Current methods for meta-analysis with dependent estimates

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Meta-Analysis

- don't need to explain this to you ...
- *"A method for statistically combining the results of similar studies which are included in a systematic review, to come to a conclusion about the overall effects of an intervention."* (https://www.spi.ox.ac.uk/research-designs)
- next slide please!

The Standard Random-Effects Model

- let y_i denote the observed outcome (e.g., log risk/odds ratio, standardized mean difference, correlation) for the ith study
- let θ_i denote the corresponding true outcome
- approximatly: $y_i = \theta_i + e_i$ where $e_i \sim N(0, \nu_i)$
- assume: $\theta_i = \mu + u_i$ where $u_i \sim N(0, \tau^2)$
- can write this as a single model

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

with the assumptions as stated above

Example: Effectiveness of CBT for Reducing Recidivism

- meta-analysis to examine if cognitive behavioral therapy (CBT) can reduce recidivism rates (Landenberger & Lipsey, 2005)
- extract from each study a table of the form:

	Non-Recidivists	Recidivists	Total
CBT	a_i	b_i	n_{1i}
Control	c_i	d_i	n_{2i}

- compute (log) odds ratio and corresponding variance
- will illustrate methods using the **metafor** package in R (Viechtbauer, 2010)

Example: Effectiveness of CBT for Reducing Recidivism

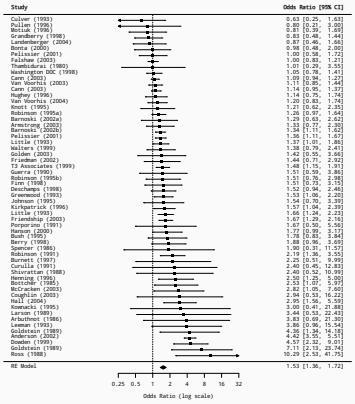
```
# load metafor package
library(metafor)
```

```
# copy dataset to 'dat'
dat <- dat.landenberger2005

# compute log odds ratios and corresponding sampling variances
dat <- escalc(measure="OR", ai=n.cbt.non,  bi=n.cbt.rec,
                            ci=n.ctrl.non, di=n.ctrl.rec, data=dat)

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

# compute average odds ratio (and corresponding 95% CI/PI)
predict(res, transf=exp, digits=2)
```


Example: Effectiveness of CBT for Reducing Recidivism

```
## Random-Effects Model (k = 58; tau^2 estimator: REML)
##
## tau^2 (estimated amount of total heterogeneity): 0.1046 (SE = 0.0352)
## tau (square root of estimated tau^2 value):      0.3234
## I^2 (total heterogeneity / total variability):   70.62%
## H^2 (total variability / sampling variability):  3.40
##
## Test for Heterogeneity:
## Q(df = 57) = 213.6898, p-val < .0001
##
## Model Results:
##
## estimate      se    zval    pval   ci.lb   ci.ub
##   0.4226  0.0605  6.9880  <.0001  0.3041  0.5411

##  pred ci.lb ci.ub pi.lb pi.ub
##  1.53  1.36  1.72  0.80  2.91
```

Example: Effectiveness of CBT for Reducing Recidivism



Independence Assumptions

- for two outcomes, y_i and $y_{i'}$, the model assumes:
  1. independent sampling errors ($\text{Cov}[e_i, e_{i'}] = 0$)
  2. independent true outcomes ($\text{Cov}[\theta_i, \theta_{i'}] = 0$)
- assumption 1. is violated when at least one participant contributes data to the computation of both y_i and $y_{i'}$
  - multiple response variables
  - multiple time points
  - use of a shared control group
- assumption 2. is often violated when y_i and $y_{i'}$ come from the same study (but ultimately this is an empirical question)

How to Deal with Dependencies

- older methods:
  - select outcomes (so that the ones selected are all independent)
  - average outcomes (so that the averages are all independent)
  - conduct separate analyses in independent subsets (for different response variables, time points, treatments, subgroups)
- problems:
  - wastes information
  - averaging often done incorrectly
  - does not allow for comparisons across subsets
  - averaging assumes homogeneity of outcomes being averaged

Example: Gender Differences in Grant and Fellowship Awards

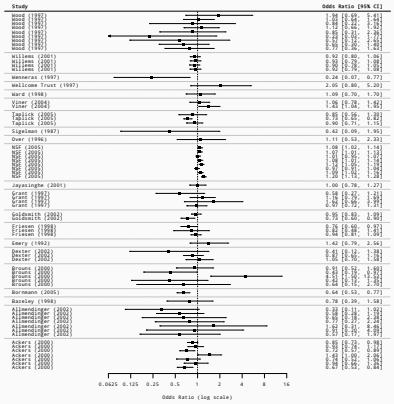
- meta-analysis to examine if the chances of receiving a grant or fellowship differs for men and women (Bornmann et al., 2007)
- extract from each study a table of the form:

	Awarded	Not Awarded	Total
Women	a_i	b_i	n_{1i}
Men	c_i	d_i	n_{2i}

- compute (log) odds ratio and corresponding variance

```
# copy dataset to 'dat'
dat <- dat.bornmann2007

# compute log odds ratios and corresponding sampling variances
dat <- escalc(measure="OR", ai=waward, n1i=wtotal,
                            ci=maward, n2i=mtotal, data=dat)
```


Example: Gender Differences in Grant and Fellowship Awards



Within-Study Averaging

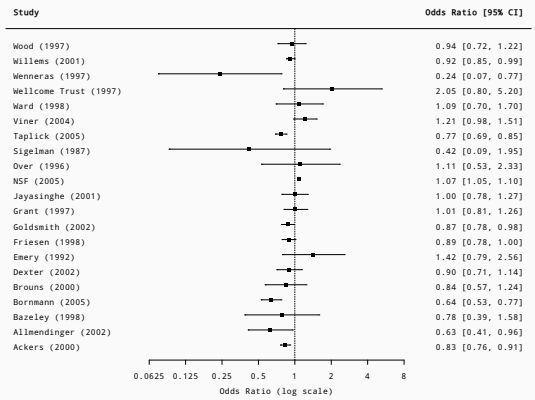
- we want to average y_1 and y_2 with variances ν_1 and ν_2
- assume that the sampling errors are independent
- let $w_1 = 1/\nu_1$ and $w_2 = 1/\nu_2$

$$\bar{y} = \frac{w_1 \times y_1 + w_2 \times y_2}{w_1 + w_2}$$

- $\text{Var}[\bar{y}] = 1/(w_1 + w_2)$

```
# within-study averaging assuming independent sampling errors
agg <- aggregate(dat, cluster=dat$study, struct="ID")

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

# compute average odds ratio (and corresponding 95% CI/PI)
predict(res, transf=exp, digits=2)
```

Example: Gender Differences in Grant and Fellowship Awards



Example: Gender Differences in Grant and Fellowship Awards

```
## Random-Effects Model (k = 21; tau^2 estimator: REML)
##
## tau^2 (estimated amount of total heterogeneity): 0.0191 (SE = 0.0105)
## tau (square root of estimated tau^2 value):      0.1384
## I^2 (total heterogeneity / total variability):   81.30%
## H^2 (total variability / sampling variability):  5.35
##
## Test for Heterogeneity:
## Q(df = 20) = 138.1045, p-val < .0001
##
## Model Results:
##
## estimate      se     zval    pval    ci.lb    ci.ub
##  -0.1028  0.0429  -2.3946  0.0166  -0.1869  -0.0187

##  pred ci.lb ci.ub pi.lb pi.ub
##  0.90  0.83  0.98  0.68  1.20
```


The Multilevel Meta-Analytic Model

- let y_{ij} denote the jth observed outcome for the ith study
- expand the standard random-effects model by adding random effects at both levels

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

where $u_i \sim N(0, \sigma_1^2)$, $u_{ij} \sim N(0, \sigma_2^2)$, $e_{ij} \sim N(0, \nu_{ij})$

- model implies

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

for the true outcomes within studies

Example: Gender Differences in Grant and Fellowship Awards

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

```
## Multivariate Meta-Analysis Model (k = 66; method: REML)
##
## Variance Components:
##
##             estim    sqrt  nlvls  fixed     factor
## sigma^2.1  0.0161  0.1268     21     no      study
## sigma^2.2  0.0038  0.0613     66     no  study/obs
##
## Model Results:
##
## estimate      se     zval    pval    ci.lb    ci.ub
##  -0.1010  0.0417  -2.4196  0.0155  -0.1828  -0.0192
```

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

```
## [1] 0.81
```


Assuming Homogeneity Within Studies

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

```
## Multivariate Meta-Analysis Model (k = 66; method: REML)
##
## Variance Components:
##
##             estim    sqrt  nlvls  fixed  factor
## sigma^2    0.0191  0.1384     21     no   study
##
## Model Results:
##
## estimate      se     zval    pval    ci.lb    ci.ub
##  -0.1028  0.0429  -2.3946  0.0166  -0.1869  -0.0187
```


Assuming Homogeneity Within Studies

- within-study averaging (as described earlier) assumes that the true outcomes within studies are homogeneous
- often not an acceptable assumption
- can do a likelihood ratio test to examine this

```
res0 <- rma.mv(yi, vi, random = ~ 1 | study, data=dat)
res1 <- rma.mv(yi, vi, random = ~ 1 | study/obs, data=dat)
anova(res0, res1)
```

```
##          df     AIC     BIC    AICc   logLik     LRT   pval       QE
## Full      3 32.1678 38.6910 32.5612 -13.0839                 221.2850
## Reduced   2 42.8291 47.1778 43.0226 -19.4145 12.6613 0.0004 221.2850
```

Multivariate Meta-Analysis

- when multiple outcomes are computed for the same subjects, the sampling errors cannot be assumed to be independent
- the underlying true outcomes might also be correlated
- need to construct matrix with the sampling variances and covariances of each study
- let y_{ij} denote the jth observed outcome for the ith study

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

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

Surgical vs Non-Surgical Treatment for Periodontal Disease

- meta-analysis on the effectiveness of surgical vs non-surgical treatment for periodontal disease (Berkey et al., 1998)
- included 5 trials that each measured two outcomes (probing depth and attachment level)

Surgical vs Non-Surgical Treatment for Periodontal Disease

```
# copy data into 'dat' and examine data
dat <- dat.berkey1998
dat
```

```
##    trial           author year ni outcome      yi     vi    v1i    v2i
## 1      1 Pihlstrom et al. 1983 14      PD  0.4700 0.0075 0.0075 0.0030
## 2      1 Pihlstrom et al. 1983 14      AL -0.3200 0.0077 0.0030 0.0077
## 3      2    Lindhe et al. 1982 15      PD  0.2000 0.0057 0.0057 0.0009
## 4      2    Lindhe et al. 1982 15      AL -0.6000 0.0008 0.0009 0.0008
## 5      3   Knowles et al. 1979 78      PD  0.4000 0.0021 0.0021 0.0007
## 6      3   Knowles et al. 1979 78      AL -0.1200 0.0014 0.0007 0.0014
## 7      4  Ramfjord et al. 1987 89      PD  0.2600 0.0029 0.0029 0.0009
## 8      4  Ramfjord et al. 1987 89      AL -0.3100 0.0015 0.0009 0.0015
## 9      5    Becker et al. 1988 16      PD  0.5600 0.0148 0.0148 0.0072
## 10     5    Becker et al. 1988 16      AL -0.3900 0.0304 0.0072 0.0304
```


Surgical vs Non-Surgical Treatment for Periodontal Disease

```
# construct the variance-covariance matrices of the observed outcomes
V <- lapply(split(dat[c("v1i", "v2i")], dat$trial), as.matrix)
V <- bldiag(V)
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 multivariate model
res <- rma.mv(yi, V, mods = ~ outcome - 1, data = dat,
              random = ~ outcome | trial, struct = "UN")
res
```


Surgical vs Non-Surgical 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  0.6088     -  no
## PD  0.6088       1     5   -
##
## 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
```


Surgical vs Non-Surgical Treatment for Periodontal Disease

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

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

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

```
## Hypothesis:
## 1: outcomeAL - outcomePD = 0
##
## Results:
##    estimate     se    zval    pval
## 1:  -0.6926 0.0744 -9.3120 <.0001
##
## Test of Hypothesis:
## QM(df = 1) = 86.7139, p-val < .0001
```

Surgical vs Non-Surgical Treatment for Periodontal Disease

```
res.AL <- rma(yi, vi, data=dat, subset=outcome=="AL")
res.AL
```

```
## Random-Effects Model (k = 5; tau^2 estimator: REML)
##
## tau^2 (estimated amount of total heterogeneity): 0.0331 (SE = 0.0275)
##
## estimate      se     zval    pval    ci.lb    ci.ub
##  -0.3457  0.0885  -3.9058  <.0001  -0.5191  -0.1722
```

```
res.PD <- rma(yi, vi, data=dat, subset=outcome=="PD")
res.PD
```

```
## Random-Effects Model (k = 5; tau^2 estimator: REML)
##
## tau^2 (estimated amount of total heterogeneity): 0.0119 (SE = 0.0123)
##
## estimate      se    zval    pval   ci.lb   ci.ub
##   0.3606  0.0592  6.0905  <.0001  0.2445  0.4766
```


Constructing the V matrix

- computation of the covariances is difficult and requires information often not reported in articles
- equations can be found in Gleser & Olkin (2009), Wei & Higgins (2013), Steiger (1980), ...
- some alternative methods
  1. fit multilevel model ignoring the covariances (Moeyaert et al., 2017; Van den Noortgate et al., 2013, 2015)
  2. use cluster-robust inference methods (Hedges et al., 2010; Tipton, 2015)
  3. approximate the V matrix + sensitivity analyses
  4. combine approaches 2. and 3. (Pustejovsky & Tipton, 2021)

Association between Recidivism and Mental Health

- meta-analysis on the difference in recidivism between delinquent juveniles with vs without a mental health disorder (Assink & Wibbelink, 2016)
- results of studies are expressed in terms of standardized mean differences, with positive values indicating a higher prevalence of recidivism in the group with a mental health disorder

Association between Recidivism and Mental Health

```
# copy data into 'dat' and examine first 10 rows
dat <- dat.assink2016
head(dat, 10)
```

```
##    study esid id      yi     vi pubstatus year deltype
## 1      1    1  1  0.9066 0.0740         1  4.5 general
## 2      1    2  2  0.4295 0.0398         1  4.5 general
## 3      1    3  3  0.2679 0.0481         1  4.5 general
## 4      1    4  4  0.2078 0.0239         1  4.5 general
## 5      1    5  5  0.0526 0.0331         1  4.5 general
## 6      1    6  6 -0.0507 0.0886         1  4.5 general
## 7      2    1  7  0.5117 0.0115         1  1.5 general
## 8      2    2  8  0.4738 0.0076         1  1.5 general
## 9      2    3  9  0.3544 0.0065         1  1.5 general
## 10     3    1 10  2.2844 0.3325         1 -8.5 general
```


Association between Recidivism and Mental Health

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

```
## Multivariate Meta-Analysis Model (k = 100; method: REML)
##
## Variance Components:
##
##             estim    sqrt  nlvls  fixed      factor
## sigma^2.1  0.1879  0.4334     17     no       study
## sigma^2.2  0.1120  0.3347    100     no  study/esid
##
## Test for Heterogeneity:
## Q(df = 99) = 809.4611, p-val < .0001
##
## Model Results:
##
## estimate      se    zval    pval   ci.lb   ci.ub
##   0.4268  0.1184  3.6038  0.0003  0.1947  0.6589
```


Association between Recidivism and Mental Health

```
# use cluster-robust inference methods
robust(res, cluster=dat$study)
```

```
## Number of outcomes:   100
## Number of clusters:   17
## Outcomes per cluster: 1-22 (mean: 5.88, median: 5)
##
## Model Results:
##
## estimate      se    tval  df    pval   ci.lb   ci.ub
##   0.4268  0.1183  3.6076  16  0.0024  0.1760  0.6776
```

```
library(clubSandwich)
coef_test(res, vcov="CR2", cluster=dat$study)
```

```
##     Coef. Estimate    SE t-stat d.f. p-val (Satt) Sig.
## 1 intrcpt    0.427 0.119    3.6 15.4      0.00253   **
```

Association between Recidivism and Mental Health

```
# construct approx V matrix assuming r=0.6 for the sampling errors
V <- impute_covariance_matrix(dat$vi, cluster=dat$study, r=0.6)
```

```
##        1      2      3      4      5      6      7      8      9    ...
## 1 0.0740 0.0326 0.0358 0.0252 0.0297 0.0486    ...    ...    ...    ...
## 2 0.0326 0.0398 0.0263 0.0185 0.0218 0.0356    ...    ...    ...    ...
## 3 0.0358 0.0263 0.0481 0.0203 0.0239 0.0392    ...    ...    ...    ...
## 4 0.0252 0.0185 0.0203 0.0239 0.0169 0.0276    ...    ...    ...    ...
## 5 0.0297 0.0218 0.0239 0.0169 0.0331 0.0325    ...    ...    ...    ...
## 6 0.0486 0.0356 0.0392 0.0276 0.0325 0.0886    ...    ...    ...    ...
## 7    ...    ...    ...    ...    ...    ... 0.0115 0.0056 0.0052    ...
## 8    ...    ...    ...    ...    ...    ... 0.0056 0.0076 0.0042    ...
## 9    ...    ...    ...    ...    ...    ... 0.0052 0.0042 0.0065    ...
## .    ...    ...    ...    ...    ...    ...    ...    ...    ...    ...
```


Association between Recidivism and Mental Health

```
# fit multivariate model
res <- rma.mv(yi, V, random = ~ factor(esid) | study, data=dat)
res
```

```
## Multivariate Meta-Analysis Model (k = 100; method: REML)
##
## Variance Components:
##
## outer factor: study        (nlvls = 17)
## inner factor: factor(esid) (nlvls = 22)
##
##             estim    sqrt  fixed
## tau^2      0.2353  0.4851     no
## rho        0.3431             no
##
## Model Results:
##
## estimate      se    zval    pval   ci.lb   ci.ub
##   0.3678  0.0965  3.8097  0.0001  0.1786  0.5570
```


Association between Recidivism and Mental Health

```
# use cluster-robust inference methods
robust(res, cluster=dat$study)
```

```
## Number of outcomes:   100
## Number of clusters:   17
## Outcomes per cluster: 1-22 (mean: 5.88, median: 5)
##
## Model Results:
##
## estimate      se    tval  df    pval   ci.lb   ci.ub
##   0.3678  0.0962  3.8210  16  0.0015  0.1637  0.5718
```

```
coef_test(res, vcov="CR2", cluster=dat$study)
```

```
##     Coef. Estimate    SE t-stat d.f. p-val (Satt) Sig.
## 1 intrcpt    0.368 0.097   3.79 14.5      0.00186   **
```


Conclusions

- no longer need to rely on selecting/averaging outcomes
- subsetting limits comparative analyses / reduces efficiency
- multilevel/multivariate analyses are the gold standard
- when calculation of covariances is difficult, can use an approximate V matrix followed by cluster-robust inference methods

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