Tutorial On Meta-Analysis In R

R useR! Conference 2013

Stephanie Kovalchik
Research Fellow, National Cancer Institute

Tutorial Outline

- Overview
- Searching The Literature
- Fixed Effects Model
- Random Effects Model
- Evaluating Heterogeneity
- Meta-Regression
- Publication Bias
- Comparing R Packages For Standard Meta-Analysis
- Some Advanced Topics

Overview

What Is Meta-Analysis?

> "The analysis of analyses."
>
> -- Gene V. Glass
>
> Primary, secondary and meta-analysis of research, Educational Researcher, 1976.

What Is Meta-Analysis?

More formally...a meta-analysis is the synthesis of:

- K **compatible effects** (Y_i)
- (Preferably, but not necessarily, from randomized controlled trials)

Giving greater weight to studies with:

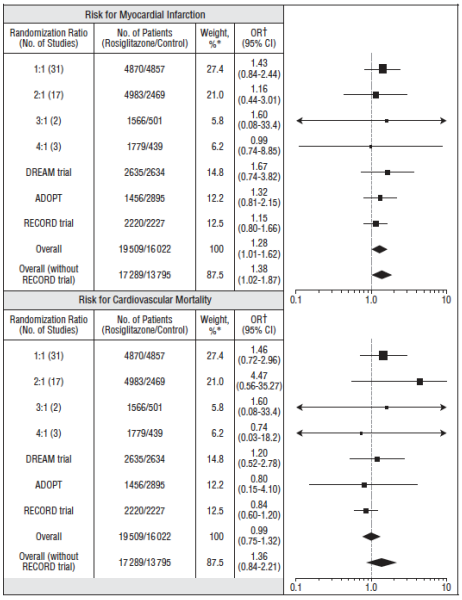
- **Less variance** (V_i), and
- **More precision** ($W_i = 1/V_i$)

Types Of Effects

An "effect" could be almost any aggregate statistic of interest:

- Mean, Mean difference, Mean change
- Risk ratio, Odds ratio, Risk difference
- Incidence rate, Prevalence, Proportion
- Correlation

A High-Impact Example: Fall Of Avandia



Risk for Myocardial Infarction			
Randomization Ratio (No. of Studies)	No. of Patients (Rosiglitazone/Control)	Weight, %*	OR† (95% CI)
1:1 (31)	4870/4857	27.4	1.43 (0.84-2.44)
2:1 (17)	4983/2469	21.0	1.16 (0.44-3.01)
3:1 (2)	1566/501	5.8	1.60 (0.08-33.4)
4:1 (3)	1779/439	6.2	0.99 (0.74-8.85)
DREAM trial	2635/2634	14.8	1.67 (0.74-3.82)
ADOPT	1456/2895	12.2	1.32 (0.81-2.15)
RECORD trial	2220/2227	12.5	1.15 (0.80-1.66)
Overall	19509/16022	100	1.28 (1.01-1.62)
Overall (without RECORD trial)	17289/13795	87.5	1.38 (1.02-1.87)
0.1	1.0	10	

Risk for Cardiovascular Mortality			
Randomization Ratio (No. of Studies)	No. of Patients (Rosiglitazone/Control)	Weight, %*	OR† (95% CI)
1:1 (31)	4870/4857	27.4	1.46 (0.72-2.96)
2:1 (17)	4983/2469	21.0	4.47 (0.56-35.27)
3:1 (2)	1566/501	5.8	1.60 (0.08-33.4)
4:1 (3)	1779/439	6.2	0.74 (0.03-18.2)
DREAM trial	2635/2634	14.8	1.20 (0.52-2.78)
ADOPT	1456/2895	12.2	0.80 (0.15-4.10)
RECORD trial	2220/2227	12.5	0.84 (0.60-1.20)
Overall	19509/16022	100	0.99 (0.75-1.32)
Overall (without RECORD trial)	17289/13795	87.5	1.36 (0.84-2.21)
0.1	1.0	10	

Source: Nissen SE, Wolski K. N Engl J Med 2007;356:2457-71.

Conducting Meta-Analyses in R

First...Getting Started With R

- Official home page: http://www.R-project.org
- Introduction under **"What is R?"**
- Download base system at: http://cran.r-project.org
- Extend with user-contributed packages -> `install.packages`
- Find further introductory material with `help.start`

Why Perform Meta-Analyses In R?

- R is a free, open-source, & powerful statistical environment
- Run on Windows, Mac OS, and Linux platforms
- Has 20+ meta-analytic packages on CRAN
- Tools for meta-regression, Bayesian meta-analysis, multivariate meta-analyses, etc.
- Easy (in most cases) to customize and extend these tools

Warning: Still...Do Not Begin Here!

- A meta-analysis **starts with a systematic review**.
- A systematic review is a scientific summary of all available evidence on a specific research question.
- An exhaustive search of the literature will require more than R.
- **Note:** If available studies are too few or too different **a meta-analysis may not be appropriate**.

Searching The Literature With R

Package `RISmed`

- Not many packages for helping with early stages of a systematic review.
- But, I created the RISmed package to import metadata from NCBI databases into `R`.
- Using this package, one can search, store, and easily mine metadata on PubMed articles.
- `RISmed` tools are not comprehensive enough to complete a systematic review but may be a helpful aid.

Importing PubMed Data With `RISmed`

1. Create `EUtilsSummary` object for specified query.
2. Retrieve matching records with `EUtilsGet`.

Importing PubMed Data With `RISmed`

Syntax

```
EUtilsSummary( [query], [db], [search.limits])
```

- `query`: String query as given on PubMed site
- `db`: String name of NCBI database
- `search.limits`: Additional arguments to restrict search

Example: EUtilsSummary

```
library(RISmed)  # Load Package
```

The following code performs a PubMed query of all BMJ articles with "rofecoxib" in the title.

```
fit <- EUtilsSummary("rofecoxib[ti]+British Medical Journal[jo]", db = "pubmed")
```

Example: Methods For `EUtilsSummary`

```
QueryTranslation(fit)  # Extract the translated query
```

```
## [1] "rofecoxib[ti] AND (\"Br Med J\"[Journal] OR \"Br Med J (Clin Res Ed)
\"[Journal] OR \"BMJ\"[Journal])"
```

```
QueryCount(fit)  # Extract the number of matched records
```

```
## [1] 16
```

Example: `EUtilsGet`

Now we can extract the metadata for the queried records.

```
fetch <- EUtilsGet(fit)
fetch  # Medline Object
```

```
## PubMed query:  rofecoxib[ti] AND ("Br Med J"[Journal] OR "
## Br Med J (Clin Res Ed)"[Journal] OR "BMJ"[Journal])
##
## Records:  16
```

Methods For `Medline` Object

```
getSlots("Medline")  # Available methods
```

```
##               Query                PMID                Year 
##         "character"         "character"           "numeric" 
##               Month                 Day              Author 
##           "numeric"           "numeric"              "list" 
##                ISSN               Title        ArticleTitle 
##         "character"         "character"         "character" 
##         ELocationID        AbstractText         Affiliation 
##         "character"         "character"         "character" 
##            Language     PublicationType           MedlineTA 
##         "character"         "character"         "character" 
##         NlmUniqueID         ISSNLinking                Hour 
##         "character"         "character"           "numeric" 
##              Minute   PublicationStatus           ArticleId 
##           "numeric"         "character"         "character" 
##              Volume               Issue     ISOAbbreviation 
##         "character"         "character"         "character" 
##          MedlinePgn CopyrightInformation             Country 
##         "character"         "character"         "character" 
##             GrantID             Acronym              Agency 
##         "character"         "character"         "character" 
##      RegistryNumber           RefSource      CollectiveName 
##         "character"         "character"         "character" 
##                Mesh 
##              "list"
```

Example: `Medline` Object

```
ArticleTitle(fetch)[1:5]
```

```
## [1] "Merck pays $1bn penalty in relation to promotion of rofecoxib."
## [2] "Merck to pay $58m in settlement over rofecoxib advertising."
## [3] "94% of patients suing Merck over rofecoxib agree to company's offer."
## [4] "Merck to pay $5bn in rofecoxib claims."
## [5] "Merck appeals rofecoxib verdict."
```

Example: `Medline` Object

```
Author(fetch)[[1]]
```

```
##   LastName       ForeName Initials order
## 1    Tanne Janice Hopkins       JH     1
```

```
Year(fetch)
```

```
##  [1] 2011 2008 2008 2007 2007 2006 2005 2005 2004 2004 2004 2004 2004 2003
## [15] 2002 2001
```

Your Turn: Working With `Medline` Object

Using the "rofecoxib" `Medline` object,

1. Determine the first year a matching article appeared.
2. What was the title of this article?
3. Do some authors have multiple matching records?
4. If so, which authors?

Working With `Medline` Object

```
min(Year(fetch))  # Earliest year
```

```
## [1] 2001
```

```
ArticleTitle(fetch)[Year(fetch) == 2001]  # Title of earliest record(s)
```

```
## [1] "FDA warns Merck over its promotion of rofecoxib."
```

Working With `Medline` Object

```
AuthorList <- Author(fetch)  # Extract list of authors
LastFirst <- sapply(AuthorList, function(x) paste(x$LastName, x$ForeName))
sort(table(unlist(LastFirst)), dec = TRUE)[1:3]  # Tabulate & Sort
```

```
## Tanne Janice Hopkins        Charatan Fred      Abenhaim Lucien
##                    4                    3                    1
```

Basic Meta-Analysis In R

R Packages For Standard Meta-Analysis

In no particular order...

- `meta` (Author: Guido Schwarzer)
- `metafor` (Author: Wolfgang Viechtbauer)
- `rmeta` (Author: Thomas Lumley)

Datasets For Package Examples

1. BCG vaccine trials (from `metafor`)
2. Amlodipine angina treatment trials (from `meta`)

Dataset 1: BCG Vaccine Trials

- **Overview:** 13 vaccine trials of Bacillus Calmette–Guérin (BCG) vaccine vs. no vaccine
- **Treatment goal:** Prevention of tuberculosis
- **Primary endpoint:** Tuberculosis infection
- **Possible explanatory variables:**
  - latitude of study region
  - treatment allocation method
  - year published

Loading BCG Dataset

A version of the BCG dataset is provided by package `metafor`

```
library(metafor)  # Load package
data(dat.bcg)  # BCG meta-analytic dataset
str(dat.bcg)  # Describe meta-analysis structure
```

```
## 'data.frame':    13 obs. of  9 variables:
##  $ trial : int  1 2 3 4 5 6 7 8 9 10 ...
##  $ author: chr  "Aronson" "Ferguson & Simes" "Rosenthal et al" "Hart & Sutherland" ...
##  $ year  : int  1948 1949 1960 1977 1973 1953 1973 1980 1968 1961 ...
##  $ tpos  : int  4 6 3 62 33 180 8 505 29 17 ...
##  $ tneg  : int  119 300 228 13536 5036 1361 2537 87886 7470 1699 ...
##  $ cpos  : int  11 29 11 248 47 372 10 499 45 65 ...
##  $ cneg  : int  128 274 209 12619 5761 1079 619 87892 7232 1600 ...
##  $ ablat : int  44 55 42 52 13 44 19 13 27 42 ...
##  $ alloc : chr  "random" "random" "random" "random" ...
```

Dataset 2: Amlodipine Treatment Trials

- **Overview:** 8 randomized controlled trials (RCTs) of amlodipine vs. placebo
- **Treatment goal:** Reduce harms of angina (chest pain)
- **Primary endpoint:** Work capacity (ratio of exercise time after to before intervention)

Loading `amlodipine` Dataset

A version of the amlodipine dataset is provided by package `meta`

```
library(meta)  # Load package
data(amlodipine)  # amlodipine meta-analytic dataset
str(amlodipine)  # Describe meta-analysis structure
```

```
## 'data.frame':    8 obs. of  7 variables:
##  $ study    : Factor w/ 8 levels "Protocol 154",..: 1 2 3 4 5 6 7 8
##  $ n.amlo   : int  46 30 75 12 32 31 27 46
##  $ mean.amlo: num  0.232 0.281 0.189 0.093 0.162 ...
##  $ var.amlo : num  0.2254 0.1441 0.1981 0.1389 0.0961 ...
##  $ n.plac   : int  48 26 72 12 34 31 27 47
##  $ mean.plac: num  -0.0027 0.027 0.0443 0.2277 0.0056 ...
##  $ var.plac : num  0.0007 0.1139 0.4972 0.0488 0.0955 ...
```

Effect Sizes (ESs)

- An **effect size** could be almost any summary statistic (e.g. a mean, a difference in proportions, an adjusted odds ratio, etc.)
- Conventional meta-analytic models **assume normality** of ESs.
- Because of the CLT, this will holds for most ESs given large enough samples.
- To normalize ESs, a log-transform is common.

Example: Log Odds Ratio

	Event	Non-Event	Sample Size
Group A	a_i	b_i	n_{iA}
Group B	c_i	d_i	n_{iB}

Example: Log Odds Ratio

Effect Size

$$LOR = \log(\frac{a * d}{b * c})$$

Variance

$$V = 1/a + 1/b + 1/c + 1/d$$

Calculating: Log Odds Ratio

```
Y <- with(dat.bcg, log(tpos * cneg/(tneg * cpos)))
V <- with(dat.bcg, 1/tpos + 1/cneg + 1/tneg + 1/cpos)
cbind(Y, V)
```

```
##              Y       V
##  [1,] -0.93869 0.357125
##  [2,] -1.66619 0.208132
##  [3,] -1.38629 0.433413
##  [4,] -1.45644 0.020314
##  [5,] -0.21914 0.051952
##  [6,] -0.95812 0.009905
##  [7,] -1.63378 0.227010
##  [8,]  0.01202 0.004007
##  [9,] -0.47175 0.056977
## [10,] -1.40121 0.075422
## [11,] -0.34085 0.012525
## [12,]  0.44663 0.534162
## [13,] -0.01734 0.071635
```

Using `metafor` For ES Calculation

- `escalc` does the work of calculating ESs.
- Give the necessary data components (i.e. sample size, events in each treatment group, etc.).
- Indicate the ES you want with `measure`.
- Many, many, types of single group and between-group ESs.

Using `metafor` For ES Calculation

Syntax

```
ES <- escalc(endpoints, variances, measure, data, ...)
```

- `endpoints`: arguments or formula containing endpoint values
- `variances`: arguments containing endpoint variances
- `measure`: character value indicating type of ES
- `data`: data frame containing named variables

Effect Size: Log Odds Ratio

```
ES <- escalc(ai = tpos, bi = tneg, ci = cpos, di = cneg,
    data = dat.bcg,
    measure = "OR")
```

```
cbind(ES$yi, ES$vi)
```

Effect Size: Log Odds Ratio

```
##           [,1]     [,2]
##  [1,] -0.93869 0.357125
##  [2,] -1.66619 0.208132
##  [3,] -1.38629 0.433413
##  [4,] -1.45644 0.020314
##  [5,] -0.21914 0.051952
##  [6,] -0.95812 0.009905
##  [7,] -1.63378 0.227010
##  [8,]  0.01202 0.004007
##  [9,] -0.47175 0.056977
## [10,] -1.40121 0.075422
## [11,] -0.34085 0.012525
## [12,]  0.44663 0.534162
## [13,] -0.01734 0.071635
```

Formula-Based Specification

- What if my data is in a "long" format?
- That is, what if I have multiple rows per study, corresponding to difference treatment groups?
- In that case, you may prefer specifying the variables for the ES calculation using a formula.

Formula-Based Specification

Syntax

```
escalc(formula = outcome ~ group | study, data = data, weights = n)
```

Note: The exact syntax will vary a bit depending on the ES type.

Example: Formula-Based Specification

```
library(reshape2)  # Load package for data reshaping
```

```
bcg.long <- melt(dat.bcg[, c("trial", "tpos", "tneg", "cpos", "cneg")], id = "trial")
bcg.long$pos <- ifelse(bcg.long$var == "tpos" | bcg.long$var == "cpos", 1, 0)
bcg.long$group <- ifelse(bcg.long$var == "tpos" | bcg.long$var == "tneg", 1, 0)
head(bcg.long)
```

```
##   trial variable value pos group
## 1     1     tpos     4   1     1
## 2     2     tpos     6   1     1
## 3     3     tpos     3   1     1
## 4     4     tpos    62   1     1
## 5     5     tpos    33   1     1
## 6     6     tpos   180   1     1
```

Example: Formula-Based Specification

```
escalc(factor(pos) ~ factor(group) | factor(trial),
    weights = value,
    data = bcg.long,
    measure = "OR")
```

Example: Formula-Based Specification

```
##         yi     vi
## 1  -0.9387 0.3571
## 2  -1.6662 0.2081
## 3  -1.3863 0.4334
## 4  -1.4564 0.0203
## 5  -0.2191 0.0520
## 6  -0.9581 0.0099
## 7  -1.6338 0.2270
## 8   0.0120 0.0040
## 9  -0.4717 0.0570
## 10 -1.4012 0.0754
## 11 -0.3408 0.0125
## 12  0.4466 0.5342
## 13 -0.0173 0.0716
```

`escalc` & `rma`

- `rma` is the main modeling function of `metafor`.
- `rma` is also a wrapper for `escalc`, and will compute ESs before modeling (if you like).
- You usually won't work with `escalc` directly.
- But if you want the ESs (`yi`) and variances (`vi`) without modeling, use `escalc`.
- By default, `escalc` appends the `yi` and `vi` to the dataset.
- To return only `yi` and `vi` set `append=TRUE`.

Summarizing Effects

Summarizing Effects: Basic Framework

Normal Assumption

$$Y_i \sim N(\theta, V_i)$$

Summary Effect Size is a **Weighted Average**

$$\hat{\theta} = \sum_i Y_i W_i / \sum_i W_i, \ \mathrm{Var}(\hat{\theta}) = 1 / \sum_i W_i$$

Each Study's Contribution

$$\lambda_i = W_i / \sum_i W_i$$

Modeling Approaches

- **Fixed**

  -> Same mean ES, zero between-study variance

- **Random**

  -> Different mean ES, between-study variance

- **Mixed**

  -> Study-level regression for mean ES

Fixed Effects Model

- Same mean ES, known variance

$$Y_i = \theta + e_i,$$

$$e_i \sim N(0, V_i).$$

Random Effects Model

- Different mean ES, between-study variance

$$Y_i = \theta + \theta_i + e_i,$$

$$\theta_i \sim N(0, \tau^2),$$

$$e_i \sim N(0, V_i).$$

Mixed Effects Model (Meta-Regression)

- Study-level regression for mean ES

$$Y_i = \boldsymbol{\beta}' \mathbf{x}_i + \theta_i + e_i,$$

$$\theta_i \sim N(0, \tau^2),$$

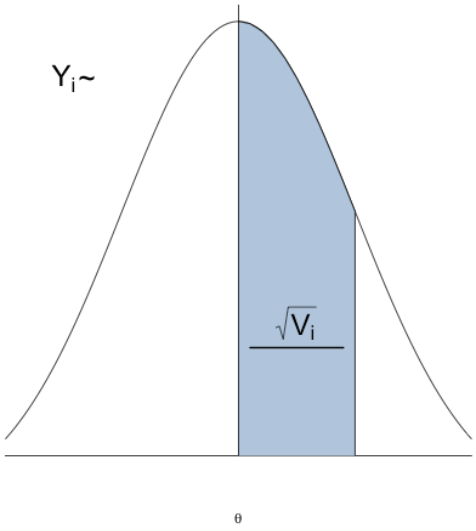
$$e_i \sim N(0, V_i).$$

$\mathbf{x}_i$ = Study-level covariates

Fixed Versus Random Effects

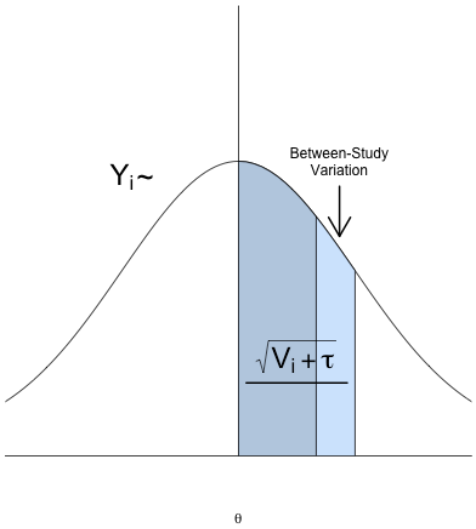
- The **FE model** is a description of the K studies.
- The **RE model** regards the K studies as a sample of a larger universe of studies.
- The **RE model** can be used to infer what would likely happen if a new study were performed, the **FE model** cannot.
- Common practice is to report **both** fixed and random effects model results.

Fixed Effects



Random Effects

Summary ES has more uncertainty because of between-study variance.



Fixed Effects With `metafor`

- All model summaries are made with the `rma` function.
- `rma` stands for **r**andom effects **m**eta-**a**nalysis
- The default method is a REML RE model, but the FE model can also be fit.

REML = Restricted Maximum Likelihood

Function `rma`

Syntax

```
rma(yi, vi, method, ...)
```

- `yi` effect size
- `vi` variances
- `method` type of model approach

Modeling Methods For `rma` Include:

- "FE" = Fixed Effects
- "DL" = DerSimonian-Laird
- "HE" = Hedges estimator
- "ML" = Maximum Likelihood
- "REML" = Restricted ML

Fitting The Fixed Effects Model

Example: BCG FE Model

```
result.or <- rma(yi = Y, vi = V, method = "FE")  # Log Odds Ratio
```

```
summary(result.or)
```

```
## Fixed-Effects Model (k = 13)
##
##   logLik  deviance       AIC       BIC
## -76.0290  163.1649  154.0580  154.6229
##
## Test for Heterogeneity:
## Q(df = 12) = 163.1649, p-val < .0001
##
## Model Results:
##
## estimate       se     zval     pval    ci.lb    ci.ub
##  -0.4361   0.0423 -10.3190   <.0001  -0.5190  -0.3533      ***
```

Wrapper For `escalc`

```
args(rma)
```

```
## function (yi, vi, sei, weights, ai, bi, ci, di, n1i, n2i, x1i,
##     x2i, t1i, t2i, m1i, m2i, sd1i, sd2i, xi, mi, ri, ti, sdi,
##     ni, mods, measure = "GEN", intercept = TRUE, data, slab,
##     subset, add = 1/2, to = "only0", drop00 = FALSE, vtype = "LS",
##     method = "REML", weighted = TRUE, knha = FALSE, level = 95,
##     digits = 4, btt, tau2, verbose = FALSE, control)
## NULL
```

Have `rma` calculate the ESs, if you haven't done it yourself.

Example: Mean Difference

```
result.md <- rma(m1 = mean.amlo, m2 = mean.plac,
    sd1 = sqrt(var.amlo), sd2 = sqrt(var.plac),
    n1 = n.amlo, n2 = n.plac,
    method = "FE", measure = "MD",
    data = amlodipine)
```

What Is Returned? `rma` Class

-> The function `rma` returns an object of the class `rma`.

-> This object behaves like a list.

-> You can use the function `names` to see available elements.

```
names(result.md)  # Components of rma
```

Components Of `rma`

```
names(result.md)
```

```
##  [1] "b"          "se"         "zval"       "pval"       "ci.lb"
##  [6] "ci.ub"      "vb"         "tau2"       "se.tau2"    "k"
## [11] "k.f"        "k.eff"      "p"          "p.eff"      "parms"
## [16] "m"          "QE"         "QEp"        "QM"         "QMp"
## [21] "I2"         "H2"         "int.only"   "int.incl"   "allvipos"
## [26] "yi"         "vi"         "X"          "yi.f"       "vi.f"
## [31] "X.f"        "ai.f"       "bi.f"       "ci.f"       "di.f"
## [36] "x1i.f"      "x2i.f"      "t1i.f"      "t2i.f"      "ni"
## [41] "ni.f"       "ids"        "not.na"     "slab"       "slab.null"
## [46] "measure"    "method"     "weighted"   "knha"       "robust"
## [51] "s2w"        "btt"        "intercept"  "digits"     "level"
## [56] "control"    "add"        "to"         "drop00"     "fit.stats"
```

Frequently Used Elements

Name	Description
`b`	Summary effect
`ci.lb`	Left endpoint of CI
`ci.ub`	Right endpoint of CI
`vb`	Variance-covariance of summary effects
`fit.stats`	Model fit statistics
`yi`	Vector of study effect sizes
`vi`	Vector of effect size variances

Your Turn: Fixed Effects, Mean Difference

For the mean difference in the amlodipine trial determine:

1. The summary effect
2. The 95% confidence interval

Your Turn: Fixed Effects, Mean Difference

```
result.md$b
```

```
##           [,1]
## intrcpt 0.1619
```

```
c(result.md$ci.lb, result.md$ci.ub)
```

```
## [1] 0.0986 0.2252
```

Your Turn: Study Contributions

1. Determine the percentage each study contributed to the overall effect size summary.
2. Which study contributes the most? How much?
3. Use a `barplot` to show the percentages graphically.

Your Turn: Study Contributions

```
contributions <- 1/result.md$vi/sum(1/result.md$vi) * 100
```

```
cbind(contributions)
```

```
##      contributions
## [1,]        21.219
## [2,]        11.355
## [3,]        10.923
## [4,]         6.667
## [5,]        17.943
## [6,]        10.848
## [7,]         1.661
## [8,]        19.385
```

Your Turn: Study Contributions

```
max(contributions)
```

```
## [1] 21.22
```

```
amlodipine$study[which(contributions == max(contributions))]
```

```
## [1] Protocol 154
## 8 Levels: Protocol 154 Protocol 156 Protocol 157 ... Protocol 306
```

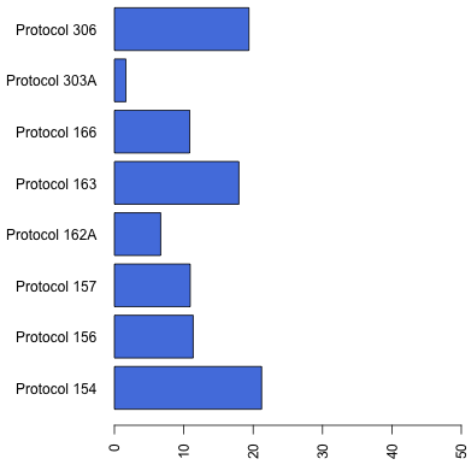
Your Turn: Study Contributions

```
contributions <- 1/result.md$vi/sum(1/result.md$vi) * 100

par(mar = c(5, 10, 5, 5))

barplot(contributions, names = amlodipine$study,
        xlim = c(0, 50), las = 2, horiz = T,
        col = "royalblue")
```

Your Turn: Study Contributions



Methods For `rma` Object

Name	Description
`coef`	Summary effect
`confint`	Confidence interval
`summary`	Summary table of meta-analytic model

Methods For `rma` Object

```
summary(result.md)
```

```
## Fixed-Effects Model (k = 8)
##
##   logLik  deviance       AIC       BIC
##   4.7834   12.3311   -7.5669   -7.4874
##
## Test for Heterogeneity:
## Q(df = 7) = 12.3311, p-val = 0.0902
##
## Model Results:
##
## estimate       se     zval     pval    ci.lb    ci.ub
##   0.1619   0.0323   5.0134   <.0001   0.0986   0.2252      ***
```

Methods For `rma` Object

```
coef(result.md)
```

```
## intrcpt
##  0.1619
```

Methods For `rma` Object

```
confint(result.md)  # Heterogeneity measures do not apply for FE model
```

```
##
##        estimate  ci.lb   ci.ub
## tau^2        NA 0.0000  0.1667
## tau          NA 0.0000  0.4082
## I^2(%)       NA 0.0000 95.0658
## H^2          NA 1.0000 20.2667
```

Fitting The Random Effects Model

Random Effects Model

- Suppose between-study variance (τ^2) is non-zero.
- Methods differ on how they estimate τ^2.
- Many iterative and non-iterative approaches to estimating τ^2 have been proposed.

Estimators of τ^2

The `rma` function offers the following estimators:

Method	Estimator
DL	DerSimonian-Laird (Most Common)
HE	Hedges
HS	Hunter-Schmidt
SJ	Sidik-Jonkman
ML	Maximum-likelihood
REML	Restricted maximum-likelihood (Default)
EB	Empirical Bayes

Between-Study Variance

The `rma` function offers the following estimators:

Method	Estimator
DL	DerSimonian-Laird (Most Common)
HE	Hedges
HS	Hunter-Schmidt
SJ	Sidik-Jonkman
ML	Maximum-likelihood
REML	Restricted maximum-likelihood (Default)
EB	Empirical Bayes

No method is universally superior, but Viechtbauer's simulation study (2002) suggests REML has the most recommendable properties.

Example: RE Model, Mean Difference

```
result.md <- rma(m1 = mean.amlo, m2 = mean.plac,
    sd1 = sqrt(var.amlo), sd2 = sqrt(var.plac),
    n1 = n.amlo, n2 = n.plac,
    method = "REML", measure = "MD",
    data = amlodipine)
```

Example: RE Model, Mean Difference

```
summary(result.md)
```

```
## Random-Effects Model (k = 8; tau^2 estimator: REML)
##
##   logLik  deviance       AIC       BIC
##   3.3094   -6.6188   -2.6188   -2.7270
##
## tau^2 (estimated amount of total heterogeneity): 0.0001 (SE = 0.0042)
## tau (square root of estimated tau^2 value):      0.0116
## I^2 (total heterogeneity / total variability):   1.54%
## H^2 (total variability / sampling variability):  1.02
##
## Test for Heterogeneity:
## Q(df = 7) = 12.3311, p-val = 0.0902
##
## Model Results:
##
## estimate       se     zval     pval    ci.lb    ci.ub
##   0.1617   0.0326   4.9584   <.0001   0.0978   0.2257      ***
```

Get Between-Study Variance & Its Error

```
result.md$tau2
```

```
## [1] 0.0001353
```

```
result.md$se.tau2
```

```
## [1] 0.004239
```

```
result.md$tau2 + 1.96 * c(-1, 1) * result.md$se.tau2  #95% CI
```

```
## [1] -0.008173  0.008444
```

How Much Can Estimates Of τ^2 Differ?

```
estimators <- c("DL", "REML", "HE", "HS", "SJ", "ML", "EB")

taus <- sapply(estimators, function(method) {
    rma(m1 = mean.amlo, m2 = mean.plac,
         sd1 = sqrt(var.amlo), sd2 = sqrt(var.plac),
        n1 = n.amlo, n2 = n.plac,
        method = method, measure = "MD",
        data = amlodipine)$tau2
})
```

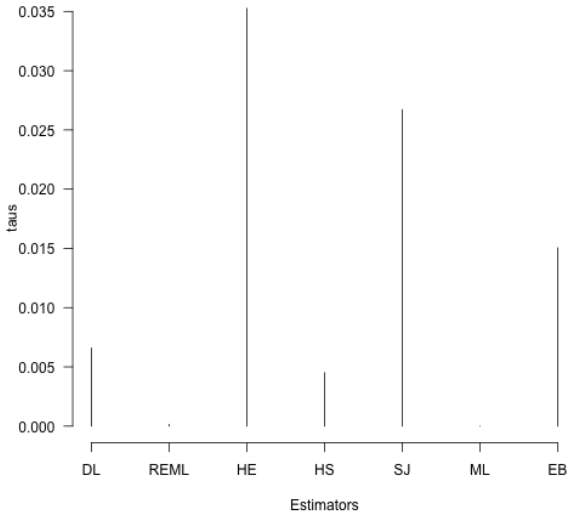
Plot Of τ^2 Estimates

```
plot(y = taus, x = 1:length(taus),
    type = "h", pch = 19,
    axes = FALSE, xlab = "Estimators")

axis(2, las = 1)

axis(1, at = 1:length(taus), lab = estimators)
```

Plot Of τ^2 Estimates



DerSimonian-Laird

Method of moments estimator; Most popular approach

$$\hat{\tau}^2 = \max\{0, \frac{Q - (K-1)}{\sum_i W_i - \sum_i W_i^2 / \sum_i W_i}\}$$

$$Q = \sum_i W_i (Y_i - \bar{Y})^2$$

$$\bar{Y}_W = \sum W_i Y_i / \sum W_i$$

REML

Best properties, in general

$$\hat{\tau}^2 = \frac{\sum_i \tilde{W}_i^2 \left[\frac{K}{K-1} (Y_i - \hat{\theta})^2 - V_i \right]}{\sum_i \tilde{W}_i^2}$$

K = Number of trials

$\tilde{W} = (V_i + \hat{\tau}^2)^{-1}$

$\hat{\theta}$ = Effect size

Maximum-Likelihood

$$\hat{\tau}^2 = \frac{\sum_i W_i^2 \left[(Y_i - \hat{\theta})^2 - V_i \right]}{\sum_i W_i^2}$$

Hedges

$$\hat{\tau}^2 = \frac{\sum_i (Y_i - \bar{Y})^2}{(K-1)} - \frac{\sum_i V_i}{K}$$

Sidik-Jonkman

$$\hat{\tau}_0^2 = k^{-1} \sum_i (Y_i - \bar{Y})^2$$

$$\hat{\theta} = (\sum_i \tilde{W}_i)^{-1} \sum_i \tilde{W}_i Y_i$$

$$\hat{\tau}_2 = \hat{\tau}_0^2 / (K-1) \sum_i \tilde{W}_i (Y_i - \hat{\theta})^2$$

10-minute Break

Evaluating Heterogeneity

Testing For Heterogeneity: Q Test

$$Q = \sum_i W_i (Y_i - \hat{\theta})^2$$

- Q is the weighted deviations about the summary effect size.
- Larger values of Q reflect greater between-study heterogeneity.
- When $\tau^2 = 0$, $Q \sim \chi^2(K-1)$, which leads to a chi-squared test for heterogeneity.

Example: Q-test, Mean Differences

```
MD <- with(amlodipine, mean.amlo - mean.plac)
```

```
W <- 1/with(amlodipine, var.amlo/n.amlo + var.plac/n.plac)
```

```
Q <- sum(W * (MD - sum(W * MD)/sum(W))^2)
```

Example: Q-test, Mean Differences

```
Q
```

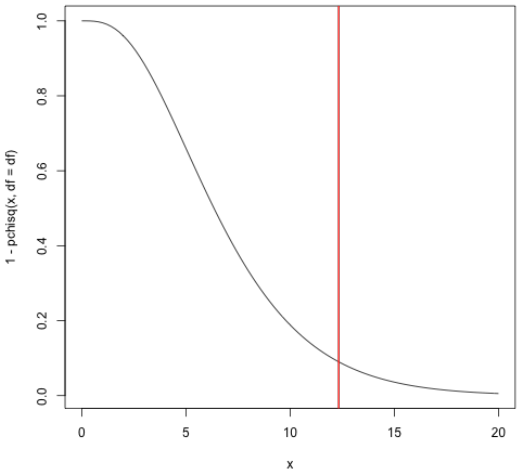
```
## [1] 12.33
```

```
df <- length(MD) - 1
pchisq(Q, df = df, lower = FALSE)  # HOW LIKELY UNDER NULL?
```

```
## [1] 0.09018
```

Example: Q-test, Mean Differences

```
curve(1 - pchisq(x, df = df), 0, 20)
abline(v = Q, col = "red", lwd = 2)
```



Q-test Comes With `rma` Object

```
result.md$QE
```

```
## [1] 12.33
```

```
result.md$QEp
```

```
## [1] 0.09018
```

Your Turn: Q-test, Log Odds Ratio

1. Obtain the Q-test for the meta-analysis of log odds ratios with the BCG Vaccine Trials.
2. What does the test suggest about between-study heterogeneity?

Your Turn: Q-test, Log Odds Ratio

```
result.or <- rma(yi = Y, vi = V, method = "DL")  # DerSimonian-Laird
```

```
result.or$QE
```

```
## [1] 163.2
```

```
result.or$QEp
```

```
## [1] 1.189e-28
```

Remarks On Q-test

- The chi-squared approximation is **valid** when study sample sizes are **large**.
- Type I error is generally accurate if normal distribution assumption and sample sizes are **not too small**.
- **Q-test has low power (<0.80)** when the number of studies and/or sample sizes is small.

Remarks On Q-test

Bottom Line: If there are few trials in the meta-analysis (as is usually the case), the Q-test is **likely underpowered for detecting true heterogeneity**.

Indices Of Heterogeneity

- τ^2
- Higgins' I^2
- H^2, H Index
- Intra-class correlation (ICC)

Higgins' I^2

$$I^2 = (Q - df)/Q \times 100$$

Interpretation = Percentage of "unexplained" variance

df = Degrees of Freedom

For random-effects meta-analysis, df = $K - 1$

Thresholds For I^2

Judging the severity of measured heterogeneity is subjective, however Higgins suggests these rules of thumb:

- 0% to 30% $\rightarrow$ Low
- 30% to 60% $\rightarrow$ Moderate
- 50% to 90% $\rightarrow$ Substantial
- 75% to 100% $\rightarrow$ Considerable

Example: I^2, Mean Differences

```
(Q - df)/Q * 100
```

```
## [1] 43.23
```

```
# From rma object
I2 <- with(result.md, (QE - (k - 1))/QE * 100)
I2
```

```
## [1] 43.23
```

H^2

Is the ratio of Q to the Q-test's degrees of freedom,

$$H^2 = \frac{Q}{df},$$

$$1/H^2 = 1 - \frac{I^2}{100}.$$

H index is the $\sqrt{H^2}$.

$H > 1$ suggests there is unexplained heterogeneity.

Example: H^2

```
Q/df
```

```
## [1] 1.762
```

```
1/(1 - I2/100)
```

```
## [1] 1.762
```

Intra-Class Correlation

After fitting RMA and getting measure of τ^2, we can compute the intra-class correlation (ICC)

$$ICC = \frac{\tau^2}{\tau^2 + S^2}$$

$$S^2 = \frac{\sum W_i(K-1)}{(\sum W_i)^2 - \sum W_i^2}$$

Example: Intra-Class Correlation

```
S2 <- sum(W * (length(W) - 1))/(sum(W)^2 - sum(W^2))
```

```
result.md$tau2/(result.md$tau2 + S2)
```

```
## [1] 0.0154
```

```
result.md$I2
```

```
## [1] 1.54
```

Relationship Between ICC, I^2, H^2

- What happened in the previous example?
- We saw that $I^2 = ICC \times 100$
- This is because `metafor` uses the more general definitions of I^2 and H^2, which are based on τ^2.
- To get the conventional estimates, which do not depend on τ^2, use method `DL`.

I^2 & H^2 In metafor

$$I^2 = ICC \times 100$$

$$H^2 = (\tau^2 + \sigma^2)/\sigma^2$$

where, σ^2 is the weighted numerator of the DL τ^2 estimator

$$\sigma^2 = \left[(K-1)(\sum W_i - \sum W_i^2 / \sum W_i)\right]^{-1}$$

Example: I^2 In `metafor`

```
result.md$tau2/(result.md$tau2 + S2) * 100
```

```
## [1] 1.54
```

```
result.md$I2
```

```
## [1] 1.54
```

Example: H^2 In `metafor`

```
sigma2 <- (length(Y) - 1) * (sum(W) - sum(W^2)/sum(W))^(-1)
```

```
result.md$tau2/sigma2 + 1  #H2
```

```
## [1] 1.009
```

```
result.md$H2
```

```
## [1] 1.016
```

Example: I^2 & H^2 Conventional Estimates

```
result.md <- rma(m1 = mean.amlo, m2 = mean.plac,
    sd1 = sqrt(var.amlo), sd2 = sqrt(var.plac),
    n1 = n.amlo, n2 = n.plac,
    method = "DL", measure = "MD", data = amlodipine)
```

```
result.md$I2
```

```
## [1] 43.23
```

```
result.md$H2
```

```
## [1] 1.762
```

Confidence Intervals For Indices

- A Q-profile method for an exact confidence interval for τ^2 is provided with the `confint` method of `rma` objects.
- The CI for τ^2 is used to derive CIs for the remaining heterogeneity indices, which are all monotonic transformations of τ^2.

Example: Confidence Intervals For Indices

```
confint(result.md)
```

```
##
##        estimate  ci.lb   ci.ub
## tau^2    0.0066 0.0000  0.1667
## tau      0.0812 0.0000  0.4082
## I^2(%)  43.2328 0.0000 95.0658
## H^2      1.7616 1.0000 20.2667
```

Your Turn: Confidence Intervals For ICC

1. Use the `confint` method to obtain a 95% CI for the ICC of the mean difference DL meta-analysis.

Your Turn: Confidence Intervals For ICC

```
names(confint(result.md))
```

```
## [1] "random"   "digits"   "tau2.min"
```

```
I2CI <- confint(result.md)$random[3, ]
```

```
I2CI/100
```

```
## estimate    ci.lb    ci.ub
##   0.4323   0.0000   0.9507
```

Visualizing Heterogeneity

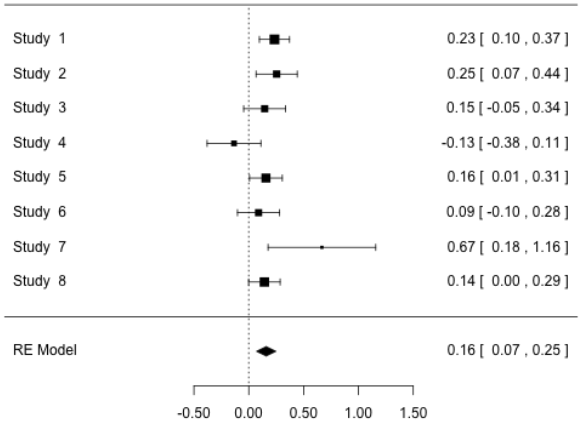
The Forest Plot

"Seeing the forest through the trees..."

- Is a plot of effect sizes and their precisions
- Is the most common way to report the results of a meta-analysis
- Can help identify patterns across effects
- Can help spot large variation in effects or possible outliers

Forest Plot For `rma` Objects

```
forest(result.md)  # DEFAULT PLOT
```



Arguments Of `forest`

```
args(forest.rma)
```

```
## function (x, annotate = TRUE, addfit = TRUE, addcred = FALSE,
##     showweight = FALSE, xlim, alim, ylim, at, steps = 5, level = x$level,
##     digits = 2, refline = 0, xlab, slab, mlab, ilab, ilab.xpos,
##     ilab.pos, order, transf = FALSE, atransf = FALSE, targs,
##     rows, efac = 1, pch = 15, psize, col = "darkgray", border = "darkgray",
##     cex, cex.lab, cex.axis, ...)
## NULL
```

Customizing Forest Plot

Some typical modifications:

- `order`: Sort by "obs", "fit", "prec", etc.
- `slab`: Change study labels
- `ilab`: Add study information
- `transf`: Apply function to effects
- `psize`: Symbol sizes

Example: Customizing Forest Plot

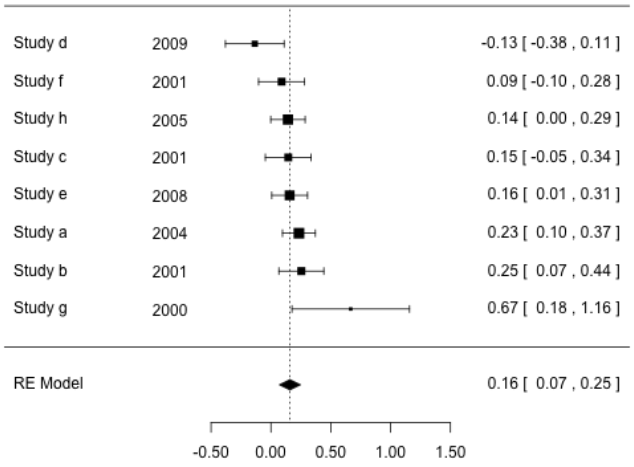
In the following, we modify the study labels and add the (fake) year of publication.

```
study.names <- paste("Study", letters[1:8])

study.year <- 2000 + sample(0:9, 8, replace = T)

forest(result.md, order = "obs",
         slab = study.names,
         ilab = study.year,
         ilab.xpos = result.md$b - 1,
         refline = result.md$b)
```

Example: Customizing Forest Plot

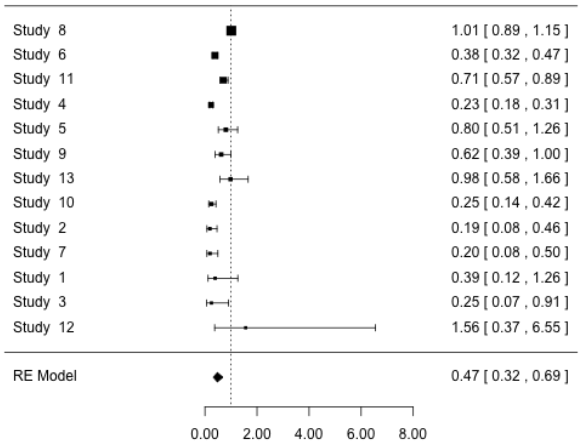


Example: Customizing Forest Plot

In the following, we plot the ORs of the BCG trials and order the studies by precision.

```
forest(result.or, order = "prec", transf = exp, refline = 1)
```

Example: Customizing Forest Plot



Your Turn: Customizing Forest Plot

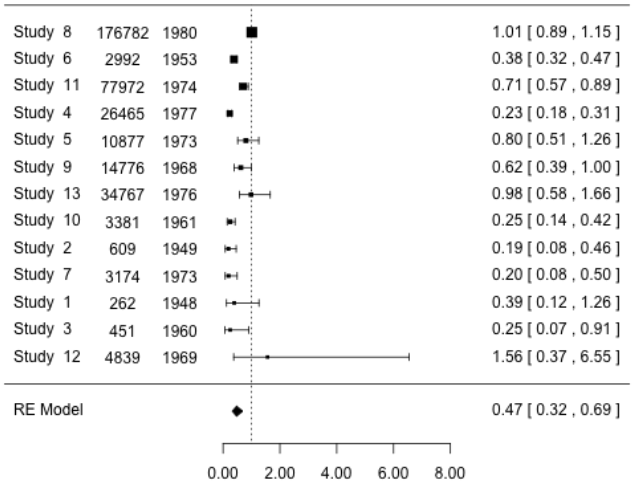
1. Modify the previous plot by adding the sample size and year of the studies.

Your Turn: Customizing Forest Plot

```
dat.bcg$n <- with(dat.bcg, tpos + tneg + cpos + cneg)
```

```
forest(result.or, order = "prec",
         ilab = dat.bcg[, c("n", "year")],
         ilab.xpos = exp(result.or$b) - c(4, 2),
         transf = exp, refline = 1)
```

Your Turn: Customizing Forest Plot



130/204

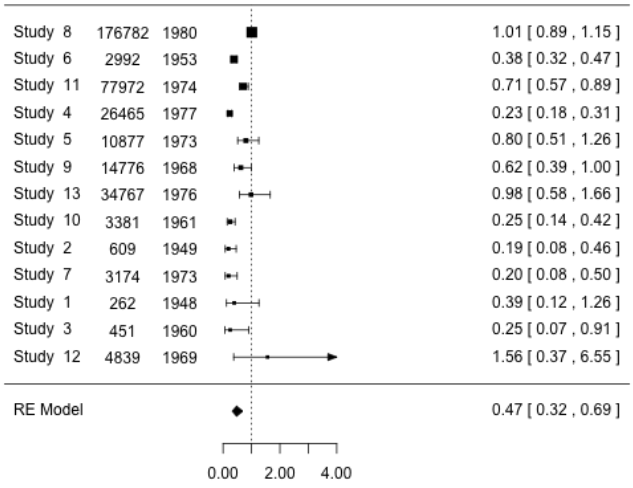
Adjusting Limits

- You can change the min and max of the drawn region with the argument `alim`.
- This must include all effects.
- CIs will be clipped if outside the restricted area.
- An arrow will indicate clipped CIs.

Example: Adjusting Limits

```
forest(result.or, order = "prec",
    ilab = dat.bcg[, c("n", "year")],
    ilab.xpos = exp(result.or$b) - c(4, 2),
    transf = exp, refline = 1,
    alim = c(0, 4))
```

Example: Adjusting Limits



Sensitivity Analyses

Case Diagnostics

- A single outlying trial could be the source of substantial heterogeneity.
- To identify suspicious cases, a leave-one-out method can be used whereby we rerun the meta-analysis, iteratively removing studies.
- In the `metafor` package this is accomplished with the `leave1out` function.

Example: Case Diagnostics

```
leave1out(result.md)
```

```
##   estimate     se   zval   pval  ci.lb  ci.ub       Q     Qp   tau2
## 1   0.1434 0.0516 2.7759 0.0055 0.0421 0.2446 10.9770 0.0891 0.0080
## 2   0.1449 0.0497 2.9156 0.0036 0.0475 0.2423 11.2868 0.0799 0.0076
## 3   0.1610 0.0519 3.1045 0.0019 0.0593 0.2626 12.2979 0.0556 0.0090
## 4   0.1833 0.0345 5.3173 0.0000 0.1158 0.2509  6.3053 0.3899 0.0004
## 5   0.1595 0.0541 2.9494 0.0032 0.0535 0.2655 12.3252 0.0551 0.0099
## 6   0.1689 0.0505 3.3429 0.0008 0.0699 0.2679 11.7178 0.0686 0.0082
## 7   0.1481 0.0387 3.8295 0.0001 0.0723 0.2239  8.2003 0.2238 0.0028
## 8   0.1623 0.0543 2.9908 0.0028 0.0559 0.2687 12.2425 0.0568 0.0099
##        I2     H2
## 1 45.3404 1.8295
## 2 46.8405 1.8811
## 3 51.2112 2.0496
## 4  4.8426 1.0509
## 5 51.3192 2.0542
## 6 48.7959 1.9530
## 7 26.8316 1.3667
## 8 50.9905 2.0404
```

Your Turn: Case Diagnostics, BCG Trials

1. Which trial contributes the most to the BCG OR meta-analysis?
2. Do any of the trials reduce I^2 to $< 30\%$?
3. Does the removal of any trial change the main conclusion about the efficacy of BCG?

Your Turn: Case Diagnostics, BCG Trials

```
cases <- leave1out(result.or)
```

```
which(cases$I2 == min(cases$I2))
```

```
## [1] 8
```

```
sum(cases$I2 < 30)  # Number with low heterogeneity
```

```
## [1] 0
```

Your Turn: Case Diagnostics, BCG Trials

```
cbind(exp(cases$estimate), cases$pval < 0.05)
```

```
##         [,1] [,2]
##  [1,] 0.4784    1
##  [2,] 0.5047    1
##  [3,] 0.4885    1
##  [4,] 0.5173    1
##  [5,] 0.4493    1
##  [6,] 0.4835    1
##  [7,] 0.5025    1
##  [8,] 0.4379    1
##  [9,] 0.4605    1
## [10,] 0.5033    1
## [11,] 0.4510    1
## [12,] 0.4499    1
## [13,] 0.4424    1
```

Explaining Heterogeneity: Meta-Regression

Meta-Regression With `rma`

- Specify study covariates through the `mods` argument
- The `mods` argument takes a matrix of p covariates

Example: Latitude And BCG Trial Results

```
result.ormr <- rma(ai = tpos, bi = tneg, ci = cpos, di = cneg,
    data = dat.bcg,
    mods = dat.bcg[, "ablat"],
    measure = "OR",
    method = "DL")
```

Example: Latitude And BCG Trial Results

```
summary(result.ormr)
```

```
## Mixed-Effects Model (k = 13; tau^2 estimator: DL)
##
## tau^2 (estimated amount of residual heterogeneity):     0.0480 (SE = 0.0451)
## tau (square root of estimated tau^2 value):             0.2191
## I^2 (residual heterogeneity / unaccounted variability): 56.17%
## H^2 (unaccounted variability / sampling variability):   2.28
##
## Test for Residual Heterogeneity:
## QE(df = 11) = 25.0954, p-val = 0.0088
##
## Test of Moderators (coefficient(s) 2):
## QM(df = 1) = 26.1628, p-val < .0001
##
## Model Results:
##
##          estimate      se     zval    pval    ci.lb    ci.ub
## intrcpt    0.3030  0.2109   1.4370  0.1507  -0.1103   0.7163
## mods      -0.0316  0.0062  -5.1150  <.0001  -0.0437  -0.0195  ***
```

Change In Estimate & Heterogeneity

```
exp(c(result.or$b, result.ormr$b[1]))
```

```
## [1] 0.4736 1.3540
```

```
c(result.or$I2, result.ormr$I2)
```

```
## [1] 92.65 56.17
```

Change In Estimate & Heterogeneity

- What happened?
- The effect of treatment changed direction.
- **Remember**: This is a linear not logistic regression.
- As fit, the intercept (treatment log-odds) corresponds to a study conducted in a region with latitude = 0.

Your Turn: Meta-Regression

1. Determine to what extent the study design (`alloc`) explains the remaining heterogeneity in the BCG vaccine trials.
2. Center latitude on the median, so that the intercept corresponds to the log-odds effect of BCG at the median latitude.
3. What is the percentage change in I^2 as compared to the RE model?

Example: Allocation And BCG Trial Results

```
dat.bcg$random <- ifelse(dat.bcg$alloc == "random", 1, 0)
dat.bcg$cablat <- dat.bcg$ablat - median(dat.bcg$ablat)
```

```
result.ormr <- rma(ai = tpos, bi = tneg, ci = cpos, di = cneg,
         data = dat.bcg,
         mods = dat.bcg[, c("ablat", "random")],
         measure = "OR",
         method = "DL")
```

Example: Allocation And BCG Trial Results

```
summary(result.ormr)
```

```
## Mixed-Effects Model (k = 13; tau^2 estimator: DL)
##
## tau^2 (estimated amount of residual heterogeneity):     0.0732 (SE = 0.0677)
## tau (square root of estimated tau^2 value):             0.2706
## I^2 (residual heterogeneity / unaccounted variability): 60.10%
## H^2 (unaccounted variability / sampling variability):   2.51
##
## Test for Residual Heterogeneity:
## QE(df = 10) = 25.0624, p-val = 0.0052
##
## Test of Moderators (coefficient(s) 2,3):
## QM(df = 2) = 20.0425, p-val < .0001
##
## Model Results:
##
##          estimate      se     zval    pval    ci.lb    ci.ub
## intrcpt    0.3643  0.2596   1.4037  0.1604  -0.1444   0.8731
## ablat     -0.0307  0.0072  -4.2829  <.0001  -0.0447  -0.0166  ***
## random    -0.2029  0.2124  -0.9551  0.3395  -0.6191   0.2134
```

Example: Allocation And BCG Trial Results

```
c(result.ormr$I2, result.or$I2)
```

```
## [1] 60.10 92.65
```

```
(result.or$I2 - result.ormr$I2)/result.or$I2 * 100
```

```
## [1] 35.13
```

Publication Bias

`The File-Drawer' Problem

- It is possible that studies showing a significant intervention effect are more often published than studies with null results.
- When a meta-analysis is based only on studies reported in the literature, null studies relegated to the file-drawer could bias the summary intervention effect in the direction of efficacy.

Detecting Publication Bias: Funnel Plot

- A funnel plot is a scatter plot of the intervention effect estimates against a measure of study precision.
- Asymmetry (gaps) in the funnel may be indicative of publication bias.
- Some authors argue that judging asymmetry is **too subjective to be useful**.
- Spurious asymmetry can result from heterogeneity or when ESs are correlated with precision.

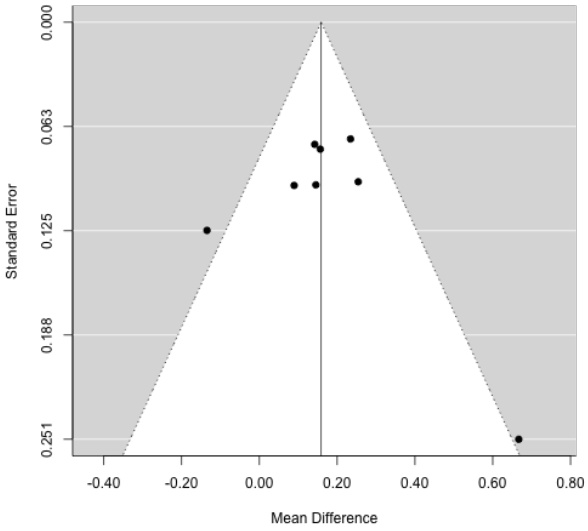
Example: Funnel Plot

`metafor` method for generating funnel plots from `rma` objects.

```
funnel(result.md)
```

Use `addtau2=TRUE` to add between-study error.

Example: Funnel Plot



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Sensitivity Analyses For Publication Bias

- Judging asymmetry in the funnel plot **can be difficult**.
- So you will usually want to consider some additional ways of assessing the threat of publication bias.
- Sensitivity Analyses:
  - Trim-and-Fill
  - Fail Safe N

Trim-and-Fill Method

- The trim and fill method estimates the number of missing NULL studies from the meta-analysis.
- The method `trimfill` of the `metafor` package augments the observed data and returns the fitted `rma` object with the missing studies included.
- These points can be added to the funnel plot.

Example: Trim-and-Fill Method

```
result.rd <- rma(ai = tpos, bi = tneg, ci = cpos, di = cneg,
    data = dat.bcg,
    measure = "RD",
    method = "DL")  # Risk Differences
```

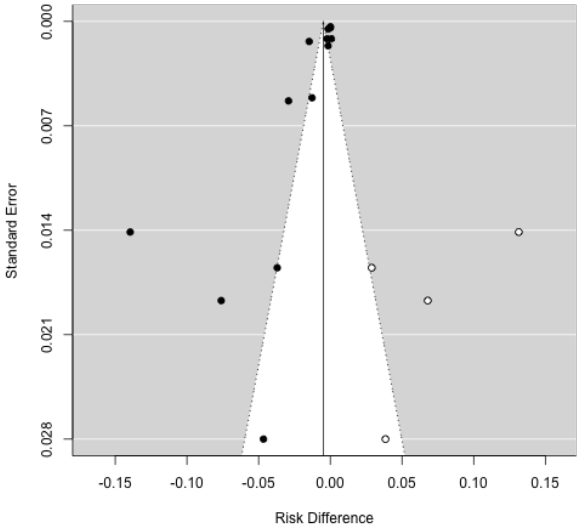
```
trimfill(result.rd)  # Only applicable for FE or RE objects
```

Example: Trim-and-Fill Method

```
## Estimated number of missing studies on the right side: 4
##
## Random-Effects Model (k = 17; tau^2 estimator: DL)
##
## tau^2 (estimated amount of total heterogeneity): 0.0000 (SE = 0.0000)
## tau (square root of estimated tau^2 value):      0.0051
## I^2 (total heterogeneity / total variability):   95.83%
## H^2 (total variability / sampling variability):  23.98
##
## Test for Heterogeneity:
## Q(df = 16) = 383.6062, p-val < .0001
##
## Model Results:
##
## estimate       se     zval     pval    ci.lb    ci.ub
##  -0.0049   0.0018  -2.7858   0.0053  -0.0084  -0.0015       **
```

Example: Trim-and-Fill Method

```
funnel(trimfill(result.rd))
```



Fail-Safe N

- Rosenthal method (sometimes called a 'file drawer analysis')
- Is the number of NULL studies that have to be added to reduce the significance of the meta-analysis to α (usually 0.05)

Example: Fail-Safe Method

```
value <- fsn(y = result.md$yi, v = result.md$vi)
```

```
value
```

```
##
## Fail-safe N Calculation Using the Rosenthal Approach
##
## Observed Significance Level: <.0001
## Target Significance Level:   0.05
##
## Fail-safe N: 65
```

Example: Fail-Safe Method

```
value$fsnum
```

```
## [1] 65
```

```
value$alpha  # Target Significance Level
```

```
## [1] 0.05
```

Other R Packages for Meta-Analysis

Packages `rmeta` And `meta`

- Package `metafor` is the most comprehensive of currently available `R` packages for performing meta-analysis, but some may find its design overly complex (think iTunes)
- The package `meta` has a lot of overlap in provided methods, but it separates modeling functions by endpoint type
- The package `rmeta` only has DSL random effects modeling and no meta-regression modeling functions, which might be fine for some purposes
- The reliability of all of these packages is very good

```
library(meta)  # Package meta
```

Main Functions:

- `metabin`: Meta-analysis for binary outcome
- `metacont`: Meta-analysis for continuous outcome
- `metareg`: Meta-regression
- `forest`: Forest plot
- `funnel`: Funnel plot
- `trimfill`: Trim-and-fill method
- `metabias`: Test of asymmetry in funnel plot

Example Of `metabin`

```
dat.bcg$tn <- dat.bcg$tpos + dat.bcg$tneg
dat.bcg$cn <- dat.bcg$cpos + dat.bcg$cneg
result.or.meta <- metabin(event.e = tpos, n.e = tn, event.c = cpos, n.c = cn,
         data = dat.bcg,
         sm = "OR",
         method = "Inverse",
         method.tau = "REML")
```

Returned Object Has Many Components

```
names(result.or.meta)
```

```
##  [1] "event.e"      "n.e"          "event.c"      "n.c"
##  [5] "studlab"      "TE"           "seTE"         "w.fixed"
##  [9] "w.random"     "TE.fixed"     "seTE.fixed"   "lower.fixed"
## [13] "upper.fixed"  "zval.fixed"   "pval.fixed"   "TE.random"
## [17] "seTE.random"  "lower.random" "upper.random" "zval.random"
## [21] "pval.random"  "k"            "Q"            "tau"
## [25] "se.tau2"      "Q.CMH"        "sm"           "method"
## [29] "sparse"       "incr"         "allincr"      "addincr"
## [33] "allstudies"   "MH.exact"     "RR.cochrane"  "incr.e"
## [37] "incr.c"       "level"        "level.comb"   "comb.fixed"
## [41] "comb.random"  "hakn"         "df.hakn"      "method.tau"
## [45] "tau.preset"   "TE.tau"       "method.bias"  "title"
## [49] "complab"      "outclab"      "label.e"      "label.c"
## [53] "label.left"   "label.right"  "call"         "warn"
## [57] "print.byvar"  "print.CMH"    "version"
```

Key Components

- `w.fixed, w.random`: Weight of individual studies
- `TE.fixed, TE.random`: Estimated overall treatment effect
- `lower.fixed, upper.fixed`: Lower and upper confidence intervals
- `lower.random, upper.random`: Lower and upper confidence intervals
- `k`: Number of studies
- `tau`: Estimated between-study variance
- `Q`: Heterogeneity statistic

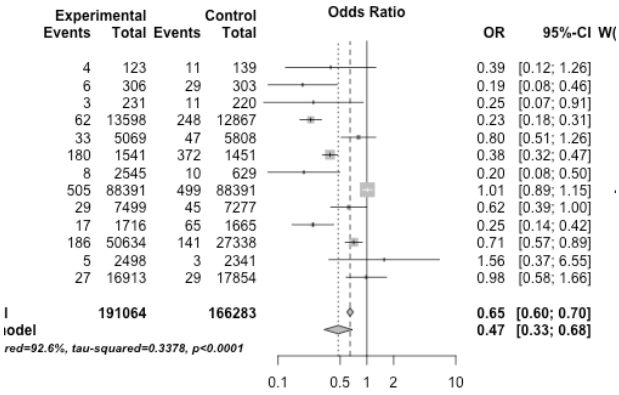
Example Of `metabin`

```
summary(result.or.meta)
```

```
## Number of studies combined: k=13
##
##                         OR          95%-CI       z  p.value
## Fixed effect model   0.647  [0.595; 0.702] -10.319 < 0.0001
## Random effects model 0.475  [0.330; 0.683]  -4.006 < 0.0001
##
## Quantifying heterogeneity:
## tau^2 = 0.3378; H = 3.69 [3.04; 4.47]; I^2 = 92.6% [89.2%; 95%]
##
## Test of heterogeneity:
##       Q d.f.  p.value
##  163.16   12 < 0.0001
##
## Details on meta-analytical method:
## - Inverse variance method
## - restricted maximum-likelihood estimator for tau^2
```

Forest Plot With `metabin`

```
forest(result.or.meta)  # Default like Cochrane forest plot
```



Funnel Plot Asymmetry Test `metabin`

```
metabias(result.or.meta, method = "rank")  # Rank-correlation test
```

```
##
##  Rank correlation test of funnel plot asymmetry
##
## data:  result.or.meta
## z = 0.122, p-value = 0.9029
## alternative hypothesis: asymmetry in funnel plot
## sample estimates:
##    ks se.ks
##  2.00 16.39
```

No indication of asymmetry for OR analysis.

```
library(rmeta)  # rmeta package
```

Key Functions:

- `meta.DSL`: RE meta-analysis (Binary only)
- `meta.MH`: FE meta-analysis (Mantel-Haenszel)
- `meta.summaries`: Fixed/Random given ES and weights
- `forestplot`: Forest plot
- `funnelplot`: Funnel plot

Mantel-Haenszel OR

- `rmeta` has the fewest features of the packages we have discussed.
- One potential advantage is the fixed-effects Mantel-Haenszel method for combined ORs.
- Like Peto's OR, this is a FE model that can be advantageous for handling studies with rare events.

Example: meta.MH

```
dat.bcg$tn <- with(dat.bcg, tpos + tneg)
dat.bcg$cn <- with(dat.bcg, cpos + cneg)
dat.bcg$tp <- with(dat.bcg, tpos/tn)
dat.bcg$cp <- with(dat.bcg, cpos/cn)
```

```
result.mh <- meta.MH(tn, cn, tp, cp, data = dat.bcg)
```

Returned Object Of `meta.MH`

```
names(result.mh)
```

```
##  [1] "logOR"      "selogOR"    "logMH"      "selogMH"    "MHtest"
##  [6] "het"        "call"       "names"      "conf.level" "statistic"
```

Key Components

- `logOR`: Log odds ratio
- `logMH`: Estimated overall log OR
- `selogMH`: Standard error of overall log OR
- `MHtest`: Mantel-Haenszel χ^2-test that OR=1
- `het`: Woolf's chi-square for heterogeneity, df, p-value

Example: meta.MH

```
summary(result.mh)
```

```
## Fixed effects ( Mantel-Haenszel ) meta-analysis
## Call: meta.MH(ntrt = tn, nctrl = cn, ptrt = tp, pctrl = cp, data = dat.bcg)
## ------------------------------------
##         OR (lower  95% upper)
##  [1,] 0.46       0  1.881e+05
##  [2,] 0.20       0  9.548e+05
##  [3,] 0.25       0  5.984e+07
##  [4,] 0.22       0  2.332e+13
##  [5,] 0.92       0  1.368e+14
##  [6,] 0.43       0  4.339e+02
##  [7,] 0.05       0  2.016e+15
##  [8,] 1.01       0  9.527e+15
##  [9,] 0.61       0  1.713e+17
## [10,] 0.25       0  9.272e+08
## [11,] 0.38       0  9.164e+17
## [12,] 1.46       0  4.151e+30
## [13,] 1.04       0  1.035e+30
## ------------------------------------
## Mantel-Haenszel OR =0.36 95% CI ( 0,47.42 )
## Test for heterogeneity: X^2( 12 ) = 0.03 ( p-value 1 )
```

Example: meta.MH

```
c(exp(result.or$b), exp(result.mh$logMH))  # Compare with RE model
```

```
## [1] 0.4736 0.3635
```

```
result.mh$MHtest
```

```
## [1] 0.1825 0.6692
```

Comparing `metafor`, `rmeta`, `meta`

Overall

Feature	`metafor`	`rmeta`	`meta`
Comprehensive modeling options	✓		✓
Simple, well-designed syntax		✓	✓
Documentation: Thorough	✓		✓
Documentation: Easy to follow	✓		
Provides tools for meta-regression	✓		✓ (from `rma`)
Publication-ready graphics	✓		✓
Provides tools to assess threat of publication bias	✓	✓	✓
Provides tools to perform sensitivity analyses	✓		

Calculated Effect Sizes

Effect Size	metafor	rmeta	meta
Relative Risk	✓		✓
Odds Ratio	✓	✓	✓
Risk Difference	✓		✓
Mean Difference	✓		✓
Standardized Mean Difference	✓		✓
Correlation Coefficient	✓		✓

Synthesis Methods

Method	`metafor`	`rmeta`	`meta`
Peto's OR	✓		✓
Mantel-Haenszel OR		✓	✓
DerSimonian-Laird RE	✓		✓
REML RE	✓		✓
Hedges	✓		✓
Sidik-Jonkman	✓		✓
Meta-Regression	✓		✓

Computed & Accesible Heterogeneity Measures

Heterogeneity Index	`metafor`	`rmeta`	`meta`
τ^2	✓	✓	✓
I^2	✓		
H^2	✓		

Computed & Accesible Confidence Intervals

Estimate	metafor	rmeta	meta
Study Effects	✓		
Summary Effect	✓	✓	✓
τ^2	✓		
I^2	✓		

Graphics

Plot	metafor	rmeta	meta
Forest Plot	✓	✓	✓
Funnel Plot	✓	✓	✓
Galbraith (Radial) Plot	✓		✓
L'Abbe Plot	✓		✓
Trim-and-Fill Plot	✓		✓

Some Advanced Topics

Zero Counts

- No events in one or both treatment groups can create computational problems in standard meta-analytic approaches.
- Most proprietary programs handle this by adding 0.5 to zero counts.
- Mantel-Haenszel only requires correction if zero counts occur for same treatment arm in all studies.
- Peto's odds ratio only requires correction if zero counts in both arms of one or more studies.

Patient-Level Meta-Analysis

- Always preferred but are rarely possible to undertake.
- More often only some studies have IPD and focusing only on these can introduce selection bias.
- If bias is not of concern, synthesize with hierarchical modeling.
- glmm and coxme packages are commonly used for hierarchical modeling in R.
- I have written the ipdmeta package for assessing the power of subgroup effects with IPD meta-analysis.

Meta-Analyses Of Observational Studies

- Great care is needed in assessing compatibility of effects when considering meta-analysis of non-randomized studies.
- When "treatment" is not randomized, greater heterogeneity between studies is expected.
- The reason for this is that outcomes will be more sensitive to the sample characteristics and adjustment methods a study has used.
- In general, one should use the most fully-adjusted measure of effect.

Confidence Distribution Method

- We have focused on the summary of effect sizes.
- It is also possible to summarize evidence across trials by combining confidence intervals, the so-called **"confidence distribution method"**.
- Some advantages of combining CDs:
  - Robust to outlying studies
  - Yields exact CI for combining 2 by 2 tables, even with rare events

Meta-Analysis Of Genomic Data

- Standard FE or RE methodology can be applied to perform meta-analyses of genomic data (e.g., GWAS, microarray, etc.).
- But these data introduce further issues:
  - Missing data
  - Platform discrepancies between studies
  - Multiplicity
  - Efficiency

Multivariate Meta-Analysis

- There may be multiple endpoints of interest.
- A multivariate meta-analysis combines estimates of multiple outcomes, accounting for their correlation.
- Multivariate meta-regression can also incorporate the effects of study-level predictors.

Network Meta-Analysis

- A disease may have multiple trial-tested treatments.
- In general, only a subset of treatments will have been considered in any given trial.
- When there is interest in comparing the efficacy among all trials, when not all have been directly compared in available trials, a network (or mixed-treatment) meta-analysis can be performed.
- Proposed network meta-analysis methods usually involve Bayesian approaches and require careful assessment of consistency in treatment comparisons.

Bayesian Meta-Analysis

- Bayesian meta-analysis focuses on estimating a posterior distribution of effect rather than a summary effect estimate.
- A Bayesian framework can be advantageous for:
  - Accounting for possible bias
  - Making mixed-treatment comparisons
  - Conducting multivariate analyses

Packages For Advanced Meta-Analyses

Topic	Related Packages
Confidence Distribution Method	gmeta (Not yet on CRAN)
Network Meta-Analysis	gemtc
Multivariate Meta-Analysis	mmeta, mvmeta, bamdit, mada, HSROC, metamisc
Bayesian Meta-Analysis	bamdit, bspmma
Genomic Meta-Analysis	metABEL, gap, MAMA

Key Messages

Remember...

1. Not to begin here!
2. That meta-analytic summaries are all about weighted averages
3. That evaluating bias and heterogeneity are essential steps of meta-analysis
4. You now have a basic knowledge of how to use multiple `R` packages to perform conventional meta-analyses

Resources For Systematic Reviews

- Cochrane Collaboration Handbook
- Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA Statement)
- Meta-analysis of Observational Studies in Epidemiology (MOOSE Statement)

Further Reading

Overview (1)

- Cochrane Handbook
- CRAN Task View on Meta-Analysis.
- Chen D-G, Peace KE. Applied meta-analysis with R. Boca Raton, Florida: Taylor & Francis Group; 2013.
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Overview (2)

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Heterogeneity

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- Hardy RJ, et al. Detecting and describing heterogeneity in meta-analysis. Stat Med 1998;17:841-56.
- Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21:1539-58.
- Knapp G, Biggerstaff BJ, Hartung J. Assessing the amount of heterogeneity in random-effects meta-analysis. Biom J 2006;48:271-85.
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Advanced Topics (1)

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- Dukic V, Gatsonis C. Meta-analysis of diagnostic test accuracy assessment studies with varying number of thresholds. Biometrics 2003;59:936-46.
- Gasparrini A, Armstrong B, Kenward MG. Multivariate meta-analysis for non-linear and other multi-parameter associations. Stat Med 2012;31:3821-39.
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Advanced Topics (1)

- Lin DY, Zeng D. On the relative efficiency of using summary statistics versus individual-level data in meta-analysis. Biometrika 2010;97:321-32.
- Singh K, Xie M, Strawdermann. Combining information from independent sources through confidence distribution. Annals of Statistics 2005;33:159-183.
- Thompson SG, Higgins JP. How should meta-regression analyses be undertaken and interpreted? Stat Med 2002;21:1559-73.
- van Houwelingen HC, Arends LR, Stijnen T. Advanced methods in meta-analysis: multivariate approach and meta-regression. Stat Med 2002;21:589-624.

Applications

- Colditz GA, Brewer TF, Berkey CS, et al. Efficacy of BCG vaccine in the prevention of tuberculosis. Meta-analysis of the published literature. JAMA 1994;271:698-702.
- Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med 2007;356:2457-71.