

## Meta-Analysis in R with the metafor Package

Oslo useR! Group Meetup

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2021-08-26

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### First of all ...

- thank you for the invitation!
- would like to talk about the development of metafor
- do a small tutorial on its basic functionality
- highlight some interesting applications
- for those who want to follow along with the demo later on:  
[https://www.wvbauer.com/lib/exe/fetch.php/talks:2021\\_viechtbauer\\_oslo\\_user\\_metafor.r](https://www.wvbauer.com/lib/exe/fetch.php/talks:2021_viechtbauer_oslo_user_metafor.r)

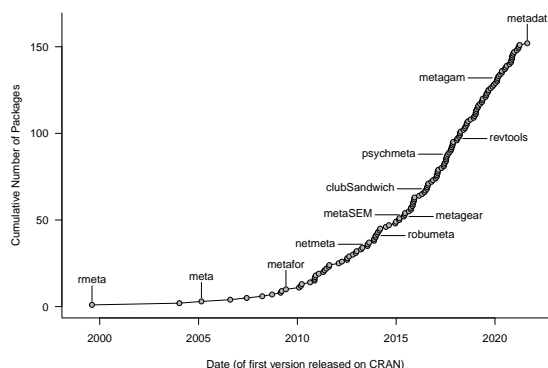
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### Software for Meta-Analysis

- 1990's: DSTAT [1], True Epistat [2], FAST\*PRO [3], macros, ...
- 1993: RevMan released (not R) [4]
- 1997: MetaWin released (also not R) [5]
- 1998: Comprehensive Meta-Analysis released (still no R) [6]
- 1999: rmeta package, but no 'meta-regression' capabilities
- ~2000: wrote function for fitting random/mixed-effects models
- ~2005: put function on my personal website
- ~2005: meta package
- 2006-2009: a few other packages
- 2009: published metafor package
- 2009-now: lots of new packages (current count: 152)  
based on CRAN Task View on Meta-Analysis:  
<https://cran.r-project.org/view=MetaAnalysis>

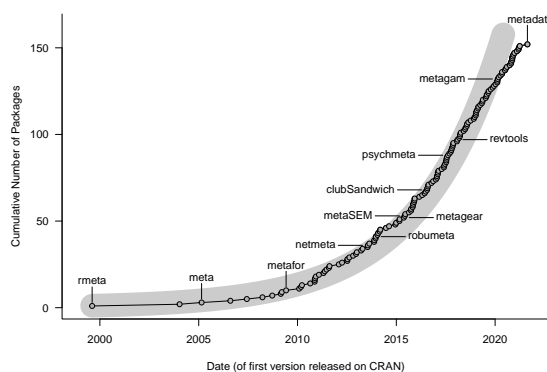
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### First Releases of Meta-Analysis R Packages



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### Exponential Growth (might be slowing down)



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### Development of the metafor Package

- first version (0.5-0) released 2009-06-04
- a total of 30 versions released so far
- latest is 3.0-2 released 2021-06-09
- full changelog:  
<https://wvbauer.github.io/metafor/news/index.html>

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## Some Milestones

Version	Date	Notes / Changes
0.5-0	2009-06-04	• first version released on CRAN • <code>rma.uni()</code> , <code>rma.mh()</code> , <code>rma.peto()</code>
0.5-4	2009-09-18	• <code>regtest()</code> and <code>ranktest()</code> functions • <code>anova()</code> function (LRTs, contrasts)
0.5-5	2009-10-08	• <code>cumul()</code> and <code>leave1out()</code> functions
0.5-7	2009-12-06	• <code>permutest()</code> function
1.0-1	2010-02-02	• version 1 released
1.4-0	2010-07-30	• various improvements for JSS paper
	2010-08-05	• JSS paper published [7]
1.5-0	2010-12-16	• started metafor website
1.7-0	2013-02-06	• <code>rma.glmm()</code> function

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## Some Milestones

Version	Date	Notes / Changes
1.9-2	2013-10-07	• <code>rma.mv()</code> and <code>profile()</code> functions
1.9-3	2014-05-05	• models with user-defined weights • sparse matrices for <code>rma.mv()</code> • autoregressive structures for <code>rma.mv()</code>
1.9-6	2015-05-07	• multiple correlated random effects • parallel processing for <code>profile()</code>
1.9-8	2015-09-28	• <code>robust()</code> function
1.9-9	2016-09-25	• started using git and GitHub • <code>raneft()</code> and <code>gosh()</code> functions • permutation-based CIs of model coefficients

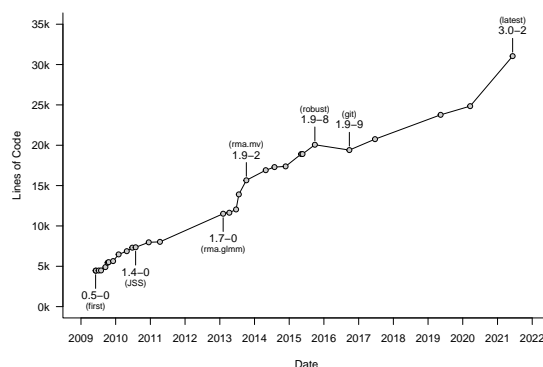
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## Some Milestones

Version	Date	Notes / Changes
2.1-0	2019-05-13	• <code>reporter()</code> function • cluster-level outlier/influence statistics • more parallel processing capabilities • spatial correlation structures
2.4-0	2020-03-19	• <code>to.wide()</code> and <code>contrmat()</code> for NMA
3.0-2	2021-06-09	• <code>selmodel()</code> , <code>tes()</code> , PET/PEESE • location-scale models

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## Lines of Code



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## Package Features: Effect Sizes and Outcome Measures

- measures for 2×2 table data (e.g., RD, RR, OR)
- measures for two-group person-time data (e.g., IRR, IRD)
- raw/standardized mean differences and response ratios
- conversions of 2×2 table data / ORs to SMDs and vice-versa
- raw and Fisher's r-to-z transformed correlation coefficients
- (semi)partial correlations and biserial/tetrachoric correlations
- proportions and transformations thereof
- incidence rates and transformations thereof
- raw/standardized mean change measures
- measures of change in 2×2 table data
- reliability measures (Cronbach's alpha and transformations)
- measures to quantify variability (and group differences thereof)

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## Package Features: Models and Analysis Approaches

- fixed-, random-, and mixed-effects (meta-regression) models
- Mantel-Haenszel and Peto's (one-step) method
- generalized linear (mixed-effects) models
- multilevel and multivariate meta-analytic models
- network meta-analysis / mixed treatment comparisons
- phylogenetic meta-analysis
- spatio-temporal meta-analytic models
- models with user-defined weights
- location-scale models

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## Package Features: Plots and Figures

- forest plots
- funnel plots
- bubble plots
- Baujat plots
- L'Abbé plots
- radial (Galbraith) plots
- GOSH plots
- profile likelihood plots
- normal quantile-quantile plots

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## Package Features: Publication Bias

- rank correlation test
- Egger's regression test (PET / PEESE methods)
- trim and fill method
- Henmi and Copas approach
- file drawer analysis
- test of excess significance
- selection models

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## Package Features: Inference Methods

- Wald-type and likelihood ratio tests
- Knapp and Hartung method
- prediction intervals
- confidence intervals for heterogeneity statistics
- permutation tests / confidence intervals
- (cluster) robust tests and confidence intervals
- cumulative meta-analysis
- best linear unbiased predictions for random effects
- model fit / information criteria
- bootstrapping (via **boot** package) ([website](#))
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- raw, standardized, and studentized residuals
- DFFITS, DFBETAS values, Cook's distances, covariance ratios
- cluster-level outlier/influence statistics
- model weights and hat values
- leave-one-out analyses

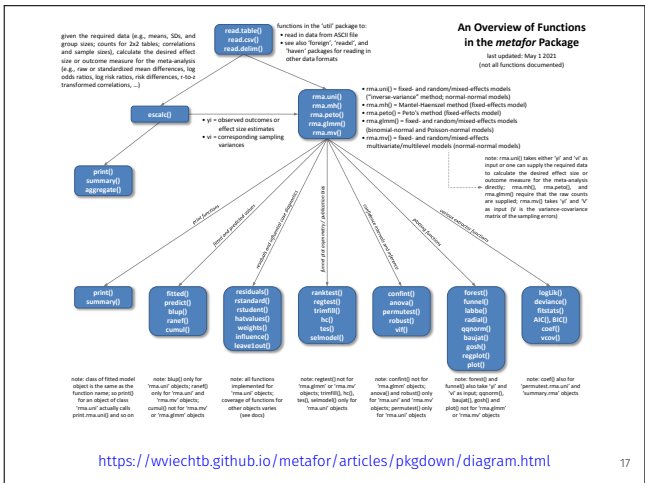
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## Demo: Random-Effects Model

```
# load the metafor package
library(metafor)

# look at the BCG dataset
dat.bcg
```

trial	author	year	tpos	tneg	cpos	cneg	ablat	alloc
1	Aronson	1948	4	119	11	128	44	random
2	Ferguson & Simes	1949	6	300	29	274	55	random
3	Rosenthal et al	1960	3	228	11	209	42	random
4	Hart & Sutherland	1977	62	13536	248	12619	52	random
5	Frimodt-Moller et al	1973	33	5036	47	5761	13	alternate
6	Stein & Aronson	1953	180	1361	372	1079	44	alternate
7	Vandiviere et al	1973	8	2537	10	619	19	random
8	TPT Madras	1980	505	87886	499	87892	13	random
9	Coetzee & Berjak	1968	29	7470	45	7232	27	random
10	Rosenthal et al	1961	17	1699	65	1600	42	systematic
11	Comstock et al	1974	186	50448	141	27197	18	systematic
12	Comstock & Webster	1969	5	2493	3	2338	33	systematic
13	Comstock et al	1976	27	16886	29	17825	33	systematic

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## Demo: Random-Effects Model

```
# calculate log risk ratios and corresponding sampling variances
dat <- escalc(measure="RR", ai=tpos, bi=tneg,
              ci=cpos, di=cneg, data=dat.bcg)
dat
```

trial	author	year	...	yi	vi
1	Aronson	1948	...	-0.8893	0.3256
2	Ferguson & Simes	1949	...	-1.5854	0.1946
3	Rosenthal et al	1960	...	-1.3481	0.4154
4	Hart & Sutherland	1977	...	-1.4416	0.0200
5	Frimodt-Moller et al	1973	...	-0.2175	0.0512
6	Stein & Aronson	1953	...	-0.7861	0.0069
7	Vandiviere et al	1973	...	-1.6209	0.2230
8	TPT Madras	1980	...	0.0120	0.0040
9	Coetzee & Berjak	1968	...	-0.4694	0.0564
10	Rosenthal et al	1961	...	-1.3713	0.0730
11	Comstock et al	1974	...	-0.3394	0.0124
12	Comstock & Webster	1969	...	0.4459	0.5325
13	Comstock et al	1976	...	-0.0173	0.0714

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## Demo: Random-Effects Model

```
# random-effects model (using log risk ratios and variances as input)
res <- rma(yi, vi, data=dat)
res

## Random-Effects Model (k = 13; tau^2 estimator: REML)
##
## tau^2 (estimated amount of total heterogeneity): 0.3132 (SE = 0.1664)
## tau (square root of estimated tau^2 value): 0.5597
## I^2 (total heterogeneity / total variability): 92.22%
## H^2 (total variability / sampling variability): 12.86
##
## Test for Heterogeneity:
## Q(df = 12) = 152.2330, p-val < .0001
##
## Model Results:
##
## estimate      se      zval      pval      ci.lb      ci.ub
## -0.7145  0.1798  -3.9744  <.0001  -1.0669  -0.3622
```

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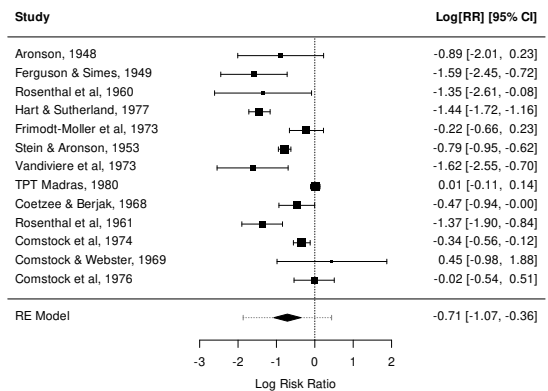
## Demo: Random-Effects Model

```
# then do lots more stuff ...
forest(res)
funnel(res)
influence(res)
plot(influence(res))
leavelout(res)
baujat(res)
ranktest(res)
regtest(res)
trimfill(res)
funnel(trimfill(res))
cumul(res)
forest(cumul(res))
radial(res)
labbe(res)
plot(gosh(res))
selmodel(res)

# note: the following plots are based on various datasets
```

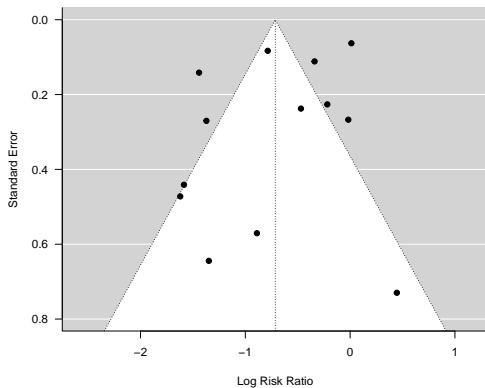
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## Demo: Forest Plot



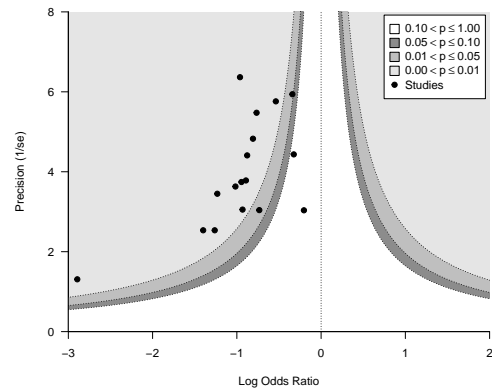
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## Demo: Funnel Plot



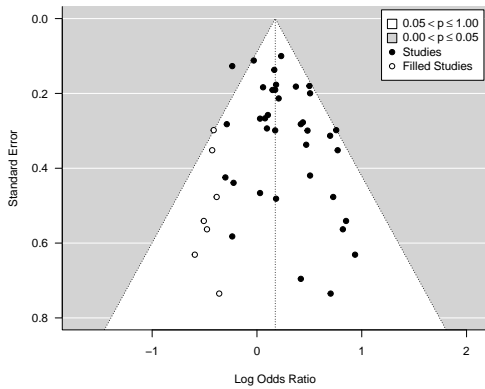
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## Demo: Contour-Enhanced Funnel Plot [8]



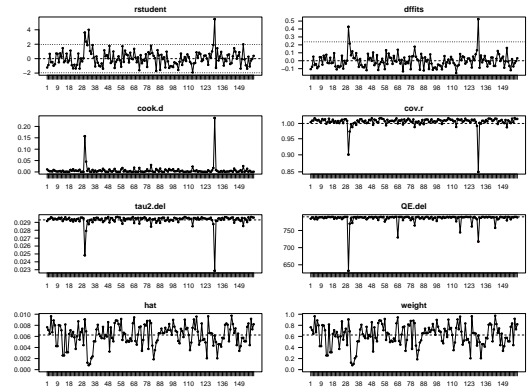
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### Demo: Trim-and-Fill [9, 10]



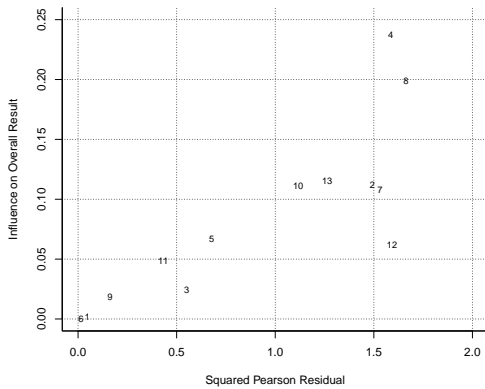
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### Demo: Outlier / Influence Diagnostics [11, 12]



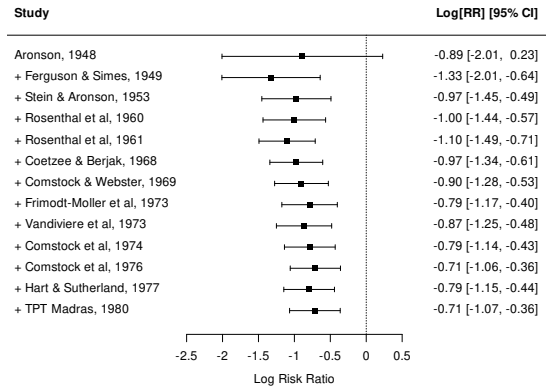
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### Demo: Baujat Plot [12, 13]



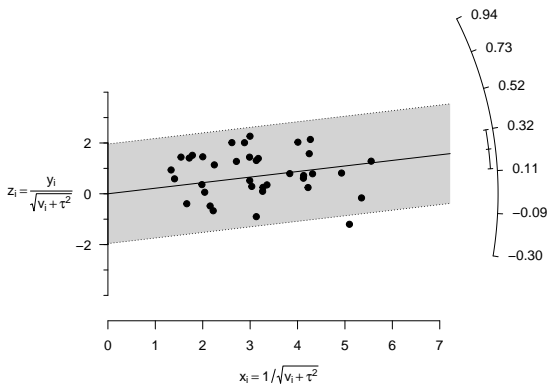
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### Demo: Cumulative Meta-Analysis [14]



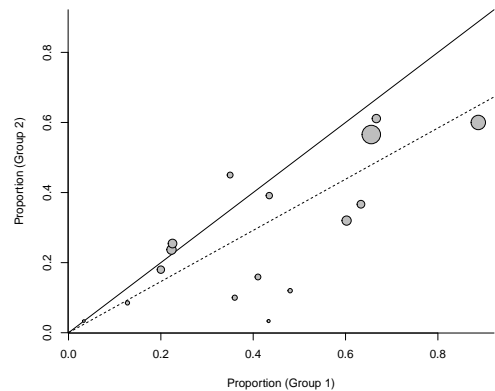
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### Demo: Radial (Galbraith) Plot [15]



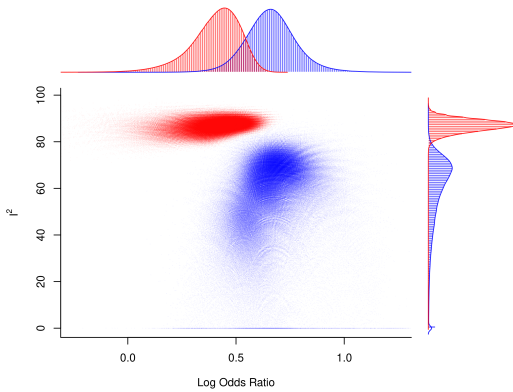
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### Demo: L'Abbé Plot [16]



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## Demo: GOSH Plot [17]



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## Demo: Meta-Regression

```
# mixed-effects meta-regression model
res <- rma(yi, vi, mods = ~ ablat + alloc, data=dat)
res

## Mixed-Effects Model (k = 13; tau^2 estimator: REML)
##
## tau^2 (estimated amount of residual heterogeneity):      0.1446
## tau (square root of estimated tau^2 value):             0.3803
## I^2 (residual heterogeneity / unaccounted variability): 70.11%
## H^2 (unaccounted variability / sampling variability):    3.35
## R^2 (amount of heterogeneity accounted for):            53.84%
##
## Test for Residual Heterogeneity:
## QE(df = 9) = 26.2034, p-val = 0.0019
##
## ...
```

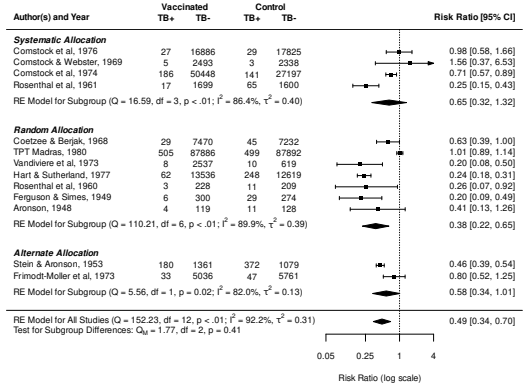
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## Demo: Meta-Regression

```
## ...
##
## Test of Moderators (coefficients 2:4):
## QM(df = 3) = 11.0605, p-val = 0.0114
##
## Model Results:
##
##               estimate    se      zval    pval    ci.lb    ci.ub
## intrcpt           0.2932  0.4050   0.7239  0.4691  -0.5006   1.0870
## ablat             -0.0273  0.0092  -2.9650  0.0030  -0.0453  -0.0092
## allocrandom      -0.2675  0.3504  -0.7633  0.4453  -0.9543   0.4193
## allocsystematic   0.0585  0.3795   0.1540  0.8776  -0.6854   0.8023
```

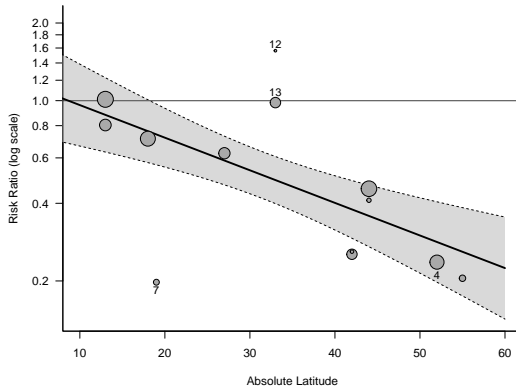
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## Demo: Forest Plot with Subgroups



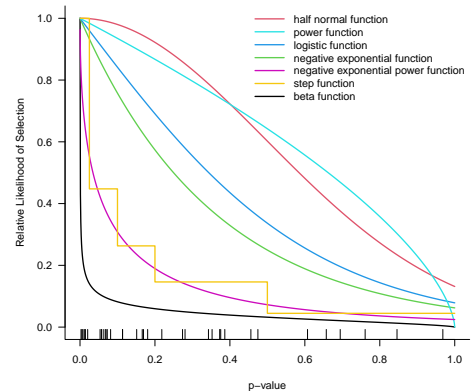
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## Demo: Meta-Analytic Scatterplot [18]



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## Demo: Selection Models [19-21]



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## The reporter() Function

- automatically generates a report based on `rma.uni` objects
- describes the statistical methods used
- gives a natural language summary of the results
- includes a forest and a funnel plot
- gives references for all methods used
- output can be html, pdf, or docx

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## Demo: Using reporter()

```
dat <- escalc(measure="RR", ai=tpos, bi=tneg,
              ci=cpos, di=cneg,
              slab=paste(author, " ", year, sep=" "),
              data=dat.bcg)
res <- rma(yi, vi, data=dat)
reporter(res)
```

Directory for generating the report is: `/tmp/Rtmpusq5ns`

Copying references.bib and apa.csl to report directory ...  
Saving model object to report\_res.rdata ...  
Creating report\_res.rmd file ...  
Rendering report\_res.rmd file ...  
Generated `/tmp/Rtmpusq5ns/report_res.html` ...  
Opening report ...

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## Demo: Using reporter()

### Analysis Report

Generated with the reporter() Function of the metafor Package  
19 January, 2021

#### Methods

The analysis was carried out using the log risk ratio as the outcome measure. A random-effects model was fitted to the data. The amount of heterogeneity (i.e.,  $\tau^2$ ), was estimated using the restricted maximum-likelihood estimator (Viechtbauer, 2005). In addition to the estimate of  $\tau^2$ , the  $Q$ -test for heterogeneity (Cochran, 1954) and the  $I^2$  statistic (Higgins & Thompson, 2002) are reported. In case any amount of heterogeneity is detected (i.e.,  $\tau^2 > 0$ , regardless of the results of the  $Q$ -test), a prediction interval for the true outcomes is also provided (Riley et al., 2011). Studentized residuals and Cook's distances are used to examine whether studies may be outliers and/or influential in the context of the model (Viechtbauer & Cheung, 2010). Studies with a studentized residual larger than the  $100 \times (1 - 0.05/(2 \times k))$ th percentile of a standard normal distribution are considered potential outliers (i.e., using a Bonferroni correction with two-sided  $\alpha = 0.05$  for  $k$  studies included in the meta-analysis). Studies with a Cook's distance larger than the median plus six times the interquartile range of the Cook's distances are considered to be influential. The rank correlation test (Begg & Mazumdar, 1994) and the regression test (Sterne & Egger, 2005), using the standard error of the observed outcomes as predictor, are used to check for funnel plot asymmetry. The analysis was carried out using R (version 4.0.3) (R Core Team, 2020) and the `metafor` package (version 2.5.70) (Viechtbauer, 2010).

#### Results

A total of  $k = 13$  studies were included in the analysis. The observed log risk ratios ranged from  $-1.6209$  to  $0.4450$ , with the majority of estimates being negative (85%). The estimated average log risk ratio based on the random-effects model was  $\hat{\mu} = -0.7145$  (95% CI:  $-1.0609$  to  $-0.3622$ ). Therefore, the average outcome differed significantly from zero ( $z = -3.9744$ ,  $p < 0.0001$ ). A forest plot showing the observed outcomes and the estimate based on the random-effects model is shown in Figure 1.

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## Demo: Using reporter()

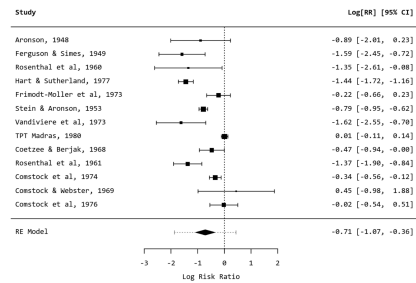


Figure 1: Forest plot showing the observed outcomes and the estimate of the random-effects model

According to the  $Q$ -test, the true outcomes appear to be heterogeneous ( $Q(12) = 152.2330$ ,  $p < 0.0001$ ,  $\tau^2 = 0.3132$ ,  $I^2 = 92.2214\%$ ). A 95% prediction interval for the true outcomes is given by  $-1.8667$  to  $0.4376$ . Hence, although the average outcome is estimated to be negative, in some studies the true outcome may in fact be positive.

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## Demo: Using reporter()

An examination of the studentized residuals revealed that none of the studies had a value larger than  $\pm 2.8905$  and hence there was no indication of outliers in the context of this model. According to the Cook's distances, none of the studies could be considered to be overly influential.

A funnel plot of the estimates is shown in Figure 2. Neither the rank correlation nor the regression test indicated any funnel plot asymmetry ( $p = 0.9524$  and  $p = 0.4218$ , respectively).

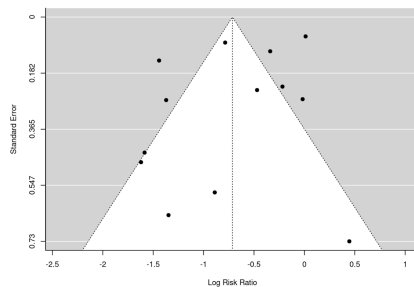


Figure 2: Funnel plot

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## Demo: Using reporter()

### Notes

This analysis report was dynamically generated for model object 'res' with the `reporter()` function of the `metafor` package. The model call that was used to fit the model was `rma(yi = yi, vi = vi, data = dat)`. This report provides an illustration of how the results of the model can be reported, but is not a substitute for a careful examination of the results.

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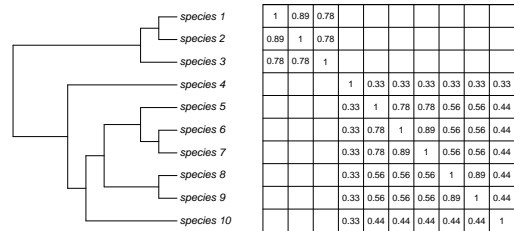
## Validation / Testing

- extensive comparisons with other R/software packages
- comparisons with published results (e.g., [analysis examples](#))
- testing via simulation studies
- appreciable user base
- automated testing + code coverage (~70%)
- plus a 100% money-back guarantee if you find a bug!

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## Phylogenetic Meta-Analysis [22–24]

- meta-analyses in ecology and evolutionary biology often contain studies conducted with different species
- these species share an evolutionary history (= phylogeny)
- effects for species that are more similar to each other might also correlate more strongly

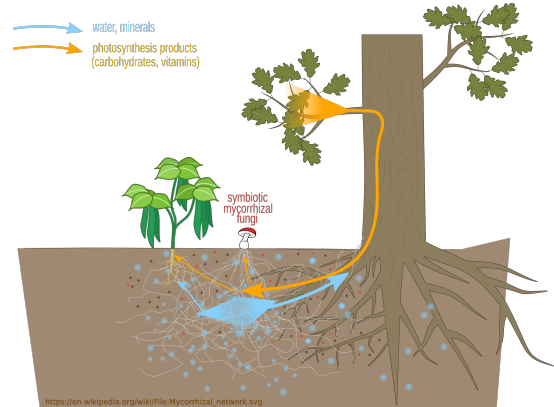


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## Phylogenetic Meta-Analysis [22–24]

- in 2012, I was invited by Jason Hoeksema (University of Mississippi) to participate in a NESCent (National Evolutionary Synthesis Center) working group to develop methods/software for phylogenetic meta-analysis
- over the course of 5 meetings developed `rma.mv()` and its ability to incorporate known correlation matrices
- applied in a meta-analysis on the effects of inoculating plants with mycorrhizal fungi [25, 26]

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## Effects of Mycorrhizal Fungi Inoculation

- focus here on plants inoculated with arbuscular mycorrhizal fungi belonging to one or more fungal genera (359 papers, 2984 effects, 1776 control conditions, 293 plant species)
- model includes random effects for papers, control conditions, effect sizes, plant species, and plant species with its phylogenetic correlation matrix

```
rma.mv(EffectSize, Var, data = dat,
       random = list(~ 1 | Paper/Control/Effect,
                     ~ 1 | PlantSpecies,
                     ~ 1 | PlantSpecies.phyl),
       R = list(PlantSpecies.phyl=R.PS))
```

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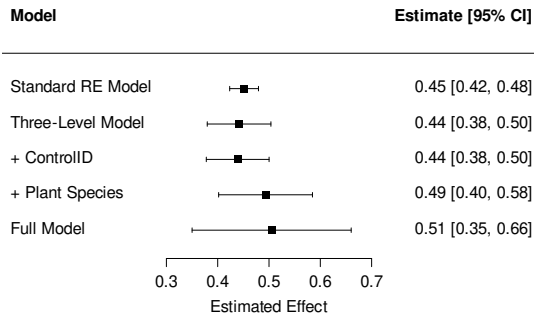
## Effects of Mycorrhizal Fungi Inoculation

```
## Multivariate Meta-Analysis Model (k = 2984; method: REML)
##
## Variance Components:
##
##      estim  sqrt  nlvls  fixed      factor  R
## sigma^2.1 0.1799 0.4242   359    no      PaperID no
## sigma^2.2 0.1434 0.3786  1776    no      ControlID no
## sigma^2.3 0.1224 0.3498  2984    no      EffectID no
## sigma^2.4 0.1618 0.4023   293    no      PlantSpecies no
## sigma^2.5 0.1000 0.3162   293    no PlantSpecies.phyl yes
##
## Test for Heterogeneity:
## Q(df = 2983) = 66515.4758, p-val < .0001
##
## Model Results:
##
## estimate    se    zval    pval    ci.lb    ci.ub
## 0.5051    0.0791  6.3858  <.0001  0.3501  0.6601
```

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## Effects of Mycorrhizal Fungi Inoculation

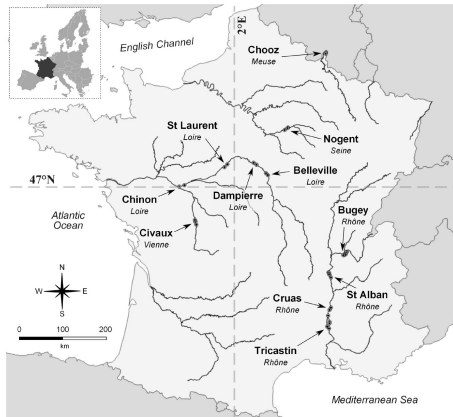


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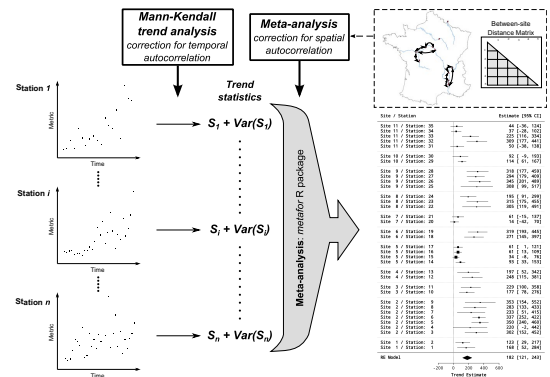
## Spatial Correlation Structures in Meta-Analysis

- was contacted in 2017 by researchers doing a meta-analysis on changes in fish abundance/diversity in French rivers
- had derived trend statistics based on repeated measures of fish abundance/diversity at 35 sampling stations (11 general sites)
- expected strong spatial correlation in these trend estimates
- implemented spatial correlation structures in `rma.mv()` to account for this and helped with the analysis [27]

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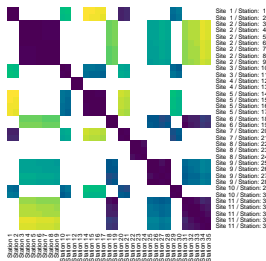
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## Trends in Fish Abundance/Diversity in French Rivers

- $35 \times 35$  distance matrix derived based on the 'river distance' between the stations (min = 1km, max = 423km)
- pairs of stations not connected through the river network assumed to be uncorrelated



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## Trends in Fish Abundance/Diversity in French Rivers

- Gaussian spatial correlation structure:

$$\text{Cov}[u_i, u_j] = \tau^2 \times \exp(-d_{i,j}^2/\rho^2),$$

where  $d_{i,i'}$  is their distance

- model includes random effects for sites, stations, and correlated random effects for stations assuming an exponential or Gaussian spatial correlation structure

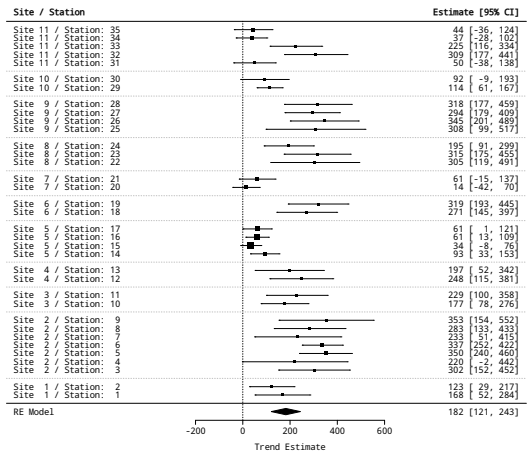
```
rma.mv(EffectSize, Var, data = dat,
      random = list(~ 1 | site/station,
                    ~ station | const),
      struct="SPGAU", dist=list(dmat))
```

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## Trends in Fish Abundance/Diversity in French Rivers

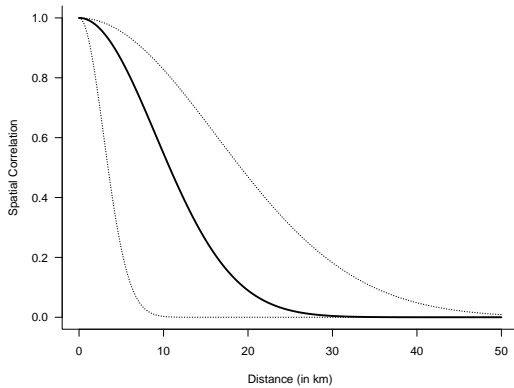
```
## Multivariate Meta-Analysis Model (k = 35; method: REML)
##
## Variance Components:
##
##      estim  sqrt  nlvls  fixed    factor
## sigma^2.1 7158.35 84.61   11    no      site
## sigma^2.2   0.00   0.00   35    no site/station
##
## outer factor: const (nlvls = 1)
## inner term:  ~station (nlvls = 35)
##
##      estim  sqrt  fixed
## tau^2    3425.59 58.53   no
## rho       12.88    no
##
## Model Results:
##
## estimate    se  zval  pval  ci.lb  ci.ub
## 182.12    31.28  5.82  <.01 120.81 243.43
```

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## Trends in Fish Abundance/Diversity in French Rivers



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## Complex Random-Effects Structures

- 2016-2020 I was involved in a meta-analysis on the 'generation effect' (= information is better remembered if it is generated from one's own mind rather than simply read) [28]
- a study might ask participants to recall words that were read versus words self-generated from word fragments
- studies often report multiple experiments and examine various conditions using a mix of within- and between-subject designs

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## Complex Random-Effects Structures

Article	Experiment	Sample	Pairing	Condition	Id	Recall
1	1	1	1	read	1	0.31
1	1	2	1	generate	2	0.45
2	1	3	2	read	3	0.45
2	1	3	2	generate	4	0.61
3	1	4	3	read	5	0.61
3	1	4	3	generate	6	0.72
3	1	4	3	generate	7	0.95
4	1	5	4	read	8	0.28
4	1	5	4	generate	9	0.38
4	1	5	5	read	10	0.36
4	1	5	5	generate	11	0.55
...	...	...	...	...	...	...

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## Complex Random-Effects Structures

- dataset included 126 articles reporting on 310 experiments with 582 samples, yielding 1653 recall estimates for 804 pairings
- model includes random effects for articles, experiments, samples, estimates, and a crossed random effect for pairing
- so a five-level model with an additional crossed random effect

```
rma.mv(Recall, Var, mods = ~ Condition,
       random = list(~ 1 | article/experiment/sample/id,
                     ~ 1 | pairing),
       data=dat, sparse=TRUE)
```

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## Complex Random-Effects Structures

```
## Multivariate Meta-Analysis Model (k = 1653; method: REML)
##
## Variance Components:
##
##           estim  sqrt  nlvls  fixed  factor
## sigma^2.1  0.0219  0.1479   126    no   Article
## sigma^2.2  0.0060  0.0777   310    no  Experiment
## sigma^2.3  0.0000  0.0000   582    no   Sample
## sigma^2.4  0.0064  0.0798  1653    no     Id
## sigma^2.5  0.0165  0.1285   804    no   Pairing
##
## [...]
##
## Model Results:
##
##           estimate      se      zval      pval      ci.lb      ci.ub
## intrcpt      0.4785    0.0157    30.4456    <.0001    0.4477    0.5093
## generate      0.1021    0.0042    24.0422    <.0001    0.0938    0.1104
```

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## Sparse Matrix Structures

- `rma.mv()` works by default internally with  $k \times k$  matrices, where  $k$  denotes the number of rows in the dataset
- model fitting can be painfully slow when  $k$  is large
- was contacted around 2013 about this issue by people from Vanderbilt University (i.e., Joshua Polanin, Mark Lipsey and Sandra Wilson) who were running models with  $k > 8000$  rows!
- this led to the implementation of the `sparse=TRUE` option so 'sparse matrix representations' are used to speed things up

$$W = \begin{bmatrix} a & b & 0 & 0 \\ c & d & 0 & 0 \\ 0 & 0 & e & f \\ 0 & 0 & g & h \end{bmatrix}^{-1} = \begin{bmatrix} a & b \\ c & d \end{bmatrix}^{-1} \cdot \begin{bmatrix} e & f \\ g & h \end{bmatrix}^{-1}$$

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## Philosophy

- build a toolbox, not individuals tools
- try to avoid special cases / figure out logical generalizations
- coherent and general modeling framework; e.g., `rma.mv()` for:
  - multilevel meta-analysis (e.g., [29], [website](#))
  - multivariate meta-analysis (e.g., [ex 1](#), [ex 2](#), [ex 3](#), [ex 4](#))
  - network meta-analysis (e.g., [24, 26], [ex 1](#), [ex 2](#))
  - phylogenetic meta-analysis (e.g., [27], [ex 1](#), [ex 2](#), [ex 3](#))
  - spatio-temporal models (e.g., [27], [ex 1](#), [ex 2](#), [ex 3](#))
  - dose-response models (e.g., [ex 1](#))
  - all can be combined with (cluster) robust variance estimation (using `robust()` or the `clubSandwich` package)
- listen to users

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# Thank You for Your Attention!

## Questions, Comments, Suggestions?

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🌐 <https://www.wvbauer.com/>

🌐 <https://www.metafor-project.org/>

🐦 [@wwiechthb](https://twitter.com/wwiechthb)

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