Phaco meta analysis

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14/02/2017

Load data

We load data from a CSV exported from Stata. The `Mo` variables refer to what happens after 6 months. The letter variables `Z`, `AA` etc. refer to what happens after 12 months. That's a bug in how Stata exports names of variables which start with a number - the columns were named `6mo...` and `12mo...`.

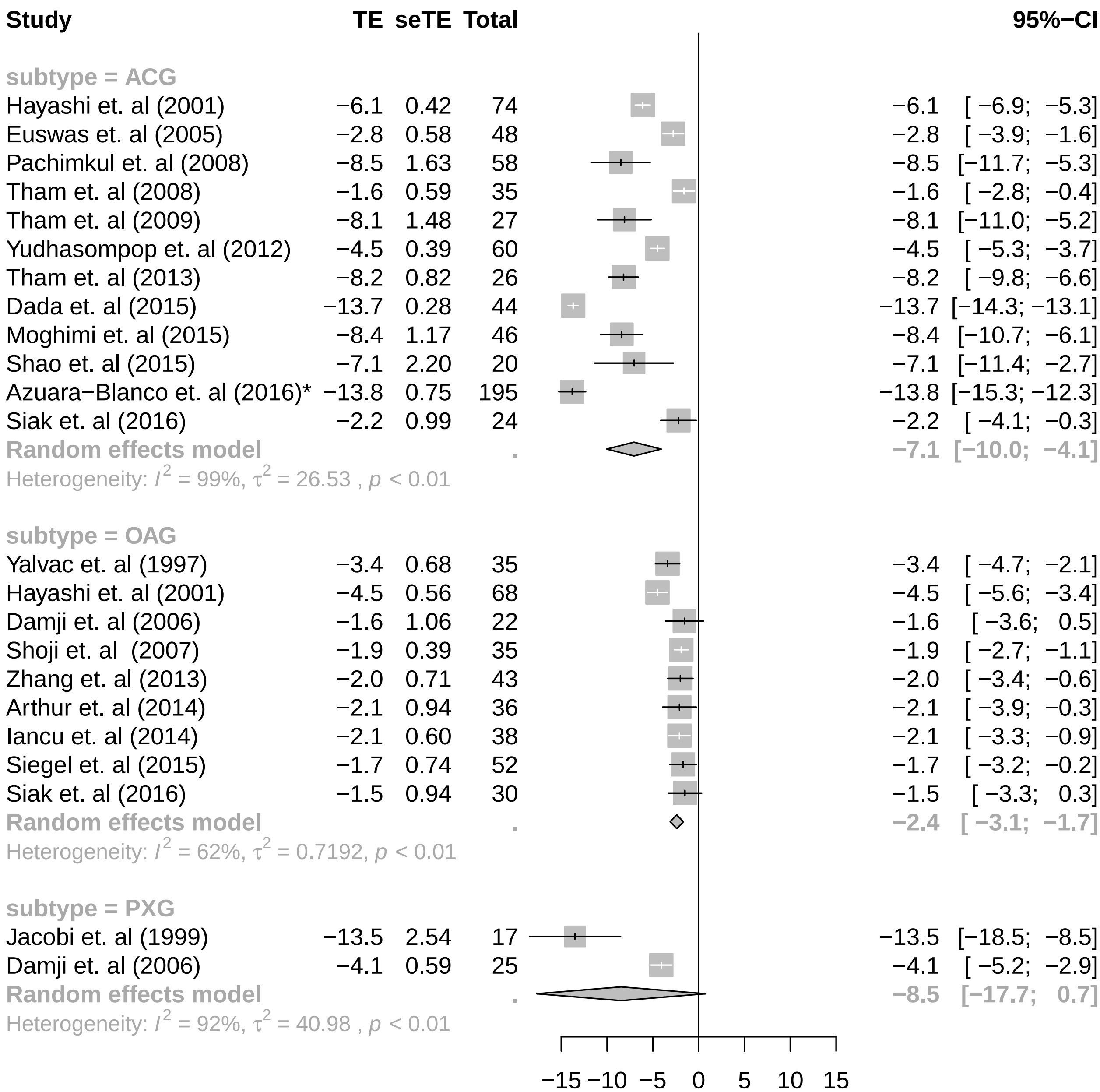
```
## Loading tidyverse: ggplot2
## Loading tidyverse: tibble
## Loading tidyverse: tidyr
## Loading tidyverse: readr
## Loading tidyverse: purrr
## Loading tidyverse: dplyr

## Conflicts with tidy packages ----------------------------------------------

## filter(): dplyr, stats
## lag():    dplyr, stats

## Loading 'meta' package (version 4.7-0).
## Type 'help("meta-package")' for a brief overview.

##
## Attaching package: 'testthat'

## The following object is masked from 'package:dplyr':
##
##     matches

## The following object is masked from 'package:purrr':
##
##     is_null

## In anonymous test function
## This study only has some eye number information missing, fix it:
## Vold et.al (2016)*

## This study only has some eye number information missing, fix it:
## Vold et.al (2016)*
```

Full analysis

6 month follow-up

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

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

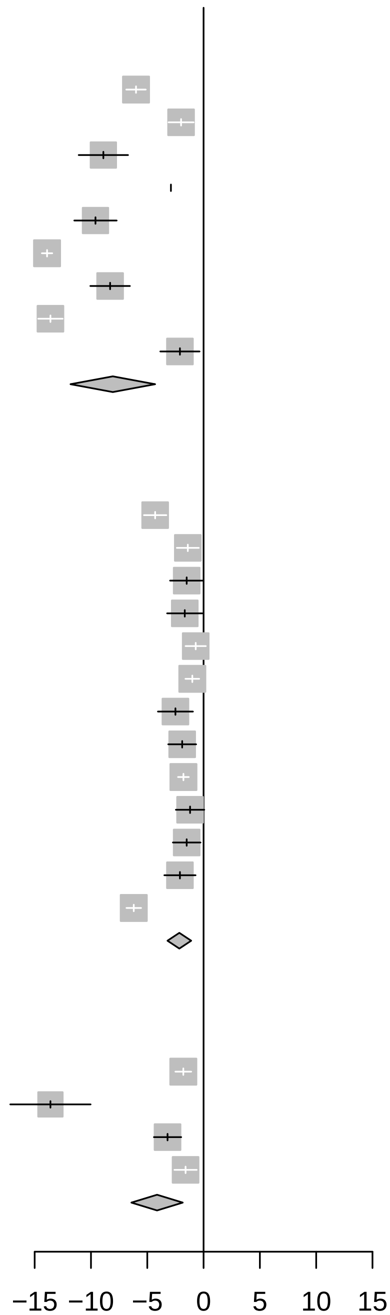


12-month follow up

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

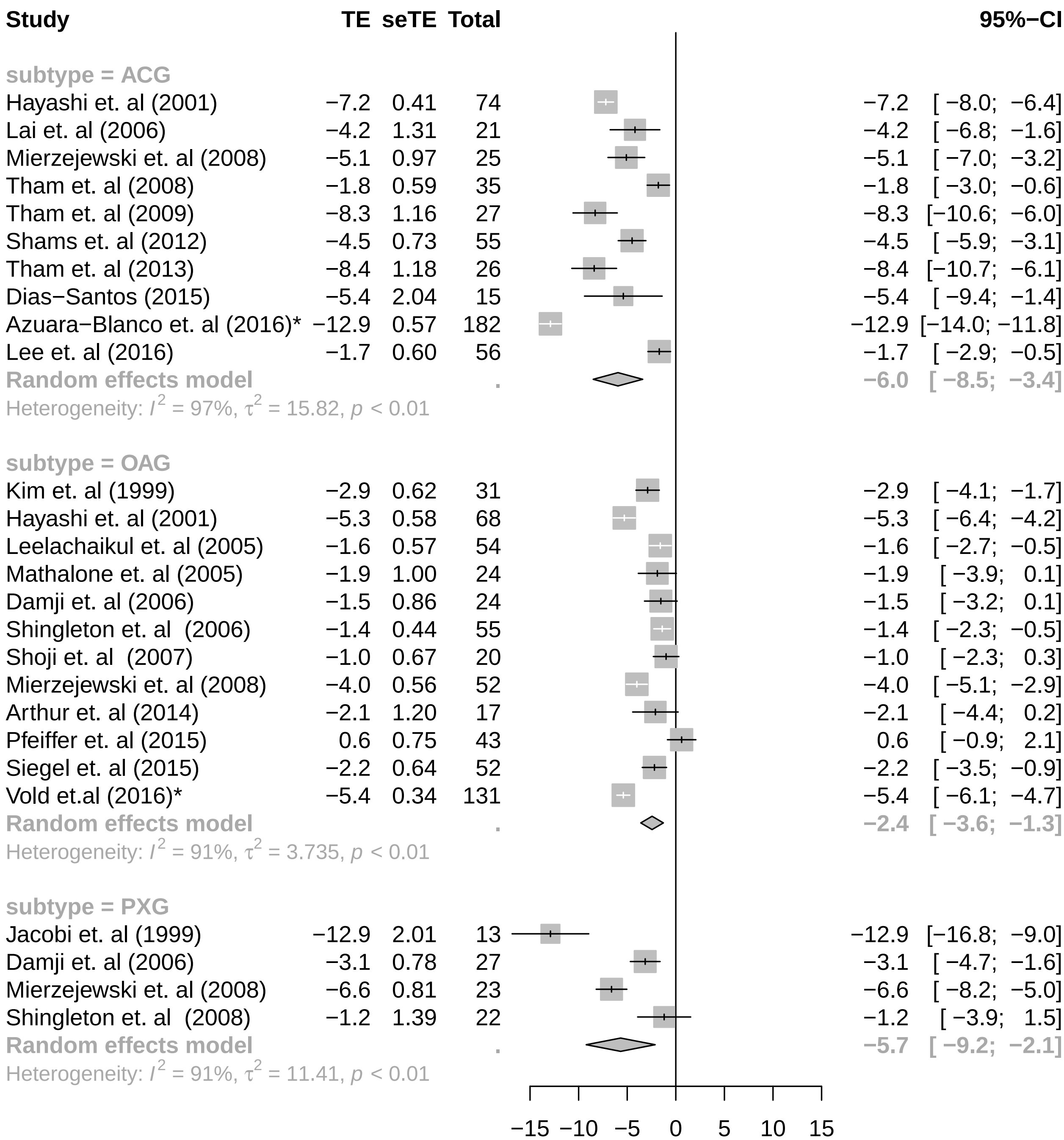
```
              OneYAbsIOPChangeStdDev / sqrt(OneYEyes),
              study.name,
              data=df_,
              byvar=subtype,
              n.e=OneYEyes)
forest(m,
       comb.fixed=FALSE,
       digits=1,
       digits.se = 2,
       overall=FALSE,
       leftcols=c("studlab", "TE", "seTE",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

Study	TE	seTE	Total	95%−CI
subtype = ACG				
Hayashi et. al (2001)	−6.0	0.44	74	−6.0 [−6.9; −5.1]
Tham et. al (2008)	−2.0	0.57	35	−2.0 [−3.1; −0.9]
Tham et. al (2009)	−8.9	1.12	27	−8.9 [−11.1; −6.7]
Liu et. al (2011)	−2.9	.	56	−2.9
Tham et. al (2013)	−9.6	0.96	26	−9.6 [−11.5; −7.7]
Dada et. al (2015)	−13.9	0.24	44	−13.9 [−14.4; −13.4]
Moghimi et. al (2015)	−8.3	0.90	46	−8.3 [−10.1; −6.5]
Azuara−Blanco et. al (2016)*	−13.6	0.55	192	−13.6 [−14.7; −12.5]
Siak et. al (2016)	−2.1	0.89	24	−2.1 [−3.8; −0.4]
Random effects model			.	**−8.1 [−11.8; −4.3]**
Heterogeneity: $I^2 = 99\%$, $\tau^2 = 28.83$, $p < 0.01$				
subtype = OAG				
Hayashi et. al (2001)	−4.3	0.51	68	−4.3 [−5.3; −3.3]
Leelachaikul et. al (2005)	−1.4	0.50	58	−1.4 [−2.4; −0.4]
Mathalone et. al (2005)	−1.5	0.75	34	−1.5 [−3.0; 0.0]
Damji et. al (2006)	−1.7	0.80	21	−1.7 [−3.2; −0.1]
Shoji et. al (2007)	−0.7	0.46	32	−0.7 [−1.6; 0.2]
Samuelson et. al (2011)	−1.0	0.31	112	−1.0 [−1.6; −0.4]
Arthur et. al (2014)	−2.5	0.79	34	−2.5 [−4.1; −0.9]
Iancu et. al (2014)	−1.9	0.63	38	−1.9 [−3.1; −0.7]
Slabaugh et. al (2014)	−1.8	0.25	157	−1.8 [−2.3; −1.3]
Pfeiffer et. al (2015)	−1.2	0.64	44	−1.2 [−2.5; 0.1]
Siegel et. al (2015)	−1.5	0.63	52	−1.5 [−2.7; −0.3]
Siak et. al (2016)	−2.1	0.71	30	−2.1 [−3.5; −0.7]
Vold et.al (2016)*	−6.2	0.33	131	−6.2 [−6.9; −5.5]
Random effects model			.	**−2.2 [−3.2; −1.1]**
Heterogeneity: $I^2 = 94\%$, $\tau^2 = 3.419$, $p < 0.01$				
subtype = PXG				
Perasalo et. al (1997)	−1.8	0.36	127	−1.8 [−2.5; −1.1]
Jacobi et. al (1999)	−13.6	1.82	16	−13.6 [−17.2; −10.0]
Damji et. al (2006)	−3.2	0.62	27	−3.2 [−4.4; −2.0]
Shingleton et. al (2008)	−1.6	0.51	111	−1.6 [−2.6; −0.6]
Random effects model			.	**−4.1 [−6.4; −1.8]**
Heterogeneity: $I^2 = 93\%$, $\tau^2 = 4.647$, $p < 0.01$				



Last period

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



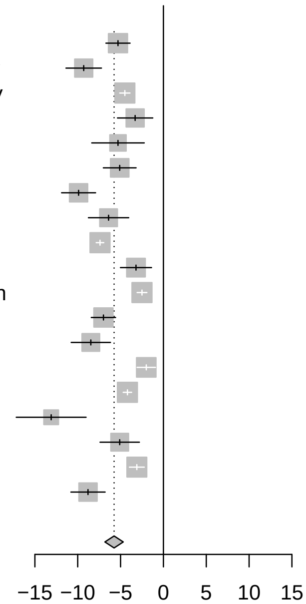
MIGS

```
df_ <- df %>%
  filter(!is.na(df$LastPeriodAbsIOPChangeMean), df$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)
```

```r
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	0.72	49	2 site Microbypass Stent	−5.3 [−6.7; −3.9]	5.6%
Klamann et. al (2013)	−9.3	1.06	27	Ab interno trabeculectomy	−9.3 [−11.4; −7.2]	5.0%
Neiweem et. al (2016)	−4.5	0.31	352	Ab Interno Trabeculectomy	−4.5 [−5.1; −3.9]	6.1%
Khan et. al (2015)	−3.3	1.05	52	Ab interno Trabeculotomy	−3.3 [−5.4; −1.2]	5.0%
Arthur et. al (2014)	−5.3	1.56	11	Canaloplasty	−5.3 [−8.4; −2.2]	4.1%
Schoenberg et. al (2015)	−5.1	0.98	36	Canaloplasty	−5.1 [−7.0; −3.2]	5.2%
Tetz et. al (2015)	−9.9	1.01	27	Canaloplasty	−9.9 [−11.9; −7.9]	5.1%
Rekas et. al (2015)	−6.4	1.20	29	Canoloplasty	−6.4 [−8.8; −4.0]	4.8%
Vold et.al (2016)*	−7.4	0.23	374	Cypass	−7.4 [−7.8; −7.0]	6.1%
Sheybani et. al (2015)	−3.2	0.93	83	ECP	−3.2 [−5.0; −1.4]	5.3%
Siegel et. al (2015)	−2.5	0.29	261	Endocyclophotocoagulation	−2.5 [−3.1; −1.9]	6.1%
Sheybani et. al (2015)	−7.0	0.72	34	Gelatin stent	−7.0 [−8.4; −5.6]	5.6%
Shao et. al (2015)	−8.5	1.17	23	Goniosynechialysis	−8.5 [−10.8; −6.2]	4.8%
Pfeiffer et. al (2015)	−2.0	0.55	47	Hydrus Microstent	−2.0 [−3.1; −0.9]	5.8%
Parikh et. al (2016)	−4.2	0.25	498	Trabectome	−4.2 [−4.7; −3.7]	6.1%
Jacobi et. al (1999)	−13.1	2.08	13	Trabecular Aspiration	−13.1 [−17.2; −9.0]	3.3%
Klamann et. al (2013)	−5.1	1.17	28	Trabecular Aspiration	−5.1 [−7.4; −2.8]	4.8%
Shoji et. al (2007)	−3.1	0.44	16	Viscocanalostomy	−3.1 [−4.0; −2.2]	6.0%
Moghimi et. al (2015)	−8.8	1.02	45	Viscogonioplasty	−8.8 [−10.8; −6.8]	5.1%
Random effects model			**2005**		**−5.8 [−6.8; −4.7]**	**100.0%**

Heterogeneity: $I^2 = 95\%$, $\tau^2 = 4.82$, $p < 0.01$



Acute

```r
cat("===========================================================================\n")
```

```
## ===========================================================================
```

```r
cat("Six months: \n")
```

```
## Six months:
```

```r
cat("===========================================================================\n")
```

```
## ===========================================================================
```

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

```
##                                          95%-CI %W(random)
## Lam et. al (2008) -47.0000 [-51.0521; -42.9479]       50.2
## Hou et. al (2015) -38.2000 [-42.4159; -33.9841]       49.8
```

```
##
## Number of studies combined: k = 2
##
##                                           95%-CI     z  p-value
## Random effects model -42.62 [-51.2438; -33.9963] -9.69 < 0.0001
##
## Quantifying heterogeneity:
##  tau^2 = 34.2694; H = 2.95; I^2 = 88.5%;
##  Rb = 88.5%
##
## Test of heterogeneity:
##     Q d.f.  p-value
##  8.70    1   0.0032
##
## Details on meta-analytical method:
## - Inverse variance method
## - DerSimonian-Laird estimator for tau^2
```

```r
cat("========================================================================\n")
```

```
## ========================================================================
```

```r
cat("One year: \n")
```

```
## One year:
```

```r
cat("========================================================================\n")
```

```
## ========================================================================
```

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

```
##                                          95%-CI %W(random)
## Lam et. al (2008) -47.6000 [-50.4731; -44.7269]       50.1
## Hou et. al (2015) -35.9600 [-38.9540; -32.9660]       49.9
##
## Number of studies combined: k = 2
##
##                                             95%-CI     z  p-value
## Random effects model -41.7879 [-53.1949; -30.3809] -7.18 < 0.0001
##
## Quantifying heterogeneity:
##  tau^2 = 65.5036; H = 5.50; I^2 = 96.7%;
##  Rb = 96.7%
##
## Test of heterogeneity:
##      Q d.f.  p-value
##  30.23    1 < 0.0001
##
```

```
## Details on meta-analytical method:
## - Inverse variance method
## - DerSimonian-Laird estimator for tau^2
```

```r
cat("========================================================================\n")
```

```
## ========================================================================
```

```r
cat("Last period: \n")
```

```
## Last period:
```

```r
cat("========================================================================\n")
```

```
## ========================================================================
```

```r
df_ <- df %>%
  filter(!is.na(df$LastPeriodAbsIOPChangeMean), df$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]       25.6
## Lam et. al (2008)    -47.1000 [-49.9970; -44.2030]       25.3
## Lee et. al (2010)    -35.8000 [-39.5586; -32.0414]       25.1
## Husain et. al (2012) -44.5000 [-51.8668; -37.1332]       24.0
##
## Number of studies combined: k = 4
##
##                                           95%-CI     z  p-value
## Random effects model -37.399 [-51.7586; -23.0395] -5.10 < 0.0001
##
## Quantifying heterogeneity:
##  tau^2 = 209.7798; H = 10.00 [8.16; 12.24]; I^2 = 99.0% [98.5%; 99.3%];
##  Rb = 97.7% [93.2%; 100.0%]
##
## Test of heterogeneity:
##       Q d.f.  p-value
##  299.84    3 < 0.0001
##
## Details on meta-analytical method:
## - Inverse variance method
## - DerSimonian-Laird estimator for tau^2
```

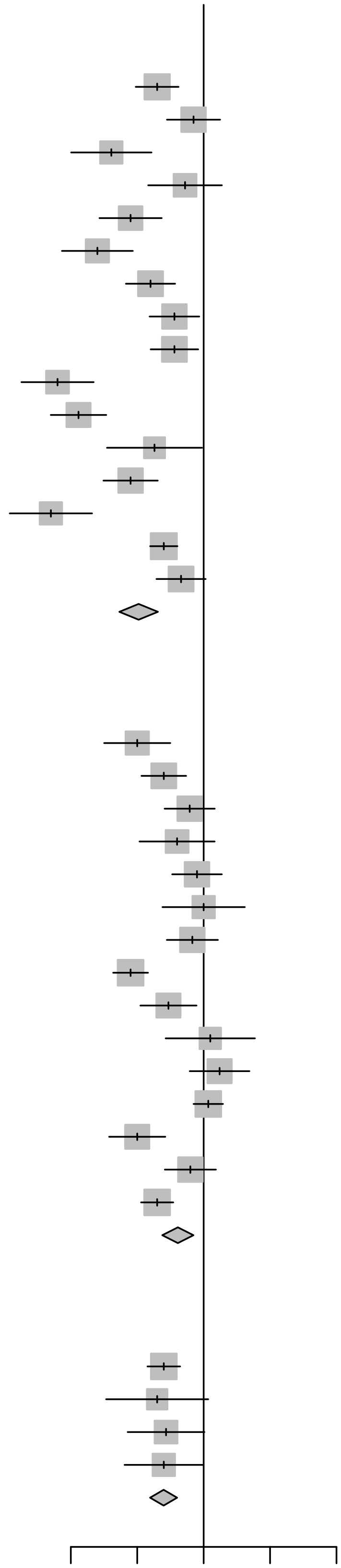
Meds

TODO(Patrick): Figure out a less hacky way of doing this. Wait for answers on this question

```r
df_ <- df %>%
  filter(!is.na(df$RxPostOpMean), !is.na(df$RxPreOpMean), df$subtype != "acute", MIGsYorN == 'N') %>%
  mutate(subtype=factor(subtype), LastPeriodEyes = ifelse(is.na(LastPeriodEyes), OneYEyes, LastPeriodEy
m <- metagen(RxPostOpMean - RxPreOpMean,
```

```
             sqrt(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"))
```

Study	TE	seTE	Total		95%−CI
subtype = ACG					
Hayashi et. al (2001)	−0.7	0.16	74	−0.7	[−1.0; −0.4]
Euswas et. al (2005)	−0.2	0.20	48	−0.2	[−0.6; 0.2]
Lai et. al (2006)	−1.4	0.31	21	−1.4	[−2.0; −0.8]
Mierzejewski et. al (2008)	−0.3	0.28	25	−0.3	[−0.8; 0.3]
Tham et. al (2008)	−1.1	0.24	35	−1.1	[−1.6; −0.6]
Tham et. al (2009)	−1.6	0.27	27	−1.6	[−2.1; −1.1]
Liu et. al (2011)	−0.8	0.19	56	−0.8	[−1.2; −0.4]
Shams et. al (2012)	−0.4	0.19	55	−0.4	[−0.8; −0.1]
Yudhasompop et. al (2012)	−0.4	0.18	60	−0.4	[−0.8; −0.1]
Tham et. al (2013)	−2.2	0.28	26	−2.2	[−2.7; −1.7]
Dada et. al (2015)	−1.9	0.21	44	−1.9	[−2.3; −1.5]
Dias−Santos (2015)	−0.7	0.37	15	−0.7	[−1.5; 0.0]
Moghimi et. al (2015)	−1.1	0.21	46	−1.1	[−1.5; −0.7]
Shao et. al (2015)	−2.3	0.32	20	−2.3	[−2.9; −1.7]
Azuara−Blanco et. al (2016)*	−0.6	0.10	182	−0.6	[−0.8; −0.4]
Lee et. al (2016)	−0.3	0.19	56	−0.3	[−0.7; 0.0]
Random effects model			.	**−1.0**	**[−1.3; −0.7]**
Heterogeneity: $I^2 = 88\%$, $\tau^2 = 0.2966$, $p < 0.01$					
subtype = OAG					
Kim et. al (1999)	−1.0	0.25	31	−1.0	[−1.5; −0.5]
Hayashi et. al (2001)	−0.6	0.17	68	−0.6	[−0.9; −0.3]
Leelachaikul et. al (2005)	−0.2	0.19	54	−0.2	[−0.6; 0.2]
Mathalone et. al (2005)	−0.4	0.29	24	−0.4	[−1.0; 0.2]
Shingleton et. al (2006)	−0.1	0.19	55	−0.1	[−0.5; 0.3]
Shoji et. al (2007)	0.0	0.32	20	0.0	[−0.6; 0.6]
Mierzejewski et. al (2008)	−0.2	0.20	52	−0.2	[−0.6; 0.2]
Samuelson et. al (2011)	−1.1	0.13	112	−1.1	[−1.4; −0.8]
Zhang et. al (2013)	−0.5	0.22	43	−0.5	[−1.0; −0.1]
Arthur et. al (2014)	0.1	0.34	17	0.1	[−0.6; 0.8]
Iancu et. al (2014)	0.2	0.23	38	0.2	[−0.2; 0.7]
Slabaugh et. al (2014)	0.1	0.11	157	0.1	[−0.2; 0.3]
Pfeiffer et. al (2015)	−1.0	0.22	43	−1.0	[−1.4; −0.6]
Siegel et. al (2015)	−0.2	0.20	52	−0.2	[−0.6; 0.2]
Vold et.al (2016)*	−0.7	0.12	131	−0.7	[−0.9; −0.5]
Random effects model			.	**−0.4**	**[−0.6; −0.2]**
Heterogeneity: $I^2 = 83\%$, $\tau^2 = 0.1701$, $p < 0.01$					
subtype = PXG					
Perasalo et. al (1997)	−0.6	0.13	127	−0.6	[−0.8; −0.4]
Jacobi et. al (1999)	−0.7	0.39	13	−0.7	[−1.5; 0.1]
Mierzejewski et. al (2008)	−0.6	0.29	23	−0.6	[−1.1; 0.0]
Shingleton et. al (2008)	−0.6	0.30	22	−0.6	[−1.2; 0.0]
Random effects model			.	**−0.6**	**[−0.8; −0.4]**
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.99$					



Retrospective only

TODO(Patrick): Do this analysis.

Sensitivity analysis

TODO(Patrick): Do this analysis.

Correlation between meds and drop in IOP

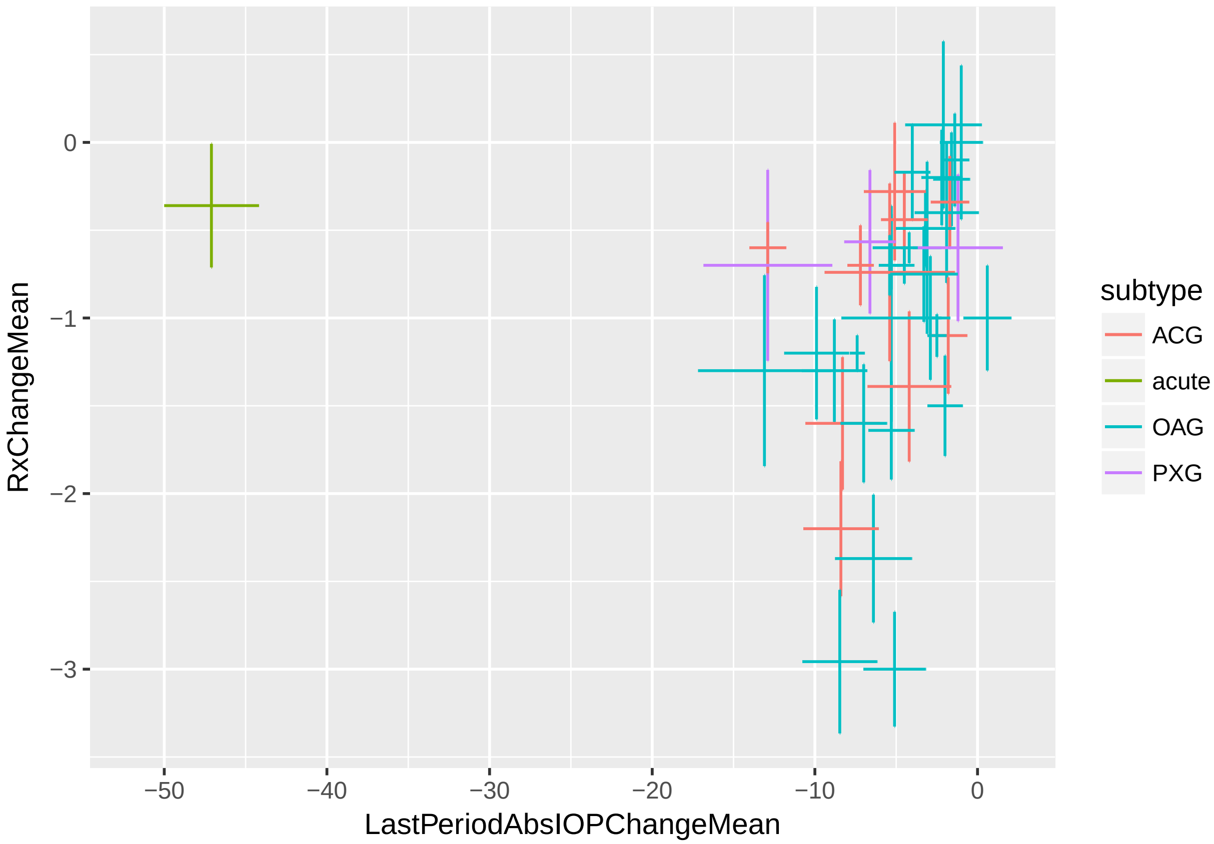
How is IOP drop related to change in meds? Two hypotheses:

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

So which is it?

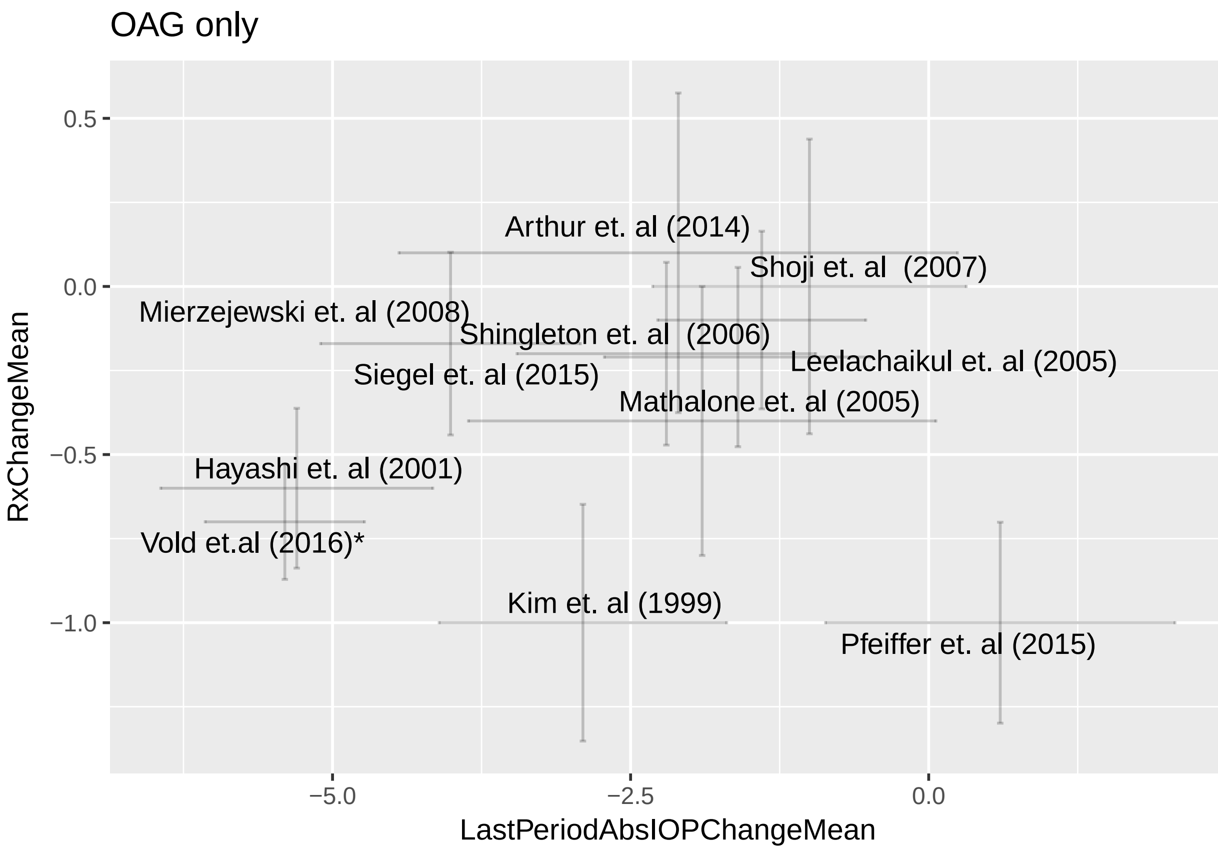
```
df_ <- df %>% mutate(RxChangeMean = RxPostOpMean - RxPreOpMean,
                     RxChangeSEM  = sqrt(1 / ifelse(is.na(LastPeriodEyes), OneYEyes, LastPeriodEyes)),
                     LastPeriodAbsIOPChangeSEM = LastPeriodAbsIOPChangeStdDev / sqrt(LastPeriodEyes))

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

```
## Warning: Removed 24 rows containing missing values (geom_errorbar).

## Warning: Removed 24 rows containing missing values (geom_errorbarh).
```




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

```
## Warning: Removed 7 rows containing missing values (geom_errorbar).

## Warning: Removed 7 rows containing missing values (geom_errorbarh).

## Warning: Removed 7 rows containing missing values (geom_text_repel).
```



In fact, apart from the Pfeiffer et al. (2015) study, 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, without Pfeiffer et al\n")
```

```
## Mean +- SE correlation, without Pfeiffer et al
```

```
df_ <- df %>% filter(!(study.name %in% c("Pfeiffer et. al (2015)")), subtype=='OAG', MIGsYorN == 'N')
drawn.corrs <- with(df_, replicate(n = 100,
                                   draw.corr(LastPeriodAbsIOPChangeMean,
                                             LastPeriodAbsIOPChangeStdDev / sqrt(LastPeriodEyes),
                                             RxPostOpMean - RxPreOpMean,
                                             1 / sqrt(LastPeriodEyes))))
mean(drawn.corrs)
```

```
## [1] 0.5040158
```

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

```
## [1] 0.1691644
```

```
cat("Mean +- SE correlation, with Pfeiffer et al\n")
```

```
## Mean +- SE correlation, with Pfeiffer et al
```

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

```
## [1] 0.1153128
```

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

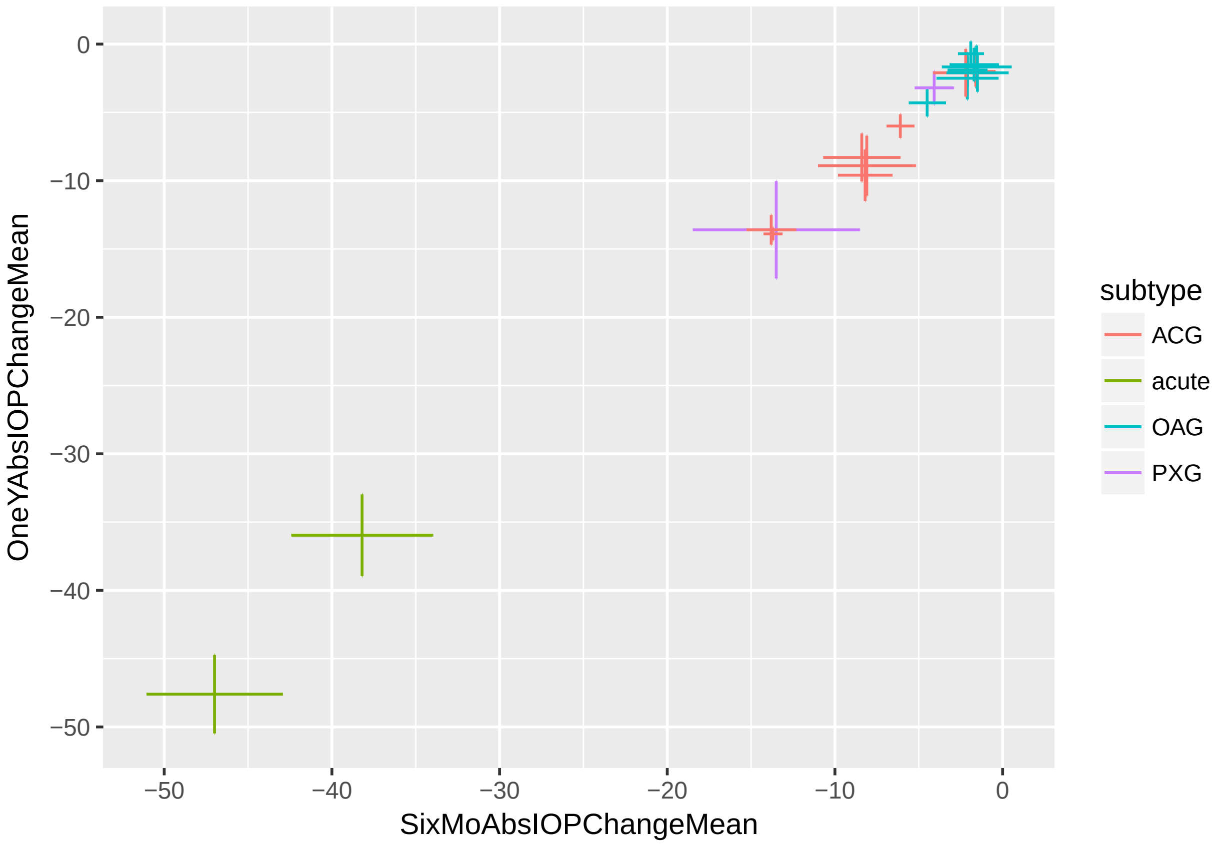
```
## [1] 0.1568103
```

Joint inferences

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

```r
ggplot(df, aes(x    =SixMoAbsIOPChangeMean,
               xmin=SixMoAbsIOPChangeMean - 1.96*SixMoAbsIOPChangeStdDev / sqrt(SixMoEyes),
               xmax=SixMoAbsIOPChangeMean + 1.96*SixMoAbsIOPChangeStdDev / sqrt(SixMoEyes),
               y    = OneYAbsIOPChangeMean,
               ymin= OneYAbsIOPChangeMean - 1.96*OneYAbsIOPChangeStdDev / sqrt(OneYEyes),
               ymax= OneYAbsIOPChangeMean + 1.96*OneYAbsIOPChangeStdDev / sqrt(OneYEyes),
               label=study.name,
               color=subtype
               )) + geom_errorbar() + geom_errorbarh()
```

```
## Warning: Removed 47 rows containing missing values (geom_errorbar).

## Warning: Removed 47 rows containing missing values (geom_errorbarh).
```



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

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

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

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

```
## [1] 0.5800933
```

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

```
## [1] 0.1949443
```

```
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] 0.9925106
```

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

```
## [1] 0.003868571
```

That's really high. 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)
  }
  S
}

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

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

summary(thefit)
```

```
## Call:  mvmeta(formula = cbind(SixMoAbsIOPChangeMean, OneYAbsIOPChangeMean,
##     LastPeriodAbsIOPChangeMean) ~ subtype, S = get.correlation.matrices.tri(df_$SixMoAbsIOPChangeStdI
##     df_$OneYAbsIOPChangeStdDev/sqrt(df_$OneYEyes), df_$LastPeriodAbsIOPChangeStdDev/sqrt(df_$LastPeri
##     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)   -6.1992      0.7259  -8.5402    0.0000   -7.6219   -4.7765
## subtypeOAG     3.6467      0.9944   3.6672    0.0002    1.6977    5.5956
##
## (Intercept)  ***
## subtypeOAG   ***
## OneYAbsIOPChangeMean :
##              Estimate  Std. Error        z  Pr(>|z|)  95%ci.lb  95%ci.ub
## (Intercept)   -6.4438      0.7290  -8.8395    0.0000   -7.8726   -5.0150
## subtypeOAG     4.1465      0.9873   4.2000    0.0000    2.2115    6.0815
##
## (Intercept)  ***
## subtypeOAG   ***
## LastPeriodAbsIOPChangeMean :
##              Estimate  Std. Error        z  Pr(>|z|)  95%ci.lb  95%ci.ub
## (Intercept)   -6.2258      0.7086  -8.7856    0.0000   -7.6147   -4.8369
## subtypeOAG     3.9724      0.9639   4.1212    0.0000    2.0832    5.8616
##
## (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          2.7239  SixMoAbsIOPChangeMean
## OneYAbsIOPChangeMean           2.7247                 0.9949
## LastPeriodAbsIOPChangeMean     2.6038                 0.9735
##
## SixMoAbsIOPChangeMean       OneYAbsIOPChangeMean
## OneYAbsIOPChangeMean
## LastPeriodAbsIOPChangeMean                0.9601
##
## Multivariate Cochran Q-test for residual heterogeneity:
## Q = 1431.9589 (df = 58), p-value = 0.0000
## I-square statistic = 95.9%
##
## 35 studies, 64 observations, 6 fixed and 6 random-effects parameters
##    logLik        AIC        BIC
## -113.8315   251.6630   276.3884
```

```
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]
```

```r
newdata$LastPeriodAbsIOPChangeSEM <- pred$se[,3]

library(reshape2)
```

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

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

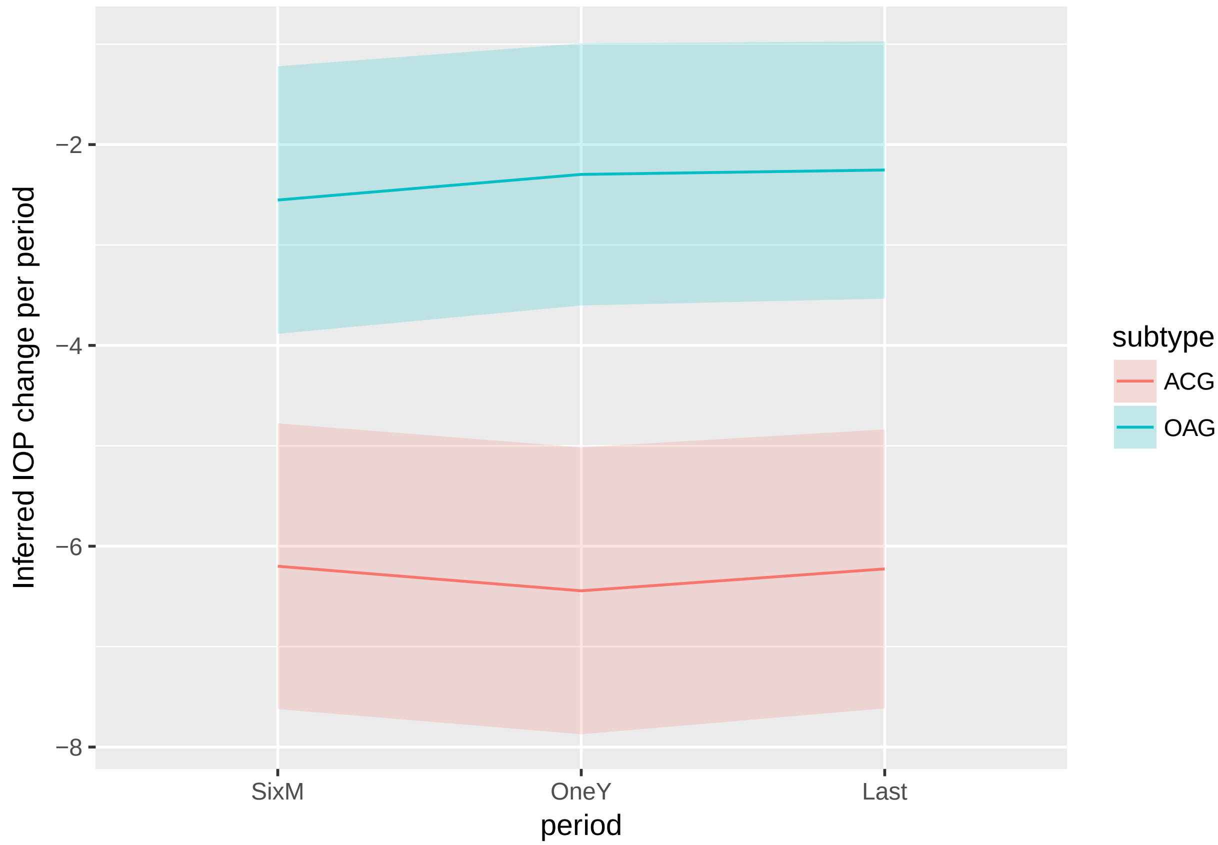
```r
nd <- melt(newdata)
```

```
## 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))
nd
```

```
##    subtype                   variable      value period metric
## 1      OAG      SixMoAbsIOPChangeMean -2.5525274   SixM   Mean
## 2      ACG      SixMoAbsIOPChangeMean -6.1991907   SixM   Mean
## 3      OAG       OneYAbsIOPChangeMean -2.2973087   OneY   Mean
## 4      ACG       OneYAbsIOPChangeMean -6.4438172   OneY   Mean
## 5      OAG LastPeriodAbsIOPChangeMean -2.2533934   Last   Mean
## 6      ACG LastPeriodAbsIOPChangeMean -6.2257786   Last   Mean
## 7      OAG       SixMoAbsIOPChangeSEM  0.6796425   SixM   eSEM
## 8      ACG       SixMoAbsIOPChangeSEM  0.7258840   SixM   eSEM
## 9      OAG        OneYAbsIOPChangeSEM  0.6657829   OneY   eSEM
## 10     ACG        OneYAbsIOPChangeSEM  0.7289839   OneY   eSEM
## 11     OAG  LastPeriodAbsIOPChangeSEM  0.6533949   Last   eSEM
## 12     ACG  LastPeriodAbsIOPChangeSEM  0.7086335   Last   eSEM
```

```r
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

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

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

```
## Warning in metafor::rma.uni(yi = TE, sei = seTE, data = dataset, mods =
## formula, : Studies with NAs omitted from model fitting.
```

```
##
## Mixed-Effects Model (k = 25; tau^2 estimator: DL)
##
## tau^2 (estimated amount of residual heterogeneity):     26.0988 (SE = 10.3971)
## tau (square root of estimated tau^2 value):             5.1087
## I^2 (residual heterogeneity / unaccounted variability): 99.06%
## H^2 (unaccounted variability / sampling variability):   106.36
## R^2 (amount of heterogeneity accounted for):            0.00%
##
```

```
## Test for Residual Heterogeneity:
## QE(df = 23) = 2446.2014, p-val < .0001
##
## Test of Moderators (coefficient(s) 2):
## QM(df = 1) = 0.1338, p-val = 0.7146
##
## Model Results:
##
##          estimate      se     zval    pval    ci.lb    ci.ub
## intrcpt   -3.9455  1.7253  -2.2869  0.0222  -7.3269  -0.5640  *
## OneYEyes  -0.0080  0.0220  -0.3657  0.7146  -0.0512   0.0351
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

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

```
## Warning in metafor::rma.uni(yi = TE, sei = seTE, data = dataset, mods =
## formula, : Studies with NAs omitted from model fitting.

##
## Mixed-Effects Model (k = 25; tau^2 estimator: DL)
##
## tau^2 (estimated amount of residual heterogeneity):     12.0443 (SE = 5.1857)
## tau (square root of estimated tau^2 value):             3.4705
## I^2 (residual heterogeneity / unaccounted variability): 97.78%
## H^2 (unaccounted variability / sampling variability):   45.10
## R^2 (amount of heterogeneity accounted for):            51.39%
##
## Test for Residual Heterogeneity:
## QE(df = 19) = 856.8799, p-val < .0001
##
## Test of Moderators (coefficient(s) 2,3,4,5,6):
## QM(df = 5) = 20.5253, p-val = 0.0010
##
## Model Results:
##
##                      estimate      se     zval    pval     ci.lb    ci.ub
## intrcpt               -1.2844  1.7626  -0.7287  0.4662   -4.7390   2.1702
## OneYEyes              -0.0136  0.0233  -0.5832  0.5597   -0.0593   0.0321
## subtypeACG            -4.4122  2.5780  -1.7115  0.0870   -9.4651   0.6407
## subtypePXG            -8.2707  3.6917  -2.2403  0.0251  -15.5063  -1.0350
## OneYEyes:subtypeACG   -0.0266  0.0332  -0.7996  0.4240   -0.0917   0.0386
## OneYEyes:subtypePXG    0.0812  0.0436   1.8632  0.0624   -0.0042   0.1665
##
## intrcpt
## OneYEyes
## subtypeACG           .
## subtypePXG           *
## OneYEyes:subtypeACG
## OneYEyes:subtypePXG  .
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

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

```
## Warning in metafor::rma.uni(yi = TE, sei = seTE, data = dataset, mods =
## formula, : Studies with NAs omitted from model fitting.
```

```
##
## Mixed-Effects Model (k = 25; tau^2 estimator: DL)
##
## tau^2 (estimated amount of residual heterogeneity):     23.1680 (SE = 9.5806)
## tau (square root of estimated tau^2 value):             4.8133
## I^2 (residual heterogeneity / unaccounted variability): 98.96%
## H^2 (unaccounted variability / sampling variability):   96.34
## R^2 (amount of heterogeneity accounted for):            6.49%
##
## Test for Residual Heterogeneity:
## QE(df = 23) = 2215.8187, p-val < .0001
##
## Test of Moderators (coefficient(s) 2):
## QM(df = 1) = 0.1409, p-val = 0.7074
##
## Model Results:
##
##          estimate        se     zval    pval      ci.lb     ci.ub
## intrcpt  121.7955  336.3525   0.3621  0.7173  -537.4433  781.0343
## Year      -0.0628    0.1674  -0.3753  0.7074    -0.3908    0.2652
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

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

```
## Warning in metafor::rma.uni(yi = TE, sei = seTE, data = dataset, mods =
## formula, : Studies with NAs omitted from model fitting.
```

```
##
## Mixed-Effects Model (k = 25; tau^2 estimator: DL)
##
## tau^2 (estimated amount of residual heterogeneity):     8.2783 (SE = 3.6738)
## tau (square root of estimated tau^2 value):             2.8772
## I^2 (residual heterogeneity / unaccounted variability): 96.75%
## H^2 (unaccounted variability / sampling variability):   30.79
## R^2 (amount of heterogeneity accounted for):            66.59%
##
## Test for Residual Heterogeneity:
## QE(df = 19) = 584.9775, p-val < .0001
##
## Test of Moderators (coefficient(s) 2,3,4,5,6):
## QM(df = 5) = 23.6796, p-val = 0.0003
##
## Model Results:
##
##                   estimate        se     zval    pval       ci.lb
## intrcpt            49.1972  329.6992   0.1492  0.8814   -597.0013
## Year               -0.0255    0.1640  -0.1557  0.8763     -0.3469
## subtypeACG        609.6700  535.4101   1.1387  0.2548   -439.7146
```

```
## subtypePXG       -757.0909  725.7824  -1.0431  0.2969  -2179.5983
## Year:subtypeACG    -0.3060    0.2662  -1.1496  0.2503     -0.8278
## Year:subtypePXG     0.3768    0.3621   1.0405  0.2981     -0.3329
##                      ci.ub
## intrcpt           695.3958
## Year                0.2958
## subtypeACG       1659.0545
## subtypePXG        665.4165
## Year:subtypeACG     0.2157
## Year:subtypePXG     1.0865
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

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

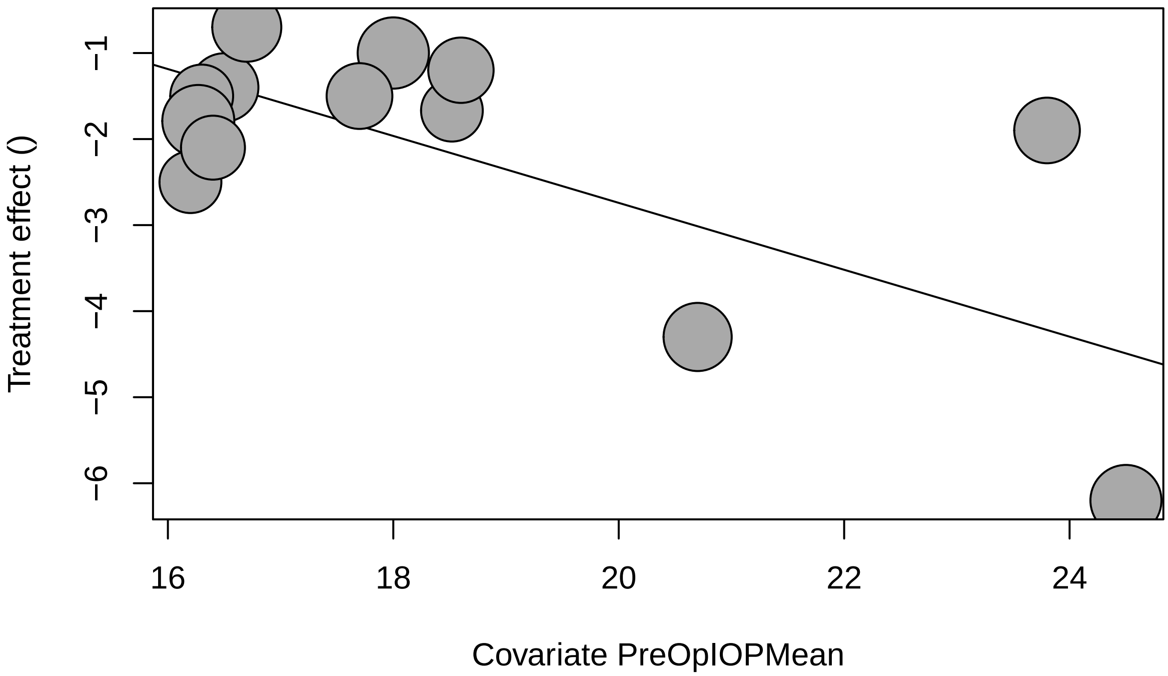
```
## Warning in metafor::rma.uni(yi = TE, sei = seTE, data = dataset, mods =
## formula, : Studies with NAs omitted from model fitting.

##
## Mixed-Effects Model (k = 25; tau^2 estimator: DL)
##
## tau^2 (estimated amount of residual heterogeneity):     3.6153 (SE = 1.4695)
## tau (square root of estimated tau^2 value):             1.9014
## I^2 (residual heterogeneity / unaccounted variability): 93.46%
## H^2 (unaccounted variability / sampling variability):   15.29
## R^2 (amount of heterogeneity accounted for):            85.41%
##
## Test for Residual Heterogeneity:
## QE(df = 23) = 351.6605, p-val < .0001
##
## Test of Moderators (coefficient(s) 2):
## QM(df = 1) = 84.7648, p-val < .0001
##
## Model Results:
##
##               estimate      se     zval    pval    ci.lb    ci.ub
## intrcpt        13.4065  1.9653   6.8218  <.0001   9.5547  17.2584  ***
## PreOpIOPMean   -0.8807  0.0957  -9.2068  <.0001  -1.0682  -0.6932  ***
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

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

```
## Warning in metafor::rma.uni(yi = TE, sei = seTE, data = dataset, mods =
## formula, : Studies with NAs omitted from model fitting.

##
## Mixed-Effects Model (k = 25; tau^2 estimator: DL)
##
## tau^2 (estimated amount of residual heterogeneity):     1.0943 (SE = 0.5213)
## tau (square root of estimated tau^2 value):             1.0461
## I^2 (residual heterogeneity / unaccounted variability): 80.19%
## H^2 (unaccounted variability / sampling variability):   5.05
## R^2 (amount of heterogeneity accounted for):            95.58%
```

```
##
## Test for Residual Heterogeneity:
## QE(df = 19) = 95.9215, p-val < .0001
##
## Test of Moderators (coefficient(s) 2,3,4,5,6):
## QM(df = 5) = 260.3196, p-val < .0001
##
## Model Results:
##
##                          estimate      se     zval    pval    ci.lb
## intrcpt                    5.0459  2.2208   2.2721  0.0231   0.6931
## PreOpIOPMean              -0.3894  0.1184  -3.2903  0.0010  -0.6214
## subtypeACG                 8.9217  3.2024   2.7860  0.0053   2.6452
## subtypePXG                 7.1956  3.7322   1.9280  0.0539  -0.1194
## PreOpIOPMean:subtypeACG   -0.5827  0.1542  -3.7794  0.0002  -0.8849
## PreOpIOPMean:subtypePXG   -0.4109  0.1925  -2.1348  0.0328  -0.7882
##                            ci.ub
## intrcpt                   9.3986    *
## PreOpIOPMean             -0.1575   **
## subtypeACG               15.1983   **
## subtypePXG               14.5105    .
## PreOpIOPMean:subtypeACG  -0.2805  ***
## PreOpIOPMean:subtypePXG  -0.0336    *
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

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

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



Treatment effect ()
−1
−2
−3
−4
−5
−6
16
18
20
22
24
Covariate PreOpIOPMean