

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

A screenshot of the Review Manager 5 software interface. The menu bar includes 'File', 'Edit', 'Format', 'View', 'Tools', 'Table', 'Window', and 'Help'. The 'File' menu has options like 'New', 'Open...', 'Recent Files', 'Save', 'Save As...', 'Check Out...', 'Check In...', 'Import', 'Export', 'Reports', 'Page Setup...', 'Print...', and 'Exit'. The 'Export' option is highlighted. The main window shows a 'Text of Review' section with the heading 'Examples from Fleiss 1993' and a 'Review information' section. Under 'Review information', there are sections for 'Authors' (with a note '[Empty name]'), 'Contact person' (with a note '[Empty name]'), and 'Dates' (with fields for 'Assessed as Up-to-date' and 'Date of Search').

The screenshot shows the RevMan 5 software interface. The main window displays a project titled 'Fleiss93.rms5' with sections like 'Intervention review', 'Review information', 'Main text', 'Tables', 'Studies and references', 'Data and analyses', 'Sources of support', 'Feedback', and 'Appendices'. A red arrow points from the text 'Set tickmark' to the 'Export Analysis Data Wizard' dialog box. This dialog box is titled 'Export Analysis Data Wizard' and asks 'Which fields do you want to include?'. It lists several options with checkboxes: 'Comparison Number', 'Outcome Number', 'Subgroup Number', 'Name', 'Data Type', 'Statistical Method', 'Effect Measure', 'Analysis Model', 'Events 1', 'Mean 1', 'SD 1', 'Total 1', and 'Events 2'. Most checkboxes are checked. At the bottom are 'Cancel', '< back', 'Next >', and 'Finish' buttons. Below the dialog, status bars show 'Assessed as Up-to-date.' and 'Date of Search:'. The top menu bar includes 'Background', 'R packages for meta-analysis', 'R in Action', and 'Summary'.

Background R packages for meta-analysis R in Action Summary

Do meta-analysis for outcome from Cochrane review

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

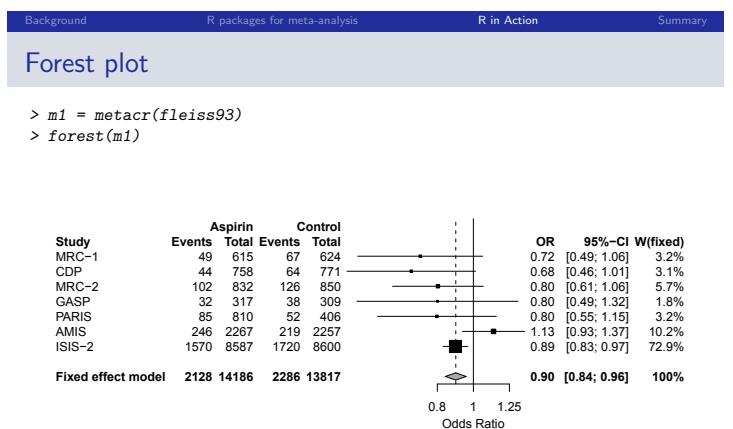
Review: Examples from Fleiss 1993
Comparison: i Examples from Fleiss (1993)
Outcome: 1.1 Aspirin for Preventing Death after Myocardial Infarction

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:
tau^2 = 0.0096; H = 1.29 [1; 1.99]; I^2 = 39.7% [0%; 74.6%]
```



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Funnel plot

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

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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
```

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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.

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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
```

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Trim-and-fill method

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

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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)
```