University of Zurich[UZH]

Biostatistics

Publication Bias in Meta-Analysis

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Cochrane Library

Database of high-quality, systematic reviews in clinical science.

Currently $\sim$ 8,000 reviews, prepared by independent groups.

Reviews are peer-reviewed and prepared after guidelines.

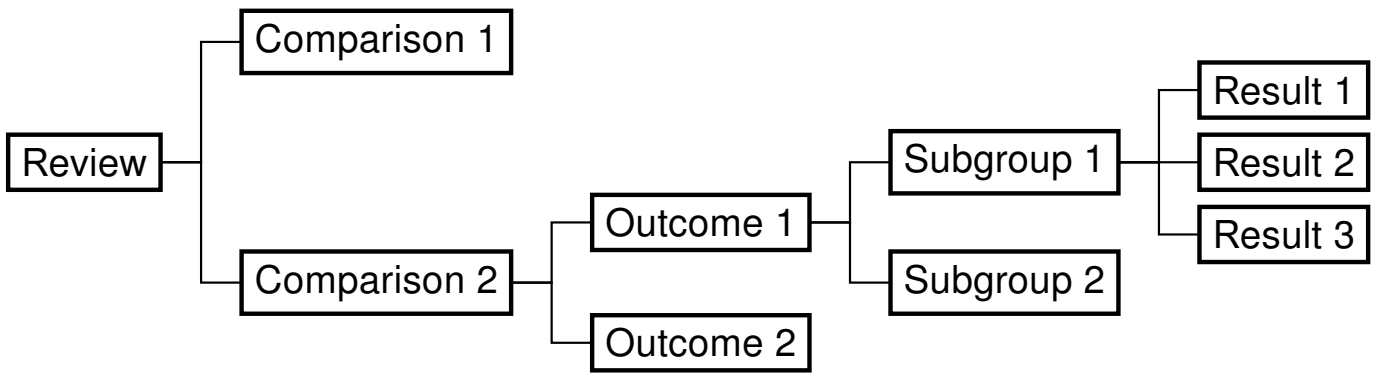
Cochrane Library Dataset

5,016 systematic reviews with studies published until 2018.

52,995 studies.

463,820 study results.

Dataset Structure



Dataset Structure

- Comparison: What is compared, e.g. treatment vs. control
- Outcome: How it is compared
- Subgroup: Subgroup affiliation
- Meta-Analysis ~~Group~~: Results from same comparison, outcome and subgroup

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 Properties

Missing data:

Missing mean values and mean differences	984
Missing standard deviations and standard errors	1300
Missing sample sizes	12173
Missing study year	44649

Dataset Properties

Review and study properties:

	5% quantile	median	mean	95% quantile
Study number	1	7	12	40
Comparison number	1	2	4	12
~~Group~~ number	2	19	37	132
Study years	1981	2002	2000	2013
Study sample size	13	78	750	890

Pooling Studies - Meta-Analysis

Multiple results in a meta-analysis group can be pooled:

n	Number of groups	Cumulative sum of groups
1	102344	188079
2	31686	85735
3	16072	54049
4	9628	37977
5	6444	28349
6	4230	21905
7	2961	17675
8	2114	14714
9	1592	12600
10	11008	11008

Meta-analysis

Benefits:

- Summary of evidence (e.g. of a treatment)
- 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 large effects
- Bias in smaller studies
- Systematical differences in study settings
- ...

Small Study Effect Tests

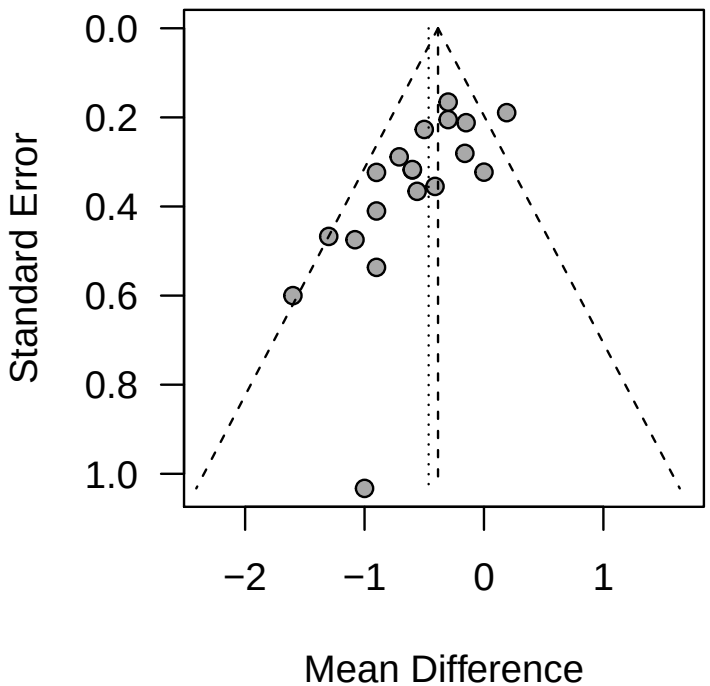
Tests applicable if:

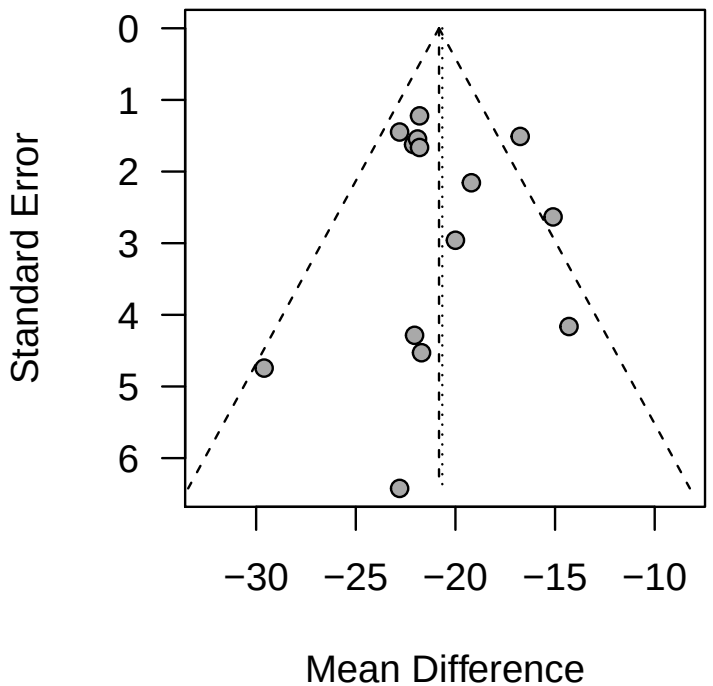
- ~~*n* large~~
- variation in the estimated variances of effects
  (here: $\frac{\sigma_{\max}}{\sigma_{\min}} > 4$)

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

Small Study Effect Tests

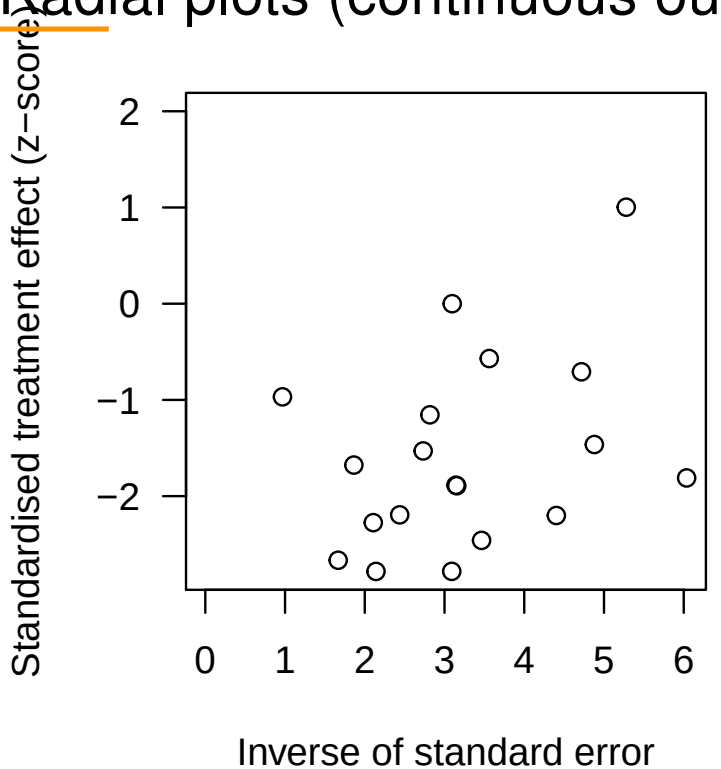
Funnel plots (continuous outcome examples):

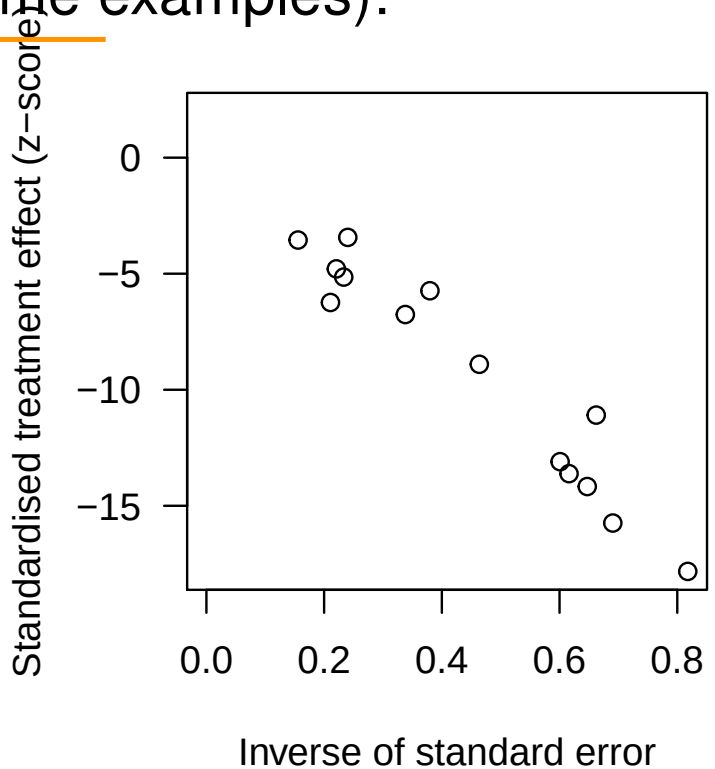




Regression based Tests

Radial plots (continuous outcome examples):





Regression based Tests

Continuous outcomes tests:

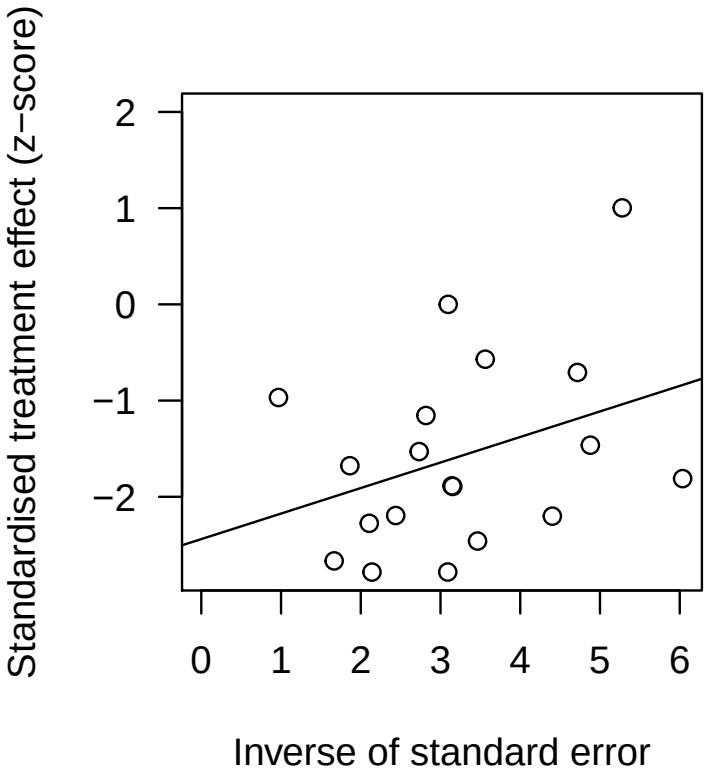
i being the ith study in a meta-analysis:

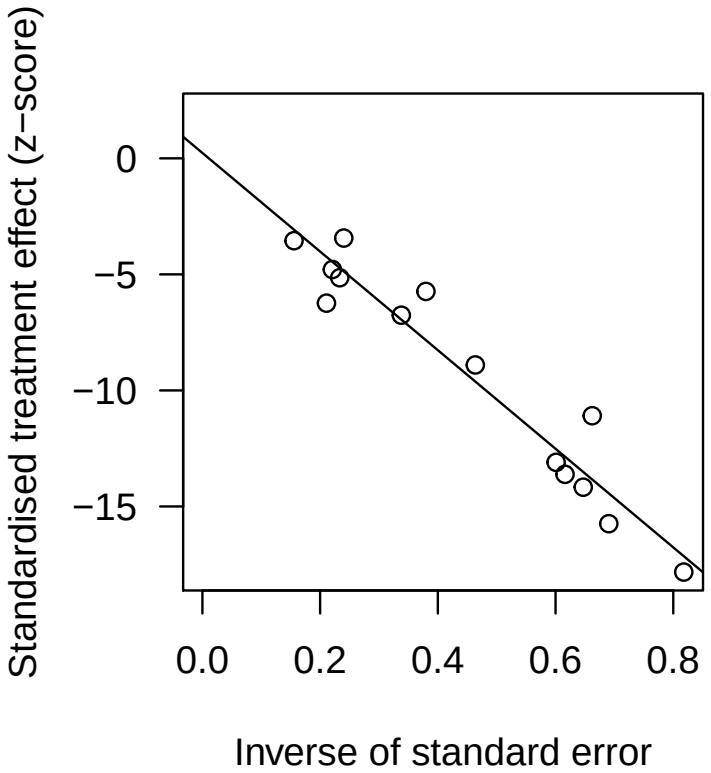
Let $y_i = \text{effect}_i/\text{se}_i$ and $x_i = 1/\text{se}_i$

- Egger et al. (1997) :
  $y_i \sim N(\beta_0 + \beta_1 x_i, v_i)$
- Thompson and Sharp (1999) :
  $y_i \sim N(\beta_0 + \beta_1 x_i, v_i + \tau^2)$

```
## sample estimates:
##       bias    se.bias      slope
## -2.4398295  0.5958069  0.2653786
```

Egger's Tests

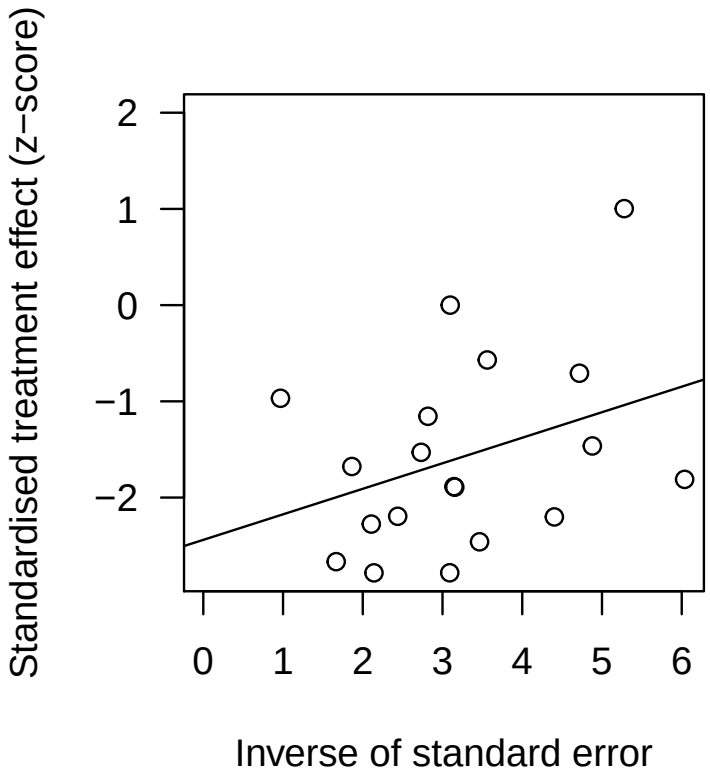


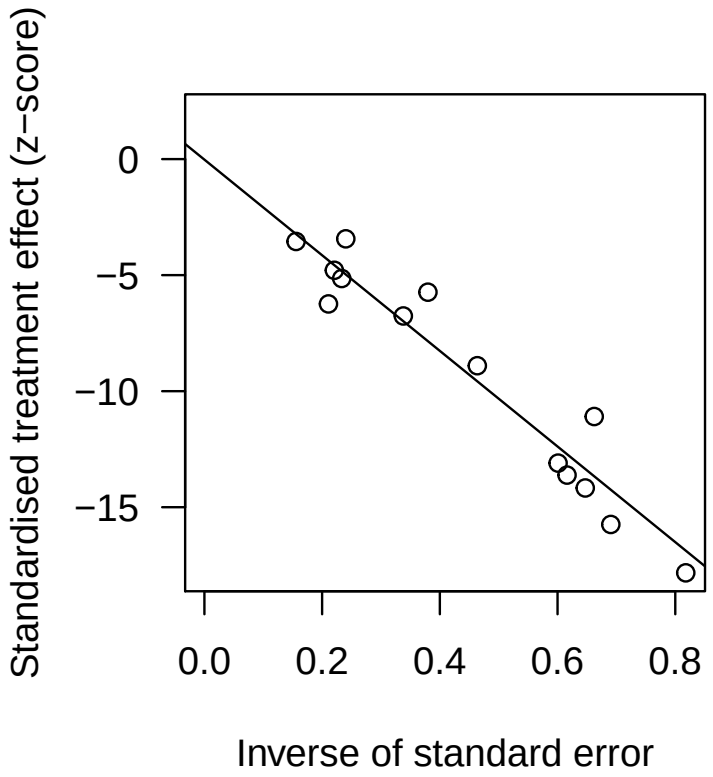



```
##
## Linear regression test of funnel plot asymmetry
```

```
## sample estimates:
##       bias    se.bias      slope
## -2.4398295  0.6210298  0.2653786
```

Thompson and Sharp's Tests






```
##
## Linear regression test of funnel plot asymmetry (metho
```

Regression based Tests

Adjustments for binary outcomes:

- Peters et al. (2006) :x_i = inverse of total sample size, variance_i as weight.
- Harbord et al. (2006) :$x : i$ = score of the log-likelihood of a proportion, variance_i as weight.
- ? :Use arcsine variance stabilizing transformation for variances and effects, do e.g. Egger's test.

Rank based tests

Begg (1988) Let y_i the standardized effect size of a study i, v_i it's variance and n the number of studies

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

$Z = (u - l)/\sqrt{n(n-1)(2n+5)/18}$
can be used as a test statistic (based on Kendall's Tau)

Rank based tests

Schwarzer et al. (2007) Let e_t the number of events in the treatment group

Given constant log odds ratio, E_t follows a hypergeometric distribution.

$\mathbb{E}(E_t)$ and the variance can be estimated and used as in Begg (1988)

Test Results

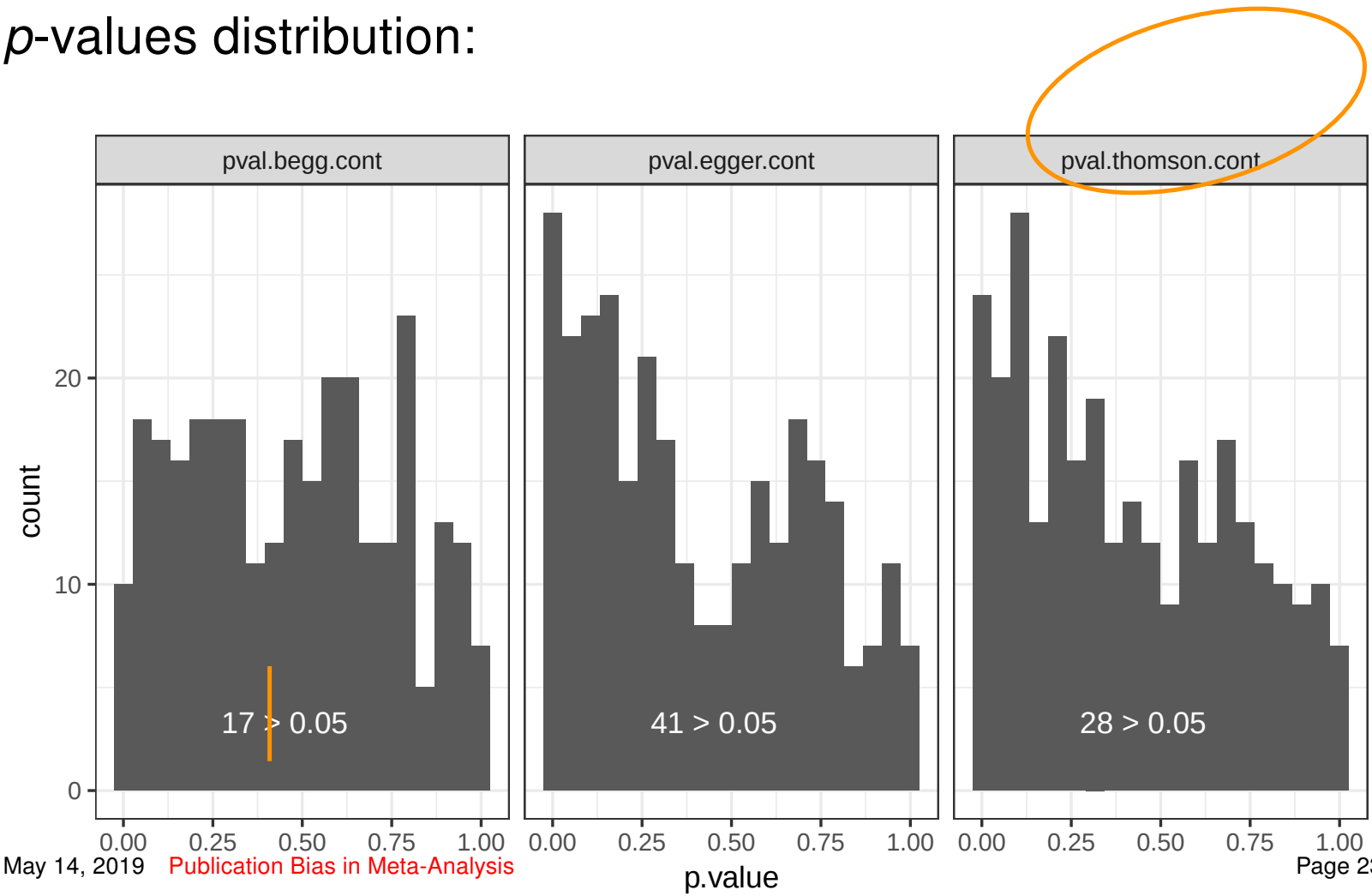
Application of tests if:

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

From 5338 with $n \geq 10$, 1602 remain.

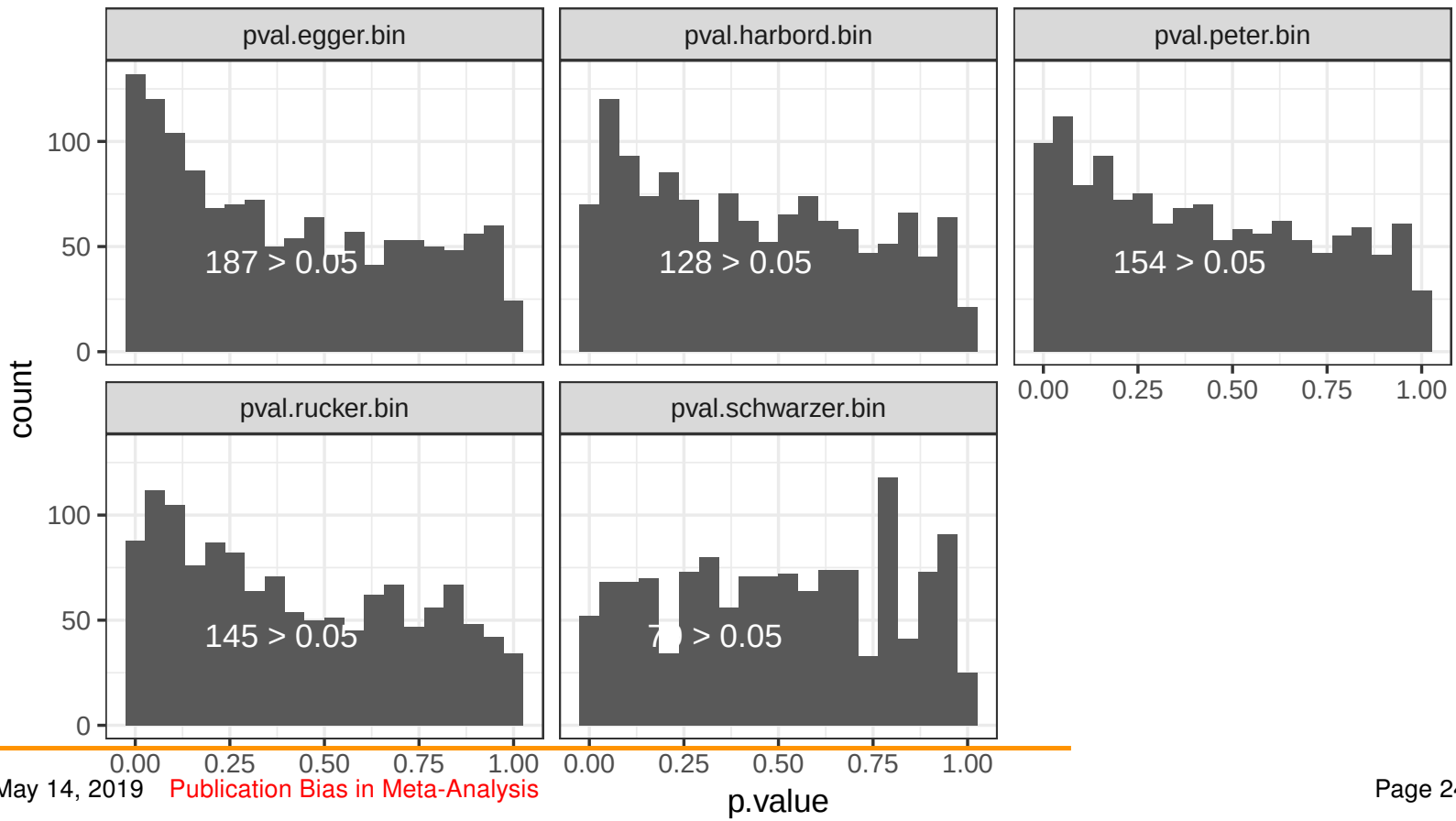
Continuous Outcome Test Results

p-values distribution:



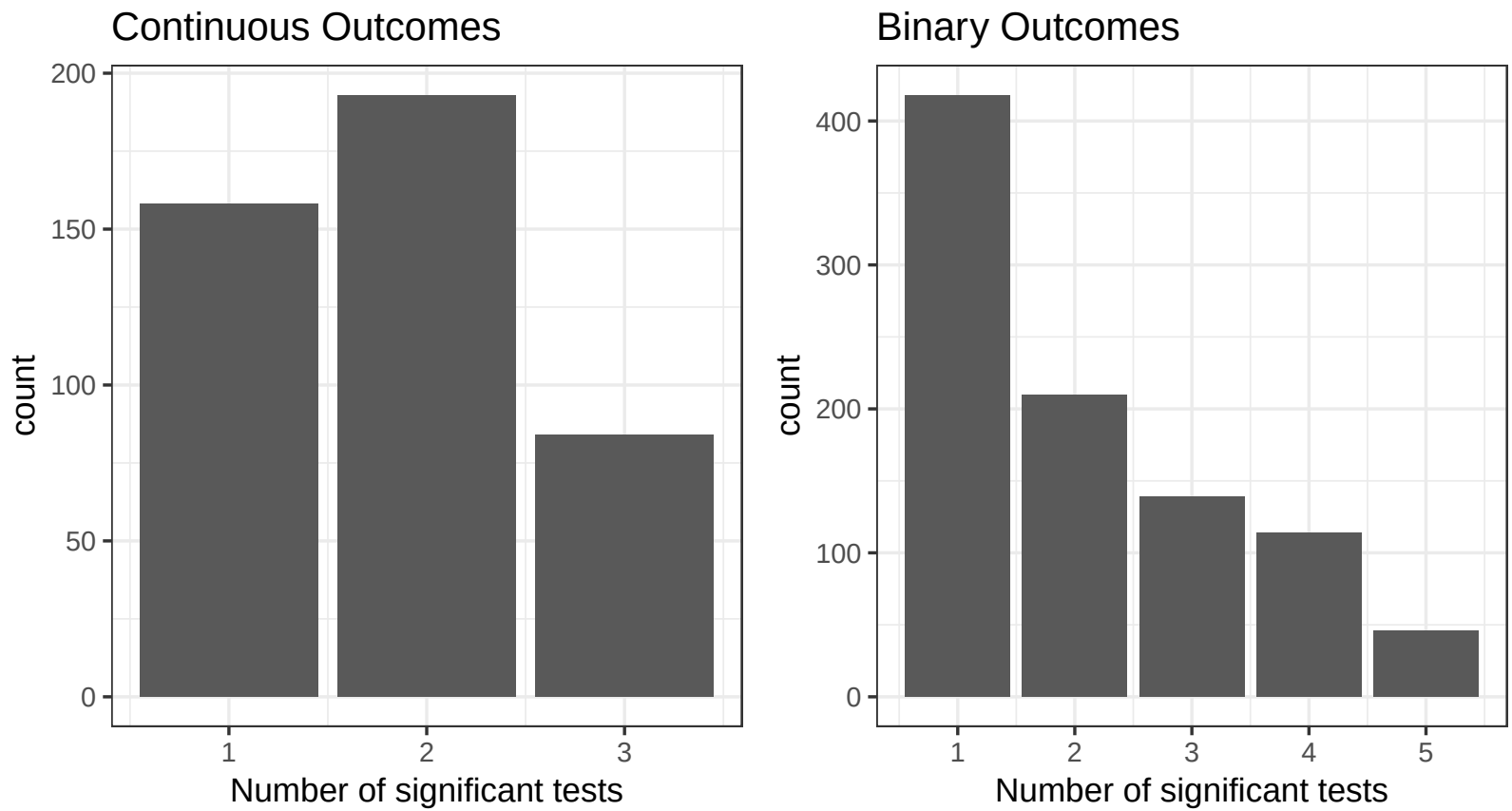
Binary Outcome Test Results

p-values distribution:



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

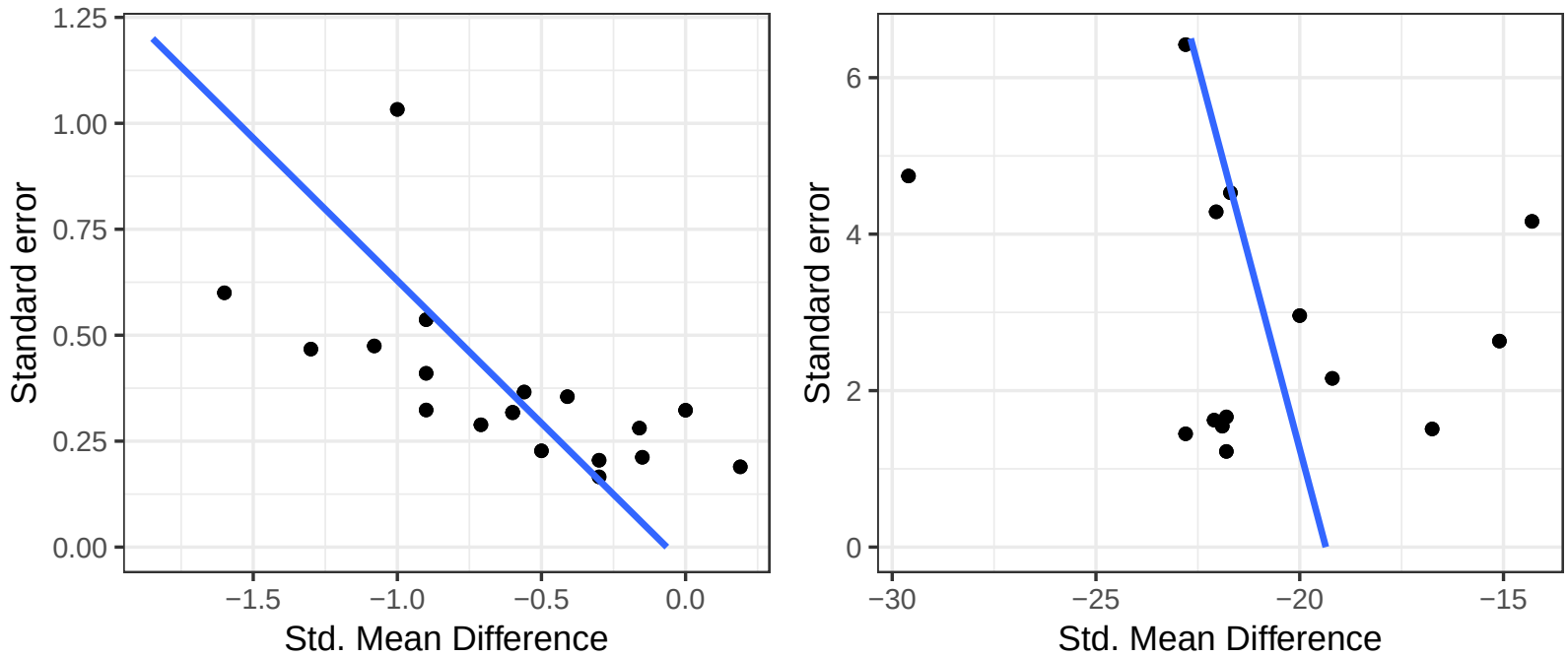
Similar to the tests, but with unnormalized effect y_i:

$$y_i = \beta_0 + \beta_1 x_i \tag{1}$$

β_0 corresponds to y_i with $x_i = 0$

Adjustment by regression

Linear regression method:



Shrinkage Regression

Extended random effects model:

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

$$\mathbb{E}(y_i) \to \beta_0 + \beta_1\tau \text{ if } \sqrt{v_i} \to 0$$

β_0, β_1 and τ can be estimated e.g. by ML and REML.

Shrinkage Regression

shrinking the within study variance:

$$y_i = \beta_0^\star + \beta_1^\star(\sqrt{v_i/M + \tau^2}) + \epsilon_i(\sqrt{s_i/M + \tau^2})$$

Letting $M \to \infty$ and substituting for all parameters and the observed residual

$$y_{\infty,i} = \beta_0^\star + \sqrt{\frac{\tau^2}{v_i + \tau^2}}(y_i - \beta_0^\star) \tag{2}$$

Shrinkage Regression

Three different treatment effect estimates:

$$y_{\infty,i} = \beta_0^\star + \sqrt{\frac{\tau^2}{v_i + \tau^2}}(y_i - \beta_0^\star) \tag{3}$$

References

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.

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