Practical 1: Indirect and mixed treatment effects

R packages

We will use the package **readxl** to import excel data and the package **meta** to run meta-analyses.

```
library(readxl)
library(meta)
```

Results (treatment estimates and confidence intervals) should be rounded to three digits (default is four digits).

```
settings.meta(digits = 3)
```

Dataset

Open the dataset PHOpairwise.xls by using the *Import Dataset* tab or type

```
PHOpairwise = read_excel("PHOpairwise.xls")
```

This network includes studies from three comparisons; Olanzapine versus Haloperidol, Placebo versus Haloperidol and Placebo versus Olanzapine. The outcome is efficacy measured using a symptoms scale (mean, sd and ncont for arms 1 and 2). The lower the outcome, the better the efficacy of the treatment. The treatments for arms 1 and 2 can be seen in variables t1, t2. Some studies report endpoint values but most studies report change from baseline. Because studies might use different scales to measure the outcome, we will synthesize the data using the standardized mean difference (SMD). This is a very simple 'triangular' network.

The aim of the first part of the practical is to fill-in the following table. The next commands will help you fill it in.

Direct evidence from pairwise (subgroup) meta-analyses

Summarize the SMDs from studies grouped by comparison using metacont and the option 'byvar' for subgroups. Then fill in the respective columns of the table considering the results from the random-effects model using the default DerSimonian-Laird estimator.

```
pooledSMD = metacont(ncont1, mean1, sd1, ncont2, mean2, sd2,
                     data = PHOpairwise, studlab = author, sm = "SMD",
                     byvar = contrast, print.byvar = FALSE,
                     comb.fixed = FALSE)
summary(pooledSMD)

## Number of studies combined: k = 17
##
##                          SMD           95%-CI     z  p-value
```

```
## Random effects model -0.453 [-0.563; -0.343] -8.05 < 0.0001
##
## Quantifying heterogeneity:
## tau^2 = 0.0309; H = 1.60 [1.23; 2.08]; I^2 = 60.8% [33.4%; 76.9%]
##
## Quantifying residual heterogeneity:
## H = 1.35 [1.00; 1.82]; I^2 = 44.8% [0.0%; 69.8%]
##
## Test of heterogeneity:
##      Q d.f. p-value
##  40.77   16  0.0006
##
## Results for subgroups (random effects model):
##                             k    SMD           95%-CI     Q  tau^2   I^2
## Haloperidol - Olanzapine    2 -0.149 [-0.322;  0.025]  0.01      0  0.0%
## Haloperidol - Placebo       6 -0.581 [-0.770; -0.393] 12.07 0.0311 58.6%
## Olanzapine - Placebo        9 -0.439 [-0.560; -0.318] 13.28 0.0133 39.7%
##
## Test for subgroup differences (random effects model):
##                      Q d.f. p-value
## Between groups   11.99    2  0.0025
##
## Details on meta-analytical method:
## - Inverse variance method
## - DerSimonian-Laird estimator for tau^2
## - Hedges' g (bias corrected standardised mean difference)
```

Consider your input in Table 1. Both drugs are better than Placebo – the SMDs should be (and are) negative.

Note, we can extract the direct treatment effect of the comparison of Haloperidol and Olanzapine and its standard error from R object pooledSMD:

```
directHO = pooledSMD$TE.random.w[pooledSMD$bylevs == "Haloperidol -
Olanzapine"]
se.directHO = pooledSMD$seTE.random.w[pooledSMD$bylevs == "Haloperidol -
Olanzapine"]
```

We will need this information later to compare direct with indirect evidence for the comparison between Haloperidol and Olanzapine.

Indirect comparison between Haloperidol and Olanzapine

How much does Haloperidol and how much does Olanzapine reduce the symptoms of acute mania?

Which of the two active drugs is better?

Can you derive an indirect SMD for the comparison Haloperidol versus Olanzapine? You can do so by subtracting the two SMDs from the comparisons with Placebo.

First, we extract the direct treatment effects of the comparisons of Haloperidol and Olanzapine with Placebo

```
directHP = pooledSMD$TE.random.w[pooledSMD$bylevs == "Haloperidol - Placebo"]
directOP = pooledSMD$TE.random.w[pooledSMD$bylevs == "Olanzapine - Placebo"]
```

and the corresponding standard errors

```
se.directHP = pooledSMD$seTE.random.w[pooledSMD$bylevs == "Haloperidol -
Placebo"]
se.directOP = pooledSMD$seTE.random.w[pooledSMD$bylevs == "Olanzapine -
Placebo"]
```

Then, we can calculate the indirect estimate

```
indirectHO = directHP - directOP
```

We can also estimate a standard error for the indirect SMD (as the variances of the direct estimates are independent and thus always add-up).

```
se.indirectHO = sqrt(se.directHP**2 + se.directOP**2)
```

We can use these quantities to estimate a 95% confidence interval for the indirect SMD:

```
metagen(indirectHO, se.indirectHO, sm = "SMD")

##     SMD          95%-CI     z p-value
##  -0.142 [-0.366; 0.082] -1.24  0.2136
##
## Details:
## - Inverse variance method
```

Go and add this information into the Table (forth column of results) - it is the SMD and 95% confidence interval of the indirect comparison Haloperidol – Olanzapine.

Compare direct and indirect evidence

The heterogeneity is estimated to be zero – what do you think about this? Are you confident that there is no heterogeneity?

How does the direct summary SMD compares with indirect SMD? Are they in reasonable agreement?

Compare the 95% confidence intervals between direct and indirect evidence. What do you conclude?

Which evidence is more precise and why?

Note that these two pieces of evidence (direct and indirect) are independent because they have been estimated using different sets of studies; Placebo – Olanzapine and Placebo – Haloperidol studies for the indirect and Olanzapine – Haloperidol studies for the direct.

Consequently, they can be pooled into a single summary SMD using a new, 'second-level' meta-analysis to estimate a mixed treatment effect.

Combine direct and indirect evidence into a mixed treatment effect

Create a dataset called DirectIndirect with two new "studies"; direct and indirect evidence about the comparison Haloperidol vs Olanzapine.

Use two variables named 'SMD' and 'seSMD' (with values those in the Table)

```
DirectIndirectHO = data.frame(source = c("indirect"   , "direct"),
                              SMD    = c(indirectHO   , directHO),
                              seSMD  = c(se.indirectHO, se.directHO))
```

These two SMDs can be meta-analyzed. The metagen function can take effect sizes and their standard errors as arguments. Meta-analysis of these two sources of evidence will produce a mixed SMD.

```
metagen(SMD, seSMD, data = DirectIndirectHO, studlab = source,
        comb.random = FALSE)
```

```
##                           95%-CI %W(fixed)
## indirect -0.142 [-0.366; 0.082]      37.5
## direct   -0.149 [-0.322; 0.025]      62.5
##
## Number of studies combined: k = 2
##
##                                      95%-CI     z p-value
## Fixed effect model -0.146 [-0.283; -0.009] -2.09  0.0369
##
## Quantifying heterogeneity:
## tau^2 = 0; H = 1.00; I^2 = 0.0%
##
## Test of heterogeneity:
##     Q d.f. p-value
##  0.00    1  0.9650
##
## Details on meta-analytical method:
## - Inverse variance method
```

Now add the values of the mixed SMD and the 95% CI to complete the table.