Multilevel, multivariate, and network meta-analysis with the *metafor* package in R

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Purpose of Talk

- describe how multilevel and multivariate structures can arise in meta-analytic data
- illustrate how to fit multilevel, multivariate, and network meta-analyses with the *metafor* package in R

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Meta-Analytic Data

- $i = 1, \ldots, k$ studies
- have y_i and corresponding v_i
- assume:

$$\boxed{y_i \mid \theta_i \sim N(\theta_i, v_i)}$$

- and independence of the estimates (for now)
- approx. 95% CI for θ_i: $y_i \pm 1.96\sqrt{v_i}$

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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

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Example: BCG Vaccine

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

$$p_T = 4/123 = .0325$$

$$p_C = 11/139 = .0791$$

$$RR = \frac{4/123}{11/139} = .41$$

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

$$v = \frac{1}{4} - \frac{1}{123} + \frac{1}{11} - \frac{1}{139} = .326$$

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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

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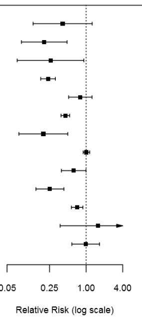
Example: BCG Vaccine

Author(s) and Year	Vaccinated TB+	Vaccinated TB-	Control TB+	Control TB-	Rel. Risk [95% CI]
Aronson, 1948	4	119	11	128	0.41 [0.13 , 1.26]
Ferguson & Simes, 1949	6	300	29	274	0.20 [0.09 , 0.49]
Rosenthal et al, 1960	3	228	11	209	0.26 [0.07 , 0.92]
Hart & Sutherland, 1977	62	13536	248	12619	0.24 [0.18 , 0.31]
Frimodt-Moller et al, 1973	33	5036	47	5761	0.80 [0.52 , 1.25]
Stein & Aronson, 1953	180	1361	372	1079	0.46 [0.39 , 0.54]
Vandiviere et al, 1973	8	2537	10	619	0.20 [0.08 , 0.50]
TPT Madras, 1980	505	87886	499	87892	1.01 [0.89 , 1.14]
Coetzee & Berjak, 1968	29	7470	45	7232	0.63 [0.39 , 1.00]
Rosenthal et al, 1961	17	1699	65	1600	0.25 [0.15 , 0.43]
Comstock et al, 1974	186	50448	141	27197	0.71 [0.57 , 0.89]
Comstock & Webster, 1969	5	2493	3	2338	1.56 [0.37 , 6.53]
Comstock et al, 1976	27	16886	29	17825	0.98 [0.58 , 1.66]



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

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

Marginal Variance-Covariance Matrix

$$Var\begin{bmatrix} y_1 \\ y_2 \\ y_3 \\ y_4 \\ y_5 \\ \vdots \\ y_k \end{bmatrix} = \begin{bmatrix} \tau^2+v_1 & & & & & & \\ & \tau^2+v_2 & & & & & \\ & & \tau^2+v_3 & & & & \\ & & & \tau^2+v_4 & & & \\ & & & & \tau^2+v_5 & & \\ & & & & & \ddots & \\ & & & & & & \tau^2+v_k \end{bmatrix}$$

Meta-Analysis with R

- ***metafor:*** meta-analysis package for R
- install with: `install.packages("metafor")`
- load with: `library(metafor)`
- 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)
```

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,
                             ci=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)
```

name of variable for the observed outcomes

name of variable for the corresponding sampling variances

to select the τ^2 estimator (DL, ML, REML, PM, EB, …)

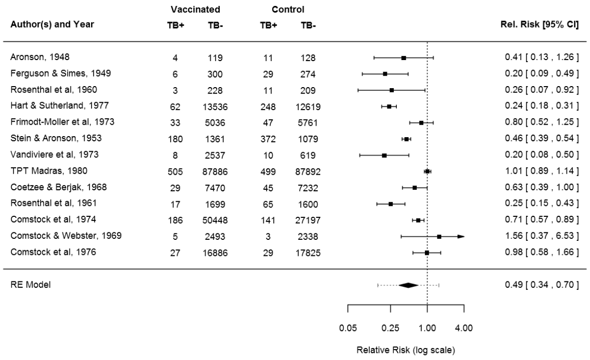
name of data frame containing the variables

- 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

(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:
  - $y_i = \beta_0 + \beta_1 x_{i1} + \cdots + \beta_p x_{ip} + u_i + e_i$
  - $u_i \sim N(0, \tau^2)$ (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

`anova(res, btt=<>)`

vector of numbers indicating which coefficients to test

`anova(res, L=c())`

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


```
> ### omnibus test of the 'alloc' factor
> 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
```



```
> ### 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


```
> ### 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
```


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`)

```
> ### 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
```

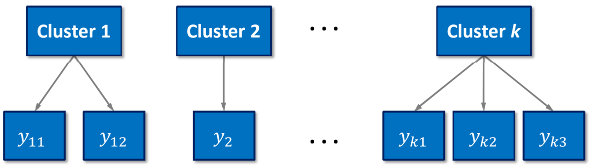


```
> ### load data
> dat <- get(data(dat.konstantopoulos2011))
>
> ### show data
> dat

    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

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

Marginal Variance-Covariance Matrix

$$Var\begin{bmatrix} y_{11} \\ y_{12} \\ y_{13} \\ y_2 \\ y_{31} \\ y_{32} \\ \vdots \end{bmatrix} = \begin{bmatrix} \sigma_B^2+\sigma_W^2+v_{11} & \sigma_B^2 & \sigma_B^2 & & & & \\ & \sigma_B^2+\sigma_W^2+v_{12} & \sigma_B^2 & & & & \\ & & \sigma_B^2+\sigma_W^2+v_{13} & & & & \\ & & & \sigma_B^2+\sigma_W^2+v_2 & & & \\ & & & & \sigma_B^2+\sigma_W^2+v_{31} & \sigma_B^2 & \\ & & & & & \sigma_B^2+\sigma_W^2+v_{32} & \\ & & & & & & \ddots \end{bmatrix}$$

marginal variance-covariance matrix with a block-diagonal structure

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
> res <- rma.mv(yi, vi, data = dat,
                random = ~ 1 | district/school)
> 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: $0.0651 + 0.0327 = 0.0978$

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

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

Marginal Variance-Covariance Matrix

$$Var\begin{bmatrix} y_{11} \\ y_{12} \\ y_{13} \\ y_2 \\ y_{31} \\ y_{32} \\ \vdots \end{bmatrix} = \begin{bmatrix} \tau^2 + v_{11} & \rho\tau^2 & \rho\tau^2 & & & & \\ & \tau^2 + v_{12} & \rho\tau^2 & & & & \\ & & \tau^2 + v_{13} & & & & \\ & & & \tau^2 + v_2 & & & \\ & & & & \tau^2 + v_{31} & \rho\tau^2 & \\ & & & & & \tau^2 + v_{32} & \\ & & & & & & \ddots \end{bmatrix}$$

The rma.mv() Function

- `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)


```
> ### 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
```

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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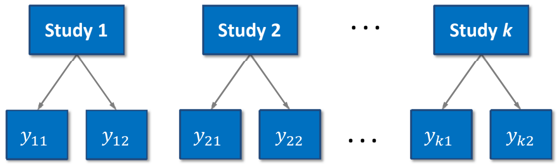
Multiple (Correlated) Outcomes

- 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

$y_{ij} \;=\; \mu_j$ — average true outcome for jth 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

   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
```

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

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```
> ### construct var-cov matrix of the sampling errors
> 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)


```
> ### 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       0.6088                    no

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

Model Results:

           estimate      se     zval    pval    ci.lb    ci.ub
outcomeAL   -0.3392  0.0879  -3.8588  0.0001  -0.5115  -0.1669
outcomePD    0.3534  0.0588   6.0056  <.0001   0.2381   0.4688
```


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" are the same)


```
> ### 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
```


Multiple Time Points

- multivariate data also arise when an outcome is measured at multiple time points
- the sampling errors will again be correlated
- true outcomes may also be correlated
- can consider auto-regressive structures for the sampling errors and random effects (Ishak et al., 2007; Trikalinos & Olkin, 2012)

Random Effects Structures

struct="AR"

$$\begin{bmatrix} \tau^2 & \rho\tau^2 & \rho^2\tau^2 & \rho^3\tau^2 \\ & \tau^2 & \rho\tau^2 & \rho^2\tau^2 \\ & & \tau^2 & \rho\tau^2 \\ & & & \tau^2 \end{bmatrix}$$

struct="HAR"

$$\begin{bmatrix} \tau_1^2 & \rho\tau_1\tau_2 & \rho^2\tau_1\tau_3 & \rho^3\tau_1\tau_4 \\ & \tau_2^2 & \rho\tau_2\tau_3 & \rho^2\tau_2\tau_4 \\ & & \tau_3^2 & \rho\tau_3\tau_4 \\ & & & \tau_4^2 \end{bmatrix}$$

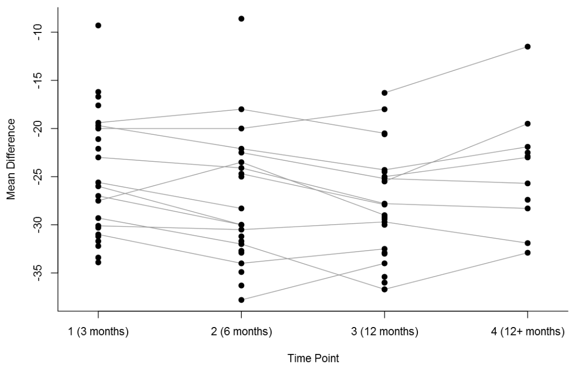
```
> ### load data
> dat <- get(data(dat.ishak2007))
>
> ### create long format dataset
> dat.long <- reshape(dat, direction="long", idvar="study",
                      v.names=c("yi","vi"),
                      varying=list(c(2,4,6,8), c(3,5,7,9)))
> dat.long <- dat.long[order(dat.long$study, dat.long$time),]
> rownames(dat.long) <- 1:nrow(dat.long)
>
> ### remove missing measurement occasions from dat.long
> is.miss  <- is.na(dat.long$yi)
> dat.long <- dat.long[!is.miss,]
>
> ### construct full (block diagonal) V matrix with AR(1) structure
> rho.within <- .97
> V <- lapply(split(with(dat, cbind(v1i, v2i, v3i, v4i)),
         dat$study), diag)
> V <- lapply(V, function(v) sqrt(v) %*%
         toeplitz(ARMAacf(ar=rho.within, lag.max=3)) %*% sqrt(v))
> V <- bldiag(V)
> V <- V[!is.miss,!is.miss]
```



```
> ### show data
> dat.long
```

mean differences and corresponding sampling variances

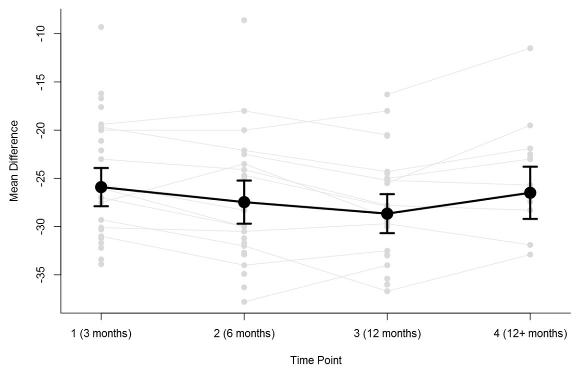
```
                  study  time     yi     vi
1        Alegret (2001)     1  -33.4   14.3
5     Barichella (2003)     1  -20.0    7.3
7     Barichella (2003)     3  -30.0    5.7
9         Berney (2002)     1  -21.1    7.3
13      Burchiel (1999)     1  -20.0    8.0
14      Burchiel (1999)     2  -20.0    8.0
15      Burchiel (1999)     3  -18.0    5.0
18          Chen (2003)     2  -32.9  125.0
91                  ...   ...    ...    ...
173  Vingerhoets (2002)     1  -19.7   18.5
174  Vingerhoets (2002)     2  -22.1   18.1
175  Vingerhoets (2002)     3  -24.3   18.2
176  Vingerhoets (2002)     4  -21.9   16.7
178      Volkman (2001)     2  -37.8   20.9
179      Volkman (2001)     3  -34.0   26.4
181  Weselburger (2002)     1  -22.1   40.8
```


```
> ### show var-cov matrix of sampling errors for rows 1-8
> V[1:8,1:8]

       [,1]   [,2]   [,3]   [,4]   [,5]   [,6]   [,7]    [,8]
[1,] 14.300
[2,]         7.300  6.069
[3,]         6.069  5.700
[4,]                       7.300
[5,]                              8.000  7.760  5.951
[6,]                              7.760  8.000  6.135
[7,]                              5.951  6.135  5.000
[8,]                                                   125.000
```



```
> ### multivariate model with HAR(1) structure
> res <- rma.mv(yi, V, mods = ~ factor(time) - 1, data = dat.long,
                random = ~ time | study, struct = "HAR")
> res

Multivariate Meta-Analysis Model (k = 82; method: REML)

Variance Components:

            estim    sqrt  k.lvl  fixed  level
tau^2.1    22.724   4.767     24     no      1
tau^2.2    33.755   5.810     22     no      2
tau^2.3    26.167   5.115     25     no      3
tau^2.4    31.207   5.586     11     no      4
rho         0.883                    no

Test for Residual Heterogeneity:
QE(df = 78) = 856.164, p-val < .001

Model Results:

               estimate     se     zval   pval    ci.lb    ci.ub
factor(time)1   -25.905  1.012  -25.605  <.001  -27.888  -23.922
factor(time)2   -27.461  1.141  -24.072  <.001  -29.697  -25.225
factor(time)3   -28.656  1.032  -27.756  <.001  -30.680  -26.633
factor(time)4   -26.494  1.382  -19.172  <.001  -29.202  -23.785
```

```
> ### comparison of effects between pairs of time points
> anova(res, L=rbind(c(1,-1,0,0), c(1,0,-1,0), c(1,0,0,-1),
                     c(0,1,-1,0), c(0,1,0,-1),
                     c(0,0,1,-1)))

Hypotheses:
1: factor(time)1 - factor(time)2 = 0
2: factor(time)1 - factor(time)3 = 0
3: factor(time)1 - factor(time)4 = 0
4: factor(time)2 - factor(time)3 = 0
5: factor(time)2 - factor(time)4 = 0
6: factor(time)3 - factor(time)4 = 0

Results:
   estimate    se    zval  pval
1:    1.556 0.755   2.061 0.039    1 vs 2
2:    2.751 0.859   3.204 0.001    1 vs 3
3:    0.589 1.273   0.462 0.644    1 vs 4
4:    1.195 0.761   1.569 0.117    2 vs 3
5:   -0.967 1.217  -0.795 0.427    2 vs 4
6:   -2.163 0.968  -2.235 0.025    3 vs 4
```

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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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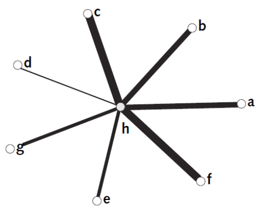
Star-Shaped Networks

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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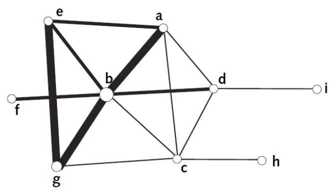
Complex Networks

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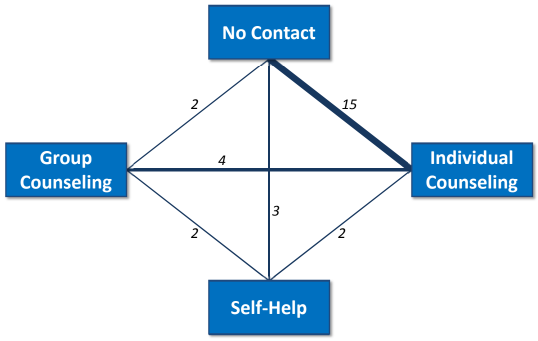
```
> ### load data
> dat <- get(data(dat.hasselblad1998))
>
> ### calculate log odds for each study arm
> dat <- escalc(measure="PLO", xi=xi, ni=ni, data=dat)
>
> ### show data
> dat
```

log odds and corresponding sampling variances

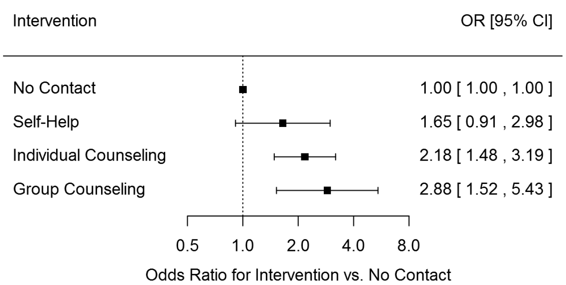
```
     id  study              trt   xi    ni      yi     vi
1     1      1       no_contact   75   731  -2.169  0.015
2     2      1  ind_counseling   363   714   0.034  0.006
3     3      2       no_contact    9   140  -2.678  0.119
4     4      2  ind_counseling    23   140  -1.627  0.052
5     5      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
```

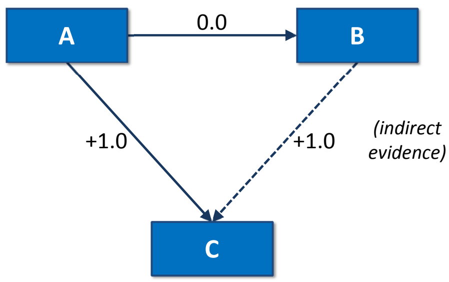

```
> ### convert trt variable to factor with desired ordering of levels
> dat$trt <- factor(dat$trt, levels=c("no_contact", "self_help",
                    "ind_counseling", "grp_counseling"))
>
> ### network meta-analysis using a multilevel model
> res <- rma.mv(yi, vi, mods = ~ trt, data = dat,
               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 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
```



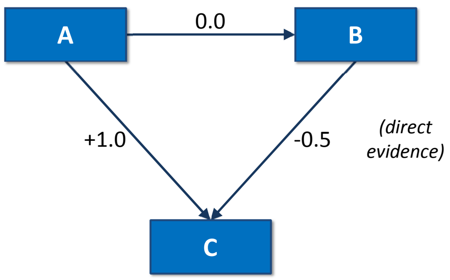
```
> ### pairwise odds ratios of interventions versus no contact
> predict(res, newmods=diag(3),
          intercept=FALSE, transf=exp, digits=2)

  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
```

Network/Loop Inconsistency



Network/Loop Inconsistency



Dealing with Inconsistency

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

Final Notes

- `rma.mv()` allows for an arbitrary number of random effects of the form `~ 1 | factor` (allows for 3/4/…-level models and crossed random effects)
- up to 2 terms of the form `~ inner | outer`
- can also specify a known correlation matrix corresponding to a `~ 1 | factor` term (e.g., for phylogenetic meta-analyses)
- website: `http://www.metafor-project.org`

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Thank You!

Questions? Comments?