Treatment effect estimates adjusted for small-study effects via a limit meta-analysis

Gerta Rücker[1], James Carpenter[1 2], Guido Schwarzer[1]

[1]Institute of Medical Biometry and Medical Informatics, University Medical Center Freiburg
[2]Medical Statistics Unit, London School of Hygiene & Tropical Medicine, London, UK
DFG Forschergruppe FOR 534

ruecker@imbi.uni-freiburg.de

MAER Net Conference, Cambridge, 18 September, 2011

Outline

Small-study effects in meta-analysis

Extended random effects model

Application to an example

Simulation study

Concluding remarks

Small-study effects in meta-analysis

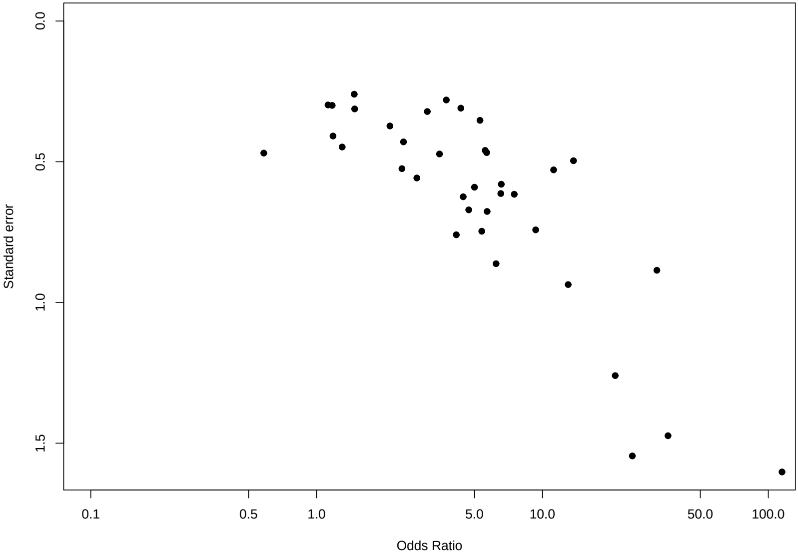
Small trials may show larger treatment effects than big trials, potentially caused by

- Publication bias:
  Small studies tend to be published only if they show a large effect
- Selective outcome reporting bias:
  Present the most significant outcome
- Clinical heterogeneity between patients in large and small trials
- For binary data, treatment effect estimate correlated with standard error

Small-study effects in meta-analysis

- Graphical representation of small-study effects: Asymmetry in funnel plot
- Numerous tests for funnel plot asymmetry available (Sterne et al., 2011)
- Treatment effect estimates adjusted for small-study effects
  - Copas selection model (Copas and Shi, 2000)
  - Trim and Fill method (Duval and Tweedie, 2000)
  - Regression-based approach (Stanley, 2008; Moreno et al., 2009)

A funnel plot showing a strong small-study effect



Extended random effects model (Rücker et al., 2010)

- Random effects model in meta-analysis:

$$x_i = \mu + \sqrt{\sigma_i^2 + \tau^2}\,\epsilon_i, \quad \epsilon_i \overset{iid}{\sim} N(0,1)$$

x_i observed effect in study i, μ global mean,
σ_i^2 within-study sampling variance, τ^2 between-study variance

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

$$x_i = \beta + \sqrt{\sigma_i^2 + \tau^2}\,(\alpha + \epsilon_i), \quad \epsilon_i \overset{iid}{\sim} N(0,1)$$

β replaces μ, and α represents bias introduced by small-study effects ('publication bias') (Stanley, 2008; Moreno et al., 2009)

Interpretation of α in the extended random effects model

$$x_i = \beta + \sqrt{\sigma_i^2 + \tau^2}\ (\alpha + \epsilon_i), \quad \epsilon_i \overset{iid}{\sim} N(0,1)$$

- α interpreted as the expected shift in the standardised treatment effect if precision is very small:

$$\mathrm{E}\left(\frac{x_i - \beta}{\sigma_i}\right) \to \alpha, \quad \sigma_i \to \infty$$

- α corresponds to the intercept in a radial (Galbraith) plot
- Egger test on publication bias based on $H_0 : \alpha = 0$

Interpretation of α in the extended random effects model

$$x_i = \beta + \sqrt{\sigma_i^2 + \tau^2}\ (\alpha + \epsilon_i), \quad \epsilon_i \overset{iid}{\sim} N(0,1)$$

- $\beta_0 = \beta + \tau\alpha$ interpreted as the limit treatment effect if precision is infinite:
$$E(x_i) \rightarrow \beta + \tau\alpha, \quad \sigma_i \rightarrow 0$$
- Interpretation of β changes as α is included in the model: In the presence of a small-study effect, the treatment effect is represented by $\beta + \tau\alpha$ instead of β alone
- $\beta + \tau\alpha$ corresponds to a point at the top of the funnel plot

ML estimation of α and β

- Use inverse variance weighting: $w_i = 1/(s_i^2 + \hat{\tau}^2)$
- ML estimates $\hat{\beta}$ and $\hat{\alpha}$ can be interpreted as slope and intercept in linear regression on so-called generalised radial (Galbraith) plots
- α and β often estimated with large standard error, particularly if
  - there are only few studies, or
  - there are small studies (large random error) with extreme results

  $\Rightarrow$ Potentially false positive finding of small-study effects
- Idea: Shrinkage by inflation of precision, based on extended model

Inflation of precision, based on extended model

$$x_i = \beta + \sqrt{\sigma_i^2 + \tau^2}\ (\alpha + \epsilon_i), \quad \epsilon_i \overset{iid}{\sim} N(0,1)$$

- Imagine each study has an *M*-fold increased precision:

$$x_{M,i} = \beta + \sqrt{\sigma_i^2/M + \tau^2}\ (\alpha + \epsilon_i), \quad \epsilon_i \overset{iid}{\sim} N(0,1)$$

- *Limit meta-analysis*:
  Let $M \to \infty$, substitute estimates for $\beta, \tau^2, \sigma_i^2$ and ϵ_i

$$x_{\infty,i} = \hat{\beta} + \sqrt{\frac{\hat{\tau}^2}{s_i^2 + \hat{\tau}^2}}\,(x_i - \hat{\beta})$$

- Limit meta-analysis compared to empirical Bayes estimation
  - Takes account for bias correction
  - Shrinkage factor $\sqrt{\frac{\hat{\tau}^2}{s_i^2+\hat{\tau}^2}}$ less marked than for empirical Bayes $\left(\frac{\hat{\tau}^2}{s_i^2+\hat{\tau}^2}\right)$

Application: NSAIDS example

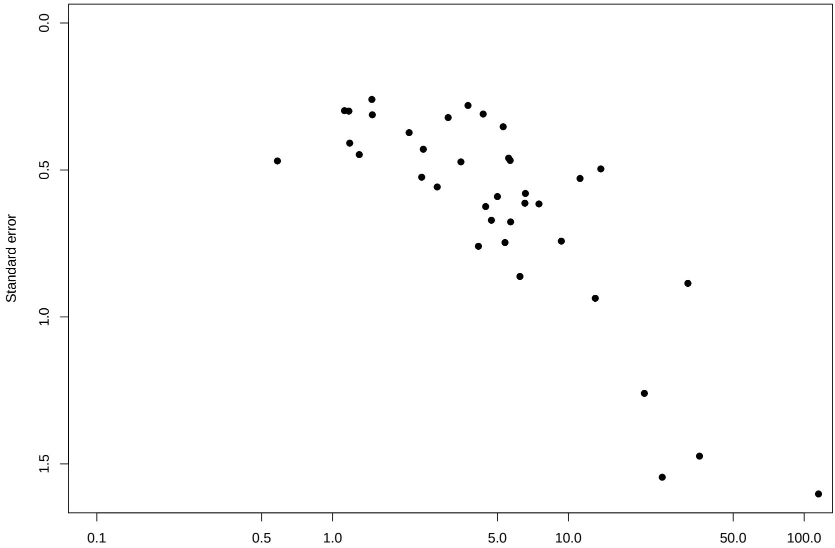
Example

- 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)

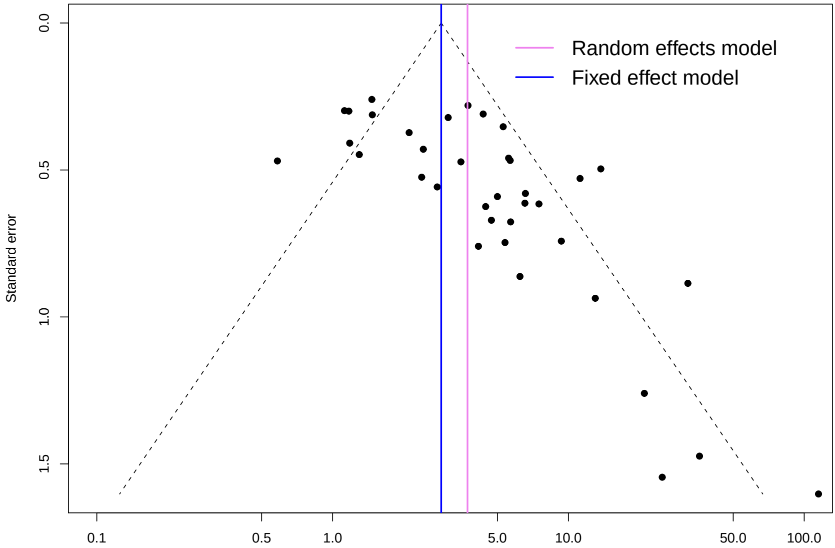
Models compared

- Fixed and random effects model
- Three estimates based on limit meta-analysis (Rücker et al., 2010)
  - Expectation $\beta_0 = \beta + \tau\alpha$
  - Model including bias parameter
  - Model without bias parameter
- Copas selection model (Copas and Shi, 2000)
- Trim and Fill method (Duval and Tweedie, 2000)
- Peters method (Moreno et al., 2009)

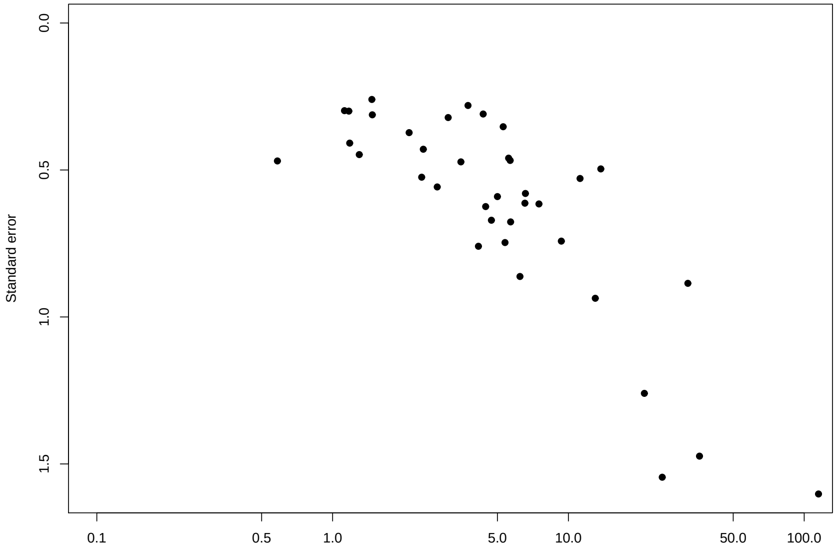
NSAIDS example (Moore et al., 1998): Funnel plot



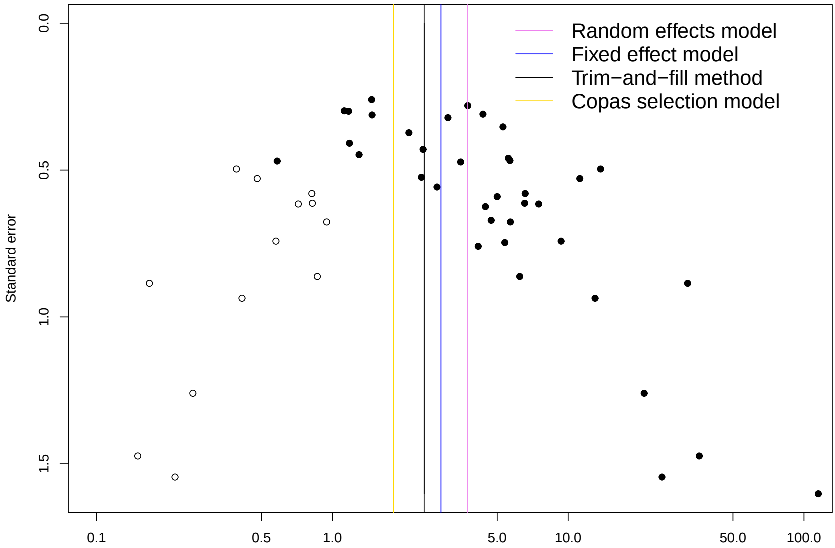
NSAIDS example (Moore et al., 1998)



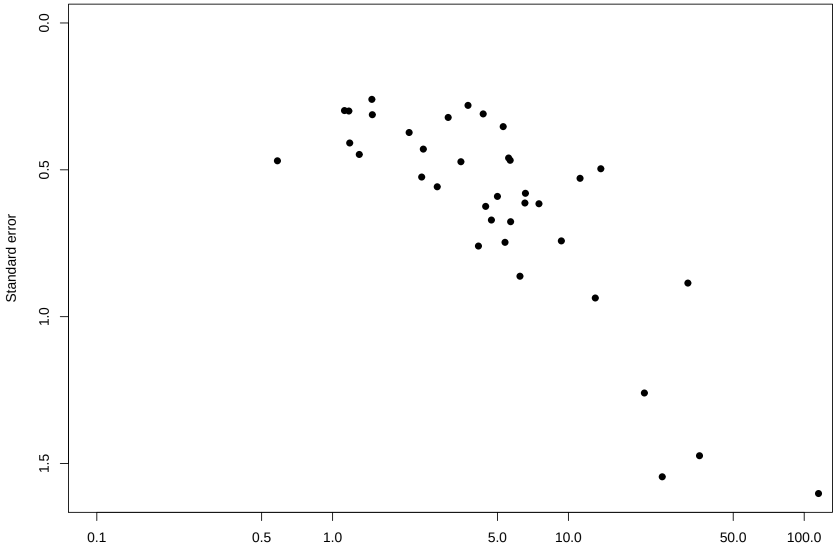
NSAIDS example (Moore et al., 1998)



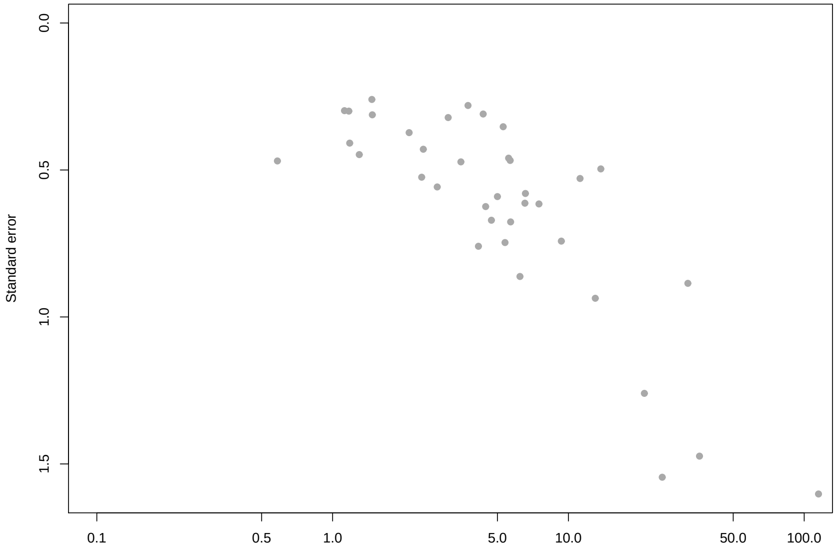
NSAIDS example (Moore et al., 1998)



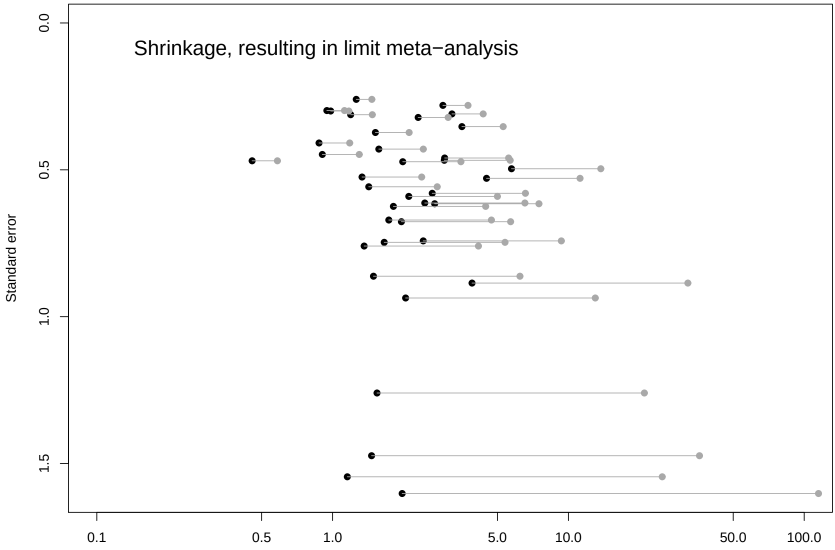
NSAIDS example (Moore et al., 1998)



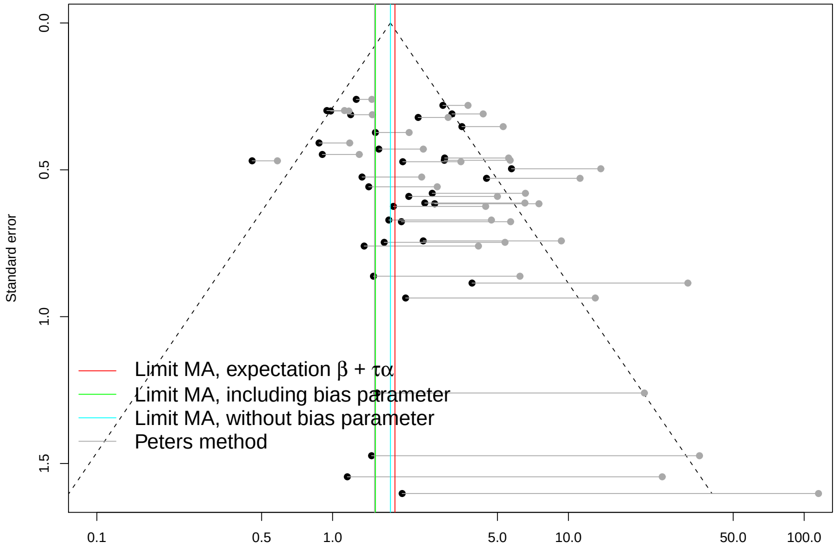
NSAIDS example (Moore et al., 1998)



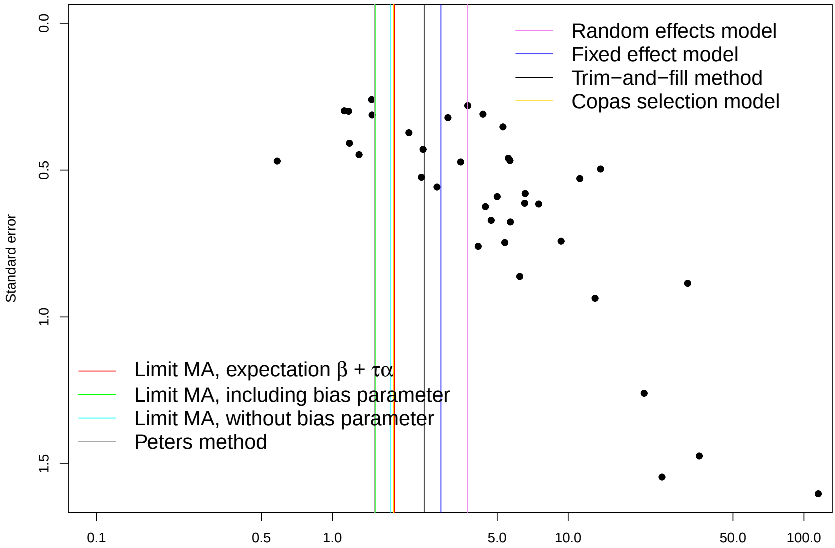
NSAIDS example (Moore et al., 1998)



NSAIDS example (Moore et al., 1998)



NSAIDS example (Moore et al., 1998)



NSAIDS example (Moore et al., 1998): Effect estimates

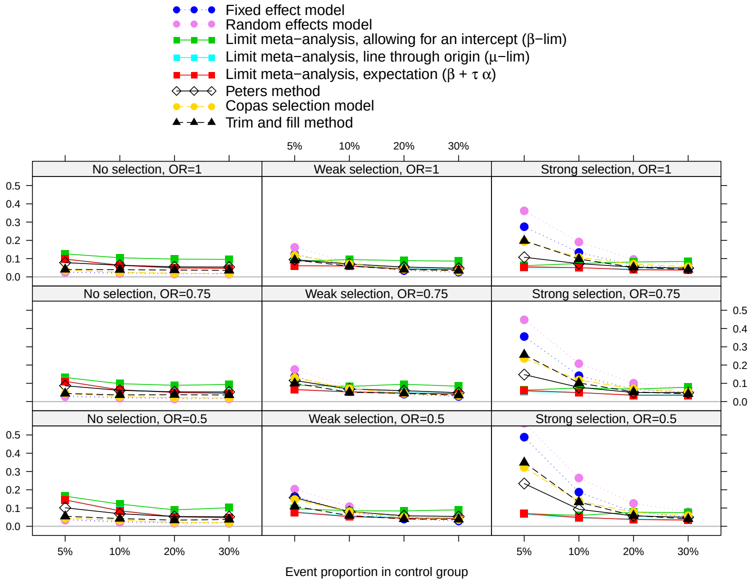
Model	Odds ratio [95% CI]
Fixed effect model	2.89 [2.49; 3.35]
Random effects model	3.73 [2.80; 4.97]
Trim and fill (random effects estimate)	2.45 [1.83; 3.28]
Copas selection model	1.82 [1.46; 2.26]
Limit meta-analysis, expectation ($\beta_0 = \beta + \tau\alpha$)	1.84 [1.26; 2.68]
Limit meta-analysis, including bias parameter	1.52 [1.04; 2.21]
Limit meta-analysis, without bias parameter	1.76 [1.52; 2.04]
Peters method	1.51 [1.03; 2.20]

Simulation study (Rücker et al., 2011)

36 Scenarios, based on binary response data, each repeated 1000 times, setting

- the number of trials in the meta-analysis: 10 (trial sizes drawn from a log-normal distribution)
- heterogeneity variance $\tau^2 = 0.10$
- true odds ratio: 0.5, 0.75, 1
- control group event probability: 0.05, 0.10, 0.20, 0.30
- small-study effects simulated based on Copas selection model (Copas and Shi, 2000), with selection parameter ρ^2 : 0, 0.36, 1

Simulation results: Mean Squared Error (MSE)



Simulation study: Summary of results

- In the absence of small-study effects
  - Conventional models worked best
  - Copas selection model preferable to Trim and Fill
  - Extended random effects model not optimal
- In the presence of strong selection
  - Limit meta-analysis without bias parameter had smallest MSE
  - Limit meta-analysis including bias parameter had smallest bias
  - Limit meta-analysis expectation and Peters method had best coverage
- Estimates robust against varying estimators for τ^2
  (Diploma thesis Dominik Struck, Freiburg)

Concluding remarks

Modelling and philosophy

- Extend the random effects model by a parameter for bias caused by potential small-study effects
- Limit meta-analysis yields shrunken estimates of individual study effects — can also be justified from an empirical Bayesian viewpoint
- Consistent with the philosophy of random effects modelling, that *'inference for each particular study is performed by 'borrowing strength' from the other studies'* (Higgins et al., 2009)
- For adjusting it doesn't matter where small-study effects come from (Moreno et al., 2009)
- Large studies are more reliable than small studies
  'Could it be better to discard 90% of the data? A statistical paradox' (Stanley et al., 2010)

References

Copas, J. and Shi, J. Q. (2000). Meta-analysis, funnel plots and sensitivity analysis. *Biostatistics*, 1:247–262.

Duval, S. and Tweedie, R. (2000). Trim and Fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics*, 56:455–463.

Higgins, J. P., Thompson, S. G., and Spiegelhalter, D. J. (2009). A re-evaluation of random-effects meta-analysis. *Journal of the Royal Statistical Society*, 172:137–159.

Moore, R. A., Tramer, M. R., Carroll, D., Wiffen, P. J., and McQuay, H. J. (1998). Quantitive systematic review of topically applied non-steroidal anti-inflammatory drugs. *British Medical Journal*, 316(7128):333–338.

Moreno, S., Sutton, A., Ades, A., Stanley, T., Abrams, K., Peters, J., and Cooper, N. (2009). Assessment of regression-based methods to adjust for publication bias through a comprehensive simulation study. *BMC Medical Research Methodology*, 9:2.

Rücker, G., Carpenter, J., and Schwarzer, G. (2011). Detecting and adjusting for small-study effects in meta-analysis. *Biometrical Journal*, 53(2):351–368.

Rücker, G., Schwarzer, G., Carpenter, J., Binder, H., and Schumacher, M. (2010). Treatment effect estimates adjusted for small-study effects via a limit meta-analysis. *Biostatistics*, 12(1):122–142. Doi:10.1136/jme.2008.024521.

Stanley, T., Jarrell, S. B., and Doucouliagos, H. (2010). Could it be better to discard 90% of the data? A statistical paradox. *The American Statistician*, 64(1):70–77.

Stanley, T. D. (2008). Meta-regression methods for detecting and estimating empirical effects in the presence of publication selection. *Oxford Bulletin of Economics and Statistics*, 70(105–127).

Sterne, J. A. C. et al. (2011). Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *British Medical Journal*, 343:d4002. doi: 10.1136/bmj.d4002.

Appendix: ML estimation of α and β

- Writing $w_i = 1/(s_i^2 + \hat{\tau}^2)$ (inverse variance weighting), obtain estimates

$$\hat{\beta} = \frac{\sum_{i=1}^k w_i x_i - \frac{1}{k}\sum_{i=1}^k \sqrt{w_i}\sum_{i=1}^k \sqrt{w_i} x_i}{\sum_{i=1}^k w_i - \frac{1}{k}(\sum_{i=1}^k \sqrt{w_i})^2}$$

$$\hat{\alpha} = \frac{1}{k}\sum_{i=1}^k \sqrt{w_i}(x_i - \hat{\beta}).$$

- $\hat{\beta}$ and $\hat{\alpha}$ can be interpreted as slope and intercept in linear regression on so-called generalised radial plots

Appendix: ML estimation of α and β – Variance estimates

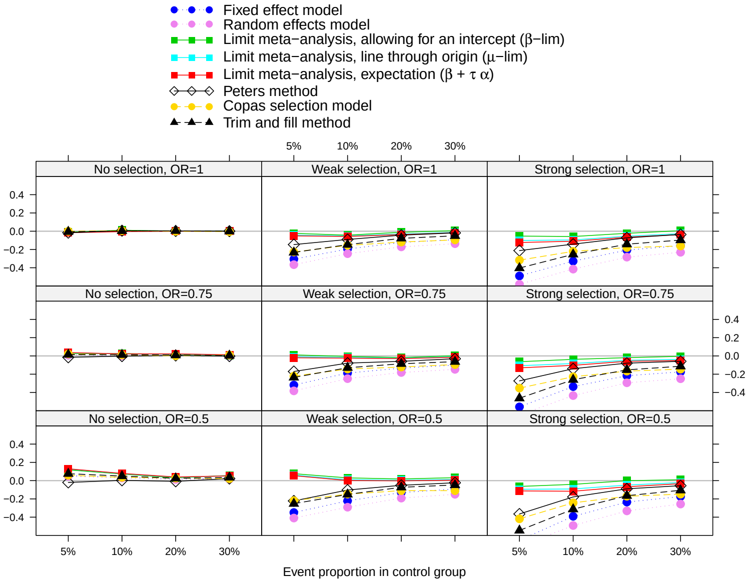
- Variance estimates:

$$\widehat{\text{Var}}\ (\hat{\beta}) = \frac{1}{\sum w_i - \frac{1}{k}\left(\sum \sqrt{w_i}\right)^2}$$

$$\widehat{\text{Var}}\ (\hat{\alpha}) = \frac{\frac{1}{k}\sum w_i}{\sum w_i - \frac{1}{k}\left(\sum \sqrt{w_i}\right)^2}$$

- Both variance estimates inversely proportional to variance of the observed study precisions $\sqrt{w_i} = 1/s_i$
  $\Rightarrow$ Estimation is the more precise, the more precision (size) varies between studies

Appendix: Simulation results for bias $\log \widehat{OR} - \log OR$



Appendix: Simulation results for coverage of 95% CI