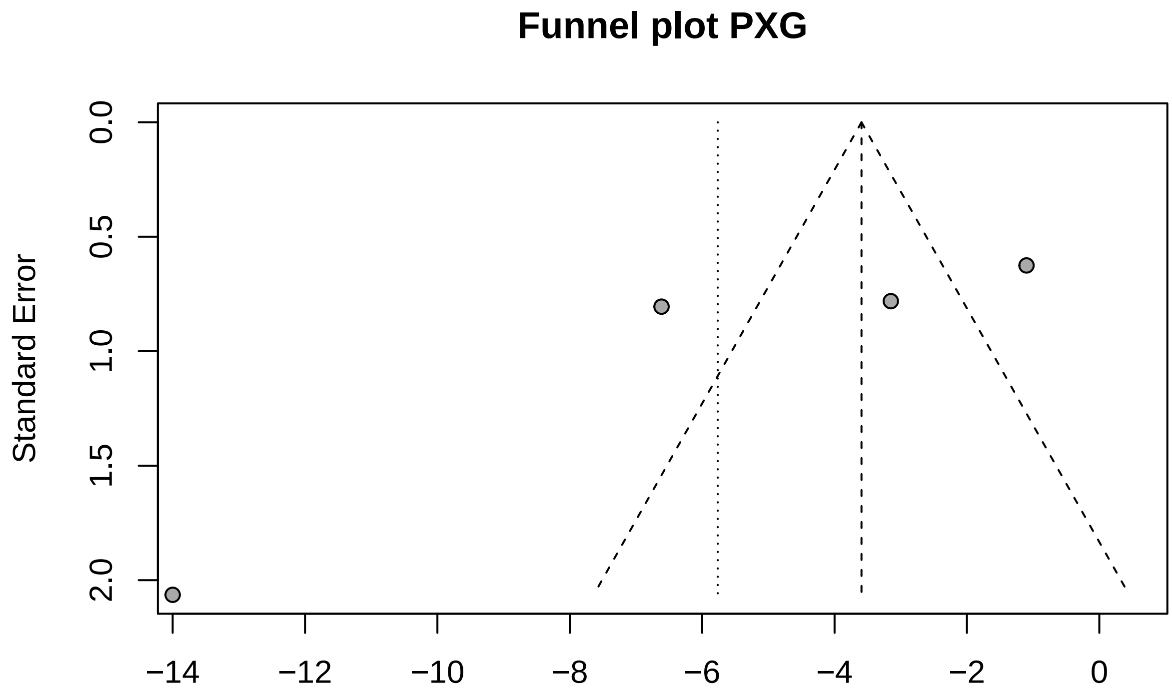


Small study bias

```
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
Standard Error
0.0
0.5
1.0
1.5
2.0
−14
−12
−10
−8
−6
−4
−2

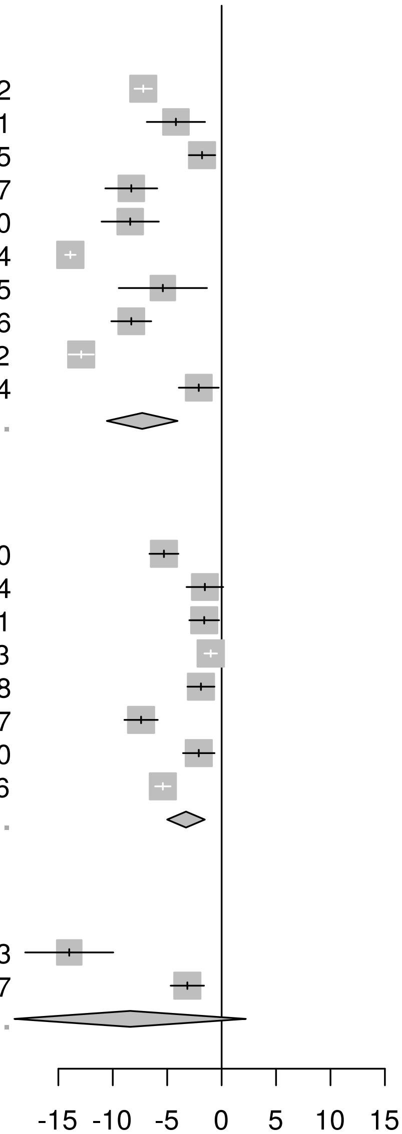

Funnel plot OAG
Standard Error
0.0
0.2
0.4
0.6
0.8
1.0
1.2
−7
−6
−5
−4
−3
−2
−1
0


Funnel plot PXG
Standard Error
0.0
0.5
1.0
1.5
2.0
−14
−12
−10
−8
−6
−4
−2
0

Alternative filterings of the data

Prospective studies only

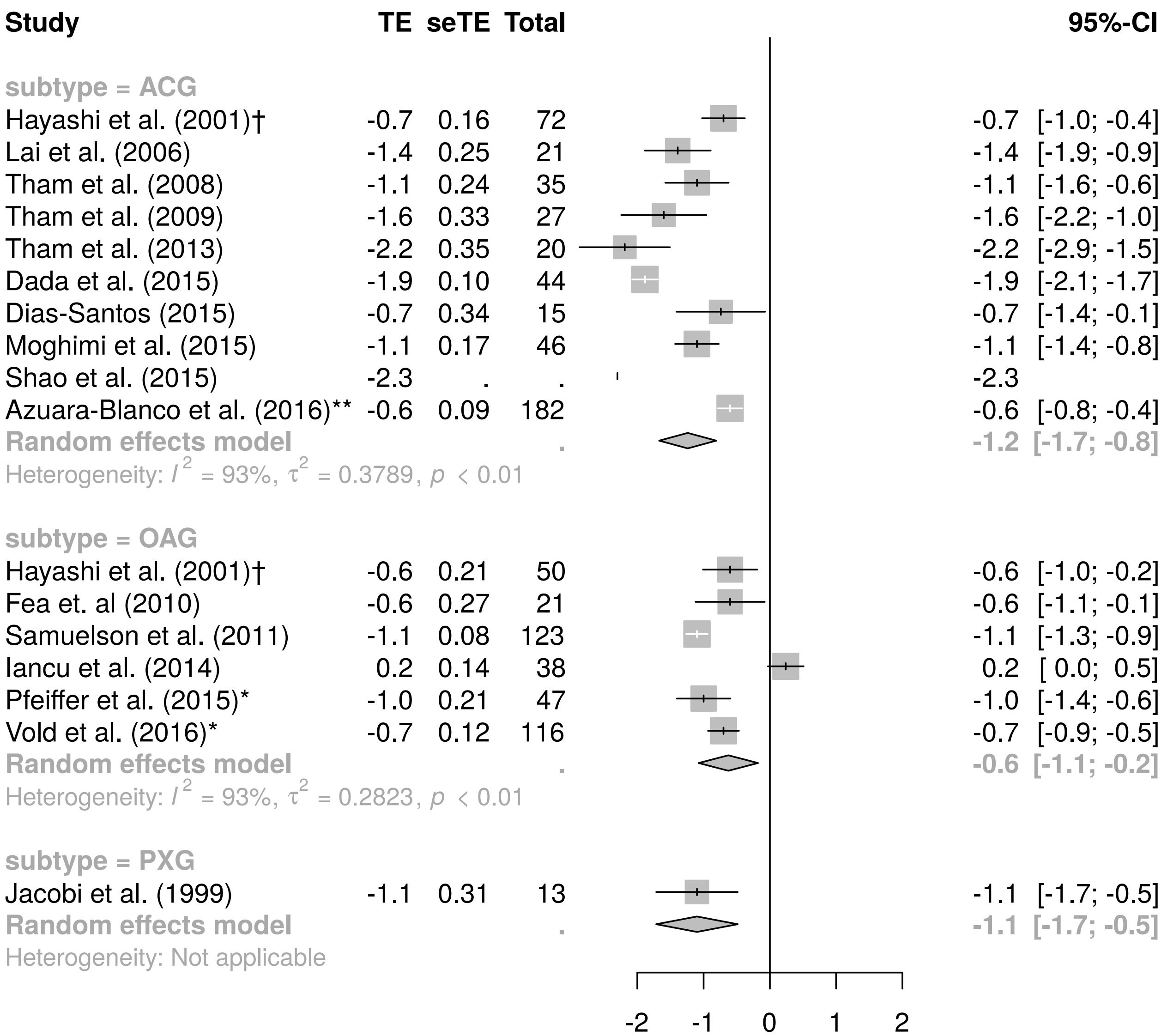
Study	TE	seTE	Total	95%-CI
subtype = ACG				
Hayashi et al. (2001)†	-7.2	0.41	72	-7.2 [-8.0; -6.4]
Lai et al. (2006)	-4.2	1.36	21	-4.2 [-6.9; -1.5]
Tham et al. (2008)	-1.8	0.62	35	-1.8 [-3.0; -0.6]
Tham et al. (2009)	-8.3	1.22	27	-8.3 [-10.7; -5.9]
Tham et al. (2013)	-8.4	1.34	20	-8.4 [-11.0; -5.8]
Dada et al. (2015)	-13.9	0.25	44	-13.9 [-14.4; -13.4]
Dias-Santos (2015)	-5.4	2.07	15	-5.4 [-9.5; -1.3]
Moghimi et al. (2015)	-8.3	0.94	46	-8.3 [-10.1; -6.5]
Azuara-Blanco et al. (2016)**	-12.9	0.59	182	-12.9 [-14.1; -11.7]
Siak et al. (2016)	-2.1	0.94	24	-2.1 [-3.9; -0.3]
Random effects model			.	**-7.3 [-10.5; -4.0]**
Heterogeneity: $I^2 = 98\%$, $\tau^2 = 26.29$, $p < 0.01$				
subtype = OAG				
Hayashi et al. (2001)†	-5.3	0.68	50	-5.3 [-6.6; -4.0]
Damji et al. (2006)	-1.5	0.86	24	-1.5 [-3.2; 0.1]
Fea et. al (2010)	-1.6	0.70	21	-1.6 [-3.0; -0.2]
Samuelson et al. (2011)	-1.0	0.30	123	-1.0 [-1.6; -0.4]
Iancu et al. (2014)	-1.9	0.63	38	-1.9 [-3.1; -0.7]
Pfeiffer et al. (2015)*	-7.4	0.78	47	-7.4 [-8.9; -5.9]
Siak et al. (2016)	-2.1	0.74	30	-2.1 [-3.5; -0.7]
Vold et al. (2016)*	-5.4	0.36	116	-5.4 [-6.1; -4.7]
Random effects model			.	**-3.3 [-5.0; -1.5]**
Heterogeneity: $I^2 = 95\%$, $\tau^2 = 5.788$, $p < 0.01$				
subtype = PXG				
Jacobi et al. (1999)	-14.0	2.06	13	-14.0 [-18.0; -10.0]
Damji et al. (2006)	-3.1	0.78	27	-3.1 [-4.7; -1.6]
Random effects model			.	**-8.4 [-19.0; 2.2]**
Heterogeneity: $I^2 = 96\%$, $\tau^2 = 56.43$, $p < 0.01$				



Meds

```r
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"))
```



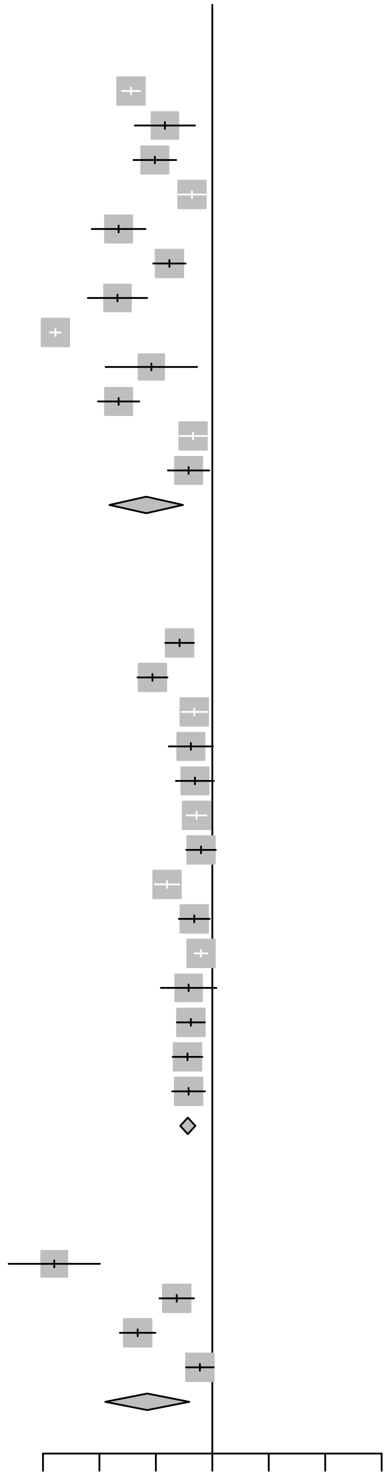
Excluding washout studies

Last period

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

```r
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"))
```

Study	TE	seTE	Total		95%-CI
subtype = ACG					
Hayashi et al. (2001)†	-7.2	0.41	72	-7.2	[-8.0; -6.4]
Lai et al. (2006)	-4.2	1.36	21	-4.2	[-6.9; -1.5]
Mierzejewski et al. (2008)	-5.1	0.97	25	-5.1	[-7.0; -3.2]
Tham et al. (2008)	-1.8	0.62	35	-1.8	[-3.0; -0.6]
Tham et al. (2009)	-8.3	1.22	27	-8.3	[-10.7; -5.9]
Liu et al. (2011)	-3.8	0.73	30	-3.8	[-5.2; -2.4]
Tham et al. (2013)	-8.4	1.34	20	-8.4	[-11.0; -5.8]
Dada et al. (2015)	-13.9	0.25	44	-13.9	[-14.4; -13.4]
Dias-Santos (2015)	-5.4	2.07	15	-5.4	[-9.5; -1.3]
Moghimi et al. (2015)	-8.3	0.94	46	-8.3	[-10.1; -6.5]
Lee et al. (2016)	-1.7	0.62	56	-1.7	[-2.9; -0.5]
Siak et al. (2016)	-2.1	0.94	24	-2.1	[-3.9; -0.3]
Random effects model			.	**-5.9**	**[-9.1; -2.6]**
Heterogeneity: $I^2 = 99\%$, $\tau^2 = 32.07$, $p < 0.01$					
subtype = OAG					
Kim et al. (1999)	-2.9	0.65	31	-2.9	[-4.2; -1.6]
Hayashi et al. (2001)†	-5.3	0.68	50	-5.3	[-6.6; -4.0]
Leelachaikul et al. (2005)	-1.6	0.57	54	-1.6	[-2.7; -0.5]
Mathalone et al. (2005)	-1.9	1.00	24	-1.9	[-3.9; 0.1]
Damji et al. (2006)	-1.5	0.86	24	-1.5	[-3.2; 0.1]
Shingleton et al. (2006)	-1.4	0.44	55	-1.4	[-2.3; -0.5]
Shoji et al. (2007)	-1.0	0.67	20	-1.0	[-2.3; 0.3]
Mierzejewski et al. (2008)	-4.0	0.56	52	-4.0	[-5.1; -2.9]
Fea et. al (2010)	-1.6	0.70	21	-1.6	[-3.0; -0.2]
Samuelson et al. (2011)	-1.0	0.30	123	-1.0	[-1.6; -0.4]
Arthur et al. (2014)	-2.1	1.26	17	-2.1	[-4.6; 0.4]
Iancu et al. (2014)	-1.9	0.63	38	-1.9	[-3.1; -0.7]
Siegel et al. (2015)	-2.2	0.67	52	-2.2	[-3.5; -0.9]
Siak et al. (2016)	-2.1	0.74	30	-2.1	[-3.5; -0.7]
Random effects model			.	**-2.2**	**[-2.8; -1.5]**
Heterogeneity: $I^2 = 76\%$, $\tau^2 = 1.17$, $p < 0.01$					
subtype = PXG					
Jacobi et al. (1999)	-14.0	2.06	13	-14.0	[-18.0; -10.0]
Damji et al. (2006)	-3.1	0.78	27	-3.1	[-4.7; -1.6]
Mierzejewski et al. (2008)	-6.6	0.81	23	-6.6	[-8.2; -5.0]
Shingleton et al. (2008)	-1.1	0.63	51	-1.1	[-2.3; 0.1]
Random effects model			.	**-5.8**	**[-9.5; -2.0]**
Heterogeneity: $I^2 = 95\%$, $\tau^2 = 13.11$, $p < 0.01$					



Meds

```
df_ <- df %>%
  filter(!is.na(RxChangeMean), !is.na(RxChangeStdDev),
```

```r
         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"))
```

```
## Warning in grid.Call(L_textBounds, as.graphicsAnnot(x$label), x$x, x
## $y, : conversion failure on 'Hayashi et al. (2001)†' in 'mbcsToSbcs': dot
## substituted for <e2>
```

```
## Warning in grid.Call(L_textBounds, as.graphicsAnnot(x$label), x$x, x
## $y, : conversion failure on 'Hayashi et al. (2001)†' in 'mbcsToSbcs': dot
## substituted for <80>
```

```
## Warning in grid.Call(L_textBounds, as.graphicsAnnot(x$label), x$x, x
## $y, : conversion failure on 'Hayashi et al. (2001)†' in 'mbcsToSbcs': dot
## substituted for <a0>
```

```
## Warning in grid.Call(L_textBounds, as.graphicsAnnot(x$label), x$x, x
## $y, : conversion failure on 'Hayashi et al. (2001)†' in 'mbcsToSbcs': dot
## substituted for <e2>
```

```
## Warning in grid.Call(L_textBounds, as.graphicsAnnot(x$label), x$x, x
## $y, : conversion failure on 'Hayashi et al. (2001)†' in 'mbcsToSbcs': dot
## substituted for <80>
```

```
## Warning in grid.Call(L_textBounds, as.graphicsAnnot(x$label), x$x, x
## $y, : conversion failure on 'Hayashi et al. (2001)†' in 'mbcsToSbcs': dot
## substituted for <a0>
```

```
## Warning in grid.Call.graphics(L_text, as.graphicsAnnot(x$label), x$x, x
## $y, : conversion failure on 'Hayashi et al. (2001)†' in 'mbcsToSbcs': dot
## substituted for <e2>
```

```
## Warning in grid.Call.graphics(L_text, as.graphicsAnnot(x$label), x$x, x
## $y, : conversion failure on 'Hayashi et al. (2001)†' in 'mbcsToSbcs': dot
## substituted for <80>
```

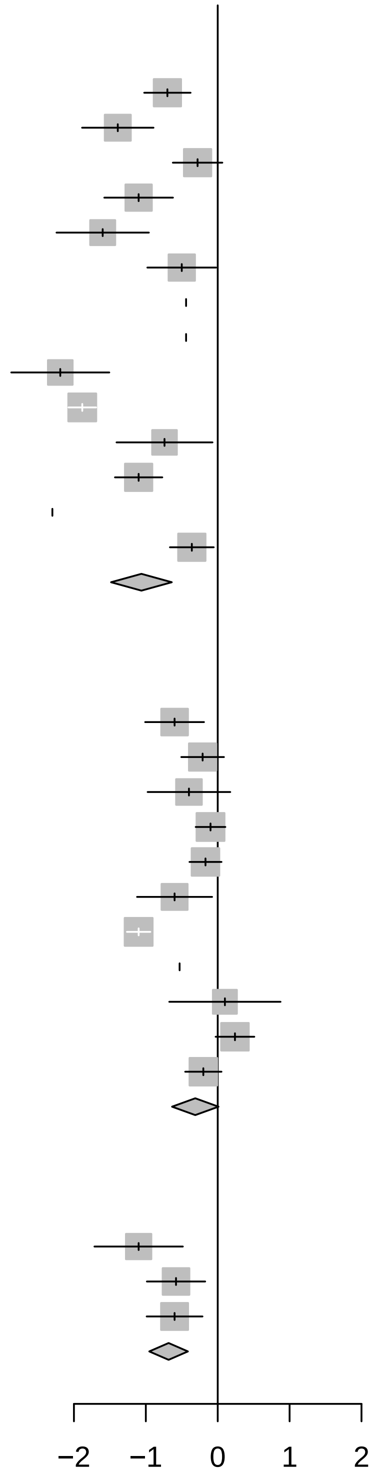
```
## Warning in grid.Call.graphics(L_text, as.graphicsAnnot(x$label), x$x, x
## $y, : conversion failure on 'Hayashi et al. (2001)†' in 'mbcsToSbcs': dot
## substituted for <a0>
```

```
## Warning in grid.Call.graphics(L_text, as.graphicsAnnot(x$label), x$x, x
## $y, : conversion failure on 'Hayashi et al. (2001)†' in 'mbcsToSbcs': dot
## substituted for <e2>
```

```
## Warning in grid.Call.graphics(L_text, as.graphicsAnnot(x$label), x$x, x
## $y, : conversion failure on 'Hayashi et al. (2001)†' in 'mbcsToSbcs': dot
## substituted for <80>
```

```
## Warning in grid.Call.graphics(L_text, as.graphicsAnnot(x$label), x$x, x
## $y, : conversion failure on 'Hayashi et al. (2001)†' in 'mbcsToSbcs': dot
## substituted for <a0>
```

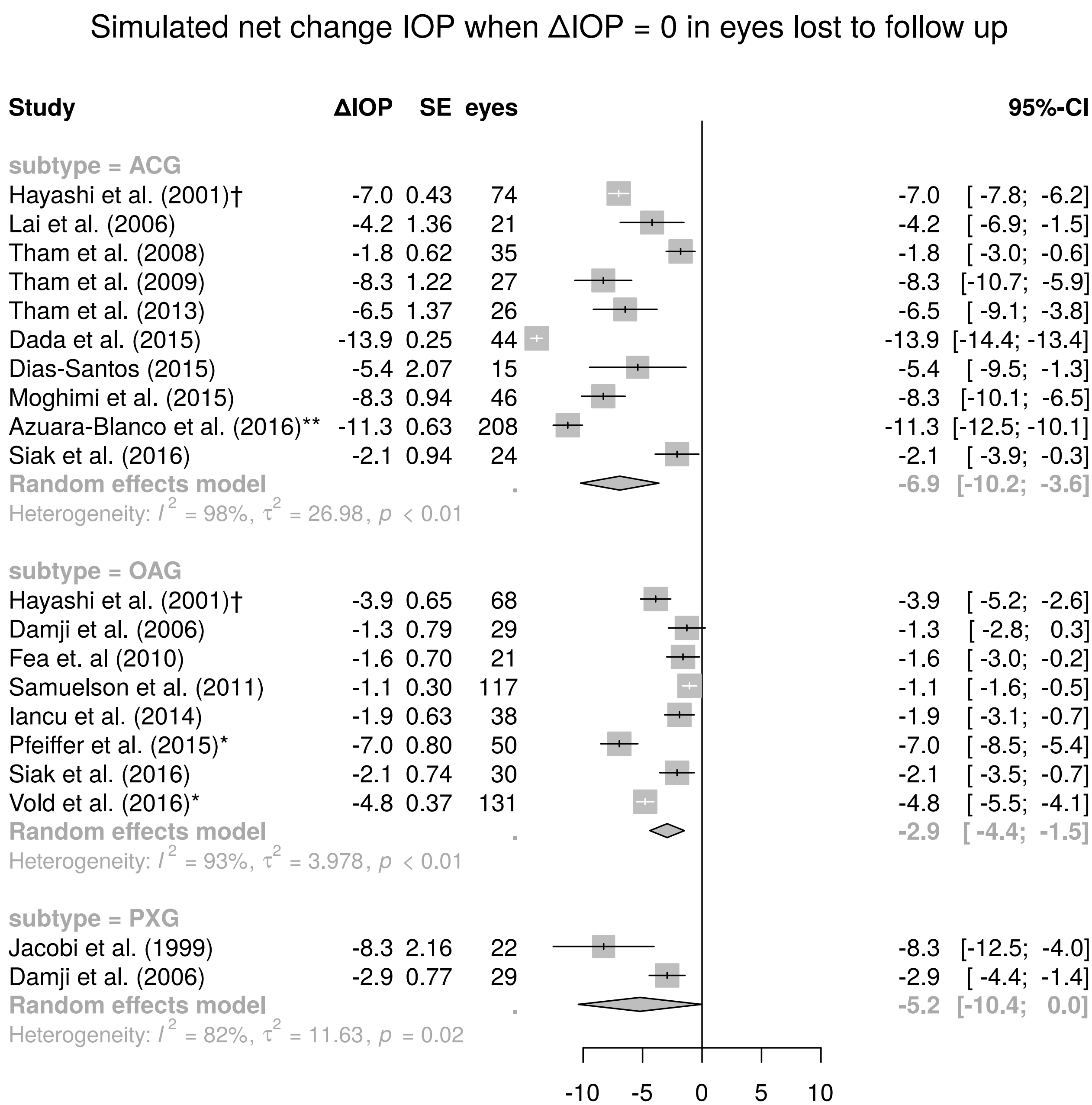
Study	TE	seTE	Total		95%−CI
subtype = ACG					
Hayashi et al. (2001)...	−0.7	0.16	72		−0.7 [−1.0; −0.4]
Lai et al. (2006)	−1.4	0.25	21		−1.4 [−1.9; −0.9]
Mierzejewski et al. (2008)	−0.3	0.18	25		−0.3 [−0.6; 0.1]
Tham et al. (2008)	−1.1	0.24	35		−1.1 [−1.6; −0.6]
Tham et al. (2009)	−1.6	0.33	27		−1.6 [−2.2; −1.0]
Liu et al. (2011)	−0.5	0.24	30		−0.5 [−1.0; 0.0]
Shams et al. (2012)	−0.4	.	.		−0.4
Yudhasompop et al. (2012)	−0.4	.	.		−0.4
Tham et al. (2013)	−2.2	0.35	20		−2.2 [−2.9; −1.5]
Dada et al. (2015)	−1.9	0.10	44		−1.9 [−2.1; −1.7]
Dias−Santos (2015)	−0.7	0.34	15		−0.7 [−1.4; −0.1]
Moghimi et al. (2015)	−1.1	0.17	46		−1.1 [−1.4; −0.8]
Shao et al. (2015)	−2.3	.	.		−2.3
Lee et al. (2016)	−0.4	0.16	56		−0.4 [−0.7; −0.1]
Random effects model			.		**−1.1 [−1.5; −0.6]**
Heterogeneity: I^2 = 93%, τ^2 = 0.4553, p < 0.01					
subtype = OAG					
Hayashi et al. (2001)...	−0.6	0.21	50		−0.6 [−1.0; −0.2]
Leelachaikul et al. (2005)	−0.2	0.15	54		−0.2 [−0.5; 0.1]
Mathalone et al. (2005)	−0.4	0.29	24		−0.4 [−1.0; 0.2]
Shingleton et al. (2006)	−0.1	0.11	55		−0.1 [−0.3; 0.1]
Mierzejewski et al. (2008)	−0.2	0.11	52		−0.2 [−0.4; 0.1]
Fea et. al (2010)	−0.6	0.27	21		−0.6 [−1.1; −0.1]
Samuelson et al. (2011)	−1.1	0.08	123		−1.1 [−1.3; −0.9]
Zhang et al. (2013)	−0.5	.	.		−0.5
Arthur et al. (2014)	0.1	0.39	17		0.1 [−0.7; 0.9]
Iancu et al. (2014)	0.2	0.14	38		0.2 [0.0; 0.5]
Siegel et al. (2015)	−0.2	0.13	52		−0.2 [−0.5; 0.1]
Random effects model			.		**−0.3 [−0.6; 0.0]**
Heterogeneity: I^2 = 92%, τ^2 = 0.2339, p < 0.01					
subtype = PXG					
Jacobi et al. (1999)	−1.1	0.31	13		−1.1 [−1.7; −0.5]
Mierzejewski et al. (2008)	−0.6	0.21	23		−0.6 [−1.0; −0.2]
Shingleton et al. (2008)	−0.6	0.20	51		−0.6 [−1.0; −0.2]
Random effects model			.		**−0.7 [−1.0; −0.4]**
Heterogeneity: I^2 = 9%, τ^2 = 0.0051, p = 0.33					



Sensitivity to missingness

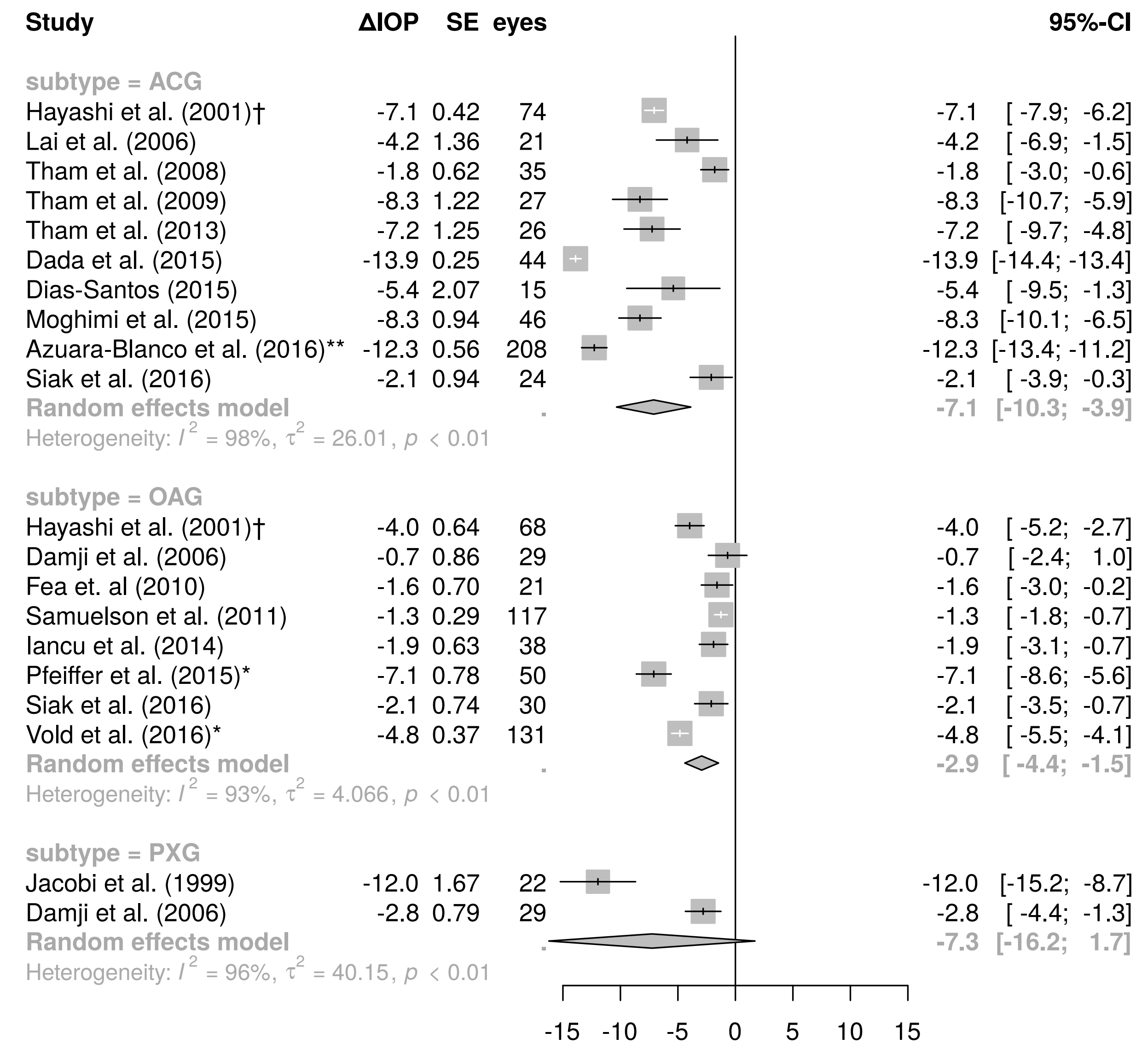
Simulate what the results would look like if there was no effect in the eyes lost to follow up ($\Delta IOP = 0$).

```
meta.analysis.with.sensitivity <- function(missingness='zero') {
  df <- read.data()
  df <- filter.data(df, 'prospective')

  df_ <- df %>%
    filter(!is.na(LastPeriodAbsIOPChangeMean), subtype != "acute") %>%
    mutate(subtype=factor(subtype))

  # Simulate a 0 effect in the unobserved fraction.
  df.missing <- df_
  if(missingness == 'zero') {
    # Zero out.
    df.missing <- df.missing %>% mutate(LastPeriodEyes = PreOpEyes - LastPeriodEyes,
                            LastPeriodAbsIOPChangeMean = 0)
  } else {
    # Add 5 mm Hg to each missing eye.
    df.missing <- df.missing %>% mutate(LastPeriodEyes = PreOpEyes - LastPeriodEyes,
                            LastPeriodAbsIOPChangeMean = LastPeriodAbsIOPChangeMean + 5)
  }

  df_ <- rbind(df_, df.missing)
  # Aggregate two by two
  for(i in seq(nrow(df.missing), 1)) {
    idx <- rep(FALSE, nrow(df_))
    idx[i] <- TRUE
    idx[i*2] <- TRUE
    df_ <- agg.arms(df_, idx)
  }

  df_ <- df_ %>% dplyr::arrange(Year, study.name)

  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"))
}

meta.analysis.with.sensitivity()
grid.text(paste0("Simulated net change IOP when ΔIOP = 0 in eyes lost to follow up"), .5, .97, gp=gpar(
```




```
meta.analysis.with.sensitivity('five')
grid.text(paste0("Simulated net change IOP when ΔIOP = 5 mm Hg higher in eyes lost to follow up"), .5,
```

Simulated net change IOP when ΔIOP = 5 mm Hg higher in eyes lost to follow up



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"))
```

Study	TE	seTE	Total	Type	95%-CI	Weight
Khan et al. (2015)	-5.3	0.75	49	2 site iStent	-5.3 [-6.8; -3.8]	5.4%
Klamann et al. (2013)	-9.3	1.09	27	Ab interno trabeculectomy	-9.3 [-11.4; -7.2]	5.0%
Neiweem et al. (2016)	-4.5	0.32	352	Ab Interno Trabeculectomy	-4.5 [-5.1; -3.9]	5.8%
Khan et al. (2015)	-3.3	1.11	52	Ab interno Trabeculotomy	-3.3 [-5.5; -1.1]	5.0%
Shoji et al. (2007)	-3.1	0.45	16	Canaloplasty	-3.1 [-4.0; -2.2]	5.8%
Arthur et al. (2014)	-5.3	1.64	11	Canaloplasty	-5.3 [-8.5; -2.1]	4.2%
Schoenberg et al. (2015)	-5.1	1.02	36	Canaloplasty	-5.1 [-7.1; -3.1]	5.1%
Tetz et al. (2015)	-9.9	1.06	27	Canaloplasty	-9.9 [-12.0; -7.8]	5.0%
Rekas et al. (2015)	-6.4	1.24	29	Canoloplasty	-6.4 [-8.8; -4.0]	4.8%
Vold et al. (2016)*	-7.4	0.24	332	Cypass	-7.4 [-7.9; -6.9]	5.9%
Siegel et al. (2015)	-2.5	0.31	261	Endocyclophotocoagulation	-2.5 [-3.1; -1.9]	5.8%
Sheybani et al. (2015)	-7.0	0.76	34	Gelatin stent	-7.0 [-8.5; -5.5]	5.4%
Pfeiffer et al. (2015)*	-9.4	0.72	43	Hydrus Microstent	-9.4 [-10.8; -8.0]	5.5%
Fea et. al (2010)	-3.2	0.87	12	iStent	-3.2 [-4.9; -1.5]	5.3%
Samuelson et al. (2011)	-1.5	0.28	117	iStent	-1.5 [-2.0; -1.0]	5.9%
Parikh et al. (2016)	-4.2	0.26	498	Trabectome	-4.2 [-4.7; -3.7]	5.9%
Jacobi et al. (1999)	-13.1	1.51	26	Trabecular Aspiration	-13.1 [-16.1; -10.1]	4.4%
Klamann et al. (2013)	-5.1	1.22	28	Trabecular Aspiration	-5.1 [-7.5; -2.7]	4.8%
Moghimi et al. (2015)	-8.8	1.05	45	Viscogonioplasty	-8.8 [-10.9; -6.7]	5.1%
Random effects model			**1995**		**-5.9 [-7.1; -4.7]**	**100.0%**

Heterogeneity: $I^2 = 96\%$, $\tau^2 = 6.317$, $p < 0.01$