Evidence Synthesis / Meta-analysis

Session 3, Lecture 6: Small study effects

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Overview Lecture 6

- ▶ Types of bias
  - ▶ Publication bias and related biases
  - ▶ Small-study effects
- ▶ Diagnosis of small-study effects
  - ▶ Funnel plot
  - ▶ Funnel plot tests
- ▶ Adjustment for small-study effects
  - ▶ Trim and fill method
  - ▶ Copas selection model (short description of method)
  - ▶ Adjustment by regression

Bias in meta-analyses: Small-study effects

- ▶ Publication bias (Easterbrook et al., 1991; Rothstein et al., 2005): Small studies tend to be published only if they show a large effect
- ▶ Related types of bias: Studies having 'significant' results tend to be
  - ▶ published in high-ranking English language journals
    (Language bias) (Egger et al., 1997b)
  - ▶ published faster than studies without a 'significant' result
    (Time lag bias) (Higgins and Green, 2009)
  - ▶ published more than once
    (Multiple publication bias) (Gøtzsche, 1989)
  - ▶ cited more often than studies without a 'significant' result, and therefore are more easily detectable in literature searches
    (Citation bias) (Nieminen et al., 2007)

Small-study effects

Smaller trials show different, often larger, treatment effects than large ones (Sterling et al., 1995; Sterne et al., 2000; Rothstein et al., 2005)
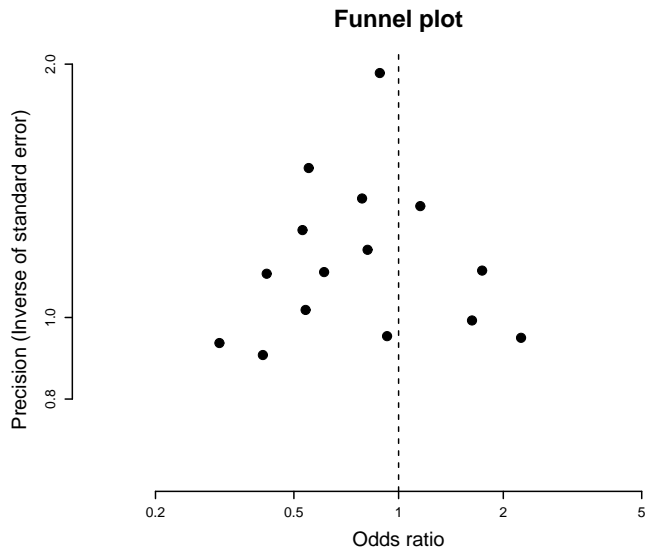
- ▶ Potential causes of small-study effects
  - ▶ Publication bias: Small studies tend to be published preferably if they show a large effect (Easterbrook et al., 1991)
  - ▶ Selective outcome reporting bias: Studies present selected outcomes (Chan et al., 2004a,b; Williamson and Gamble, 2005)
  - ▶ Selective analysis reporting bias: Studies choose a method of analysis that leads to larger effects (Ioannidis et al., 2014)
  - ▶ Clinical heterogeneity between patients in large and small trials
  - ▶ For binary data: Statistical correlation between treatment effect estimate and its variance (Schwarzer et al., 2002)
  - ▶ Coincidence
- ▶ Graphical representation of small-study effects
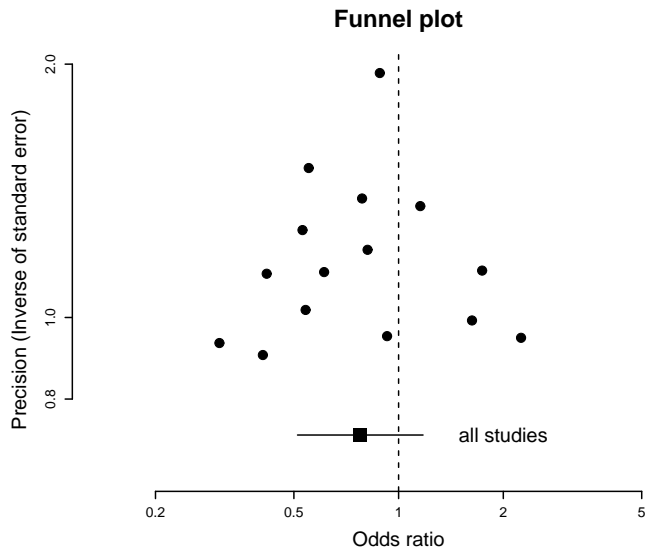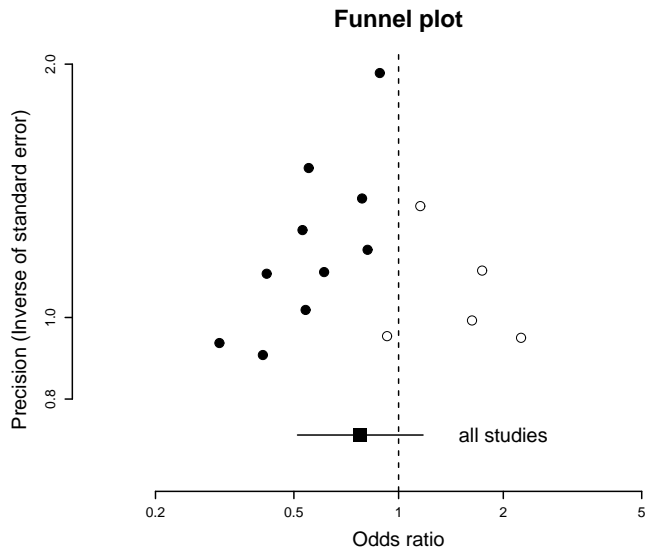 - ▶ Funnel plot (Light and Pillemer, 1984; Sterne and Egger, 2001)

Funnel plot

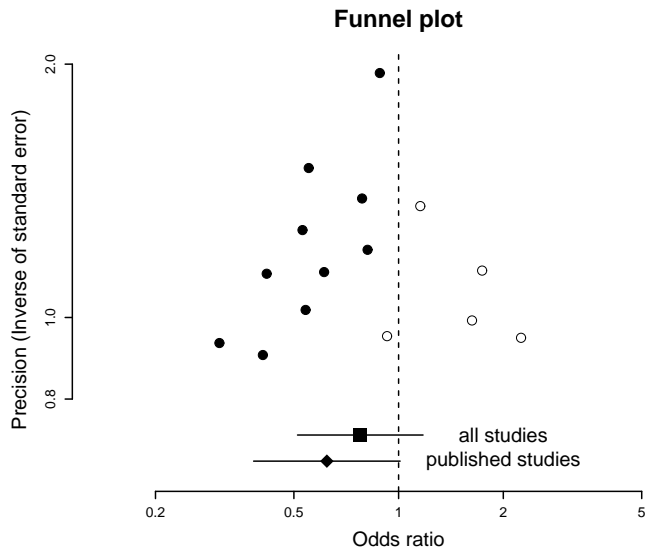Horizontal axis: (log) treatment effect

Vertical axis: a measure of precision; various versions in the literature:

- ▶ Sample size
- ▶ Inverse variance
- ▶ Standard error on a reversed axis (preferred, Sterne and Egger (2001))
  - ▶ confidence intervals increasing linearly
  - ▶ sufficient space for imprecise (small) studies (particularly interesting for diagnosis of small-study effects)
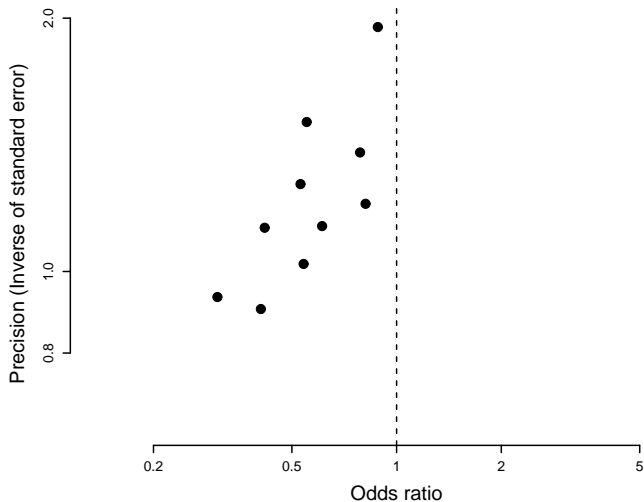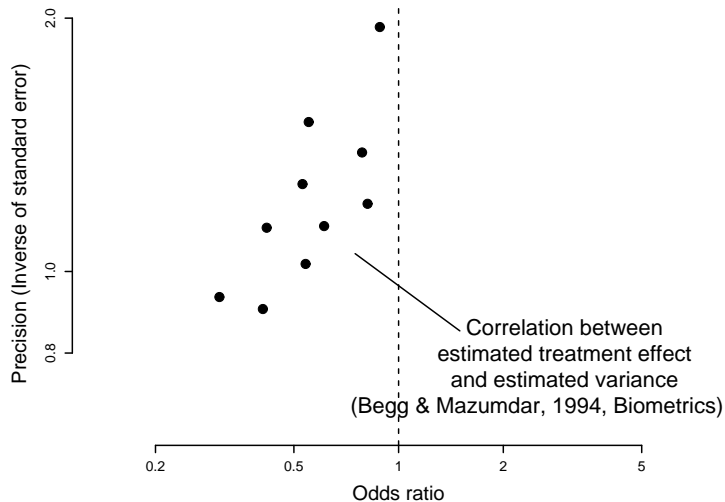
Funnel plot

Funnel plot

Funnel plot

Precision (Inverse of standard error)

all studies

Odds ratio

Funnel plot

Bias in meta−analysis <=> Asymmetry in funnel plot

Bias in meta−analysis <=> Asymmetry in funnel plot

Funnel plot

Example: NSAIDS data

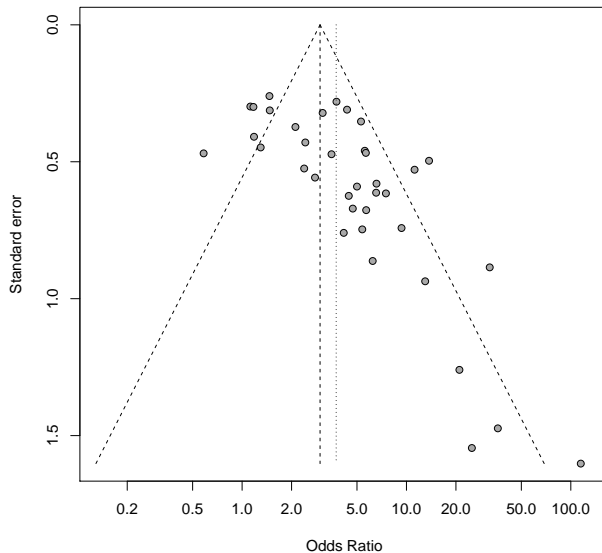Meta-analysis of 37 placebo-controlled randomized trials on the effectiveness and safety of topical non-steroidal anti-inflammatory drugs (NSAIDS) in acute pain (Moore et al., 1998)

Part of R package **metasens**

```
# Perform meta-analysis
ms1 <- metabin(Ee, Ne, Ec, Nc, data = nsaids, sm = "OR")
```

```
# Create funnel plot
funnel(ms1)
```

Funnel plot of NSAIDS data

Contour-enhanced funnel plot of NSAIDS data

Funnel plot-based tests for small-study effects

- ▶ Idea: Test for asymmetry in the funnel plot as an indication for bias
- ▶ Method: Test for association between treatment effect and standard error
- ▶ Assumption: No association between treatment effect and standard error (or precision) if there is no small-study effect
- ▶ Limitation: Strictly valid only for normally distributed outcomes
- ▶ Criticised by some authors (Terrin et al., 2005; Lau et al., 2006)

Funnel plot tests for asymmetry: Overview

Rank correlation tests (not considered here)

- ▶ Test by Begg and Mazumdar (1994)
    - ▶ Modification for binary data: Test by Schwarzer et al. (2007)

Regression tests

- ▶ Test by Egger et al. (1997a)
- ▶ Modifications for binary data
    - ▶ Test by Harbord et al. (2006)
    - ▶ Test by Macaskill et al. (2001)
    - ▶ Test by Peters et al. (2006)
    - ▶ Arcsine test (Rücker et al., 2008)

Regression tests: Basic idea

Choose an effect measure, say, the mean difference

Null-hypothesis (*'No small study effects'*): Treatment effect does not depend on precision

1. Regress the treatment effect on the standard error, using inverse variance weights
2. Test null-hypothesis of zero slope

Often called Egger's test (Egger et al., 1997a)

Note: Strictly valid only for continuous data (data normally distributed)!

Nevertheless often applied to binary data, preferably in a modified version

Egger's test and its modifications for binary data in R

- ▶ Egger's test (Egger et al., 1997a)
    - ▶ Use R: **metabias**(ms1, method = "linreg")
- ▶ Harbord's score test (Harbord et al., 2006)
    - ▶ Uses a score-based estimate for the odds ratio
    - ▶ Advantage: Variance estimate depends only on marginal totals
    - ▶ Use R: **metabias**(ms1, method = "score")
- ▶ Peters' test (Peters et al., 2006)
    - ▶ Uses the usual odds ratio estimate and $1/n$ as regressor
    - ▶ Advantage: Study weights depending only on marginal totals
    - ▶ Use R: **metabias**(ms1, method = "peters")
- ▶ Arcsine test (Rücker et al., 2008)
    - ▶ Uses the arcsine difference instead of the odds ratio
    - ▶ Advantage: Variance depends only on group sample sizes
    - ▶ Use R: ms1.asd <- **update**(ms1, sm = "ASD")
              metabias(ms1.asd, method = "linreg")

Recommendations on testing for funnel plot asymmetry

Sterne et al. (2011), BMJ:

- ▶ Funnel plot tests only when there are at least 10 studies (rule of thumb; argument `k.min` in function `metabias`)
- ▶ Recommendation for continuous outcomes:
  Linear regression test (Egger et al., 1997a)
- ▶ For binary outcomes:
  Use one of the modifications of Egger's test (Harbord et al., 2006; Peters et al., 2006; Rücker et al., 2008)
- ▶ Bias cannot be excluded if test for funnel plot asymmetry is non-significant
- ▶ Test performance deteriorates if between-study heterogeneity increases

Adjusting for small-study effects

Three approaches

- ▶ **Trim and fill method**
  (Duval and Tweedie, 2000a,b)

- ▶ **Copas selection model for publication bias**
  (Copas, 1999; Copas and Shi, 2000, 2001)

- ▶ **Adjustment by regression**
  (Copas and Malley, 2008; Stanley, 2008; Moreno et al., 2009a,b;
  Rücker et al., 2010)

Trim and fill method

1. Estimate the number of studies in the outlying part of the funnel plot using rank-based methods;
2. remove (trim) these studies and do meta-analysis on the remaining studies;
3. consider the estimate from the 'trimmed' meta-analysis as the true center of the funnel;
4. for each 'trimmed' study, create (fill) an additional study as the mirror image about the center of funnel plot;
5. do meta-analysis on original and filled studies.

```
# Perform Trim and fill analysis
tf1 <- trimfill(ms1)
```

```
# Create funnel plot including filled-in studies
funnel(tf1)
```

Trim and fill plot of NSAIDS data

Trim and fill method

```
# Print results of Trim and fill analysis
print(tf1, digits = 2)

##                 OR           95%-CI %W(random)
## 1           6.57 [2.11;   20.48]       2.13
*** Output truncated ***
## 37          5.69 [1.51;   21.42]       1.91
## Filled: 37  0.95 [0.25;    3.56]       1.91
## Filled: 27  0.86 [0.16;    4.68]       1.53
## Filled: 16  0.82 [0.25;    2.73]       2.05
*** Output truncated ***
## Filled: 32  0.05 [0.00;    1.08]       0.68
##
## Number of studies combined: k=51 (with 14 added studies)
##
##                      OR       95%-CI z  p-value
## Random effects model 2.45 [1.83; 3.28] 6 < 0.0001
##
## Quantifying heterogeneity:
## tau^2 = 0.7113; H = 1.93 [1.68; 2.22]; I^2 = 73.2% [64.7%; 79.7%]
*** Output truncated ***
```

Copas selection model

Combine two models:

1. Usual random effects model for treatment effect
2. A model for the selection process with a parameter controlling how chance of publication depends on precision $1/s_k$ (where s_k is the within-study standard error)

Selection/publication bias is modelled by a parameter representing the correlation between effect size and selection probability

- Implemented in function **copas** of R package **metasens** (earlier: **copas**) (Carpenter et al., 2009a)
- Sensitivity analysis necessary
- Details given in (Copas, 1999; Copas and Shi, 2001)

Adjustment by regression (Rücker et al., 2010)

▶ Random effects model

$$\hat{\theta}_k = \theta_k + \sigma_k\,\eta_k, \qquad\qquad \eta_k \ \sim \ N(0,1)$$
$$\theta_k = \theta + \tau\,\delta_k, \qquad\qquad \delta_k \ \sim \ N(0,1)$$

- ▶ $\hat{\theta}_k$ observed treatment effect in study k ($k = 1,\ldots,K$)
- ▶ θ_k true treatment effect in study k
- ▶ θ overall treatment effect
- ▶ σ_k^2 within-study sampling variance, τ^2 between-study variance

▶ Equivalent:

$$\hat{\theta}_k = \theta + \sqrt{\sigma_k^2 + \tau^2}\,\epsilon_k, \qquad\qquad \epsilon_k \ \sim \ N(0,1)$$

Adjustment by regression

► Random effects model:

$$\hat{\theta}_k = \theta + \sqrt{\sigma_k^2 + \tau^2}\, \epsilon_k, \qquad\qquad \epsilon_k \ \sim\ N(0,1)$$

► Extended random effects model taking account of possible small study effects by allowing the effect to depend on the standard error:

$$\hat{\theta}_k = \theta + \sqrt{\sigma_k^2 + \tau^2}\ (\alpha + \epsilon_k), \qquad\qquad \epsilon_k \ \sim\ N(0,1)$$

Additional parameter α represents bias introduced by small-study effects ('publication bias')

Adjustment by regression

▶ Extended random effects model, taking account of possible small study effects by allowing the effect to depend on the standard error:

$$\hat{\theta}_k = \theta + \sqrt{\sigma_k^2 + \tau^2} \ (\alpha + \epsilon_k), \qquad \epsilon_k \sim N(0, 1)$$

▶ Additional parameter α represents bias introduced by small-study effects ('publication bias')

  ▶ For a very small study k, we have $\sigma_k^2 \to \infty$ and therefore

  $$\mathsf{E}\left(\frac{\hat{\theta}_k - \theta}{\sigma_k}\right) \to \alpha \ \text{Small study bias}$$

  ▶ For a very large study k, we have $\sigma_k^2 \to 0$ and therefore

  $$\mathsf{E}\left(\hat{\theta}_k\right) \to \theta + \tau \, \alpha \ \text{Adjusted effect of large study}$$
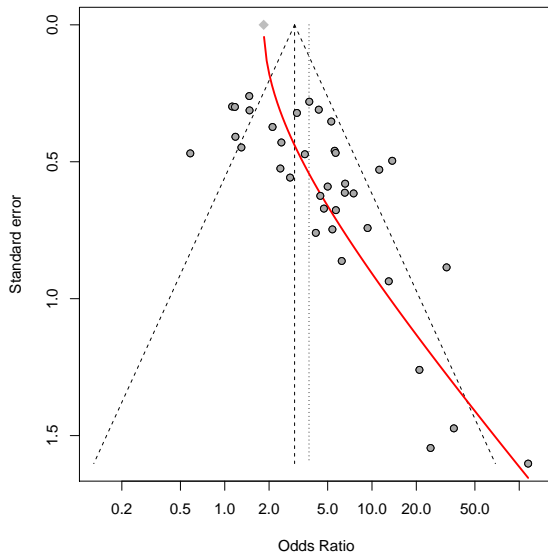
▶ Implemented in function **limitmeta** of R package **metasens** (Carpenter et al., 2009a)

Adjustment by regression

```
# Perform limit meta-analysis
l1 <- limitmeta(ms1)
```

```
# Create funnel plot with adjusted regression line
funnel(l1, col.line = "red", lwd.line = 2)
```

Funnel plot with adjusted regression line for NSAIDS data

Adjustment by regression

```
# Print results of regression adjustment (limit meta-analysis)
print(summary(l1), digits = 2)

## Result of limit meta-analysis:
##
##  Random effects model    OR       95%-CI    z      pval
##     Adjusted estimate  1.84  [1.26; 2.68]  3.17    0.0015
##   Unadjusted estimate  3.73  [2.80; 4.97]  9.01  < 0.0001
##
## Quantifying heterogeneity:
## tau^2 = 0.4670; I^2 = 68.3% [55.5%; 77.4%]; G^2 = 91.5%
##
## Test of heterogeneity:
##       Q d.f.  p.value
##  113.52   36  < 0.0001
##
## Test of small-study effects:
##    Q-Q' d.f.  p.value
##   44.20    1  < 0.0001
##
## Test of residual heterogeneity beyond small-study effects:
##      Q' d.f.  p.value
##   69.32   35   0.0005
```

Compare estimates for NSAIDS example

Model	Odds ratio [95% CI]
Fixed effect model	2.89 [2.49; 3.35]
Random effects model	3.73 [2.80; 4.97]
Trim and fill (random effects estimate)	2.45 [1.83; 3.28]
Copas selection model	1.82 [1.46; 2.26]
Regression adjustment	1.84 [1.26; 2.68]

Adjusting for small-study effects: Summary

Three approaches

- ▶ Trim and fill method
    - ▶ R function **trimfill** in R package **meta**
    - ▶ Not model-based, somewhat ad hoc
- ▶ Copas selection model for publication bias
    - ▶ R function **copas**, implemented in R package **metasens**
    - ▶ Model-based, needs sensitivity analysis
    - ▶ Sometimes associated with estimation problems (Carpenter et al., 2009b)
- ▶ Adjustment by regression
    - ▶ R function **limitmeta**, implemented in R package **metasens**
    - ▶ Model-based, extension of the regression test

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Binary outcome: Notation

Result of study k

Event	yes	no	Total
Treatment	a_k	b_k	$a_k + b_k$
Control	c_k	d_k	$c_k + d_k$
Total	$a_k + c_k$	$b_k + d_k$	n_k

Modification I: Harbord's score test

- Take the efficient score

$$Z_k = a_k - (a_k + b_k)(a_k + c_k)/n_k$$

  of the log odds ratio with variance (Fisher's information)

$$V_k = (a_k + b_k)(a_k + c_k)(b_k + d_k)(c_k + d_k)/[n_k^2(n_k - 1)]$$

- Z_k/V_k is an estimate for the log odds ratio, if the true value of θ is not too far from 0 (standard likelihood theory)
- 1. Regress treatment effect estimate Z/V (with variance $1/V$) on its standard error $1/\sqrt{V}$ with study weights V
  2. Test null-hypothesis of zero slope
- Advantage: Variance estimate depends only on marginal totals

Modification II: Macaskill's/Peters' test

- ► Choose as effect measure the log odds ratio
- ► Let $\hat{\theta}_k$ be the effect estimate of study k, $a_k + c_k$ the number of events, $b_k + d_k$ the number of non-events in study k
  1. Regress treatment effect $\hat{\theta}$ on sample size n (Macaskill) or inverse sample size $1/n$ (Peters) with study weights $(1/(a + c) + 1/(b + d))^{-1}$ (both)
  2. Test null-hypothesis of zero slope
- ► Advantage: Variance estimate depends only on marginal totals

Modification III: Arcsine test

► With

$$p_{T,i} = \frac{a_k}{a_k + b_k} \quad \text{and} \quad p_{C,i} = \frac{c_k}{c_k + d_k}$$

choose as effect measure the arcsine difference

$$\Delta_k = \arcsin \sqrt{p_{T,i}} - \arcsin \sqrt{p_{C,i}}$$

►   1. Regress treatment effect Δ on standard error $\sqrt{\frac{1}{a+b} + \frac{1}{c+d}}$

       with weights $1/(\frac{1}{a+b} + \frac{1}{c+d})$

   2. Test null-hypothesis of zero slope

► Advantage: Variance estimate independent of mean treatment effect

Overview: Regression tests

Test	Measure	Regressor	Weights
Egger's test	$\hat{\theta}$	$\text{SE}(\hat{\theta})$	$1/\widehat{\text{Var}}(\hat{\theta})$
Harbord's score test	Z/V	$1/\sqrt{V}$	V
Peters' test	$\hat{\theta}$	$1/n$	$1/(\frac{1}{a+c} + \frac{1}{b+d})$
Arcsine test	Δ	$\sqrt{\frac{1}{a+b} + \frac{1}{c+d}}$	$1/(\frac{1}{a+b} + \frac{1}{c+d})$

Compare results of fixed effect and random effects model

```
summary(ms1)

## Number of studies combined: k=37
##
##                        OR          95%-CI        z   p-value
## Fixed effect model   2.9809  [2.5854; 3.4368]  15.0409 < 0.0001
## Random effects model 3.7345  [2.8039; 4.9740]   9.0105 < 0.0001
##
## Quantifying heterogeneity:
## tau^2 = 0.4670; H = 1.78 [1.5; 2.1]; I^2 = 68.3% [55.5%; 77.4%]
##
## Test of heterogeneity:
##       Q d.f.  p-value
##  113.52   36  < 0.0001
##
## Details on meta-analytical method:
## - Mantel-Haenszel method
## - DerSimonian-Laird estimator for tau^2
## - Continuity correction of 0.5 in studies with zero cell frequencies
```

Funnel plot and contour-enhanced funnel plot

```r
# Load the data
data(nsaids)
```

```r
# Perform meta-analysis
ms1 <- metabin(Ee, Ne, Ec, Nc, data = nsaids, sm = "OR")
```

```r
# Create funnel plot
funnel(ms1)
```

```r
# Create contour-enhanced funnel plot
funnel(ms1, comb.random = FALSE, pch = 16,
       contour = c(0.9, 0.95, 0.99),
       col.contour = c("green", "yellow", "pink"))
legend(0.25, 1.25,
       c("0.1 > p > 0.05", "0.05 > p > 0.01", "< 0.01"),
       fill = c("green", "yellow", "pink"), bty = "n")
```

Copas selection model

Combine two models:

1. Usual random effects model for treatment effect
2. A model for the selection process with a parameter controlling how chance of publication depends on precision $1/s_k$ (where s_k is the within-study standard error)
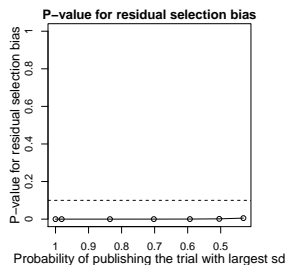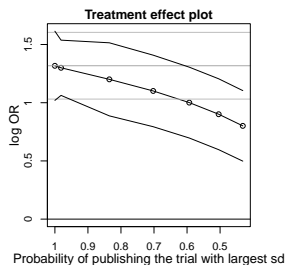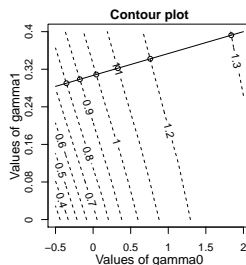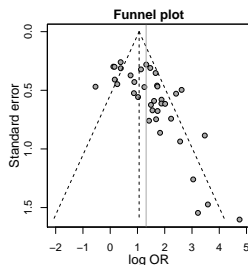
Selection/publication bias is modelled by a parameter representing the correlation between effect size and selection probability

- Implemented in function **copas** of R package **metasens** (earlier: **copas**) (Carpenter et al., 2009a)
- Sensitivity analysis necessary

```
# Use Copas selection model
c1 <- copas(ms1)
```

```
# Create plots for sensitivity analysis
plot(c1)
```

Copas selection model plot of NSAIDS data

Copas selection model

```
# Print results of Copas selection model
print(summary(c1), digits = 2)

## Summary of Copas selection model analysis:
##
##              publprob    OR        95%-CI pval.treat pval.rsb N.unpubl
##                  1.00 3.73 [2.77; 5.02]   < 0.0001 < 0.0001        0
##                  0.98 3.67 [2.89; 4.65]   < 0.0001 < 0.0001        0
##                  0.84 3.32 [2.43; 4.55]   < 0.0001 < 0.0001        3
##                  0.70 3.01 [2.21; 4.09]   < 0.0001 < 0.0001        8
##                  0.59 2.72 [2.01; 3.69]   < 0.0001   0.0004       14
##                  0.50 2.46 [1.82; 3.34]   < 0.0001   0.0014       20
##                  0.43 2.23 [1.65; 3.02]   < 0.0001   0.0054       28
##
##      Copas model (adj)
## Random effects model 3.73 [2.80; 4.97]   < 0.0001
##
## Significance level for test of residual selection bias: 0.1
##
## Legend:
## publprob  - Probability of publishing study with largest standard error
## pval.treat - P-value for hypothesis of overall treatment effect
## pval.rsb  - P-value for hypothesis that no selection remains unexplained
```
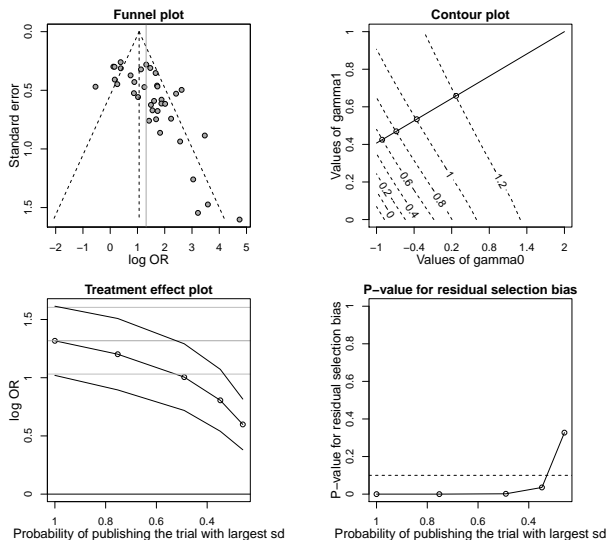
Copas selection model: Change sensitivity parameters

```
# Use Copas selection model, range of (gamma0, gamma1) modified
c2 <- copas(ms1, gamma0.range = c(-1, 2), gamma1.range = c(0, 1))


# Create plots for sensitivity analysis
plot(c2)
```

Copas selection model plot of NSAIDS data

Copas selection model

```
# Print results of Copas selection model
print(summary(c2), digits = 2)

## Summary of Copas selection model analysis:
##
##              publprob  OR       95%-CI pval.treat pval.rsb N.unpubl
##                  1.00 3.73 [2.77; 5.02]  < 0.0001 < 0.0001        0
##                  0.75 3.33 [2.45; 4.52]  < 0.0001 < 0.0001        4
##                  0.49 2.73 [2.05; 3.64]  < 0.0001   0.0018       15
##                  0.35 2.24 [1.72; 2.92]  < 0.0001   0.0356       30
##                  0.26 1.82 [1.46; 2.26]  < 0.0001   0.3273       48
##
##     Copas model (adj) 1.82 [1.46; 2.26]  < 0.0001   0.3273       48
##   Random effects model 3.73 [2.80; 4.97]  < 0.0001
##
##   Significance level for test of residual selection bias: 0.1
##
##   Legend:
##   publprob   - Probability of publishing study with largest standard error
##   pval.treat - P-value for hypothesis of overall treatment effect
##   pval.rsb   - P-value for hypothesis that no selection remains unexplained
##   N.unpubl   - Approximate number of unpublished studies suggested by model
```