Meta-analysis

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Overview

- What is meta-analysis?
- When can/should I use meta-analysis?
- What are the steps in meta-analysis?
- Meta-analysis in R
- Pitfalls and limitations of meta-analysis

Suggested reading:

Viechtbauer, W. (2010). Conducting meta-analyses in R with the metafor package. Journal of Statistical Software, 36(3), 1–48. Available at: https://www.jstatsoft.org/article/view/v036i03

What is meta-analysis?

- A meta-analysis = systematic review with quantitative analysis of the extracted data:
    - *Single summary of the effect*
    - *Heterogeneity of effects*
    - *How effects differ depending on features of primary studies*
    - *Whether studies with more favourable findings are more likely to be published (‘publication bias’)*

When can/should I use meta-analysis?

- Best for well-defined and relatively narrow research questions e.g., a group difference, intervention effect, or association between two variables
- Primary studies must be quantitative
- Technically requires only two studies but greatest value when there are enough studies to conduct moderator analysis

Steps in meta-analysis

- Specify research question, search, and eligibility criteria
- Systematic search
- Assess against inclusion/exclusion criteria
- Quality assessment and **data extraction**
- **Data analysis**
    - ***Calculate/convert effect sizes***
    - ***Meta-analytic model(s)***
        - **Pooled effect size estimate**
        - **Heterogeneity**
        - **Meta-regression**
    - ***Assess publication bias***

Data extraction - effect sizes

- Need to extract **effect size** measure and associated sampling variance
- Effect sizes = standardised metric to facilitate comparisons across studies
- Appropriate effect size measure depends on study designs
- Examples:
  - ***Odds ratio, relative risk ratio, risk difference*** *for 2x2 data (e.g., two groups with binary outcome)*
  - ***Standardised mean difference*** *for comparing two groups on continous outcome (e.g., sex differences in neuroticism)*
  - *Raw and transformed* ***correlation coefficient*** *for assessing strength of association*
  - ***Proportion*** *(e.g., for prevalence studies)*

Data extraction - additional study information

- Also extract/derive other study information for descriptive purposes and/or moderator analysis
  - *Study year*
  - *Quality*
  - *Lab of origin*
  - *Type of intervention*
  - *Study design features*

Fitting the meta-analysis model

- Calculated using either a **fixed-effect** or **random-effects** model
- Weighted estimation can be used to up-weight studies with greater precision (lower SEs/bigger sample size)
- Effect sizes can be regressed on predictors to estimate moderator effects

Choosing a fixed-effect versus random-effects model

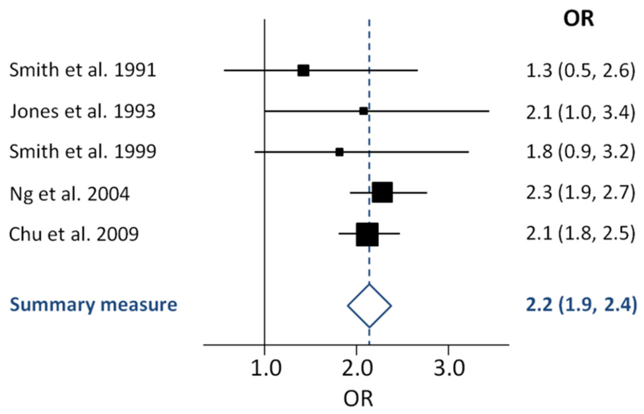
- Fixed-effect model assumes all studies estimate a common effect
  - *Variation in effect sizes assumed to be due only to sampling variation*
- Random-effects model assumes that the sampled studies come from a broader population of studies varying in true effect
  - *Variation due to true variation in effect sizes* τ^2 *AND sampling variation*
- Common misconception that you should examine heterogeneity and choose random effects if high heterogeneity
- Choice between fixed or random should be made *a priori*, not based on estimated heterogeneity
  - *Choose fixed-effect model if you believe all studies estimate the same true effect size*
  - *Choose random-effects model if you believe there are a range of true effect sizes estimated by your studies*

Results from meta-analytic models

- **Pooled effect size estimate** provides estimate of true effect (or average true effect for random-effects meta-analysis)
- I^2 = % of variation between studies
  - *Bigger I^2 means greater heterogeneity*
- β **coefficients** and associated p-values estimate effect and significance of moderators

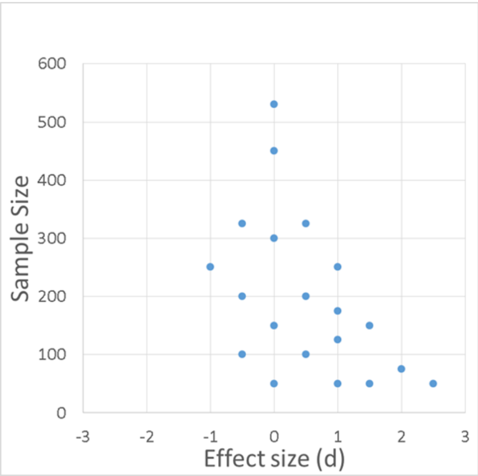
Plotting meta-analytic results

- Forest plots used to display meta-analytic results



Publication bias

- Funnel plots can be used to help identify publication bias
- x-axis is effect size, y-axis is N, SE, or sampling variance
- Should be symmetrical with greater variation in effect sizes for smaller Ns (larger SEs) i.e. funnel-shaped
- Publication bias indicated if there is asymmetry (studies missing from small N-small effect size quadrant)



Statistical methods to assess publication bias

- Statistical tests of the relation between effect size and precision also possible
  - *Egger test (regression-based method)*
  - *Rank correlation test*
- Trim and fill method
  - *Estimates the number of 'missing' studies due to publication bias*
  - *Estimates what the pooled effect size would be were they not missing*

Meta-analysis in R

- Several software options but best option in R is metafor package
- Functions for:
  - *calculating effect sizes*
  - *Fitting meta-analytic models (including moderators)*
  - *Plotting results*
  - *Statistically assessing publication bias*

Example: the effectiveness of BCG vaccination against tuberculosis

```
library(metafor)
data("dat.bcg", package="metafor")
print(dat.bcg)
```

```
##    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
```

- 13 primary studies
- In each study two groups (treated vs control) with a binary outcome (tested positive vs negative for TB)
  - *We can use OR, RR, RD as our effect size measure*
- Additional information about study design and latitude of study

Calculate effect sizes

- We can calculate the effect sizes and associated sampling variation using escalc() function
- We supply the Ns in each of the four cells of the 2-by-2 table:

	TB+	TB-
Treated	ai	bi
Control	ci	di

```
dat.bcg<-escalc(measure="OR", ai=tpos, bi=tneg, ci=cpos, di=cneg, data=dat.bcg, append=T)
head(dat.bcg)
```

```
##   trial               author year tpos  tneg cpos  cneg ablat     alloc      yi
## 1     1              Aronson 1948    4   119   11   128    44    random -0.9387
## 2     2     Ferguson & Simes 1949    6   300   29   274    55    random -1.6662
## 3     3      Rosenthal et al 1960    3   228   11   209    42    random -1.3863
## 4     4    Hart & Sutherland 1977   62 13536  248 12619    52    random -1.4564
## 5     5 Frimodt-Moller et al 1973   33  5036   47  5761    13 alternate -0.2191
## 6     6      Stein & Aronson 1953  180  1361  372  1079    44 alternate -0.9581
##       vi
## 1 0.3571
## 2 0.2081
## 3 0.4334
## 4 0.0203
## 5 0.0520
## 6 0.0099
```

Fit random-effects model

- We can fit a random-effects model using the rma() function, supplying the newly calculated ORs and sampling variance:

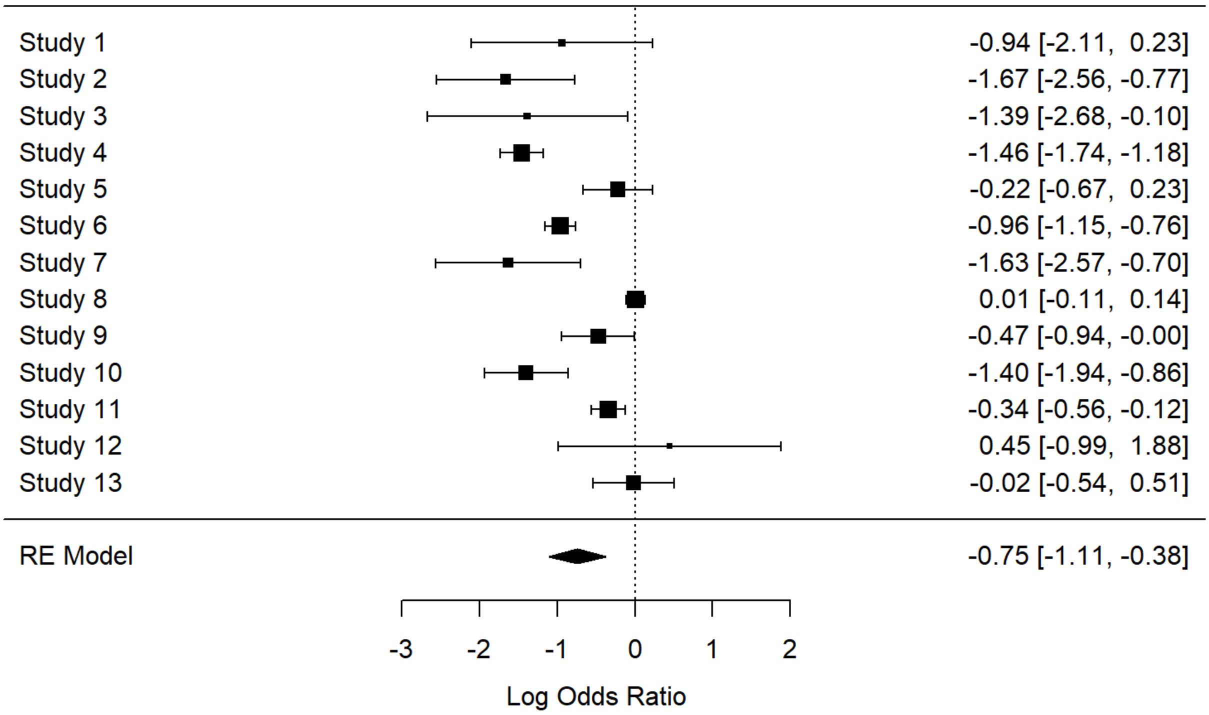
```
rEffs<-rma(yi=yi, vi=vi, data=dat.bcg) #yi is the effect size measures, vi is their sampling variance
rEffs  #NB will use log OR
```

```
##
## 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  ***
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

- Significant pooled effect [exponentiate coefficients using exp() to convert to ORs]
- Substantial heterogeneity

Visualise using forest plot

```
forest(rEffs)
```



Include moderators in model

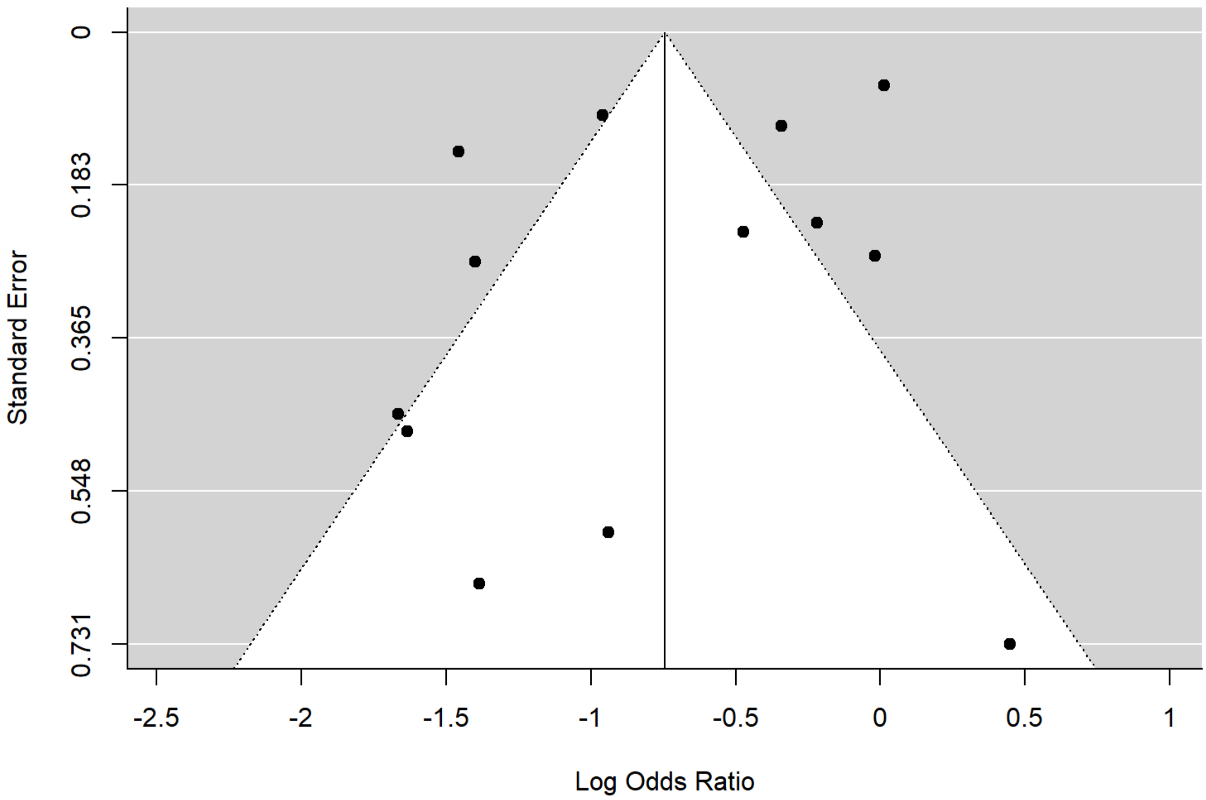
```
mEffs<- rma(yi=yi, vi=vi, mods= ~ablat+year, data=dat.bcg) #ablot and year are moderators; specified
  lm()-style
mEffs
```

```
##
## Mixed-Effects Model (k = 13; tau^2 estimator: REML)
##
## tau^2 (estimated amount of residual heterogeneity):     0.0913 (SE = 0.0745)
## tau (square root of estimated tau^2 value):             0.3022
## I^2 (residual heterogeneity / unaccounted variability): 67.29%
## H^2 (unaccounted variability / sampling variability):   3.06
## R^2 (amount of heterogeneity accounted for):            72.96%
##
## Test for Residual Heterogeneity:
## QE(df = 10) = 25.0121, p-val = 0.0053
##
## Test of Moderators (coefficients 2:3):
## QM(df = 2) = 16.2533, p-val = 0.0003
##
## Model Results:
##
##          estimate       se     zval    pval     ci.lb    ci.ub
## intrcpt  -10.5347  27.3739  -0.3848  0.7004  -64.1865  43.1172
## ablat     -0.0288   0.0095  -3.0311  0.0024   -0.0475  -0.0102  **
## year       0.0055   0.0138   0.3949  0.6929   -0.0216   0.0325
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

- Sig effect of latitute
- No sig effect of study year

Examine publication bias

```
funnel(rEffs)
```



Statistical evaluation of publication bias

```r
regtest(rEffs, model='lm')  #regress effect sizes on standard error
```

```
##
## Regression Test for Funnel Plot Asymmetry
##
## model:     weighted regression with multiplicative dispersion
## predictor: standard error
##
## test for funnel plot asymmetry: t = -1.5070, df = 11, p = 0.1600
```

- regtest() tells us no significant relation between standard error and effect size

Trim and fill method

```r
trimfill(rEffs)  #trim & fill method
```

```
##
## Estimated number of missing studies on the right side: 0 (SE = 2.3309)
##
## 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  ***
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

- Trim and fill method suggests that accounting for publication bias would not make result non-significant

Pitfalls and limitations

- Garbage in, garbage out
- Typically able to include fewer studies than a systematic review
- Comparing apples and oranges
- File-drawer problem
- Subjectivity
- Structured/mechanical approach does not lend itself well to all research questions

Summary

- Meta-analysis provides quantitative summary across multiple studies
- Can give greater weight to more precise studies
- Can answer questions that individual studies can't
  - *Presence of publication bias*
  - *Sources of heterogeneity*
- Doesn't solve problem of poor primary study quality/publication bias etc.