

Beyond RevMan 5: Meta-analysis with R

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What is R?

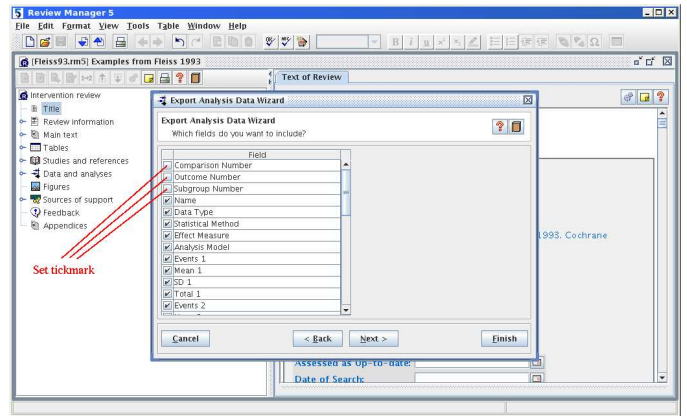
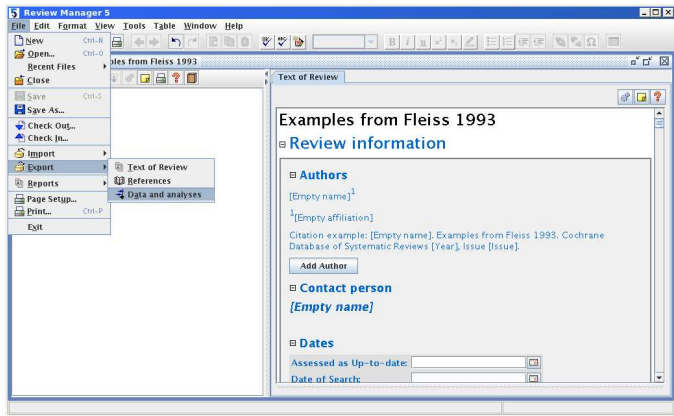
- ▶ General purpose statistical package (<http://www.r-project.org/>)
- ▶ Based on statistical programming language S (→ S-PLUS)
- ▶ 15 years old, actively developed and maintained
- ▶ Available for Windows, Linux, Unix, Mac OS
- ▶ Released under the GNU General Public License (GPL) version 2
- ▶ Licence costs: **0\$ / 0€ / 0 SGD**
- ▶ R can be used in regulated clinical trial environments (<http://www.r-project.org/doc/R-FDA.pdf>)
- ▶ More than 2000 add-on packages available on CRAN (<http://cran.at.r-project.org/>)
- ▶ Short introductions / reviews of add-on packages in *The R Journal* (<http://journal.r-project.org/>) – successor of *R News*

R packages for meta-analysis on CRAN

- ▶ **rmeta** (Thomas Lumley, Washington, USA)
 - ▶ Fixed and random effects meta-analysis (Mantel-Haenszel, Peto, DerSimonian-Laird)
- ▶ **metafor** (Wolfgang Viechtbauer, Maastricht, Netherlands)
 - ▶ Fixed and random effects meta-analysis (Mantel-Haenszel, Peto, DerSimonian-Laird)
 - ▶ Tests for funnel plot asymmetry / Trim and fill method
 - ▶ General linear (mixed-effects) model approach for meta-regression
- ▶ **meta** (Guido Schwarzer, Freiburg, Germany)
 - ▶ Fixed and random effects meta-analysis (Mantel-Haenszel, Peto, DerSimonian-Laird)
 - ▶ Tests for funnel plot asymmetry / Trim and fill method
 - ▶ Import data from RevMan5
- ▶ **copas** (James Carpenter, London, UK; Guido Schwarzer)
 - ▶ Add-on package to R package meta
 - ▶ Copas selection model to adjust for bias in meta-analysis

R package meta

Function	Comment
metabin	Meta-analysis of binary outcome data
metacont	Meta-analysis of continuous outcome data
metagen	Generic inverse variance meta-analysis
read.rm5	Import RevMan 5 data files (.csv)
metacr	Meta-analysis of outcome data from Cochrane review
forest	Forest plot
funnel	Plot to assess funnel plot asymmetry
metabias	Test for funnel plot asymmetry
trimfill	Trim and fill method for meta-analysis
metacum	Cumulative meta-analysis
metainf	Influence analysis in meta-analysis



```
> fleiss93 = read.rm5("Examples from Fleiss 1993.csv")
> metacr(fleiss93)

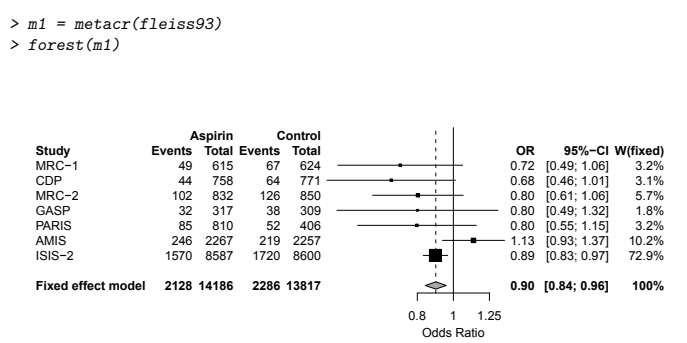
Review:      Examples from Fleiss 1993
Comparison: 1 Examples from Fleiss (1993)
Outcome:    1.1 Aspirin for Preventing Death after Myocardial Infarction

      OR      95%-CI  %W(fixed)
MRC-1 0.7197 [0.4890; 1.0593]  3.18
CDP    0.6808 [0.4574; 1.0132]  3.10
MRC-2 0.8029 [0.6065; 1.0629]  5.68
GASP   0.8007 [0.4863; 1.3186]  1.80
PARIS  0.7981 [0.5526; 1.1529]  3.22
AMIS   1.1327 [0.9347; 1.3728]  10.15
ISIS-2 0.8950 [0.8294; 0.9657]  72.88

Number of trials combined: 7

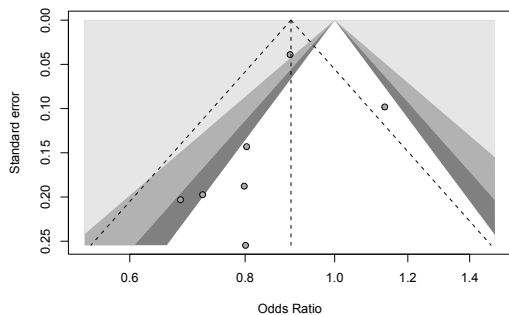
      OR      95%-CI      z p.value
Fixed effect model 0.8969 [0.8405; 0.957] -3.2876  0.001

Quantifying heterogeneity:
tau² = 0.0096; I² = 1.29 [1; 1.99]; I² = 39.7% [0%; 74.6%]
```



Funnel plot

```
> funnel(m1, contour.levels=c(0.9, 0.95, 0.99))
```



Test for funnel plot asymmetry

Linear regression test by Harbord et al. (2006), *Stat Med*, **25**, 3443–57:

```
> metabias(m1, method="score")
```

```
Review:      Examples from Fleiss 1993
Comparison:  1 Examples from Fleiss (1993)
Outcome:     1.1 Aspirin for Preventing Death after Myocardial Infarction
```

Linear regression test of funnel plot asymmetry (efficient score)

```
data: m1
t = -0.9214, df = 5, p-value = 0.3991
alternative hypothesis: asymmetry in funnel plot
sample estimates:
      bias      se.bias      slope
-0.72587833  0.78775820 -0.05932016
```

Summary

- ▶ Modern statistical packages for data analysis, management & graphics
- ▶ Use of additional software easily possible
- ▶ Use of command line necessary
- ▶ Extended documentation available (Online, Use-R books, ...)
- ▶ R package meta:
 - ▶ Can be used without RevMan5
 - ▶ Further additions to come
- ▶ Literature:
 - ▶ An Introduction to R. <http://cran.r-project.org/doc/manuals/R-intro.pdf>
 - ▶ Guido Schwarzer (2007): meta: An R package for Meta-Analysis, *R News*, **7**, 40–45. http://cran.r-project.org/doc/Rnews/Rnews_2007-3.pdf
 - ▶ James Carpenter, Gerta Rücker, Guido Schwarzer (2009): copas: An R package for fitting the Copas selection model, *The R Journal*, 2009, accepted for publication.

Do meta-analysis for different outcome types

```
> # Binary outcome:
> metabin(event.e=49, n.e=615, event.c=67, n.c=624, sm="OR", studlab="MRC-1")

      OR      95%-CI      z p.value
0.7197 [0.489; 1.0593] -1.6677 0.0954

Method: Inverse variance method

> # Continuous outcome:
> metacont(13, 5, 4.7, 13, 6.5, 3.8, studlab="Davis")

      MD      95%-CI      z p.value
-1.5 [-4.7855; 1.7855] -0.8948 0.3709

Method: Inverse variance method

> # Generic inverse variance outcome:
> OR = (49/(615-49)) / (67/(624-67))
> selogOR = sqrt(1/49 + 1/615 + 1/67 + 1/624)
> metagen(log(OR), selogOR, sm="OR", studlab="Davis")

      OR      95%-CI      z p.value
0.7197 [0.4898; 1.0576] -1.6749 0.094

Method: Inverse variance method
```

Trim-and-fill method

```
> tf1 = trimfill(m1)
> summary(tf1)

Number of trials combined: 10

      OR      95%-CI      z p.value
Fixed effect model 0.914 [0.8587; 0.9727] -2.829 0.0047

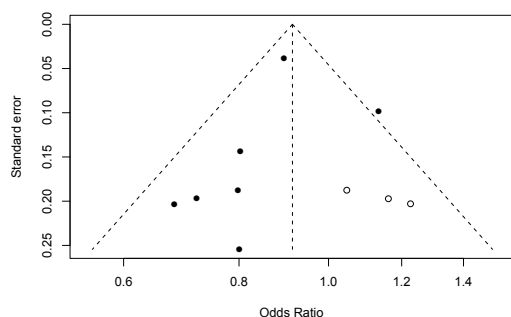
Quantifying heterogeneity:
tau^2 = 0.0102; H = 1.26 [1; 1.83]; I^2 = 37.4% [0%; 70.1%]

Test of heterogeneity:
  Q d.f. p.value
14.37  9 0.1099

Method: Inverse variance method
```

Trim-and-fill method

```
> funnel(tf1, pch=ifelse(tf1$trimfill, 1, 16))
```



Installing / Updating / Loading R packages

Install R package meta via Internet:

```
> install.packages("meta")
```

Update installed R packages via Internet:

```
> update.packages()
```

Make R package available in R session:

```
> library(meta)
```