STA 404: Clinical Biostatistics

Fall Semester 2018

University of Zurich

All Course Material on OLAT

Leonhard Held

Lecture 14: Meta-Analysis

Systematic Review

Meta-Analysis

- Fixed Effect Model
- Test for Homogeneity
- Random Effects Model
- Cumulative Meta-Analysis

Publication Bias

- Funnel Plot
- The Trim and Fill Method
- Tests for Funnel Plot Asymmetry

Network Meta-Analysis

- Introduction
- Inconsistency and Node-Splitting

Systematic Review

- Analyse the results from a number of clinical studies on the same problem and integrate findings:
  - Review systematically the available evidence
  - Provide quantitative summaries of the results from each study
  - Combine these results across studies, if appropriate
  - Provide overall interpretation

$\rightarrow$ Evidence-based medicine

- The studies entering a systematic review should be sufficiently homogeneous regarding in- and exclusion criteria and should use the same measure of treatment effect.
- Pre-registration of systematic reviews on www.crd.york.ac.uk/prospero

Measures of Treatment Effect

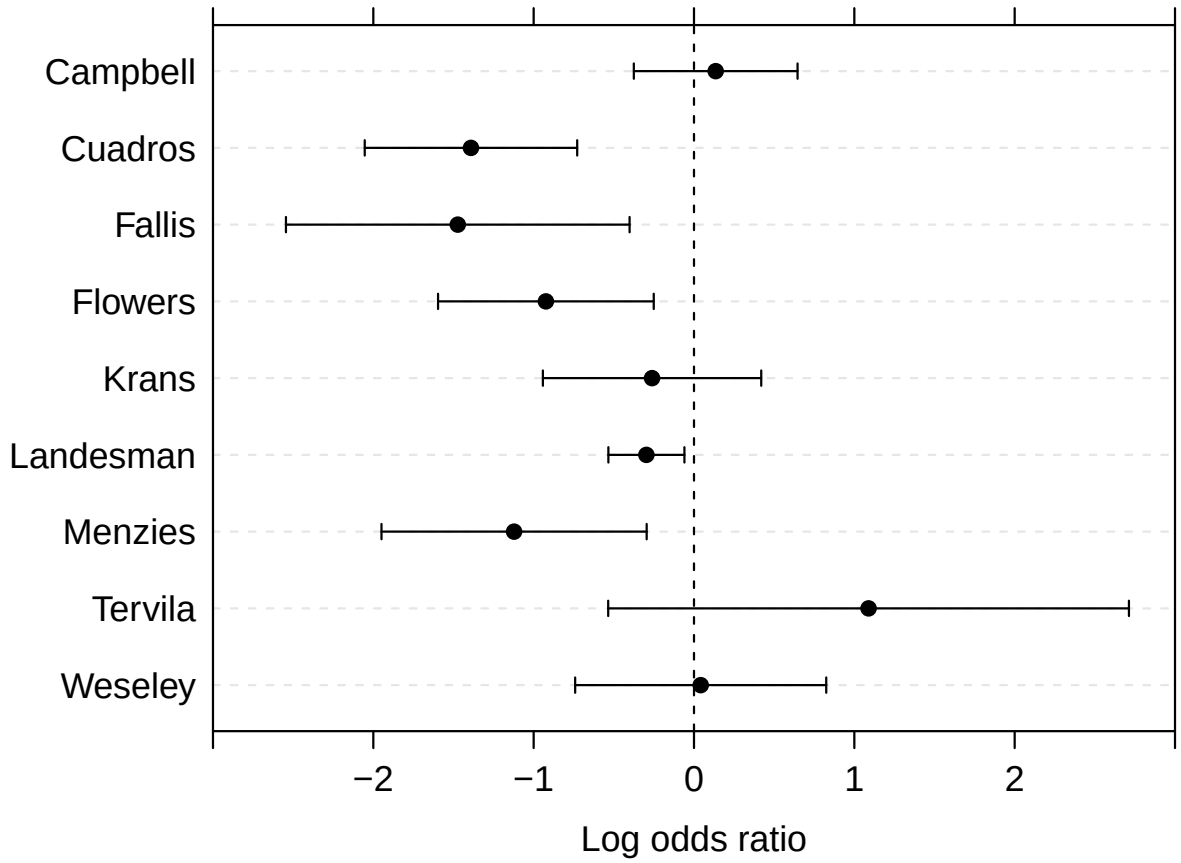
- For continuous outcomes
  - Mean difference θ between treatment groups
- For binary/event outcomes relative treatment effects are preferred:
  - Relative risk RR
  - Odds ratio OR
  - Hazard ratio HR
- These are usually considered on a log-scale:
  $\theta = \log(\text{RR})$, $\theta = \log(\text{OR})$, $\theta = \log(\text{HR})$

Example: Treatment of Preeclampsia with Diuretica

Nine placebo-controlled RCTs

```
##       study diur_pre diur_tot plac_pre plac_tot oddsRatio
## 1   Weseley       14      131       14      136      1.04
## 2   Flowers       21      385       17      134      0.40
## 3   Menzies       14       57       24       48      0.33
## 4    Fallis        6       38       18       40      0.23
## 5   Cuadros       12     1011       35      760      0.25
## 6 Landesman      138     1370      175     1336      0.74
## 7     Krans       15      506       20      524      0.77
## 8   Tervila        6      108        2      103      2.97
## 9  Campbell       65      153       40      102      1.14
```

Graphical Summary with 95% CIs



Fixed Effect Model

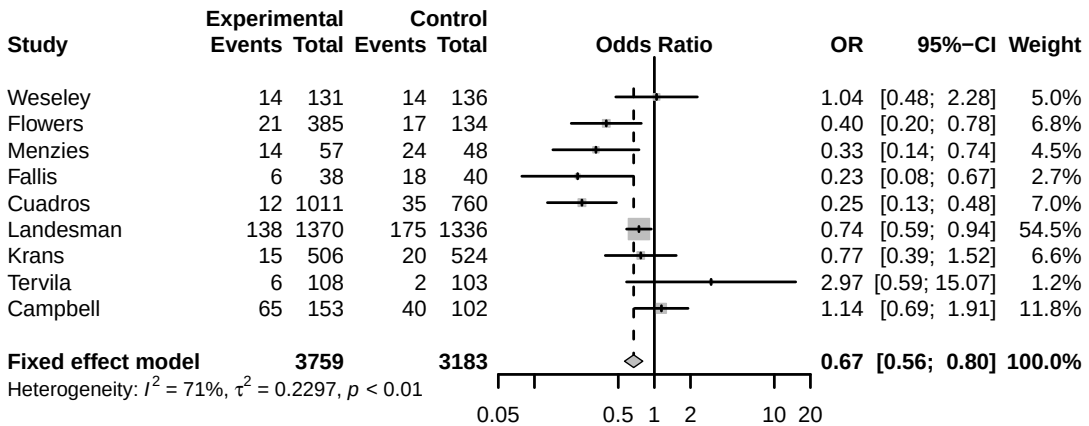
- Notation:
  - $i = 1, \ldots, n$ trials
  - $\hat{\theta}_i$: estimated treatment effect (*e. g.* log odds ratio)
  - $v_i = \text{se}(\hat{\theta}_i)^2$: variance of $\hat{\theta}_i$
  - $w_i = 1/v_i$: precision of $\hat{\theta}_i$
- The estimate of the overall treatment effect θ is a weighted average of the study-specific estimates:

$$\hat{\theta} = \frac{\sum w_i \hat{\theta}_i}{\sum w_i} \text{ with } \text{se}(\hat{\theta}) = 1/\sqrt{\sum w_i}.$$

$\rightarrow$ Confidence interval and a p-value for H_0: $\theta = 0$.

Fixed Effect Model and Forest Plot

```
library(meta)
meta1 <- metabin(event.e = diur_pre, n.e = diur_tot,
                 event.c = plac_pre, n.c = plac_tot, data=pree,
                 sm = "OR", method = "Inverse", studlab = study)
forest(meta1, comb.fixed=T, comb.random=FALSE, xlim=c(0.05, 20),
       scale.square=1.5, cex.lab=1.5, cex.comb=1.5, lwd = 2)
```



Test for Homogeneity

- Cochran's Q test: Under the homogeneity assumption, we have

$$Q = \sum_{i=1}^{n} w_i(\hat{\theta}_i - \hat{\theta})^2 \underset{H_0}{\sim} \chi^2_{n-1}$$

- For the preeclampsia data, this test yields $Q = 27.3$ at $n - 1 = 8$ degrees of freedom ($p = 0.0006$, `metabin` reports "$p < 0.01$").

$\rightarrow$ Strong evidence for heterogeneity between studies.

- Higgins's I^2 test statistic (here 71%) represents the proportion of variation between the sample estimates that is due to heterogeneity rather than to sampling error.

Random Effects Model

– Now assume that the individual study effects θ_i come from a normal distribution with mean θ and heterogeneity variance τ^2:

$$\hat{\theta}_i \,|\, \theta_i \sim \mathrm{N}(\theta_i, v_i) \quad \text{and} \quad \theta_i \sim \mathrm{N}(\theta, \tau^2),$$

so marginally $\hat{\theta}_i \sim \mathrm{N}(\theta, v_i + \tau^2)$.

– The estimate of the overall treatment effect θ is now a weighted average of the study-specific estimates with different weights:

$$\hat{\theta} = \frac{\sum w_i \hat{\theta}_i}{\sum w_i}, \text{ where } w_i = \frac{1}{v_i + \tau^2}.$$

→ Small studies obtain more weight, large studies obtain less weight than in the fixed effect model.

→ $\mathrm{se}(\hat{\theta}) = 1/\sqrt{\sum w_i}$ can be used to calculate confidence intervals and a p-value.

Heterogeneity Variance Estimates

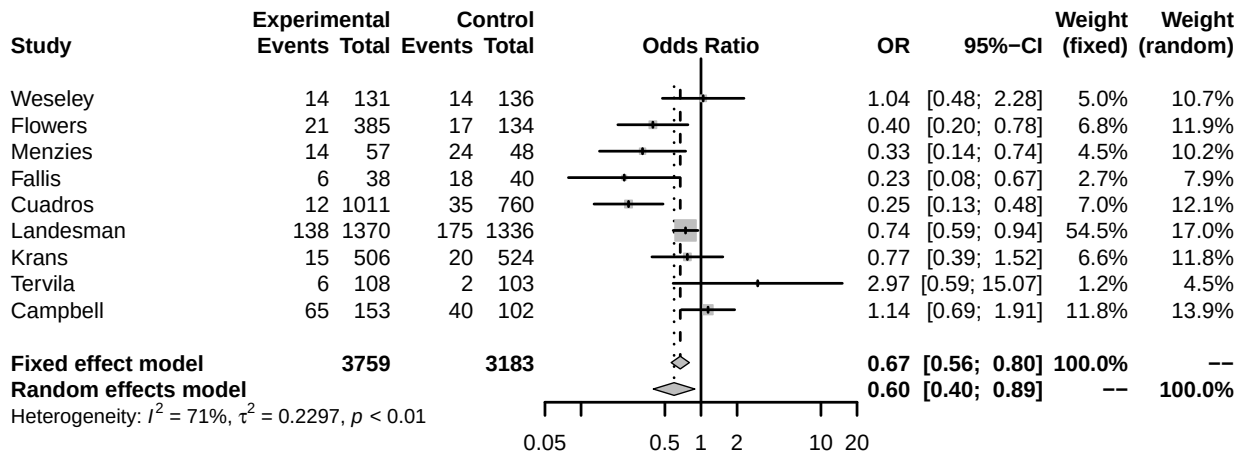
- Moment estimator

$$\tau^2 = \max\left\{0, \frac{Q-(n-1)}{\sum w_i - \sum w_i^2 / \sum w_i}\right\}$$

- Alternatively one may use a profile likelihood estimator.
- For the preeclampsia data we obtain $\tau^2 = 0.23$.

Presentation as Forest Plot

```
forest(meta1, comb.fixed=T, comb.random=T, xlim=c(0.05, 20),
       scale.square=1.5, cex.lab=1.5, cex.comb=1.5, lwd = 2)
```



Cumulative Meta-Analysis

- A cumulative meta-analysis plot shows how evidence has accumulated over time.
- The i-th line in a cumulative meta-analysis plot is the summary produced by a meta-analysis of the first i trials.

$\rightarrow$ Cumulative meta-analysis has traditionally been used to show shifts in the cumulative weight of evidence over time.

Efficacy of Antiseptic-Impregnated Central Venous Catheters in Preventing Catheter-Related Bloodstream Infection

A Meta-analysis

David L. Veenstra, PharmD, PhD
Sanjay Saint, MD, MPH
Somnath Saha, MD, MPH
Thomas Lumley, PhD
Sean D. Sullivan, PhD

Context Central venous catheters impregnated with chlorhexidine and silver sulfadiazine have recently been introduced for the prevention of catheter-related infections. However, there remains some uncertainty regarding the efficacy of these catheters because of conflicting reports in the literature.

Objective To evaluate the efficacy of chlorhexidine–silver sulfadiazine–impregnated central venous catheters in the prevention of catheter-related bloodstream infection.

Data Sources Studies identified from a computerized search of the MEDLINE database from January 1966 to January 1998, reference lists of identified articles, and queries of principal investigators and the catheter manufacturer.

Study Selection Randomized trials comparing chlorhexidine–silver sulfadiazine–impregnated central venous catheters with nonimpregnated catheters were included. The outcomes assessed were catheter colonization and catheter-related bloodstream infection confirmed by catheter culture.

Data Extraction Twelve studies met the inclusion criteria for catheter colonization and included a total of 2611 catheters. Eleven studies with a total of 2603 catheters met the inclusion criteria for catheter-related bloodstream infection. Most patients in these studies were from groups considered to be at high risk for catheter-related infections. Summary statistics were calculated using Mantel-Haenszel methods under a fixed-effects model.

Data Synthesis The summary odds ratio for catheter colonization was 0.44 (95% confidence interval [CI], 0.36-0.54; $P<.001$), indicating a significant decrease in catheter colonization associated with impregnated catheters. The studies examining the outcome of primary interest, catheter-related bloodstream infection, had a summary odds ratio of 0.56 (95% CI, 0.37-0.84; $P = .005$).

Conclusions Central venous catheters impregnated with a combination of chlorhexidine and silver sulfadiazine appear to be effective in reducing the incidence of both catheter colonization and catheter-related bloodstream infection in patients at high risk for catheter-related infections.

JAMA. 1999;281:261-267 www.jama.com

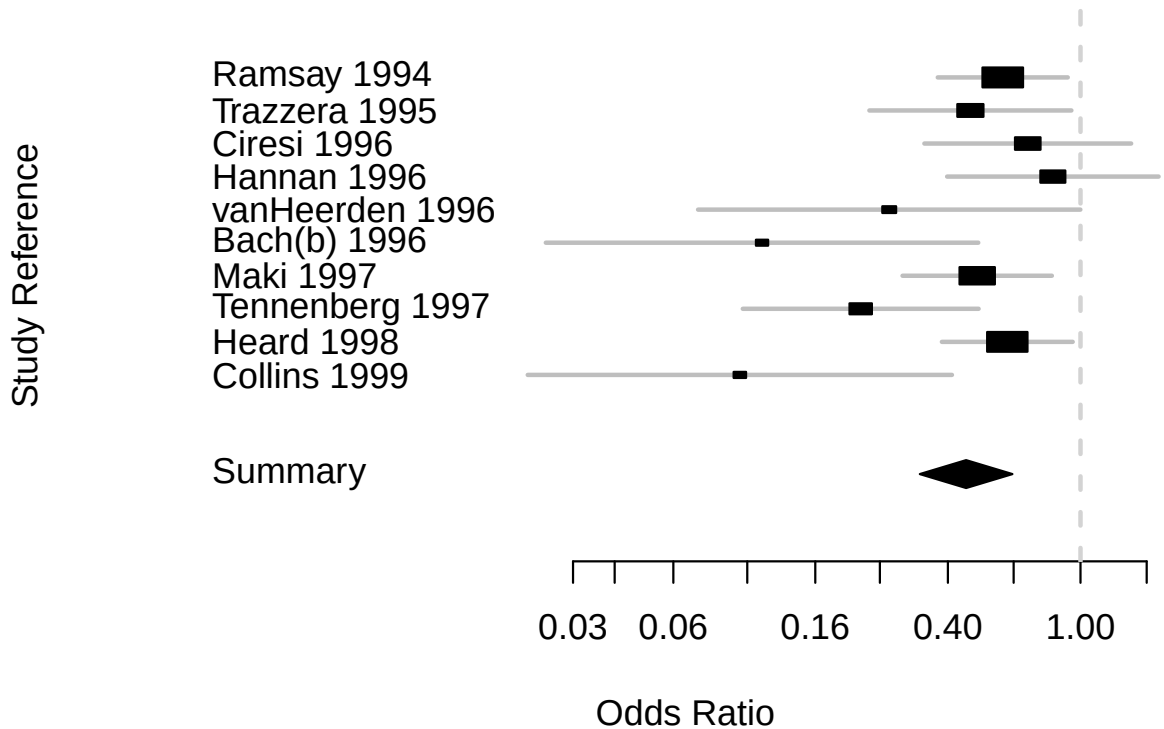
CENTRAL VENOUS CATHETERS ARE commonly used for parenteral nutrition and fluid or drug administration in a variety of hospital settings. While providing convenient and beneficial venous access, these catheters also increase the risk of nosocomial bloodstream infection, contributing to the more than 200 000 cases that occur annually in the United States.[1] Catheter-related bloodstream infection (CRBSI) can be a serious complication, leading to increases in mortality, hospital stay, and medical costs.[2]

A variety of methods have been used to prevent catheter-related infections. Aseptic insertion techniques and proper catheter care have proved effective, while silver-coated catheter cuffs have produced mixed results.[3] Recently, the use of antibiotic-coated and antiseptic-impregnated cath-

Application: Efficacy of Catheters

Normal Meta-Analysis

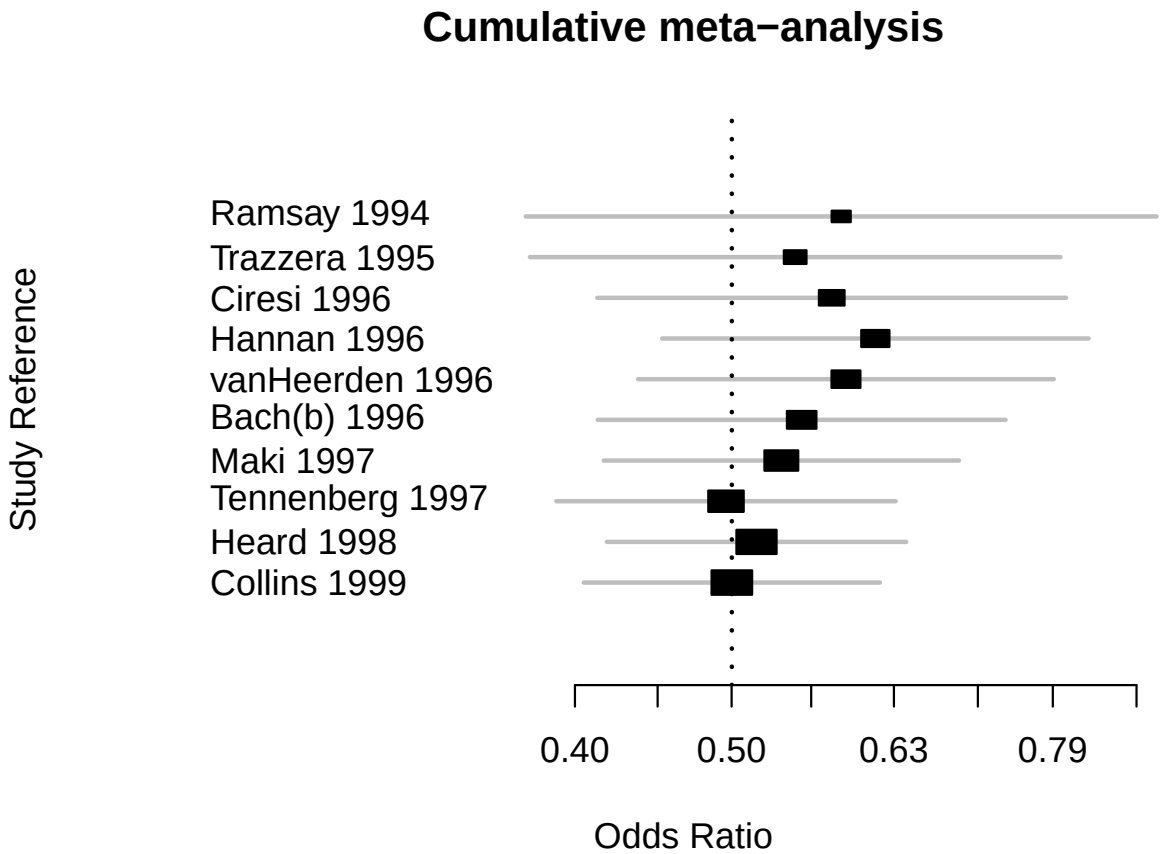
```
library(rmeta)
b2 <- meta.DSL(n.trt, n.ctrl, col.trt, col.ctrl, data=catheter2,
               names=paste(Name, year))
plot(b2, xlab="Odds Ratio", lwd = 2)
```



Application: Efficacy of Catheters

Cumulative Meta-Analysis

```
d2 <- cummeta.summaries(b2$logs, b2$selogs, names=b2$names,
                        method="fixed", logscale=TRUE)
plot(d2, xlab="Odds Ratio", lwd = 2)
```



Meta-Regression

- The investigation of sources of heterogeneity in meta-analyses may yield important insights.
- Meta-regression can be used to examine associations between study characteristics $x_{1i}, \ldots, x_{pi}$ and treatment effects θ_i:

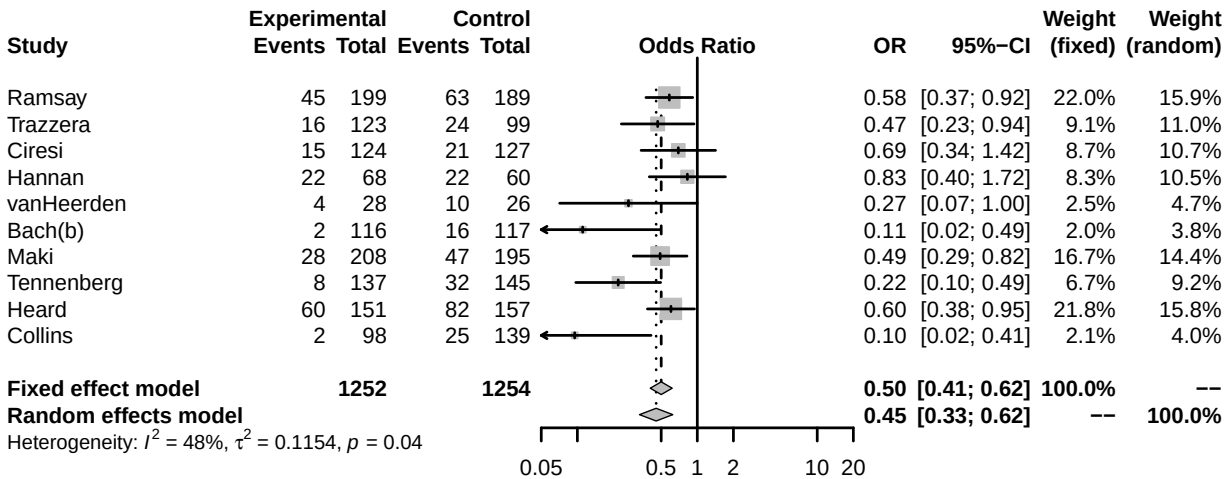
$$\theta_i \sim N(\beta_0 + \beta_1 x_{1i} + \ldots + \beta_p x_{pi}, v_i + \tau^2)$$

- The goal of meta-regression is to reduce the amount of unexplained heterogeneity (represented by τ^2) by including relevant explanatory variables.

Application: Efficacy of Catheters

Meta-Regression

```
meta2 <- metabin(event.e = col.trt, n.e = n.trt,
                 event.c = col.ctrl, n.c = n.ctrl, data=catheter2,
                 sm = "OR", method = "Inverse", studlab = Name)
forest(meta2, comb.fixed=TRUE, comb.random=TRUE, xlim=c(0.05, 20),
       scale.square=1.5, cex.lab=1.5, cex.comb=1.5, lwd = 2)
```



Application: Efficacy of Catheters

Meta-Regression

```
head(catheter2)
```

```
##          Name n.trt n.ctrl col.trt col.ctrl year durationTrt
## 8      Ramsay   199    189      45       63 1994        10.9
## 10   Trazzera   123     99      16       24 1995        11.2
## 1      Ciresi   124    127      15       21 1996         9.6
## 3      Hannan    68     60      22       22 1996         7.0
## 5  vanHeerden    28     26       4       10 1996         6.6
## 12    Bach(b)   116    117       2       16 1996         7.7
```

```
meta3 <- metareg(meta2, ~ durationTrt, method.tau = "REML")
## effect of durationTrt
printResults(meta3$beta[2], meta3$se[2])
```

```
##      Effect 95% Confidence Interval P-value
## [1,] 0.075  from -0.073 to 0.223    0.32
```

```
## heterogeneity variance estimate
print(meta3$tau2)
```

```
## [1] 0.09394178
```

Publication Bias

Publication bias occurs when the publication of research results depends on their nature and direction.

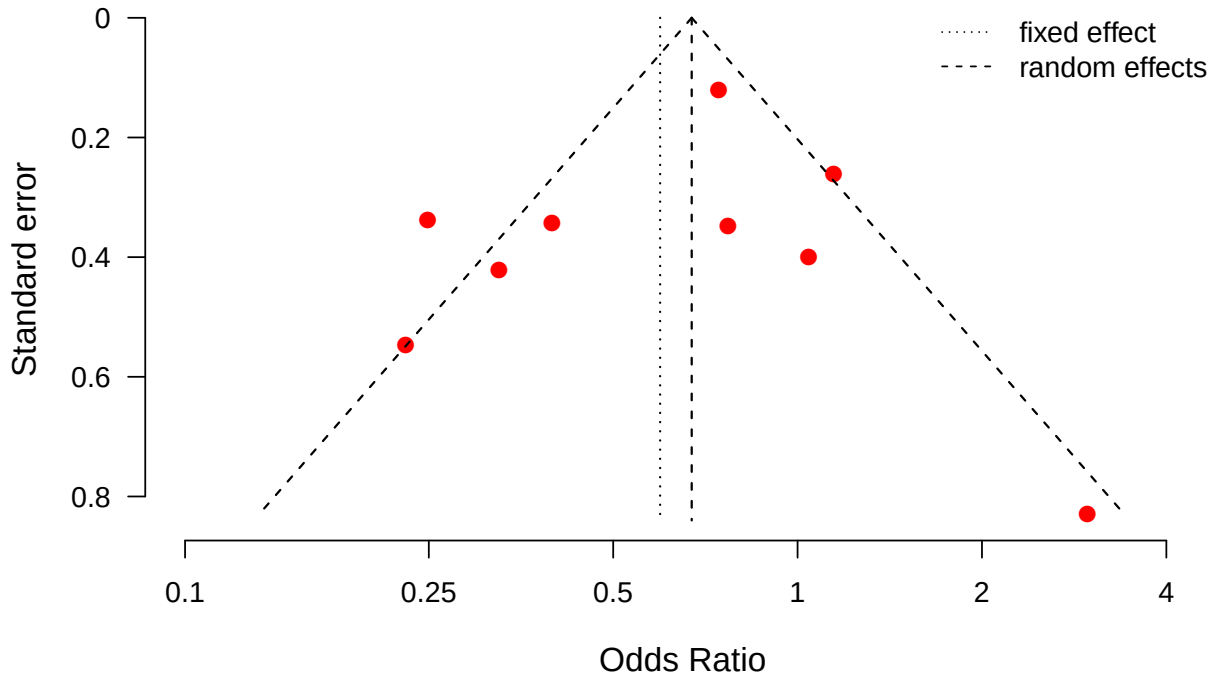
Sources of publication bias:

- Failure to publish due to negative or null findings (mostly on the side of the researchers, not editors/journals)
- Selective reporting of outcomes (e.g. due to changes in research plan)
- Selective citation of positive results

$\Longrightarrow$ danger of false conclusions and patient harm

Funnel Plot

A funnel plot is a scatter plot of a measure of study size, usually the (reversed) standard error, against the estimated treatment effects from individual studies.



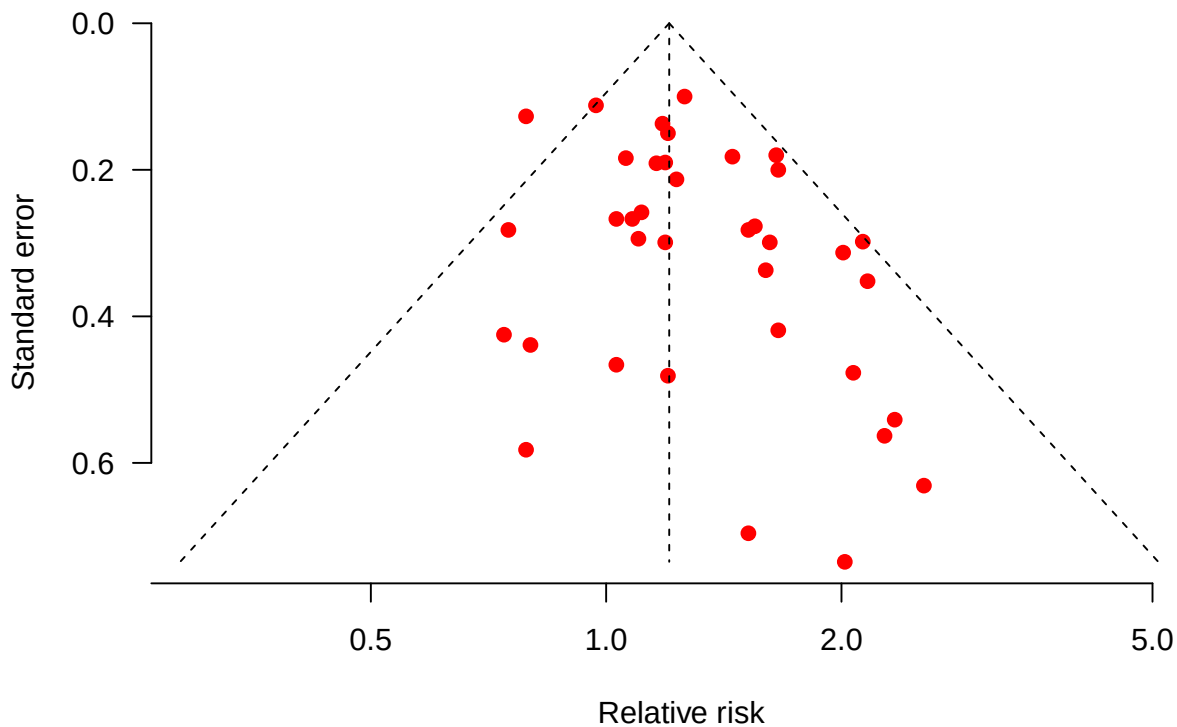
Funnel Plot cont.

- The smaller the study size, the wider the spread of the treatment effects and vice versa
- If there is no bias: form of a funnel, symmetrical
- If there is bias: asymmetrical
- Explorative tool, no quantitative information on the amount or the source of the bias
- No empirical investigations on funnel plots for continuous outcomes so far

Funnel plots and tools for meta-analysis in `R`:
packages `meta` and `rmeta`

Example: Passive Smoking

- 37 studies on the effect of passive smoking on risk of lung cancer
- Comparison of spouses of smokers and non-smokers
- Controversy: Are the results affected by publication bias?



The Trim and Fill Method

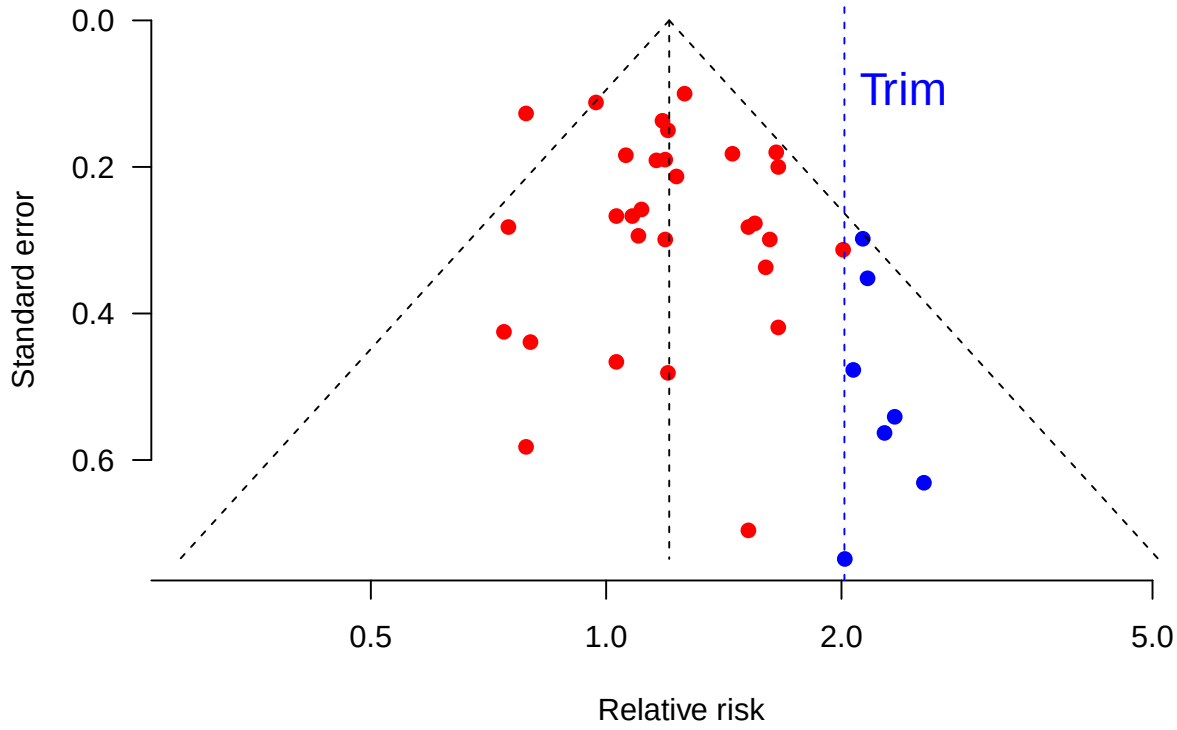
Key assumptions:

- Publication bias is reason of funnel plot asymmetry.
- Studies with negative findings are suppressed.

Idea:

1. Trim-off the “asymmetric” side of a funnel plot, after estimating the number of studies in this group.
2. Use the symmetric remainder to estimate the “true center”.
3. Replace trimmed studies and their missing “counterparts” around the center.
4. Estimate θ and its variance based on the “filled” funnel plot.

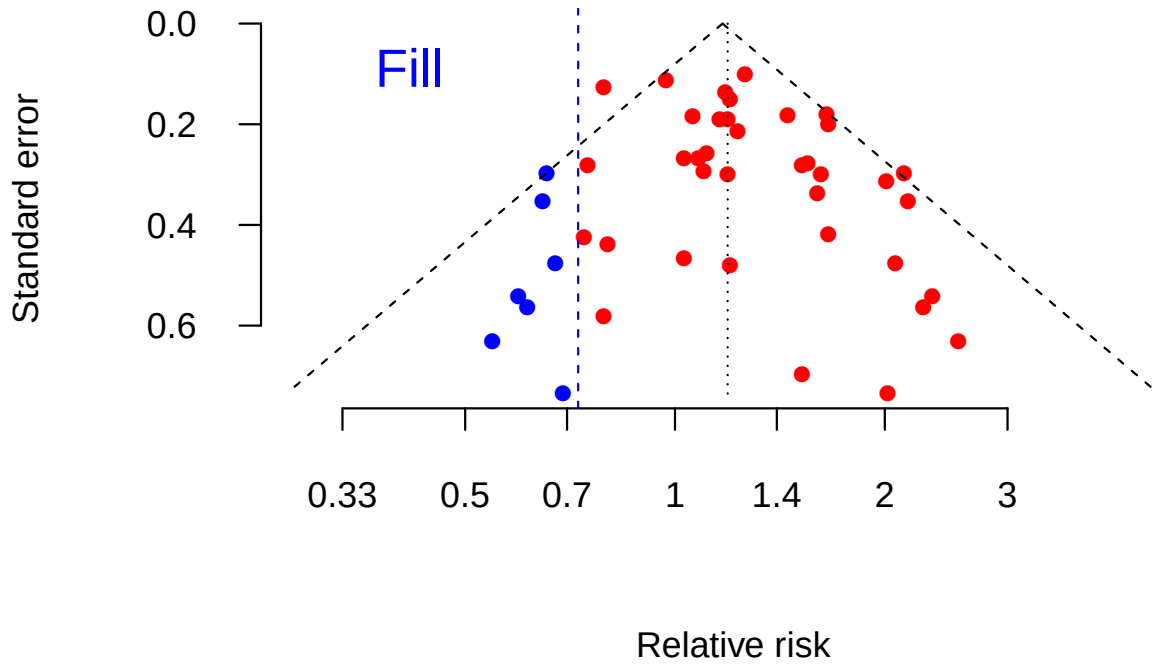
Example: Passive Smoking



Example: Passive Smoking

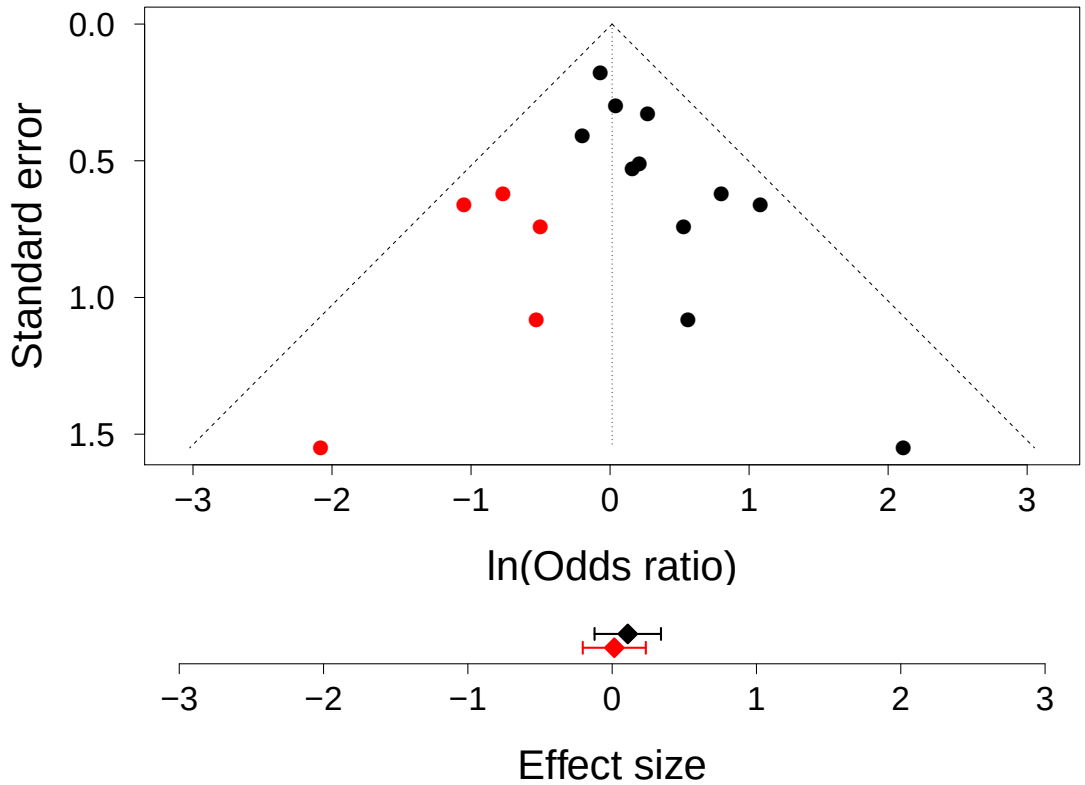
Trim-and-Fill Method

Database	Number of studies	Relative risk	95% CI
Observed	37	1.24	from 1.13 to 1.36
Trim-and-Fill	44	1.19	from 1.08 to 1.31



Example: Gangliosides and Stroke

11 studies of the effect of using gangliosides in reducing case fatality and disability in acute ischaemic stroke.



Trim and Fill with R

```
gs <- as.matrix(read.table("data/ganglioside.txt", header=T))
tf_gs <- trimfill(x=gs[,1], seTE=gs[,2],
                  ma.fixed=FALSE, type="L", silent=TRUE)
```

```
summary(tf_gs)

## Number of studies combined: k = 16 (with 5 added studies)
##
##                                         95%-CI    z p-value
## Random effects model 0.0147 [-0.2037; 0.2332] 0.13  0.8948
##
## Quantifying heterogeneity:
## tau^2 = 0; H = 1.00 [1.00; 1.44]; I^2 = 0.0% [0.0%; 51.9%]
##
## Test of heterogeneity:
##      Q d.f. p-value
##  14.88   15  0.4604
##
## Details on meta-analytical method:
## - Inverse variance method
## - DerSimonian-Laird estimator for tau^2
## - Trim-and-fill method to adjust for funnel plot asymmetry
```

Tests for Funnel Plot Asymmetry

- If visual inspection of a funnel plot is not enough:
  Perform a test

- Possibilities:
  $\rightarrow$ Rank correlation method
  $\rightarrow$ Regression method(s)

- Simplified notation:
  θ_i is effect estimate
  $s_i = \sqrt{v_i}$ is corresponding standard error

Rank Correlation Test

- Compute standardised treatment estimates

$$\theta_i^* = \frac{\theta_i - \hat{\theta}}{\sqrt{v_i^*}}$$

  where $\hat{\theta}$ is the usual fixed-effect estimate of the summary effect and v_i^* is the variance of $\theta_i - \hat{\theta}$.
- Then test H_0 that Kendell's rank correlation (Kendell's τ) between θ_i^* and v_i^* is zero.
- Test may have low power if number of studies is small.

Perform Rank Correlation Test using R

```
rc <- metabias(ps$lnRR, ps$selnRR, method="rank", correct=T)
print(rc)

##
##  Rank correlation test of funnel plot asymmetry (with continuity
##  correction)
##
## data:  m
## z = 1.2559, p-value = 0.2092
## alternative hypothesis: asymmetry in funnel plot
## sample estimates:
##       ks    se.ks
## 96.00000 76.43952
```

Weighted Regression of θ_i on s_i

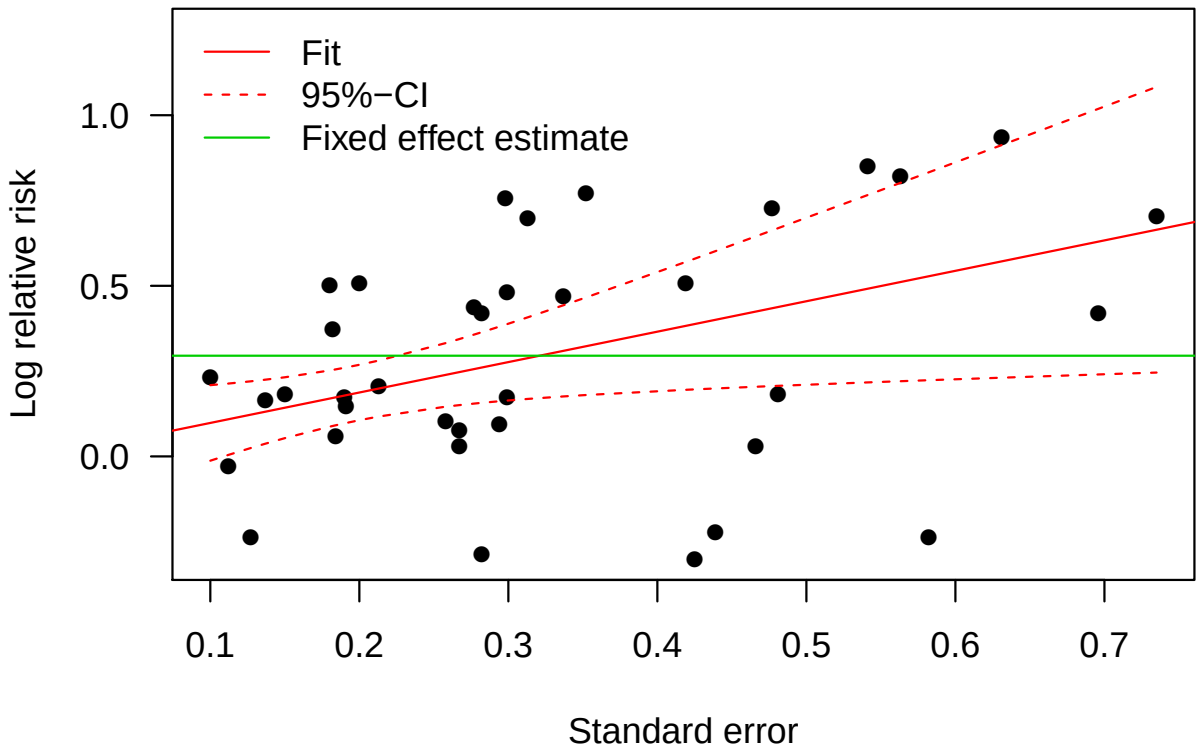
- Idea: Perform weighted regression of θ_i against s_i with weights proportional to $1/v_i$.

$\rightarrow$ Slope should be close to zero if there is no publication bias.

```
lmw <- lm(lnRR ~ selnRR, weights=1/selnRR^2, data=ps)
c <- summary(lmw)$coefficients
print(c)

##                Estimate Std. Error   t value   Pr(>|t|)
## (Intercept) 0.008992237 0.08474734 0.1061064 0.91610375
## selnRR      0.891549711 0.37679984 2.3661096 0.02364279
```

Weighted Regression: Results



Egger's Formulation

- Linear unweighted regression of
  - standardized treatment effect $z_i = \theta_i / s_i$ against
  - inverse standard error $q_i = 1/s_i$:

$$z_i = \beta_0 + \beta_1 \cdot q_i.$$

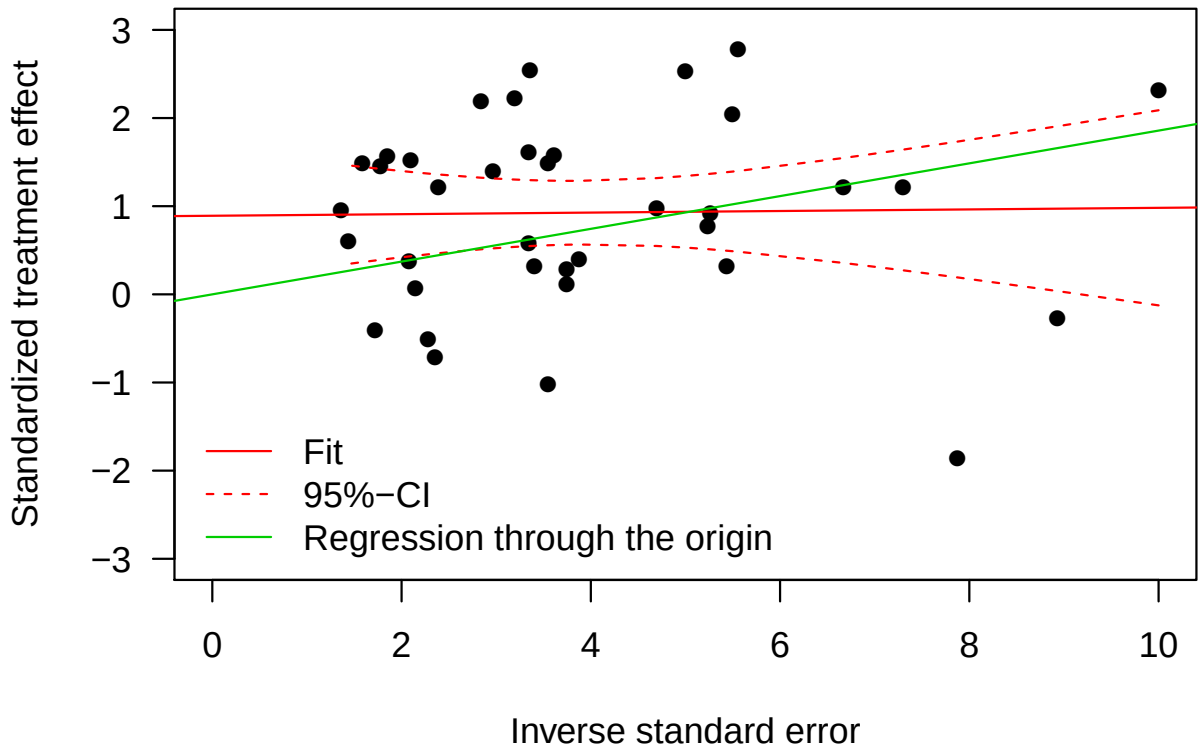
- No asymmetry: Points (q_i, z_i) scatter around a line through the origin (i.e. $\beta_0 = 0$) with slope β_1 indicating the size and direction of the treatment effect.
- Asymmetry: Line will not run through the origin, intercept β_0 provides a measure of bias.
- Formulation is equivalent to weighted regression with the role of intercept and slope reversed!

Implementation in R

```
ps <- within(ps, z <- lnRR/selnRR)
ps <- within(ps, q <- 1/selnRR)
lmuw <- lm(z ~ q, data=ps)
c2 <- summary(lmuw)$coefficients
print(c2)

##                Estimate Std. Error   t value   Pr(>|t|)
## (Intercept) 0.891549711 0.37679984 2.3661096 0.02364279
## q           0.008992237 0.08474734 0.1061064 0.91610375
```

Unweighted Regression: Results



Modelling Between-Study Heterogeneity

- Weighted linear regression model can be written as

$$\theta_i \sim N(\beta_0 + \beta_1 \cdot s_i, v_i \cdot \psi),$$

  i.e. is including a multiplicative overdispersion parameter ψ allowing for between-study heterogeneity.
- Problem of the multiplicative model: Factor ψ can be smaller than 1 ("underdispersion"), which is implausible.
- An alternative model is

$$\theta_i \sim N(\beta_0 + \beta_1 \cdot s_i, v_i + \sigma^2),$$

  including an additive between-study component of variance.

Example cont.

```
mm <- metabias(ps$lnRR,ps$selnRR,method="mm")
print(mm)

##
##  Linear regression test of funnel plot asymmetry (methods of
##  moment)
##
## data:  m
## t = 2.2497, df = 35, p-value = 0.03086
## alternative hypothesis: asymmetry in funnel plot
## sample estimates:
##       bias    se.bias      slope
## 0.85678550 0.38085277 0.01905776
```

Note: `bias` refers here to the slope β_1 in the regression model, `slope` refers to the intercept β_0.

Network Meta-Analysis

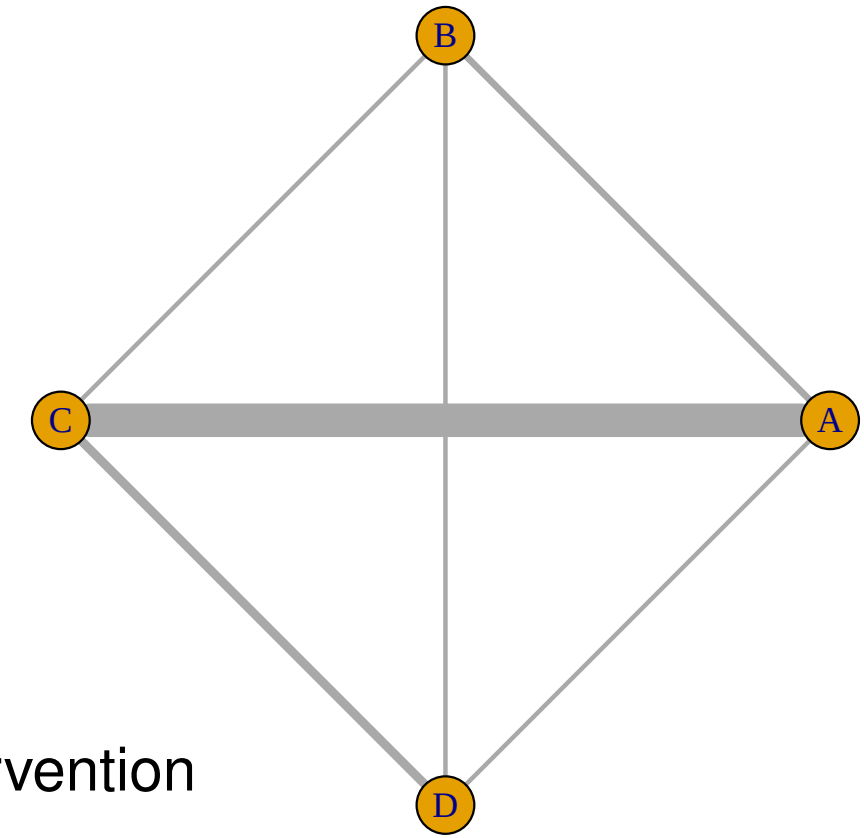
- Often there are trials/studies not only comparing treatment A vs. B but also A vs. C, A vs. D, D vs. B, etc.
- Instead of only considering pairwise comparisons, i.e. direct evidence, a network meta-analysis aggregates the evidence of all trials.
- The advantages of a network meta-analysis are:
  - Comprehensive use of all available data, including indirect evidence
  - Comparison of interventions which have not been directly compared in any experiment: indirect comparisons
  - Improved precision for each comparison

Trials on Smoking Cessation

Study	Intervention	No. Cessations	No. Participants	Proportion
1	A	9	140	0.06
1	C	23	140	0.16
1	D	10	138	0.07
2	B	11	78	0.14
2	C	12	85	0.14
2	D	29	170	0.17
3	A	79	702	0.11
3	B	77	694	0.11
4	A	18	671	0.03
4	B	21	535	0.04

- There are $K = 4$ different interventions for smoking cessation: A, B, C, D.
- In total there are $N = 24$ trials:
  - 22 two-arm trials comparing two interventions
  - 2 three-arm trials comparing three interventions

Network of Smoking Cessation Trials



- A: No intervention
- B: Self-help
- C: Individual counselling
- D: Group counselling

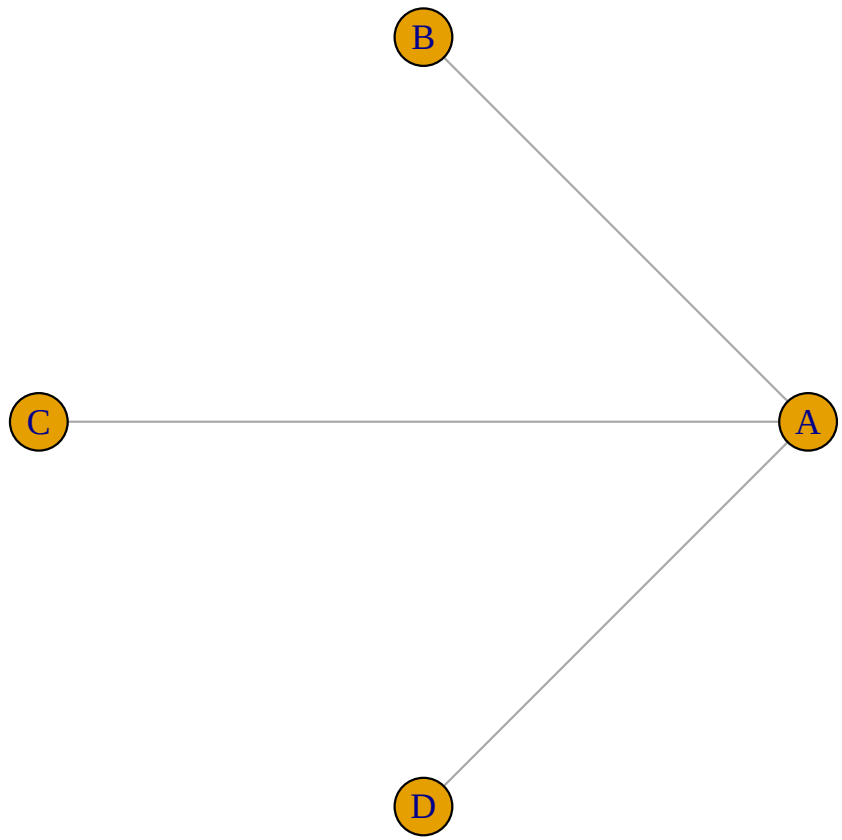
Baseline Contrasts

- Choose a baseline treatment (A) and define baseline contrasts $\theta_{AB}, \theta_{AC}, \theta_{AD}$ for all direct comparisons with the baseline treatment.
- This defines a spanning tree of the network, i.e. a connected subgraph consisting of all vertices's but without cycles.
- Under the assumption of consistency, the remaining contrasts

$$\begin{aligned} \theta_{BC} &= \theta_{AC} - \theta_{AB} \\ \theta_{BD} &= \theta_{AD} - \theta_{AB} \\ \theta_{CD} &= \theta_{AD} - \theta_{AC} \end{aligned}$$

  can be expressed as a linear combination of the baseline contrasts $\theta_{AB}, \theta_{AC}, \theta_{AD}$.

A Spanning Tree of the Smoking Cessation Network



Inference and Software for Network Meta-Analysis

- The fixed effect model ($\sigma^2 = 0$) and the random effects model can be estimated by maximum likelihood.
- There exist several `R`-packages for network meta-analysis. The `gemtc`-package implements fixed and random effect models and it is possible to do node-splitting (see later).
- `gemtc` performs Bayesian inference via Markov chain Monte Carlo (MCMC) based on `WinBUGS`, `OpenBUGS`, or `JAGS`.

Smoking Cessation: Estimates of Baseline Contrasts

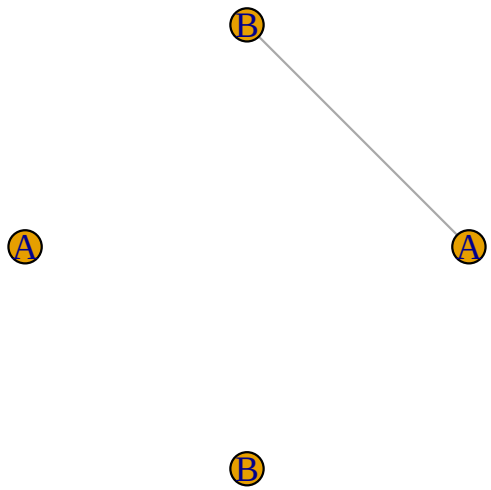
	Fixed effect model		Random effects model	
	Mean	SD	Mean	SD
d.A.B	0.228	0.120	0.486	0.390
d.A.C	0.755	0.059	0.825	0.234
d.A.D	0.820	0.175	1.062	0.448
σ^2	NA	NA	0.836	0.197

Inconsistency

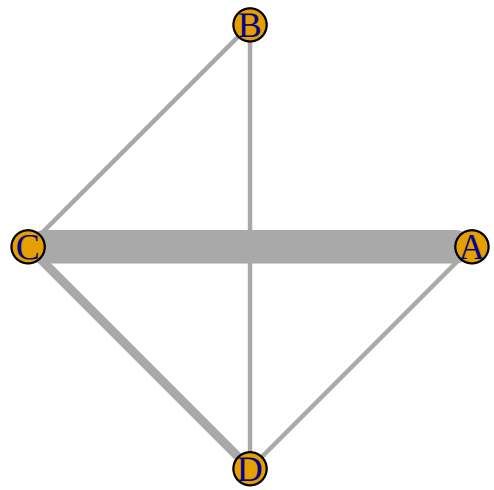
- Besides the between-trial variance (heterogeneity) it is possible to analyse the between-treatment variance (inconsistency).
- Investigate inconsistency by node-splitting: difference between estimates
  - based only on direct evidence
  - based only on indirect evidence.

Node-split for Interventions A and B

direct evidence A vs.~B



indirect evidence A vs.~B



Comparison of Direct and Indirect Estimates

- Consider direct $\hat{\theta}_{AB}^{dir}$ and indirect estimates $\hat{\theta}_{AB}^{ind}$.

$\rightarrow$ Difference $\hat{\phi}_{AB} = \hat{\theta}_{AB}^{dir} - \hat{\theta}_{AB}^{ind}$

$\rightarrow$ Standard error $\text{se}(\hat{\phi}_{AB}) = \sqrt{\text{se}(\hat{\theta}_{AB}^{dir})^2 + \text{se}(\hat{\theta}_{AB}^{ind})^2}$

	Node-split A,B		Node-split C,D	
	Estimate	se	Estimate	se
θ^{dir}	0.331	0.555	-0.067	0.473
θ^{ind}	0.617	0.672	1.858	1.003
ϕ	-0.286	0.784	-1.925	0.668