Phaco meta analysis

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Contents

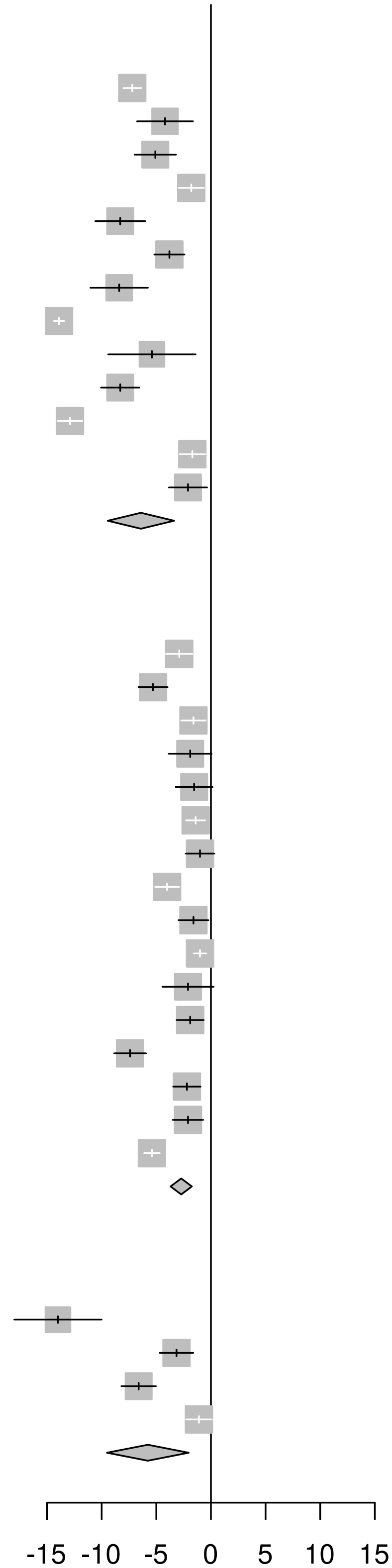
Analysis of full dataset

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	1.31	21	-4.2	[-6.8; -1.6]
Mierzejewski et al. (2008)	-5.1	0.97	25	-5.1	[-7.0; -3.2]
Tham et al. (2008)	-1.8	0.59	35	-1.8	[-3.0; -0.6]
Tham et al. (2009)	-8.3	1.16	27	-8.3	[-10.6; -6.0]
Liu et al. (2011)	-3.8	0.70	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	0.24	44	-13.9	[-14.4; -13.4]
Dias-Santos (2015)	-5.4	2.04	15	-5.4	[-9.4; -1.4]
Moghimi et al. (2015)	-8.3	0.90	46	-8.3	[-10.1; -6.5]
Azuara-Blanco et al. (2016)**	-12.9	0.57	182	-12.9	[-14.0; -11.8]
Lee et al. (2016)	-1.7	0.60	56	-1.7	[-2.9; -0.5]
Siak et al. (2016)	-2.1	0.89	24	-2.1	[-3.8; -0.4]
Random effects model			.	**-6.4**	**[-9.4; -3.4]**
Heterogeneity: $I^2 = 99\%$, $\tau^2 = 30.23$, $p < 0.01$					
subtype = OAG					
Kim et al. (1999)	-2.9	0.62	31	-2.9	[-4.1; -1.7]
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	1.20	17	-2.1	[-4.4; 0.2]
Iancu et al. (2014)	-1.9	0.63	38	-1.9	[-3.1; -0.7]
Pfeiffer et al. (2015)*	-7.4	0.74	47	-7.4	[-8.9; -5.9]
Siegel et al. (2015)	-2.2	0.64	52	-2.2	[-3.5; -0.9]
Siak et al. (2016)	-2.1	0.71	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: $I^2 = 91\%$, $\tau^2 = 3.5$, $p < 0.01$					
subtype = PXG					
Jacobi et al. (1999)	-14.0	2.04	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	0.59	51	-1.1	[-2.3; 0.1]
Random effects model			.	**-5.8**	**[-9.5; -2.0]**
Heterogeneity: $I^2 = 95\%$, $\tau^2 = 13.25$, $p < 0.01$					



Acute

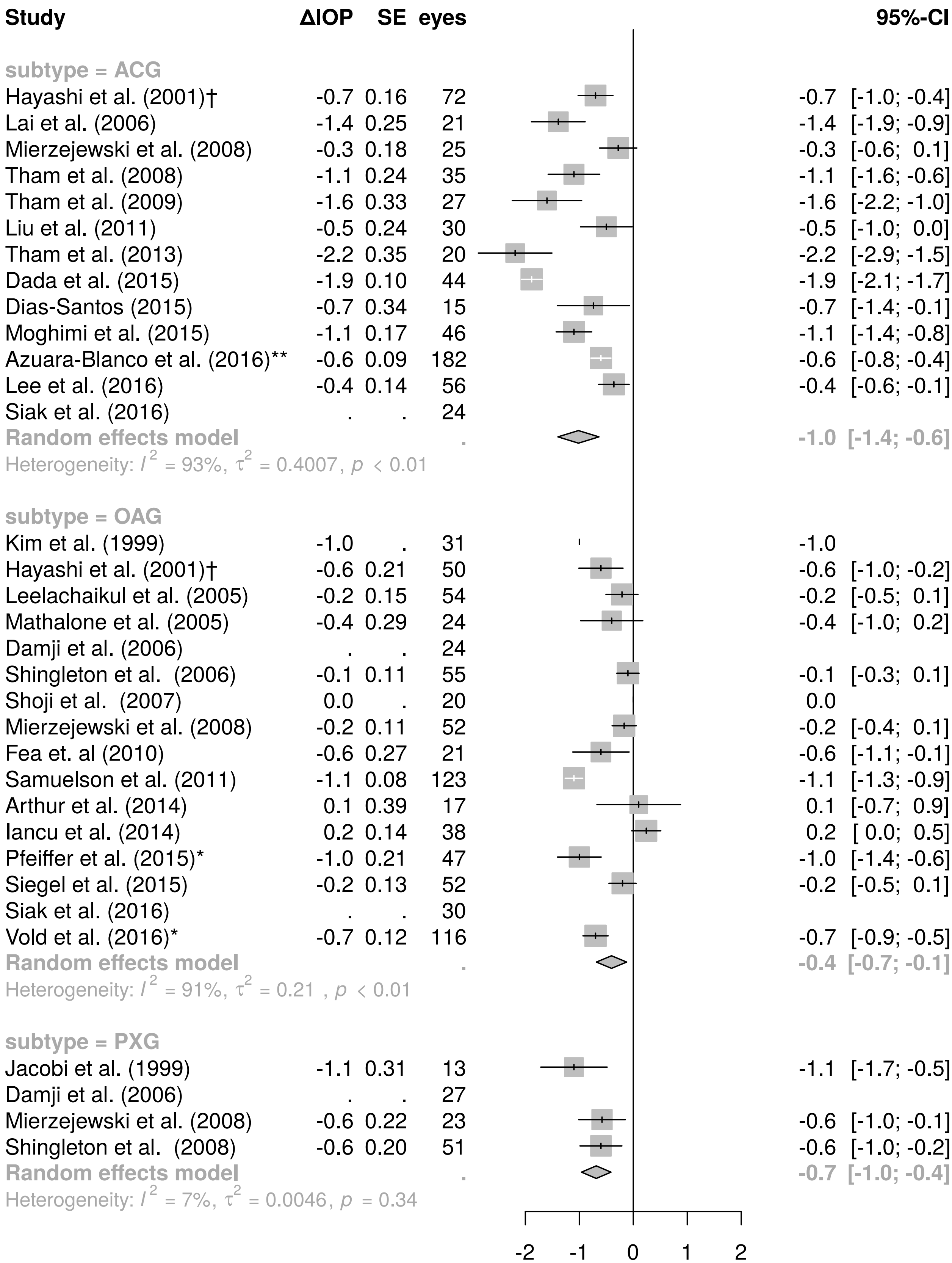
```r
df_ <- df %>%
  filter(!is.na(LastPeriodAbsIOPChangeMean), subtype == "acute", MIGsYorN == 'N') %>%
  mutate(subtype=factor(subtype)) %>% dplyr::arrange(Year)
m <- metagen(LastPeriodAbsIOPChangeMean,
             LastPeriodAbsIOPChangeStdDev / sqrt(LastPeriodEyes),
             study.name,
    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

```r
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

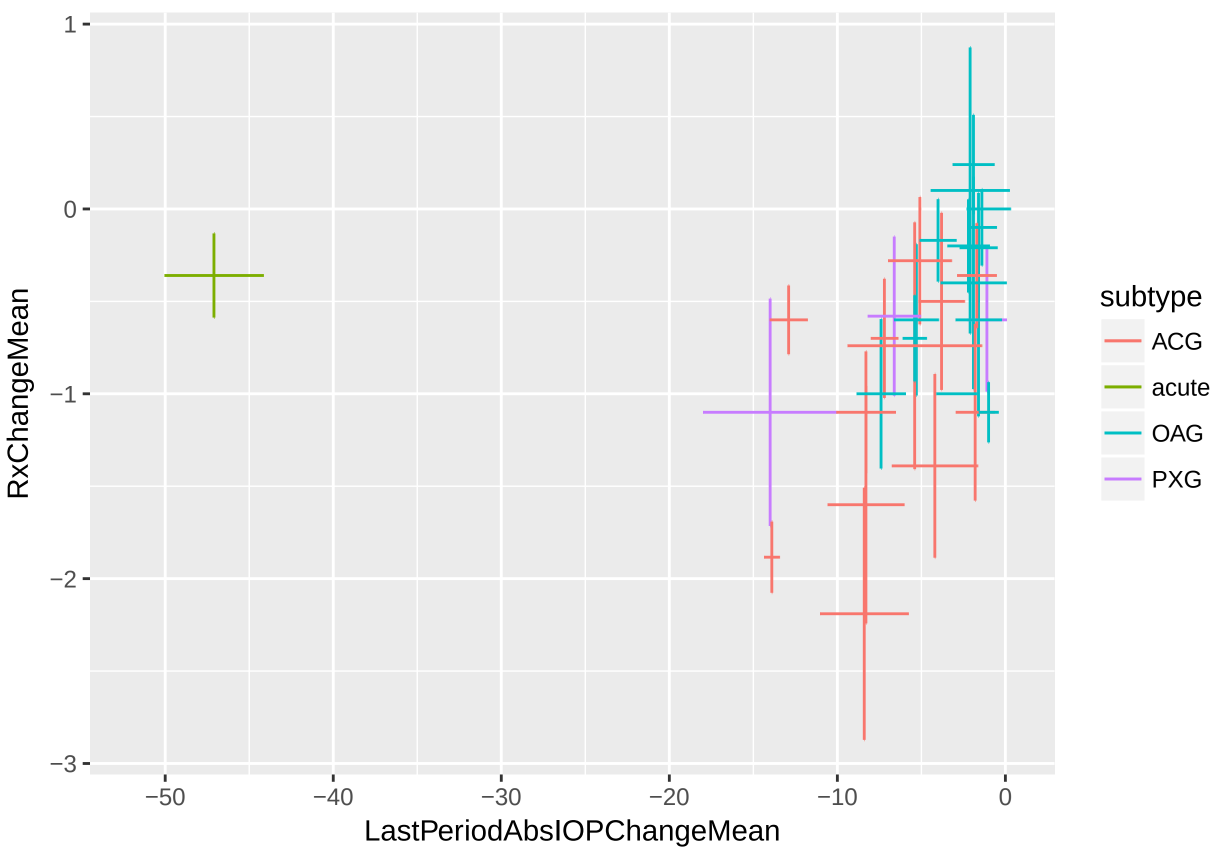
So which is it?

```
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()
```

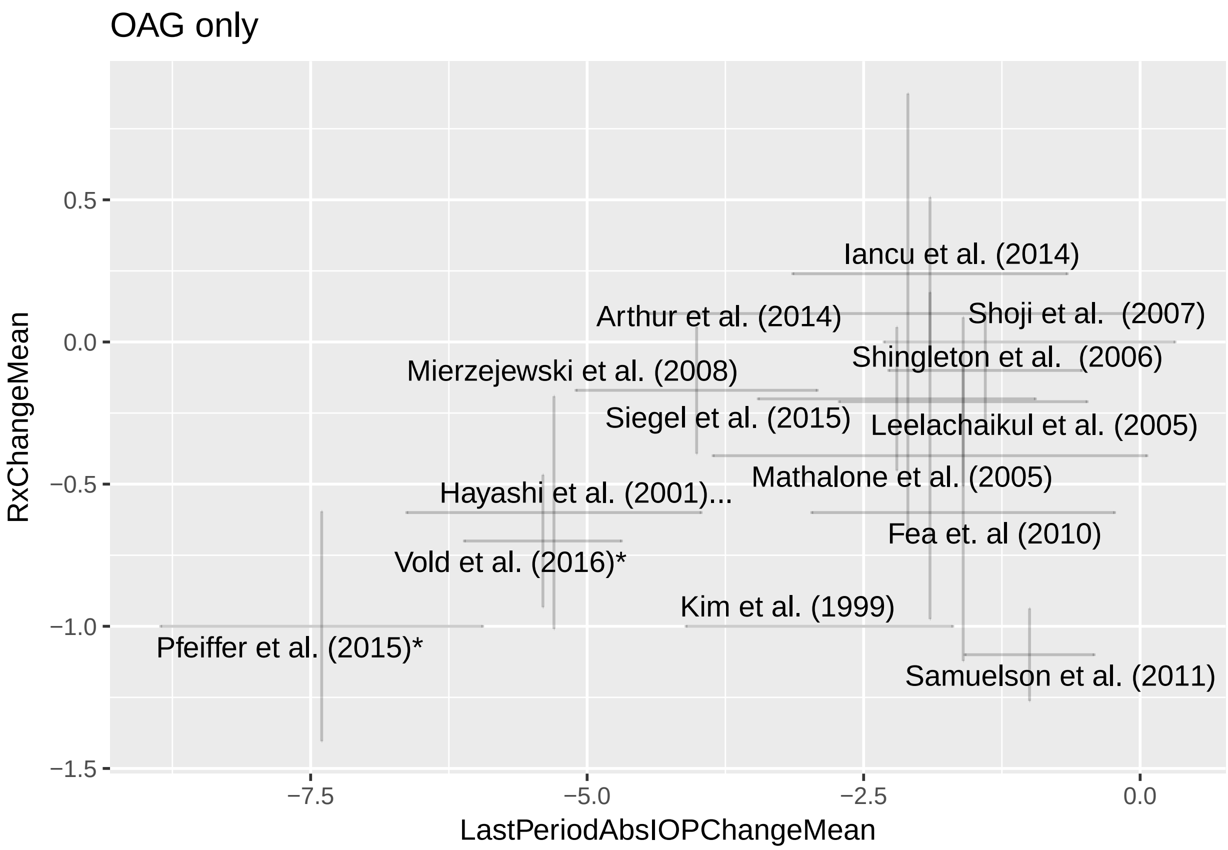
```
## Warning: Removed 17 rows containing missing values (geom_errorbar).
```

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




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

```
        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.

```
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.corrs <- with(df_, replicate(n = 100,
                                   draw.corr(LastPeriodAbsIOPChangeMean,
                                             LastPeriodAbsIOPChangeStdDev / sqrt(LastPeriodEyes),
                                             RxChangeMean,
                                             RxChangeStdDev / sqrt(LastPeriodEyes))))
mean(drawn.corrs)
```

```
## [1] 0.3816005
```

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

```
## [1] 0.1337711
```

```
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] -0.02245687
```

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

```
## [1] 0.1921681
```

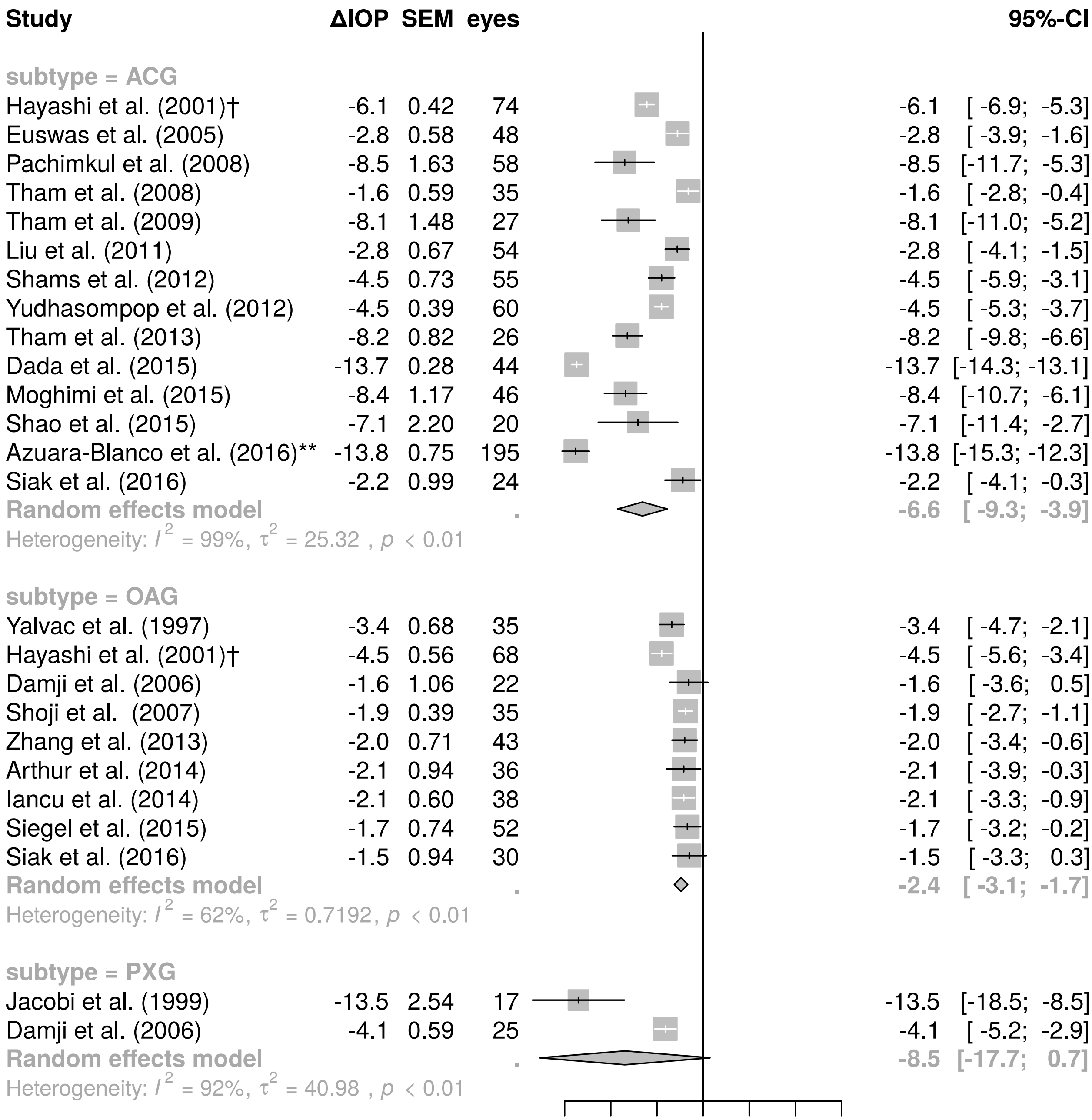
However, this effect goes away when we focus on the studies which don't have washout.

Separate meta-analysis for each time period

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

6 month follow-up

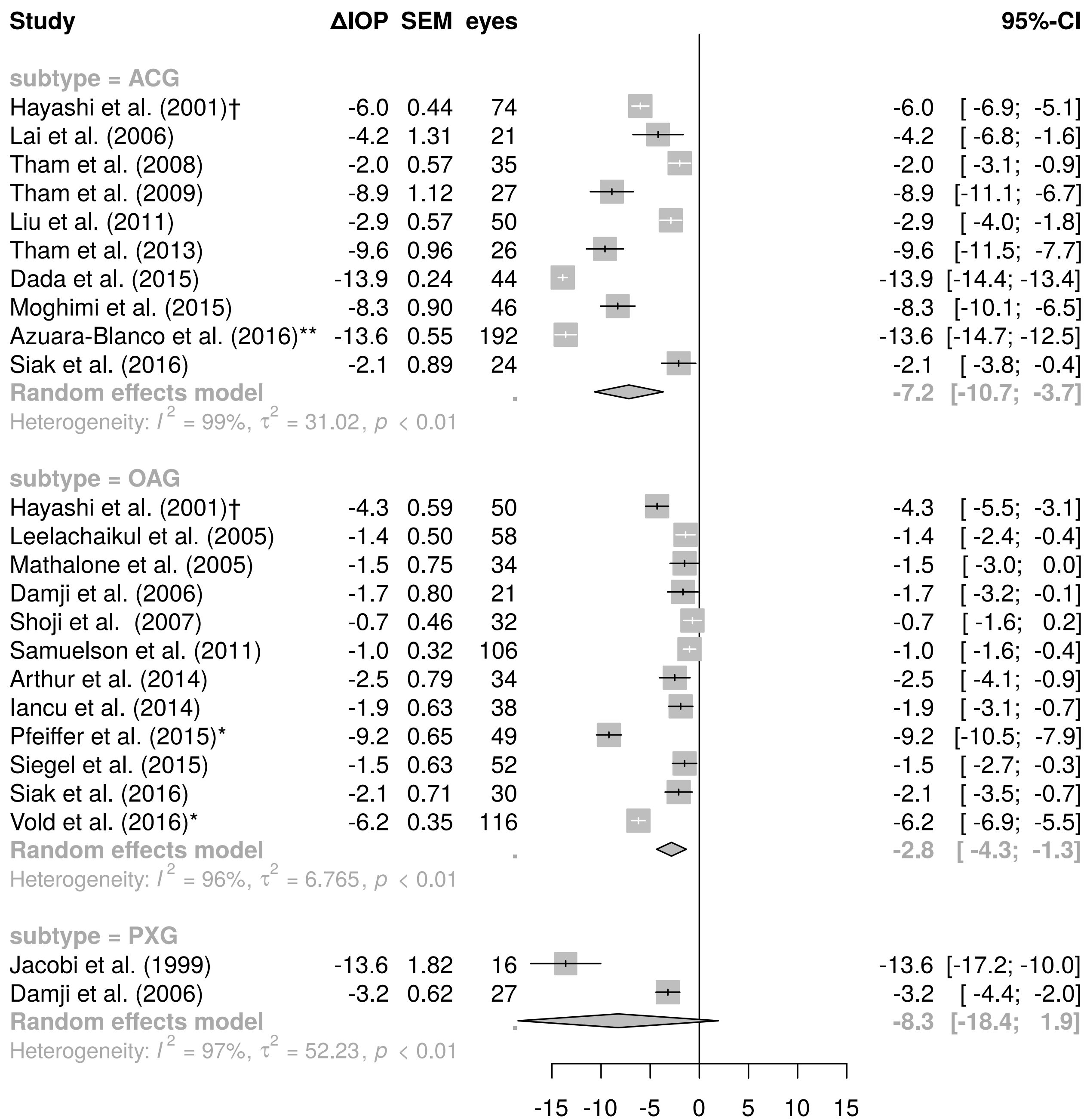
```
df_ <- df %>%
  filter(!is.na(SixMoAbsIOPChangeMean), subtype != "acute") %>%
  mutate(subtype=factor(subtype))
m <- metagen(SixMoAbsIOPChangeMean,
             SixMoAbsIOPChangeStdDev / sqrt(SixMoEyes),
             study.name,
             data=df_,
             byvar=subtype,
             n.e=SixMoEyes)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

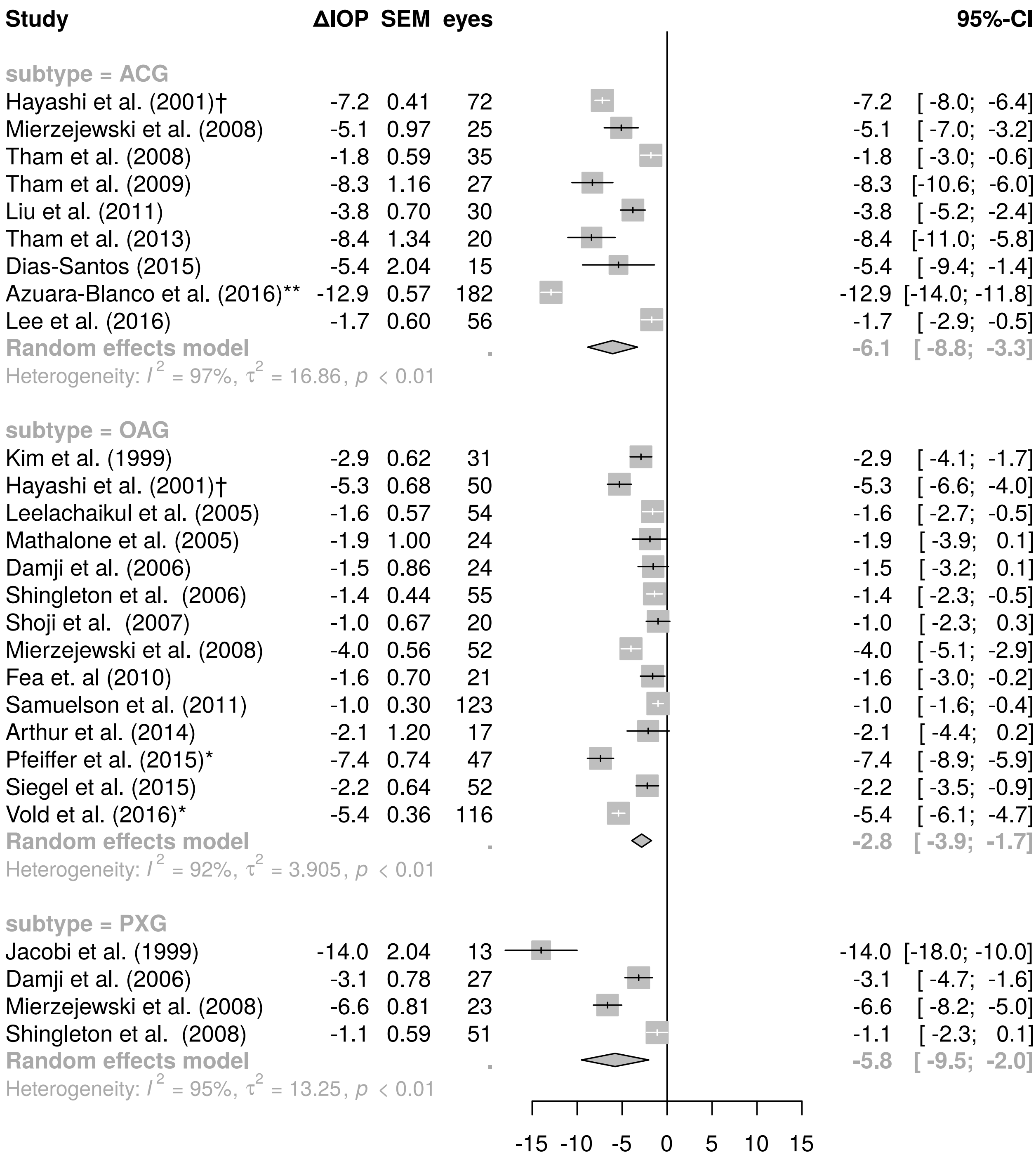
```r
df_ <- df %>%
  filter(!is.na(OneYAbsIOPChangeMean), subtype != "acute", MIGsYorN == 'N') %>%
  mutate(subtype=factor(subtype))
m <- metagen(OneYAbsIOPChangeMean,
             OneYAbsIOPChangeStdDev / sqrt(OneYEyes),
             study.name,
             data=df_,
             byvar=subtype,
  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

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## 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>

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## 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, :
```
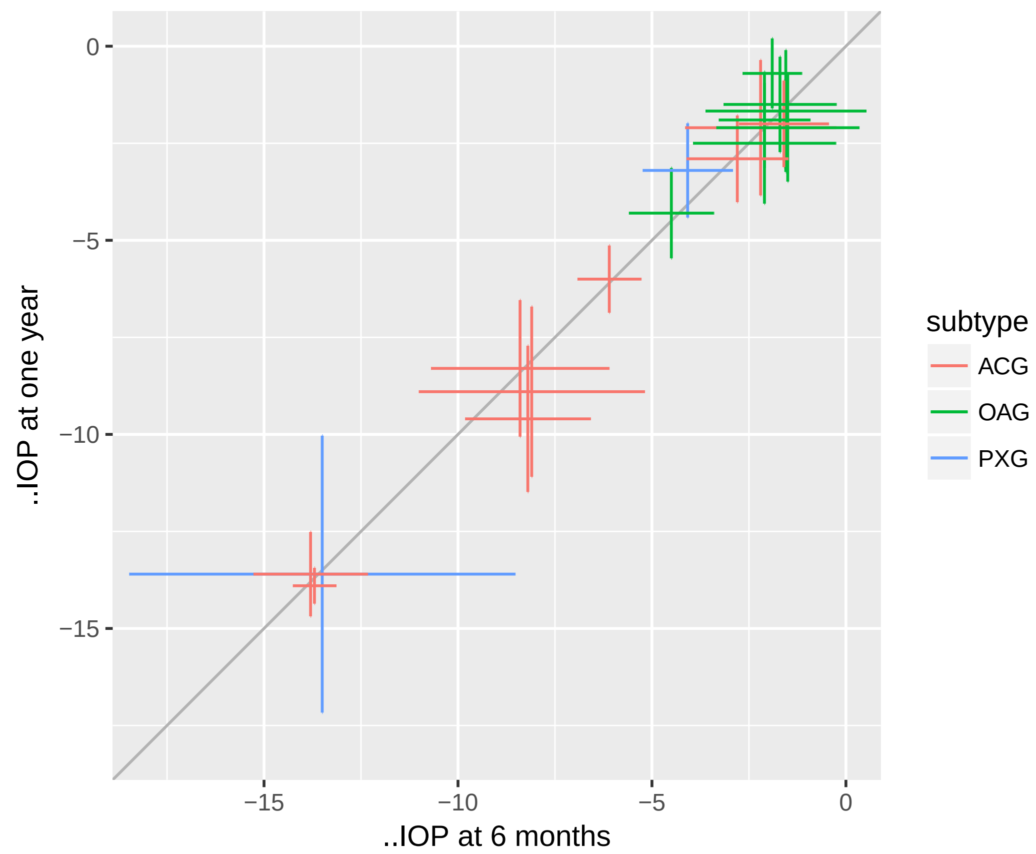

```
## conversion failure on 'ΔIOP at 6 months' in 'mbcsToSbcs': dot substituted
## for <94>

## 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>
```

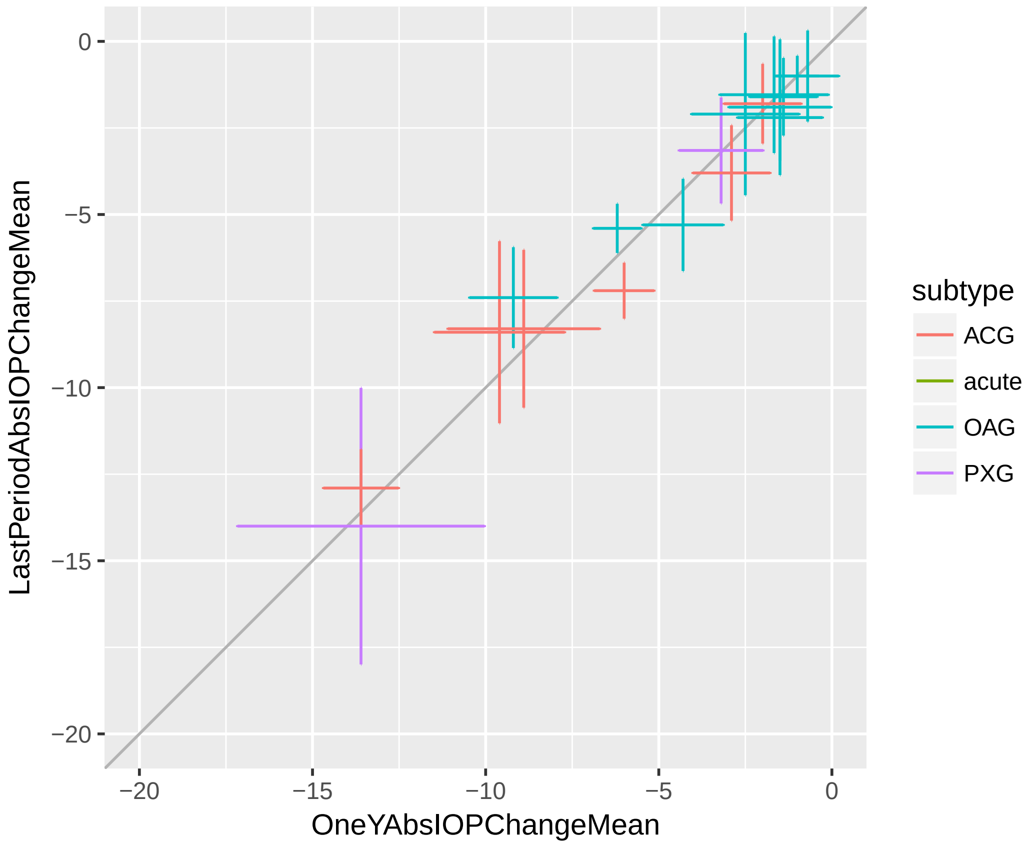


It's very clear that six months and 12 months IOP are highly correlated.

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).
```



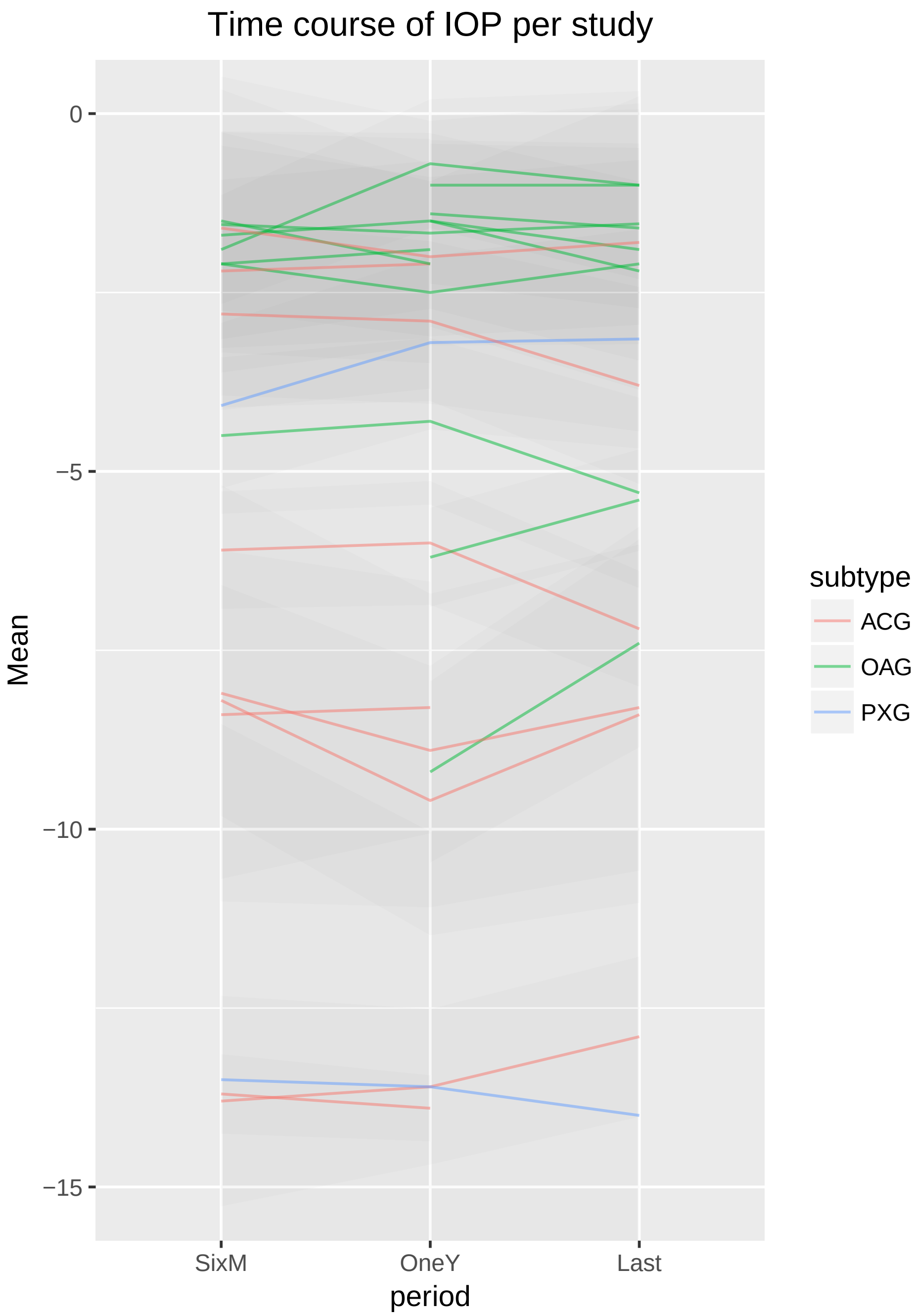
Again, correlations are very high. Present this in another way.

```
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] 0.6338953
```

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

```
## [1] 0.1782464
```

```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] 0.9922153
```

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

```
## [1] 0.00318651
```

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)
```

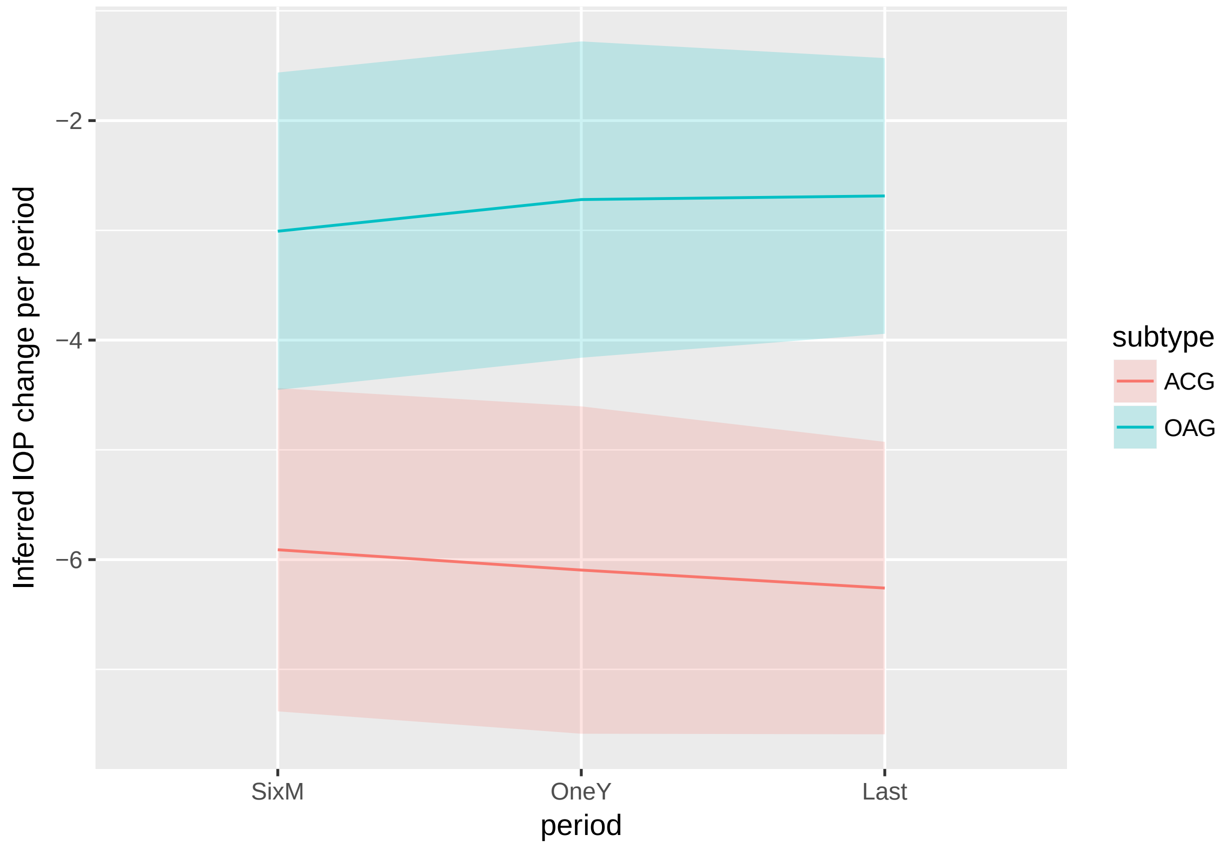
```
## Call:  mvmeta(formula = cbind(SixMoAbsIOPChangeMean, OneYAbsIOPChangeMean,
##    LastPeriodAbsIOPChangeMean) ~ subtype, S = get.correlation.matrices.tri(df_$SixMoAbsIOPChangeStdDev/
##    df_$OneYAbsIOPChangeStdDev/sqrt(df_$OneYEyes), df_$LastPeriodAbsIOPChangeStdDev/sqrt(df_$LastPerio
##      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)   -5.9098      0.7513  -7.8665    0.0000   -7.3823   -4.4374
## subtypeOAG     2.9020      1.0528   2.7565    0.0058    0.8386    4.9655
##
## (Intercept)  ***
## subtypeOAG    **
## OneYAbsIOPChangeMean :
##              Estimate  Std. Error        z  Pr(>|z|)  95%ci.lb  95%ci.ub
## (Intercept)   -6.0950      0.7609  -8.0102    0.0000   -7.5863   -4.6036
## subtypeOAG     3.3757      1.0581   3.1904    0.0014    1.3019    5.4495
##
## (Intercept)  ***
## subtypeOAG    **
## LastPeriodAbsIOPChangeMean :
##              Estimate  Std. Error        z  Pr(>|z|)  95%ci.lb  95%ci.ub
## (Intercept)   -6.2590      0.6797  -9.2084    0.0000   -7.5912   -4.9268
## subtypeOAG     3.5727      0.9342   3.8244    0.0001    1.7417    5.4036
##
## (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         2.9887  SixMoAbsIOPChangeMean
```

```
## OneYAbsIOPChangeMean          3.0250                 0.9981
## LastPeriodAbsIOPChangeMean    2.6049                 0.9918
##
## SixMoAbsIOPChangeMean       OneYAbsIOPChangeMean
## OneYAbsIOPChangeMean
## LastPeriodAbsIOPChangeMean                0.9820
##
## Multivariate Cochran Q-test for residual heterogeneity:
## Q = 1622.3062 (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
## -118.7214   261.4428   286.9685
```

```
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)
```

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

```
##
## Mixed-Effects Model (k = 33; tau^2 estimator: DL)
##
## tau^2 (estimated amount of residual heterogeneity):     26.2889 (SE = 9.7171)
## tau (square root of estimated tau^2 value):             5.1273
## I^2 (residual heterogeneity / unaccounted variability): 98.62%
## H^2 (unaccounted variability / sampling variability):   72.68
## R^2 (amount of heterogeneity accounted for):            0.00%
##
## Test for Residual Heterogeneity:
## QE(df = 31) = 2253.1681, p-val < .0001
##
## Test of Moderators (coefficient(s) 2):
## QM(df = 1) = 0.7930, p-val = 0.3732
##
## Model Results:
##
##                 estimate      se     zval    pval    ci.lb    ci.ub
## intrcpt          -3.5079  1.4751  -2.3781  0.0174  -6.3990  -0.6168  *
## LastPeriodEyes   -0.0231  0.0259  -0.8905  0.3732  -0.0739   0.0277
##
## ---
## 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):     15.5751 (SE = 5.9007)
## tau (square root of estimated tau^2 value):             3.9465
## I^2 (residual heterogeneity / unaccounted variability): 97.52%
## H^2 (unaccounted variability / sampling variability):   40.31
## R^2 (amount of heterogeneity accounted for):            36.33%
##
## Test for Residual Heterogeneity:
## QE(df = 27) = 1088.2629, p-val < .0001
##
## Test of Moderators (coefficient(s) 2,3,4,5,6):
## QM(df = 5) = 13.4471, p-val = 0.0195
##
## Model Results:
##
##                               estimate      se     zval    pval     ci.lb
## intrcpt                        -2.0693  1.8551  -1.1155  0.2646   -5.7052
## LastPeriodEyes                 -0.0135  0.0329  -0.4120  0.6804   -0.0779
## subtypeACG                     -2.2003  2.4998  -0.8802  0.3788   -7.0998
## subtypePXG                    -12.1589  5.1416  -2.3648  0.0180  -22.2362
## LastPeriodEyes:subtypeACG      -0.0323  0.0421  -0.7661  0.4436   -0.1149
## LastPeriodEyes:subtypePXG       0.2999  0.1514   1.9815  0.0475    0.0033
##                                  ci.ub
## intrcpt                         1.5666
```

```
## LastPeriodEyes              0.0509
## subtypeACG                  2.6993
## subtypePXG                 -2.0816  *
## LastPeriodEyes:subtypeACG   0.0503
## LastPeriodEyes:subtypePXG   0.5966  *
##
## ---
## 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):     22.3626 (SE = 8.2491)
## tau (square root of estimated tau^2 value):             4.7289
## I^2 (residual heterogeneity / unaccounted variability): 98.40%
## H^2 (unaccounted variability / sampling variability):   62.31
## R^2 (amount of heterogeneity accounted for):            8.59%
##
## Test for Residual Heterogeneity:
## QE(df = 31) = 1931.7117, p-val < .0001
##
## Test of Moderators (coefficient(s) 2):
## QM(df = 1) = 0.0819, p-val = 0.7747
##
## Model Results:
##
##          estimate        se     zval    pval      ci.lb     ci.ub
## intrcpt   88.5741  325.2895   0.2723  0.7854  -548.9816  726.1299
## Year      -0.0463    0.1619  -0.2862  0.7747    -0.3636    0.2709
##
## ---
## 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):     13.5468 (SE = 4.9600)
## tau (square root of estimated tau^2 value):             3.6806
## I^2 (residual heterogeneity / unaccounted variability): 97.20%
## H^2 (unaccounted variability / sampling variability):   35.66
## R^2 (amount of heterogeneity accounted for):            44.63%
##
## Test for Residual Heterogeneity:
## QE(df = 27) = 962.7471, p-val < .0001
##
## Test of Moderators (coefficient(s) 2,3,4,5,6):
## QM(df = 5) = 12.3857, p-val = 0.0299
##
## Model Results:
##
##                      estimate         se     zval    pval       ci.lb
```

```
## intrcpt            101.1538   357.3868   0.2830  0.7771   -599.3116
## Year                -0.0517     0.1779  -0.2906  0.7713     -0.4003
## subtypeACG         214.7869   582.6862   0.3686  0.7124   -927.2571
## subtypePXG       -2425.5918  1161.6203  -2.0881  0.0368  -4702.3259
## Year:subtypeACG     -0.1086     0.2898  -0.3746  0.7079     -0.6766
## Year:subtypePXG      1.2078     0.5791   2.0857  0.0370      0.0728
##                      ci.ub
## intrcpt           801.6191
## Year                0.2969
## subtypeACG       1356.8308
## subtypePXG       -148.8578  *
## Year:subtypeACG     0.4594
## Year:subtypePXG     2.3428  *
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

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

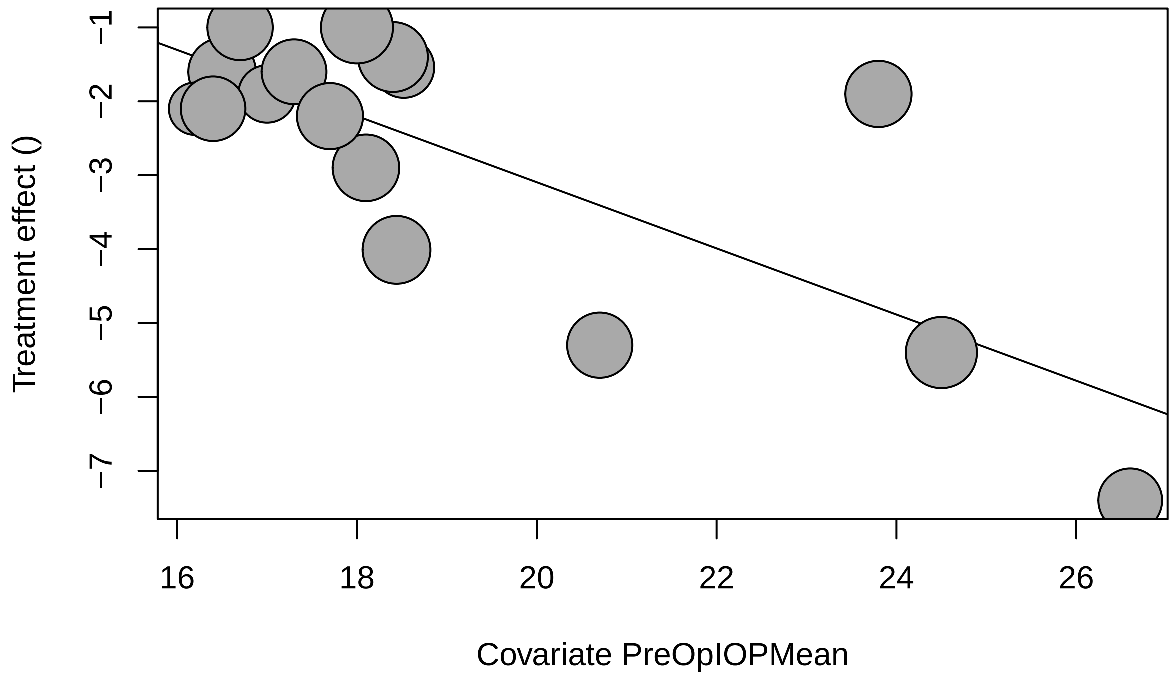
```
##
## Mixed-Effects Model (k = 33; tau^2 estimator: DL)
##
## tau^2 (estimated amount of residual heterogeneity):     5.0212 (SE = 1.8093)
## tau (square root of estimated tau^2 value):             2.2408
## I^2 (residual heterogeneity / unaccounted variability): 92.99%
## H^2 (unaccounted variability / sampling variability):   14.27
## R^2 (amount of heterogeneity accounted for):            79.48%
##
## Test for Residual Heterogeneity:
## QE(df = 31) = 442.4006, p-val < .0001
##
## Test of Moderators (coefficient(s) 2):
## QM(df = 1) = 57.3287, p-val < .0001
##
## Model Results:
##
##               estimate      se     zval    pval    ci.lb    ci.ub
## intrcpt        11.3282  2.1248   5.3314  <.0001   7.1637  15.4927  ***
## PreOpIOPMean   -0.7855  0.1037  -7.5716  <.0001  -0.9889  -0.5822  ***
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

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

```
##
## Mixed-Effects Model (k = 33; tau^2 estimator: DL)
##
## tau^2 (estimated amount of residual heterogeneity):     1.3334 (SE = 0.5546)
## tau (square root of estimated tau^2 value):             1.1547
## I^2 (residual heterogeneity / unaccounted variability): 77.07%
## H^2 (unaccounted variability / sampling variability):   4.36
## R^2 (amount of heterogeneity accounted for):            94.55%
##
## Test for Residual Heterogeneity:
```

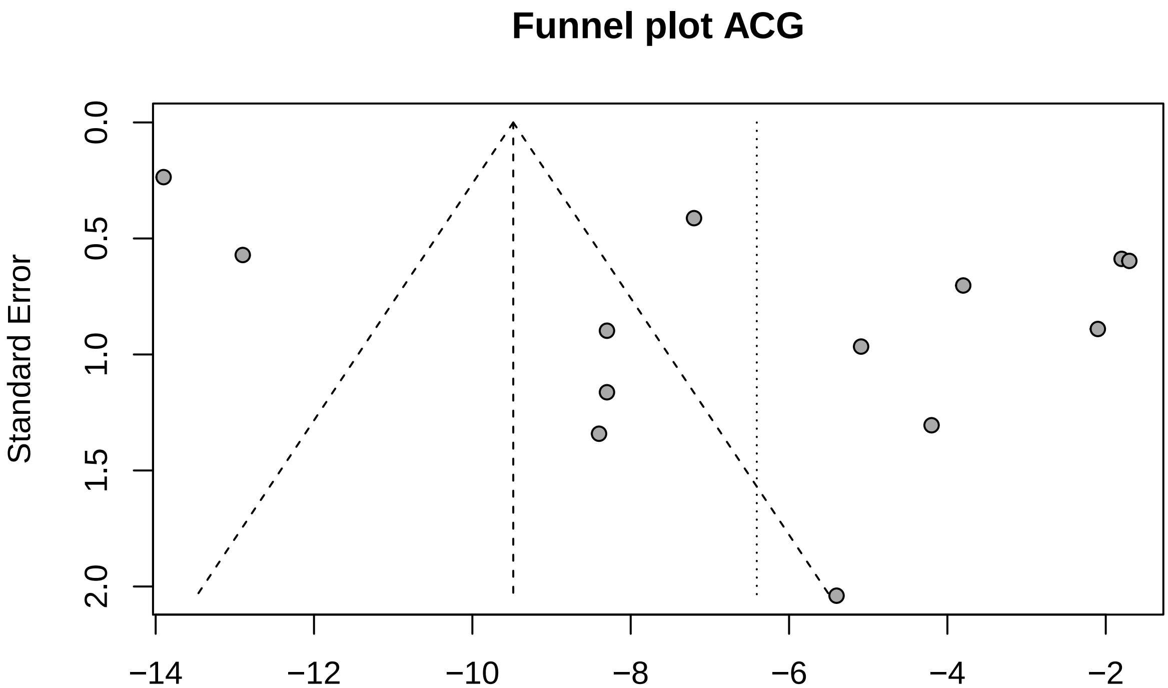
```
## QE(df = 27) = 117.7706, p-val < .0001
##
## Test of Moderators (coefficient(s) 2,3,4,5,6):
## QM(df = 5) = 202.5133, p-val < .0001
##
## Model Results:
##
##                          estimate      se     zval    pval    ci.lb
## intrcpt                    5.8523  2.1039   2.7816  0.0054   1.7287
## PreOpIOPMean              -0.4475  0.1084  -4.1298  <.0001  -0.6598
## subtypeACG                 5.6044  2.7819   2.0146  0.0439   0.1521
## subtypePXG                 8.8320  4.5158   1.9558  0.0505  -0.0189
## PreOpIOPMean:subtypeACG   -0.4148  0.1374  -3.0181  0.0025  -0.6841
## PreOpIOPMean:subtypePXG   -0.4778  0.2177  -2.1947  0.0282  -0.9046
##                            ci.ub
## intrcpt                   9.9759   **
## PreOpIOPMean             -0.2351  ***
## subtypeACG               11.0568    *
## subtypePXG               17.6829    .
## PreOpIOPMean:subtypeACG  -0.1454   **
## PreOpIOPMean:subtypePXG  -0.0511    *
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

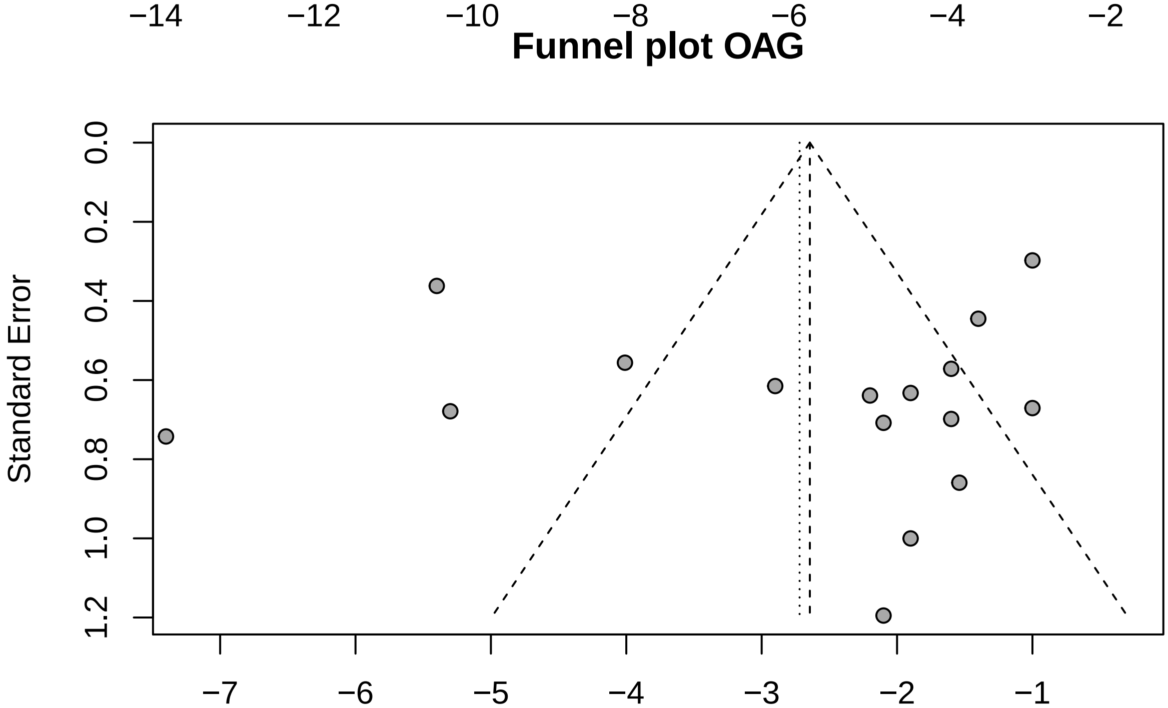
```r
# Same, restricted to OAG only
df_ <- df %>% filter(!is.na(LastPeriodAbsIOPChangeMean), subtype == "OAG", MIGsYorN == 'N') %>%
  mutate(subtype=relevel(factor(subtype), ref="OAG"))
m <- metagen(LastPeriodAbsIOPChangeMean,
             LastPeriodAbsIOPChangeStdDev / sqrt(LastPeriodEyes),
       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

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

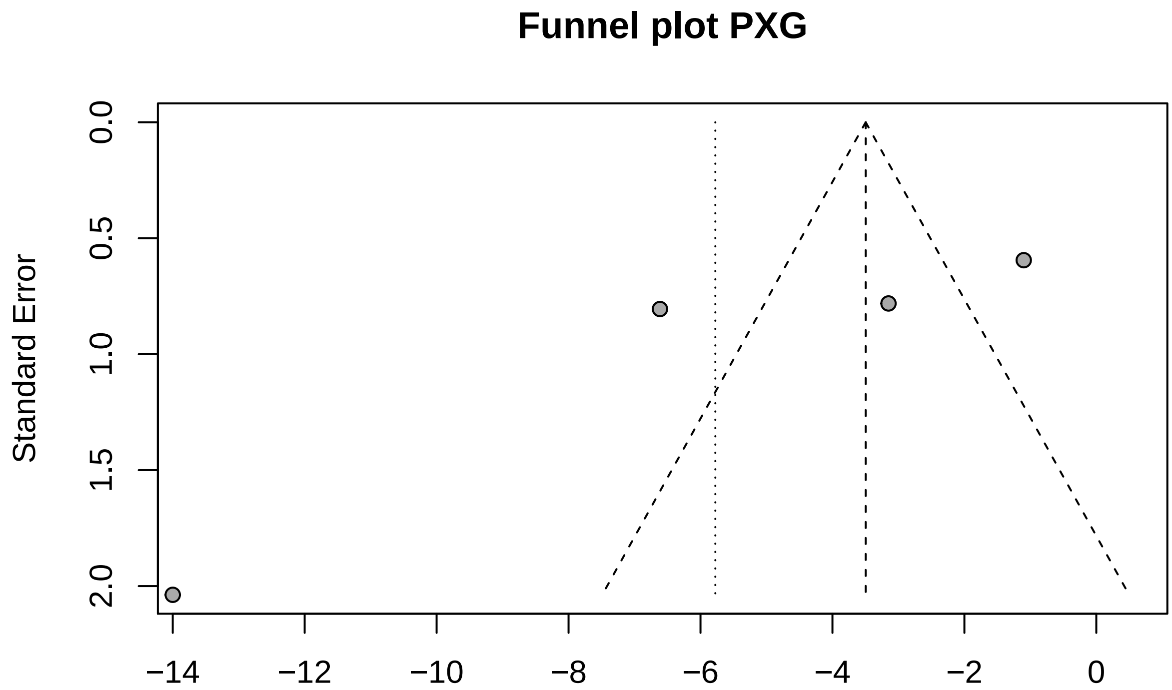


Small study bias

```
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))
}
```

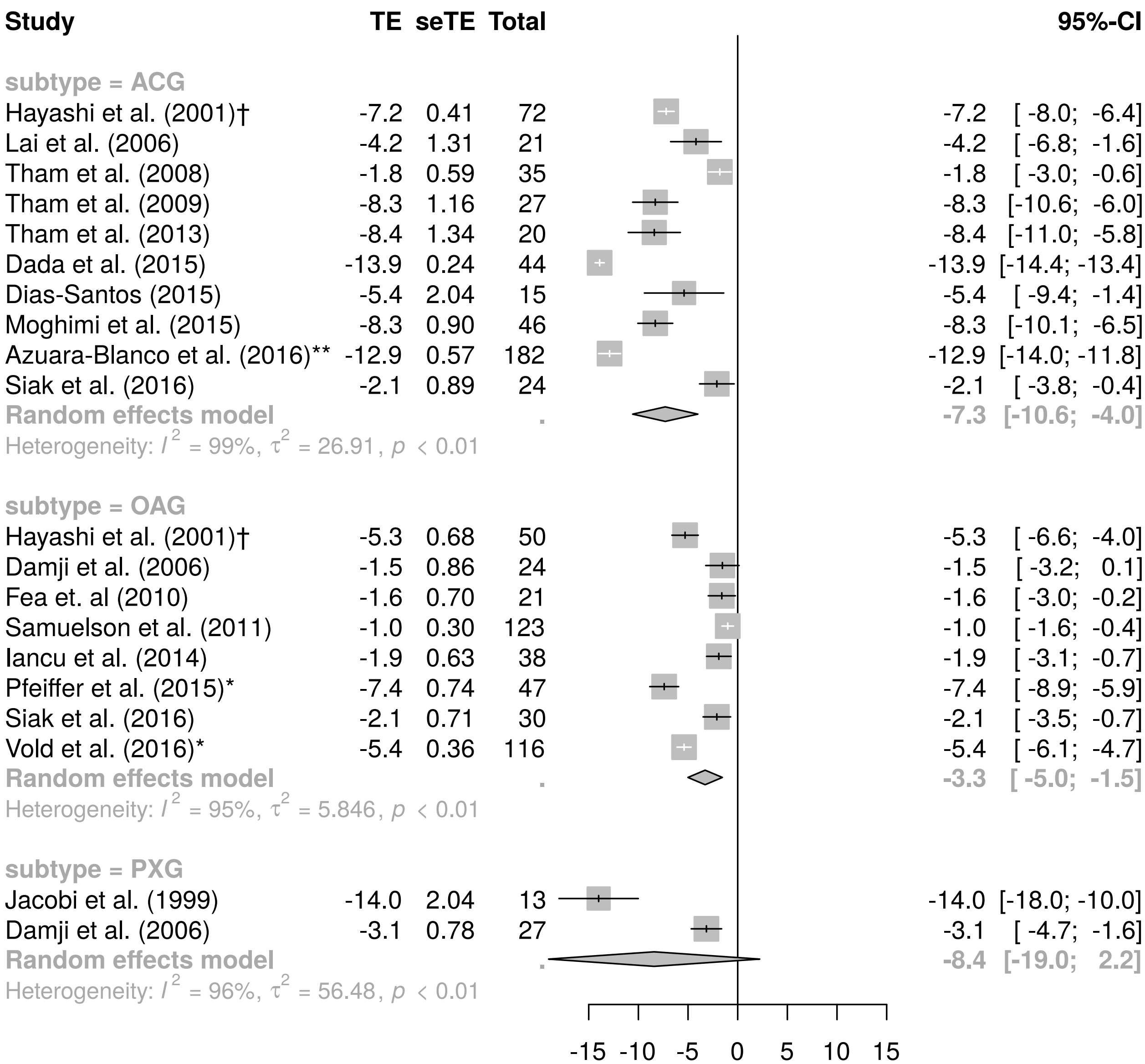

Funnel plot ACG
Standard Error
0.0
0.5
1.0
1.5
2.0
−14
−12
−10
−8
−6
−4
−2


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


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

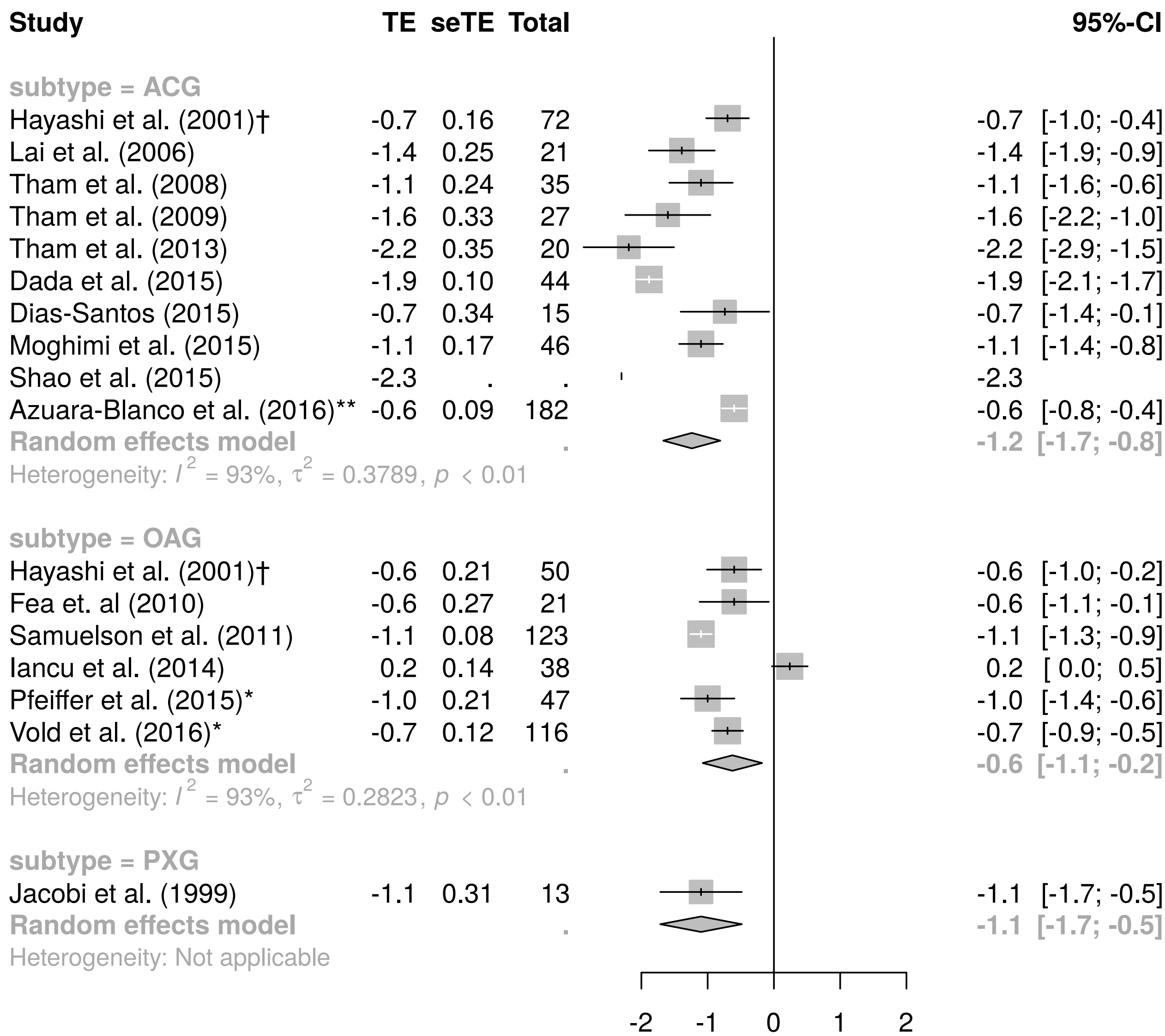
Prospective studies only



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_,
```

```r
             byvar=subtype,
             n.e=LastPeriodEyes)
forest(m,
       comb.fixed=FALSE,
       digits=1,
       digits.se = 2,
       overall=FALSE,
       leftcols=c("studlab", "TE", "seTE", "n.e"))
```



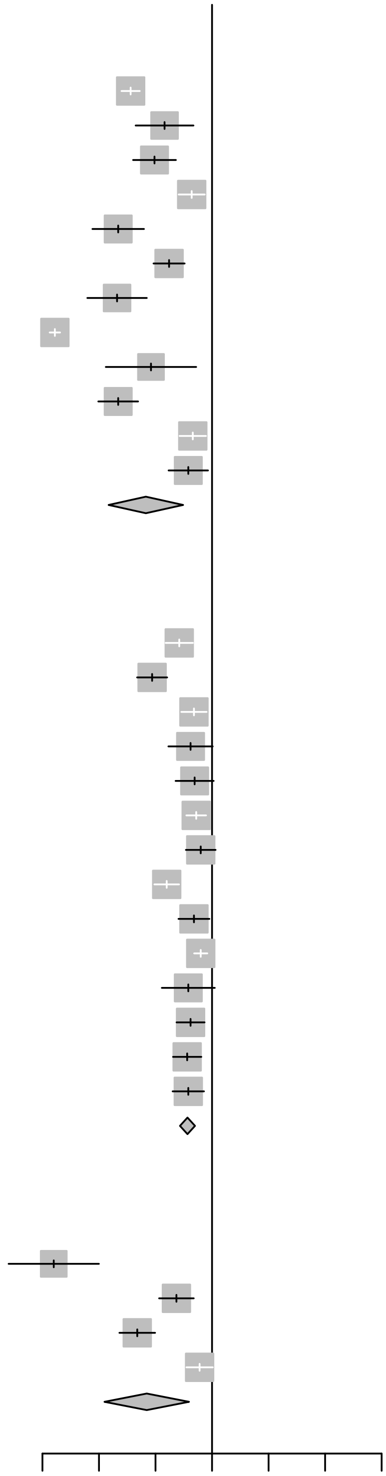
Excluding washout studies

Last period

```r
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	1.31	21	-4.2 [-6.8; -1.6]
Mierzejewski et al. (2008)	-5.1	0.97	25	-5.1 [-7.0; -3.2]
Tham et al. (2008)	-1.8	0.59	35	-1.8 [-3.0; -0.6]
Tham et al. (2009)	-8.3	1.16	27	-8.3 [-10.6; -6.0]
Liu et al. (2011)	-3.8	0.70	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	0.24	44	-13.9 [-14.4; -13.4]
Dias-Santos (2015)	-5.4	2.04	15	-5.4 [-9.4; -1.4]
Moghimi et al. (2015)	-8.3	0.90	46	-8.3 [-10.1; -6.5]
Lee et al. (2016)	-1.7	0.60	56	-1.7 [-2.9; -0.5]
Siak et al. (2016)	-2.1	0.89	24	-2.1 [-3.8; -0.4]
Random effects model			.	**-5.9 [-9.1; -2.6]**
Heterogeneity: $I^2 = 99\%$, $\tau^2 = 32.88$, $p < 0.01$				
subtype = OAG				
Kim et al. (1999)	-2.9	0.62	31	-2.9 [-4.1; -1.7]
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	1.20	17	-2.1 [-4.4; 0.2]
Iancu et al. (2014)	-1.9	0.63	38	-1.9 [-3.1; -0.7]
Siegel et al. (2015)	-2.2	0.64	52	-2.2 [-3.5; -0.9]
Siak et al. (2016)	-2.1	0.71	30	-2.1 [-3.5; -0.7]
Random effects model			.	**-2.2 [-2.8; -1.5]**
Heterogeneity: $I^2 = 76\%$, $\tau^2 = 1.154$, $p < 0.01$				
subtype = PXG				
Jacobi et al. (1999)	-14.0	2.04	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	0.59	51	-1.1 [-2.3; 0.1]
Random effects model			.	**-5.8 [-9.5; -2.0]**
Heterogeneity: $I^2 = 95\%$, $\tau^2 = 13.25$, $p < 0.01$				



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>
```

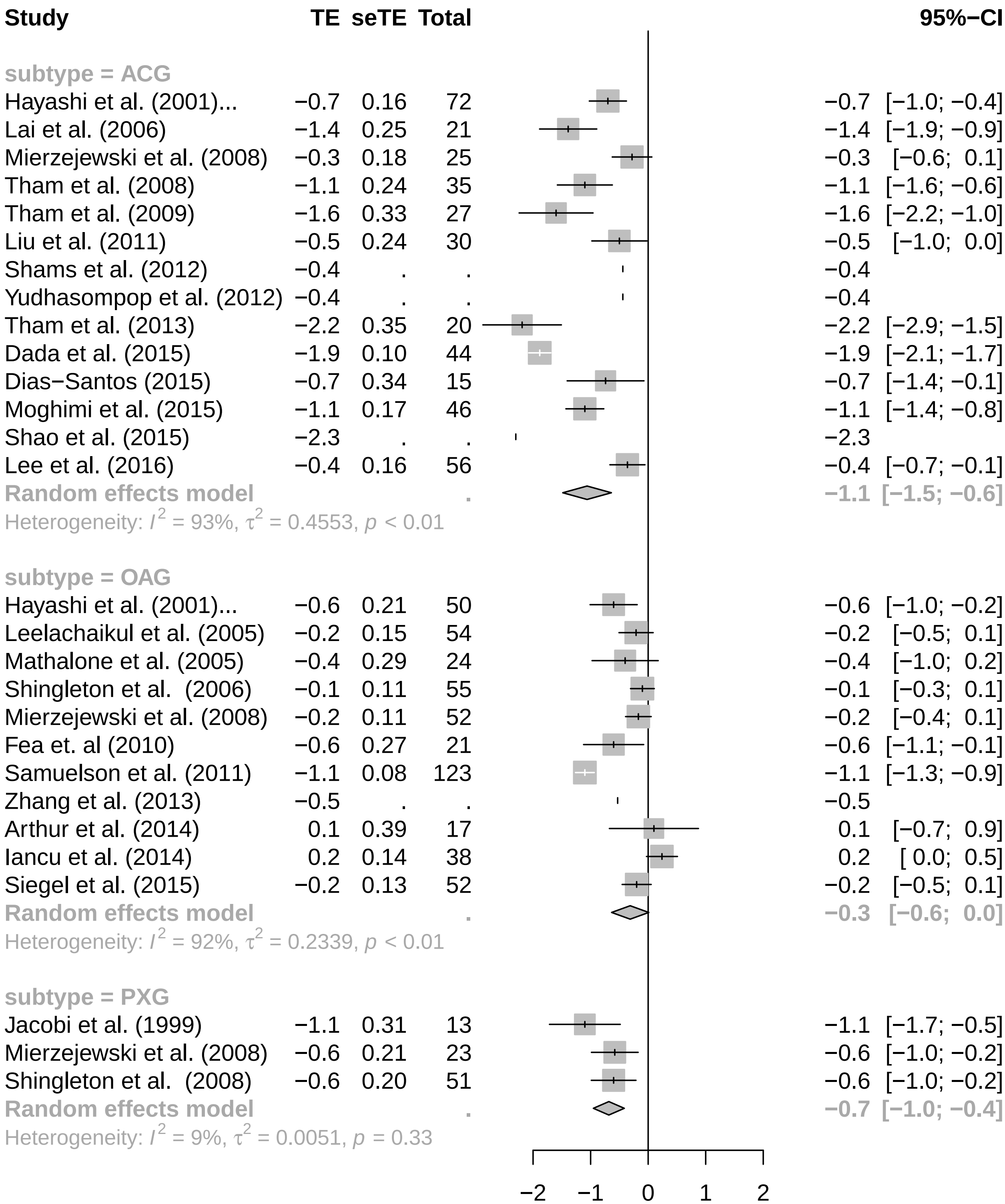
```
## Warning in grid.Call.graphics(L_text, as.graphicsAnnot(x$label), x$x, x
## $y, : conversion failure on 'Hayashi et al. (2001)†' in 'mbcsToSbcs': dot
## substituted for <80>
```

```
## 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>
```



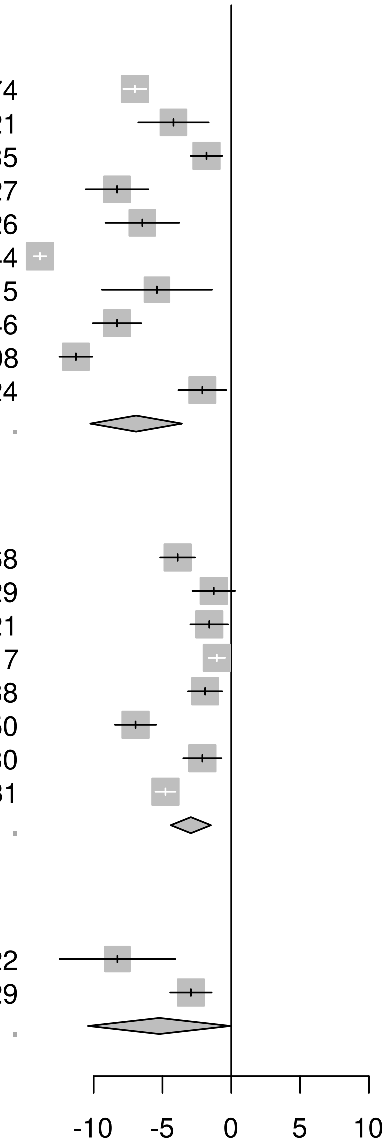
Sensitivity to missingness

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(
```

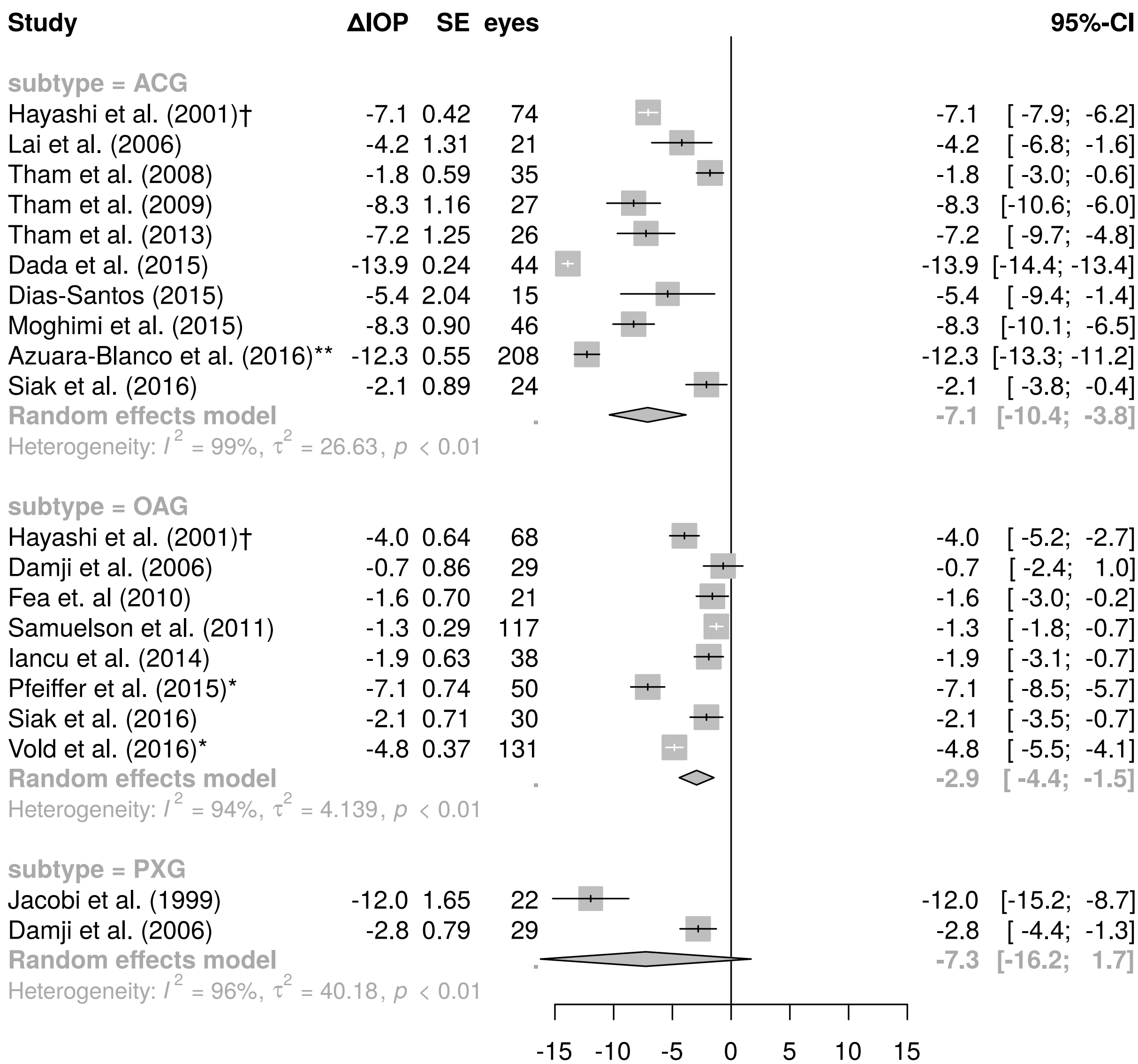
Simulated net change IOP when ΔIOP = 0 in eyes lost to follow up

Study	ΔIOP	SE	eyes	95%-CI
subtype = ACG				
Hayashi et al. (2001)†	-7.0	0.43	74	-7.0 [-7.8; -6.2]
Lai et al. (2006)	-4.2	1.31	21	-4.2 [-6.8; -1.6]
Tham et al. (2008)	-1.8	0.59	35	-1.8 [-3.0; -0.6]
Tham et al. (2009)	-8.3	1.16	27	-8.3 [-10.6; -6.0]
Tham et al. (2013)	-6.5	1.37	26	-6.5 [-9.1; -3.8]
Dada et al. (2015)	-13.9	0.24	44	-13.9 [-14.4; -13.4]
Dias-Santos (2015)	-5.4	2.04	15	-5.4 [-9.4; -1.4]
Moghimi et al. (2015)	-8.3	0.90	46	-8.3 [-10.1; -6.5]
Azuara-Blanco et al. (2016)**	-11.3	0.61	208	-11.3 [-12.5; -10.1]
Siak et al. (2016)	-2.1	0.89	24	-2.1 [-3.8; -0.4]
Random effects model			.	**-6.9 [-10.2; -3.6]**
Heterogeneity: $I^2 = 99\%$, $\tau^2 = 27.68$, $p < 0.01$				
subtype = OAG				
Hayashi et al. (2001)†	-3.9	0.65	68	-3.9 [-5.2; -2.6]
Damji et al. (2006)	-1.3	0.79	29	-1.3 [-2.8; 0.3]
Fea et. al (2010)	-1.6	0.70	21	-1.6 [-3.0; -0.2]
Samuelson et al. (2011)	-1.1	0.30	117	-1.1 [-1.6; -0.5]
Iancu et al. (2014)	-1.9	0.63	38	-1.9 [-3.1; -0.7]
Pfeiffer et al. (2015)*	-7.0	0.76	50	-7.0 [-8.4; -5.5]
Siak et al. (2016)	-2.1	0.71	30	-2.1 [-3.5; -0.7]
Vold et al. (2016)*	-4.8	0.37	131	-4.8 [-5.5; -4.1]
Random effects model			.	**-2.9 [-4.4; -1.5]**
Heterogeneity: $I^2 = 93\%$, $\tau^2 = 4.038$, $p < 0.01$				
subtype = PXG				
Jacobi et al. (1999)	-8.3	2.15	22	-8.3 [-12.5; -4.1]
Damji et al. (2006)	-2.9	0.77	29	-2.9 [-4.4; -1.4]
Random effects model			.	**-5.2 [-10.4; 0.0]**
Heterogeneity: $I^2 = 82\%$, $\tau^2 = 11.66$, $p = 0.02$				




```
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)
```

```r
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"))
```