Phaco meta analysis

Patrick Mineault

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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...`.

```
library(tidyverse)
```

```
## 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
```

```
library(meta)
```

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

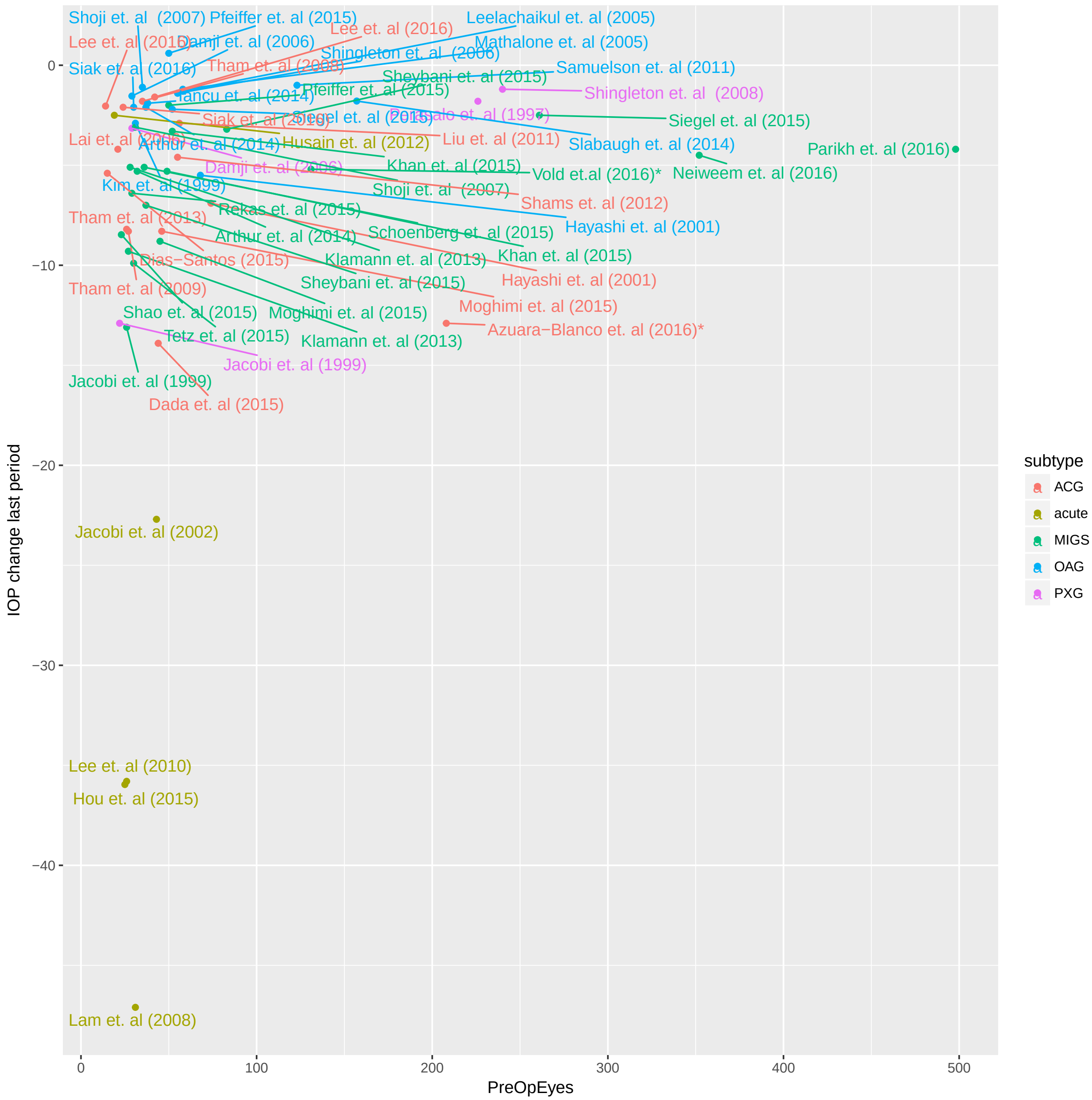
```
library(ggrepel)

setwd("~/Documents/phaco")
df <- read.csv("phaco.csv", na.strings='-')
df <- df %>% rename(SixMoEyes = MoEyes,
              SixMoIOPMean = MoIOPMean,
              SixMoIOPStdDev = MoIOPStdDev,
              SixMoAbsIOPChangeMean = MoAbsIOPChangeMean,
              SixMoAbsIOPChangeStdDev = MoAbsIOPChangeStdDev,
              OneYEyes = Y,
              OneYIOPMean = Z,
              OneYIOPStdDev = AA,
              OneYAbsIOPChangeMean = AB,
              OneYAbsIOPChangeStdDev = AC,
              LastPeriodAbsIOPChangeStdDev = LastPeriodAbsIOPChangeStd,
              LastPeriodEyes = LastPeriodofEyes
              )

df <- df %>% mutate(subtype = as.factor(
  ifelse(acuteangleclosure == 'Y', 'acute',
         ifelse(MIGsYorN == 'Y', 'MIGS',
            ifelse(OAG > 50, 'OAG',
              ifelse(ACG > 50, 'ACG',
                ifelse(PXG > 50, 'PXG', NA)))))))
```

```
df <- df %>% mutate(study.name = paste0(Author, ' (', Year, ')', ifelse(WashOut == 'Y', '*', '')))
df <- df %>% filter(Author != "Mierzejewski et. al")  # Exclude Mierzejewski studies, they're abstracts
df <- df %>% dplyr::arrange(Year, study.name)
```

Summary plot

```
ggplot(df, aes(x = PreOpEyes, y =
                 ifelse(!is.na(LastPeriodIOPMean) & !is.na(PreOpIOPMean),
                        LastPeriodIOPMean - PreOpIOPMean,
                        ifelse(!is.na(LastPeriodAbsIOPChangeMean),
                               LastPeriodAbsIOPChangeMean,
                               ifelse(!is.na(OneYAbsIOPChangeMean),
                                      OneYAbsIOPChangeMean,
                                      OneYIOPMean - PreOpIOPMean
                                      )))
                               , label = study.name, color = subtype)) + geom_point() + ylab('IOP chang
```

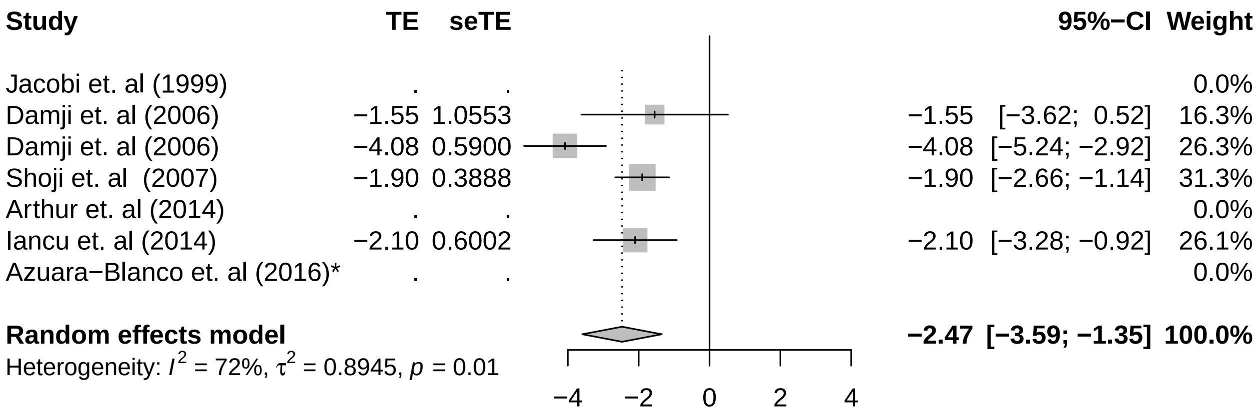
```
## Warning: Removed 8 rows containing missing values (geom_point).

## Warning: Removed 8 rows containing missing values (geom_text_repel).
```



Analysis without imputation

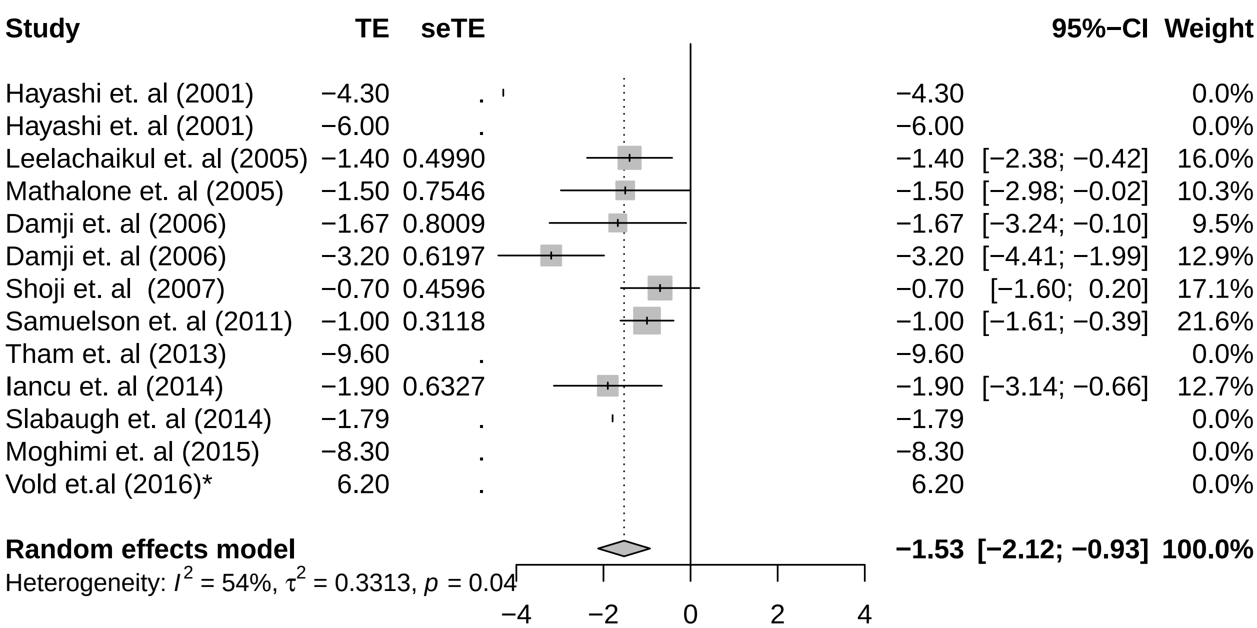
6 month follow-up

```r
m <- metagen(SixMoAbsIOPChangeMean,
             SixMoAbsIOPChangeStdDev / sqrt(SixMoEyes),
             study.name,
             data=df,
             subset=!is.na(df$SixMoEyes))
forest(m, comb.fixed=FALSE)
```



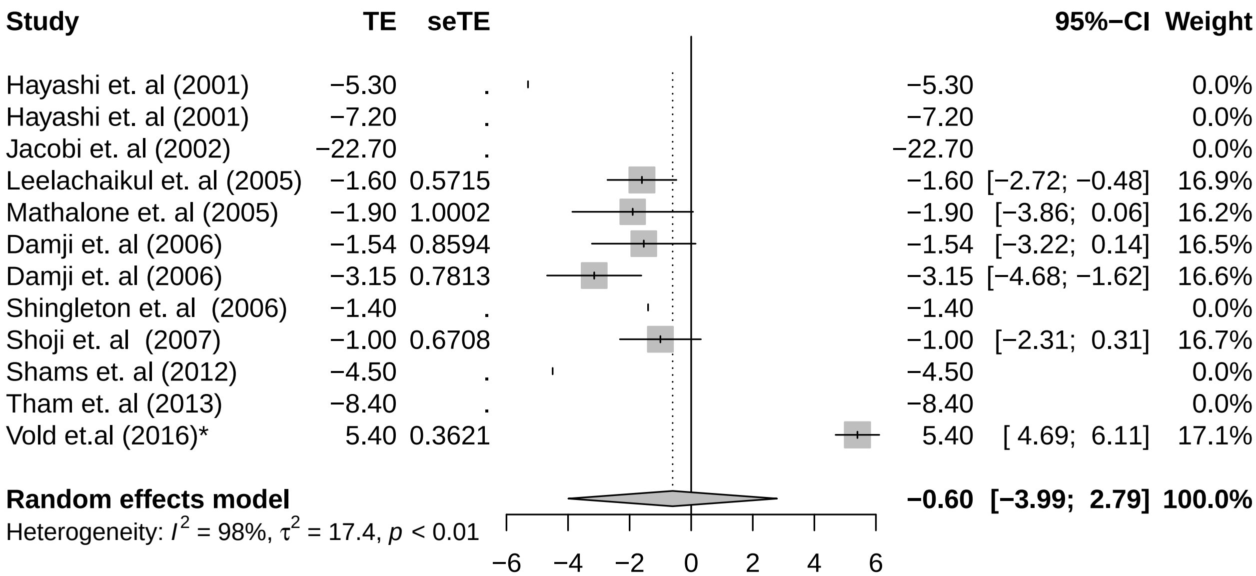
12-month follow up

```
m <- metagen(OneYAbsIOPChangeMean,
             OneYAbsIOPChangeStdDev / sqrt(OneYEyes),
             study.name,
             data=df,
             subset=!is.na(df$OneYAbsIOPChangeMean))
forest(m, comb.fixed = FALSE)
```



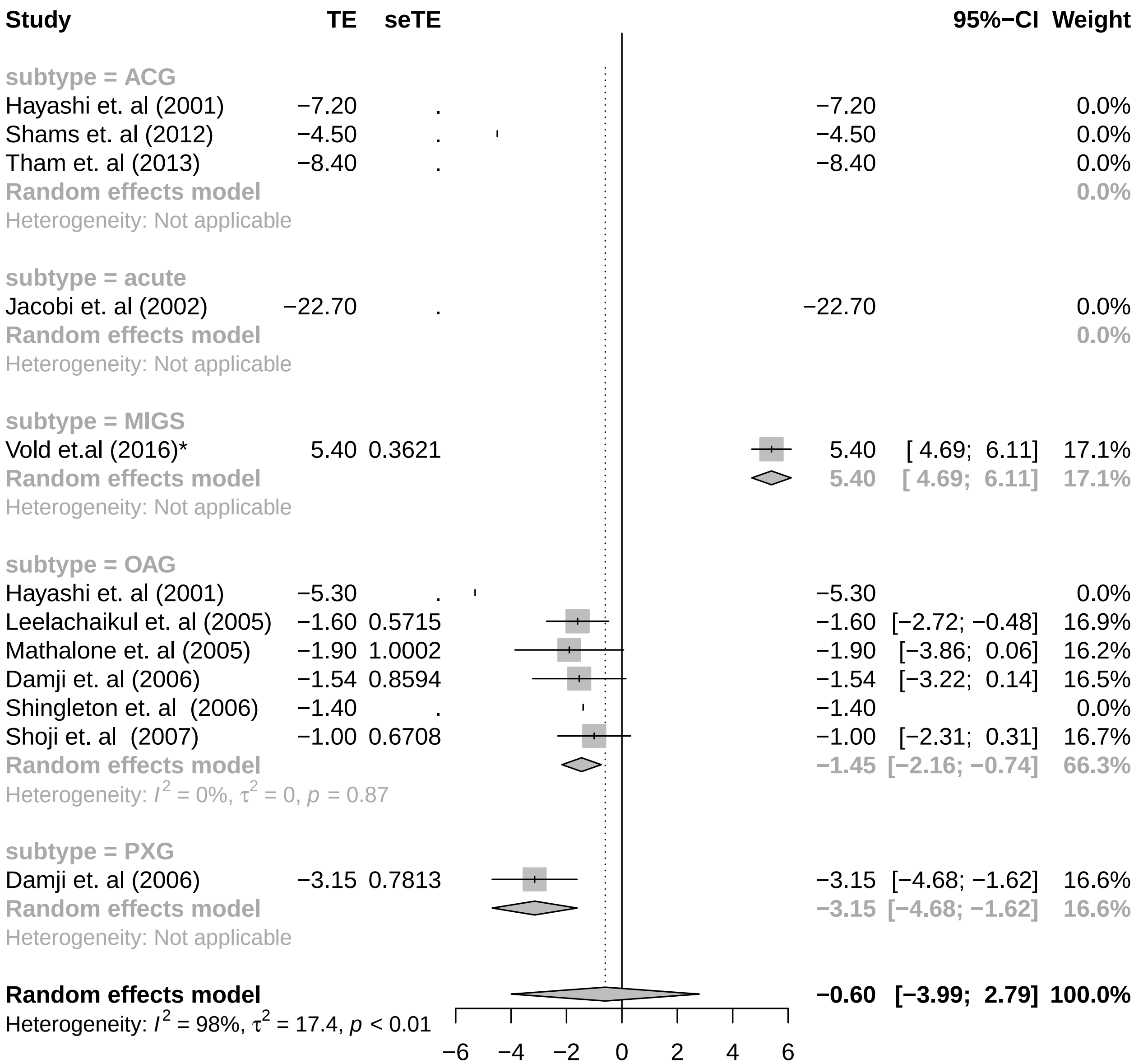
Last period

```
m <- metagen(LastPeriodAbsIOPChangeMean,
             LastPeriodAbsIOPChangeStdDev / sqrt(LastPeriodEyes),
             study.name,
             data=df,
             subset=!is.na(df$LastPeriodAbsIOPChangeMean))
forest(m, comb.fixed = FALSE)
```



Subgroup analysis

```
m <- metagen(LastPeriodAbsIOPChangeMean,
             LastPeriodAbsIOPChangeStdDev / sqrt(LastPeriodEyes),
             study.name,
             data=df,
             subset=!is.na(df$LastPeriodAbsIOPChangeMean),
             byvar=subtype)
forest(m, comb.fixed = FALSE)
```



There's too much missing data to anything useful with this data.

Analyses with imputation

I'm going to start by imputing on the basis of a low loss in follow up, high correlation between pre and post measures, and no change in relative IOP for those patients that were lost in follow up.

```
# Consider two range of loss of follow up.
losses <- list(lo=c(.94, .91, .87),
               hi=c(.82, .72, .51))

# Assume a range of correlations between PreOp and PostOp periods.
corrs <- list(lo=c(.25, .25, .25),
              hi=c(.45, .45, .45))

# And a range of outcomes for the missing eyes.
```

```r
deltas <- list(lo=c(0, 0, 0),  # Same outcome in the unseen arm.
               hi=c(5, 5, 5))  # Worse outcome in the unseen arm.

infer.mean.sem <- function(N.b, m.b, s.b, N.a, m.a, s.a, m.d, s.d, rho, m.delta) {
  # Infer the mean and SEM of the deviation in the metric measured before and after the intervention.
  # N.b, m.b, s.b: N, mean, S.D. of metric before the intervention
  # N.a, m.a, s.a: N, mean, S.D. of metric after the intervention
  # m.d, s.d: mean, S.D. of metric after intervention minus the metric before the intervention for
  #   the group of survivors (N.a). Can be NA.
  # rho: Assumed correlation between before and after scores. Will be used to infer s.d. if s.d is NA
  # m.delta: the assumed mean delta between the m.b for the non-survivors minus the survivors.
  # Use equations in Section 6.1 of Schwarzer, Carpenter & Rucker (2014), Meta-Analysis with R
  m.d <- ifelse(is.na(m.d), m.a - m.b, m.d)
  s.d <- ifelse(is.na(s.d), sqrt(s.a ** 2 + s.b ** 2 - 2 * rho * s.a * s.b), s.d)

  # Now generalize the mean difference from the observed subset to the full dataset.
  # pi := unobserved portion
  pi = (N.b - N.a) / N.b
  m.d.full <- m.d + pi * m.delta
  # Let's assume that delta ~ N(m.delta, s.d)
  sem.d.full <- sqrt(1 + pi ** 2) * s.d / sqrt(N.a)
  return(data.frame(m=m.d.full, sem=sem.d.full))
}

library(testthat)
```

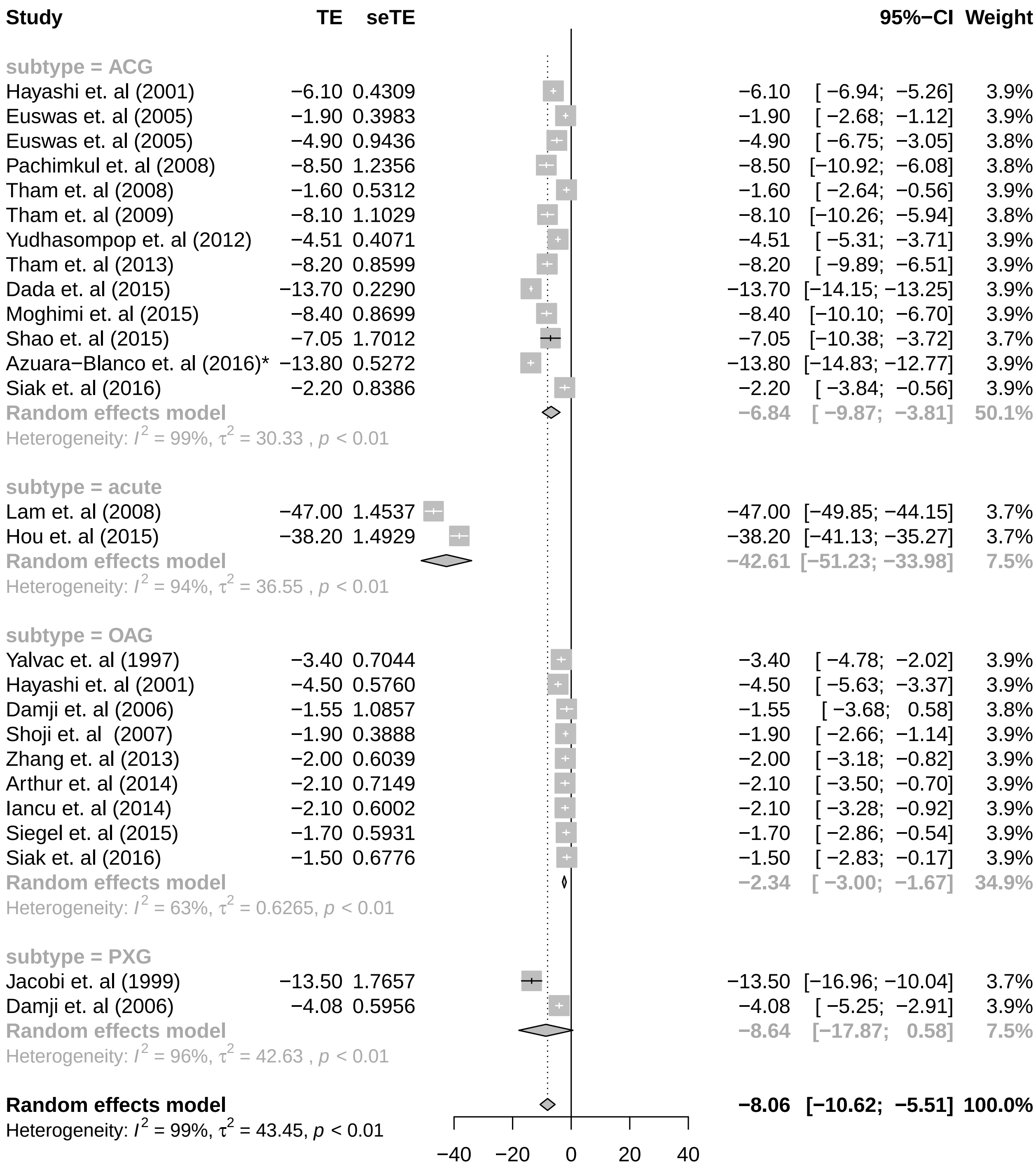
```
##
## Attaching package: 'testthat'

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

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

```r
expect_equal(infer.mean.sem(25, 0, 1, 25, 0, 1, NA, NA, 0, 0)$sem, sqrt(2)/sqrt(25))
expect_equal(infer.mean.sem(25, 0, 1, 25, 0, 1, NA, NA, 0.5, 0)$sem, 1/sqrt(25))
expect_equal(infer.mean.sem(25, 0, 1, 25, 0, 1, NA, NA, 0, 0)$m, 0)
expect_equal(infer.mean.sem(25, 0, 1, 16, 0, 1, NA, NA, 0, 0)$sem, sqrt(1 + (9 / 25) ** 2) * sqrt(2)/sq
expect_equal(infer.mean.sem(25, -1, 1, 16, 2, 1, NA, NA, 0, 0)$m, 3)
expect_equal(infer.mean.sem(25, -1, 1, 16, 2, 1, NA, NA, 0, 0)$m, 3)
expect_equal(infer.mean.sem(20, 5, 1, 20, -5, 1, NA, NA, 0, 10)$m, -10)
expect_equal(infer.mean.sem(20, 5, 1, 10, -5, 1, NA, NA, 0, 20)$m, 0)

impute.df <- function(df, loss, corr, delta) {
  # Impute missing data using the bone-headed method of just assuming the mean effect of
  # - loss of follow-up
  # - correlation between Pre and Post IOP metrics
  # - delta between IOP of eyes that were lost in follow up and eyes that were ok.
  df <- df %>% mutate(imp.SixMoEyes = ifelse(is.na(SixMoEyes), round(loss[1] * PreOpEyes), SixMoEyes),
                      imp.OneYEyes = ifelse(is.na(OneYEyes), round(loss[2] * PreOpEyes), OneYEyes),
                      imp.LastPeriodEyes = ifelse(is.na(LastPeriodEyes), round(loss[3] * PreOpEyes), La
```

```
  df_ <- with(df, infer.mean.sem(PreOpEyes, PreOpIOPMean, PreOpIOPStdDev,
                                 imp.SixMoEyes, SixMoIOPMean, SixMoIOPStdDev,
                                 SixMoAbsIOPChangeMean, SixMoAbsIOPChangeStdDev, corr[1], delta[1]))

  df$imp.SixMoIOPChangeMean <- df_$m
  df$imp.SixMoIOPChangeSEM <- df_$sem

  df_ <- with(df, infer.mean.sem(PreOpEyes, PreOpIOPMean, PreOpIOPStdDev,
                                 imp.OneYEyes, OneYIOPMean, OneYIOPStdDev,
                                 OneYAbsIOPChangeMean, OneYAbsIOPChangeStdDev, corr[2], delta[2]))
  df$imp.OneYIOPChangeMean <- df_$m
  df$imp.OneYIOPChangeSEM <- df_$sem

  df_ <- with(df, infer.mean.sem(PreOpEyes, PreOpIOPMean, PreOpIOPStdDev,
                                 imp.LastPeriodEyes, LastPeriodIOPMean, LastPeriodIOPStdDev,
                                 LastPeriodAbsIOPChangeMean, LastPeriodAbsIOPChangeStdDev, corr[3], delt
  df$imp.LastPeriodIOPChangeMean <- df_$m
  df$imp.LastPeriodIOPChangeSEM <- df_$sem

  # Patch up NAs for std dev of medications.
  df$imp.RxPreOpStdDev <- ifelse(is.na(df$RxPreOpStdDev),
                                 .5* df$RxPreOpMean + .2,
                                 pmax(df$RxPreOpStdDev, .2))

  df$imp.RxPostOpStdDev <- ifelse(is.na(df$RxPostOpStdDev),
                                 .5* df$RxPostOpMean + .2,
                                 pmax(df$RxPostOpStdDev, .2))


  return(df)
}

# Q: are we dealing properly with loss of follow-up means?
# Verify where available if the before, after measurements, and changes match up.

df <- impute.df(df, losses[['lo']], corrs[['hi']], deltas[['lo']])
```

6 month follow-up

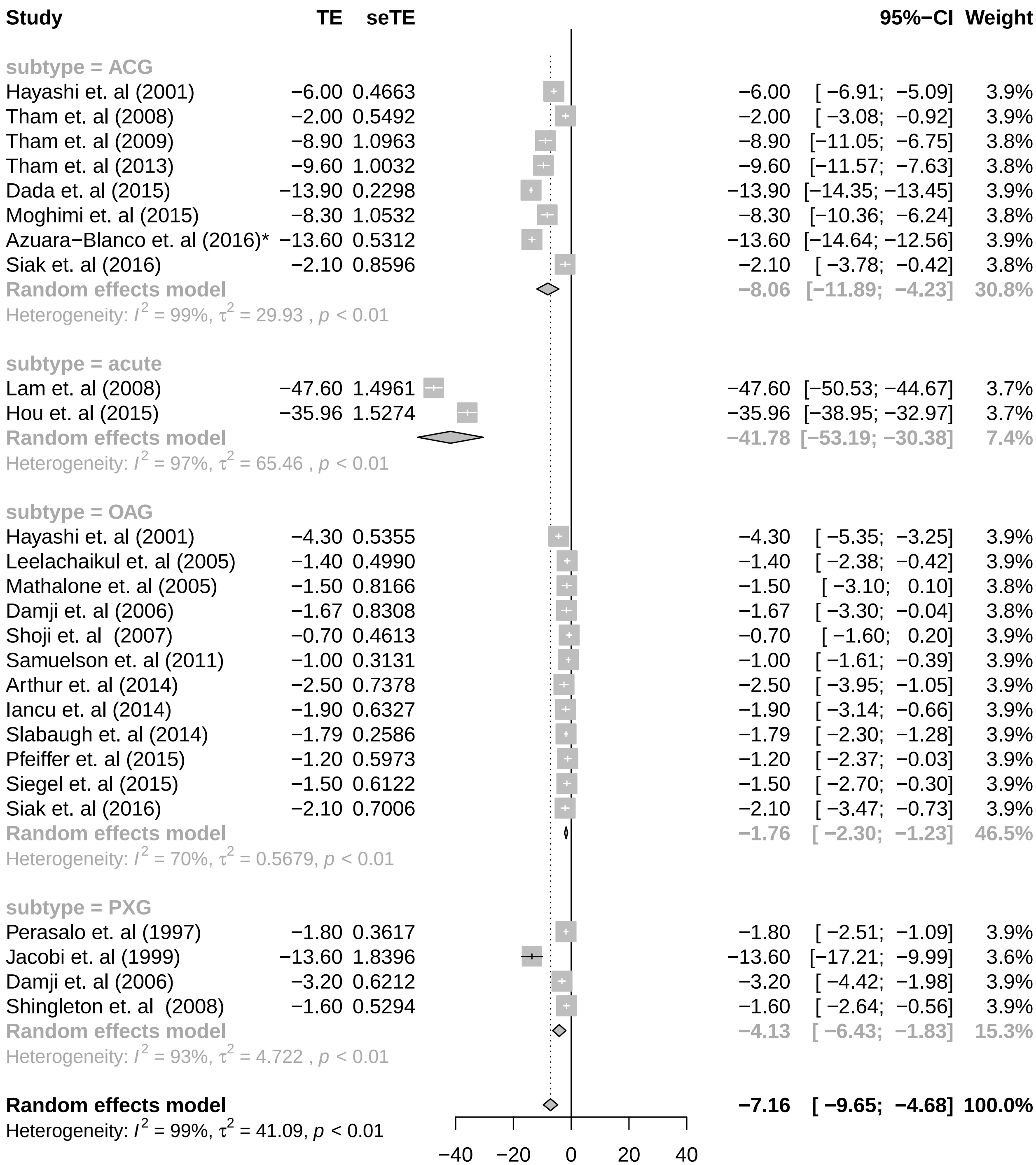
```
m <- metagen(imp.SixMoIOPChangeMean,
             imp.SixMoIOPChangeSEM,
             study.name,
             data=df %>% filter(!is.na(imp.SixMoIOPChangeSEM), subtype != 'MIGS') %>% mutate(subtype = c
             byvar=subtype)
forest(m, comb.fixed=FALSE)
```



12-month follow up

```
m <- metagen(imp.OneYIOPChangeMean,
             imp.OneYIOPChangeSEM,
             study.name,
             data=df %>% filter(!is.na(imp.OneYIOPChangeSEM), subtype != 'MIGS') %>% mutate(subtype = d
             byvar=subtype)
```

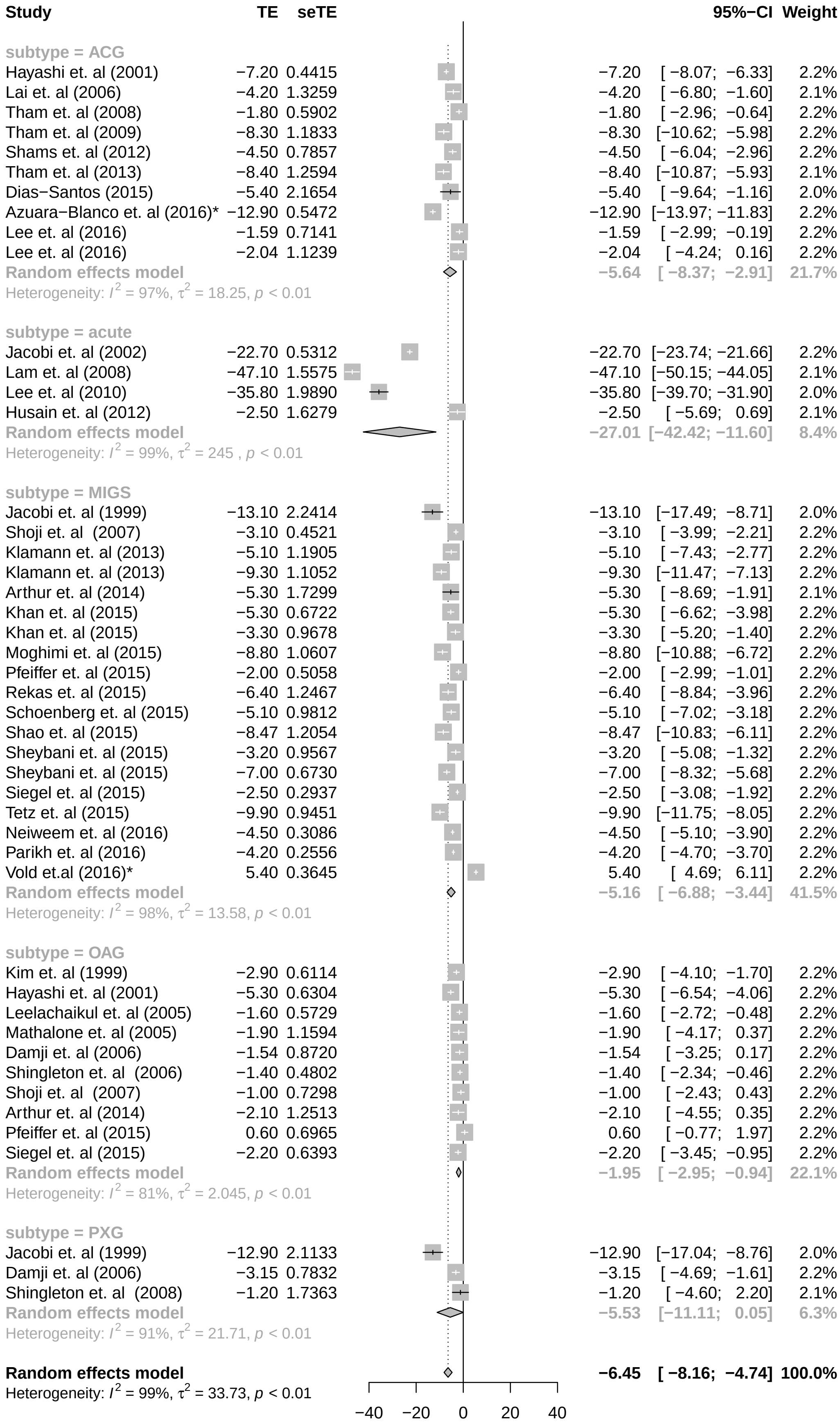
```r
forest(m, comb.fixed=FALSE)
```



Last period

```r
m <- metagen(imp.LastPeriodIOPChangeMean,
             imp.LastPeriodIOPChangeSEM,
             study.name,
             data=df %>% filter(!is.na(imp.LastPeriodIOPChangeSEM)),
             subset=!is.na(imp.LastPeriodIOPChangeSEM),
             byvar=subtype)
```

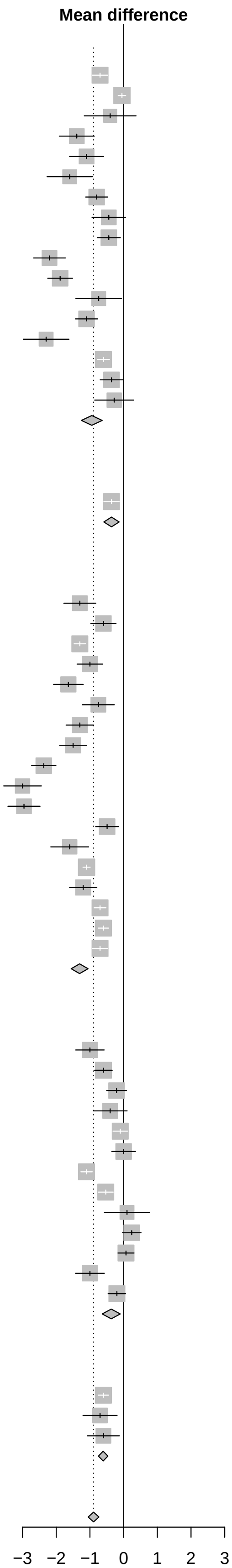
```
forest(m, comb.fixed=FALSE)
```


Study TE seTE 95%−CI Weight
subtype = ACG
Hayashi et. al (2001) −7.20 0.4415 −7.20 [−8.07; −6.33] 2.2%
Lai et. al (2006) −4.20 1.3259 −4.20 [−6.80; −1.60] 2.1%
Tham et. al (2008) −1.80 0.5902 −1.80 [−2.96; −0.64] 2.2%
Tham et. al (2009) −8.30 1.1833 −8.30 [−10.62; −5.98] 2.2%
Shams et. al (2012) −4.50 0.7857 −4.50 [−6.04; −2.96] 2.2%
Tham et. al (2013) −8.40 1.2594 −8.40 [−10.87; −5.93] 2.1%
Dias−Santos (2015) −5.40 2.1654 −5.40 [−9.64; −1.16] 2.0%
Azuara−Blanco et. al (2016)* −12.90 0.5472 −12.90 [−13.97; −11.83] 2.2%
Lee et. al (2016) −1.59 0.7141 −1.59 [−2.99; −0.19] 2.2%
Lee et. al (2016) −2.04 1.1239 −2.04 [−4.24; 0.16] 2.2%
Random effects model −5.64 [−8.37; −2.91] 21.7%
Heterogeneity: I^2 = 97%, τ^2 = 18.25, p < 0.01
subtype = acute
Jacobi et. al (2002) −22.70 0.5312 −22.70 [−23.74; −21.66] 2.2%
Lam et. al (2008) −47.10 1.5575 −47.10 [−50.15; −44.05] 2.1%
Lee et. al (2010) −35.80 1.9890 −35.80 [−39.70; −31.90] 2.0%
Husain et. al (2012) −2.50 1.6279 −2.50 [−5.69; 0.69] 2.1%
Random effects model −27.01 [−42.42; −11.60] 8.4%
Heterogeneity: I^2 = 99%, τ^2 = 245 , p < 0.01
subtype = MIGS
Jacobi et. al (1999) −13.10 2.2414 −13.10 [−17.49; −8.71] 2.0%
Shoji et. al (2007) −3.10 0.4521 −3.10 [−3.99; −2.21] 2.2%
Klamann et. al (2013) −5.10 1.1905 −5.10 [−7.43; −2.77] 2.2%
Klamann et. al (2013) −9.30 1.1052 −9.30 [−11.47; −7.13] 2.2%
Arthur et. al (2014) −5.30 1.7299 −5.30 [−8.69; −1.91] 2.1%
Khan et. al (2015) −5.30 0.6722 −5.30 [−6.62; −3.98] 2.2%
Khan et. al (2015) −3.30 0.9678 −3.30 [−5.20; −1.40] 2.2%
Moghimi et. al (2015) −8.80 1.0607 −8.80 [−10.88; −6.72] 2.2%
Pfeiffer et. al (2015) −2.00 0.5058 −2.00 [−2.99; −1.01] 2.2%
Rekas et. al (2015) −6.40 1.2467 −6.40 [−8.84; −3.96] 2.2%
Schoenberg et. al (2015) −5.10 0.9812 −5.10 [−7.02; −3.18] 2.2%
Shao et. al (2015) −8.47 1.2054 −8.47 [−10.83; −6.11] 2.2%
Sheybani et. al (2015) −3.20 0.9567 −3.20 [−5.08; −1.32] 2.2%
Sheybani et. al (2015) −7.00 0.6730 −7.00 [−8.32; −5.68] 2.2%
Siegel et. al (2015) −2.50 0.2937 −2.50 [−3.08; −1.92] 2.2%
Tetz et. al (2015) −9.90 0.9451 −9.90 [−11.75; −8.05] 2.2%
Neiweem et. al (2016) −4.50 0.3086 −4.50 [−5.10; −3.90] 2.2%
Parikh et. al (2016) −4.20 0.2556 −4.20 [−4.70; −3.70] 2.2%
Vold et.al (2016)* 5.40 0.3645 5.40 [4.69; 6.11] 2.2%
Random effects model −5.16 [−6.88; −3.44] 41.5%
Heterogeneity: I^2 = 98%, τ^2 = 13.58, p < 0.01
subtype = OAG
Kim et. al (1999) −2.90 0.6114 −2.90 [−4.10; −1.70] 2.2%
Hayashi et. al (2001) −5.30 0.6304 −5.30 [−6.54; −4.06] 2.2%
Leelachaikul et. al (2005) −1.60 0.5729 −1.60 [−2.72; −0.48] 2.2%
Mathalone et. al (2005) −1.90 1.1594 −1.90 [−4.17; 0.37] 2.2%
Damji et. al (2006) −1.54 0.8720 −1.54 [−3.25; 0.17] 2.2%
Shingleton et. al (2006) −1.40 0.4802 −1.40 [−2.34; −0.46] 2.2%
Shoji et. al (2007) −1.00 0.7298 −1.00 [−2.43; 0.43] 2.2%
Arthur et. al (2014) −2.10 1.2513 −2.10 [−4.55; 0.35] 2.2%
Pfeiffer et. al (2015) 0.60 0.6965 0.60 [−0.77; 1.97] 2.2%
Siegel et. al (2015) −2.20 0.6393 −2.20 [−3.45; −0.95] 2.2%
Random effects model −1.95 [−2.95; −0.94] 22.1%
Heterogeneity: I^2 = 81%, τ^2 = 2.045, p < 0.01
subtype = PXG
Jacobi et. al (1999) −12.90 2.1133 −12.90 [−17.04; −8.76] 2.0%
Damji et. al (2006) −3.15 0.7832 −3.15 [−4.69; −1.61] 2.2%
Shingleton et. al (2008) −1.20 1.7363 −1.20 [−4.60; 2.20] 2.1%
Random effects model −5.53 [−11.11; 0.05] 6.3%
Heterogeneity: I^2 = 91%, τ^2 = 21.71, p < 0.01
Random effects model −6.45 [−8.16; −4.74] 100.0%
Heterogeneity: I^2 = 99%, τ^2 = 33.73, p < 0.01
−40 −20 0 20 40

Meds

```
m <- metacont(imp.LastPeriodEyes,
              RxPostOpMean,
              imp.RxPostOpStdDev,
              PreOpEyes,
              RxPreOpMean,
              imp.RxPreOpStdDev,
              study.name,
              data=df,
              subset=!is.na(imp.RxPreOpStdDev) & !is.na(imp.RxPostOpStdDev),
              byvar=subtype)
forest(m, comb.fixed=FALSE)
```

Study	Experimental Total	Experimental Mean	Experimental SD	Control Total	Control Mean	Control SD	MD	95%−CI	Weight
subtype = ACG									
Hayashi et. al (2001)	64	0.600	0.500	74	1.300	0.85	−0.70	[−0.93; −0.47]	2.1%
Euswas et. al (2005)	30	0.030	0.215	34	0.080	0.24	−0.05	[−0.16; 0.06]	2.2%
Euswas et. al (2005)	12	1.400	0.900	14	1.800	1.10	−0.40	[−1.17; 0.37]	1.4%
Lai et. al (2006)	18	0.520	0.870	21	1.910	0.77	−1.39	[−1.91; −0.87]	1.8%
Tham et. al (2008)	30	1.100	1.200	35	2.200	0.80	−1.10	[−1.60; −0.60]	1.8%
Tham et. al (2009)	23	1.700	1.300	27	3.300	1.10	−1.60	[−2.27; −0.93]	1.6%
Liu et. al (2011)	49	1.000	0.700	56	1.800	1.00	−0.80	[−1.13; −0.47]	2.0%
Shams et. al (2012)	48	0.960	1.170	55	1.400	1.41	−0.44	[−0.94; 0.06]	1.8%
Yudhasompop et. al (2012)	52	1.430	1.030	60	1.870	0.77	−0.44	[−0.78; −0.10]	2.0%
Tham et. al (2013)	23	1.500	0.950	26	3.700	0.70	−2.20	[−2.67; −1.73]	1.8%
Dada et. al (2015)	38	0.136	0.268	44	2.020	1.21	−1.88	[−2.25; −1.52]	2.0%
Dias−Santos (2015)	13	0.930	0.590	15	1.670	1.18	−0.74	[−1.42; −0.06]	1.6%
Moghimi et. al (2015)	40	0.100	0.300	46	1.200	1.10	−1.10	[−1.43; −0.77]	2.0%
Shao et. al (2015)	17	0.650	1.090	20	2.950	1.00	−2.30	[−2.98; −1.62]	1.6%
Azuara−Blanco et. al (2016)*	182	0.400	0.800	208	1.000	1.00	−0.60	[−0.78; −0.42]	2.1%
Lee et. al (2016)	37	0.690	0.680	42	1.050	0.84	−0.36	[−0.70; −0.02]	2.0%
Lee et. al (2016)	12	1.430	0.540	14	1.710	0.94	−0.28	[−0.86; 0.30]	1.7%
Random effects model	**688**			**791**			**−0.94**	**[−1.25; −0.64]**	**31.4%**
Heterogeneity: $I^2 = 93\%$, $\tau^2 = 0.3667$, $p < 0.01$									
subtype = acute									
Lam et. al (2008)	27	0.030	0.200	31	0.390	0.61	−0.36	[−0.59; −0.13]	2.1%
Random effects model	**27**			**31**			**−0.36**	**[−0.59; −0.13]**	**2.1%**
Heterogeneity: Not applicable									
subtype = MIGS									
Jacobi et. al (1999)	13	0.800	0.600	26	2.100	0.90	−1.30	[−1.78; −0.82]	1.8%
Shoji et. al (2007)	16	0.400	0.400	31	1.000	0.90	−0.60	[−0.97; −0.23]	2.0%
Samuelson et. al (2011)*	106	0.200	0.600	117	1.500	0.70	−1.30	[−1.47; −1.13]	2.1%
Arthur et. al (2014)	11	0.300	0.500	32	1.300	0.70	−1.00	[−1.38; −0.62]	1.9%
Khan et. al (2015)	49	1.220	1.280	49	2.860	0.91	−1.64	[−2.08; −1.20]	1.9%
Khan et. al (2015)	52	2.150	1.350	52	2.900	1.10	−0.75	[−1.22; −0.28]	1.8%
Moghimi et. al (2015)	39	0.400	0.800	45	1.700	1.10	−1.30	[−1.71; −0.89]	1.9%
Pfeiffer et. al (2015)	47	0.500	1.000	50	2.000	1.00	−1.50	[−1.90; −1.10]	1.9%
Rekas et. al (2015)	25	0.270	0.670	29	2.640	0.68	−2.37	[−2.73; −2.01]	2.0%
Schoenberg et. al (2015)	31	0.000	0.200	36	3.000	1.70	−3.00	[−3.56; −2.44]	1.7%
Shao et. al (2015)	20	0.000	0.200	23	2.957	1.15	−2.96	[−3.44; −2.48]	1.8%
Sheybani et. al (2015)	72	1.510	0.955	83	2.000	1.20	−0.49	[−0.83; −0.15]	2.0%
Sheybani et. al (2015)	34	0.900	1.000	37	2.500	1.40	−1.60	[−2.16; −1.04]	1.7%
Siegel et. al (2015)	227	0.200	0.600	261	1.300	0.60	−1.10	[−1.21; −0.99]	2.2%
Tetz et. al (2015)	27	0.300	0.500	30	1.500	1.00	−1.20	[−1.60; −0.80]	1.9%
Neiweem et. al (2016)	306	1.700	1.200	352	2.400	1.10	−0.70	[−0.88; −0.52]	2.1%
Parikh et. al (2016)	433	1.700	1.300	498	2.300	1.10	−0.60	[−0.76; −0.44]	2.1%
Vold et.al (2016)*	116	0.600	0.800	131	1.300	1.00	−0.70	[−0.92; −0.48]	2.1%
Random effects model	**1624**			**1882**			**−1.31**	**[−1.56; −1.06]**	**35.0%**
Heterogeneity: $I^2 = 93\%$, $\tau^2 = 0.2584$, $p < 0.01$									
subtype = OAG									
Kim et. al (1999)	27	0.700	0.550	31	1.700	1.05	−1.00	[−1.42; −0.58]	1.9%
Hayashi et. al (2001)	59	0.800	0.600	68	1.400	0.90	−0.60	[−0.86; −0.34]	2.1%
Leelachaikul et. al (2005)	54	0.990	0.950	58	1.200	0.58	−0.21	[−0.50; 0.08]	2.0%
Mathalone et. al (2005)	24	1.100	1.120	58	1.500	0.90	−0.40	[−0.90; 0.10]	1.8%
Shingleton et. al (2006)	48	1.000	0.600	55	1.100	0.50	−0.10	[−0.32; 0.12]	2.1%
Shoji et. al (2007)	20	0.800	0.600	35	0.800	0.70	0.00	[−0.35; 0.35]	2.0%
Samuelson et. al (2011)	107	0.400	0.700	123	1.500	0.60	−1.10	[−1.27; −0.93]	2.1%
Zhang et. al (2013)	37	0.230	0.430	43	0.760	0.58	−0.53	[−0.75; −0.31]	2.1%
Arthur et. al (2014)	17	1.500	1.200	37	1.400	1.10	0.10	[−0.57; 0.77]	1.6%
Iancu et. al (2014)	33	2.900	0.530	38	2.660	0.66	0.24	[−0.04; 0.52]	2.0%
Slabaugh et. al (2014)	137	1.920	1.070	157	1.850	1.01	0.07	[−0.17; 0.31]	2.1%
Pfeiffer et. al (2015)	43	1.000	1.000	50	2.000	1.10	−1.00	[−1.43; −0.57]	1.9%
Siegel et. al (2015)	45	1.300	0.610	52	1.500	0.70	−0.20	[−0.46; 0.06]	2.1%
Random effects model	**651**			**805**			**−0.37**	**[−0.64; −0.10]**	**25.7%**
Heterogeneity: $I^2 = 91\%$, $\tau^2 = 0.2118$, $p < 0.01$									
subtype = PXG									
Perasalo et. al (1997)	197	0.900	0.650	226	1.500	0.95	−0.60	[−0.75; −0.45]	2.1%
Jacobi et. al (1999)	13	1.500	0.700	22	2.200	0.80	−0.70	[−1.21; −0.19]	1.8%
Shingleton et. al (2008)	22	1.000	1.100	240	1.600	0.90	−0.60	[−1.07; −0.13]	1.8%
Random effects model	**232**			**488**			**−0.61**	**[−0.75; −0.47]**	**5.8%**
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.93$									
Random effects model	**3222**			**3997**			**−0.89**	**[−1.05; −0.73]**	**100.0%**
Heterogeneity: $I^2 = 94\%$, $\tau^2 = 0.3039$, $p < 0.01$									



Multivariate model to integrate across time

Correlation between meds and drop in IOP

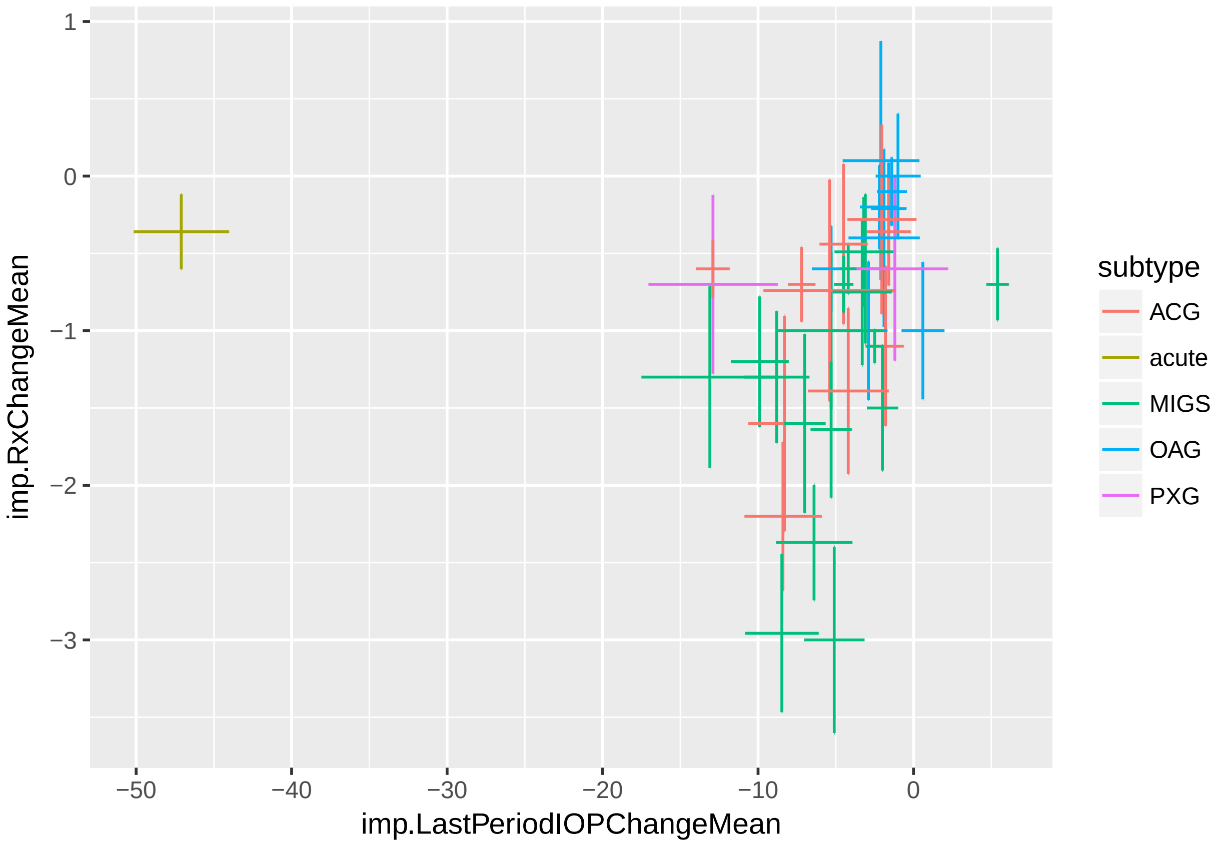
How is IOP drop related to change in meds? Two hypotheses:

- 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?

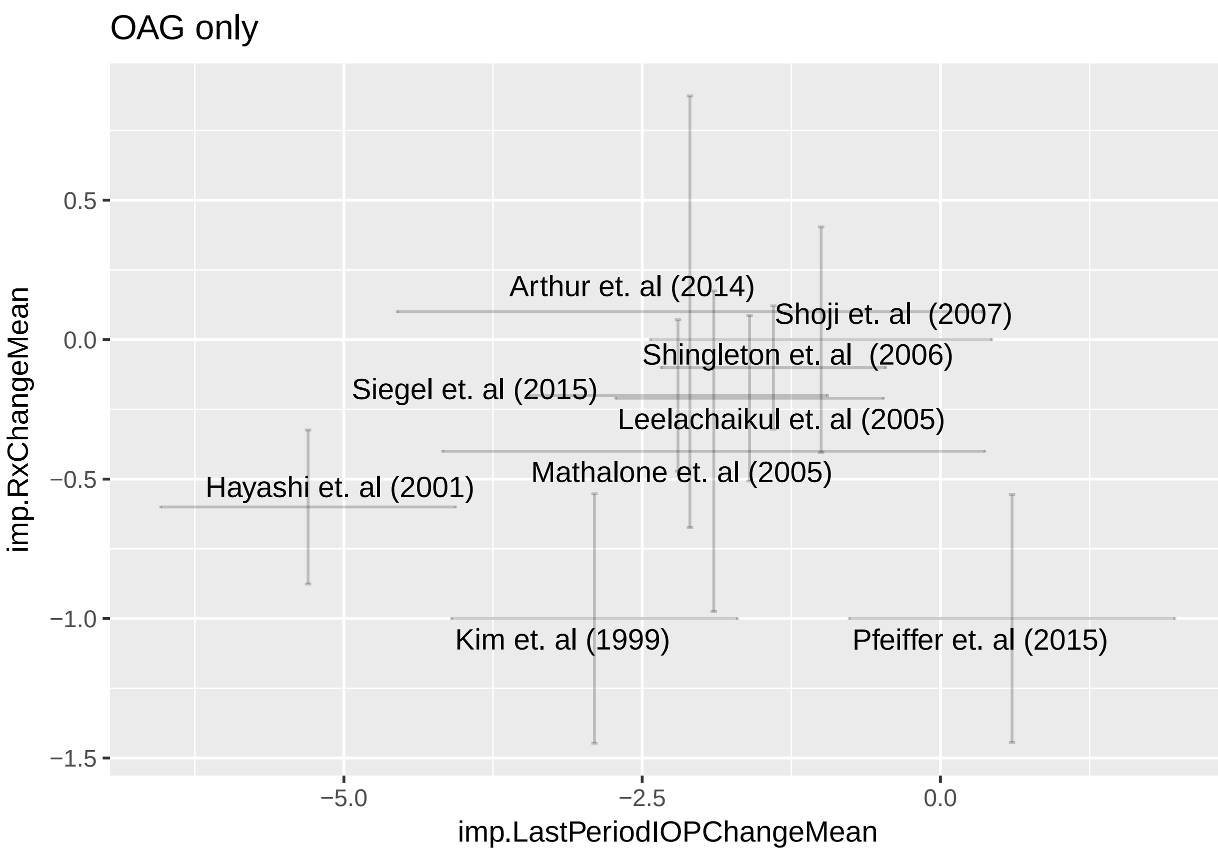
```
df <- df %>% mutate(imp.RxChangeMean = RxPostOpMean - RxPreOpMean,
              imp.RxChangeSEM  = sqrt(imp.RxPostOpStdDev ** 2 + imp.RxPreOpStdDev ** 2) / sqrt(imp.Last

ggplot(df, aes(x   =imp.LastPeriodIOPChangeMean,
               xmin=imp.LastPeriodIOPChangeMean - 1.96*imp.LastPeriodIOPChangeSEM,
               xmax=imp.LastPeriodIOPChangeMean + 1.96*imp.LastPeriodIOPChangeSEM,
               y    = imp.RxChangeMean,
               ymin= imp.RxChangeMean - 1.96*imp.RxChangeSEM,
               ymax= imp.RxChangeMean + 1.96*imp.RxChangeSEM,
               color=subtype
               )) + geom_errorbar() + geom_errorbarh()
```

```
## Warning: Removed 25 rows containing missing values (geom_errorbar).

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



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

```
## 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
```

```r
df_ <- df %>% filter(!(study.name %in% c("Pfeiffer et. al (2015)")), subtype=='OAG')
drawn.corrs <- with(df_, replicate(n = 100,
                                   draw.corr(imp.LastPeriodIOPChangeMean, imp.LastPeriodIOPChangeSEM, i
mean(drawn.corrs)
```

```
## [1] 0.4414706
```

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

```
## [1] 0.2087896
```

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

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

```r
df_ <- df %>% filter(subtype=='OAG')
drawn.corrs <- with(df_, replicate(n = 100,
                                  draw.corr(imp.LastPeriodIOPChangeMean, imp.LastPeriodIOPChangeSEM, im
mean(drawn.corrs)
```

```
## [1] 0.03711403
```

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

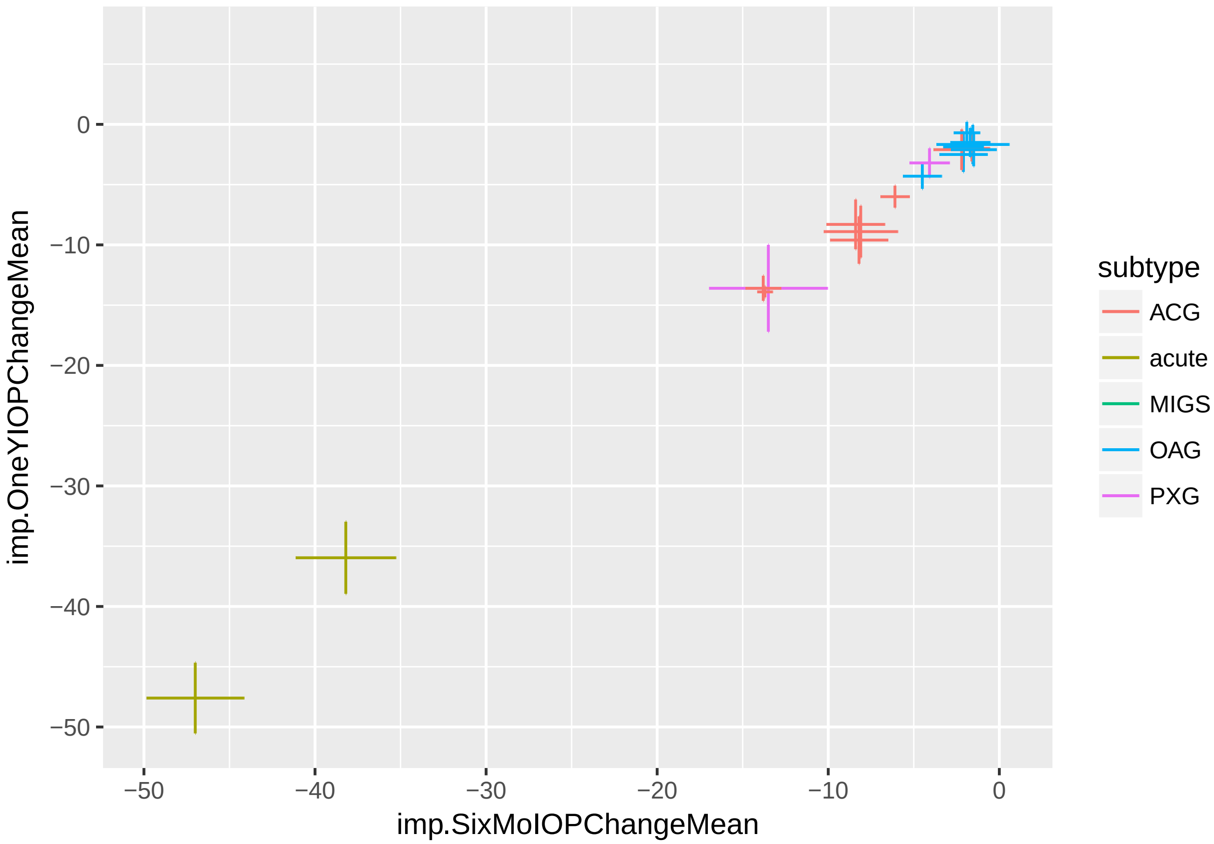
```
## [1] 0.2077679
```

Joint inferences

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

```r
ggplot(df, aes(x    =imp.SixMoIOPChangeMean,
               xmin=imp.SixMoIOPChangeMean - 1.96*imp.SixMoIOPChangeSEM,
               xmax=imp.SixMoIOPChangeMean + 1.96*imp.SixMoIOPChangeSEM,
               y    = imp.OneYIOPChangeMean,
               ymin= imp.OneYIOPChangeMean - 1.96*imp.OneYIOPChangeSEM,
               ymax= imp.OneYIOPChangeMean + 1.96*imp.OneYIOPChangeSEM,
               label=study.name,
               color=subtype
               )) + geom_errorbar() + geom_errorbarh()
```

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

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



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

```
df_ <- df %>% filter(subtype=='OAG')
drawn.corrs <- with(df_, replicate(n = 100,
                                   draw.corr(imp.SixMoIOPChangeMean, imp.SixMoIOPChangeSEM, imp.OneYIOP
cat("Mean +- SE correlation, OAG only\n")
```

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

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

```
## [1] 0.6212267
```

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

```
## [1] 0.2047245
```

```
df_ <- df
drawn.corrs <- with(df_, replicate(n = 100,
                                   draw.corr(imp.SixMoIOPChangeMean, imp.SixMoIOPChangeSEM, imp.OneYIOP
cat("Mean +- SE correlation, All subtypes\n")
```

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

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

```
## [1] 0.9935905
```

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

```
## [1] 0.00318292
```

Let's repeat the same analysis, this time for 12 months vs. last period

```
df_ <- df %>% filter(subtype=='OAG')
drawn.corrs <- with(df_, replicate(n = 100,
                          draw.corr(imp.LastPeriodIOPChangeMean, imp.LastPeriodIOPChangeSEM, imp.OneYIOP
cat("Mean +- SE correlation, OAG only\n")
```

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

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

```
## [1] 0.6635031
```

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

```
## [1] 0.1582084
```

```
df_ <- df
drawn.corrs <- with(df_, replicate(n = 100,
                          draw.corr(imp.LastPeriodIOPChangeMean, imp.LastPeriodIOPChangeSEM, imp.OneYIOP
cat("Mean +- SE correlation, All subtypes\n")
```

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

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

```
## [1] 0.9913575
```

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

```
## [1] 0.00297567
```

That's also really high! Finally, 6 months vs. last period

```
df_ <- df %>% filter(subtype=='OAG')
drawn.corrs <- with(df_, replicate(n = 100,
                          draw.corr(imp.LastPeriodIOPChangeMean, imp.LastPeriodIOPChangeSEM, imp.SixMoIOI
cat("Mean +- SE correlation, OAG only\n")
```

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

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

```
## [1] 0.7329639
```

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

```
## [1] 0.1858193
```

```
df_ <- df
drawn.corrs <- with(df_, replicate(n = 100,
                          draw.corr(imp.LastPeriodIOPChangeMean, imp.LastPeriodIOPChangeSEM, imp.SixMoIOI
cat("Mean +- SE correlation, All subtypes\n")
```

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

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

```
## [1] 0.9932244
```

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

```
## [1] 0.003924695
```

6 months is also highly correlated with the last period. Let's use mvmeta to infer the effect size for both 6 months and 12 months together.

```
library(mvmeta)
```

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

```
get.correlation.matrices.bi <- function(x, y, assumed.rho) {
  S <- list()
  for(i in 1:length(x)) {
    x[i] <- ifelse(is.na(x[i]), y[i], x[i])
    y[i] <- ifelse(is.na(y[i]), x[i], y[i])
    S[[i]] <- matrix(c(x[i] ** 2, x[i] * y[i]* assumed.rho,
                       x[i] * y[i] * assumed.rho, y[i] ** 2), ncol=2)
  }
  S
}

df_ <- df %>% filter(!is.na(imp.SixMoIOPChangeSEM) | !is.na(imp.OneYIOPChangeSEM), subtype %in% c('OAG'
thefit <- mvmeta(cbind(imp.SixMoIOPChangeMean, imp.OneYIOPChangeMean) ~ subtype,
       S=get.correlation.matrices.bi(df_$imp.SixMoIOPChangeSEM, df_$imp.OneYIOPChangeSEM, .7),
       data=df_,
       method="reml")

summary(thefit)
```

```
## Call:  mvmeta(formula = cbind(imp.SixMoIOPChangeMean, imp.OneYIOPChangeMean) ~
##     subtype, S = get.correlation.matrices.bi(df_$imp.SixMoIOPChangeSEM,
##     df_$imp.OneYIOPChangeSEM, 0.7), data = df_, method = "reml")
##
## Multivariate random-effects meta-regression
## Dimension: 2
## Estimation method: REML
##
## Fixed-effects coefficients
## imp.SixMoIOPChangeMean :
##              Estimate  Std. Error        z  Pr(>|z|)  95%ci.lb  95%ci.ub
## (Intercept)   -6.8486      0.8122  -8.4319    0.0000   -8.4406   -5.2567
## subtypeOAG     4.7346      1.1244   4.2108    0.0000    2.5308    6.9384
##
## (Intercept)  ***
## subtypeOAG   ***
## imp.OneYIOPChangeMean :
##              Estimate  Std. Error        z  Pr(>|z|)  95%ci.lb  95%ci.ub
## (Intercept)   -7.0589      0.8161  -8.6494    0.0000   -8.6584   -5.4594
## subtypeOAG     5.1950      1.1184   4.6452    0.0000    3.0031    7.3870
##
## (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
```

```
## imp.SixMoIOPChangeMean    2.8086  imp.SixMoIOPChangeMean
## imp.OneYIOPChangeMean     2.7854                  0.9946
##
## Multivariate Cochran Q-test for residual heterogeneity:
## Q = 1418.0961 (df = 38), p-value = 0.0000
## I-square statistic = 97.3%
##
## 27 studies, 42 observations, 4 fixed and 3 random-effects parameters
##   logLik       AIC       BIC
## -77.5246  169.0491  180.5123
```

```
newdata <- data.frame(subtype=c('OAG', 'ACG'))
pred <- predict(thefit, newdata, se=TRUE)
newdata$SixMoIOPChangeMean <- pred$fit[,1]
newdata$OneYIOPChangeMean <- pred$fit[,2]
newdata$SixMoIOPChangeSEM <- pred$se[,1]
newdata$OneYIOPChangeSEM <- pred$se[,2]

library(reshape2)
```

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

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

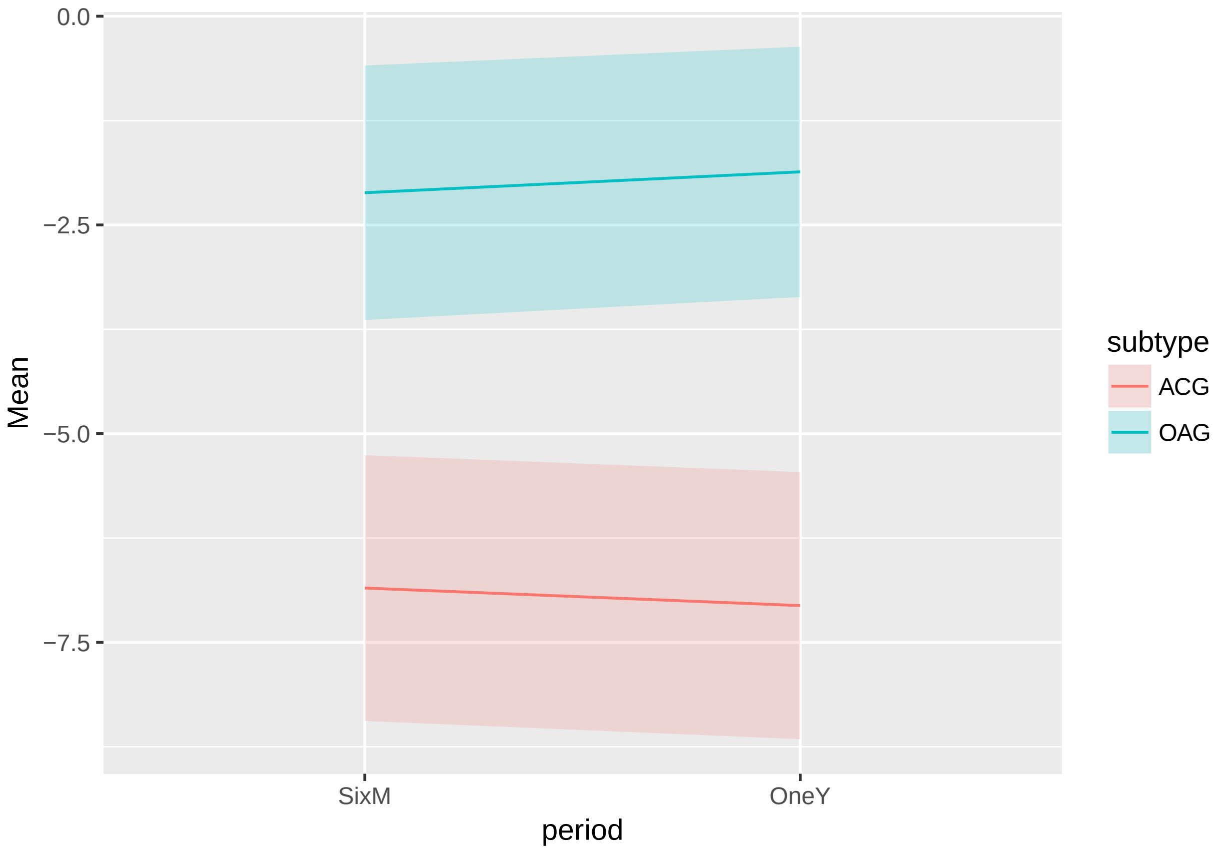
```
nd <- melt(newdata)
```

```
## 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))
nd
```

```
##   subtype           variable      value period metric
## 1     OAG SixMoIOPChangeMean -2.1140397   SixM   Mean
## 2     ACG SixMoIOPChangeMean -6.8486463   SixM   Mean
## 3     OAG  OneYIOPChangeMean -1.8638527   OneY   Mean
## 4     ACG  OneYIOPChangeMean -7.0588996   OneY   Mean
## 5     OAG  SixMoIOPChangeSEM  0.7775207   SixM   eSEM
## 6     ACG  SixMoIOPChangeSEM  0.8122344   SixM   eSEM
## 7     OAG   OneYIOPChangeSEM  0.7646785   OneY   eSEM
## 8     ACG   OneYIOPChangeSEM  0.8161110   OneY   eSEM
```

```
df_ <- dcast(nd, formula = subtype + period ~ metric)
df_$period <- relevel(as.factor(df_$period), ref='SixM')
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))
```




```
# TODO(Patrick): repeat for three time periods
```

Impute under every scenario

Look at what happens depending on how we impute the data.

```
# TODO(Patrick): Fix this.
results <- list()
for(loss in c('lo', 'hi')) {
  for(corr in c('lo', 'hi')) {
    for(delta in c('lo', 'hi')) {
      df <- impute.df(df, losses[[loss]], corrs[[corr]], deltas[[delta]])
      s <- (metagen(imp.SixMoIOPChangeMean,
                    imp.SixMoIOPChangeSEM,
                    study.name,
                    data=df,
                    subset=!is.na(imp.SixMoIOPChangeSEM) & MIGsYorN == 'N',
                    byvar=subtype))
      row <- data.frame(loss=loss, corr=corr, delta=delta, m=s$TE.random.w, ci.lo=s$upper.random.w, ci.
      results[[length(results) + 1]] <- row

      s <- (metagen(imp.OneYIOPChangeMean,
                    imp.OneYIOPChangeSEM,
                    study.name,
                    data=df,
```

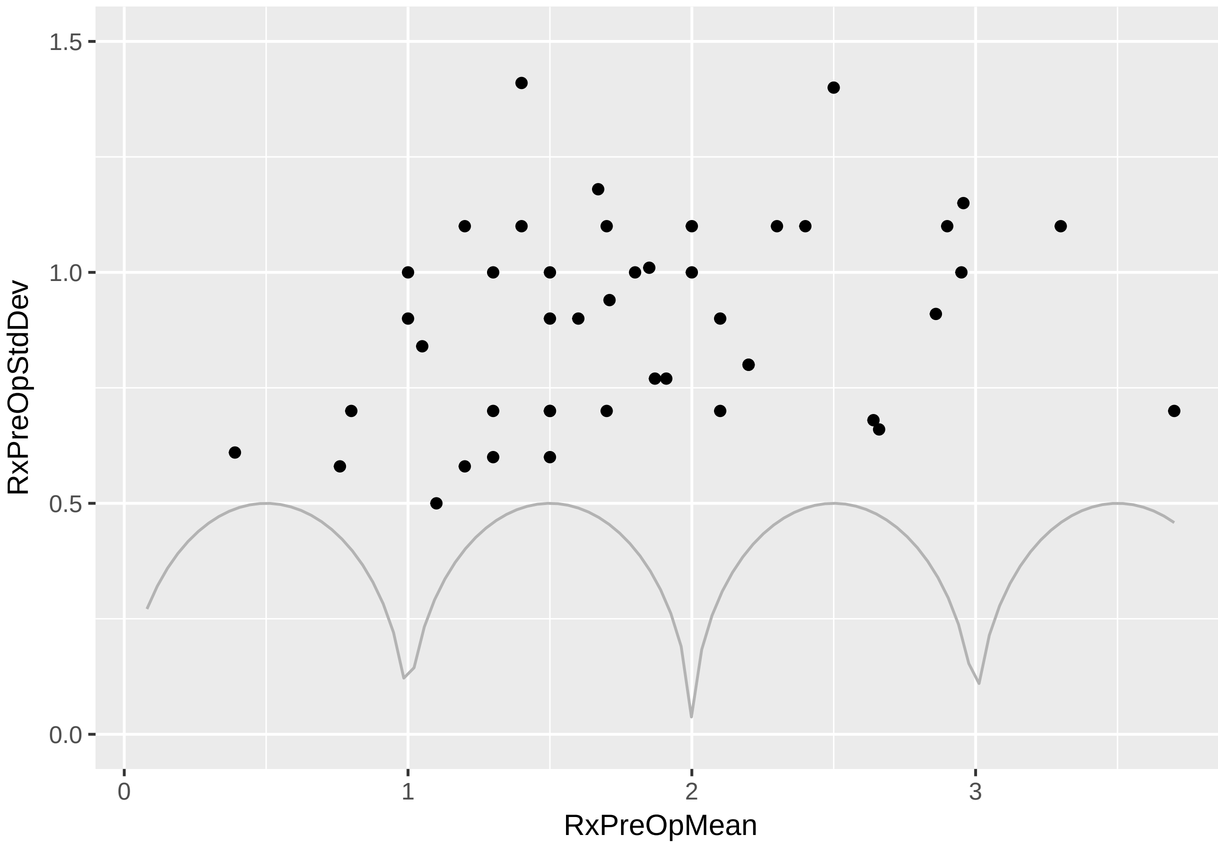
```
                   subset=!is.na(imp.OneYIOPChangeSEM) & MIGsYorN == 'N',
                   byvar=subtype))
      row <- data.frame(loss=loss, corr=corr, delta=delta, m=s$TE.random.w, ci.lo=s$upper.random.w, ci.l
      results[[length(results) + 1]] <- row

      s <- (metagen(imp.LastPeriodIOPChangeMean,
                   imp.LastPeriodIOPChangeSEM,
                   study.name,
                   data=df,
                   subset=!is.na(imp.LastPeriodIOPChangeSEM) & MIGsYorN == 'N',
                   byvar=subtype))
      row <- data.frame(loss=loss, corr=corr, delta=delta, m=s$TE.random.w, ci.lo=s$upper.random.w, ci.l
      results[[length(results) + 1]] <- row
    }
  }
}

all.df <- do.call(rbind, results)

p <- position_dodge(width=1)
ggplot(all.df, aes(x=period, y = m, ymin=ci.lo, ymax=ci.hi, color=subtype)) + geom_pointrange(position=p

summary(metagen(imp.LastPeriodIOPChangeMean,
             imp.LastPeriodIOPChangeSEM,
             study.name,
             data=df,
             subset=!is.na(imp.LastPeriodIOPChangeSEM) & MIGsYorN == 'N',
             byvar=subtype))

summary(metagen(imp.LastPeriodIOPChangeMean,
             imp.LastPeriodIOPChangeSEM,
             study.name,
             data=df,
             subset=!is.na(imp.LastPeriodIOPChangeSEM) & MIGsYorN == 'N',
             byvar=subtype))
```

Sanity check data graphically

Check the relationship between RxPreOpMean and s.d.

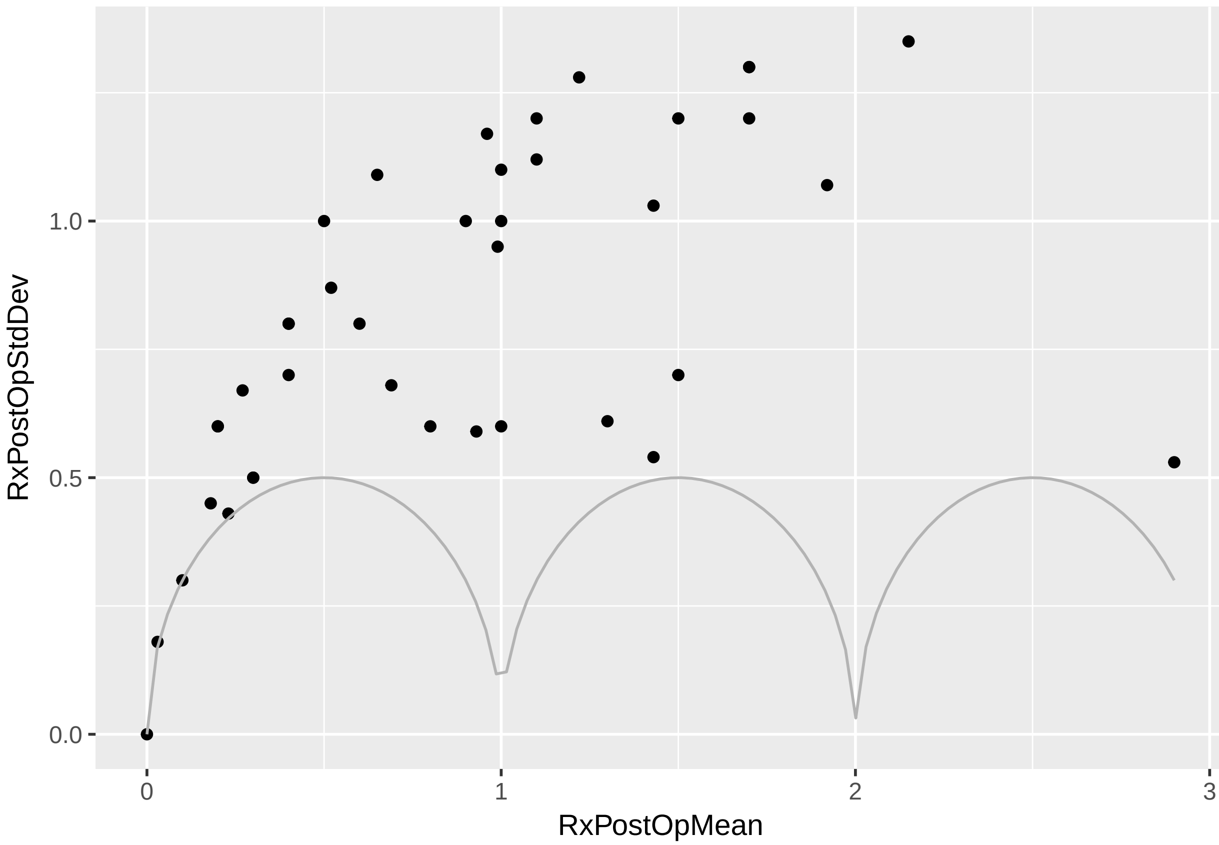
```
ggplot(df, aes(x = RxPreOpMean, y = RxPreOpStdDev)) +
  geom_point() +
  coord_cartesian(y=c(0, 1.5)) +
  stat_function(fun = function(x) sqrt((x - floor(x)) * (1 - (x - floor(x)))), color="gray70")
```

```
## Warning: Removed 19 rows containing missing values (geom_point).
```




```
ggplot(df, aes(x = RxPostOpMean, y = RxPostOpStdDev)) + geom_point() +
  stat_function(fun = function(x) sqrt((x - floor(x)) * (1 - (x - floor(x)))), color="gray70")
```

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

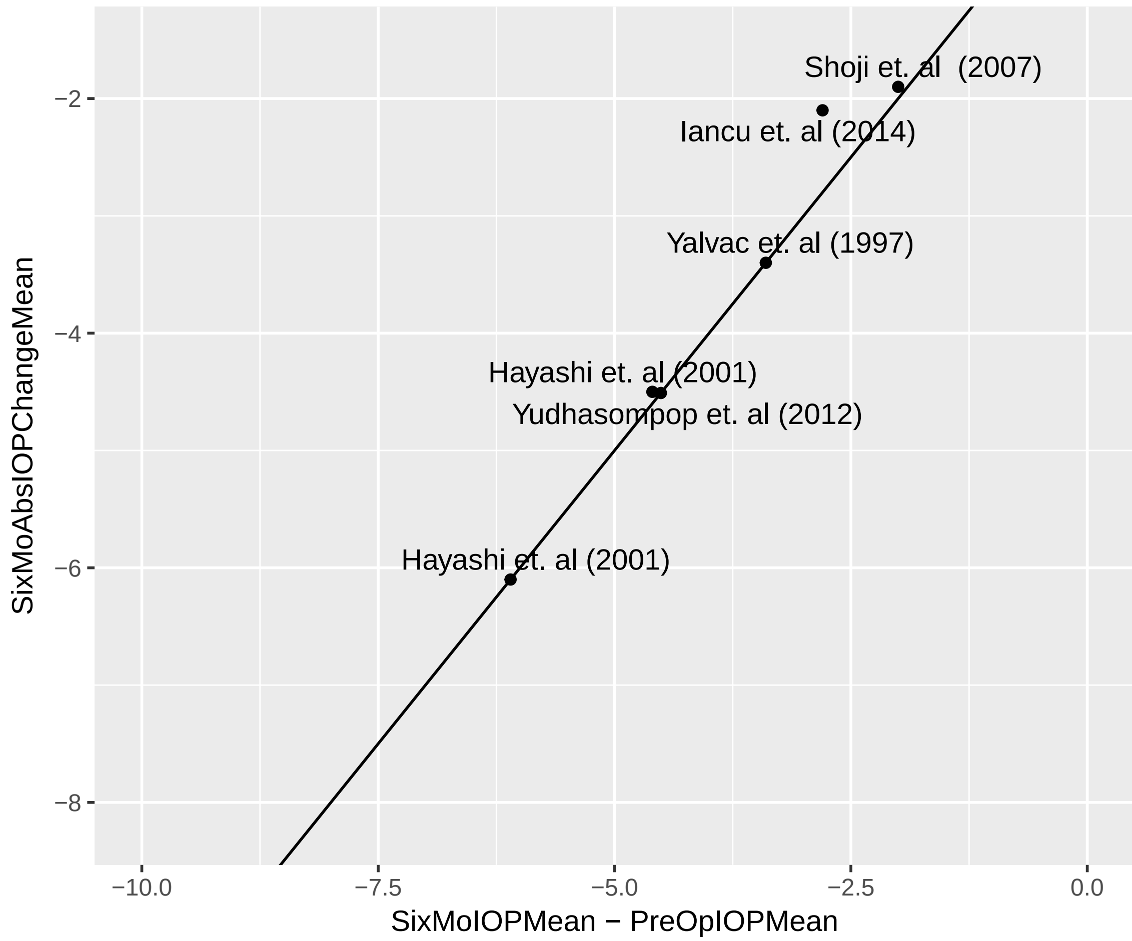


Check that changes add up.

```
ggplot(df, aes(x = SixMoIOPMean - PreOpIOPMean, y = SixMoAbsIOPChangeMean, label = study.name)) +
  geom_point() +
  coord_cartesian(xlim=c(-10, 0)) +
  geom_abline() +
  geom_text_repel()
```

```
## Warning: Removed 58 rows containing missing values (geom_point).
```

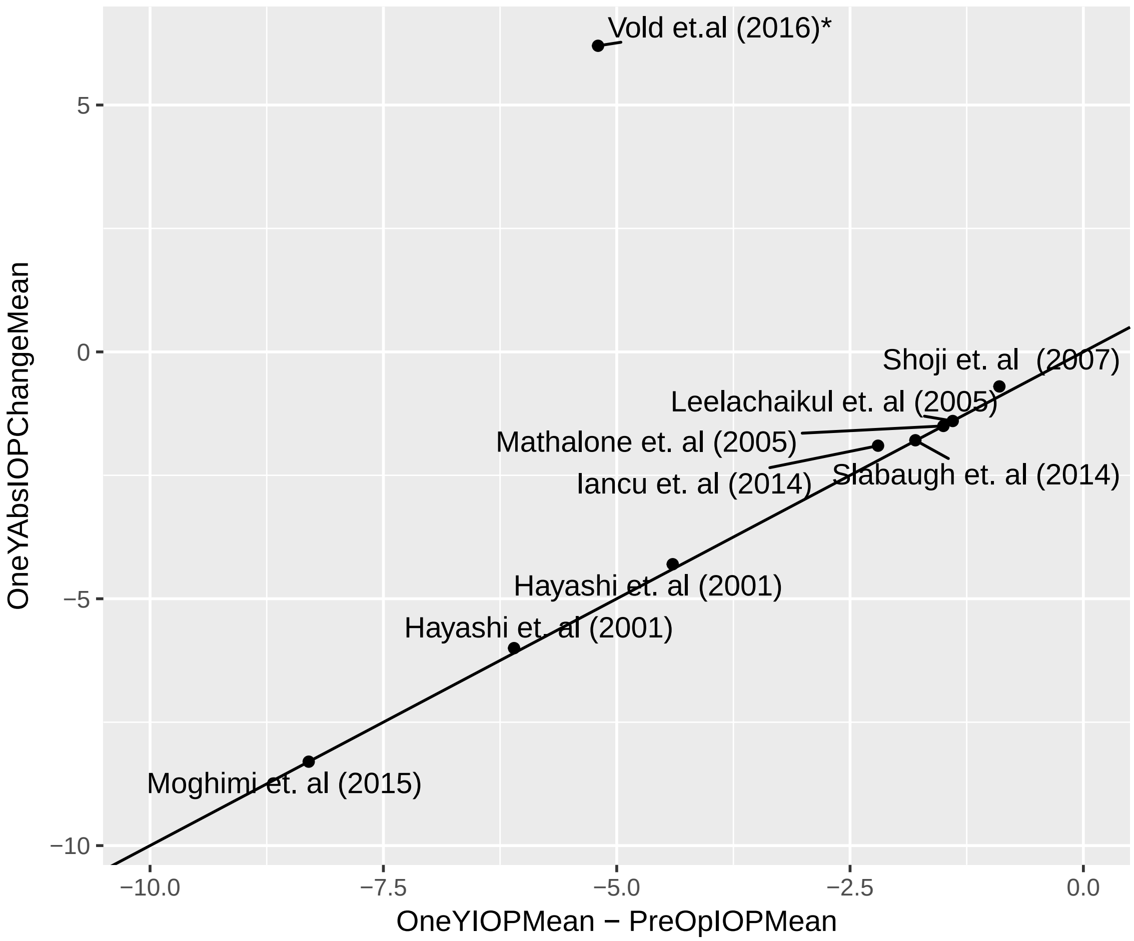
```
## Warning: Removed 58 rows containing missing values (geom_text_repel).
```




```r
ggplot(df, aes(x = OneYIOPMean - PreOpIOPMean, y = OneYAbsIOPChangeMean, label = study.name)) +
  geom_point() +
  coord_cartesian(xlim=c(-10, 0)) +
  geom_abline() +
  geom_text_repel()
```

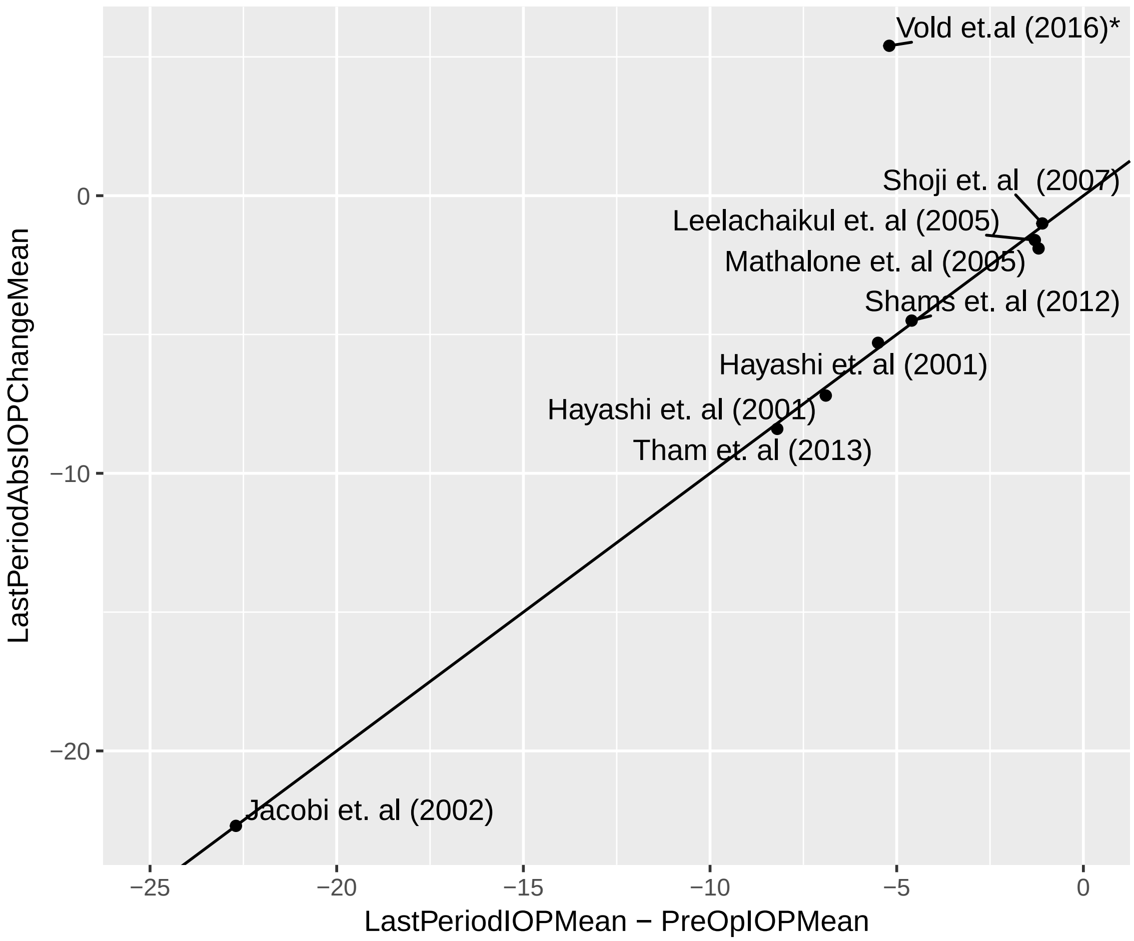
```
## Warning: Removed 55 rows containing missing values (geom_point).
```

```
## Warning: Removed 55 rows containing missing values (geom_text_repel).
```




```r
ggplot(df, aes(x = LastPeriodIOPMean - PreOpIOPMean, y = LastPeriodAbsIOPChangeMean, label = study.name
  geom_point() +
  coord_cartesian(xlim=c(-25, 0)) +
  geom_abline() +
  geom_text_repel()
```

```
## Warning: Removed 55 rows containing missing values (geom_point).
## Warning: Removed 55 rows containing missing values (geom_text_repel).
```

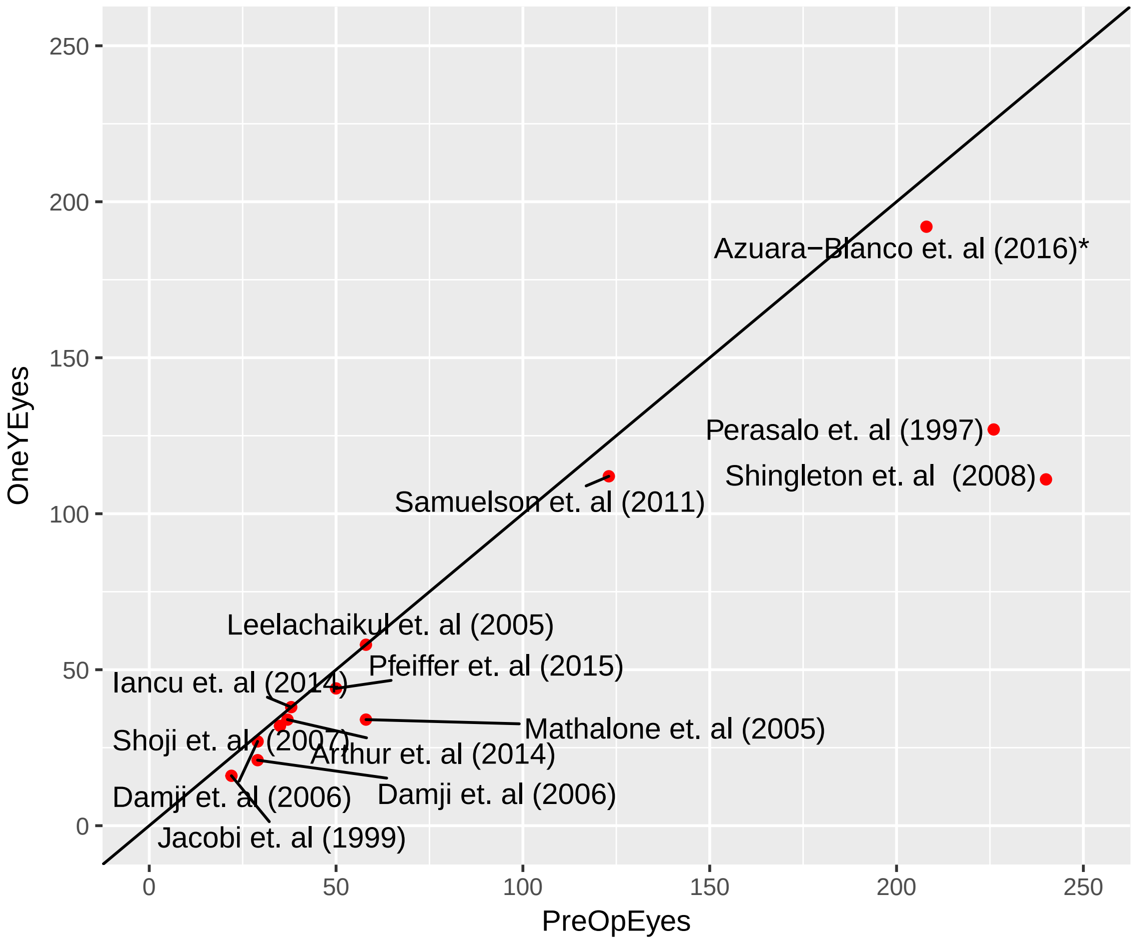


Examine loss at one year.

```
ggplot(df, aes(x=PreOpEyes, y=OneYEyes, label=study.name)) +
  geom_point(color="red") +
  geom_abline() +
  geom_text_repel() + coord_cartesian(xlim=c(0, 250), ylim=c(0, 250))
```

```
## Warning: Removed 51 rows containing missing values (geom_point).
```

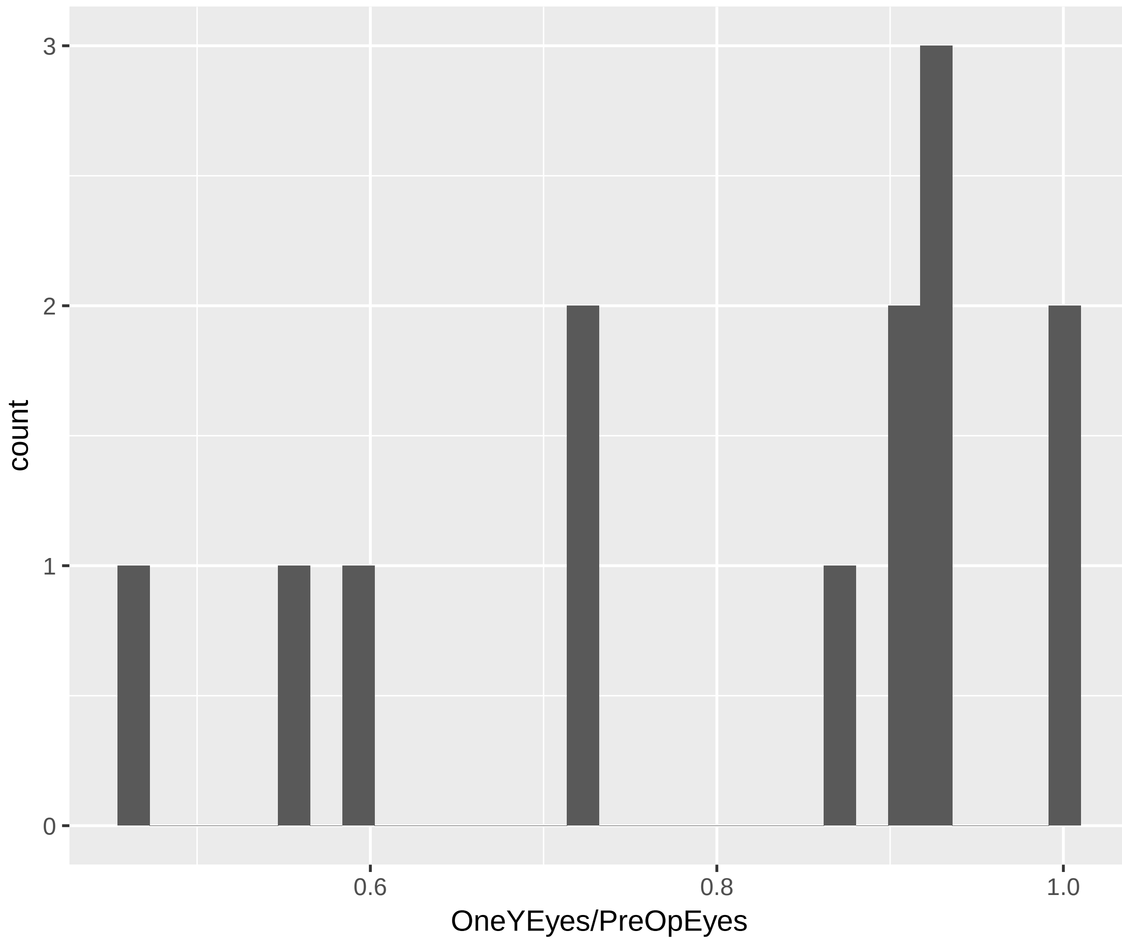
```
## Warning: Removed 51 rows containing missing values (geom_text_repel).
```




```r
ggplot(df, aes(x=OneYEyes / PreOpEyes, label=study.name)) +
  geom_histogram() +
  coord_cartesian()
```

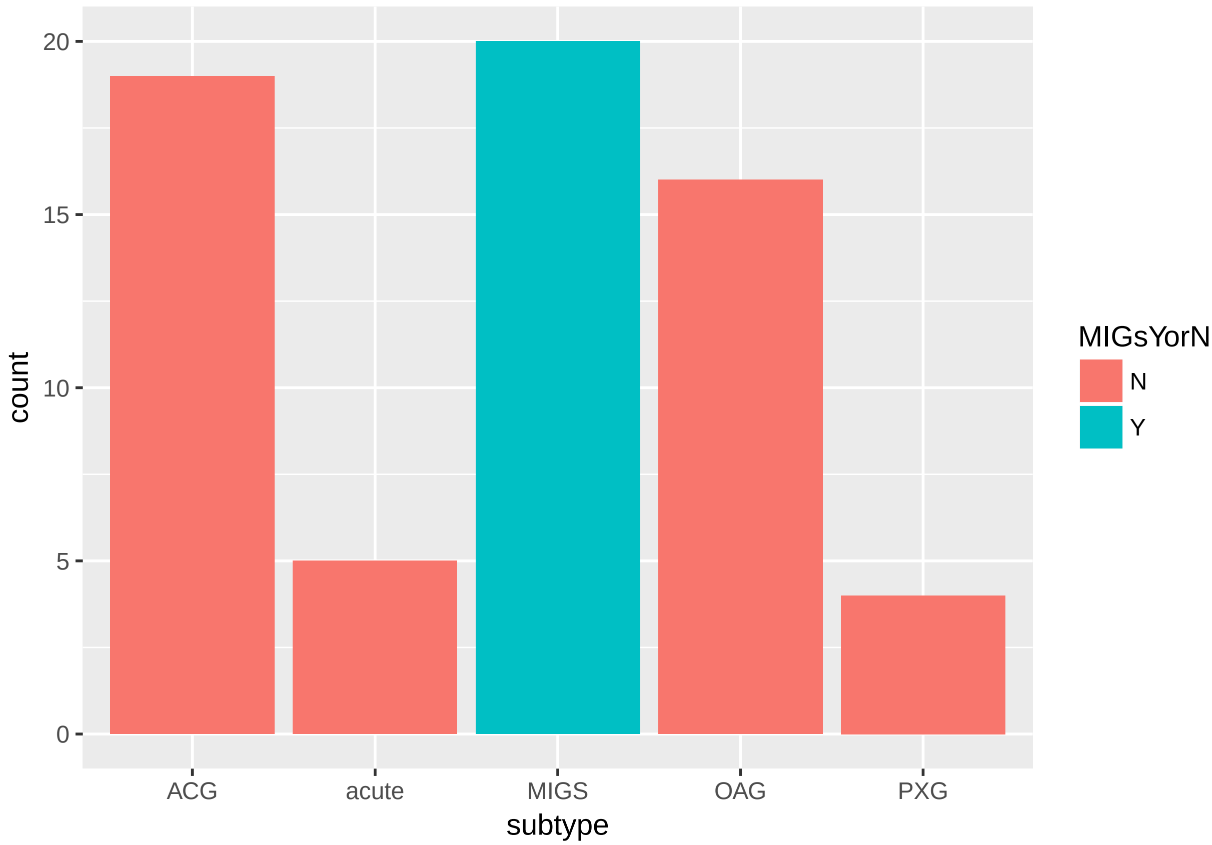
```
## `stat_bin()` using `bins = 30`. Pick better value with `binwidth`.
```

```
## Warning: Removed 51 rows containing non-finite values (stat_bin).
```



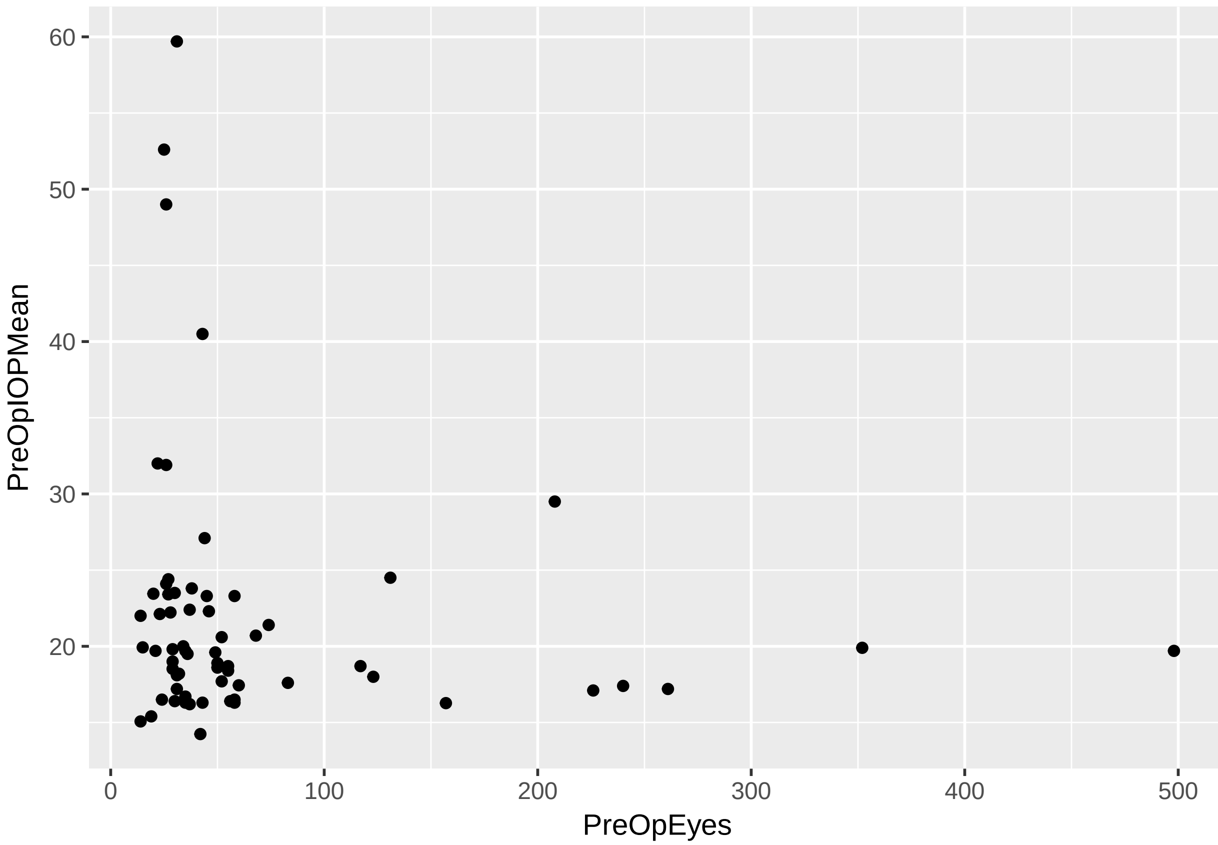

```
ggplot(df, aes(x=subtype, fill=MIGsYorN)) + geom_histogram(stat="count", position = 'dodge')
```

```
## Warning: Ignoring unknown parameters: binwidth, bins, pad
```



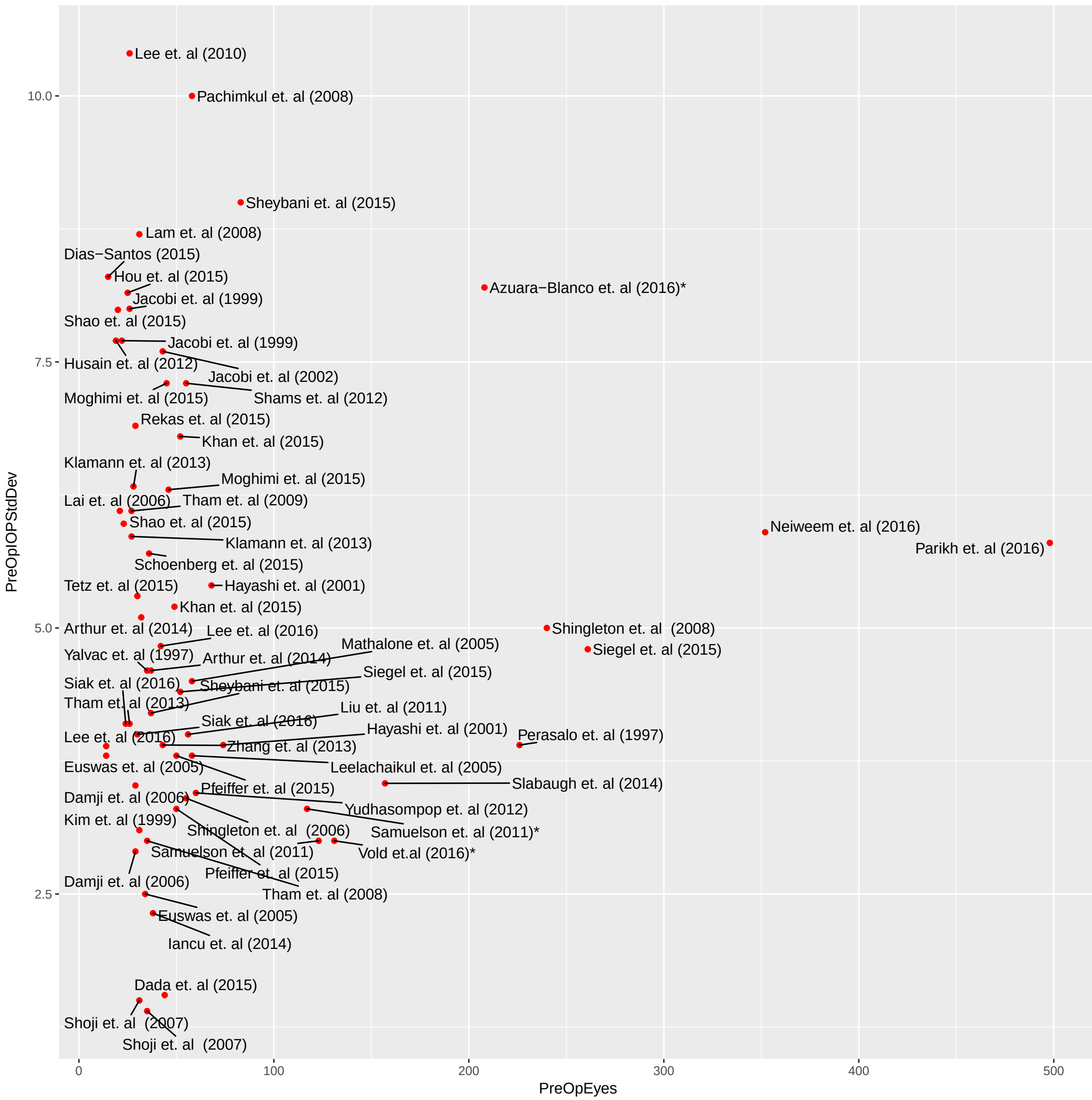
Look at the distribution of eyes and IOP means.

```
ggplot(df, aes(x=PreOpEyes, y=PreOpIOPMean)) + geom_point()
```



Look at number of eyes and standard deviation.

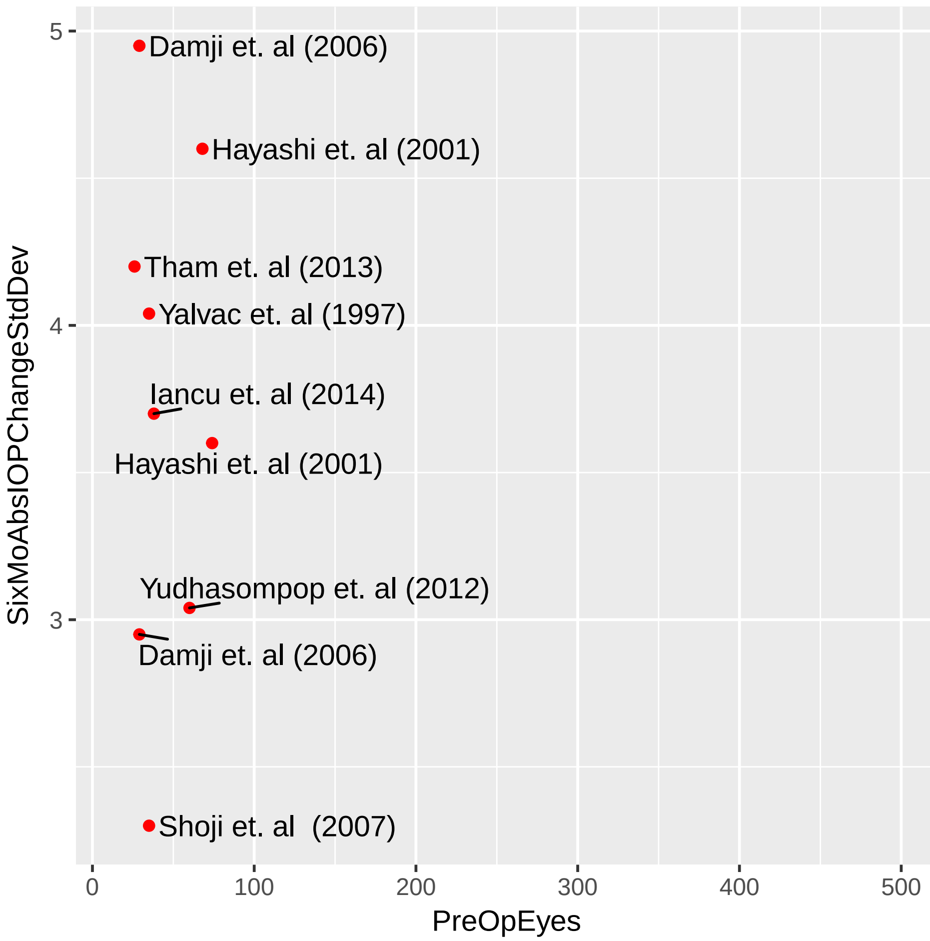
```
ggplot(df, aes(x=PreOpEyes, y=PreOpIOPStdDev, label=study.name)) + geom_point(color="red") + geom_text_
```




```
ggplot(df, aes(x=PreOpEyes, y=SixMoAbsIOPChangeStdDev, label=study.name)) + geom_point(color="red") + g
```

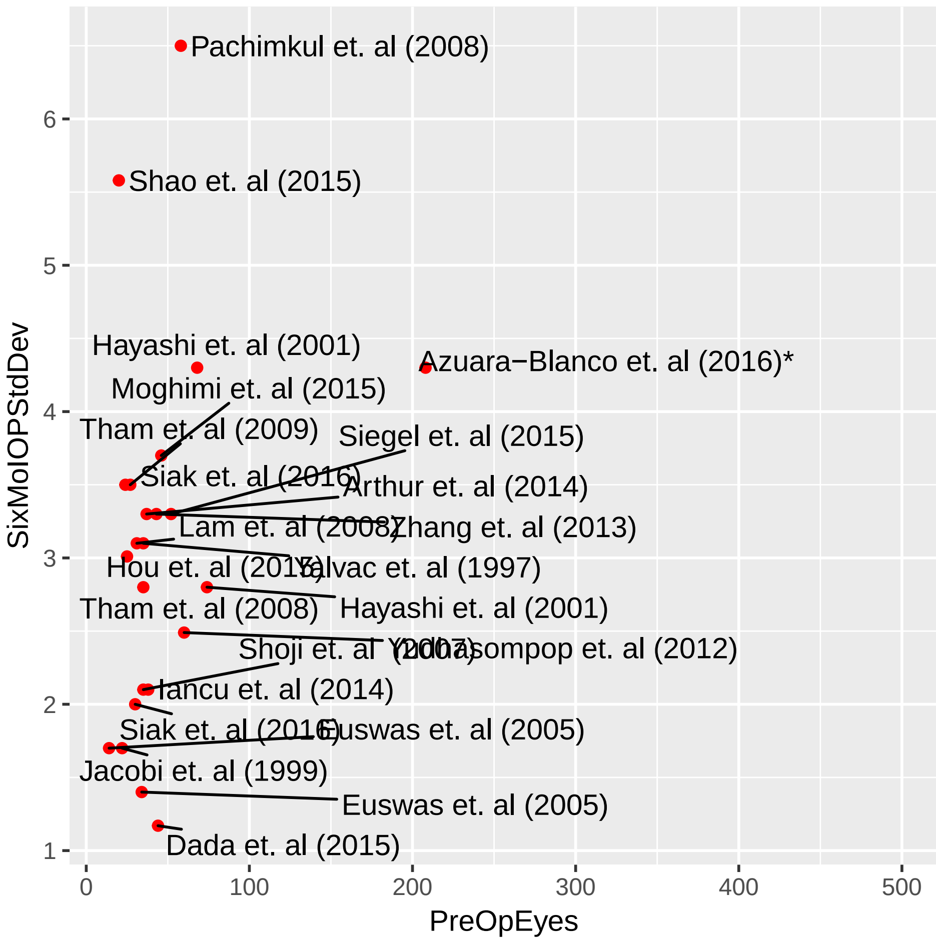
```
## Warning: Removed 55 rows containing missing values (geom_point).
```

```
## Warning: Removed 55 rows containing missing values (geom_text_repel).
```




```
ggplot(df, aes(x=PreOpEyes, y=SixMoIOPStdDev, label=study.name)) + geom_point(color="red") + geom_text_
```

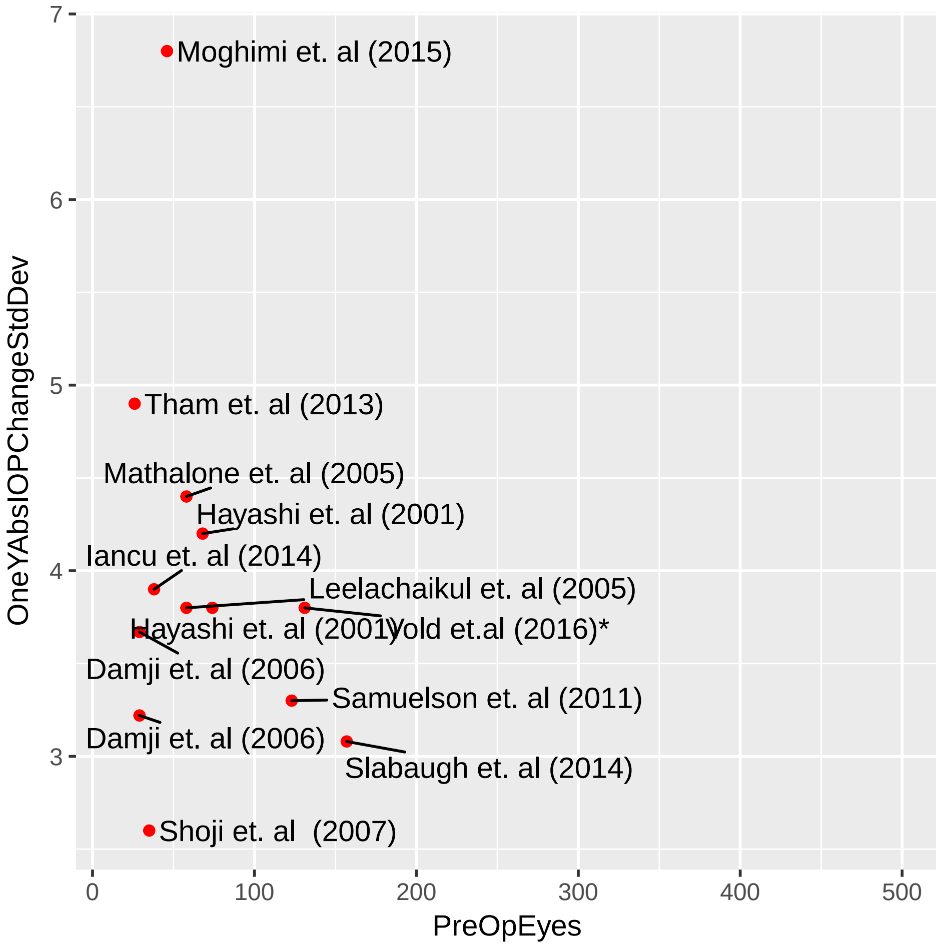
```
## Warning: Removed 41 rows containing missing values (geom_point).
## Warning: Removed 41 rows containing missing values (geom_text_repel).
```




```
ggplot(df, aes(x=PreOpEyes, y=OneYAbsIOPChangeStdDev, label=study.name)) + geom_point(color="red") + ge
```

```
## Warning: Removed 51 rows containing missing values (geom_point).
```

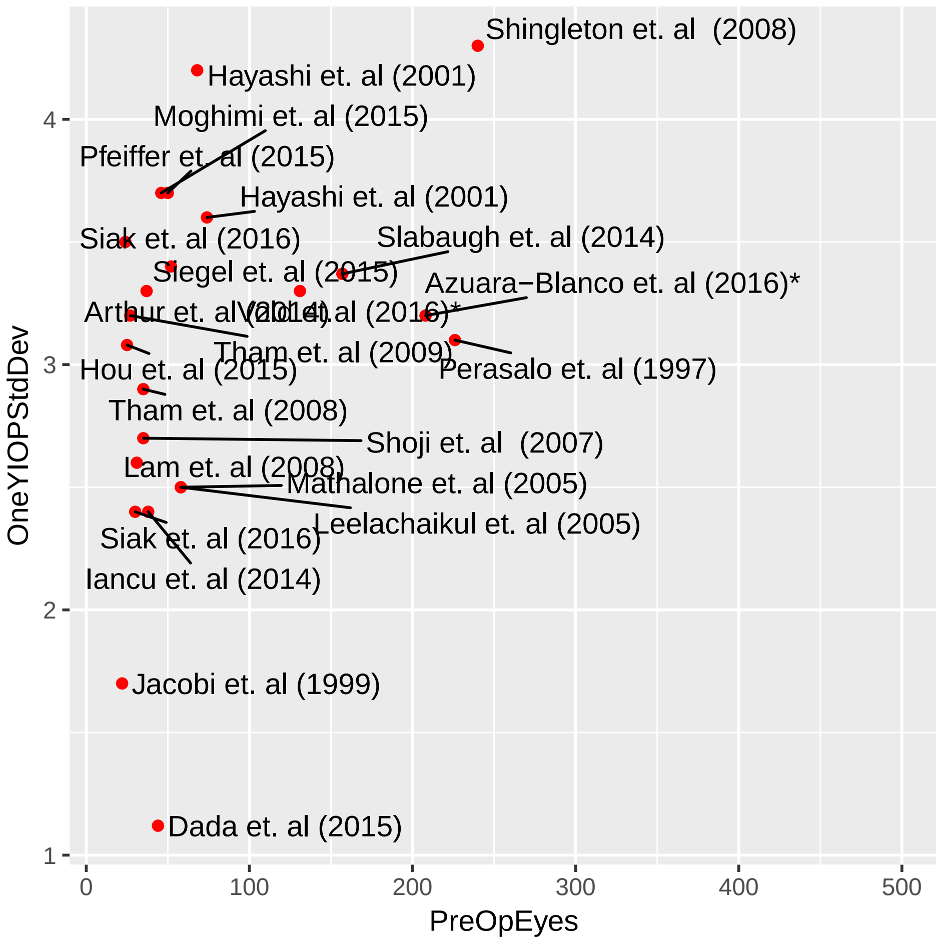
```
## Warning: Removed 51 rows containing missing values (geom_text_repel).
```




```
ggplot(df, aes(x=PreOpEyes, y=OneYIOPStdDev, label=study.name)) + geom_point(color="red") + geom_text_r
```

```
## Warning: Removed 41 rows containing missing values (geom_point).
```

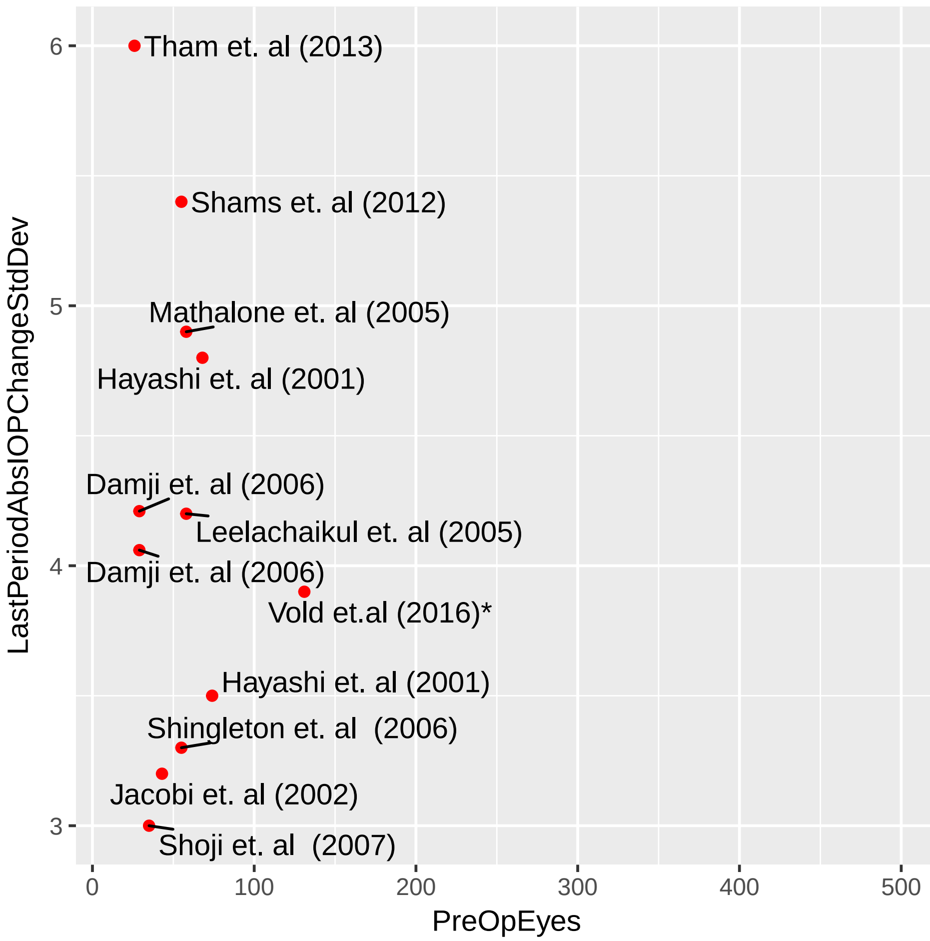
```
## Warning: Removed 41 rows containing missing values (geom_text_repel).
```




```
ggplot(df, aes(x=PreOpEyes, y=LastPeriodAbsIOPChangeStdDev, label=study.name)) + geom_point(color="red")
```

```
## Warning: Removed 52 rows containing missing values (geom_point).
```

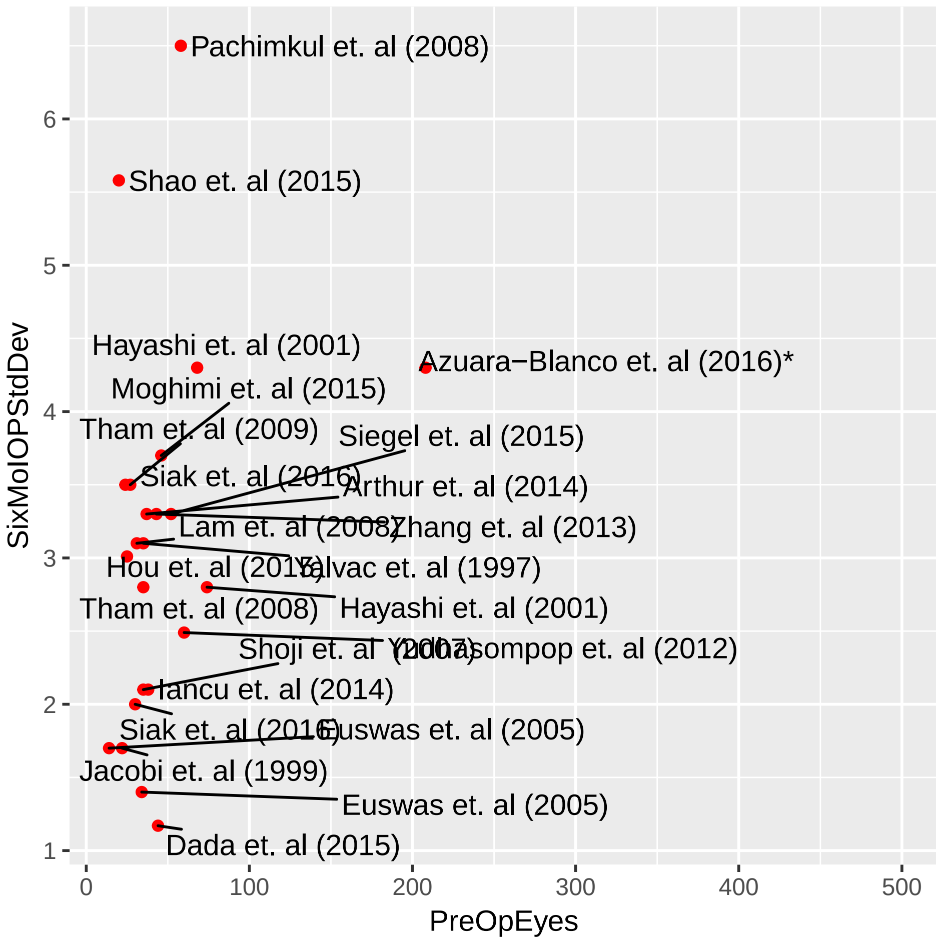
```
## Warning: Removed 52 rows containing missing values (geom_text_repel).
```




```
ggplot(df, aes(x=PreOpEyes, y=SixMoIOPStdDev, label=study.name)) + geom_point(color="red") + geom_text_
```

```
## Warning: Removed 41 rows containing missing values (geom_point).
```

```
## Warning: Removed 41 rows containing missing values (geom_text_repel).
```



Some notes on the analysis and the studies

- None of the studies are randomized, except the EAGLE one – (2016) Azuara-Bianco et al., Lancet
- There's no control arm in any of the studies
- Main outcome is IOP drop
  - The older studies are phaco + glaucoma surgery
  - The new ones are phaco + MIGS - minimally invasive glaucoma surgery

Slicings to look at

- MIGS
  - Don't look at MIGS
- Type of glaucoma:
  - OAG -> open angle glaucoma ** ~2-3mm **
  - NTG -> normal tension glaucoma ?
  - ACG -> angle closure glaucoma ** known to be effective **
  - PXG: pseudo-exfoliation ?

Dimensions to look at - meta-regression

- Initial severity (IOP before)
- Size of study (number of eyes)
- Year

Different outcomes

- Primary is IOP drop
  - time points 6 mo, 12 mo, (last time point)

  - most important is 12 months
- Number of meds
  - Huge confound, because it's controlled by the doctor
  - Meds themselves decrease the IOP
  - A handful of studies use washout pre and post (measuring the IOP without meds) to undo the confounding
    - EAGLE, Samuelson studies have washout
    - Lack of washout will have a tendency to decrease the apparent effectiveness of the studies
  - One med ~= 20% decrease in IOP
  - One med := decrease in quality of life
  - RxPostOpMean is at the same time as LastPeriod
- (visual acuity but it's kind of obvious)

Additional analyses to perform

- Funnel plot for small / medium large studies
- Deal appropriately with multiple arms of same study, e.g. Damji et al., Merz...
- Deal with three forms of lossiness:
  - Absolutes reported, relatives needed
  - Can patch up using estimate of rho – sqrt(s_1 ** 2 + s_2 ** 2 - 2 * rho * s_1 * s_2)
  - Try rho = 0, rho = 0.5
  - Loss of follow-up
  - Can deal with by assuming that follow up is either MCAR or worse than MCAR
  - Try mean_delta = 0, mean_delta = -3, mean_delta = -5
  - Not all metrics reported for every study
  - Use mvmeta