Beyond RevMan 5: Meta-analysis with R

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Background
R packages for meta-analysis

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 / 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

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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

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R package meta

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

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Export data from RevMan 5

```
> 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

<table>
<thead>
<tr>
<th>Study</th>
<th>Aspirin Events</th>
<th>Control Events</th>
<th>Total</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRC-1</td>
<td>49</td>
<td>615</td>
<td>664</td>
<td>824</td>
</tr>
<tr>
<td>CDP</td>
<td>44</td>
<td>758</td>
<td>64</td>
<td>771</td>
</tr>
<tr>
<td>MRC-2</td>
<td>102</td>
<td>832</td>
<td>126</td>
<td>850</td>
</tr>
<tr>
<td>GASP</td>
<td>32</td>
<td>517</td>
<td>38</td>
<td>555</td>
</tr>
<tr>
<td>PARIS</td>
<td>85</td>
<td>810</td>
<td>52</td>
<td>862</td>
</tr>
<tr>
<td>AMIS</td>
<td>246</td>
<td>2287</td>
<td>219</td>
<td>2327</td>
</tr>
<tr>
<td>ISIS-2</td>
<td>1570</td>
<td>8587</td>
<td>1720</td>
<td>8650</td>
</tr>
</tbody>
</table>

Number of trials combined: 7

```
> m1 = metacr(fleiss93)
> forest(m1)
```

Forest plot

```
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> metacr(fleiss93)
> forest(m1)
```

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

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

![Funnel plot](image)

Test for funnel plot asymmetry

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

```r
> 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:

<table>
<thead>
<tr>
<th>estimate</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>bias</td>
<td>0.726</td>
</tr>
<tr>
<td>se.bias</td>
<td>0.788</td>
</tr>
<tr>
<td>slope</td>
<td>-0.059</td>
</tr>
</tbody>
</table>

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
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 [-4.7585; 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

- Trim-and-fill:
  ```
  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

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)
  ```