Meta-Regression

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Meta-Regression

- In case of substantial heterogeneity between the studies, possible causes of the heterogeneity should be explored.
- In the context of meta-analysis this can be done by either covariates on the study level that could explain the differences between the studies or by covariates on the subject level.
- However, the latter approach is only possible when individual data are available.
- Since often only information on the study level is available, explaining and investigating heterogeneity by covariates on the study level has drawn much attention in applied sciences.

Meta-Regression

- Since the number of studies in a meta-analysis is usually quite small, there is a great danger of overfitting.
- So, there is only room for a few explanatory variables in a meta-regression, whereas a lot of characteristics of the studies may be identified as potential causes of heterogeneity.
- Investigations of differences between the studies and their results are observational associations and are subject to biases (such as aggregation bias) and confounding (resulting from correlation between study characteristics).
- Consequently, there is a clear danger of misleading conclusions if P-values from multiple meta-regression analyses are interpreted naïvely.

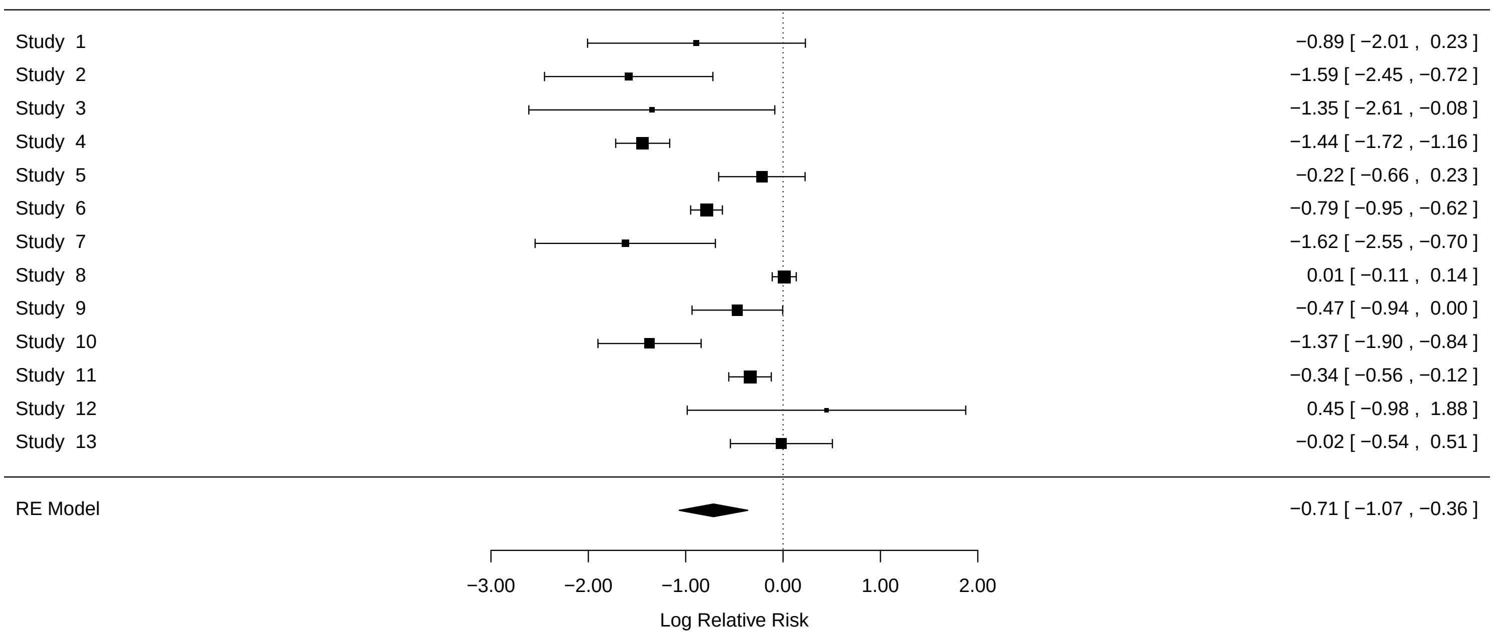
Example

Data on 13 trials on the prevention of tuberculosis using BCG vaccination

Trial	Vaccinated		Not vaccinated		Latitude
	Disease	No disease	Disease	No Disease	
1	4	119	11	128	44
2	6	300	29	274	55
3	3	228	11	209	42
4	62	13536	248	12619	52
5	33	5036	47	5761	13
6	180	1361	372	1079	44
7	8	2537	10	619	19
8	505	87886	499	87892	13
9	29	7470	45	7232	27*
10	17	1699	65	1600	42
11	186	50448	414	27197	18
12	5	2493	3	2338	33
13	27	16886	29	17825	33

Further covariates available: Year of publication, type of allocation (alternate, random, systematic)

Example



Study 1
Study 2
Study 3
Study 4
Study 5
Study 6
Study 7
Study 8
Study 9
Study 10
Study 11
Study 12
Study 13
RE Model
−0.89 [−2.01 , 0.23]
−1.59 [−2.45 , −0.72]
−1.35 [−2.61 , −0.08]
−1.44 [−1.72 , −1.16]
−0.22 [−0.66 , 0.23]
−0.79 [−0.95 , −0.62]
−1.62 [−2.55 , −0.70]
0.01 [−0.11 , 0.14]
−0.47 [−0.94 , 0.00]
−1.37 [−1.90 , −0.84]
−0.34 [−0.56 , −0.12]
0.45 [−0.98 , 1.88]
−0.02 [−0.54 , 0.51]
−0.71 [−1.07 , −0.36]
−3.00
−2.00
−1.00
0.00
1.00
2.00
Log Relative Risk

Meta-Regression (one covariate)

Let us consider k independent trials (experiments) and each trial provides an estimate, say $\hat{\theta}_i$, $i = 1, \ldots, k$, of a parameter of interest, say θ, and an estimate of the variance of $\hat{\theta}_i$, say $\hat{\sigma}_i^2$, $i = 1, \ldots, k$. Moreover, one covariate on study-level, say x_i, is known for each trial.

Normal-normal hierarchical model:

$$\hat{\theta}_i \sim N\left(\theta_i, \hat{\sigma}_i^2\right)$$

and

$$\theta_i \sim N\left(\theta_{MA}, \tau_{MA}^2\right)$$

OR

$$\theta_i \sim N\left(\theta_{MR} + \beta x_i, \tau_{MR}^2\right)$$

Meta-Regression (one covariate)

Random effects meta-analysis model

$$\hat{\theta}_i \sim N\left(\theta_{MA}, \tau^2_{MA} + \hat{\sigma}^2_i\right).$$

- θ_{MA} – mean effect size
- τ^2_{MA} – between-study variability (heterogeneity parameter)

Random effects meta-regression

$$\hat{\theta}_i \sim N\left(\theta_{MR} + \beta x_i \ , \ \tau^2_{MR} + \hat{\sigma}^2_i\right).$$

- θ_{MR} – effect size given that the covariate is zero
- τ^2_{MR} – residual heterogeneity

Meta-Regression (one covariate)

Random effects meta-regression

$$\hat{\theta}_i \sim N\left(\theta_{MR} + \beta x_i \;,\; \tau^2_{MR} + \hat{\sigma}^2_i\right).$$

Objectives:

- Fixed effects or random effects meta-regression?
  Test of $H_0 : \tau^2_{MR} = 0$!
- Estimate and confidence interval for τ^2_{MR}
- Estimates and confidence intervals for θ_{MR} and β

Extend analysis methods from meta-analysis to meta-regression:

- (conditional) restricted maximum likelihood estimation
- method of moments estimation

R Package `metafor`

- "Classical" meta-analysis and meta-regression (weighted least squares method)

- Knapp-Hartung (2003) approach for meta-analysis and meta-regression

- Q-profiling confidence interval for τ^2

- A lot of estimators for the heterogeneity parameter τ^2

- ...

Note: The $metareg$ function in R package `meta` can also be used (wrapper function that calls $rma.uni$ function from R package `metafor`).

Inference on the Fixed Effects

- Let $\tilde{\theta}$ and $\tilde{\beta}$ be the weighted least-squares estimators with known variances.

- Knapp and Hartung (2003) considered the quadratic form

$$Q_2 = \frac{1}{k-2} \sum_{i=1}^{k} w_i \, (Y_i - \tilde{\theta} - \tilde{\beta}\, x_i)^2 \, , \; k > 2 \, .$$

  that is, a mean sum of the weighted least-squares residuals.

- Under normality of Y_i, the quadratic form Q_2 is stochastically independent of the $\tilde{\theta}$ and $\tilde{\beta}$, and $(k-2)\ Q_2$ is χ^2-distributed with $k-2$ degrees of freedom.

Inference on the Fixed Effects

- Hence, unbiased and non-negative estimators of the variances of $\tilde{\theta}$ and $\tilde{\beta}$ are given by

$$Q_2(\tilde{\theta}) = \frac{1}{k-2} \sum_{i=1}^{k} g_i \, (Y_i - \tilde{\theta} - \tilde{\beta}\, x_i)^2$$

with $\quad g_i = w_i \,/\, [\sum w_j - (\sum w_j \, x_j)^2 / \sum w_j \, x_j^2], \; i = 1, \ldots, k$, and

$$Q_2(\tilde{\beta}) = \frac{1}{k-2} \sum_{i=1}^{k} h_i \, (Y_i - \tilde{\theta} - \tilde{\beta}\, x_i)^2$$

with $\quad h_i = w_i \,/\, [\sum w_j \, x_j^2 - (\sum w_j \, x_j)^2 / \sum w_j], \; i = 1, \ldots, k$.

Inference on the Fixed Effects

- Replacing the unknown variance components in $Q_2(\tilde{\theta})$ and $Q_2(\tilde{\beta})$ by appropriate estimates, Knapp and Hartung (2003) proposed the following approximate $(1-\alpha)$-confidence intervals on θ and β:

$$\hat{\theta} \pm \sqrt{\hat{Q}_2(\hat{\theta})}\, t_{k-2;\alpha/2}$$

and

$$\hat{\beta} \pm \sqrt{\hat{Q}_2(\hat{\beta})}\, t_{k-2;\alpha/2}\ .$$

Example

Results for slope with covariate latitude

Method $\hat{\tau}^2$	Estimate	95% CI (classical)	95% CI (KH)
Hunter-Schmidt	-0.0296	[-0.0398, -0.0193]	[-0.0447, -0.0144]
Hedges	-0.0282	[-0.0489, -0.0075]	[-0.0493, -0.0071]
DerSimonian-Laird	-0.0292	[-0.0424, -0.0160]	[-0.0467, -0.0118]
Sidik-Jonkman	-0.0281	[-0.0497, -0.0065]	[-0.0495, -0.0067]
ML	-0.0295	[-0.0403, -0.0188]	[-0.0452, -0.0139]
REML	-0.0291	[-0.0432, -0.0150]	[-0.0472, -0.0111]
Paule-Mandel	-0.0286	[-0.0463, -0.0108]	[-0.0485, -0.0086]

Explaining Heterogeneity

Method $\hat{\tau}^2$	MA	MR	Reduction (in %)
Hunter-Schmidt	0.2284	0.0291	87.26
Hedges	0.3285	0.2090	36.38
DerSimonian-Laird	0.3087	0.0633	79.50
Sidik-Jonkman	0.3455	0.2318	32.90
ML	0.2800	0.0344	87.73
REML	0.3132	0.0764	75.62
Paule-Mandel	0.3180	0.1421	55.31

Categorical Covariate

```
### load package
load(metafor)
### load BCG vaccine data
data(dat.bcg)
### calculate log relative risks and corresponding sampling variances
dat <- escalc(measure="RR", ai=tpos, bi=tneg, ci=cpos,
                            di=cneg, data=dat.bcg)
### using a model formula to specify the same model
rma(yi, vi, mods = ~ factor(alloc), data=dat, method="REML", btt=c(2,3))
```

Categorical Covariate

```
Mixed-Effects Model (k = 13; tau^2 estimator: REML)

tau^2 (estimated amount of residual heterogeneity):     0.3615
tau (square root of estimated tau^2 value):             0.6013
I^2 (residual heterogeneity / unaccounted variability): 88.77%
H^2 (unaccounted variability / sampling variability):   8.91
R^2 (amount of heterogeneity accounted for):            0.00%

Test for Residual Heterogeneity:
QE(df = 10) = 132.3676, p-val < .0001

Test of Moderators (coefficient(s) 2,3):
QM(df = 2) = 1.7675, p-val = 0.4132
```

Categorical Covariate

```
Model Results:

            estimate      se     zval    pval    ci.lb   ci.ub
intrcpt      -0.5180  0.4412  -1.1740  0.2404  -1.3827  0.3468
random       -0.4478  0.5158  -0.8682  0.3853  -1.4588  0.5632
systematic    0.0890  0.5600   0.1590  0.8737  -1.0086  1.1867

---
Signif. codes:  0 *** 0.001 ** 0.01 * 0.05 . 0.1   1
Results for type of allocation
```

Further Applications

- Methods can be easily extended to more than one covariate.
- Meta-regression is primarily used for explaining heterogeneity between study results.
- Meta-regression technique can be also used for other applications of combining results; e.g. combining results from controlled and uncontrolled studies in meta-regression model where the covariate indicates whether the result comes from a controlled or from an uncontrolled study