University of Zurich[UZH]

Biostatistics

# Publication Bias in Meta-Analysis

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# 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.

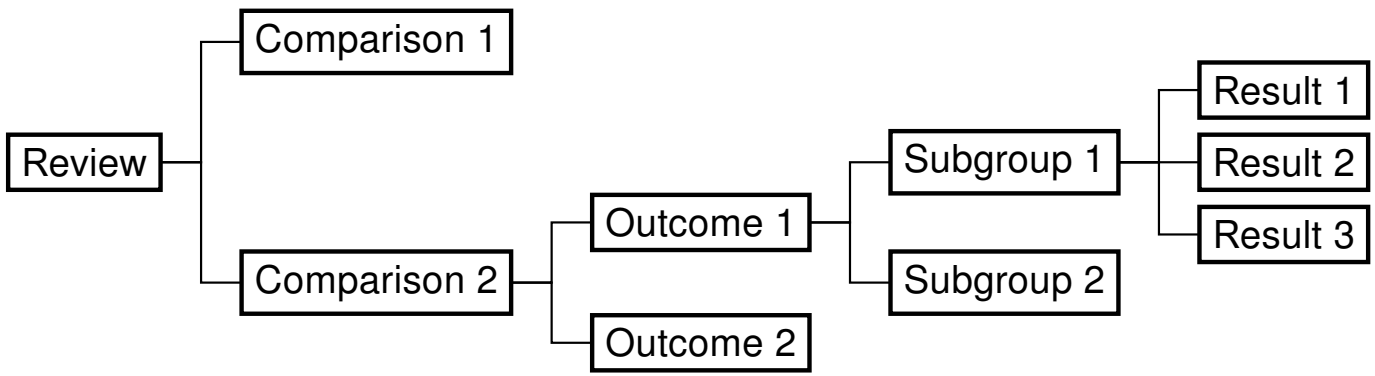
463,820 study results.

# 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
- Systematical differences in study settings

# Small Study Effect Tests

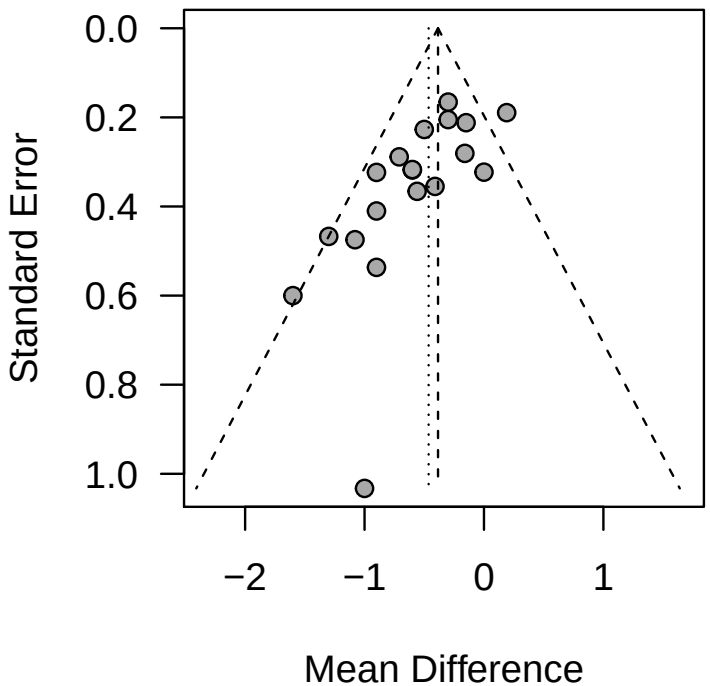
Tests applicable if:

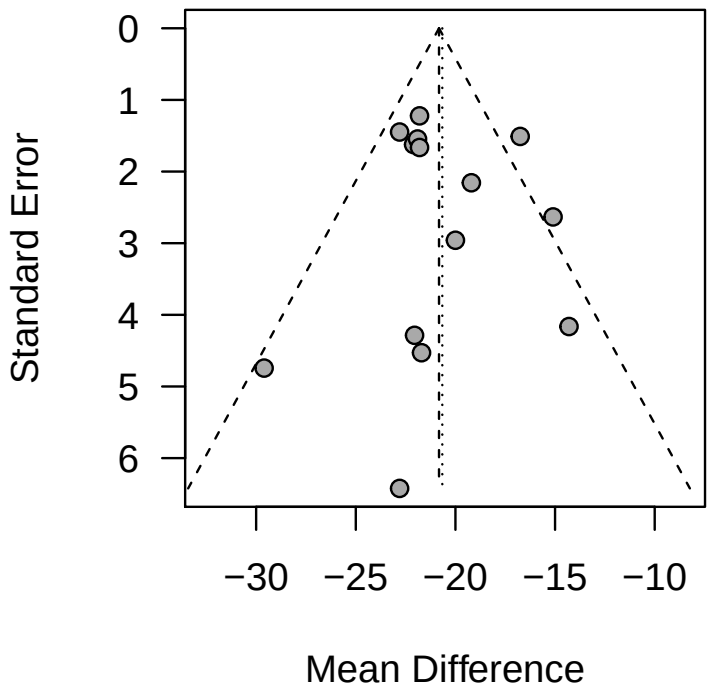
- Number of studies $n$ large
- variation in the estimated variances of effects

Adjustments required if variance is dependent on effect size (e.g. log odds ratios)

# Small Study Effect Tests

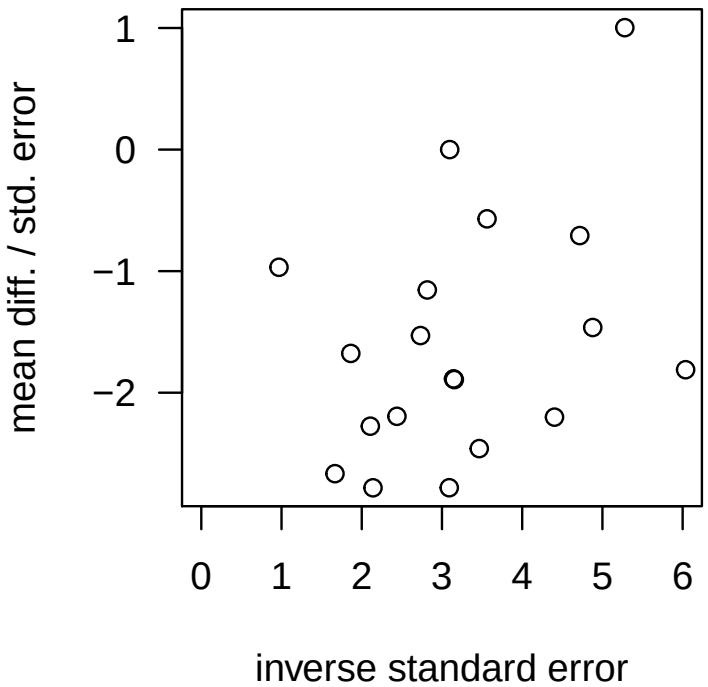
Funnel plots (continuous outcome examples):

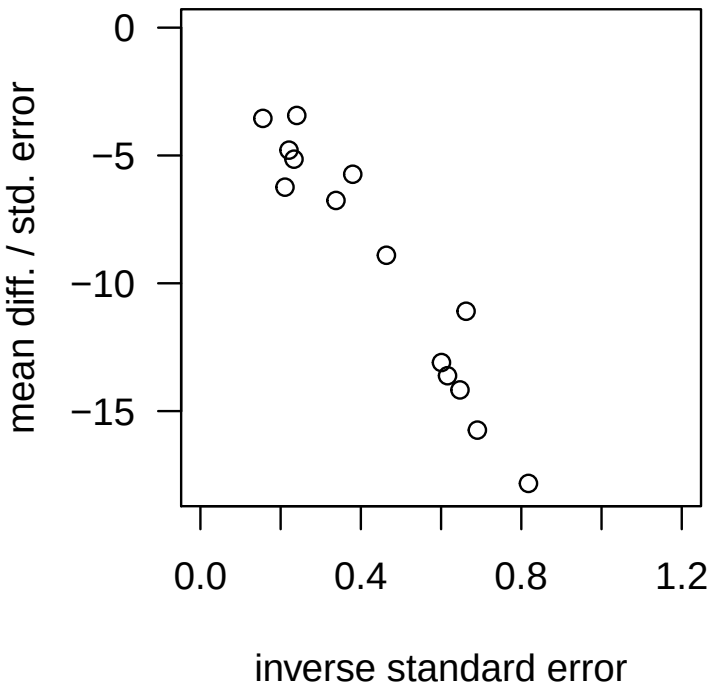


# Regression based Tests

Radial plots (continuous outcome examples):



# Regression based Tests

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

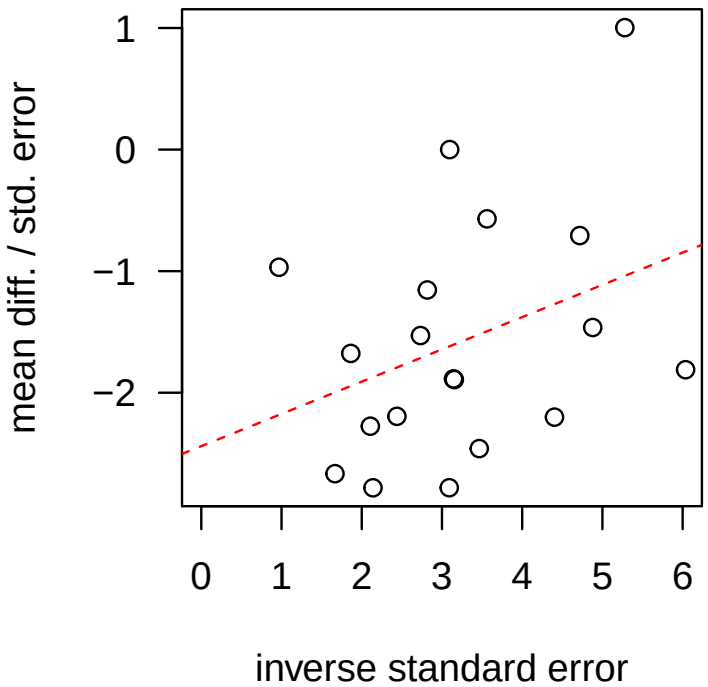
$\theta_M$ is the pooled effect and $\tau^2$ the between-study variance.

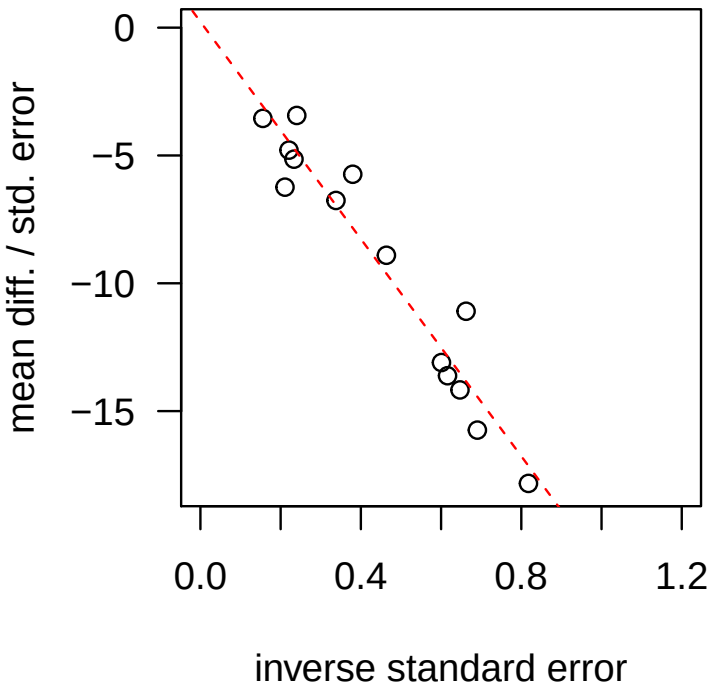
Let $y_i = \theta_i / _i$ and $x_i = 1/s_i$

- 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 $\beta_0$



# 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

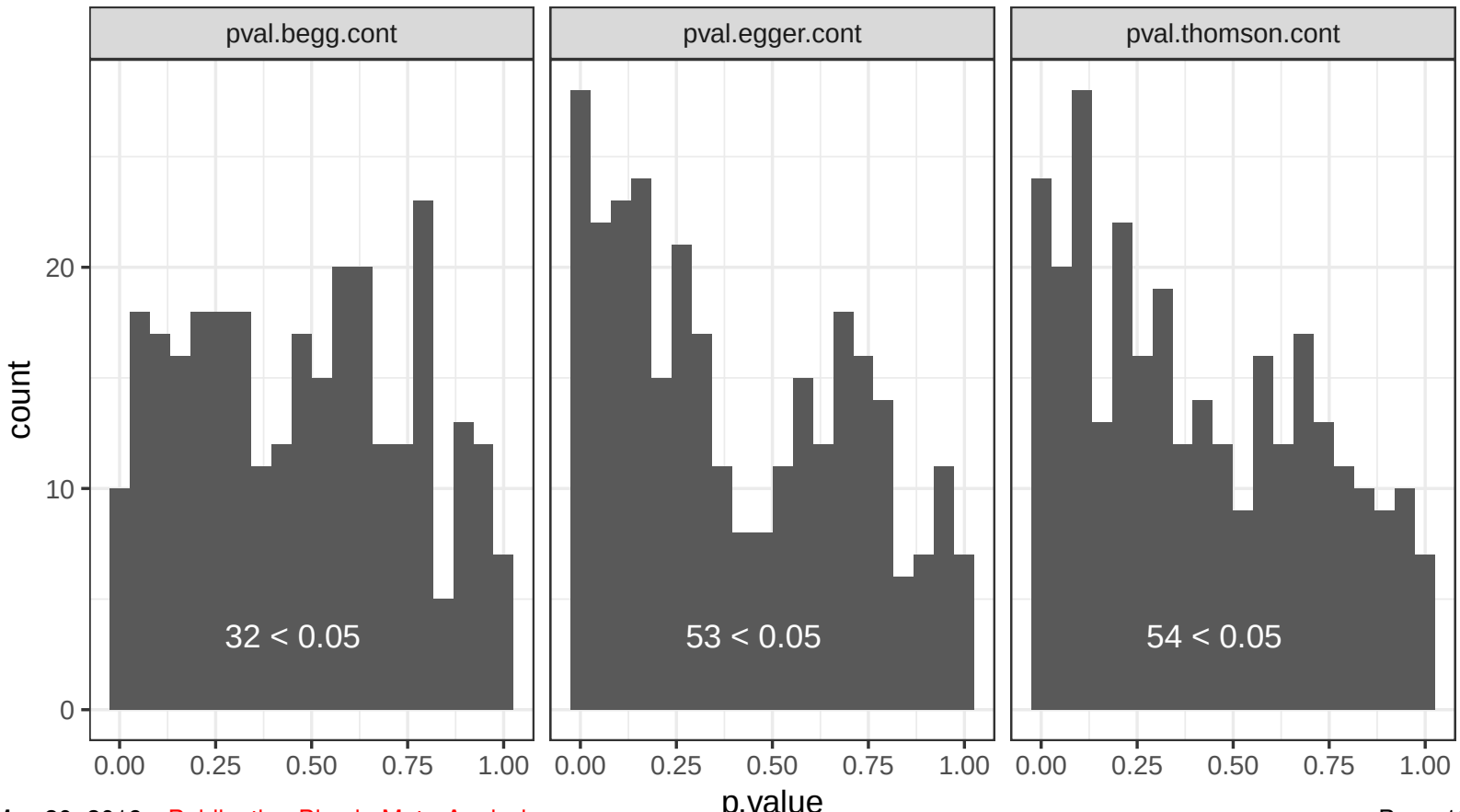
Inclusion criteria (from Ioannidis and Trikalinos (2007)):

- $n \geq 10$
- 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.

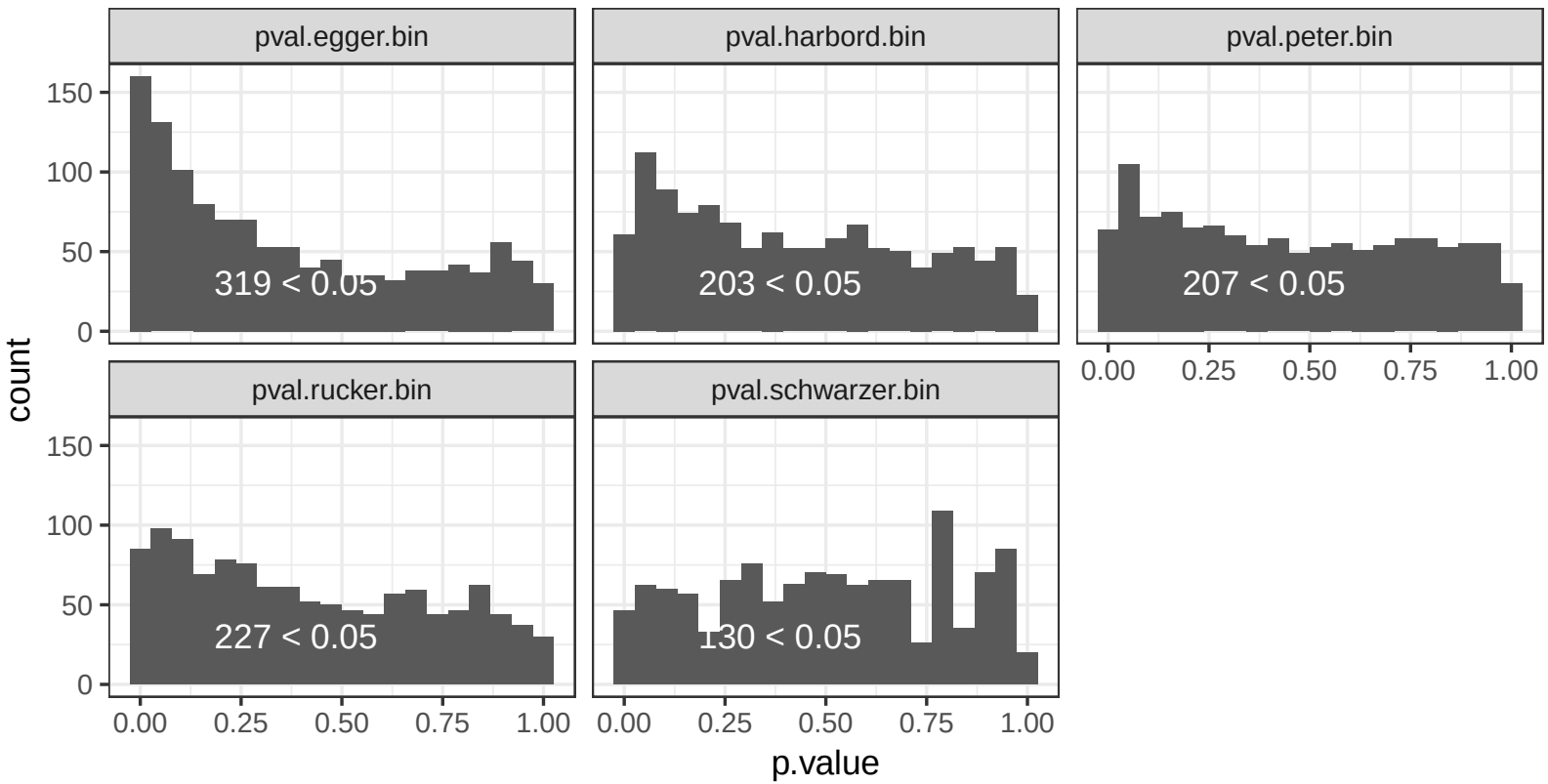
# Continuous Outcome Test Results

*p*-values distribution, *n* = 294:



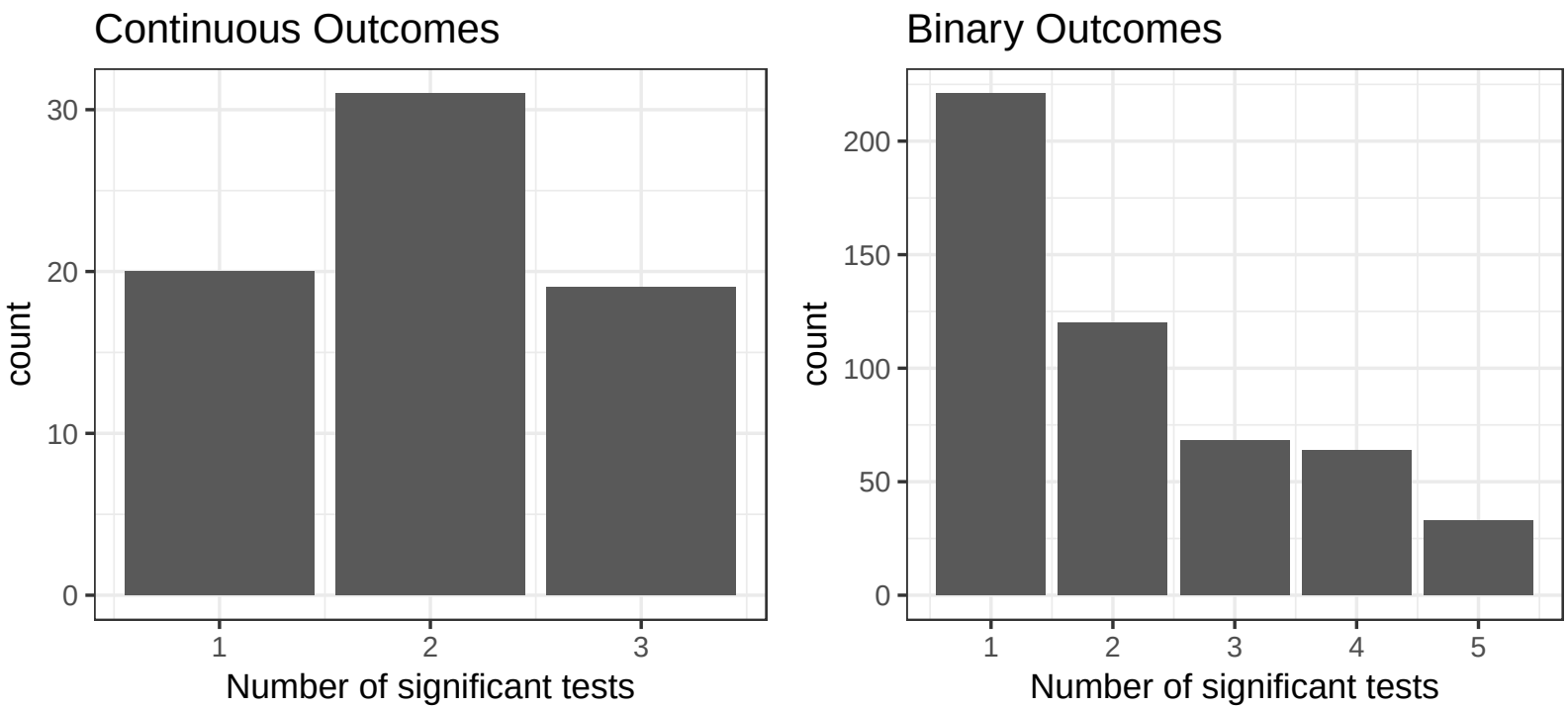
# Binary Outcome Test Results

*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

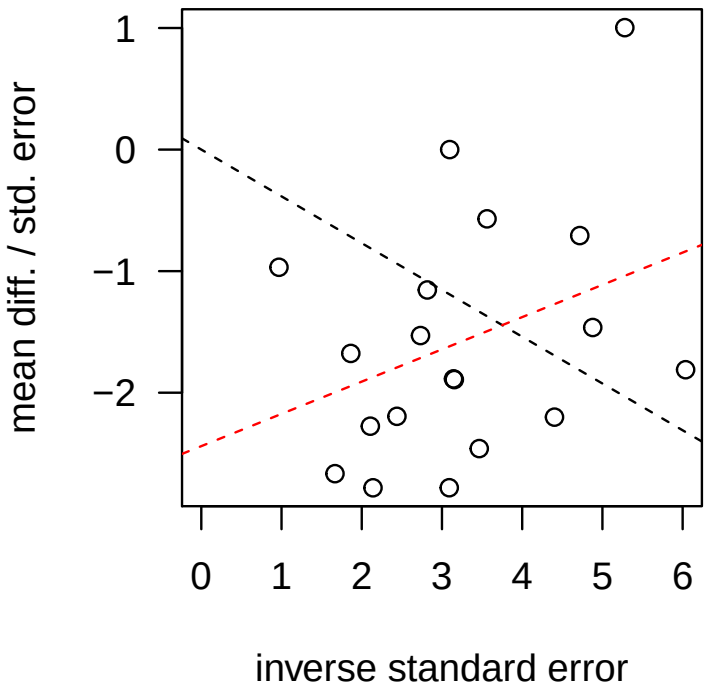
$y_i = \theta_i / s_i, x_i = 1/s_i$

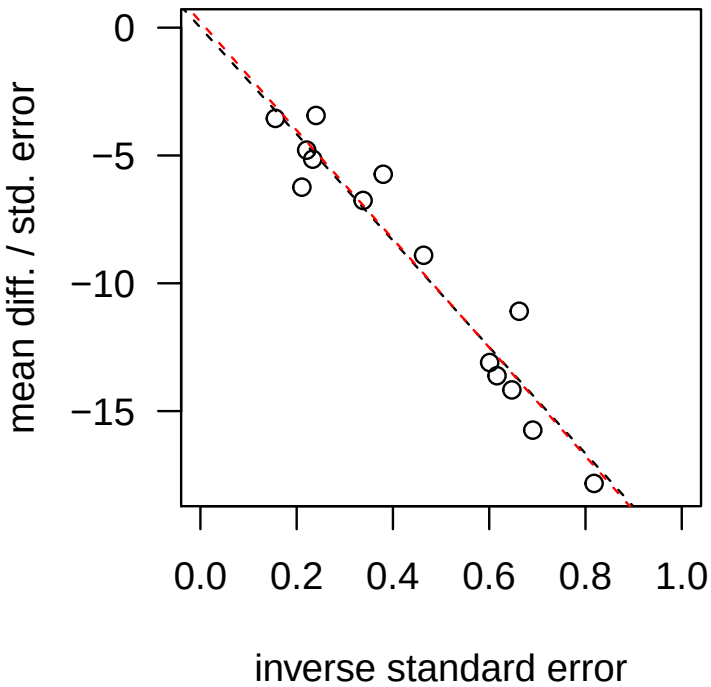
$y_i = \beta_0 + \beta_1 x_i, \epsilon_i \sim N(0, \sigma)$

$\beta_1$ is the weighted mean treatment effect if $\beta_0 = 0$

# Adjustment by regression

Radial plots (continuous outcome examples):



# Limit Meta-Analysis

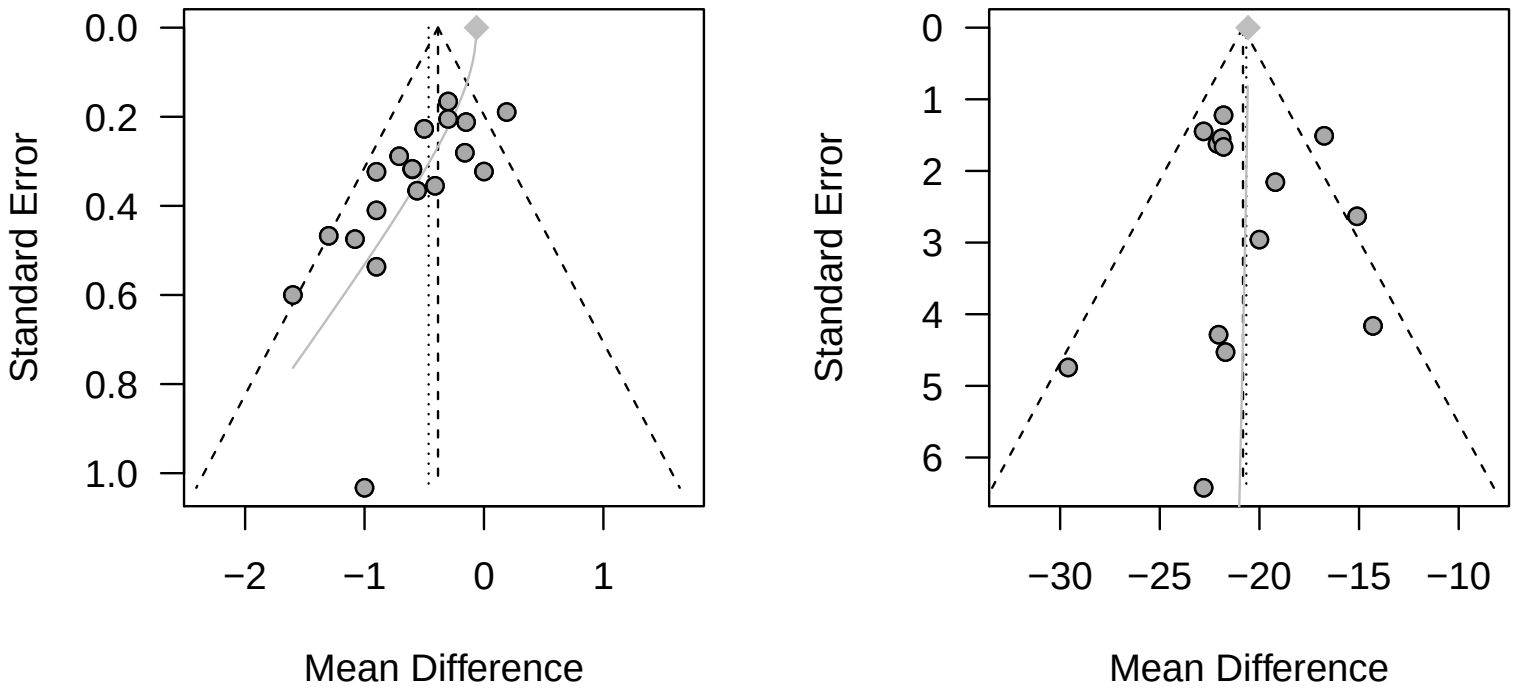
Extended random effects model:

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

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

# Shrinkage Regression

Funnel plot with effect with infinite precision:



# Copas selection model

Copas and Shi (2001): Bivariate normal model with two parts:

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

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

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

2 is called population model, 3 the selection model

$(\epsilon_i, \delta_i)$ 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

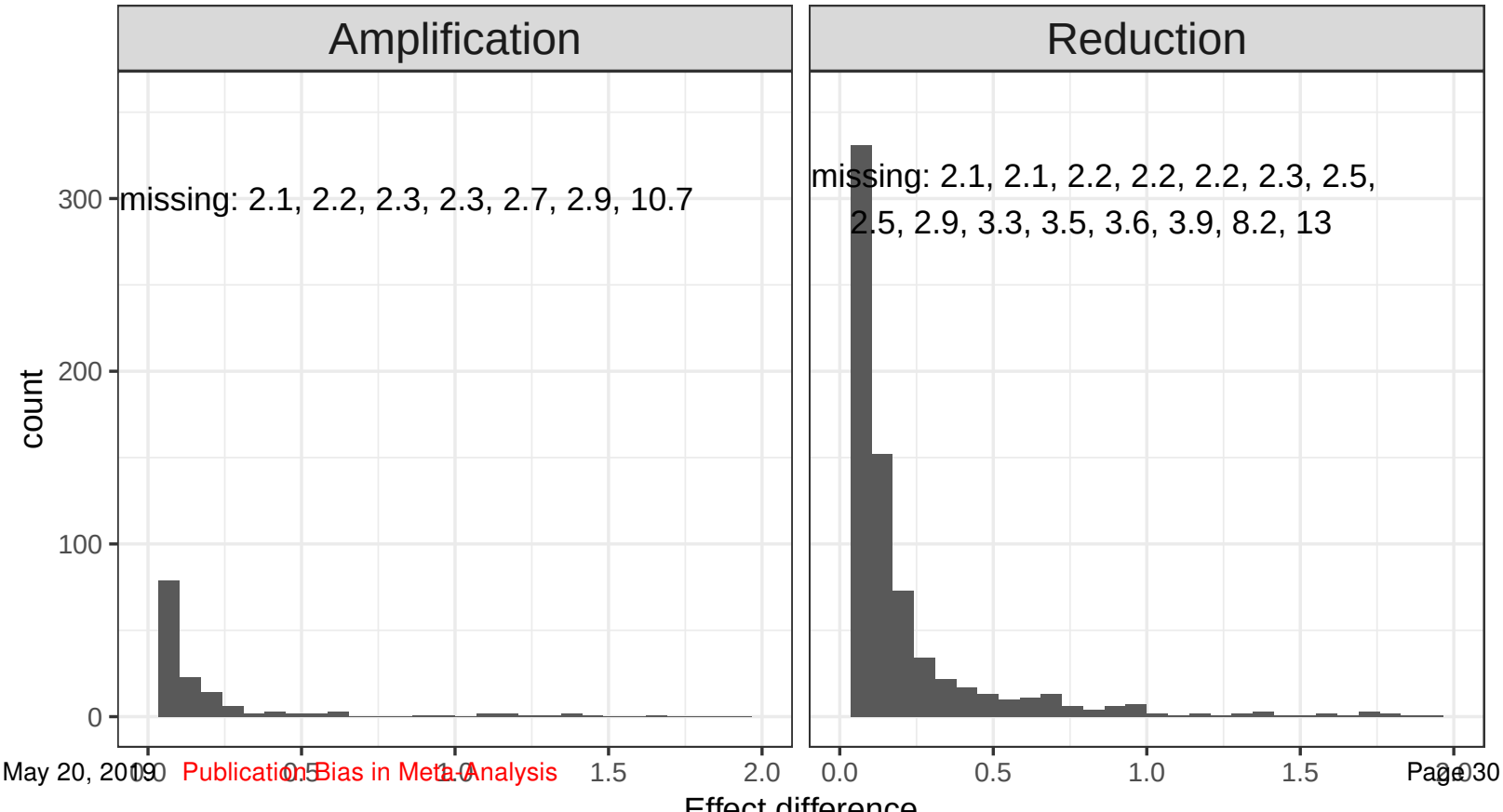
Non-parametric, iterative method:

Cut away smallest study until funnel plot is symmetric

Mirror studies that are responsible for asymmetry

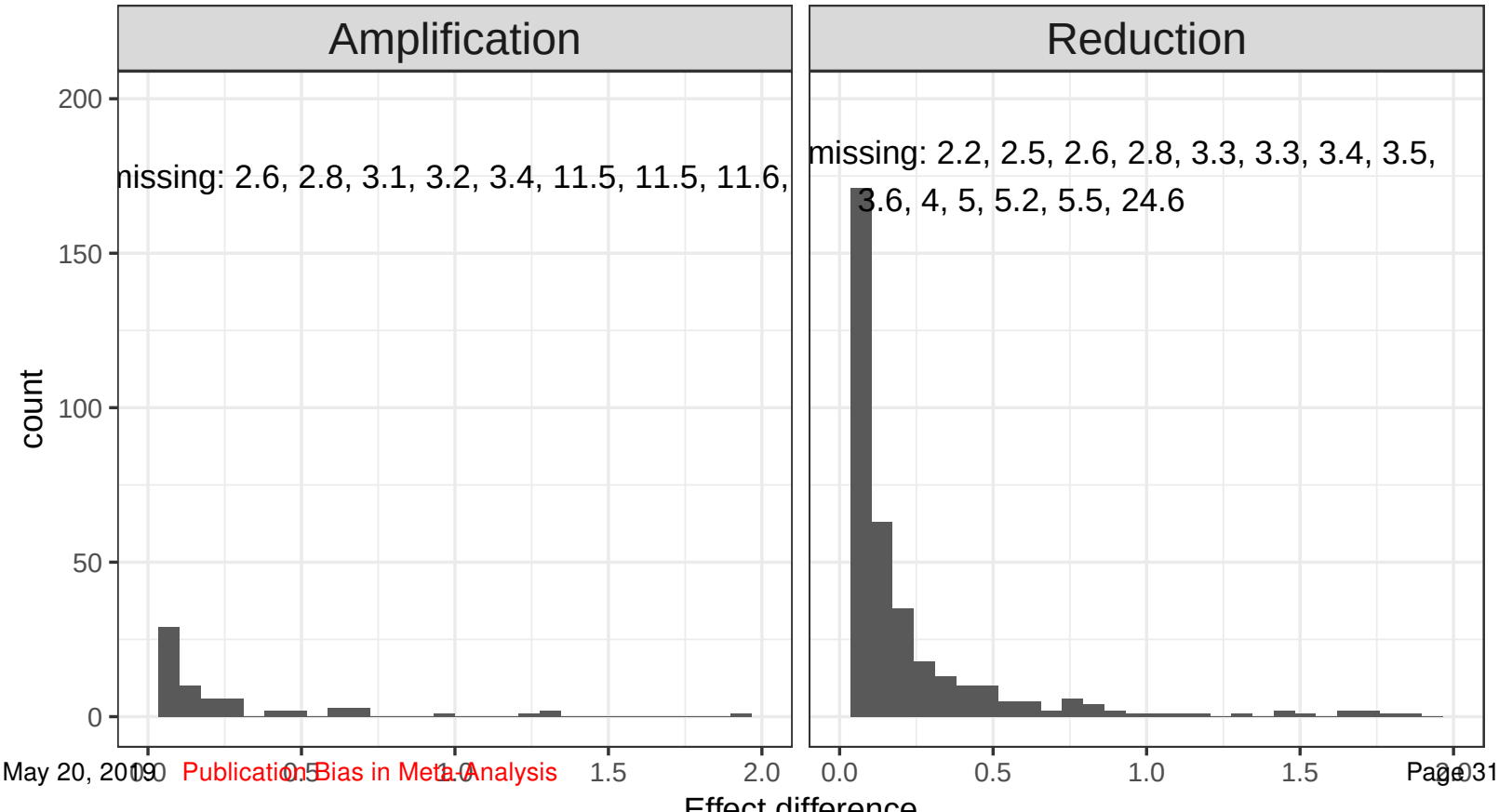
# Adjustment Results: Trim-and-fill

Difference between adjusted and fixed effects meta-analysis estimate:



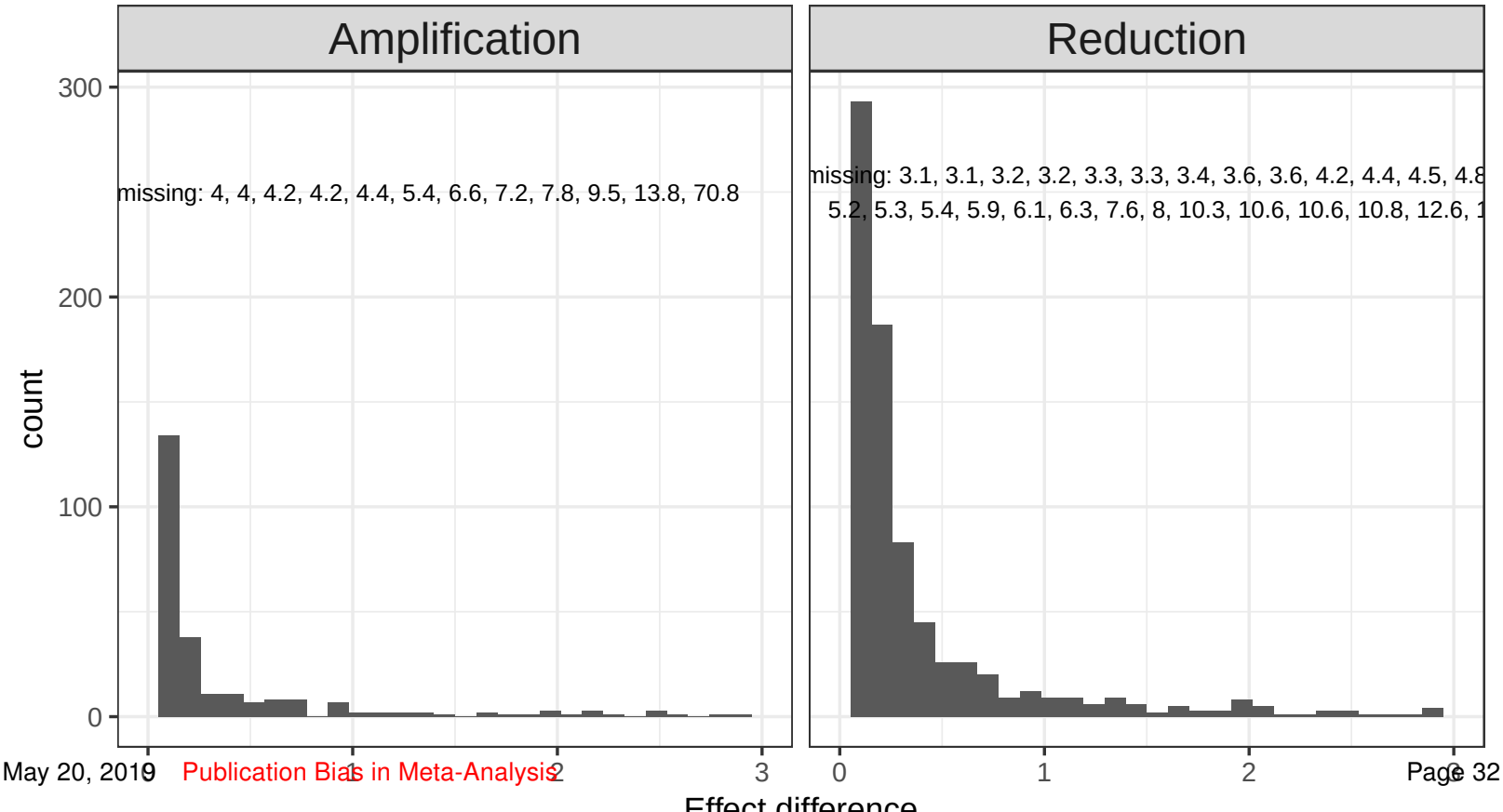
# Adjustment Results: Copas

Difference between adjusted and fixed effects meta-analysis estimate:



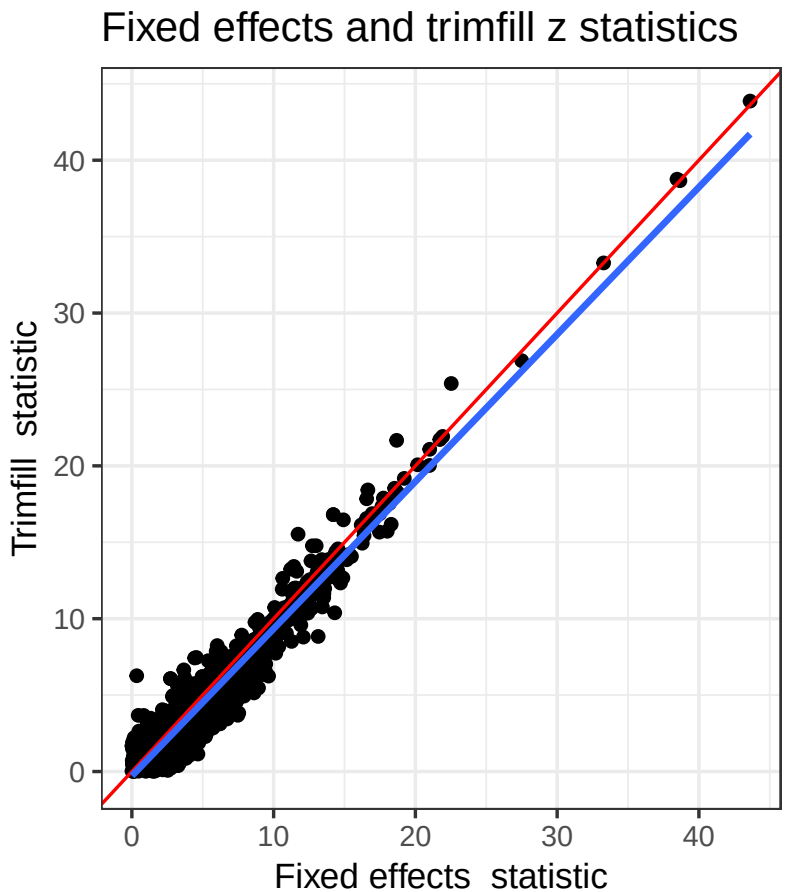
# Adjustment Results: Regression

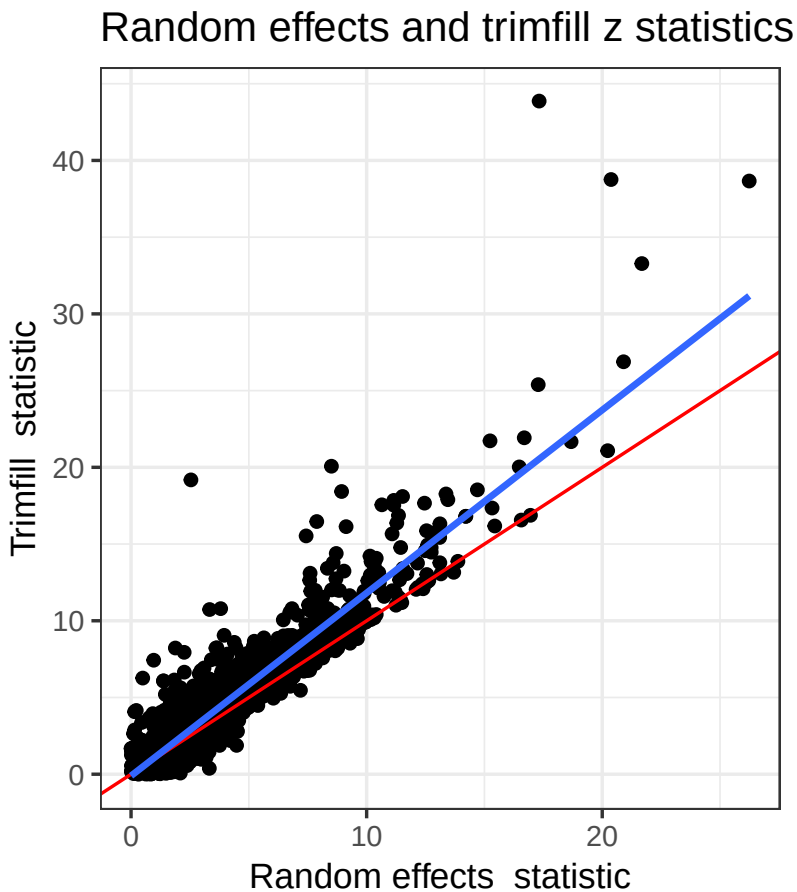
Difference between adjusted and fixed effects meta-analysis estimate:



# Adjustment Results: Trim-and-fill

Adjusted and meta-analysis test statistics:



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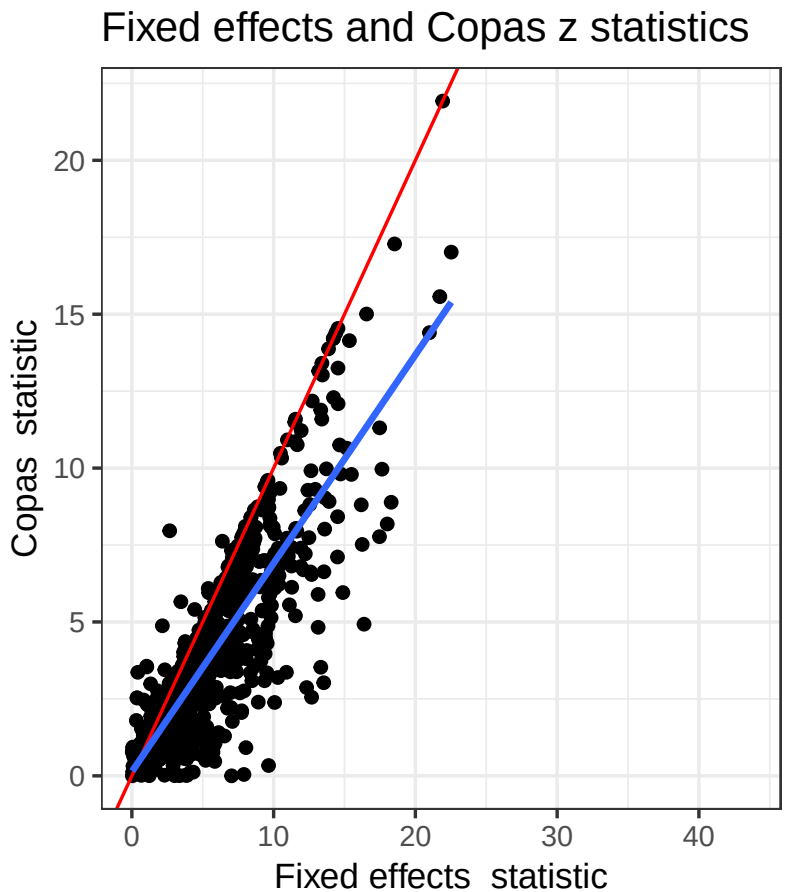
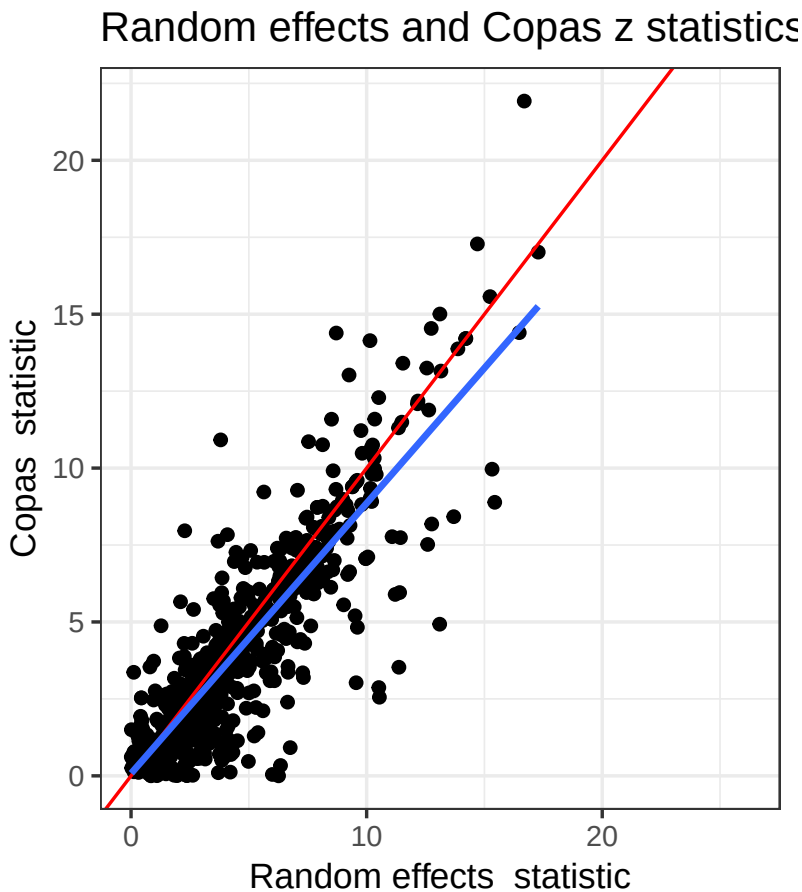
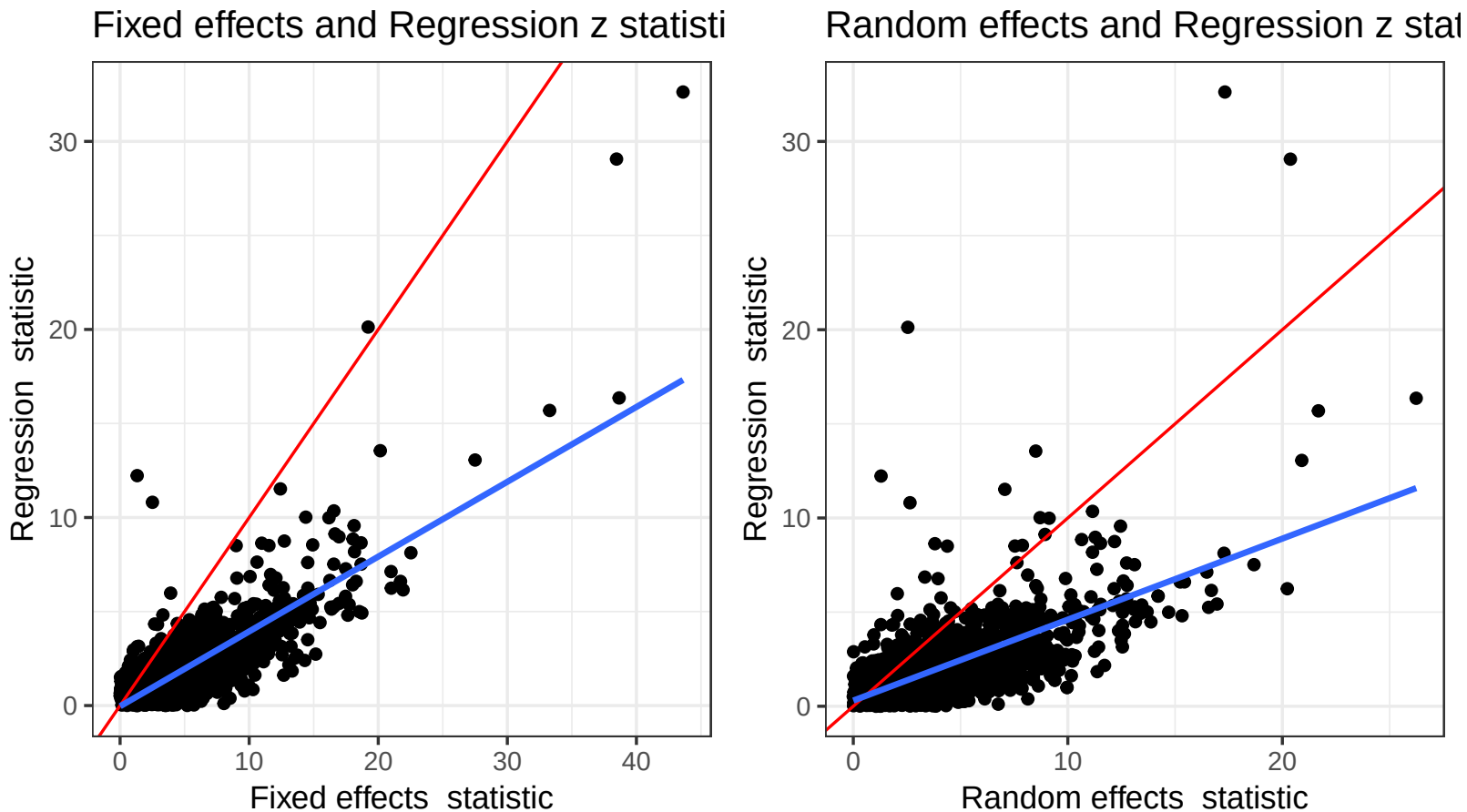


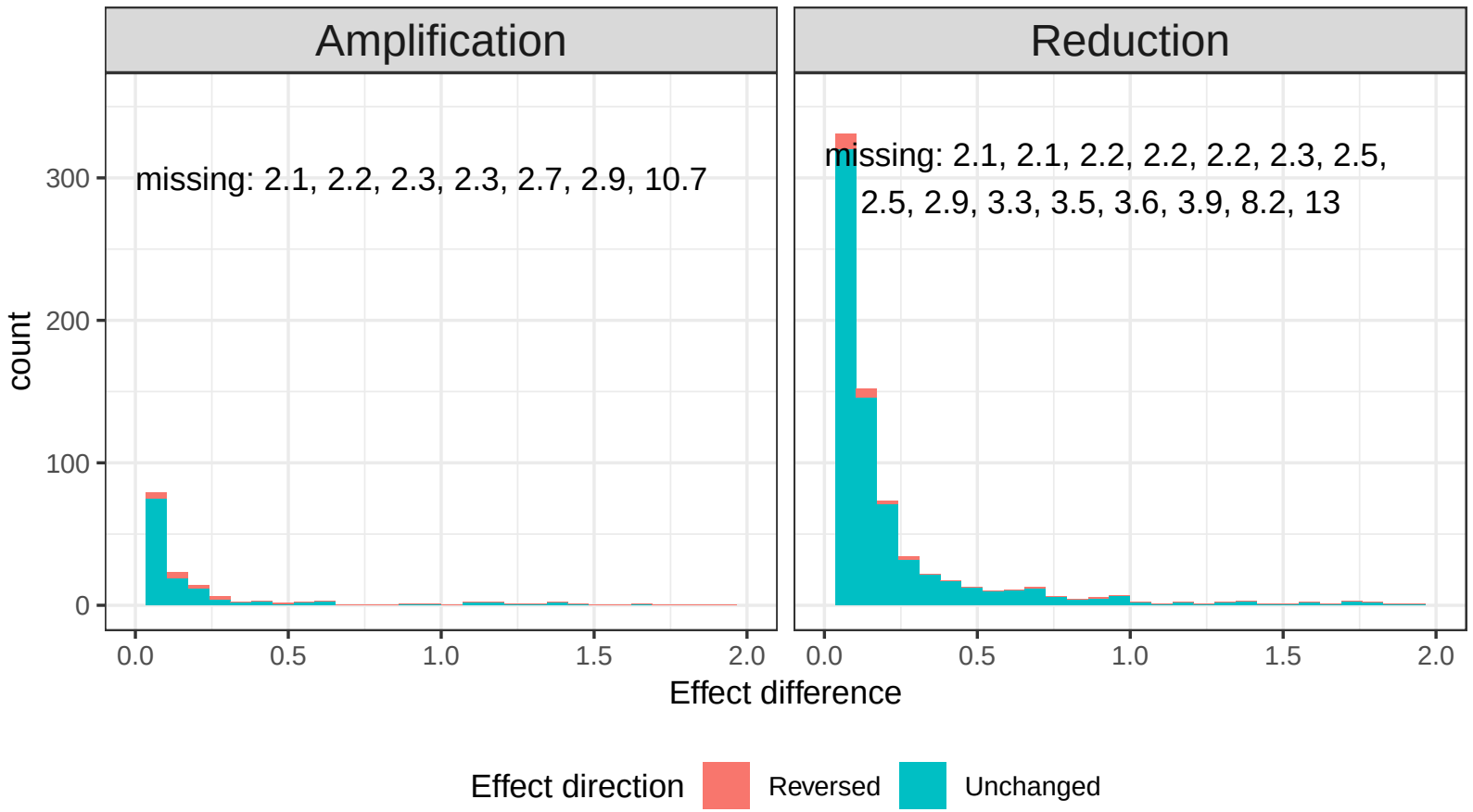
# Adjustment Results: Regression

Adjusted and meta-analysis test statistics:



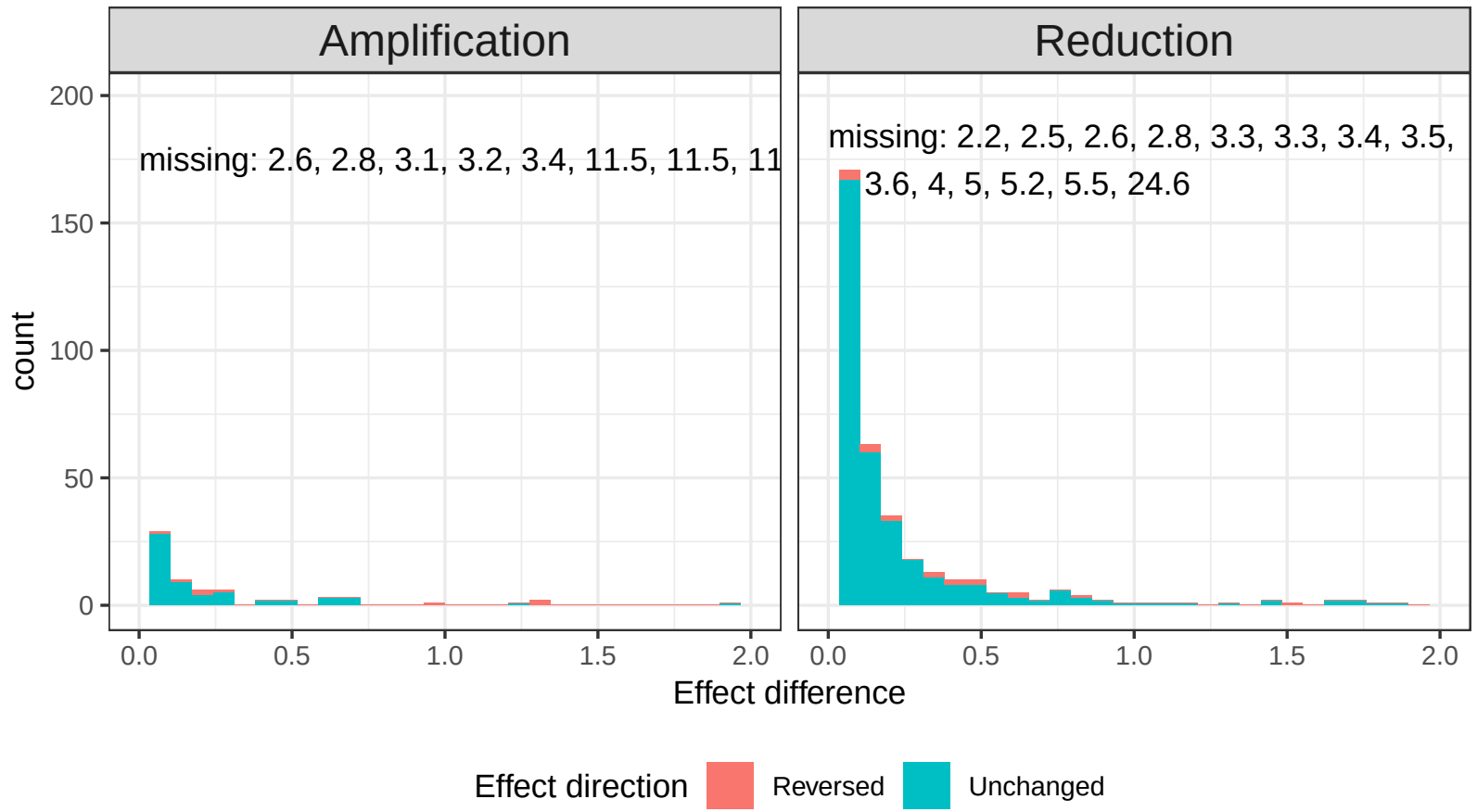
# Adjustment Results: Trim-and-fill

Treatment effect difference:



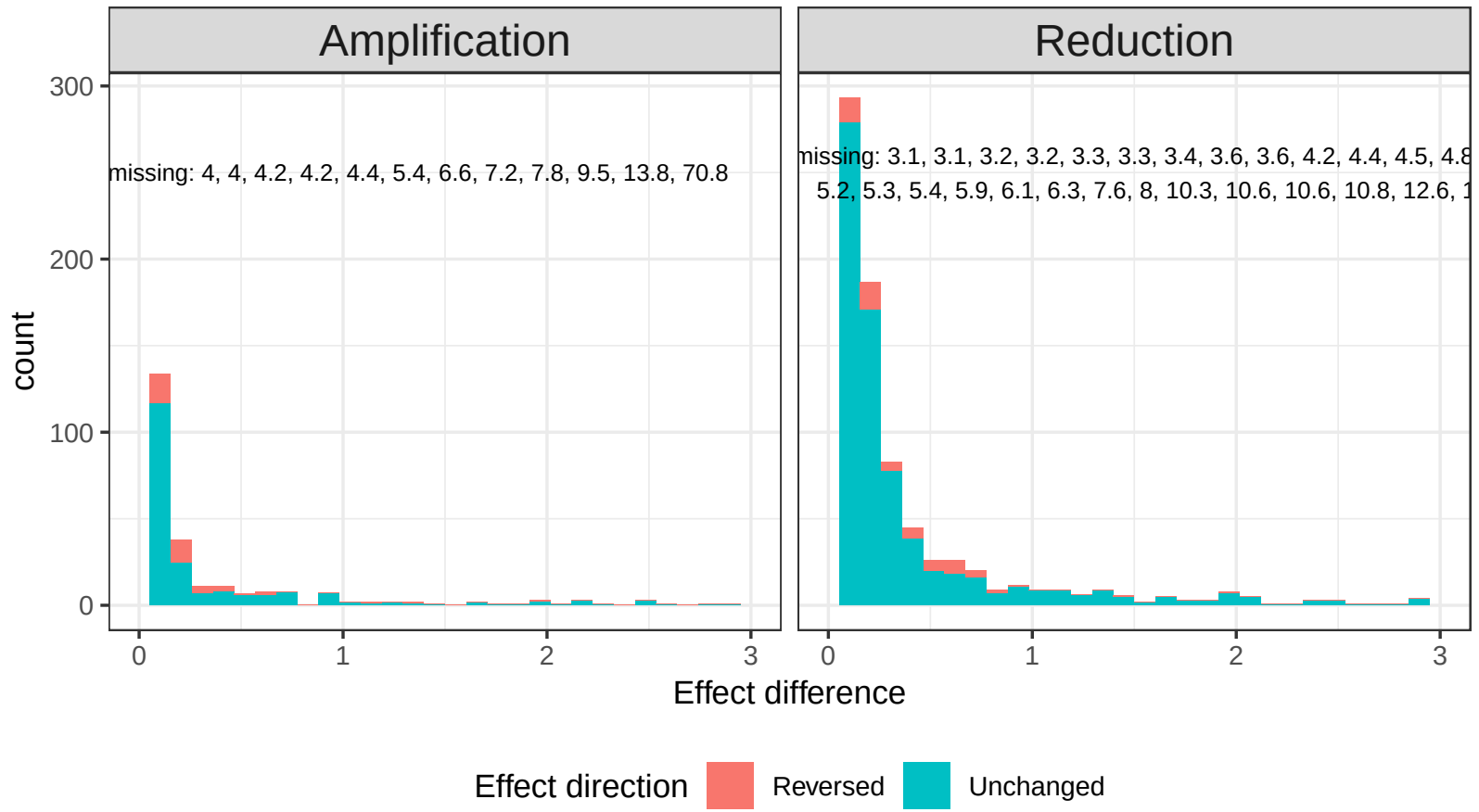
# Adjustment Results: Copas

Treatment effect difference:



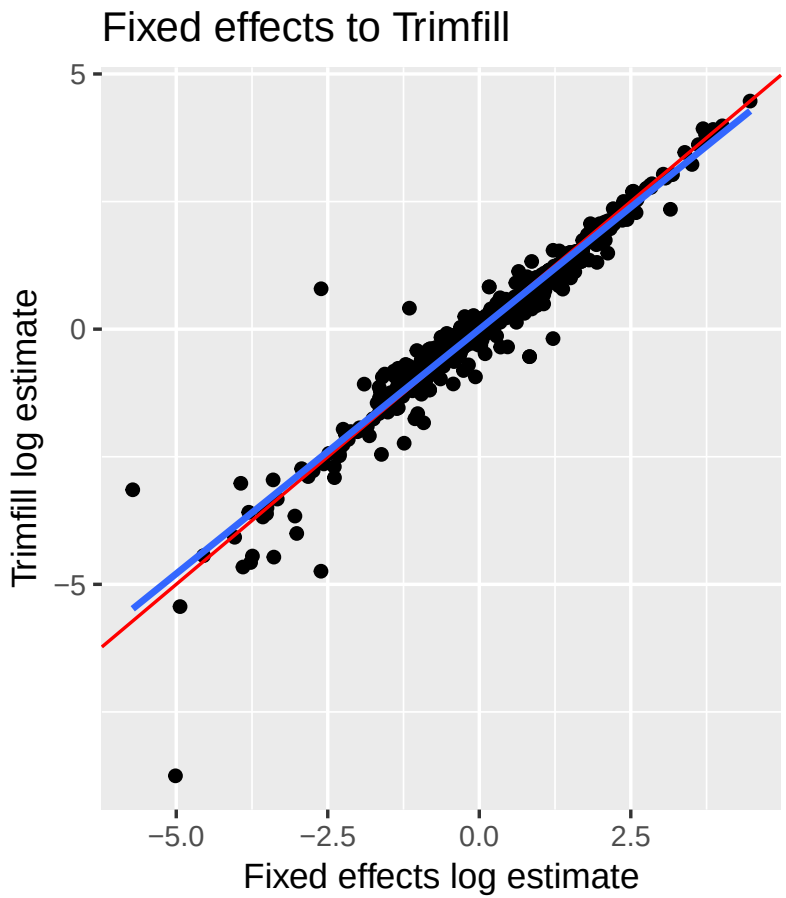
# Adjustment Results: Regression

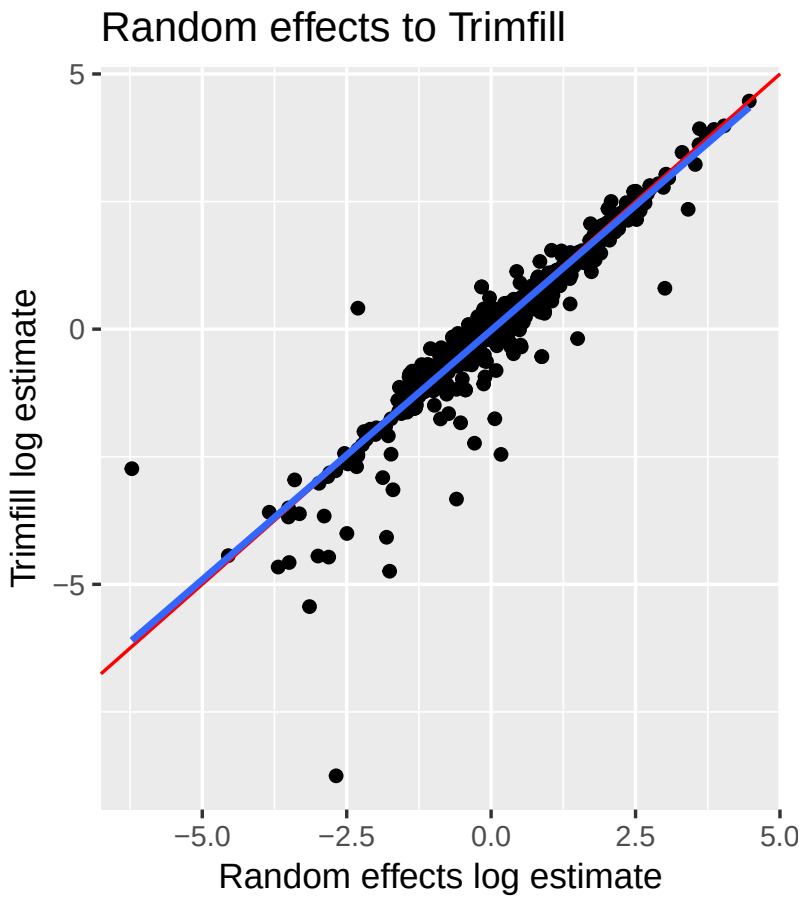
Treatment effect difference:



# Adjustment Results: Trim-and-fill

log treatment effect estimates:



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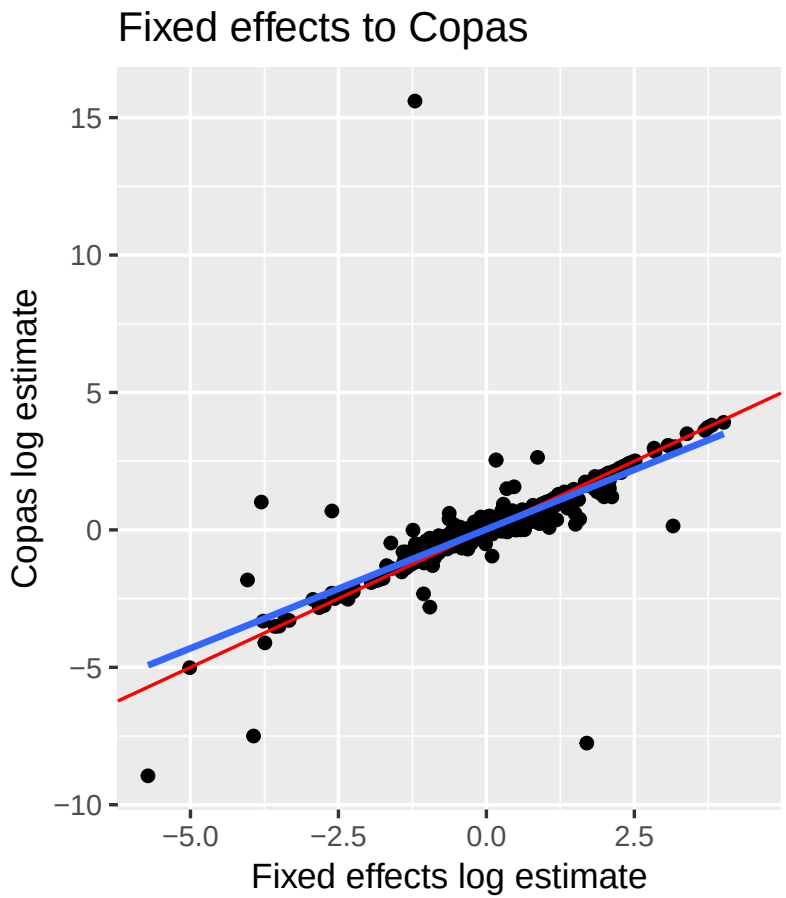
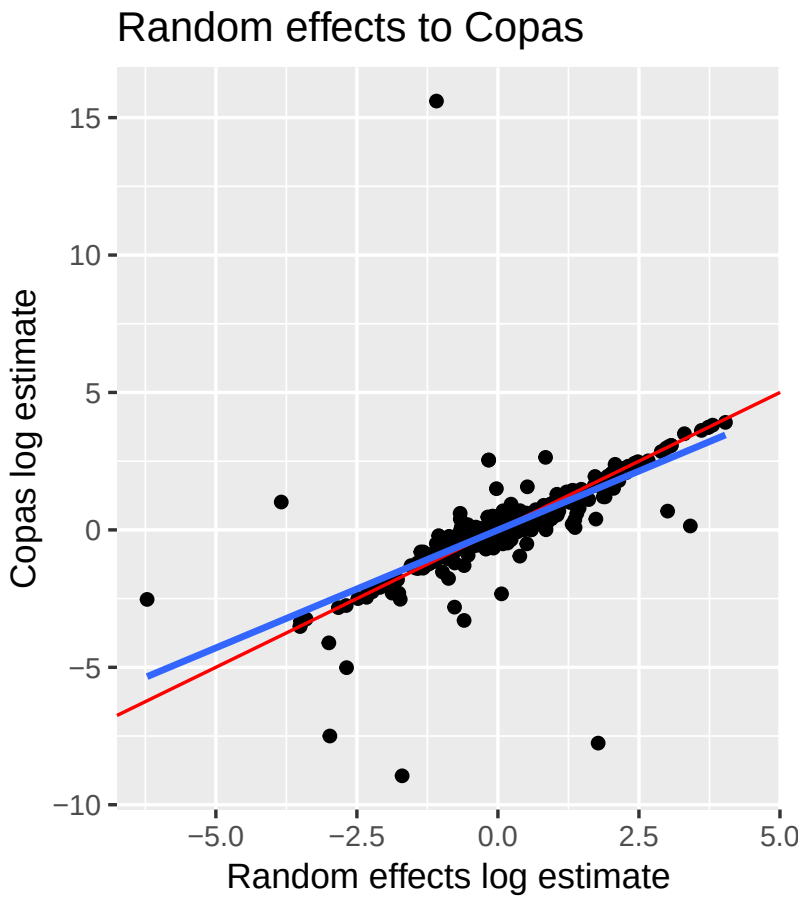
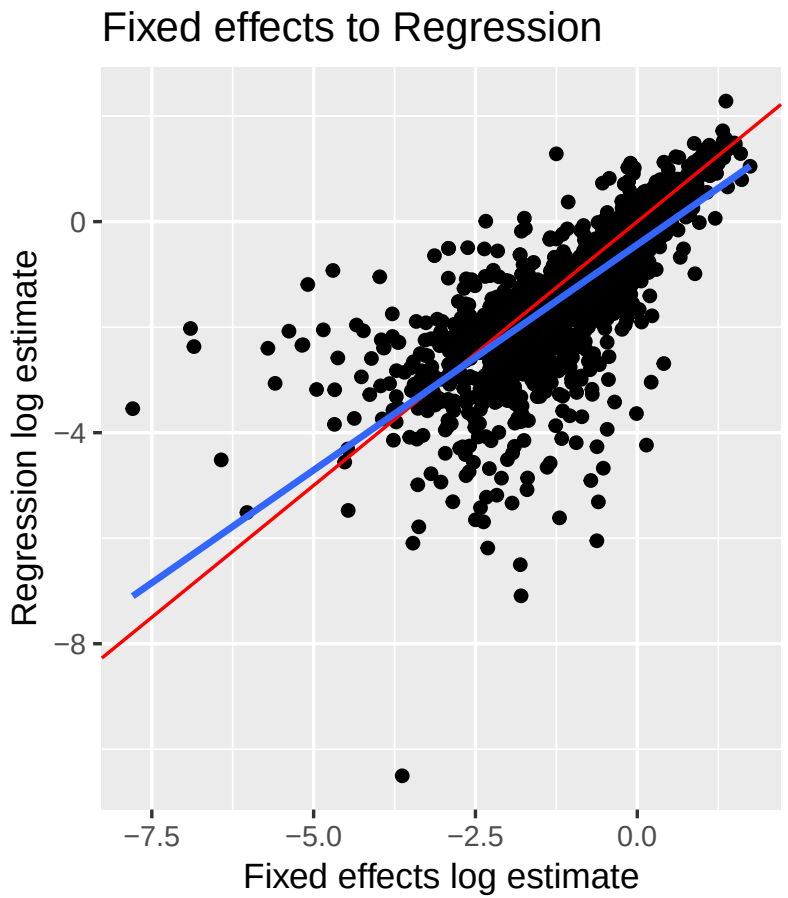
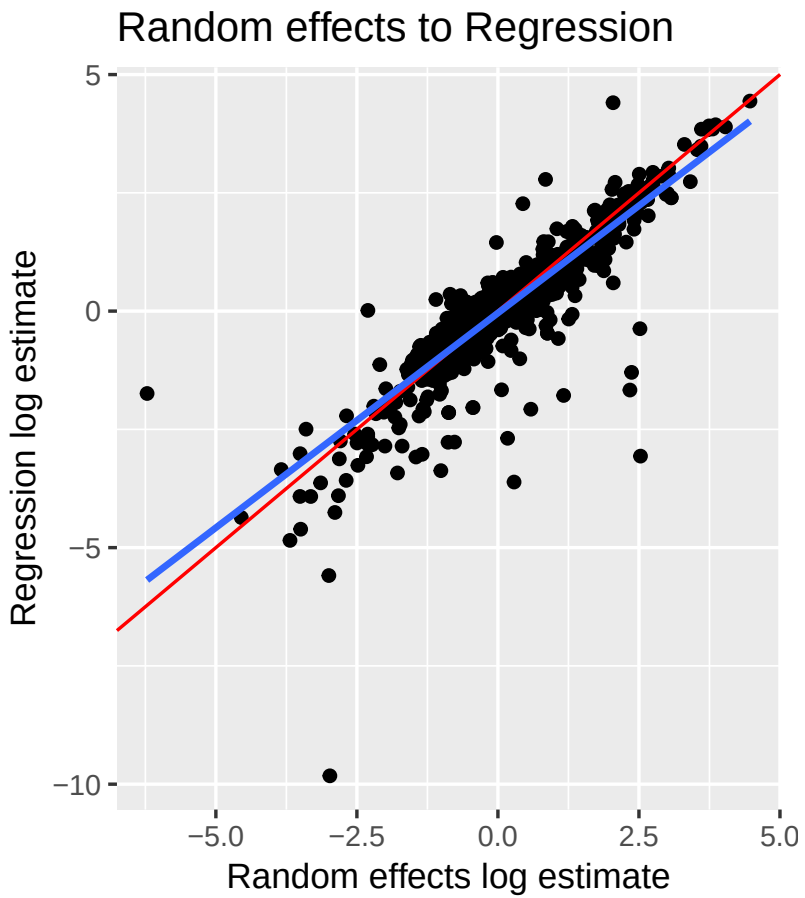


# Adjustment Results: Regression

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*,