# Meta-Analysis with R: The metafor Package

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## 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
- Viechtbauer, W. (2010). Conducting meta-analyses in R with the metafor package. *Journal of Statistical Software, 36*(3), 1-48.
- 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


Camille Guérin


Albert Calmette

BCG Vaccine



## Example: BCG Vaccine

| | Tuberculosis | | |
|---|---|---|---|
| | **Positive** | **Negative** | |
| **Vaccinated** | 4 | 119 | 123 |
| **Not Vaccinated** | 11 | 128 | 139 |

$$p_T = 4/123 = .0325$$
$$p_C = 11/139 = .0791$$
$$RR = \frac{4/123}{11/139} = .41$$

$$y = \ln[RR] = \ln\left[\frac{4/123}{11/139}\right] = -.89$$
$$v = \frac{1}{4} - \frac{1}{123} + \frac{1}{11} - \frac{1}{139} = .326$$

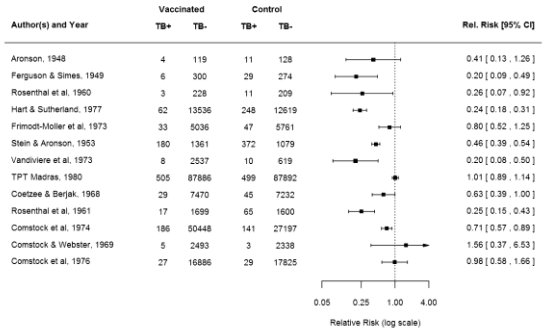


## Example: BCG Vaccine

| Study | Year | *RR* | *y* = ln(*RR*) | *v* | *Allocation* | Latitude |
|---|---|---|---|---|---|---|
| 1 | 1948 | 0.41 | -0.89 | .326 | random | 44 |
| 2 | 1949 | 0.20 | -1.59 | .195 | random | 55 |
| 3 | 1960 | 0.26 | -1.35 | .415 | random | 42 |
| 4 | 1977 | 0.24 | -1.44 | .020 | random | 52 |
| 5 | 1973 | 0.80 | -0.22 | .051 | alternate | 13 |
| 6 | 1953 | 0.46 | -0.79 | .007 | alternate | 44 |
| 7 | 1973 | 0.20 | -1.62 | .223 | random | 19 |
| 8 | 1980 | 1.01 | 0.01 | .004 | random | 13 |
| 9 | 1968 | 0.63 | -0.47 | .056 | random | 27 |
| 10 | 1961 | 0.25 | -1.37 | .073 | systematic | 42 |
| 11 | 1974 | 0.71 | -0.34 | .012 | systematic | 18 |
| 12 | 1969 | 1.56 | 0.45 | .533 | systematic | 33 |
| 13 | 1976 | 0.98 | -0.02 | .071 | systematic | 33 |



## Example: BCG Vaccine




## Standard Random-Effects Model

$$y_i = \mu$$ 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

---

$$e_i \sim N(0, v_i) \qquad u_i \sim N(0, \tau^2)$$



## Meta-Analysis with R (*metafor*)

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

```
> ### load BCG vaccine data
> dat <- get(data(dat.bcg))
>
> ### show data
> dat
```

| | TB+ | TB- |
|---|---|---|
| treated | tpos | tneg |
| control | cpos | cneg |

| | trial | author | year | tpos | tneg | cpos | cneg | ablat | alloc |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 1 | Aronson | 1948 | 4 | 119 | 11 | 128 | 44 | random |
| 2 | 2 | Ferguson & Simes | 1949 | 6 | 300 | 29 | 274 | 55 | random |
| 3 | 3 | Rosenthal et al | 1960 | 3 | 228 | 11 | 209 | 42 | random |
| 4 | 4 | Hart & Sutherland | 1977 | 62 | 13536 | 248 | 12619 | 52 | random |
| 5 | 5 | Frimodt-Moller et al | 1973 | 33 | 5036 | 47 | 5761 | 13 | alternate |
| 6 | 6 | Stein & Aronson | 1953 | 180 | 1361 | 372 | 1079 | 44 | alternate |
| 7 | 7 | Vandiviere et al | 1973 | 8 | 2537 | 10 | 619 | 19 | random |
| 8 | 8 | TPT Madras | 1980 | 505 | 87886 | 499 | 87892 | 13 | random |
| 9 | 9 | Coetzee & Berjak | 1968 | 29 | 7470 | 45 | 7232 | 27 | random |
| 10 | 10 | Rosenthal et al | 1961 | 17 | 1699 | 65 | 1600 | 42 | systematic |
| 11 | 11 | Comstock et al | 1974 | 186 | 50448 | 141 | 27197 | 18 | systematic |
| 12 | 12 | Comstock & Webster | 1969 | 5 | 2493 | 3 | 2338 | 33 | systematic |
| 13 | 13 | Comstock et al | 1976 | 27 | 16886 | 29 | 17825 | 33 | systematic |



## Computing Observed Outcomes

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

```
dat <- escalc(measure="", ..., data=dat)
```

- `measure=""`: to specify the outcome measure (RD, RR, OR, SMD, ROM, PLO, ...)
- `...`: to specify the variables needed to compute the observed outcomes



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

| | trial | author | year | ... | yi | vi |
|---|---|---|---|---|---|---|
| 1 | 1 | Aronson | 1948 | ... | -0.8893 | 0.3256 |
| 2 | 2 | Ferguson & Simes | 1949 | ... | -1.5854 | 0.1946 |
| 3 | 3 | Rosenthal et al | 1960 | ... | -1.3481 | 0.4154 |
| 4 | 4 | Hart & Sutherland | 1977 | ... | -1.4416 | 0.0200 |
| 5 | 5 | Frimodt-Moller et al | 1973 | ... | -0.2175 | 0.0512 |
| 6 | 6 | Stein & Aronson | 1953 | ... | -0.7861 | 0.0069 |
| 7 | 7 | Vandiviere et al | 1973 | ... | -1.6209 | 0.2230 |
| 8 | 8 | TPT Madras | 1980 | ... | 0.0120 | 0.0040 |
| 9 | 9 | Coetzee & Berjak | 1968 | ... | -0.4694 | 0.0564 |
| 10 | 10 | Rosenthal et al | 1961 | ... | -1.3713 | 0.0730 |
| 11 | 11 | Comstock et al | 1974 | ... | -0.3394 | 0.0124 |
| 12 | 12 | Comstock & Webster | 1969 | ... | 0.4459 | 0.5325 |
| 13 | 13 | Comstock et al | 1976 | ... | -0.0173 | 0.0714 |

*log relative risks and sampling variances*



## Random-Effects Model

- basic syntax:

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

- `yi`: name of variable for the observed outcomes
- `vi`: name of variable for the corresponding sampling variances
- `method="REML"`: to select the $\tau^2$ estimator (DL, ML, REML, PM, EB, ...)
- `data=dat`: name of data frame containing the variables

- to print results, type: **`res`**
- or use: **`print(res, digits=2)`**
- use **`predict()`** for back-transformation



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

Random-Effects Model (k = 13; tau^2 estimator: REML)

tau^2 (estimated amount of total heterogeneity): 0.3132
tau (square root of estimated tau^2 value):      0.5597
I^2 (total heterogeneity / total variability):   92.22%
H^2 (total variability / sampling variability):  12.86

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

Model Results:

estimate       se     zval     pval    ci.lb    ci.ub
 -0.7145   0.1798  -3.9744   <.0001  -1.0669  -0.3622
```

```
> ### estimated average relative risk (and 95% CI/CR)
> predict(res, transf=exp, digits=2)
 pred ci.lb ci.ub cr.lb cr.ub
 0.49  0.34  0.70  0.15  1.55
```

cr.lb/cr.ub = bounds of a 95% credibility/prediction interval



## Back-Transformation

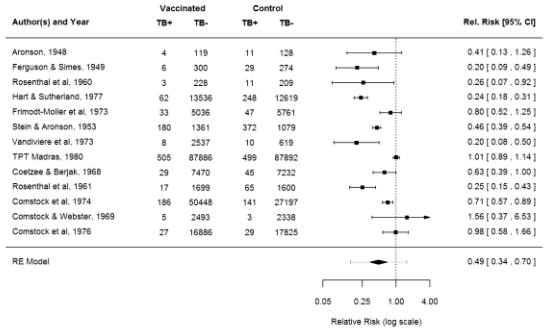
- where necessary, can use **`predict()`** to back-transform the estimate and CI/CR bounds
- basic syntax:

```
predict(res, transf=<>, digits=2)
```

- `res`: name of the model object
- `transf`: transformation function

- for exponentiation: **`exp`**
- for z-to-r transformation: **`transf.ztor`**

(forest plots like this can be created with the `forest()` command)






## 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)
  - $e_i \sim N(0, v_i)$



## Mixed-Effects Meta-Regression Model

- basic syntax as before, but now:

```
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`



```
> ### fit mixed-effects meta-regression model
> res <- rma(yi, vi, mods = ~ alloc + ablat, data=dat)
> res

Mixed-Effects Model (k = 13; tau^2 estimator: REML)

tau^2 (estimated amount of residual heterogeneity):     0.1446
tau (square root of estimated tau^2 value):             0.3803
I^2 (residual heterogeneity / unaccounted variability): 70.11%
H^2 (unaccounted variability / sampling variability):   3.35
R^2 (amount of heterogeneity accounted for):            53.84%

Test for Residual Heterogeneity:
QE(df = 9) = 26.2034, p-val = 0.0019

Test of Moderators (coefficient(s) 2,3,4):
QM(df = 3) = 11.0605, p-val = 0.0114

Model Results:

               estimate      se     zval    pval    ci.lb    ci.ub
intrcpt          0.2932  0.4050   0.7239  0.4691  -0.5006   1.0870
allocrandom     -0.2675  0.3504  -0.7633  0.4453  -0.9543   0.4193
allocsystematic  0.0585  0.3795   0.1540  0.8776  -0.6854   0.8023
ablat           -0.0273  0.0092  -2.9650  0.0030  -0.0453  -0.0092
```



## Wald-Type Tests and Contrasts

- syntax: `anova(res, btt=<>)`

  vector of numbers indicating which coefficients to test

- syntax: `anova(res, L=c())`

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



```
> ### test 'alloc' factor as a whole
> anova(res, btt=2:3)

Test of Moderators (coefficient(s) 2,3):
QM(df = 2) = 1.2850, p-val = 0.5260

> ### test random versus systematic allocation
> anova(res, L=c(0,1,-1,0))

Hypothesis:
1: allocrandom - allocsystematic = 0

Results:
   estimate      se    zval    pval
1:  -0.3260 0.3104 -1.0501 0.2937

Test of Hypothesis:
QM(df = 1) = 1.1027, p-val = 0.2937
```

## Predicted Values

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

```
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

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```
> ### predicted RR for 'random' at 10, 30, and 50 degrees
>
> predict(res, newmods = c(1,0,10), transf=exp, digits=2)

 pred ci.lb ci.ub cr.lb cr.ub
 0.78  0.44  1.38  0.31  1.99

> predict(res, newmods = c(1,0,30), transf=exp, digits=2)

 pred ci.lb ci.ub cr.lb cr.ub
 0.45  0.31  0.66  0.20  1.05

> predict(res, newmods = c(1,0,50), transf=exp, digits=2)
 pred ci.lb ci.ub cr.lb cr.ub
 0.26  0.16  0.42  0.11  0.64
```

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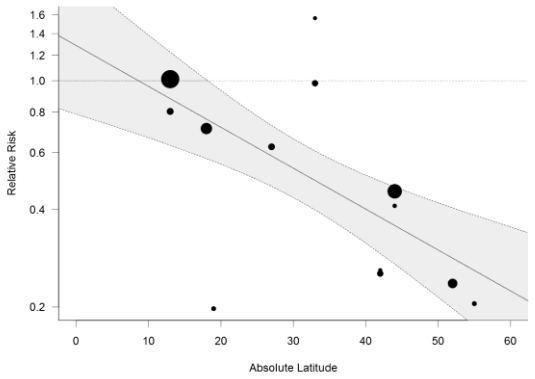


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```
> ### load data
> dat <- get(data(dat.konstantopoulos2011))
>
> ### show data
> dat
```

*standardized mean differences and sampling variances*

| | district | school | study | year | yi | vi |
|---|---|---|---|---|---|---|
| 1 | 11 | 1 | 1 | 1976 | -0.18 | 0.118 |
| 2 | 11 | 2 | 2 | 1976 | -0.22 | 0.118 |
| 3 | 11 | 3 | 3 | 1976 | 0.23 | 0.144 |
| 4 | 11 | 4 | 4 | 1976 | -0.30 | 0.144 |
| 5 | 12 | 1 | 5 | 1989 | 0.13 | 0.014 |
| 6 | 12 | 2 | 6 | 1989 | -0.26 | 0.014 |
| 7 | 12 | 3 | 7 | 1989 | 0.19 | 0.015 |
| 8 | 12 | 4 | 8 | 1989 | 0.32 | 0.024 |
| 9 | 18 | 1 | 9 | 1994 | 0.45 | 0.023 |
| 10 | 18 | 2 | 10 | 1994 | 0.38 | 0.043 |
| 11 | 18 | 3 | 11 | 1994 | 0.29 | 0.012 |
| 12 | ... | ... | ... | ... | ... | ... |
| 56 | 644 | 4 | 56 | 1994 | -0.05 | 0.067 |

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

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:

estimate       se     zval     pval    ci.lb    ci.ub
  0.1279   0.0439   2.9161   0.0035   0.0419   0.2139
```

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## The rma.mv() Function

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

```
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`**)

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```
> ### fit standard random-effects model with rma.mv()
> res <- rma.mv(yi, vi, random = ~ 1 | study, data = dat)
> res

Multivariate Meta-Analysis Model (k = 56; method: REML)

Variance Components:

            estim    sqrt  nlvls  fixed  factor
sigma^2    0.0884  0.2974     56     no   study

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

Model Results:

estimate       se     zval     pval    ci.lb    ci.ub
  0.1279   0.0439   2.9161   0.0035   0.0419   0.2139
```



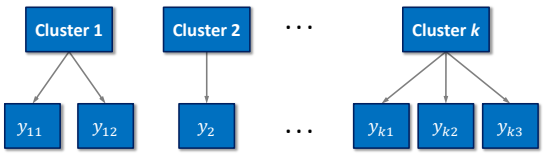
```
> ### load data
> dat <- get(data(dat.konstantopoulos2011))
>
> ### show data
> dat

    district  school  study  year     yi     vi
1         11       1      1  1976  -0.18  0.118
2         11       2      2  1976  -0.22  0.118
3         11       3      3  1976   0.23  0.144
4         11       4      4  1976  -0.30  0.144
5         12       1      5  1989   0.13  0.014
6         12       2      6  1989  -0.26  0.014
7         12       3      7  1989   0.19  0.015
8         12       4      8  1989   0.32  0.024
9         18       1      9  1994   0.45  0.023
10        18       2     10  1994   0.38  0.043
11        18       3     11  1994   0.29  0.012
12       ...     ...    ...   ...    ...    ...
56       644       4     56  1994  -0.05  0.067
```

between 3 and 11 schools within 11 different districts (56 studies in total)



## Multilevel Meta-Analytic Data

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






## Multilevel Random-Effects Model

$$y_{ij} = \mu$$ average true outcome

$$+ w_i$$ random effect that makes the true outcomes for a particular cluster larger/smaller by some amount (heterogeneity between clusters)

$$+ u_{ij}$$ random effect that makes one of the true outcomes within a particular cluster larger/smaller by some amount (heterogeneity within clusters)

$$+ e_{ij}$$ sampling error

$$w_i \sim N(0, \sigma_B^2) \qquad u_{ij} \sim N(0, \sigma_W^2) \qquad e_{ij} \sim N(0, v_{ij})$$



## 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`



```
> ### fit multilevel random-effects model
> res <- rma.mv(yi, vi, random = ~ 1 | district/school,
                data = dat)
> res

Multivariate Meta-Analysis Model (k = 56; method: REML)

Variance Components:

            estim    sqrt  nlvls  fixed           factor
sigma^2.1  0.0651  0.2551     11     no         district
sigma^2.2  0.0327  0.1809     56     no  district/school

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

Model Results:

estimate       se     zval     pval    ci.lb    ci.ub
  0.1847   0.0846   2.1845   0.0289   0.0190   0.3504
```

## Correlation due to Multilevel Structure

- the multilevel structure implies that the true outcomes within a cluster are correlated:

$$\rho = \frac{\sigma_B^2}{\sigma_B^2 + \sigma_W^2}$$

- in example:

$$\hat{\rho} = \frac{0.0651}{0.0651 + 0.0327} = .67$$

- also note: 0.0651 + 0.0327 = 0.0978

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## Multivariate Parameterization

$y_{ij} = \mu$ average true outcome

$+ u_{ij}$ correlated random effects for the true outcomes within the same cluster

$+ e_{ij}$ sampling error

$$\begin{bmatrix} u_{i1} \\ u_{i2} \\ u_{i3} \end{bmatrix} \sim MVN\left( \begin{bmatrix} 0 \\ 0 \\ 0 \end{bmatrix}, \begin{bmatrix} \tau^2 & \rho\tau^2 & \rho\tau^2 \\ & \tau^2 & \rho\tau^2 \\ & & \tau^2 \end{bmatrix} \right) \qquad e_{ij} \sim N(0, v_{ij})$$

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## 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)

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```
> ### fit multivariate random-effects model
> res <- rma.mv(yi, vi, random = ~ factor(school) | district,
                data = dat)
> res

Multivariate Meta-Analysis Model (k = 56; method: REML)

Variance Components:

outer factor: district       (nlvls = 11)
inner factor: factor(school) (nlvls = 11)

              estim    sqrt  fixed
tau^2       0.0978  0.3127     no
rho         0.6653             no

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

Model Results:

estimate       se     zval     pval    ci.lb    ci.ub
  0.1847   0.0846   2.1845   0.0289   0.0190   0.3504
```

$\tau^2 = \sigma_B^2 + \sigma_W^2$

$\rho = \frac{\sigma_B^2}{\sigma_B^2 + \sigma_W^2}$

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## 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)

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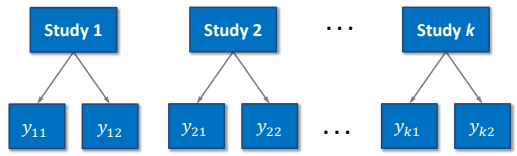
## Multiple (Correlated) Outcomes

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




***note:*** *not all studies have to measure all outcomes*

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## 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), …

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## Multivariate Random-Effects Model

$$y_{ij} = \mu_j + u_{ij} + e_{ij}$$

$\mu_j$: average true outcome for $j$th outcome

$u_{ij}$: correlated random effects corresponding to the true outcomes of the same study

$e_{ij}$: correlated sampling errors of the observed outcomes for the same study (with known var-cov matrix)

$$Var\begin{bmatrix} u_{i1} \\ u_{i2} \end{bmatrix} = \begin{bmatrix} \tau_1^2 & \rho\tau_1\tau_2 \\ & \tau_2^2 \end{bmatrix} \qquad Var\begin{bmatrix} e_{i1} \\ e_{i2} \end{bmatrix} = \begin{bmatrix} v_{i1} & \text{cov}_i \\ & v_{i2} \end{bmatrix}$$

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

*mean differences and corresponding var-cov matrix of the sampling errors*

| | trial | author | year | ni | outcome | yi | v1i | v2i |
|---|---|---|---|---|---|---|---|---|
| 1 | 1 | Pihlstrom et al. | 1983 | 14 | PD | 0.47 | 0.0075 | 0.0030 |
| 2 | 1 | Pihlstrom et al. | 1983 | 14 | AL | -0.32 | 0.0030 | 0.0077 |
| 3 | 2 | Lindhe et al. | 1982 | 15 | PD | 0.20 | 0.0057 | 0.0009 |
| 4 | 2 | Lindhe et al. | 1982 | 15 | AL | -0.60 | 0.0009 | 0.0008 |
| 5 | 3 | Knowles et al. | 1979 | 78 | PD | 0.40 | 0.0021 | 0.0007 |
| 6 | 3 | Knowles et al. | 1979 | 78 | AL | -0.12 | 0.0007 | 0.0014 |
| 7 | 4 | Ramfjord et al. | 1987 | 89 | PD | 0.26 | 0.0029 | 0.0009 |
| 8 | 4 | Ramfjord et al. | 1987 | 89 | AL | -0.31 | 0.0009 | 0.0015 |
| 9 | 5 | Becker et al. | 1988 | 16 | PD | 0.56 | 0.0148 | 0.0072 |
| 10 | 5 | Becker et al. | 1988 | 16 | AL | -0.39 | 0.0072 | 0.0304 |

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```
> ### construct var-cov matrix of the sampling errors
> dat$trial <- factor(dat$trial, levels=unique(dat$trial))
> V <- split(dat[,c("v1i","v2i")], dat$trial)
> V <- lapply(V, as.matrix)
> V <- bldiag(V)
> V
```

```
       [,1]   [,2]   [,3]   [,4]   [,5] [,6] [,7] [,8] [,9]   [,10]
 [1,] 0.0075 0.0030 0.0000 0.0000  ...  ...  ...  ...    ...    ...
 [2,] 0.0030 0.0077 0.0000 0.0000  ...  ...  ...  ...    ...    ...
 [3,] 0.0000 0.0000 0.0057 0.0009  ...  ...  ...  ...    ...    ...
 [4,] 0.0000 0.0000 0.0009 0.0008  ...  ...  ...  ...    ...    ...
 [5,]    ...    ...    ...    ...  ...  ...  ...  ...    ...    ...
 [6,]    ...    ...    ...    ...  ...  ...  ...  ...    ...    ...
 [7,]    ...    ...    ...    ...  ...  ...  ...  ...    ...    ...
 [8,]    ...    ...    ...    ...  ...  ...  ...  ...    ...    ...
 [9,]    ...    ...    ...    ...  ...  ...  ...  ... 0.0148 0.0072
[10,]    ...    ...    ...    ...  ...  ...  ...  ... 0.0072 0.0304
```

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## 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)

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```
> ### fit multivariate random-effects model
> res <- rma.mv(yi, V, mods = ~ outcome - 1, data = dat,
                random = ~ outcome | trial, struct = "UN")
> res

Multivariate Meta-Analysis Model (k = 10; method: REML)

Variance Components:

outer factor: trial   (nlvls = 5)
inner factor: outcome (nlvls = 2)

             estim    sqrt  k.lvl  fixed  level
tau^2.1    0.0327  0.1807      5     no     AL
tau^2.2    0.0117  0.1083      5     no     PD

    rho.AL  rho.PD    AL  PD
AL       1  0.6088     -  no
PD  0.6088       1     5   -

Test for Residual Heterogeneity:
QE(df = 8) = 128.2267, p-val < .0001

Test of Moderators (coefficient(s) 1,2):
QM(df = 2) = 108.8616, p-val < .0001

Model Results:

           estimate      se     zval    pval    ci.lb    ci.ub
outcomeAL   -0.3392  0.0879  -3.8589  0.0001  -0.5115  -0.1669
outcomePD    0.3534  0.0588   6.0057  <.0001   0.2381   0.4688
```

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## Random Effects Structures

**struct="CS"**
(this is the default)

$$\begin{bmatrix} \tau^2 & \rho\tau^2 & \rho\tau^2 & \rho\tau^2 \\ & \tau^2 & \rho\tau^2 & \rho\tau^2 \\ & & \tau^2 & \rho\tau^2 \\ & & & \tau^2 \end{bmatrix}$$

**struct="HCS"**

$$\begin{bmatrix} \tau_1^2 & \rho\tau_1\tau_2 & \rho\tau_1\tau_3 & \rho\tau_1\tau_4 \\ & \tau_2^2 & \rho\tau_2\tau_3 & \rho\tau_2\tau_4 \\ & & \tau_3^2 & \rho\tau_3\tau_4 \\ & & & \tau_4^2 \end{bmatrix}$$

**struct="UN"**

$$\begin{bmatrix} \tau_1^2 & \rho_{12}\tau_1\tau_2 & \rho_{13}\tau_1\tau_3 & \rho_{14}\tau_1\tau_4 \\ & \tau_2^2 & \rho_{23}\tau_2\tau_3 & \rho_{24}\tau_2\tau_4 \\ & & \tau_3^2 & \rho_{34}\tau_4\tau_4 \\ & & & \tau_4^2 \end{bmatrix}$$

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

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```
> ### contrast for differences in outcomes
> anova(res, L=c(1,-1))

Hypothesis:
1: outcomeAL - outcomePD = 0

Results:
   estimate     se    zval   pval
1:  -0.6926 0.0744 -9.3120 <.0001

Test of Hypothesis:
QM(df = 1) = 86.7139, p-val < .0001
```

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## 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

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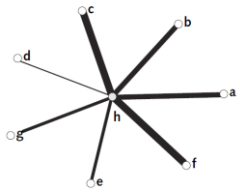
## Star-Shaped Networks

Second-generation antiepileptic drugs in partial epilepsy




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

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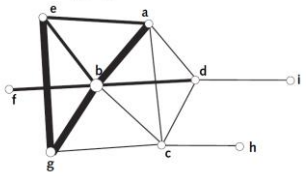
## Complex Networks

Chemotherapy regimens for ovarian cancer




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

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## 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

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## Arm-Based Network Meta-Analysis

$$y_{ij} = \beta_0 + \beta_1 T_{i1} + \ldots + \beta_p T_{ip}$$ ($T_{ij}$ = treatment indicators)

$+ w_i$ random effect that makes the true outcomes for a particular study larger/smaller by some amount (between-study heterogeneity)

$+ u_{ij}$ random effect that makes one of the true outcomes within a particular study larger/smaller by some amount (between-treatment heterogeneity)

$+ e_{ij}$ sampling error

$$w_i \sim N(0, \sigma_S^2) \qquad u_{ij} \sim N(0, \sigma_T^2) \qquad e_{ij} \sim N(0, v_{ij})$$

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```
> ### load data
> dat <- get(data(dat.hasselblad1998))
>
> ### calculate log odds for each study arm
> dat <- escalc(measure="PLO", xi=xi, ni=ni, data=dat)
>
> ### show data
> dat
```

*log odds and corresponding sampling variances*

| | id | study | trt | xi | ni | yi | vi |
|---|---|---|---|---|---|---|---|
| 1 | 1 | 1 | no_contact | 75 | 731 | -2.169 | 0.015 |
| 2 | 2 | 1 | ind_counseling | 363 | 714 | 0.034 | 0.006 |
| 3 | 3 | 2 | no_contact | 9 | 140 | -2.678 | 0.119 |
| 4 | 4 | 2 | ind_counseling | 23 | 140 | -1.627 | 0.052 |
| 5 | 5 | 2 | grp_counseling | 10 | 138 | -2.549 | 0.108 |
| 6 | 6 | 3 | no_contact | 2 | 106 | -3.951 | 0.510 |
| 7 | 7 | 3 | ind_counseling | 9 | 205 | -3.081 | 0.116 |
| 8 | ... | ... | ... | ... | ... | ... | ... |
| 9 | 49 | 24 | no_contact | 69 | 1177 | -2.776 | 0.015 |
| 10 | 50 | 24 | ind_counseling | 54 | 888 | -2.737 | 0.020 |

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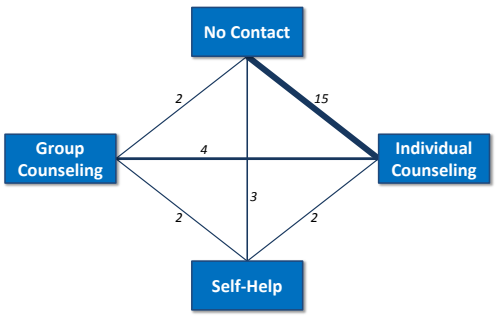


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```
> ### network meta-analysis using a multilevel model
> res <- rma.mv(yi, vi, mods = ~ trt, data = dat,
                random = ~ 1 | study/trt)
> res

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

Variance Components:

            estim   sqrt  nlvls  fixed     factor
sigma^2.1  0.195  0.441     24     no      study
sigma^2.2  0.249  0.499     50     no  study/trt

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:

                    estimate     se     zval   pval   ci.lb   ci.ub
intrcpt              -2.456  0.174  -14.129  <.001  -2.796  -2.115
trt self_help         0.501  0.302    1.657  0.098  -0.092   1.093
trt ind_counseling    0.777  0.196    3.969  <.001   0.393   1.161
trt grp_counseling    1.056  0.324    3.259  0.001   0.421   1.691
```

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

  pred ci.lb ci.ub cr.lb cr.ub
1 1.65  0.91  2.98  0.39  6.92   Self-Help versus No Contact
2 2.18  1.48  3.19  0.56  8.49   Individual Counseling versus No Contact
3 2.88  1.52  5.43  0.67 12.29   Group Counseling versus No Contact

> ### pairwise odds ratios comparing interventions
> predict(res, newmods=rbind(c(-1,1,0), c(-1,0,1), c(0,-1,1)),
          intercept=FALSE, transf=exp, digits=2)

  pred ci.lb ci.ub cr.lb cr.ub
1 1.32  0.73  2.39  0.31  5.54   Individual Counseling versus Self-Help
2 1.74  0.84  3.62  0.39  7.79   Group Counseling versus Self-Help
3 1.32  0.72  2.43  0.31  5.58   Group versus Individual Counseling
```

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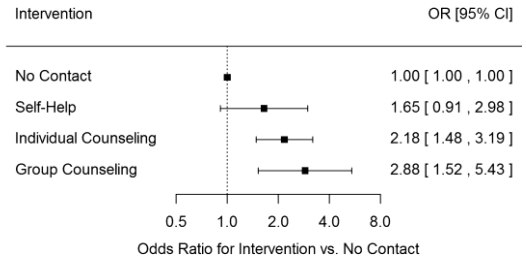


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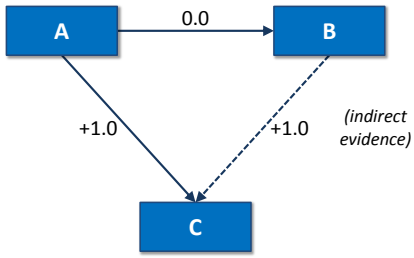
## Network/Loop Inconsistency

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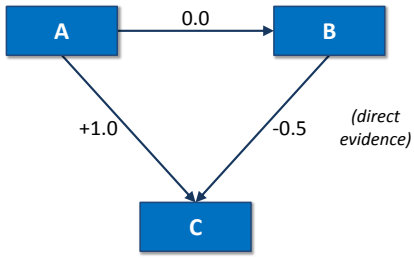
## Network/Loop Inconsistency

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## Dealing with Inconsistency

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

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## 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

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## Plots

- forest plots: `forest()`
- funnel plots: `funnel()`
- 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()`

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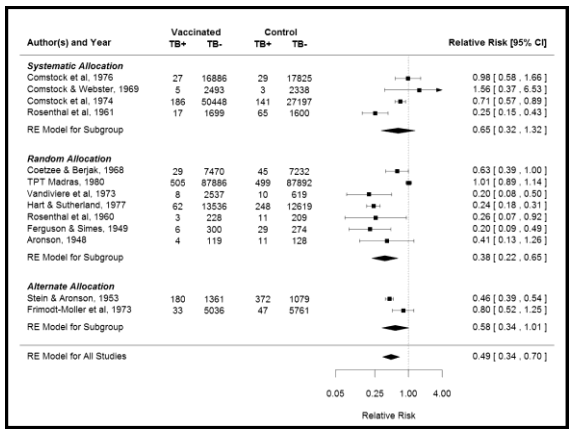

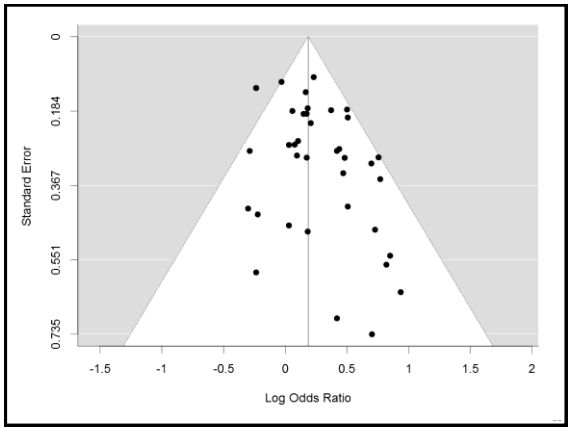


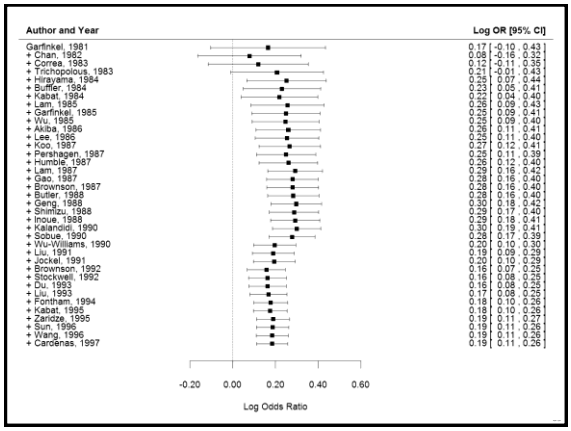


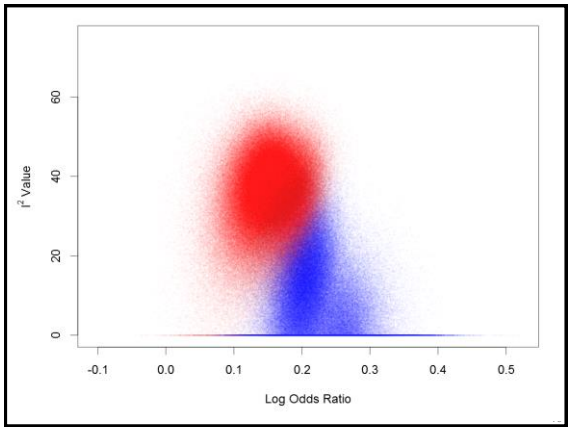


## Ongoing Development

- psychometric meta-analysis (Hunter & Schmidt)
- fully Bayesian models
- selection models
- lots of small improvements
- …

## References


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## Thank You!

Questions?