University of Zurich[UZH]

Biostatistics

Publication Bias in Meta-Analysis

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Publication Bias

Availability of studies depends on the effect sizes thereof

Thesis topic: Abundancy and extent of publication bias in clinical science

Cochrane Organisation

Aim: summarise findings in primary clinical research and health care

Provide peer-reviewed, systematic reviews

Public access (for some countries)

Cochrane Library Dataset

5,016 systematic reviews with studies published until 2018.

52,995 studies.

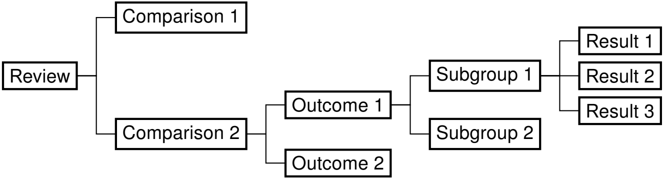
463,820 study results.

Review Example: Binary Outcome

Barbiturate efficacy for head injury treatment

Study	Comparison	Outcome	Events	Total	Events_c	Total_c
Bohn 1989	Barbiturate vs no b	Death at the end of	11	41	11	41
Bohn 1989	Barbiturate vs no b	Death or severe dis	18	41	13	41
Eisenberg 1988	Barbiturate vs no b	Uncontrolled ICP du	25	37	30	36
Eisenberg 1988	Barbiturate vs no b	Hypotension during	23	37	18	36
Perez-Barcena 2008	Pentobarbital vs Th	Death at the end of	16	21	9	21
Perez-Barcena 2008	Pentobarbital vs Th	Death or severe dis	17	21	13	21
Perez-Barcena 2008	Pentobarbital vs Th	Uncontrolled ICP du	18	22	11	22
Perez-Barcena 2008	Pentobarbital vs Th	Hypotension during	20	22	21	22
Schwartz 1984	Barbiturate vs Mann	Death at the end of	6	15	7	14
Schwartz 1984	Barbiturate vs Mann	Uncontrolled ICP du	19	28	12	31
Ward 1985	Barbiturate vs no b	Mean ICP during tre	0	27	0	26
Ward 1985	Barbiturate vs no b	Mean arterial press	0	27	0	26
Ward 1985	Barbiturate vs no b	Mean body temperatu	0	27	0	26

Dataset Structure



Dataset Properties

Review or study level:

	5% quantile	median	mean	95% quantile
Number of studies	1	7	12	40
Number of comparisons	1	2	4	12
Number of meta-analyses	2	19	37	132
Study years	1981	2002	2000	2013
Study sample size	13	78	750	890

Meta-analysis

Benefits:

- Summary of evidence (e.g. of a treatment effect)
- More reliable evidence (?)

Assumptions:

- Identical study settings (can be relaxed)
- Random sample of studies

Small Study Effects

"The tendency for the smaller studies to show larger treatment effects" (Sterne et al., 2001)

Small Study Effects

Causes:

- Selective publication of studies with significant results - publication bias
- Selective reporting of most favorable outcomes
- Systematic differences in study settings

Small Study Effect Tests

Different approaches:

- Simple linear regression
- Rank correlation

Special methods for binary outcomes

Regression based Tests

studies $i, .., n$, effects θ_i and variances v_i, s.e. s_i

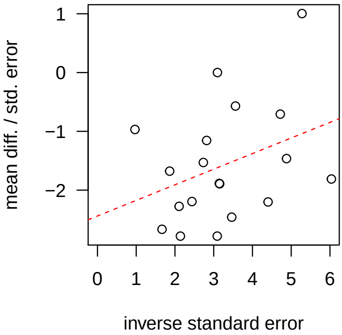
θ_M is the pooled effect and τ^2 the between-study variance.

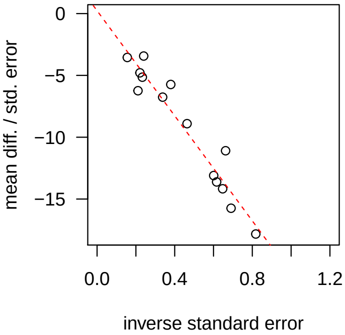
Let $y_i = \theta_i /_i$ and $x_i = 1/s_i$

- Egger et al. (1997) : Simple linear regression
  $y_i = \beta_0 + \beta_1 x_i, \epsilon_i \sim N(0, \sigma)$
- Thompson and Sharp (1999) : extension of Egger with study weights $v_i + \tau^2$

Egger's Test examples

Test for non-zero intercept β_0





Regression Tests for Binary Outcomes

- Peters et al. (2006) :$x_i = 1/n_i$ instead $1/s_i$, inverse variances as weight.
- Harbord et al. (2006) :x_i = score of the log-likelihood of a proportion and inverse variances as weights.
- **?** :Use arcsine variance stabilizing transformation for variances and effects, do e.g. Egger's test.

Rank based tests

Begg (1988):

Let y_i be $frac\theta_i - \theta_M v_i$ and x_i its variance ($\neq v_i$)

u the number of pairs (y_i, x_i) ranked in the same order, l the number of pairs in the opposite order

$Z = \frac{(u-l)}{\sqrt{n(n-1)(2n+5)/18}}$ is a test statistic

Rank based tests

Schwarzer et al. (2007):

e_t number of events in the treatment group

E_t follows hypergeometric distribution: calculate $\mathbb{E}(E_t)$ and variances

proceed as in Begg (1988)

Test Results

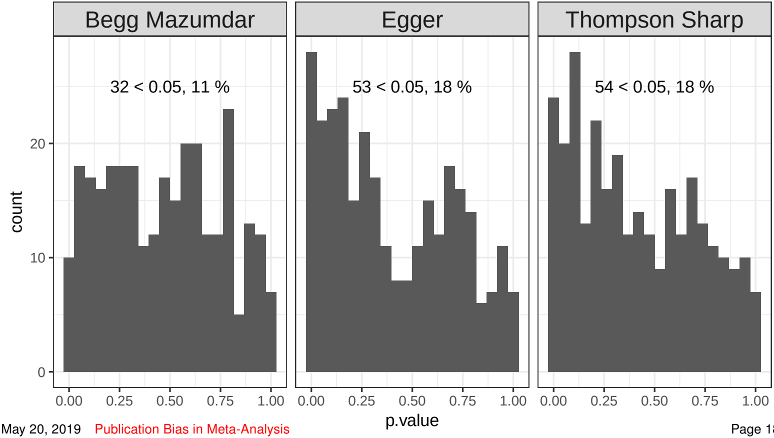
Inclusion criteria (from Ioannidis and Trikalinos (2007)):

- $n \geq 10$
- at least one statistically significant effect in a study
- $\frac{\sigma^2_{\max}}{\sigma^2_{\min}} > 4$
- $I^2 < 0.5$

From 5338 with $n \geq 10$, 1484 remain.

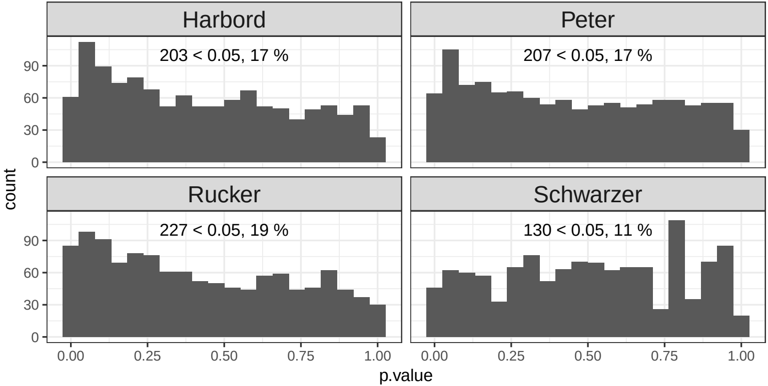
Continuous Outcome Test Results

p-values distribution, $n = 294$:



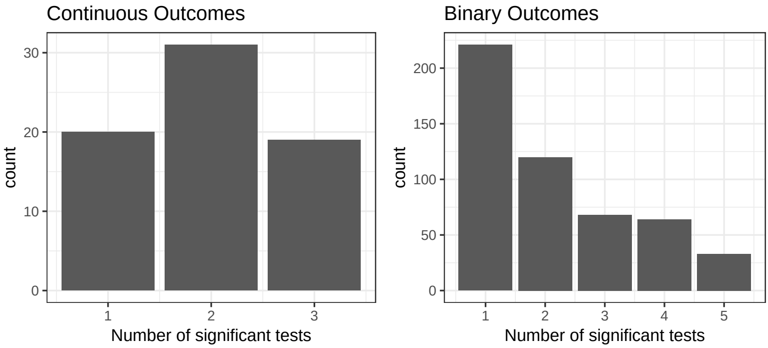
Binary Outcome Test Results

p-values distribution, n = 1190:



Agreement in significance

Number of significant test results per meta-analysis:



Small Study Effect Adjustment

Three methods:

- Regression
- Copas selection model
- Trim-and-fill

Adjustment by regression

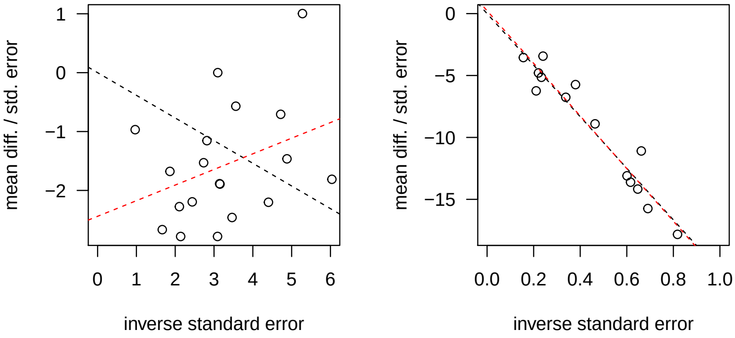
$y_i = \theta_i / s_i, x_i = 1/s_i$

$y_i = \beta_0 + \beta_1 x_i, \epsilon_i \sim N(0, \sigma)$

β_1 is the weighted mean treatment effect if $\beta_0 = 0$

Adjustment by regression

Radial plots (continuous outcome examples):



Limit Meta-Analysis

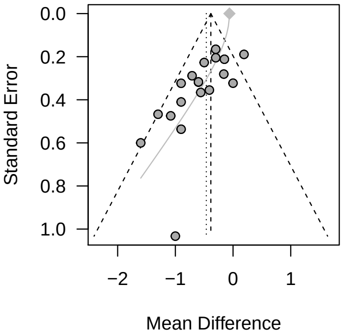
Extended random effects model:

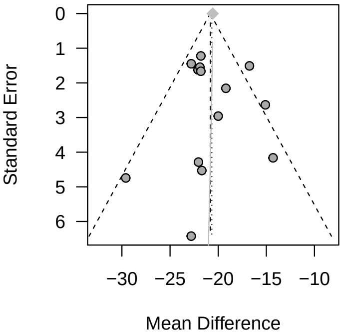
$$y_i = \beta_0 + \beta_1(\sqrt{v_i + \tau^2}) + \epsilon_i(\sqrt{v_i + \tau^2}),$$
$$\epsilon_i \overset{\text{iid}}{\sim} N(0, 1)$$

Use $\mathbb{E}(y_i) \to \beta_0 + \beta_1 \tau$ for $\sqrt{v_i} \to 0$ as corrected treatment efffect.

Limit Meta-Analysis

Funnel plot with effect with infinite precision:





Selection model

Copas and Shi (2001): model based on a bivariate normal distribution:

$$y_i = \mu_i + \sigma_i \epsilon_i \tag{1}$$

$$\mu_i \sim N(\mu, \tau^2) \tag{2}$$

$$z_i = a + b/s_i + \delta_i \tag{3}$$

2 is called population model, 3 the selection model

(ϵ_i, δ_i) are standard normal residuals with correlation $\rho = cor(y_i, z_i)$.

Sensitivity Analysis

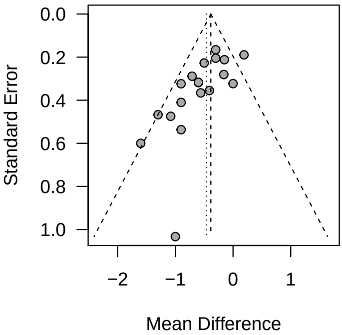
Model the selection process with different a, b

Test if small study effect is significant, by including
$y_i = \mu_i + \beta s_i + \sigma_i \epsilon_i$

Estimation: Select a, b such that $H0$ can not be rejected and estimated number of unpublished studies is minimal.

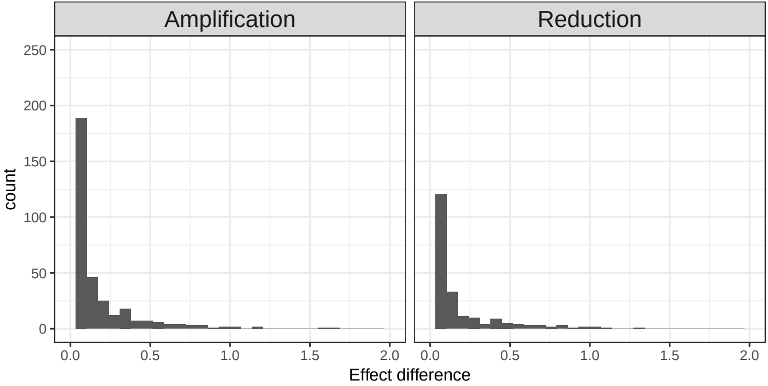
Trim-and-Fill

Mirror studies that cause asymmetry:



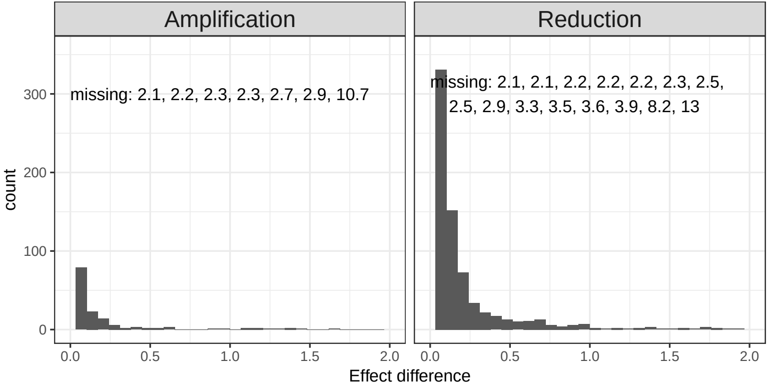
Results:

Difference between random and fixed effects meta-analysis estimate:



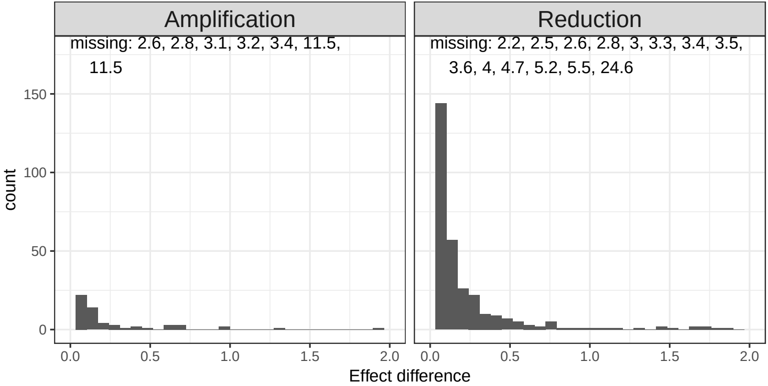
Adjustment Results: Trim-and-fill

Difference between adjusted and fixed effects meta-analysis estimate:



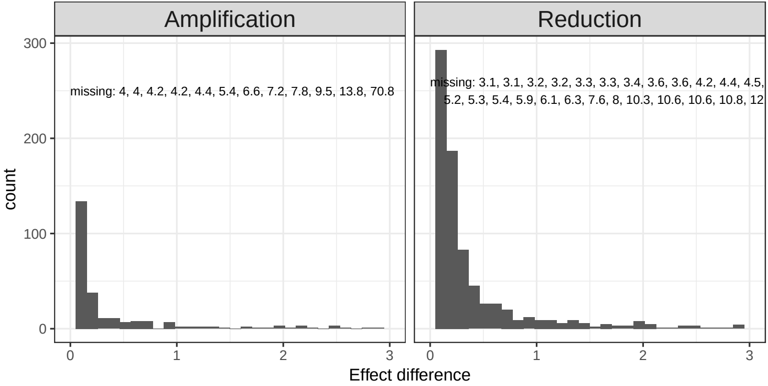
Adjustment Results: Copas

Difference between adjusted and fixed effects meta-analysis estimate:



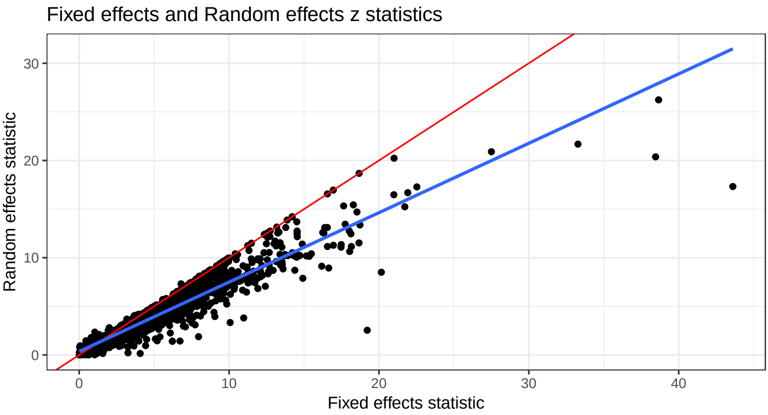
Adjustment Results: Regression

Difference between adjusted and fixed effects meta-analysis estimate:



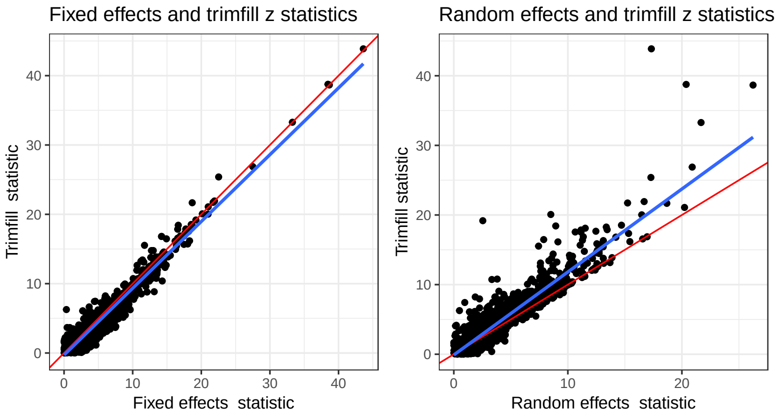
Results:

Random and fixed effects meta-analyses test statistics:



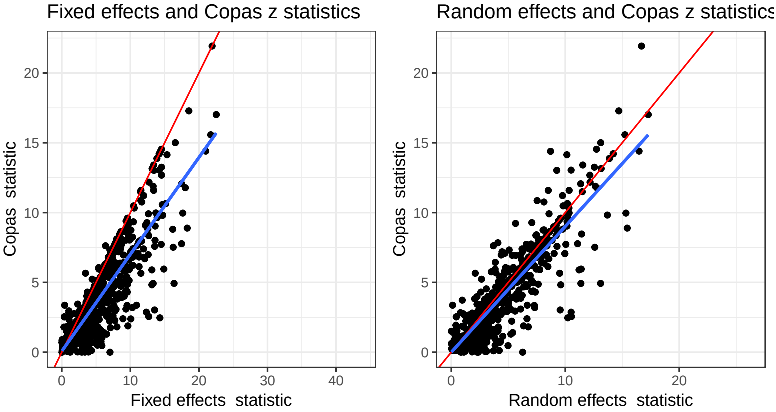
Adjustment Results: Trim-and-fill

Adjusted and meta-analysis test statistics:



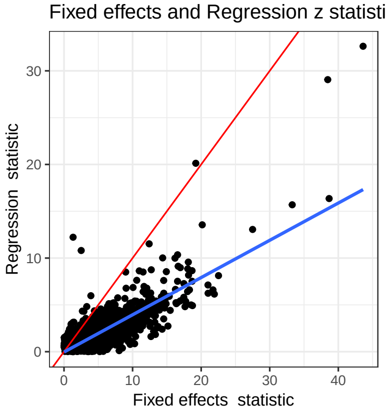
Adjustment Results: Copas

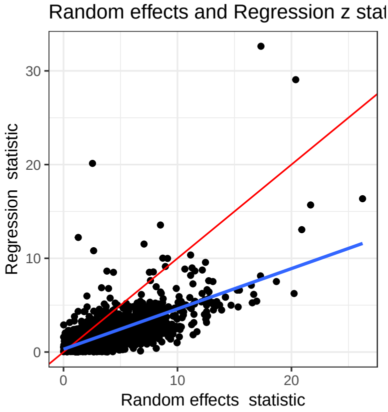
Adjusted and meta-analysis test statistics:



Adjustment Results: Regression

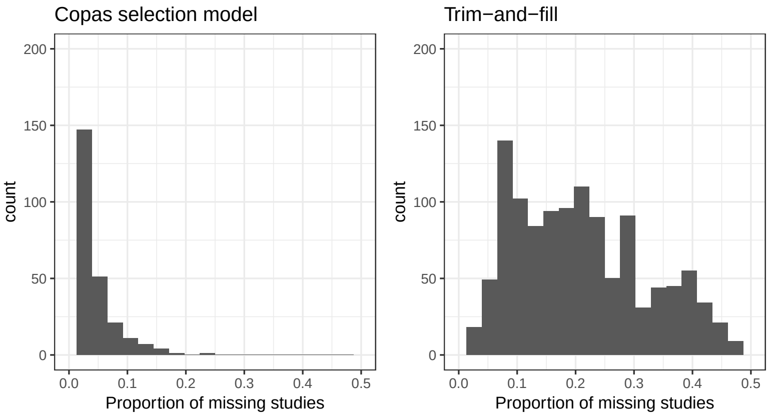
Adjusted and meta-analysis test statistics:





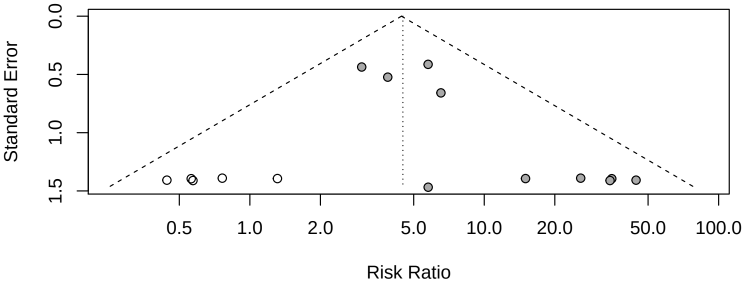
Adjustment Results

Missing study proportions:



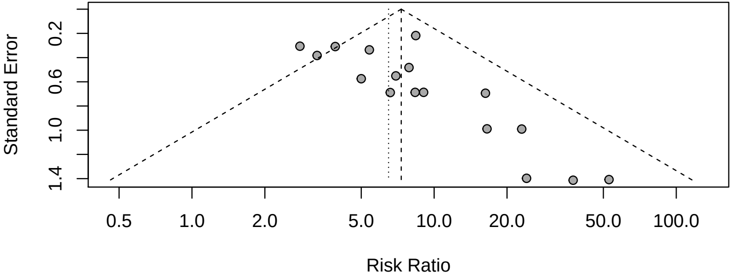
Extreme Results

RR reduction by trimfill (-3.9), side effects



Extreme Results

RR Reduction by copas selection model (-4), pain relief

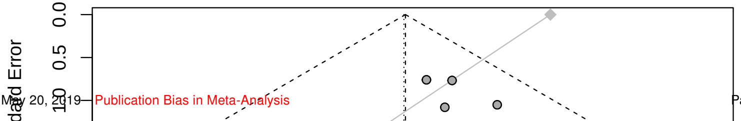


Extreme Results

RR Amplification by regression (+14), side effects

```
## Warning in summary.lm(reg):  essentially perfect
fit:  summary may be unreliable

## Warning in summary.lm(reg):  essentially perfect
fit:  summary may be unreliable
```



Discussion

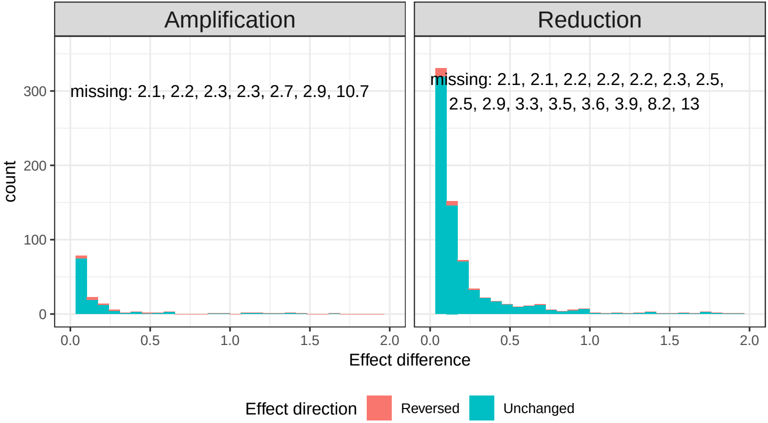
- Proportion of positive tests is well above 10%
- Effect sizes and evidence for treatment effect is diminishued
- Limitations: not only primary outcomes, adjustment methods known to perform poorly under the 0

Outlook

– Connect results with different medical fields, look for differences
– Connect results with single studies and journals (?)

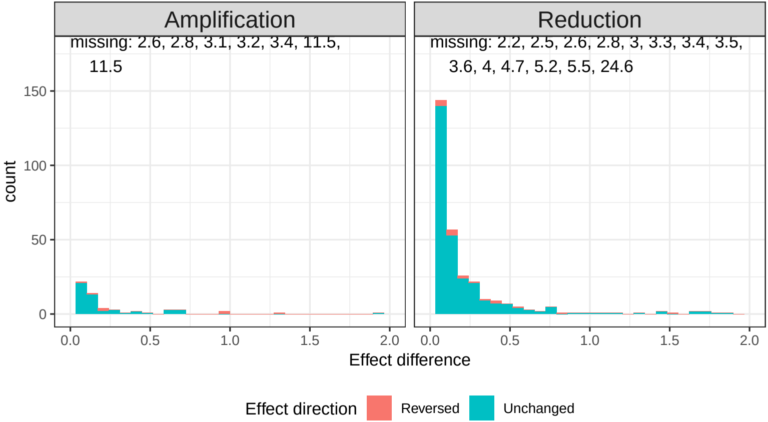
Adjustment Results: Trim-and-fill

Treatment effect difference:



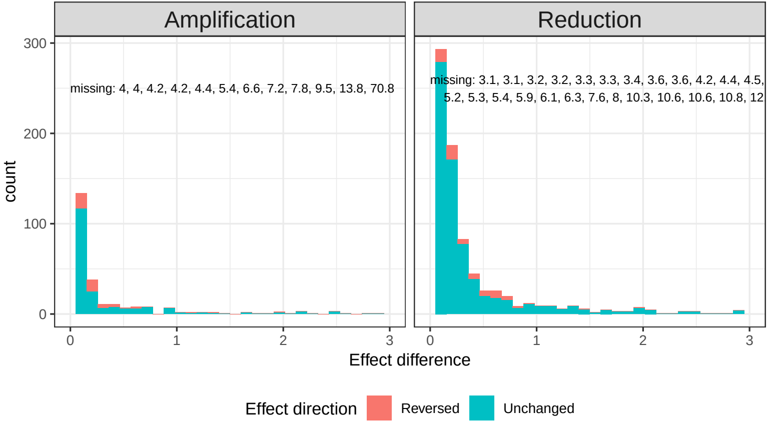
Adjustment Results: Copas

Treatment effect difference:



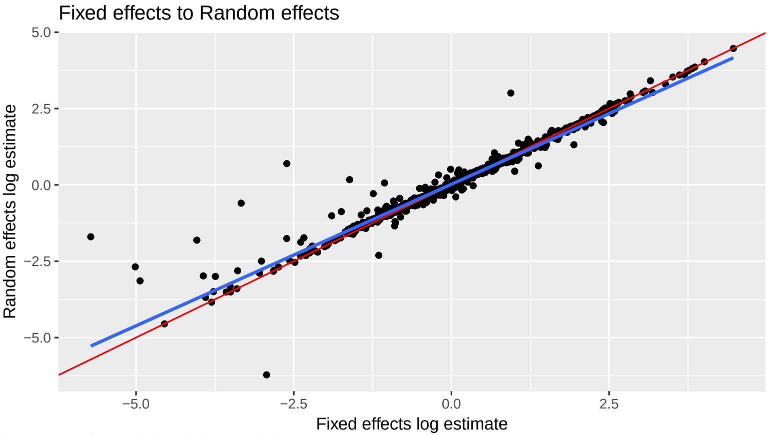
Adjustment Results: Regression

Treatment effect difference:



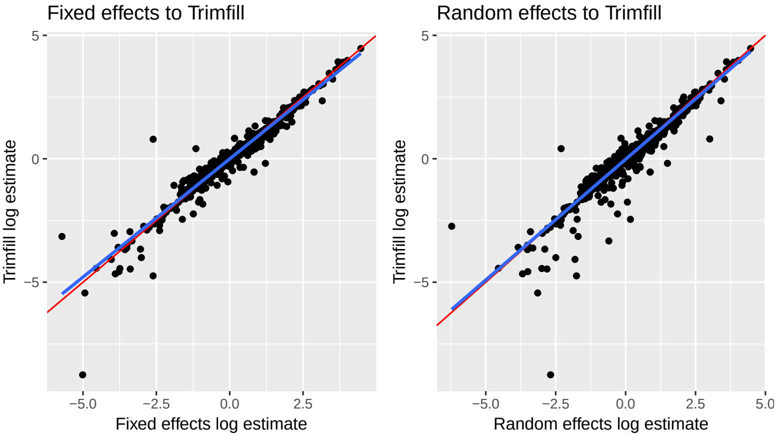
Results

log treatment effect estimates:



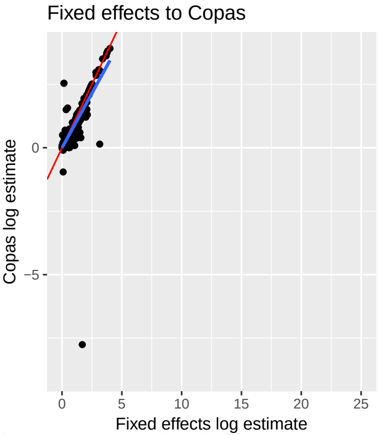
Adjustment Results: Trim-and-fill

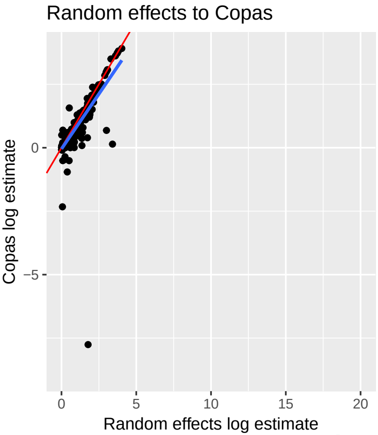
log treatment effect estimates:



Adjustment Results: Copas

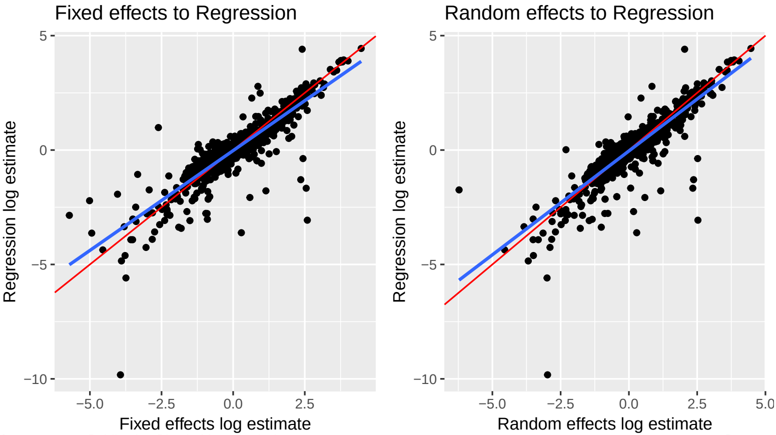
log treatment effect estimates:





Adjustment Results: Regression

log treatment effect estimates:



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Begg, C. B. (1988). Statistical methods in medical research p. armitage and g. berry, blackwell scientific publications, oxford, u.k., 1987. no. of pages: 559. price Â£22.50. *Statistics in Medicine*, 7(7):817–818.

Copas, J. B. and Shi, J. Q. (2001). A sensitivity analysis for publication bias in systematic reviews. *Statistical Methods in Medical Research*, 10(4):251–265. PMID: 11491412.

Egger, M., Smith, G. D., Schneider, M., and Minder, C. (1997). Bias in meta-analysis detected by a simple, graphical test. *BMJ*, 315(7109):629–634.

Harbord, R. M., Egger, M., and Sterne, J. A. C. (2006). A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints. *Statistics in Medicine*, 25(20):3443–3457.