Quick R Intro

- R (https://www.r-project.org)
- a programming language/environment for data processing, statistical computing, and graphics
- based on S (Bell Labs: Chambers, Becker, & Wilks)
- free & open-source (GPL)
- cross-platform (UNIX/Linux, Windows, MacOS, …)
- command-driven & object-oriented
- user community & packages (8000+)

Quick Meta-Analysis Intro

- a set of statistical methods and techniques for combining and contrasting the findings from studies examining a common phenomenon
- key idea: quantify the outcome (usually some measure of effect or association) and its variance in each study and use this data in further analyses (averaging, modeling, meta-regression, …)

Outcome Measures for Meta-Analysis

- commonly used outcome measures:
  - raw or standardized mean differences
  - risk differences, risk/odds ratios
  - correlations (raw or Fisher r-to-z transformed)
  - raw means, (logit transformed) proportions
  - …

Meta-Analysis with R

- several meta-analysis packages
- all lacked meta-regression capabilities
- wrote my own function (mima) in 2006
- turned into full package (metafor) in 2009
- http://www.metafor-project.org
- ongoing development

Meta-Analytic Data

- $i = 1, \ldots, k$ studies
- have $y_i$ and corresponding $v_i$
- assume:
  \[ y_i \mid \theta_i \sim N(\theta_i, v_i) \]
- and independence of the estimates (for now)
- approx. 95% CI for $\theta_i$: $y_i \pm 1.96 \sqrt{v_i}$
Example: BCG Vaccine

- effectiveness of the Bacillus Calmette-Guérin (BCG) vaccine against tuberculosis (TB)
- for each study, can compare the proportion of TB positive cases in the vaccinated versus the non-vaccinated group

Albert Calmette
Camille Guérin
BCG Vaccine

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>RR</th>
<th>( \log(RR) )</th>
<th>Allocation</th>
<th>Latitude</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1948</td>
<td>0.41</td>
<td>-0.89</td>
<td>random</td>
<td>44</td>
</tr>
<tr>
<td>2</td>
<td>1949</td>
<td>0.20</td>
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<td>55</td>
</tr>
<tr>
<td>3</td>
<td>1960</td>
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<td>-1.35</td>
<td>random</td>
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</tr>
<tr>
<td>4</td>
<td>1977</td>
<td>0.24</td>
<td>-1.44</td>
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<td>52</td>
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<tr>
<td>5</td>
<td>1973</td>
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<td>-0.22</td>
<td>alternate</td>
<td>13</td>
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<tr>
<td>6</td>
<td>1953</td>
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<td>44</td>
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<tr>
<td>7</td>
<td>1973</td>
<td>0.20</td>
<td>-1.62</td>
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<td>19</td>
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<tr>
<td>8</td>
<td>1980</td>
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</tr>
<tr>
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<td>1968</td>
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<td>-0.47</td>
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<td>27</td>
</tr>
<tr>
<td>10</td>
<td>1961</td>
<td>0.25</td>
<td>-1.37</td>
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<td>42</td>
</tr>
<tr>
<td>11</td>
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<td>18</td>
</tr>
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<td>12</td>
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<td>33</td>
</tr>
<tr>
<td>13</td>
<td>1976</td>
<td>0.98</td>
<td>-0.02</td>
<td>systematic</td>
<td>33</td>
</tr>
</tbody>
</table>

Standard Random-Effects Model

\[
y_i = \mu + u_i + e_i
\]

where:
- \( \mu \) = average true outcome
- \( u_i \) = random effect that makes the true outcome for a particular study larger/smaller by some amount (heterogeneity between studies)
- \( e_i \) = sampling error

\( e_i \sim N(0, \sigma_e^2) \quad u_i \sim N(0, \tau^2) \)

Example: BCG Vaccine

<table>
<thead>
<tr>
<th>Tuberculosis</th>
<th>Vaccinated</th>
<th>Not Vaccinated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuberculosis</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>TB</td>
<td>4</td>
<td>119</td>
</tr>
<tr>
<td>Not Vaccinated</td>
<td>11</td>
<td>128</td>
</tr>
<tr>
<td></td>
<td>139</td>
<td>139</td>
</tr>
</tbody>
</table>

\[
p_v = \frac{4}{123} = 0.325
\]

\[
p_c = \frac{11}{139} = 0.0791
\]

\[
RR = \frac{4}{11} = 0.364
\]

\[
y = \ln[RR] = \ln \left( \frac{4}{11} \right) = -0.591
\]

\[
v = \frac{1}{4} \left( \frac{1}{123} + \frac{1}{11} + \frac{1}{139} \right) = 0.0326
\]

Example: BCG Vaccine

Meta-Analysis with R (\texttt{metafor})

- install with: \texttt{install.packages("metafor")}
- (only need to do this once, or after reinstalling R, or to upgrade to a new package version)
- load package with: \texttt{library(metafor)}
- (have to do this each time you (re)start R)
- comments start with #
### load BCG vaccine data

```r
> dat <- get(data(dat.bcg))
```

### show data

```r
> dat
```

<table>
<thead>
<tr>
<th>trial</th>
<th>author</th>
<th>year</th>
<th>tpos</th>
<th>tneg</th>
<th>cpos</th>
<th>cneg</th>
<th>ablat</th>
<th>alloc</th>
</tr>
</thead>
<tbody>
<tr>
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<td>4</td>
<td>119</td>
<td>11</td>
<td>128</td>
<td>44</td>
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</tr>
<tr>
<td>2</td>
<td>Ferguson &amp; Simes</td>
<td>1949</td>
<td>6</td>
<td>300</td>
<td>29</td>
<td>274</td>
<td>55</td>
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<tr>
<td>3</td>
<td>Rosenthal et al</td>
<td>1953</td>
<td>3</td>
<td>228</td>
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<td>209</td>
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<td>Hart &amp; Sutherland</td>
<td>1977</td>
<td>8</td>
<td>2537</td>
<td>18</td>
<td>2359</td>
<td>42</td>
<td>random</td>
</tr>
<tr>
<td>5</td>
<td>Frimodt-Moller et al</td>
<td>1973</td>
<td>33</td>
<td>5036</td>
<td>47</td>
<td>5761</td>
<td>13</td>
<td>alternate</td>
</tr>
<tr>
<td>6</td>
<td>Stein &amp; Aronson</td>
<td>1953</td>
<td>180</td>
<td>1361</td>
<td>372</td>
<td>1079</td>
<td>44</td>
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<tr>
<td>7</td>
<td>Vandiviere et al</td>
<td>1973</td>
<td>8</td>
<td>2537</td>
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<td>2359</td>
<td>42</td>
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</tr>
<tr>
<td>8</td>
<td>TPT Madras</td>
<td>1980</td>
<td>505</td>
<td>87886</td>
<td>499</td>
<td>87892</td>
<td>13</td>
<td>random</td>
</tr>
<tr>
<td>9</td>
<td>Coetzee &amp; Berjak</td>
<td>1968</td>
<td>29</td>
<td>7470</td>
<td>45</td>
<td>7232</td>
<td>27</td>
<td>random</td>
</tr>
<tr>
<td>10</td>
<td>Rosenthal et al</td>
<td>1961</td>
<td>17</td>
<td>1699</td>
<td>65</td>
<td>1600</td>
<td>42</td>
<td>systematic</td>
</tr>
<tr>
<td>11</td>
<td>Comstock et al</td>
<td>1974</td>
<td>186</td>
<td>50448</td>
<td>141</td>
<td>27197</td>
<td>18</td>
<td>systematic</td>
</tr>
<tr>
<td>12</td>
<td>Comstock &amp; Webster</td>
<td>1969</td>
<td>5</td>
<td>2493</td>
<td>3</td>
<td>2338</td>
<td>33</td>
<td>systematic</td>
</tr>
<tr>
<td>13</td>
<td>Comstock et al</td>
<td>1976</td>
<td>27</td>
<td>16886</td>
<td>29</td>
<td>17825</td>
<td>33</td>
<td>systematic</td>
</tr>
</tbody>
</table>

### Computing Observed Outcomes

- can of course use external software for data management and preparations
- to compute outcomes: `escalc()` command

```r
### calculate log relative risks and sampling variances
> dat <- escalc(measure="RR", ai=tpos, bi=tneg, ci=cpos, di=cneg, data=dat)
```

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

### Random-Effects Model

- basic syntax:

```r
res <- rma(yi, vi, method="REML", data=dat)
```

<table>
<thead>
<tr>
<th>Random-Effects Model (k = 13; tau^2 estimator: REML)</th>
</tr>
</thead>
<tbody>
<tr>
<td>tau^2 (estimated amount of total heterogeneity): 0.3132</td>
</tr>
<tr>
<td>tau (square root of estimated tau^2 value): 0.5597</td>
</tr>
<tr>
<td>I^2 (total heterogeneity / total variability): 92.22%</td>
</tr>
<tr>
<td>H^2 (total variability / sampling variability): 12.86</td>
</tr>
</tbody>
</table>

Test for Heterogeneity:
- Q(df = 12) = 152.2330, p-val < .0001

Model Results:
- estimate: -0.7145, se: 0.1798, p-val: < .0001, ci.lb: -1.0669, ci.ub: -0.3622

### Back-Transformation

- where necessary, can use `predict()` to back-transform the estimate and CI/CR bounds

```r
### fit random-effects model
> res <- rma(yi, vi, data=dat)
> res
```

Random-Effects Model (k = 13; tau^2 estimator: REML)
- to print results, type: `res`
- or use: `print(res, digits=2)`
- use `predict()` for back-transformation

```r
### estimated average relative risk (and 95% CI/CR)
> predict(res, transf=exp, digits=2)
```

<table>
<thead>
<tr>
<th>pred</th>
<th>ci.lb</th>
<th>ci.ub</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.49</td>
<td>0.34</td>
<td>0.70</td>
</tr>
</tbody>
</table>

```r
### estimated average relative risk (and 95% CI/CR)
> predict(res, transf=exp, digits=2)
```

```r
### Back-Transformation
- for exponentiation: `exp`
- for z-to-r transformation: `transf.ztor`
```

> *** estimated average relative risk (and 95% CI/CR) ***

```r
> predict(res, transf=exp, digits=2)
```

```
> predict(res, transf=exp, digits=2)
```
Mixed-Effects Meta-Regression Model

- can include moderators/predictors/covariates in the model (to account for heterogeneity)
- mixed-effects meta-regression model:
  \[ y_i = \beta_0 + \beta_1 x_{i1} + \beta_2 x_{i2} + \cdots + \beta_p x_{ip} + u_i + e_i \]
  \[ u_i \sim N(0, \tau^2) \] (but now 'residual' heterogeneity)
  \[ e_i \sim N(0, \nu_i) \]

Mixed-Effects Meta-Regression Model

- basic syntax as before, but now:

  ```r
  res <- rma(yi, vi, mods = ~ var1, data=dat)
  ```

  for multiple predictors/moderators:
  - main effects: `mods = ~ var1 + var2 + ...`
  - interactions: `mods = ~ var1 * var2 + ...`
  - character/factor variables:
    - are automatically dummy-coded
  - to remove the intercept: `mods = ~ var1 - 1`

Wald-Type Tests and Contrasts

- syntax: ```anova(res, btt<>)```  
  vector of numbers indicating which coefficients to test

- syntax: ```anova(res, L=<())```  
  comma separated vector to specify the values to use for the contrast

```
> ### test 'alloc' factor as a whole
> anova(res, btt=3)
```

Test of Moderators (coefficient(s) 2,3):
```
QM(df = 2) = 1.2850, p-val = 0.2937
```

Hypothesis:
```
1: allocrandom - allocsystematic = 0
```

Results:
```
estimate    se   zval   pval
1: -0.3260 0.0092 -3.5300 0.0004
```

Test of Hypothesis:
```
QM(df = 1) = 1.1827, p-val = 0.2897
```
Predicted Values

- use `predict()` to compute predicted values
- basic syntax:

\[
\text{predict(res, newmods=c(), transf=\<\>)}
\]

comma separated vector to specify the values to use for the prediction

- note: intercept term is automatically included and is not part of the `c()` vector

### load data
```r
dat <- get(data(dat.konstantopoulos2011))
```

### show data
```r
dat
district school study year yi vi
1 1 11 1 1976 -0.18 0.118
2 1 11 2 1976 -0.22 0.118
3 1 11 3 1976 0.23 0.144
4 1 11 4 1976 -0.30 0.144
5 2 12 1 1989 0.13 0.014
6 2 12 2 1989 -0.26 0.014
7 2 12 3 1989 0.19 0.015
8 2 12 4 1989 0.32 0.024
9 3 18 1 1994 0.45 0.023
10 3 18 2 1994 0.38 0.043
11 3 18 3 1994 0.29 0.012
12 ... ... ... ... ...
56 4 644 4 1994 -0.85 0.067
```

### fit standard random-effects model
```r
res <- rma(yi, vi, data = dat)
```

```
Random-Effects Model (k = 56; tau^2 estimator: REML)
tau^2 (estimated amount of total heterogeneity): 0.0884
tau (square root of estimated tau^2 value): 0.2974
I^2 (total heterogeneity / total variability): 94.70%
H^2 (total variability / sampling variability): 18.89

Test for Heterogeneity:
Q(df = 55) = 578.8640, p-val < .0001

Model Results:
```
```
<table>
<thead>
<tr>
<th></th>
<th>estimate</th>
<th>se</th>
<th>zval</th>
<th>pval</th>
<th>ci.lb</th>
<th>ci.ub</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.1279</td>
<td>0.0439</td>
<td>2.9161</td>
<td>0.0035</td>
<td>0.0419</td>
<td>0.2139</td>
</tr>
</tbody>
</table>
```

The `rma.mv()` Function

- more flexible model fitting function, but must specify random effects manually
- for now, replicate previous results

```r
res <- rma.mv(yi, vi, random = ~ 1 | study, method = "REML", data = dat)
```

- `random = ~ 1 | study` adds a random effect for each level of the study variable
- `method = "REML"` is default (other option: ML)
Multilevel Meta-Analytic Data

- multilevel structures can arise when we have multiple estimates for some higher clustering variable (paper, lab, research group, ...)

\[ y_{ij} = \mu + W_i + U_{ij} + e_{ij} \]

- \( \mu \) is the average true outcome
- \( W_i \) is a random effect that makes the true outcomes for a particular cluster larger/smaller by some amount (heterogeneity between clusters)
- \( U_{ij} \) is a random effect that makes one of the true outcomes within a particular cluster larger/smaller by some amount (heterogeneity within clusters)
- \( e_{ij} \) is sampling error

\[ w_i \sim N(0, \sigma^2_w) \quad u_{ij} \sim N(0, \sigma^2_u) \quad e_{ij} \sim N(0, \sigma^2_e) \]

### The rma.mv() Function

- `rma.mv()` allows for the addition of multiple nested random effects
- `random = ~ 1 | var1/var2` adds a random effect for each level of `var1` and a random effect for each level of `var2` within each level of `var1`

---

Multilevel Random-Effects Model

\[ y_{ij} = \mu + W_i + U_{ij} + e_{ij} \]

- \( \mu \) is the average true outcome
- \( W_i \) is a random effect that makes the true outcomes for a particular cluster larger/smaller by some amount (heterogeneity between clusters)
- \( U_{ij} \) is a random effect that makes one of the true outcomes within a particular cluster larger/smaller by some amount (heterogeneity within clusters)
- \( e_{ij} \) is sampling error

\[ w_i \sim N(0, \sigma^2_w) \quad u_{ij} \sim N(0, \sigma^2_u) \quad e_{ij} \sim N(0, \sigma^2_e) \]
Correlation due to Multilevel Structure

- the multilevel structure implies that the true outcomes within a cluster are correlated:
  \[ \rho = \frac{\sigma_{\mu}^2}{\sigma_{\mu}^2 + \sigma_w^2} \]

- in example:
  \[ \hat{\rho} = \frac{0.0651}{0.0651 + 0.0327} = .67 \]

- also note: 0.0651 + 0.0327 = 0.0978

Multivariate Parameterization

- For variables \( y_{ij} \), the average true outcome is:
  \[ y_{ij} = \mu + u_{ij} + e_{ij} \]
  where:
  - \( \mu \) is the average true outcome
  - \( u_{ij} \) are correlated random effects for the true outcomes within the same cluster
  - \( e_{ij} \) is sampling error

\[ u_{ij} \sim \text{MVN}(0, \Sigma) \]

The rma.mv() Function

- `rma.mv()` allows for the addition of correlated random effects within a variable
- `random = ~ var1 | var2` adds correlated random effects for each level of `var1` within each level of `var2`
- note: `var1` must be a character/factor type variable (if it is not, use `factor()` function)

Notes

- models assume independent sampling errors within clusters (sensible if no overlap in the data/subjects used to compute outcomes)
- examples:
  - multiple independent studies reported in paper
  - multiple papers published by the same group
  - results reported for different subgroups
- but true outcomes within clusters may be more similar to each other than those from different clusters (correlated true outcomes)

Multiple (Correlated) Outcomes

- multivariate data also arise when multiple outcomes are measured within the studies

\[ Y_{11}, Y_{12}, Y_{21}, Y_{22}, \ldots, Y_{k1}, Y_{k2} \]

\text{note: not all studies have to measure all outcomes}
Multiple (Correlated) Outcomes

- since the outcomes are measured in the same subjects, the sampling errors are correlated
- true outcomes may also be correlated
- equations for the covariance between the sampling errors can be found in Gleser & Olkin (2009), Wei & Higgins (2013), Steiger (1980), ...

\[
\begin{align*}
&\text{Multivariate Random-Effects Model} \\
&y_{ij} = \mu_j + u_{ij} + e_{ij},
\end{align*}
\]

\[
\begin{bmatrix}
\tau_1^2 \\
\rho \tau_1 \tau_2 \\
\tau_2^2
\end{bmatrix}
\]

\[
\begin{bmatrix}
v_{11} & \text{cov}_{12} \\
& v_{22}
\end{bmatrix}
\]

> ### load data
> dat <- get(data(dat.berkey1998))
> ### show data
> dat
>

<table>
<thead>
<tr>
<th>trial</th>
<th>author</th>
<th>year</th>
<th>ni</th>
<th>outcome</th>
<th>yi</th>
<th>v1i</th>
<th>v2i</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pihlstrom et al. 1983</td>
<td>14</td>
<td>PD</td>
<td></td>
<td>0.47</td>
<td>0.0075</td>
<td>0.0030</td>
</tr>
<tr>
<td>2</td>
<td>Pihlstrom et al. 1983</td>
<td>14</td>
<td>AL</td>
<td></td>
<td>-0.32</td>
<td>0.0030</td>
<td>0.0077</td>
</tr>
<tr>
<td>3</td>
<td>Lindhe et al. 1982</td>
<td>15</td>
<td>PD</td>
<td></td>
<td>0.20</td>
<td>0.0057</td>
<td>0.0039</td>
</tr>
<tr>
<td>4</td>
<td>Lindhe et al. 1982</td>
<td>15</td>
<td>AL</td>
<td></td>
<td>-0.68</td>
<td>0.0009</td>
<td>0.0028</td>
</tr>
<tr>
<td>5</td>
<td>Knowles et al. 1979</td>
<td>78</td>
<td>PD</td>
<td></td>
<td>0.48</td>
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<td>0.0007</td>
</tr>
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<td>6</td>
<td>Knowles et al. 1979</td>
<td>78</td>
<td>AL</td>
<td></td>
<td>-0.12</td>
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<tr>
<td>7</td>
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<td>89</td>
<td>PD</td>
<td></td>
<td>0.26</td>
<td>0.0029</td>
<td>0.0009</td>
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<tr>
<td>8</td>
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<td></td>
<td>-0.31</td>
<td>0.0009</td>
<td>0.0035</td>
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<tr>
<td>9</td>
<td>Becker et al. 1988</td>
<td>16</td>
<td>PD</td>
<td></td>
<td>0.56</td>
<td>0.0148</td>
<td>0.0072</td>
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<td>AL</td>
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<td>-0.39</td>
<td>0.0072</td>
<td>0.0034</td>
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</table>

The rma.mv() Function

- name of object with the var-cov matrix of the sampling errors
- name of factor to indicate the outcome (and remove intercept)

res <- rma.mv(yi, V, mods = ~ outcome - 1, random = ~ outcome | study, struct = "UN", data = dat)

structure of var-cov matrix of the random effects ([UN = unstructured])

• recall: outcome must be a character/factor type variable (if it is not, use factor() function)
Random Effects Structures

\[
\text{struct} = \text{"CS"} \\
\begin{bmatrix}
\tau^2 & \rho \tau^2 & \rho \tau^2 \\
\rho \tau^2 & \tau^2 & \rho \tau^2 \\
\rho \tau^2 & \rho \tau^2 & \tau^2
\end{bmatrix}
\]

(this is the default)

\[
\text{struct} = \text{"HCS"} \\
\begin{bmatrix}
\tau_1^2 & \rho_1 \tau_1 \tau_2 & \rho_1 \tau_1 \tau_3 & \rho_1 \tau_1 \tau_4 \\
\rho_1 \tau_1 \tau_2 & \tau_2^2 & \rho_1 \tau_2 \tau_3 & \rho_1 \tau_2 \tau_4 \\
\rho_1 \tau_1 \tau_3 & \rho_1 \tau_2 \tau_3 & \tau_3^2 & \rho_1 \tau_3 \tau_4 \\
\rho_1 \tau_1 \tau_4 & \rho_1 \tau_2 \tau_4 & \rho_1 \tau_3 \tau_4 & \tau_4^2
\end{bmatrix}
\]

\[
\text{struct} = \text{"UN"} \\
\begin{bmatrix}
\tau_1^2 & \rho_1 \tau_1 \tau_2 & \rho_1 \tau_1 \tau_3 & \rho_1 \tau_1 \tau_4 \\
\rho_1 \tau_1 \tau_2 & \tau_2^2 & \rho_1 \tau_2 \tau_3 & \rho_1 \tau_2 \tau_4 \\
\rho_1 \tau_1 \tau_3 & \rho_1 \tau_2 \tau_3 & \tau_3^2 & \rho_1 \tau_3 \tau_4 \\
\rho_1 \tau_1 \tau_4 & \rho_1 \tau_2 \tau_4 & \rho_1 \tau_3 \tau_4 & \tau_4^2
\end{bmatrix}
\]

for two outcomes, "UN" and "HCS" is the same

---

Network Meta-Analysis

- often there are multiple treatments available for the same condition/disease
- studies comparing the effectiveness of these treatments form a network of comparisons
- some of the goals:
  - synthesize evidence provided by all studies and comparisons in one parsimonious model
  - obtain indirect evidence about comparisons that have not been examined head-to-head
  - determine a hierarchy of treatment effectiveness

---

Star-Shaped Networks

Second-generation antiepileptic drugs in partial epilepsy

a: levetiracetam, b: gabapentin, c: lamotrigine, d: oxcarbazepine, e: lacosamide, f: topiramate, g: zonisamide, h: placebo

---

Complex Networks

Chemotherapy regimens for ovarian cancer

a: platinum monotherapy, b: platinum-based combination, c: taxane monotherapy, d: platinum + taxane-based combination, e: nonplatinum/non-taxane monotherapy, f: taxane-based combination, g: nonplatinum/non-taxane combination, h: taxane-based combination, i: platinum/taxane-based combination (ip)

---

Network Meta-Analysis

- can analyze such data with appropriate multilevel/multivariate models
- two general approaches: arm- vs. contrast-based model (e.g., Salanti et al., 2008)
- errors are correlated in contrast-based model for studies with more than two groups
- equations for the correlation between the sampling errors can be found in Gleser and Olkin (2009) and several other papers
Arm-Based Network Meta-Analysis

\[ y_{ij} = \beta_0 + \beta_1 T_{i1} + \ldots + \beta_p T_{ip} + W_i + U_{ij} + e_{ij} \]

\[ W_i \sim N(0, \sigma_i^2) \quad U_{ij} \sim N(0, \sigma_T^2) \quad e_{ij} \sim N(0, \sigma_e^2) \]

### load data
```r
> dat <- get(data(dat.hasselblad1998))
> res <- rma.mv(yi, vi, mods = ~ trt, data = dat, 
                      random = ~ -1 | study/trt)
> res
```

Multivariate Meta-Analysis Model (k = 50; method: REML)

Variance Components:

<table>
<thead>
<tr>
<th></th>
<th>estim</th>
<th>sqrt</th>
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<tbody>
<tr>
<td>sigma^2.1</td>
<td>0.195</td>
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Test for Residual Heterogeneity:

\[ QE(df = 46) = 815.812, p-val < .001 \]

Test of Moderators (coefficient(s) 2,3,4):

\[ QM(df = 3) = 19.441, p-val < .001 \]

Model Results:

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### pairwise odds ratios of interventions versus no contact
```r
> pred(res, newmods=diag(3), intercept=FALSE, transf=exp, digits=2)
```

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Dealing with Inconsistency

- restrict analysis to a subset of studies providing consistent evidence
- try to account for it based on moderators
- model it (various proposals)

Some Other Package Features

- for 2x2 table data:
  - Mantel-Haenszel and Peto’s (one-step) method
  - generalized linear mixed-effects models (i.e., mixed-effects (conditional) logistic models)
- publication bias:
  - rank correlation test
  - Egger’s regression test
  - trim and fill method
- inference methods:
  - best linear unbiased predictions
  - permutation tests
  - (cluster) robust tests and confidence intervals

Plots

- forest plots: forest()
- funnel plots: funnel1()
- radial (Galbraith) plots: radial()
- Baujat plots: baujat()
- Q-Q normal plots: qqnorm()
- L’Abbé plots: labbe()
- cumulative forest plots: cumul() → forest()
- GOSH plots: gosh() → plot()
- diagnostics: influence() → plot()
• psychometric meta-analysis (Hunter & Schmidt)
• fully Bayesian models
• selection models
• lots of small improvements
• ...