Practicals 2 Solutions: Network meta-analysis for a star-shaped network using subgroup analysis and meta-regression

Course on network meta-analysis 2018 Kea, Greece

## R packages

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

library(readxl)  
library(meta)

## Datasets

### Acute mania dataset

The file AcuteManiaP.xls comprises data from the efficacy outcome of the network meta-analysis published in Cipriani et al. (2011). We present here only some studies that compare an active intervention versus placebo. Hence the shape of the network is a star.

AcuteManiaP = read\_excel("~/\_mydrive/Teaching/Kea NMA Course/Practicals/AcuteManiaP.xls")  
AcuteManiaP = as.data.frame(AcuteManiaP)  
str(AcuteManiaP)

## 'data.frame': 27 obs. of 15 variables:  
## $ studlab: num 51 53 54 56 58 67 50 52 61 62 ...  
## $ treat1 : chr "Placebo" "Placebo" "Placebo" "Placebo" ...  
## $ treat2 : chr "Haloperidol" "Haloperidol" "Haloperidol" "Haloperidol" ...  
## $ ncont1 : num 152 100 88 47 138 97 163 95 NA 95 ...  
## $ mean1 : num 18.6 24.2 -6.1 -8.2 22.1 ...  
## $ sd1 : num 10.6 12.4 10.7 10 10.2 ...  
## $ ncont2 : num 161 98 170 50 144 20 155 98 NA 36 ...  
## $ mean2 : num 14.7 15.9 -15.9 -13.4 17.4 ...  
## $ sd2 : num 10.6 12.4 10.7 10 10.2 ...  
## $ event1 : num 58 35 18 NA 39 43 56 26 18 NA ...  
## $ n1 : num 153 101 88 51 140 99 165 97 74 95 ...  
## $ event2 : num 80 55 93 NA 59 13 71 52 18 NA ...  
## $ n2 : num 165 99 172 53 144 20 160 98 36 36 ...  
## $ AE1 : num 2 0 0 1 3 0 5 1 0 2 ...  
## $ AE2 : num 5 2 2 1 5 1 2 5 1 0 ...

How many comparisons are present in the network? How many studies?

The dataset is in *contrast-based (pairwise) format* ; that is, each row is a study and treatment comparison.

## Analysis of the star network comparing antimanic drugs and placebo

Let’s first get some information on the studies included in the network meta-analysis.

Which treatment is the most frequently studied?

table(AcuteManiaP$treat2)

##   
## Haloperidol Lithium Olanzapine Risperidone   
## 6 7 9 5

Now synthesize the SMDs for each active intervention versus Placebo. Instead of running eight separate meta-analyses, it is easier to run a meta-analysis in subgroups using the variable contrast.  
Use random effects and complete the first three columns of the following table. Some warning messages might be generated because of missing values in the data

Starmeta=metacont(ncont1,mean1,sd1,ncont2,mean2,sd2, data=AcuteManiaP, byvar=treat2, studlab=studlab,sm="SMD",comb.fixed=F)  
summary(Starmeta)

## Number of studies combined: k = 26  
##   
## SMD 95%-CI z p-value  
## Random effects model 0.4913 [0.4151; 0.5675] 12.64 < 0.0001  
##   
## Quantifying heterogeneity:  
## tau^2 = 0.0176; H = 1.37 [1.09; 1.72]; I^2 = 46.4% [15.2%; 66.2%]  
##   
## Test of heterogeneity:  
## Q d.f. p-value  
## 46.68 25 0.0054  
##   
## Results for subgroups (random effects model):  
## k SMD 95%-CI Q tau^2 I^2  
## treat2 = Haloperidol 6 0.5841 [0.4040; 0.7642] 11.01 0.0265 54.6%  
## treat2 = Lithium 6 0.4034 [0.2612; 0.5456] 7.59 0.0107 34.1%  
## treat2 = Olanzapine 9 0.4386 [0.3187; 0.5584] 13.07 0.0128 38.8%  
## treat2 = Risperidone 5 0.5946 [0.4283; 0.7610] 6.91 0.0149 42.1%  
##   
## Test for subgroup differences (random effects model):  
## Q d.f. p-value  
## Between groups 4.67 3 0.1975  
##   
## Details on meta-analytical method:  
## - Inverse variance method  
## - DerSimonian-Laird estimator for tau^2  
## - Hedges' g (bias corrected standardised mean difference)

TABLE HERE

Compare the heterogeneity values across comparisons. Consider the number of studies per comparison to comment on the heterogeneity estimates in studies. Which is the best treatment for efficacy? Which is the worse treatment? Can you derive an indirect relative treatment effect between Haloperidol and Risperidone? How much better is Risperidone to Lithium?

Now, we will use meta-regression to do subgroup analysis. The variable treat2 will be used to create dummy variables and these will be used in the regression line.

treat2.f= factor(AcuteManiaP$treat2)  
 dummies = model.matrix(~treat2.f)  
 print(dummies)

## (Intercept) treat2.fLithium treat2.fOlanzapine treat2.fRisperidone  
## 1 1 0 0 0  
## 2 1 0 0 0  
## 3 1 0 0 0  
## 4 1 0 0 0  
## 5 1 0 0 0  
## 6 1 0 0 0  
## 7 1 1 0 0  
## 8 1 1 0 0  
## 9 1 1 0 0  
## 10 1 1 0 0  
## 11 1 1 0 0  
## 12 1 1 0 0  
## 13 1 1 0 0  
## 14 1 0 1 0  
## 15 1 0 1 0  
## 16 1 0 1 0  
## 17 1 0 1 0  
## 18 1 0 1 0  
## 19 1 0 1 0  
## 20 1 0 1 0  
## 21 1 0 1 0  
## 22 1 0 1 0  
## 23 1 0 0 1  
## 24 1 0 0 1  
## 25 1 0 0 1  
## 26 1 0 0 1  
## 27 1 0 0 1  
## attr(,"assign")  
## [1] 0 1 1 1  
## attr(,"contrasts")  
## attr(,"contrasts")$treat2.f  
## [1] "contr.treatment"

These are the variables denoting the different comparisons of drugs versus placebo. The first treatment is used as reference.

Then, subgroup analysis can be performed using the metareg command. The function takes a meta-analysis object as argument – so we have to run a meta-analysis (without subgroups this time) – we will name the object Starmeta1

Starmeta1=metacont(ncont1,mean1,sd1,ncont2,mean2,sd2, data=AcuteManiaP, studlab=studlab,sm="SMD",comb.fixed=F)  
Starmetareg=metareg(Starmeta1,dummies)  
summary(Starmetareg)

##   
## Mixed-Effects Model (k = 26; tau^2 estimator: DL)  
##   
## logLik deviance AIC BIC AICc   
## 7.6985 36.1166 -5.3969 0.8936 -2.3969   
##   
## tau^2 (estimated amount of residual heterogeneity): 0.0156 (SE = 0.0111)  
## tau (square root of estimated tau^2 value): 0.1250  
## I^2 (residual heterogeneity / unaccounted variability): 42.99%  
## H^2 (unaccounted variability / sampling variability): 1.75  
## R^2 (amount of heterogeneity accounted for): 11.27%  
##   
## Test for Residual Heterogeneity:   
## QE(df = 22) = 38.5895, p-val = 0.0157  
##   
## Test of Moderators (coefficient(s) 2:4):   
## QM(df = 3) = 4.6751, p-val = 0.1972  
##   
## Model Results:  
##   
## estimate se zval pval ci.lb  
## intrcpt 0.5811 0.0806 7.2110 <.0001 0.4231  
## dummiestreat2.fLithium -0.1784 0.1123 -1.5883 0.1122 -0.3986  
## dummiestreat2.fOlanzapine -0.1434 0.1028 -1.3953 0.1629 -0.3448  
## dummiestreat2.fRisperidone 0.0133 0.1177 0.1131 0.9100 -0.2173  
## ci.ub   
## intrcpt 0.7390 \*\*\*  
## dummiestreat2.fLithium 0.0418   
## dummiestreat2.fOlanzapine 0.0580   
## dummiestreat2.fRisperidone 0.2439   
##   
## ---  
## Signif. codes: 0 '\*\*\*' 0.001 '\*\*' 0.01 '\*' 0.05 '.' 0.1 ' ' 1

Note that meta package is smart: actually we don’t even need to create the dummies. We could have typed

Starmetareg=metareg(Starmeta1,treat2)

and it would do exactly the same job!

Write here the regression line represented by the command above

Can you interpret the intercept and slopes of the regression line? How can you derive an indirect SMD between Risperidone and Haloperidol?

Note: The default method to estimate heterogeneity in metareg is the DerSimonian and Laird. The option method.tau can be used to change estimator.

A major difference between subgroup analysis and meta-regression using a categorical variable is the default assumption about heterogeneity; in subgroup analysis subgroup-specific τ2 are estimated whereas in meta-regression a common τ2 is assumed. To make the results comparable update the subgroup analysis to estimate a single τ2

update(Starmeta, tau.common = T)

## SMD 95%-CI %W(random) treat2  
## 51 0.3658 [ 0.1423; 0.5893] 4.9 Haloperidol  
## 53 0.6687 [ 0.3822; 0.9551] 3.9 Haloperidol  
## 54 0.9186 [ 0.6491; 1.1881] 4.1 Haloperidol  
## 56 0.5145 [ 0.1095; 0.9195] 2.5 Haloperidol  
## 58 0.4610 [ 0.2244; 0.6976] 4.7 Haloperidol  
## 67 0.6190 [ 0.1310; 1.1071] 1.9 Haloperidol  
## 50 0.3004 [ 0.0792; 0.5215] 5.0 Lithium  
## 52 0.7031 [ 0.4122; 0.9941] 3.8 Lithium  
## 61 NA 0.0 Lithium  
## 62 0.1104 [-0.2735; 0.4942] 2.7 Lithium  
## 63 0.3302 [ 0.0122; 0.6483] 3.4 Lithium  
## 64 0.4448 [ 0.1796; 0.7100] 4.2 Lithium  
## 65 0.4541 [ 0.1900; 0.7183] 4.2 Lithium  
## 16 0.4248 [ 0.0847; 0.7650] 3.2 Olanzapine  
## 17 0.5238 [ 0.1434; 0.9042] 2.7 Olanzapine  
## 19 0.4536 [ 0.2247; 0.6824] 4.8 Olanzapine  
## 22 0.0289 [-0.3336; 0.3913] 2.9 Olanzapine  
## 49 0.3919 [ 0.1127; 0.6711] 4.0 Olanzapine  
## 55 0.2394 [-0.0020; 0.4808] 4.6 Olanzapine  
## 59 0.6550 [ 0.4088; 0.9011] 4.5 Olanzapine  
## 60 0.6273 [ 0.3776; 0.8770] 4.5 Olanzapine  
## 67 0.4800 [ 0.1993; 0.7607] 4.0 Olanzapine  
## 23 0.8460 [ 0.6039; 1.0881] 4.6 Risperidone  
## 24 0.3446 [ 0.0107; 0.6786] 3.2 Risperidone  
## 25 0.6086 [ 0.3528; 0.8645] 4.4 Risperidone  
## 56 0.6036 [ 0.1980; 1.0091] 2.5 Risperidone  
## 58 0.5003 [ 0.2666; 0.7340] 4.7 Risperidone  
##   
## Number of studies combined: k = 26  
##   
## SMD 95%-CI z p-value  
## Random effects model 0.4913 [0.4151; 0.5675] 12.64 < 0.0001  
##   
## Quantifying heterogeneity:  
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## Test of heterogeneity:  
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##   
## Results for subgroups (random effects model):  
## k SMD 95%-CI Q tau^2 I^2  
## treat2 = Haloperidol 6 0.5811 [0.4231; 0.7390] 11.01 0.0156 54.6%  
## treat2 = Lithium 6 0.4026 [0.2492; 0.5560] 7.59 0.0156 34.1%  
## treat2 = Olanzapine 9 0.4377 [0.3127; 0.5626] 13.07 0.0156 38.8%  
## treat2 = Risperidone 5 0.5944 [0.4263; 0.7624] 6.91 0.0156 42.1%  
##   
## Test for subgroup differences (random effects model):  
## Q d.f. p-value  
## Between groups 4.68 3 0.1972  
## Within groups 38.59 22 0.0157  
##   
## Details on meta-analytical method:  
## - Inverse variance method  
## - DerSimonian-Laird estimator for tau^2 (assuming common tau^2 in subgroups)  
## - Hedges' g (bias corrected standardised mean difference)

Now the two approaches should give identical results. How plausible it is to assume that the heterogeneity is the same in all eight comparisons?

## References

* Cipriani A et al. (2011): Comparative efficacy and acceptability of antimanic drugs in acute mania: a multiple-treatments meta-analysis. *The Lancet*, **378**(9799), 1306-15.