Model selection in complex meta-analyses

Symposium on ‘Recent Advances in Meta-Analysis’

Department of Medical Statistics

University Medical Center Göttingen

Wolfgang Viechtbauer

Maastricht University

2024-08-28

Introduction / Overview

- discuss fixed- versus random-effects models in meta-analysis

Introduction / Overview

- ~~discuss fixed- versus random-effects models in meta-analysis~~
- … not again!

Introduction / Overview

- ~~discuss fixed- versus random-effects models in meta-analysis~~
- ... not again!
- discuss the issue of model selection in complex meta-analyses
- illustrate various principles based on several example analyses (using the `metafor` package in R [1])

```
install.packages("metafor")
library(metafor)
```

Standard Random-Effects Model

- let y_i denote the estimate, θ_i the corresponding true effect, and v_i the sampling variance in the ith study (and hence $\text{SE}_i = \sqrt{v_i}$ denotes the corresponding standard error)
- **random-effects model**:

$$y_i = \theta_i + \varepsilon_i$$

  where $\theta_i \sim N(\mu, \tau^2)$ and $\varepsilon_i \sim N(0, v_i)$
- the standard 'workhorse' in many MAs for pooling estimates

Independence Assumptions

- re-write the model as:

$$y_i = \mu + u_i + \varepsilon_i$$

  where $u_i \sim N(0, \tau^2)$ and $\varepsilon_i \sim N(0, v_i)$

- model assumes **independence** between estimates:[1]

$$\begin{aligned} \mathrm{Cov}[u_i, u_{i'}] &= 0 \quad \text{(independent random effects)} \\ \mathrm{Cov}[\varepsilon_i, \varepsilon_{i'}] &= 0 \quad \text{(independent sampling errors)} \end{aligned}$$

- in more complex analyses, these assumptions are often violated

[1] There is also $\mathrm{Cov}[u_i, \varepsilon_i] = 0$ but this is a separate issue [2].

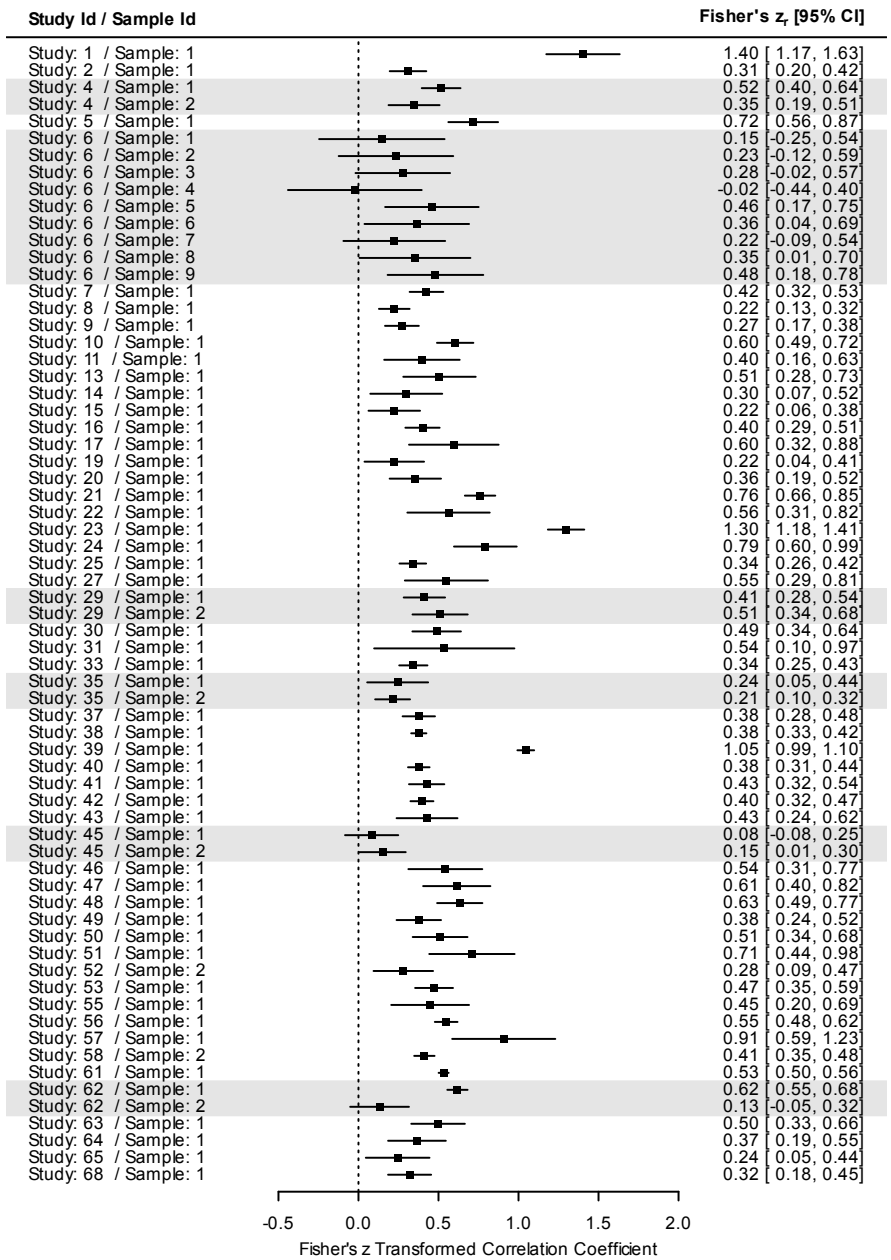
Dependent Random Effects

- when estimates from *different subsets of subjects* arise from the same study, their sampling errors can still be assumed to be independent, but not their random effects
- the true effects corresponding to estimates arising from the same study often tend to be similar to each other

Example: Relationship between Class Attendance and Grade

- meta-analysis on the relationship between class attendance of college students and their class performance (i.e., grade) [3]
- some studies examined multiple sub-samples (e.g., men versus women, different sections of the same class)
- dataset includes **54 studies** and **67 estimates** (Fisher r-to-z transformed correlations coefficients)

Example: Relationship between Class Attendance and Grade



Multilevel Random-Effects Model

- let y_{ij} denote the jth estimate from the ith study
- **multilevel random-effects model:**[2] [4]

$$y_{ij} = \mu + s_i + u_{ij} + \varepsilon_{ij}$$

where $s_i \sim N(0, \sigma_1^2)$, $u_{ij} \sim N(0, \sigma_2^2)$, $\varepsilon_{ij} \sim N(0, v_{ij})$

- implies that true effects from the same study are correlated:

$$\rho = \frac{\sigma_1^2}{\sigma_1^2 + \sigma_2^2}$$

[2] Sometimes called a 'three-level model', since the standard random-effects model can be considered a two-level model.

Example: Relationship between Class Attendance and Grade

```
dat <- subset(dat.crede2010, criterion=="grade")
dat <- escalc(measure="ZCOR", ri=ri, ni=ni, data=dat)
print(res <- rma.mv(yi, vi, random = ~ 1 | studyid/sampleid, data=dat))
```

```
## Multivariate Meta-Analysis Model (k = 67; method: REML)
##
## Variance Components:
##
##             estim    sqrt  nlvls  fixed            factor
## sigma^2.1  0.0376  0.1939     54     no           studyid
## sigma^2.2  0.0159  0.1259     67     no  studyid/sampleid
##
## Test for Heterogeneity:
## Q(df = 66) = 1068.7213, p-val < .0001
##
## Model Results:
##
## estimate      se     zval    pval   ci.lb   ci.ub
##   0.4798  0.0331  14.5167  <.0001  0.4151  0.5446
```

```
round(res$sigma2[1] / sum(res$sigma2), digits=2)
```

```
## [1] 0.7
```

Model Selection via LRT / Information Criteria

- the standard and multilevel RE models are nested (if $\sigma_1^2 = 0$, the multilevel model collapses to the standard RE model)
- comparison via likelihood ratio test and information criteria
- test H_0: $\sigma_1^2 = 0$ ($\Rightarrow$ H_0: $\rho = 0$)

```
res0 <- update(res, sigma2=c(0,NA)) # NA = estimate the component
anova(res0, res)
```

```
##         df    AIC     BIC   AICc  logLik    LRT   pval        QE
## Full     3 3.3911  9.9601 3.7782  1.3044                1068.7213
## Reduced  2 6.5060 10.8853 6.6964 -1.2530 5.1149 0.0237 1068.7213
```

- can also test H_0: $\sigma_2^2 = 0$ ($\Rightarrow$ H_0: $\rho = 1$)

```
res0 <- update(res, sigma2=c(NA,0)) # NA = estimate the component
anova(res0, res)
```

```
##         df     AIC     BIC    AICc  logLik     LRT   pval        QE
## Full     3  3.3911  9.9601  3.7782  1.3044                 1068.7213
## Reduced  2 14.8533 19.2326 15.0438 -5.4267 13.4622 0.0002 1068.7213
```

Model Selection Considerations

- this extends to more than two levels
- want to account for potential heterogeneity at each level
- there should be a random effect at the level of the individual estimates (u_i in the RE model, u_{ij} in the multilevel model)[3]
- but no simple rule for what should be considered a 'level'
- related to issue of what to consider a fixed vs. random effect [5]
- if the phenomenon of interest may vary across the units of a variable, may want to consider it as a level
- often use random effects to account for heterogeneity at a level, but there are circumstances where we also use fixed effects
- a variance component may be estimated to be ≈ 0 (ok!)

[3] So `rma.mv(yi, vi, random = ~ 1 | studyid, data=dat)` would be wrong!

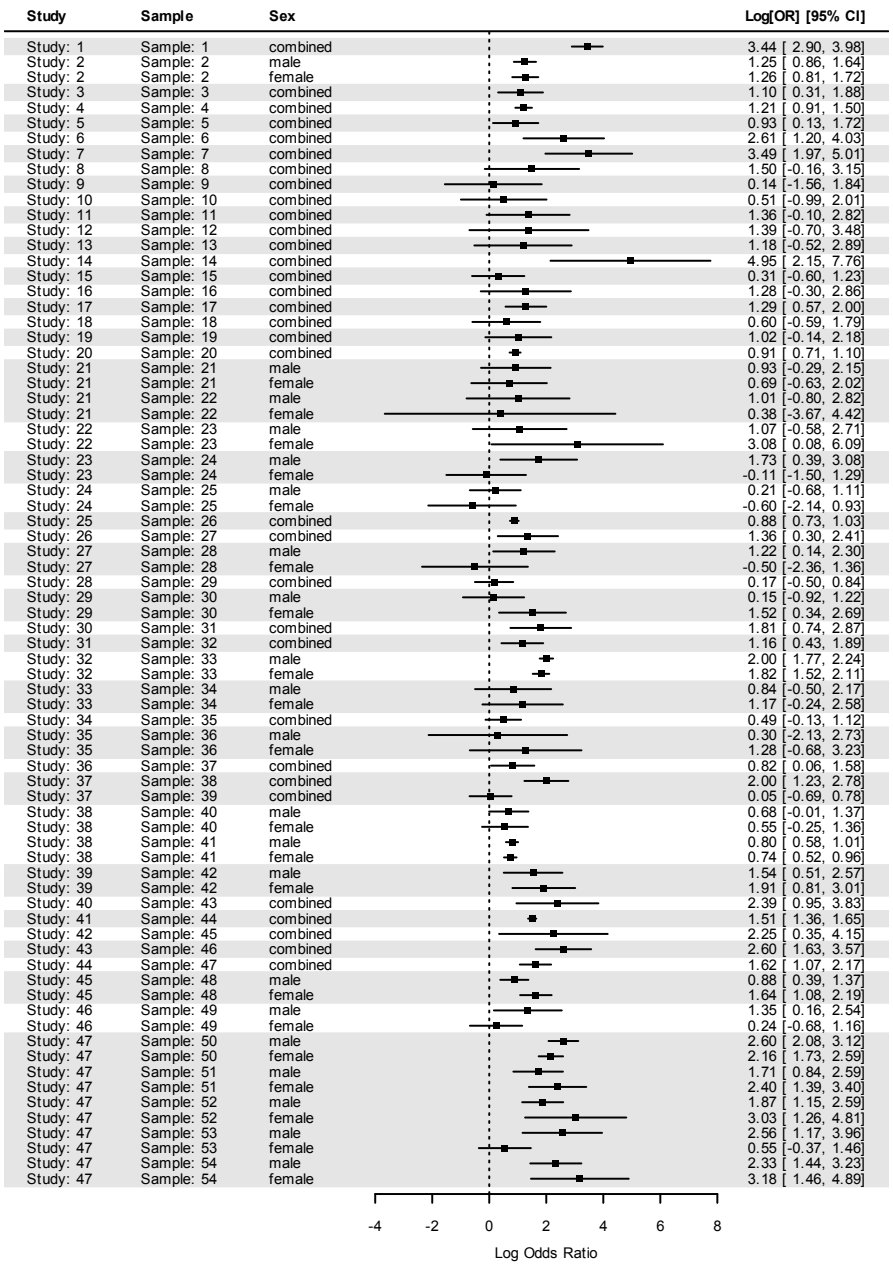
Example: Handedness and Eye-Dominance

- meta-analysis of **47 studies** on the association between handedness and eye-dominance [6]
- results are given in terms of 2×2 tables

	Right-Eyed	Left-Eyed
Right-Handed	a	b
Left-Handed	c	d

- we quantify the association in terms of log odds ratios
- some studies included multiple (independent) samples and/or reported results separately for men and women, so that the meta-analysis included **54 samples** and **75 estimates** in total

Example: Handedness and Eye-Dominance



Example: Handedness and Eye-Dominance

```
print(res <- rma.mv(yi, vi, random = ~ 1 | study/sample/sex, data=dat))
```

```
## Multivariate Meta-Analysis Model (k = 75; method: REML)
##
## Variance Components:
##
##             estim    sqrt  nlvls  fixed            factor
## sigma^2.1  0.1828  0.4276     47     no             study
## sigma^2.2  0.2259  0.4753     54     no       study/sample
## sigma^2.3  0.0000  0.0000     75     no  study/sample/sex
##
## Test for Heterogeneity:
## Q(df = 74) = 386.3457, p-val < .0001
##
## Model Results:
##
## estimate      se     zval    pval   ci.lb   ci.ub
##   1.2681  0.1130  11.2219  <.0001  1.0466  1.4895
```

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

```
##  pred ci.lb ci.ub
##  3.55  2.85  4.44
```

Bivariate Model for Independent Groups

- instead of modeling 'effect sizes' that reflect the difference between two groups ($y_i = y_i^T - y_i^C$), we can also model the arm-level outcomes (y_i^T and y_i^C) directly [7]

Wide Format

Study	y_i	v_i
1		
2		
...		

Long Format

Study	Group	y_{ij}	v_{ij}
1	T		
1	C		
2	T		
2	C		
...			

- we distinguish groups with a fixed effect
- can use fixed or random study effects

Example: BCG Vaccine against Tuberculosis

```
dat <- escalc(measure="OR", ai=tpos, bi=tneg, ci=cpos, di=cneg, data=dat.bcg)
rma(yi, vi, data=dat)
```

```
## Random-Effects Model (k = 13; tau^2 estimator: REML)
##
## tau^2 (estimated amount of total heterogeneity): 0.3378 (SE = 0.1784)
## tau (square root of estimated tau^2 value):      0.5812
## I^2 (total heterogeneity / total variability):   92.07%
## H^2 (total variability / sampling variability):  12.61
##
## Test for Heterogeneity:
## Q(df = 12) = 163.1649, p-val < .0001
##
## Model Results:
##
## estimate      se     zval    pval    ci.lb    ci.ub
##  -0.7452  0.1860  -4.0057  <.0001  -1.1098  -0.3806
```

```
# restructure into long format
dat2 <- to.long(measure="OR", ai=tpos, bi=tneg, ci=cpos, di=cneg, data=dat)
dat2$group <- factor(dat2$group, levels=c(2,1), labels=c("con","exp"))
dat2$id <- 1:nrow(dat2)
dat2 <- escalc(measure="PLO", xi=out1, mi=out2, data=dat2)
```

Example: BCG Vaccine against Tuberculosis

```
# fit model with fixed study effects
rma.mv(yi, vi, mods = ~ 0 + factor(study) + group, random = ~ 1 | id, data=dat2)
```

```
## Multivariate Meta-Analysis Model (k = 26; method: REML)
##
## Variance Components:
##
##             estim    sqrt  nlvls  fixed  factor
## sigma^2    0.1689  0.4110     26     no      id
##
## Test for Residual Heterogeneity:
## QE(df = 12) = 163.1649, p-val < .0001
##
## Model Results:
##
##           estimate      se      zval    pval    ci.lb    ci.ub
## study1     -2.5287  0.4119   -6.1386  <.0001  -3.3360  -1.7213
## ...
## study13    -6.0594  0.3330  -18.1962  <.0001  -6.7121  -5.4067
## groupexp   -0.7452  0.1860   -4.0057  <.0001  -1.1098  -0.3806
```

Example: BCG Vaccine against Tuberculosis

```r
# fit model with random study effects
rma.mv(yi, vi, mods = ~ group, random = ~ 1 | study/group, data=dat2)
```

```
## Multivariate Meta-Analysis Model (k = 26; method: REML)
##
## Variance Components:
##
##             estim    sqrt  nlvls  fixed       factor
## sigma^2.1  1.9109  1.3824     13     no        study
## sigma^2.2  0.1720  0.4147     26     no  study/group
##
## Test for Residual Heterogeneity:
## QE(df = 24) = 5270.3863, p-val < .0001
##
## Model Results:
##
##           estimate      se      zval    pval    ci.lb    ci.ub
## intrcpt    -4.0831  0.4050  -10.0826  <.0001  -4.8768  -3.2894
## groupexp   -0.7566  0.1873   -4.0393  <.0001  -1.1238  -0.3895
```

Bivariate Model for Independent Groups

- with fixed study effects, *identical* to the standard RE model; often quite similar when using random study effects[4]
- fixed versus random study effects is a debated issue [8–10]
- most important: need to account for study-level differences

[4] Estimate of τ^2 (with fixed study effects) or σ_2^2 (with random study effects) needs to be doubled to match the amount of heterogeneity from the standard RE model.

Dependent Sampling Errors

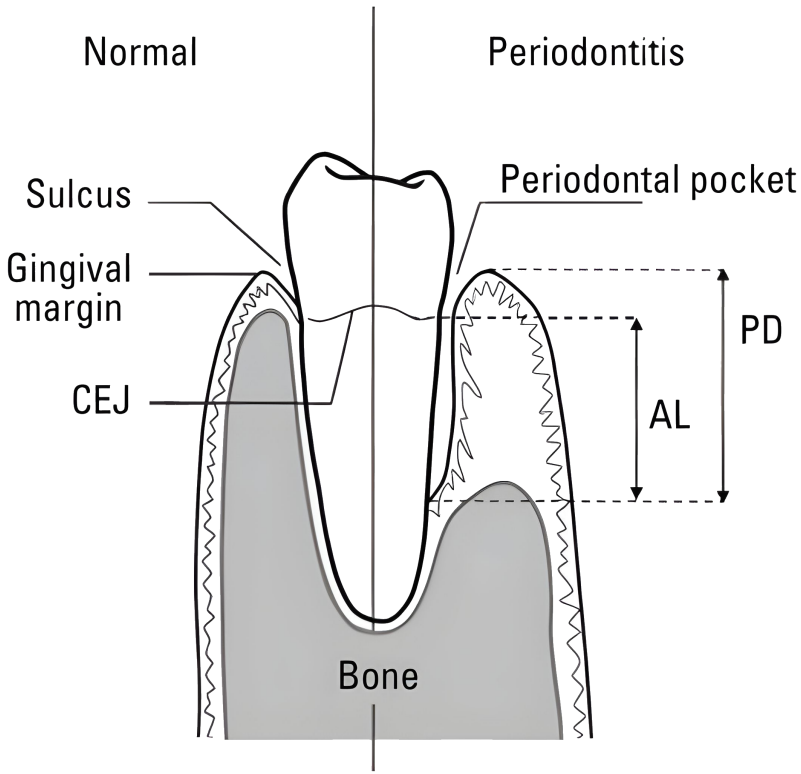
- when multiple estimates are computed for the *same subjects*, the sampling errors cannot be assumed to be independent
- can account for this by computing the covariance between dependent estimates (i.e., construct var-cov matrix of the ε_{ij})
- **note:** since we then have multiple estimates from the same study, this is an issue in addition to dependent random effects
- often multiple estimates reflect different constructs/outcomes
  - include outcome type as a fixed effect
  - allow the amount of heterogeneity to differ between types
- **multivariate random-effects model:** [11,12]

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

where $u_{ij} \sim N(0, G)$ and $\varepsilon_{ij} \sim N(0, V)$

Example: Treatment for Periodontal Disease

- meta-analysis on the effectiveness of surgical versus non-surgical treatment for periodontal disease [12,13]
- included 5 trials that each measured two outcomes: probing depth (PD) and attachment level (AL)



Example: Treatment for Periodontal Disease

```
# examine the dataset
dat <- dat.berkey1998
dat
```

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

Example: Treatment for Periodontal Disease

```
# construct the variance-covariance matrix of the observed outcomes
V <- vcalc(vi=1, cluster=author, rvars=c(v1i, v2i), data=dat)
V
```

```
##         1      2      3      4      5      6    ...      9     10
##  1 0.0075 0.0030    ...    ...    ...    ...    ...    ...    ...
##  2 0.0030 0.0077    ...    ...    ...    ...    ...    ...    ...
##  3    ...    ... 0.0057 0.0009    ...    ...    ...    ...    ...
##  4    ...    ... 0.0009 0.0008    ...    ...    ...    ...    ...
##  5    ...    ...    ...    ... 0.0021 0.0007    ...    ...    ...
##  6    ...    ...    ...    ... 0.0007 0.0014    ...    ...    ...
##  .    ...    ...    ...    ...    ...    ...    ...    ...    ...
##  9    ...    ...    ...    ...    ...    ...    ... 0.0148 0.0072
## 10    ...    ...    ...    ...    ...    ...    ... 0.0072 0.0304
```

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

Example: Treatment for Periodontal Disease

```
## 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               -   5
## PD  0.6088       1    no   -
##
## 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
```

Example: Treatment for Periodontal Disease

```r
# estimate the difference between the two pooled effects
predict(res, newmods=c(1,-1))
```

```
##     pred     se   ci.lb   ci.ub
##  -0.6926 0.0744 -0.8384 -0.5469
```

```r
# test the difference between the two pooled effects
anova(res, L=c(1,-1))
```

```
## Hypothesis:
## 1: outcomeAL - outcomePD = 0
##
##    estimate     se    zval   pval
## 1:  -0.6926 0.0744 -9.3120 <.0001
```

```r
# test the correlation among the true effects
res0 <- update(res, rho=0)
anova(res0, res)
```

```
##         df    AIC    BIC    AICc logLik    LRT   pval       QE
## Full     5 2.6165 3.0137 32.6165 3.6918                128.2267
## Reduced  4 1.5975 1.9153 14.9308 3.2012 0.9810 0.3219 128.2267
```

Dependent Sampling Errors

- when multiple groups are compared against a common comparator, need to account for dependent sampling errors

$$y_1 = y^{T_1} - y^C \quad \text{with} \quad \mathrm{Var}[y_1] = \mathrm{Var}[y^{T_1}] + \mathrm{Var}[y^C]$$
$$y_2 = y^{T_2} - y^C \quad \text{with} \quad \mathrm{Var}[y_2] = \mathrm{Var}[y^{T_2}] + \mathrm{Var}[y^C]$$

$$\mathrm{Cov}[y_1, y_2] = \mathrm{Var}[y^C]$$

- a common issue especially in network meta-analyses
- sidenote: as a rough approximation, $\mathrm{Cov}[y_1, y_2] \approx 1/n^C$

Dependent Sampling Errors

- **problem:** computation of the covariance between the sampling errors requires information that is often not reported
- **solution:** use an approximate var-cov matrix (as a working model) and then use cluster-robust inference methods [14]
- results will be similar when the working model is an adequate approximation to the data generating mechanism

Example: Association between Recidivism and Mental Health

- meta-analysis on the difference in recidivism between delinquent juveniles with/without a mental health disorder [15]
- results are given in terms of standardized mean differences, with positive values indicating a higher prevalence of recidivism in those with a mental health disorder
- multiple effect size estimates could be extracted from most studies (e.g., for different types of delinquent behaviors)
- but no information about the correlation among the estimates

Example: Association between Recidivism and Mental Health

```
# copy the dataset to dat
dat <- dat.assink2016

# assume a correlation of 0.7 for effect sizes corresponding to the same
# type of delinquent behavior and a correlation of 0.5 for effect sizes
# corresponding to different types of delinquent behavior
V <- vcalc(vi, cluster=study, type=deltype, obs=esid,
           data=dat, rho=c(0.7, 0.5))

# fit multilevel model using this approximate V matrix
res <- rma.mv(yi, V, random = ~ 1 | study/esid, data=dat)
res
```

Example: Association between Recidivism and Mental Health

```
## Multivariate Meta-Analysis Model (k = 100; method: REML)
##
## Variance Components:
##
##             estim    sqrt  nlvls  fixed      factor
## sigma^2.1  0.0704  0.2654     17     no       study
## sigma^2.2  0.1508  0.3883    100     no  study/esid
##
## Test for Heterogeneity:
## Q(df = 99) = 840.9174, p-val < .0001
##
## Model Results:
##
## estimate      se    zval    pval   ci.lb   ci.ub
##   0.3618  0.0933  3.8794  0.0001  0.1790  0.5446
```

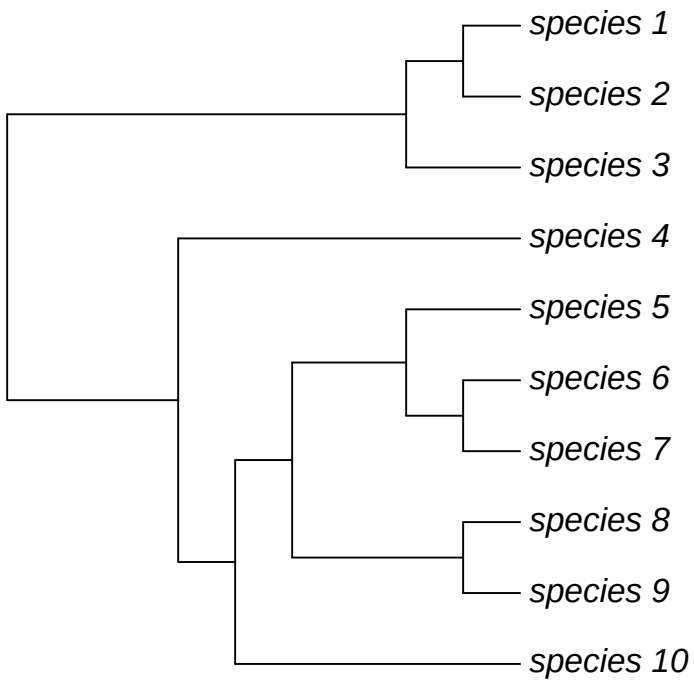
```
# use cluster-robust inference methods
robust(res, cluster=study, clubSandwich=TRUE)
```

Example: Association between Recidivism and Mental Health

```
## Multivariate Meta-Analysis Model (k = 100; method: REML)
##
## Variance Components:
##
##             estim    sqrt  nlvls  fixed      factor
## sigma^2.1  0.0704  0.2654     17     no       study
## sigma^2.2  0.1508  0.3883    100     no  study/esid
##
## Test for Heterogeneity:
## Q(df = 99) = 840.9174, p-val < .0001
##
## Model Results:
##
## estimate      se[1]    tval[1]     df[1]    pval[1]   ci.lb[1]   ci.ub[1]
##   0.3618  0.0938   3.8567   14.34   0.0017   0.1611   0.5626
##
## ---
## 1) results based on cluster-robust inference (var-cov estimator: CR2,
##    approx t-test and confidence interval, df: Satterthwaite approx)
```

Phylogenetic Meta-Analysis [16–19]

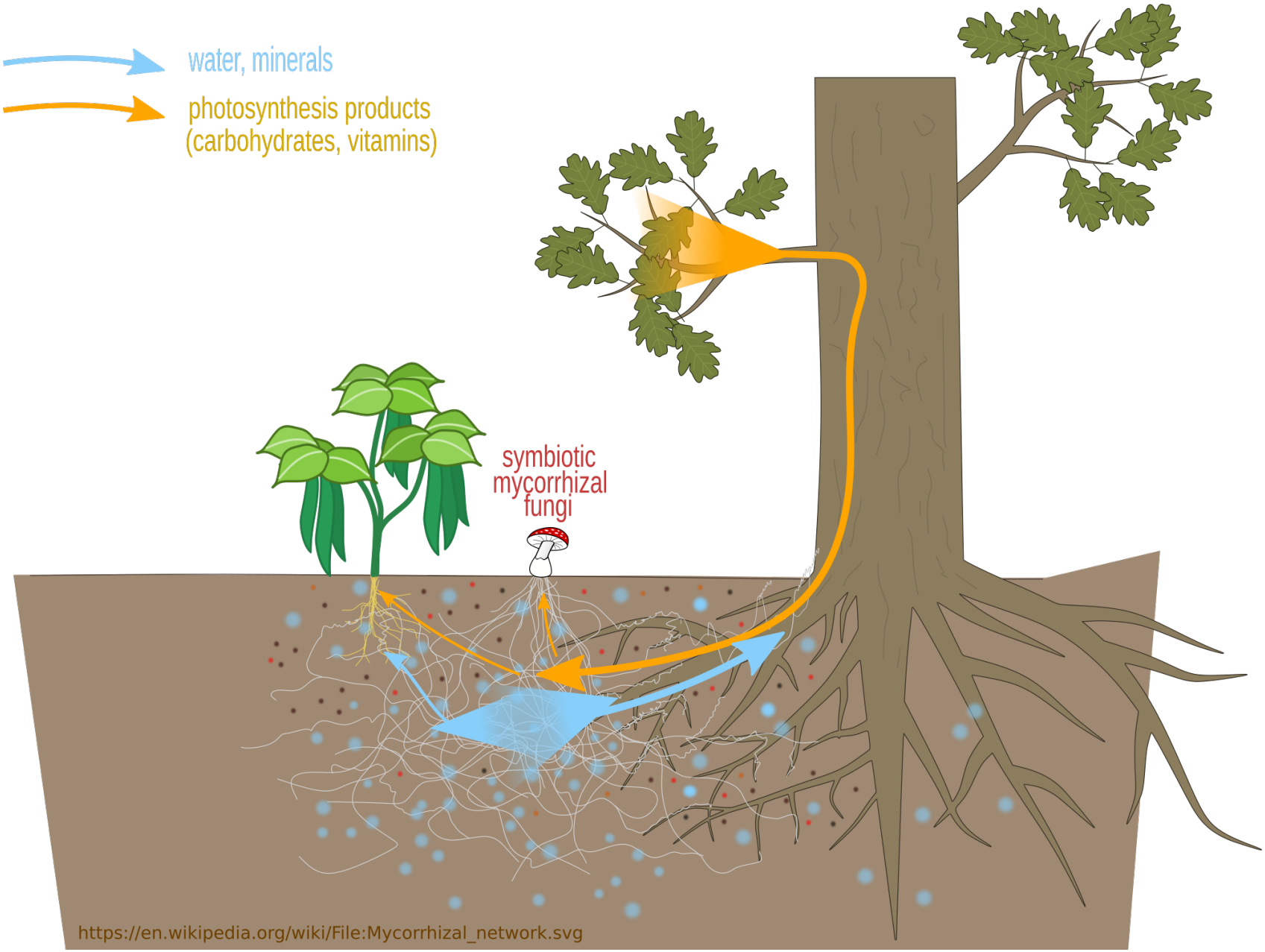
- meta-analyses in ecology and evolutionary biology often contain studies conducted with different species
- these species share an evolutionary history (= phylogeny)
- effects for species that are more similar to each other might also correlate more strongly



1	0.89	0.78							
0.89	1	0.78							
0.78	0.78	1							
			1	0.33	0.33	0.33	0.33	0.33	0.33
			0.33	1	0.78	0.78	0.56	0.56	0.44
			0.33	0.78	1	0.89	0.56	0.56	0.44
			0.33	0.78	0.89	1	0.56	0.56	0.44
			0.33	0.56	0.56	0.56	1	0.89	0.44
			0.33	0.56	0.56	0.56	0.89	1	0.44
			0.33	0.44	0.44	0.44	0.44	0.44	1

Example: Effects of Mycorrhizal Fungi Inoculation

- mycorrhiza are fungi that attach to the root of plants
- typically form a symbiotic relationships with their host (supplying the plant with water and minerals and receiving photosynthesis products in exchange)


water, minerals
photosynthesis products
(carbohydrates, vitamins)
symbiotic
mycorrhizal
fungi
https://en.wikipedia.org/wiki/File:Mycorrhizal_network.svg

Example: Effects of Mycorrhizal Fungi Inoculation

- as a result, plants often show improved growth and resistance to drought, diseases, and insects
- meta-analysis on the effects of inoculating plants with mycorrhizal fungi [20–22]
- focus here on plants inoculated with arbuscular mycorrhizal fungi belonging to one or more fungal genera (359 papers, 2984 effects, 1776 control conditions, 293 plant species)
- growth response in treatment vs. control groups quantified in terms of log transformed ratios of means (response ratios) [23]

Example: Effects of Mycorrhizal Fungi Inoculation

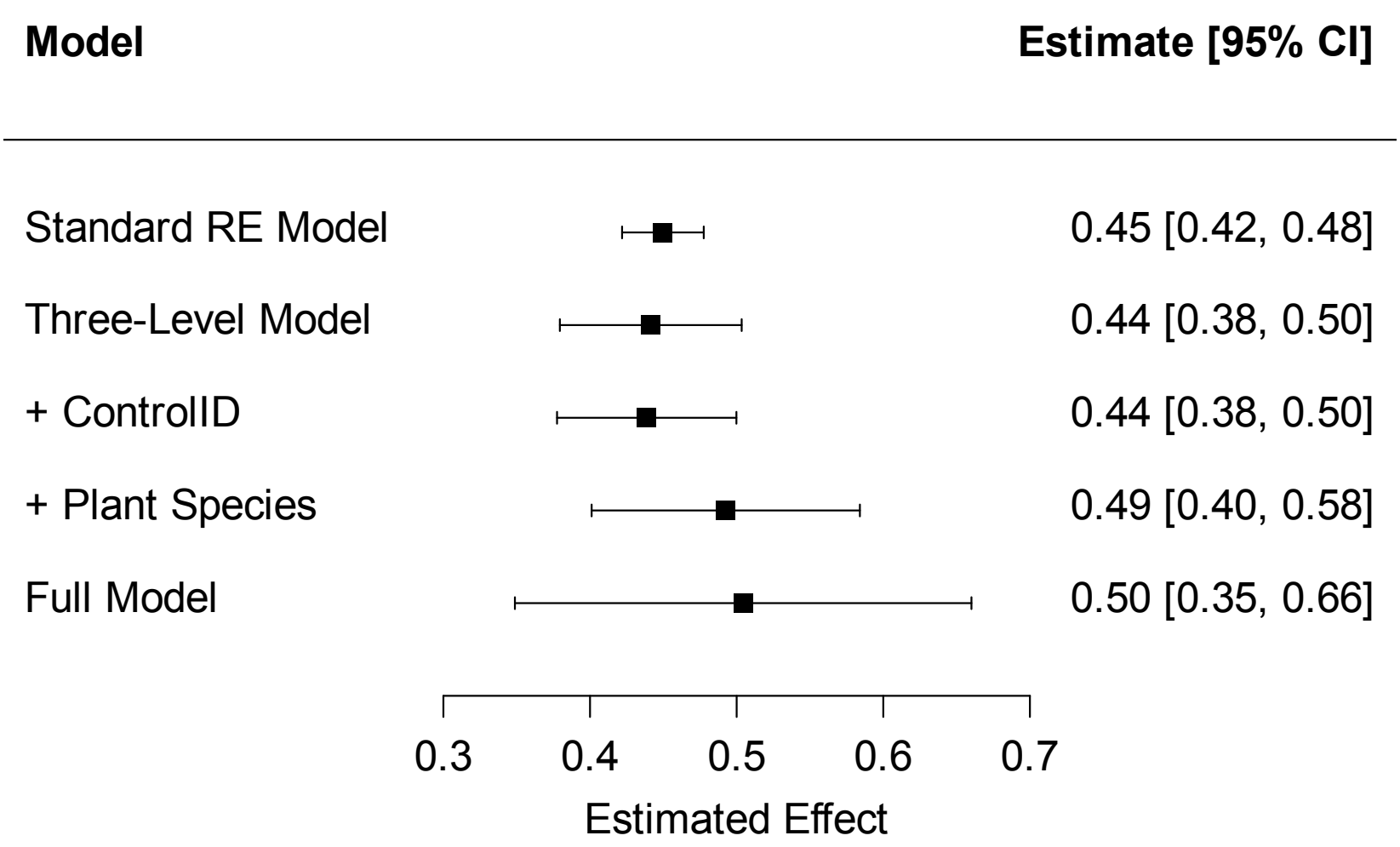
- model includes random effects for papers, control conditions, effect sizes, and plant species without and with its phylogenetic correlation matrix (and the covariance for estimates sharing a control condition)
- plant species are *crossed random effects* (a heightened or reduced response for a species should hold across studies)

```
rma.mv(EffectSize, V, data = dat,
       random = list(~ 1 | PaperID/ControlID/EffectID,
                     ~ 1 | PlantSpecies,
                     ~ 1 | PlantSpecies.phyl),
       R = list(PlantSpecies.phyl=R.PS))
```

Example: Effects of Mycorrhizal Fungi Inoculation

```
## Multivariate Meta-Analysis Model (k = 2984; method: REML)
##
## Variance Components:
##
##             estim    sqrt  nlvls  fixed             factor    R
## sigma^2.1  0.1799  0.4242    359     no            PaperID   no
## sigma^2.2  0.1434  0.3786   1776     no          ControlID   no
## sigma^2.3  0.1224  0.3498   2984     no           EffectID   no
## sigma^2.4  0.1618  0.4023    293     no       PlantSpecies   no
## sigma^2.5  0.1000  0.3162    293     no  PlantSpecies.phyl  yes
##
## Test for Heterogeneity:
## Q(df = 2983) = 66515.4758, p-val < .0001
##
## Model Results:
##
## estimate      se    zval    pval   ci.lb   ci.ub
##   0.5051  0.0791  6.3858  <.0001  0.3501  0.6601
```

Example: Effects of Mycorrhizal Fungi Inoculation



Example: Generation Effect

- meta-analysis on the ‘generation effect’ (= information is better remembered if it is generated from one’s own mind rather than simply read) [24]
- a study might ask participants to recall words that were read vs. words self-generated from word fragments
- studies often report multiple experiments and examine various conditions using a mix of within- and between-subject designs

Example: Generation Effect

Article	Experiment	Sample	Pairing	Condition	Id	Recall
1	1	1	1	read	1	0.31
1	1	2	1	generate	2	0.45
2	1	3	2	read	3	0.45
2	1	3	2	generate	4	0.61
3	1	4	3	read	5	0.61
3	1	4	3	generate	6	0.72
3	1	4	3	generate	7	0.95
4	1	5	4	read	8	0.28
4	1	5	4	generate	9	0.38
4	1	6	5	read	10	0.36
4	1	6	5	generate	11	0.55
...	...	...	...	...	...	...

Example: Generation Effect

- dataset included 126 articles reporting on 310 experiments with 582 samples, yielding 1653 recall estimates for 804 pairings
- model includes random effects for articles, experiments, samples, estimates, and a crossed random effect for pairing
- so a five-level model with an additional crossed random effect

```
rma.mv(Recall, Var, data = dat,
       mods = ~ Condition,
       random = list(~ 1 | article/exp/sample/id,
                     ~ 1 | pairing))
```

Example: Generation Effect

```
## Multivariate Meta-Analysis Model (k = 1653; method: REML)
##
## Variance Components:
##
##             estim    sqrt  nlvls  fixed      factor
## sigma^2.1  0.0219  0.1479    126     no     Article
## sigma^2.2  0.0060  0.0777    310     no  Experiment
## sigma^2.3  0.0000  0.0000    582     no      Sample
## sigma^2.4  0.0064  0.0798   1653     no          Id
## sigma^2.5  0.0165  0.1285    804     no     Pairing
##
## [...]
##
## Model Results:
##
##           estimate      se     zval    pval   ci.lb   ci.ub
## intrcpt     0.4785  0.0157  30.4456  <.0001  0.4477  0.5093
## generate    0.1021  0.0042  24.0422  <.0001  0.0938  0.1104
```

Summary of Considerations

- want to account for potential heterogeneity at each level
- there should be a random effect at the estimate level
- when modeling arm-level outcomes, need to include fixed/random effect for studies (contrasts/pairings)
- when multiple groups are compared against a common comparator, need to account for dependent sampling errors (can avoid this issue by modeling arm-level outcomes)
- when multiple estimates are computed for the same subjects, need to account for dependent sampling errors
- cluster-robust inference methods can be a remedy when we know that the working model is inaccurate

References [1]

1. Viechtbauer, W. (2010). Conducting meta-analyses in R with the metafor package. *Journal of Statistical Software*, *36*(3), 1–48. https://doi.org/10.18637/jss.v036.i03
2. Viechtbauer, W. (2021). Model checking in meta-analysis. In C. H. Schmid, T. Stijnen, & I. R. White (Eds.), *Handbook of meta-analysis* (pp. 219–254). CRC Press. https://doi.org/10.1201/9781315119403
3. Credé, M., Roch, S. G., & Kieszczynka, U. M. (2010). Class attendance in college: A meta-analytic review of the relationship of class attendance with grades and student characteristics. *Review of Educational Research*, *80*(2), 272–295. https://doi.org/10.3102/0034654310362998
4. Konstantopoulos, S. (2011). Fixed effects and variance components estimation in three-level meta-analysis. *Research Synthesis Methods*, *2*(1), 61–76. https://doi.org/10.1002/jrsm.35
5. Gelman, A. (2005). Analysis of variance: Why it is more important than ever. *Annals of Statistics*, *33*(1), 1–53. https://doi.org/10.1214/009053604000001048
6. Bourassa, D. C., McManus, I. C., & Bryden, M. P. (1996). Handedness and eye-dominance: A meta-analysis of their relationship. *Laterality*, *1*(1), 5–34. https://doi.org/10.1080/713754206
7. Houwelingen, H. C. van, Arends, L. R., & Stijnen, T. (2002). Advanced methods in meta-analysis: Multivariate approach and meta-regression. *Statistics in Medicine*, *21*(4), 589–624. https://doi.org/10.1002/sim.1040

References [2]

8. Jackson, D., Law, M., Stijnen, T., Viechtbauer, W., & White, I. R. (2018). A comparison of seven random-effects models for meta-analyses that estimate the summary odds ratio. *Statistics in Medicine*, *37*(7), 1059–1085. https://doi.org/10.1002/sim.7588
9. White, I. R., Turner, R. M., Karahalios, A., & Salanti, G. (2019). A comparison of arm-based and contrast-based models for network meta-analysis. *Statistics in Medicine*, *38*(27), 5197–5213. https://doi.org/10.1002/sim.8360
10. Senn, S. (2000). The many modes of meta. *Drug Information Journal*, *34*, 535–549. https://doi.org/10.1177/009286150003400222
11. Kalaian, H. A., & Raudenbush, S. W. (1996). A multivariate mixed linear model for meta-analysis. *Psychological Methods*, *1*(3), 227–235. https://doi.org/10.1037/1082-989X.1.3.227
12. Berkey, C. S., Hoaglin, D. C., Antczak-Bouckoms, A., Mosteller, F., & Colditz, G. A. (1998). Meta-analysis of multiple outcomes by regression with random effects. *Statistics in Medicine*, *17*(22), 2537–2550. https://doi.org/10.1002/(sici)1097-0258(19981130)17:22%3C2537::aid-sim953%3E3.0.co;2-c
13. Berkey, C. S., Antczak-Bouckoms, A., Hoaglin, D. C., Mosteller, F., & Pihlstrom, B. L. (1995). Multiple-outcomes meta-analysis of treatments for periodontal disease. *Journal of Dental Research*, *74*(4), 1030–1039. https://doi.org/10.1177/00220345950740040201

References [3]

14. Pustejovsky, J. E., & Tipton, E. (2022). Meta-analysis with robust variance estimation: Expanding the range of working models. *Prevention Science*, *23*, 425–438. https://doi.org/10.1007/s11121-021-01246-3
15. Assink, M., & Wibbelink, C. J. M. (2016). Fitting three-level meta-analytic models in R: A step-by-step tutorial. *The Quantitative Methods for Psychology*, *12*(3), 154–174. https://doi.org/10.20982/tqmp.12.3.p154
16. Adams, D. C. (2008). Phylogenetic meta-analysis. *Evolution*, *62*(3), 567–572. https://doi.org/10.1111/j.1558-5646.2007.00314.x
17. Lajeunesse, M. J. (2009). Meta-analysis and the comparative phylogenetic method. *The American Naturalist*, *174*(3), 369–381. https://doi.org/10.1086/603628
18. Nakagawa, S., & Santos, E. S. A. (2012). Methodological issues and advances in biological meta-analysis. *Evolutionary Ecology*, *26*(5), 1253–1274. https://doi.org/10.1007/s10682-012-9555-5
19. Cinar, O., Nakagawa, S., & Viechtbauer, W. (2022). Phylogenetic multilevel meta-analysis: A simulation study on the importance of modelling the phylogeny. *Methods in Ecology and Evolution*, *13*(2), 383–395. https://doi.org/10.1111/2041-210X.13760

References [4]

20. Hoeksema, J. D., Chaudhary, V. B., Gehring, C. A., Johnson, N. C., Karst, J., Koide, R. T., Pringle, A., Zabinski, C., Bever, J. D., Moore, J. C., Wilson, G. W., Klironomos, J. N., & Umbanhowar, J. (2010). A meta-analysis of context-dependency in plant response to inoculation with mycorrhizal fungi. *Ecology Letters*, *13*(3), 394–407. https://doi.org/10.1111/j.1461-0248.2009.01430.x
21. Chaudhary, V. B., Rúa, M. A., Antoninka, A., Bever, J. D., Cannon, J., Craig, A., Duchicela, J., Frame, A., Gardes, M., Gehring, C., Ha, M., Hart, M., Hopkins, J., Ji, B., Collins Johnson, N., Kaonongbua, W., Karst, J., Koide, R. T., Lamit, L. J., … Hoeksema, J. D. (2016). MycoDB, a global database of plant response to mycorrhizal fungi. *Scientific Data*, *3*, 160028. https://doi.org/10.1038/sdata.2016.28
22. Hoeksema, J. D., Bever, J. D., Chakraborty, S., Chaudhary, V. B., Gardes, M., Gehring, C. A., Hart, M. M., Housworth, E. A., Kaonongbua, W., Klironomos, J. N., Lajeunesse, M. J., Meadow, J., Milligan, B. G., Piculell, B. J., Pringle, A., Rúa, M. A., Umbanhowar, J., Viechtbauer, W., Wang, Y.-W., … Zee, P. C. (2018). Evolutionary history of plant hosts and fungal symbionts predicts the strength of mycorrhizal mutualism. *Communications Biology*, *1*(1), 116. https://doi.org/10.1038/s42003-018-0120-9
23. Hedges, L. V., Gurevitch, J., & Curtis, P. S. (1999). The meta-analysis of response ratios in experimental ecology. *Ecology*, *80*(4), 1150–1156. https://doi.org/10.1890/0012-9658(1999)080%5B1150:TMAORR%5D2.0.CO;2

References [5]

24. McCurdy, M. P., Viechtbauer, W., Sklenar, A. M., Frankenstein, A. N., & Leshikar, E. D. (2020). Theories of the generation effect and the impact of generation constraint: A meta-analytic review. *Psychonomic Bulletin & Review*, *27*(6), 1139–1165. https://doi.org/10.3758/s13423-020-01762-3

Thank You for Your Attention!

Questions, Comments, Suggestions?

wolfgang.viechtbauer@maastrichtuniversity.nl

https://www.wvbauer.com

https://www.metafor-project.org

@wviechtb