

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

Wolfgang Viechtbauer  
Maastricht University  
The Netherlands

## 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

## Meta-Analytic Data

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

$$y_i | \theta_i \sim N(\theta_i, v_i)$$

- 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

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

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

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

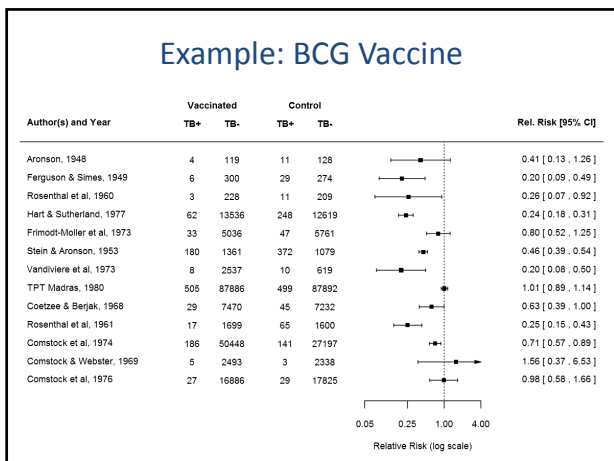
$$y = \ln[RR] = \ln\left[\frac{4/123}{11/139}\right] = -.89$$

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

## 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

$$y_i = \mu + u_i + e_i$$

average true outcome  
 random effect that makes the true outcome for a particular study larger/smaller by some amount (heterogeneity between studies)  
 sampling error

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

### 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

```

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

```
dat <- esalc(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 <- esalc(cmeasure="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  $\tau^2$  estimator (DL, ML, REML, PM, EB, ...)

- 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

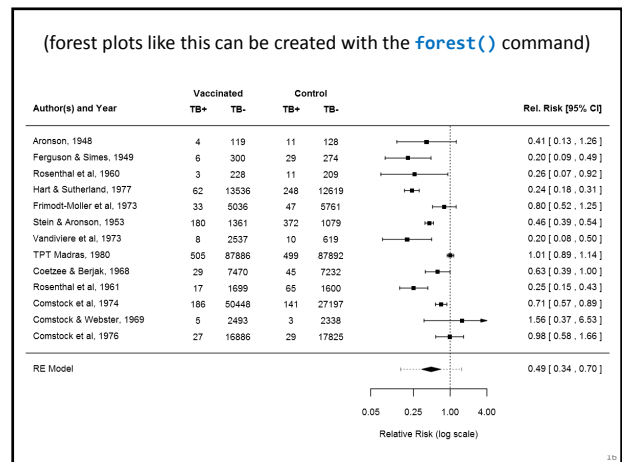
Test for Heterogeneity:
Q(df = 12) = 152.2330, p-val < .0001

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



### Mixed-Effects Meta-Regression Model

- can include moderators/predictors/covariates in the model (to account for heterogeneity)
- mixed-effects meta-regression model:
  - $y_i = \beta_0 + \beta_1 x_{i1} + \dots + \beta_p x_{ip} + u_i + e_i$
  - $u_i \sim N(0, \tau^2)$  (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<sup>2</sup> 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
alloccsystematic	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

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## 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

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```
> ### 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 - alloccsystematic = 0
```

Results:

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

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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<sup>2</sup> 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

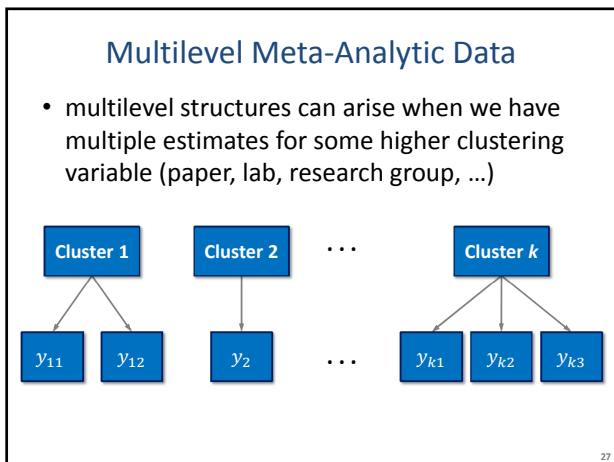
Model Results:

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)



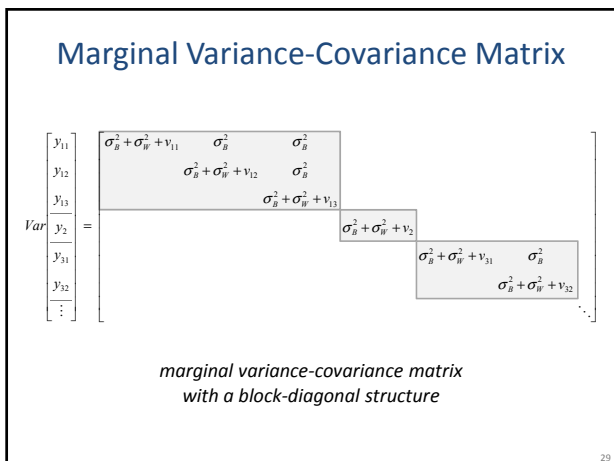
### Multilevel Random-Effects Model

$$y_{ij} = \mu + w_i + u_{ij} + e_{ij}$$

$\mu$ : 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

---


$$w_i \sim N(0, \sigma_w^2) \quad u_{ij} \sim N(0, \sigma_u^2) \quad e_{ij} \sim N(0, v_{ij})$$



### 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`

```

> ### 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

---


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

### 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
    
```

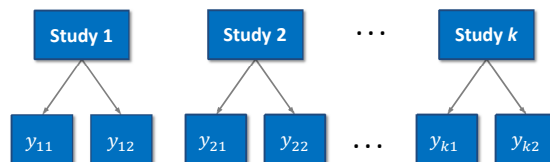
### Notes

- 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

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

$\mu_j$  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)

$$Var \begin{bmatrix} u_{i1} \\ u_{i2} \end{bmatrix} = \begin{bmatrix} \tau_1^2 & \rho\tau_1\tau_2 \\ & \tau_2^2 \end{bmatrix} \quad Var \begin{bmatrix} e_{i1} \\ e_{i2} \end{bmatrix} = \begin{bmatrix} v_{i1} & cov_i \\ & v_{i2} \end{bmatrix}$$

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```

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

```

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

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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

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

name of object with the var-cov matrix of the sampling errors

name of factor to indicate the outcome (and remove intercept)

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.lv1	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"

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

(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]

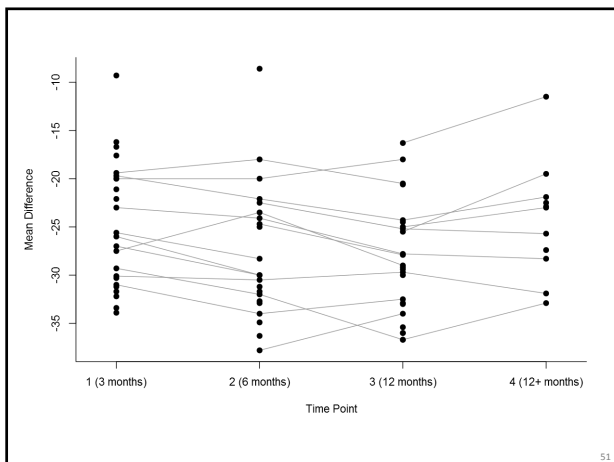
```

```

> ### show data
> dat.long

```

	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)

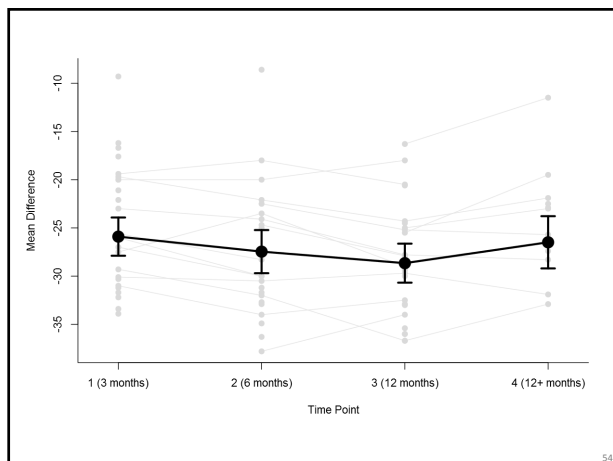
Variance Components:

	estim	sqrt	k.lv1	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

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

+  $w_i$  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

---


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

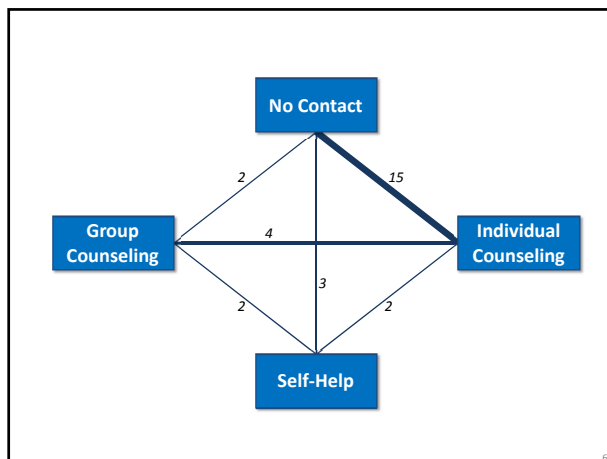
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```

> ### 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	no_contact	75	731	-2.169	0.015	
2	2	ind_counseling	363	714	0.034	0.006	
3	3	no_contact	9	140	-2.678	0.119	
4	4	ind_counseling	23	140	-1.627	0.052	
5	5	grp_counseling	10	138	-2.549	0.108	
6	6	no_contact	2	106	-3.951	0.510	
7	7	ind_counseling	9	205	-3.081	0.116	
8	...	...	...	...	...	...	...
9	49	no_contact	69	1177	-2.776	0.015	
10	50	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)

```

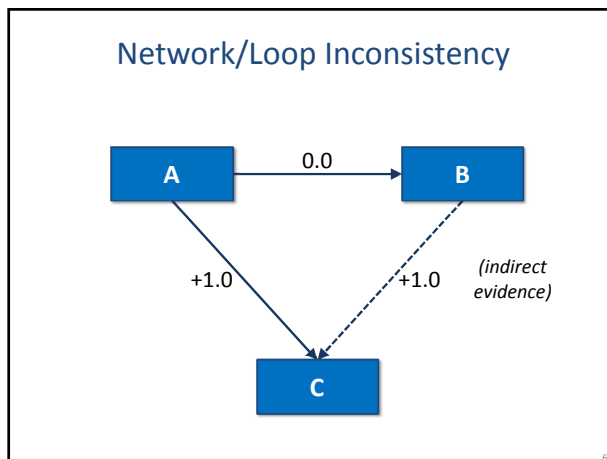
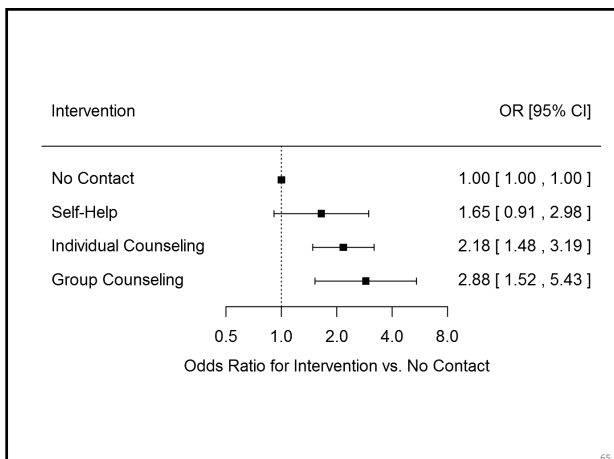
	pred	ci.lb	ci.ub	cr.lb	cr.ub	
1	1.65	0.91	2.98	0.39	6.92	Self-Help versus No Contact
2	2.18	1.48	3.19	0.56	8.49	Individual Counseling versus No Contact
3	2.88	1.52	5.43	0.67	12.29	Group Counseling versus No Contact

```

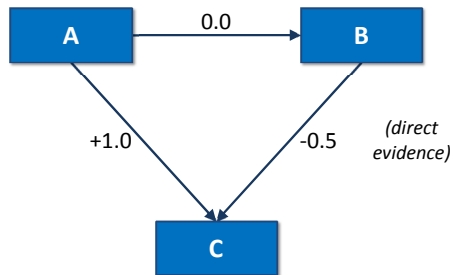
> ### pairwise odds ratios comparing interventions
> predict(res, newmods=rbind(c(-1,1,0), c(-1,0,1), c(0,-1,1)),
  intercept=FALSE, transf=exp, digits=2)

```

	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



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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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### 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?

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