

Evidence Synthesis / Meta-analysis

Session 3, Lecture 6: Small study effects

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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)

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

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)

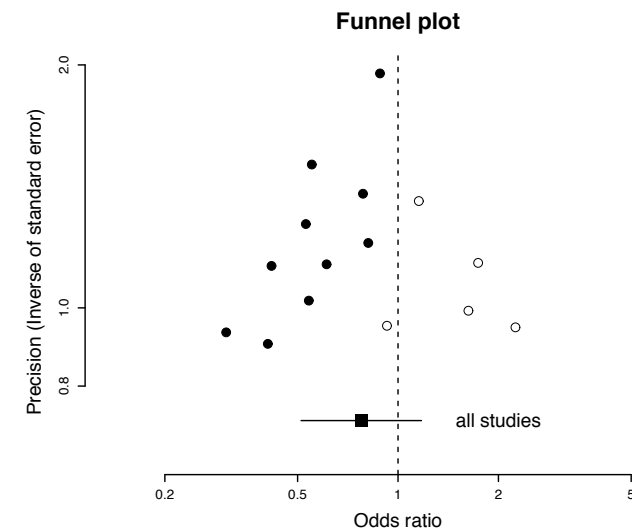
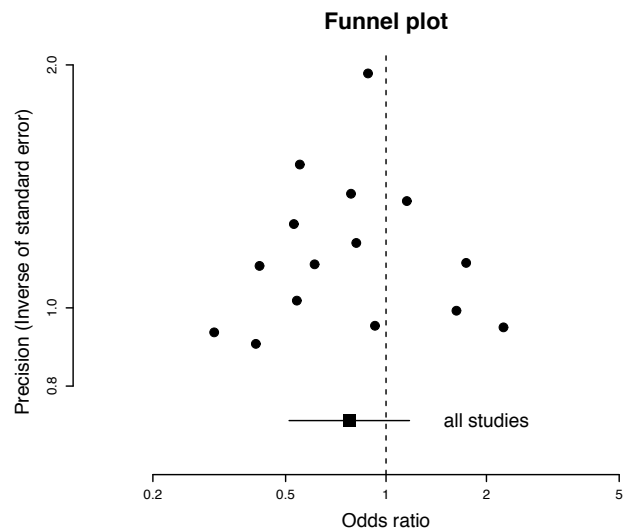
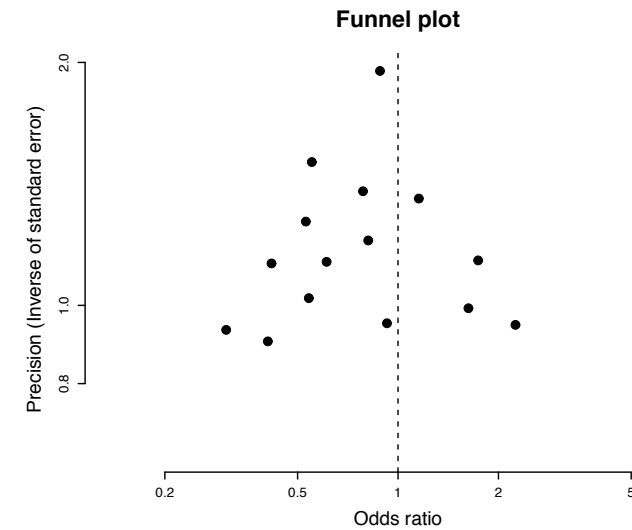
- ▶ Potential causes of small-study effects
 - ▶ **Publication bias**: Small studies tend to be published preferably if they show a large effect (Easterbrook et al., 1991)
 - ▶ **Selective outcome reporting bias**: Studies present selected outcomes (Chan et al., 2004a,b; Williamson and Gamble, 2005)
 - ▶ **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)

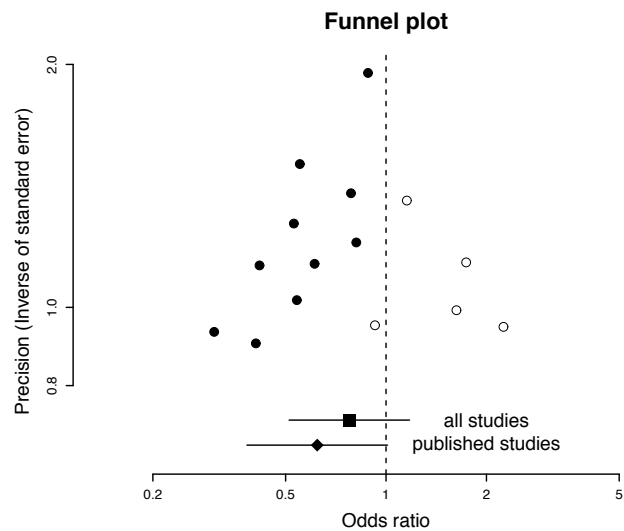
Funnel plot

Horizontal axis: (log) treatment effect

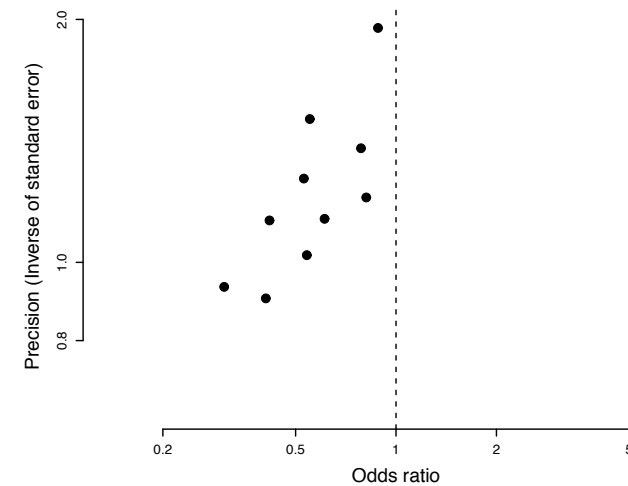
Vertical axis: a measure of precision; various versions in the literature:

- ▶ 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)

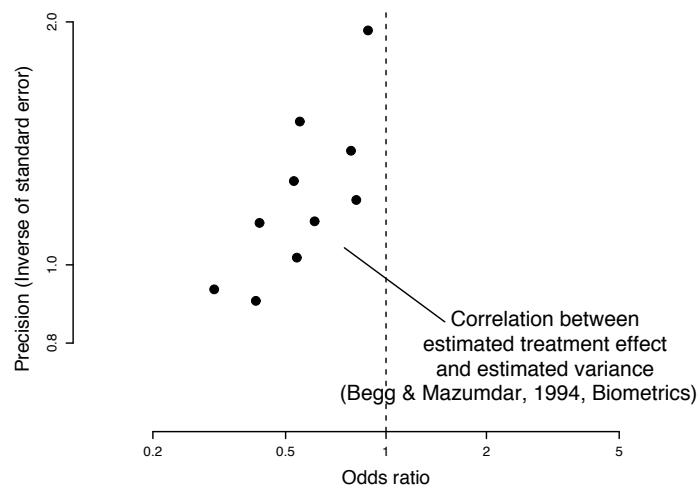




Bias in meta-analysis \Leftrightarrow Asymmetry in funnel plot



Bias in meta-analysis \Leftrightarrow Asymmetry in funnel plot



Funnel plot

Example: NSAIDS data

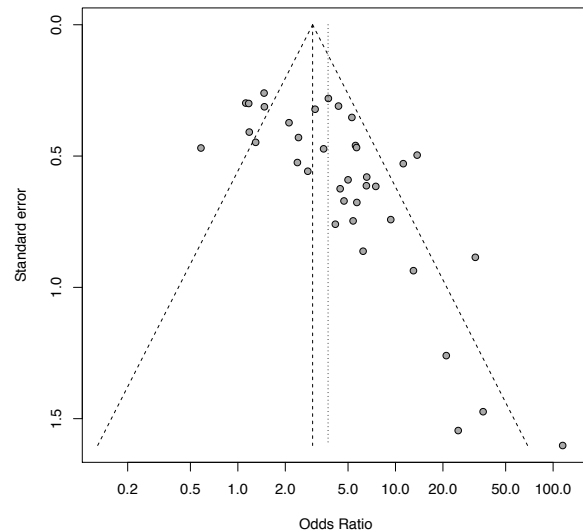
Meta-analysis of 37 placebo-controlled randomized trials on the effectiveness and safety of topical non-steroidal anti-inflammatory drugs (NSAIDS) in acute pain (Moore et al., 1998)

Part of R package **metasens**

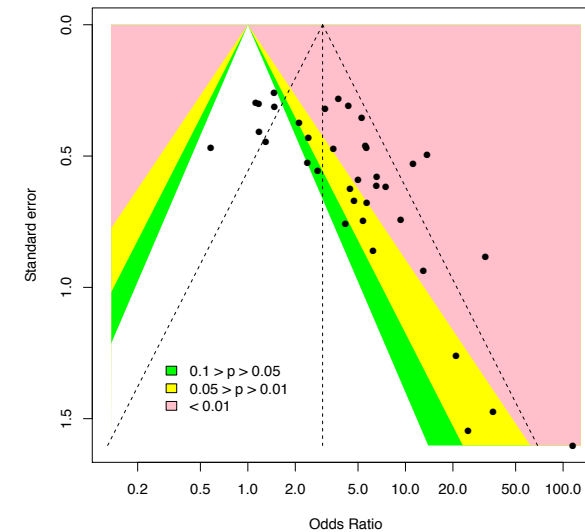
```
# Perform meta-analysis
ms1 <- metabin(Ee, Ne, Ec, Nc, data = ns aids, sm = "OR")
```

```
# 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)

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

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

- ▶ 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")`

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
tfl <- trimfill(ms1)
```

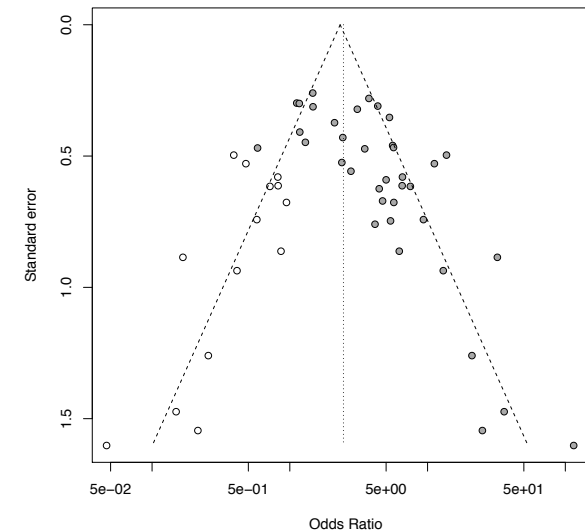
```
# Create funnel plot including filled-in studies
funnel(tfl)
```

Trim and fill method

```
# Print results of Trim and fill analysis
print(tfl, 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 ***
```

Trim and fill plot of NSAIDS data



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

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

- $\hat{\theta}_k$ observed treatment effect in study k ($k = 1, \dots, K$)
- 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:

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

Adjustment by regression

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

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

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

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

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

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

$$E(\hat{\theta}_k) \rightarrow \theta + \tau \alpha \text{ Adjusted effect of large study}$$

► Implemented in function **limitmeta** of R package **metasens** (Carpenter et al., 2009a)

Adjustment by regression

► Random effects model:

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

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

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

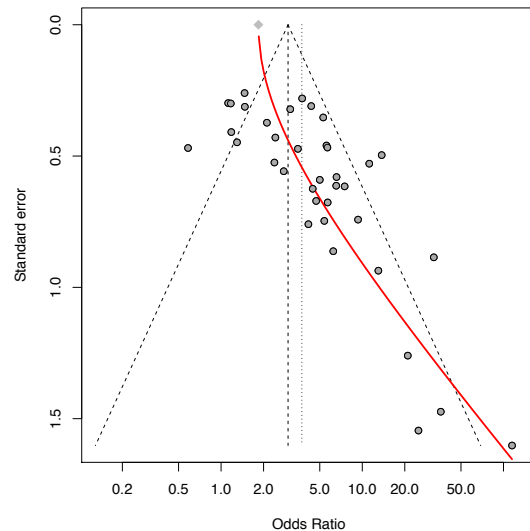
Additional parameter α represents bias introduced by small-study effects ('publication bias')

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



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]

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
```

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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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

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 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

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
```

Overview: Regression tests

Test	Measure	Regressor	Weights
Egger's test	$\hat{\theta}$	$SE(\hat{\theta})$	$1/\widehat{Var}(\hat{\theta})$
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	$\sqrt{\frac{1}{a+b} + \frac{1}{c+d}}$	$1/(\frac{1}{a+b} + \frac{1}{c+d})$

Funnel plot and contour-enhanced funnel plot

```
# Load the data
data(nsaid)
```

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

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

```
# Create contour-enhanced funnel plot
funnel(ms1, comb.random = FALSE, pch = 16,
        colour = 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)

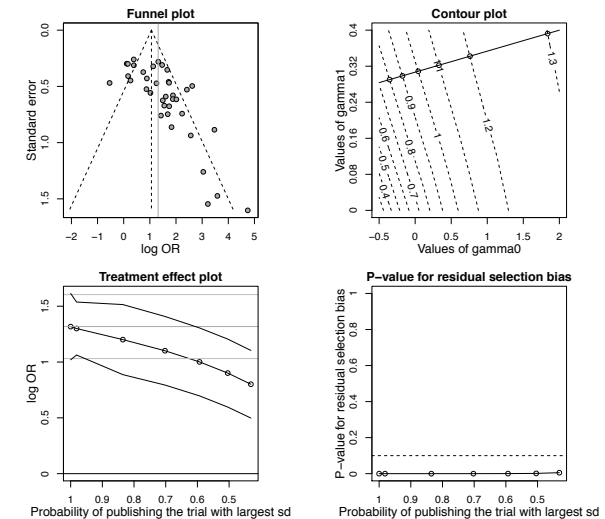
Selection/publication bias is modelled by a parameter representing the **correlation** between effect size and selection probability

- 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)
```

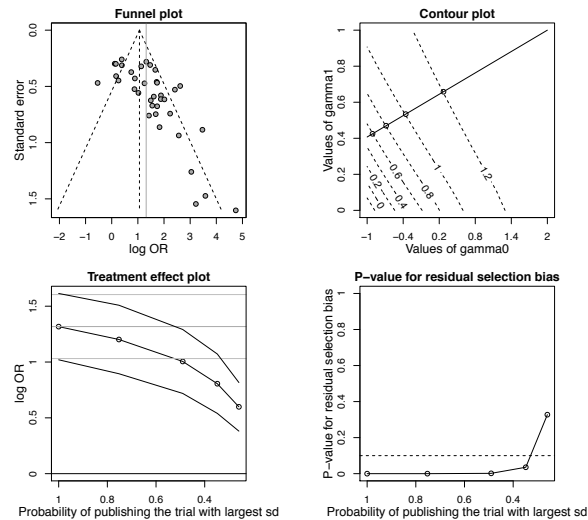
```
## Summary of Copas selection model analysis:
##
##      publprob  OR      95%-CI  pval.treat  pval.rsb  N.unpubl
##      1.00  3.73 [2.77; 5.02] < 0.0001 < 0.0001      0
##      0.98  3.67 [2.89; 4.65] < 0.0001 < 0.0001      0
##      0.84  3.32 [2.43; 4.55] < 0.0001 < 0.0001      3
##      0.70  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					