Heterogeneity- Subgroup Analysis and Meta-Regression

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# Introduction

Bassler et.al (Bassler et al. 2004) conducted a Cochrane Review to evaluate the effects of Ketotifen alone or in combination with other co=interventions in children with asthma and/or wheezing. The primary outcome was the reduction in use of rescue bronchodilators. Secondary clinical endpoints included physician’s judgement on the overall efficacy of Ketotifen. In the systematic review, a random effects model with the risk ratio as measure of treatment effect was used throughout. The meta-analysis of the clinical judgement data contains 10 trials.

Let’s import the data in to start our analysis. In order to do that we have to call the *readxl* package using the library(“readxl”) command. If a package is not installed in your computer you can install by using the *install.packages(‘name of the package’)* command

library("readxl")  
Ketotifen = read\_xlsx("Data/Ketotifen.xlsx")

We can see the first rows of our data with the *head()* command.

head(Ketotifen,   
 n =10 # number of row we want to print  
 )

# A tibble: 10 x 6  
 study Ee Ne Ec Nc blind   
 <chr> <dbl> <dbl> <dbl> <dbl> <chr>   
 1 Chay 1 10 6 10 Blinded  
 2 Rackam 31 68 38 65 Blinded  
 3 Van Asperen 16 52 19 51 Blinded  
 4 Croce 19 39 17 36 unclear  
 5 de Benedictis 7 34 35 41 unclear  
 6 Longo 10 18 15 18 unclear  
 7 Montoya 6 20 14 20 unclear  
 8 Mulhern 6 16 8 15 unclear  
 9 Salmon 8 28 16 34 unclear  
10 Spicak 9 25 20 25 unclear

Our assumption is that the treatment effects come from a larger distribution rather than a common effect. Therefore, since we want to generalise our conclusions to broader populations, we will perform a random=effect model. We will use the *meta* package. The primary function for dichotomous outcomes is *metabin()*

library("meta")

An easy way to check the help file of any package and/or functions is to use the *?* or *??* and then the name of the function or package, for instance *??metabin*. *meta* package has an excellent help file, take advantage of it. In your computer please fill the … , in the following command with the appropriate variables from the data.

**Reminder** *We want to perform a random-effect meta-analysis with risk ratio as an effect size, using the empirical Bayes (EB) as a estimator*

res.RE = metabin(event.e = .. , ## Events of treated  
 n.e = .. , ## Total number of treated  
 event.c = .. , ## Events of control  
 n.c = .., ## Total number of treated  
 sm = .., ## Effect size  
 method = .., ## weight calculation method  
 data = .., ## the data-set  
 studlab = .., ## The trial names  
 method.tau=.. ## tau estimator method  
   
 )  
  
forest(res.RE)

**Interpret this output**

**What is our outcome?**

**Does the Ketotifen help the patients?**

**Describe what Q , , and H are and the report the estimated values**

**Do our data agree with the random-effects model assumption?**

**Is the heterogeneity large?**

## Subgroup analysis

*Until now we 1) did a systematic review, 2) gathered the Ketotifen data, 3) conducted a meta-analysis, in order to find out whether the use of Ketotifen is beneficial or not and therefore 4) we pooled our treatment effects using a random-effects model, because we assumed that the treatment effects of the trials come from a greater distribution. Finally, we realised that there is significant heterogeneity, which justifies the random-effects assumption we made.*

This is one side of meta-analysis. Another is to investigate our data in order to understand where do these differences come from. We observed, that some trials had a common design. Particularly Chay et al., Rackham et al., and Van Asperen et al. used blinding method. We wonder if we can explain some heterogeneity, by splitting the trials into two meta-analyses. One for the blinded and one for not-blinded trials.

**Blinding is a trial characteristic not a patient characteristic, therefore we can perform subgroup analysis. If the categorical variable was a patient characteristic, for instance gender then we SHOULD not split the trial and perform a Subgroup analysis. We will discuss this case later on**

This is easily done using the same function **metabin()**, but adding also the option **byvar**.

res.SA = metabin(event.e = .. , ## Events of treated  
 n.e = .. , ## Total number of treated  
 event.c = .. , ## Events of control  
 n.c = .., ## Total number of treated  
 sm = .., ## Effect size  
 method = .., ## weight calculation method  
 data = .., ## the data-set  
 studlab = .., ## The trial names  
 method.tau=.., ## tau estimator method  
 byvar = .., ## The splitting variable   
 comb.fixed = F ## A logical variable (True/False) indicating   
 ## whether a fixed effect meta-analysis should be conducted.  
 )  
  
forest(res.SA)

**Note: for better looking forest-plots see the help file ( ??forest.meta )**

The subgroup analysis shows that method of blinding does not explain adequately the statistical heterogeneity between trials. *Why?*

**What are the values of , , H and now?**

**Report the Test for subgroup differences**

Subgroup analysis has a lot in common with a meta-regression with a categorical independent variable. We can also perform a subgroup analysis in a “linear” meta-regression framework. Particularly, we can use the *metareg()* function to fit a meta-regression, using the log risk ratios as a dependent variable and the blinding as an independent one. The options takes need a *meta* object (the random effects meta-analysis we performed earlier is one) and the categorical variable we wish to use (in our case blinding).

**Fill the ….**

res.MR.SA =metareg(x = .... , ## an object of class meta  
 formula = ....,  
 hakn = T)

Compare the subgroup analysis with the meta-regression output. There some minor differences, but this is due the fact that the within the blinded and unclear groups are different in subgroup analysis, while in meta-regression they are the same. If we choose the to be the same meta-regression is equal to the SA.

res.SA.2 = metabin(event.e = Ee , ## Events of treated  
 n.e = Ne , ## Total number of treated  
 event.c = Ec , ## Events of control  
 n.c = Nc, ## Total number of treated  
 sm = "RR", ## Effect size  
 method = "Inverse", ## weight calculation method  
 data = Ketotifen, ## the data-set  
 studlab = study, ## The trial names  
 method.tau="EB", ## tau estimator method  
 byvar = blind, ## The splitting variable   
 comb.fixed = F, ## A logical variable (True/False) indicating   
 ## whether a fixed effect meta-analysis should be conducted.  
 tau.common = T  
 )  
  
# forest(res.SA)

## Meta-regression with a continuous covariate

In this section we will try to explain again part of the heterogeneity, but instead of using a categorical variable we will use a continuous.

We will use a meta-analysis of Colditz et al. (Colditz 1994), where he evaluated the overall effectiveness of the Bacillus Calmette-Guerin vaccine against tuberculosis. In addition, covariates that may potentially influence the effect of vaccination were examined.

**Note: we using again a variable that is a trial characteristic**

library(metafor)  
dat <- dat.colditz1994  
head(dat)

trial author year tpos tneg cpos cneg ablat alloc  
1 1 Aronson 1948 4 119 11 128 44 random  
2 2 Ferguson & Simes 1949 6 300 29 274 55 random  
3 3 Rosenthal et al 1960 3 228 11 209 42 random  
4 4 Hart & Sutherland 1977 62 13536 248 12619 52 random  
5 5 Frimodt-Moller et al 1973 33 5036 47 5761 13 alternate  
6 6 Stein & Aronson 1953 180 1361 372 1079 44 alternate

We believe that part of our data heterogeneity can be due to the country’s place on the world map. That is a resonable thing in epidemic, since the climate may affect the disease. Therefore, we will fit a meta-regression using the logRR as dependent variable and he absolute geographical latitude

res.RE = metabin(event.e = tpos,  
 n.e = tpos+tneg ,  
 event.c = cpos,  
 n.c = cpos+cneg,  
 data = dat,   
 studlab = paste(author, year),   
 sm = "RR")  
  
res.RE

RR 95%-CI %W(fixed) %W(random)  
Aronson 1948 0.4109 [0.1343; 1.2574] 0.7 5.0  
Ferguson & Simes 1949 0.2049 [0.0863; 0.4864] 1.9 6.4  
Rosenthal et al 1960 0.2597 [0.0734; 0.9186] 0.7 4.4  
Hart & Sutherland 1977 0.2366 [0.1793; 0.3121] 16.2 9.7  
Frimodt-Moller et al 1973 0.8045 [0.5163; 1.2536] 2.8 8.9  
Stein & Aronson 1953 0.4556 [0.3871; 0.5362] 24.3 10.1  
Vandiviere et al 1973 0.1977 [0.0784; 0.4989] 1.0 6.0  
TPT Madras 1980 1.0120 [0.8946; 1.1449] 31.7 10.2  
Coetzee & Berjak 1968 0.6254 [0.3926; 0.9962] 2.9 8.7  
Rosenthal et al 1961 0.2538 [0.1494; 0.4310] 4.2 8.4  
Comstock et al 1974 0.7122 [0.5725; 0.8860] 11.6 9.9  
Comstock & Webster 1969 1.5619 [0.3737; 6.5284] 0.2 3.8  
Comstock et al 1976 0.9828 [0.5821; 1.6593] 1.8 8.4  
  
Number of studies combined: k = 13  
  
 RR 95%-CI z p-value  
Fixed effect model 0.6353 [0.5881; 0.6862] -11.53 < 0.0001  
Random effects model 0.4896 [0.3448; 0.6952] -3.99 < 0.0001  
  
Quantifying heterogeneity:  
tau^2 = 0.3095; H = 3.57 [2.93; 4.34]; I^2 = 92.1% [88.3%; 94.7%]  
  
Test of heterogeneity:  
 Q d.f. p-value  
 152.57 12 < 0.0001  
  
Details on meta-analytical method:  
- Mantel-Haenszel method  
- DerSimonian-Laird estimator for tau^2

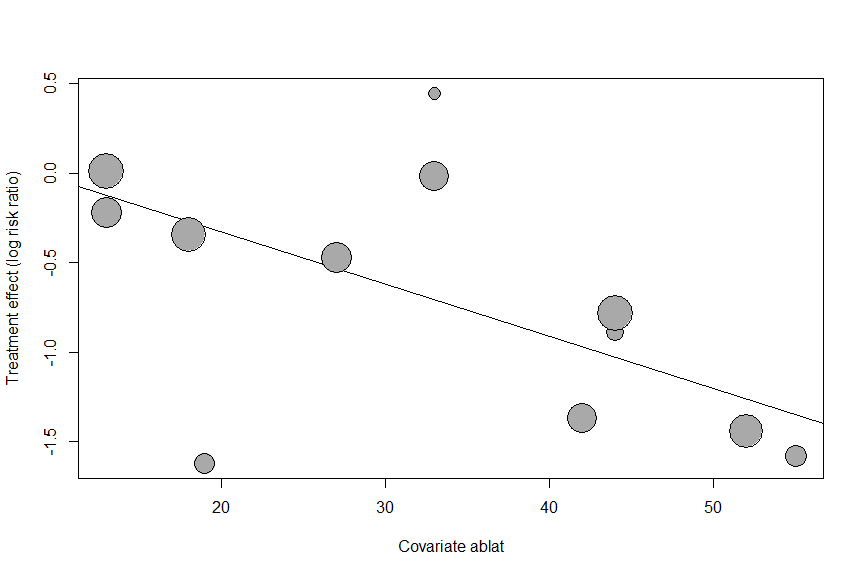
res.RE.MR = metareg(res.RE, ablat)

**Report the Test for Residual Heterogeneity and the Test for Moderators**

**What are our conclusions?**

We can also plot the effect estimates over the range of the absolute geographical latitude, so that we may have a visual represantion, using the *bubble()* command. See the help file (*??bubble.metareg*).

bubble(res.RE.MR)



**Based on our model calculate the predicted logRR (and then RR) for Nijmegen (or any other city you like)**

**What are the absolute geographical latitude ranges we can safely predict?**

# References

Bassler, Dirk, Andrew AD Mitra, Francine M Ducharme, Johannes Forster, and Guido Schwarzer. 2004. “Ketotifen Alone or as Additional Medication for Long-Term Control of Asthma and Wheeze in Children.” *Cochrane Database of Systematic Reviews*, January. <https://doi.org/10.1002/14651858.cd001384.pub2>.

Colditz, Graham A. 1994. “Efficacy of BCG Vaccine in the Prevention of Tuberculosis.” *JAMA* 271 (9): 698. <https://doi.org/10.1001/jama.1994.03510330076038>.