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Biostatistics

Publication Bias in Cochrane Meta-Analyses

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Publication Bias

– Preference of journal editors to publish significant study results

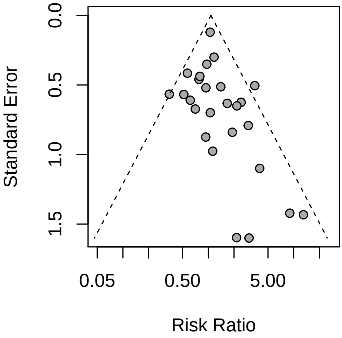
$\rightarrow$ non-significant results remain in file-drawer

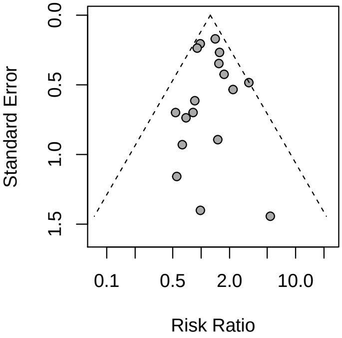
Systematic Reviews

- Summarize all evidence with regard to treatment with meta-analysis
- Biased if non-significant results are not available and included

Funnel Plot

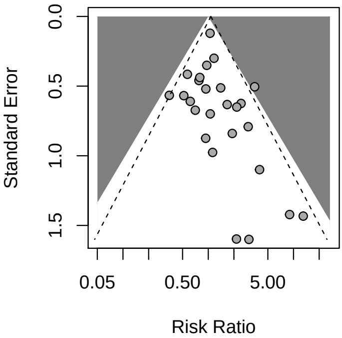
Look for funnel plot asymmetry:

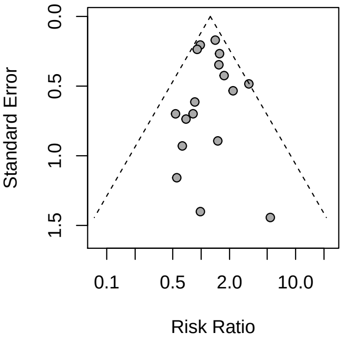




Funnel Plot

Effects with large standard errors have larger effect sizes (because they are only published if significant)





Detect Publication Bias

– Small study effect tests (funnel plot asymmetry)
– Excess significance tests

Excess Significance Test

Calculate power of each study, given that true effect size is fixed effects meta-analysis estimate.

Calculate:

$$p = \sum_{i=O}^{n} \left(\binom{n}{i} p^i (1-p)^{n-i} \right)$$

$O =$ observed no. of significant results, E expected based on power of studies, $p = E/n$.

Analysis

- Use meta-analyses from Cochrane.
- “The single most reliable source of evidence in clinical science

Analyse meta-analyses with publication bias tests.

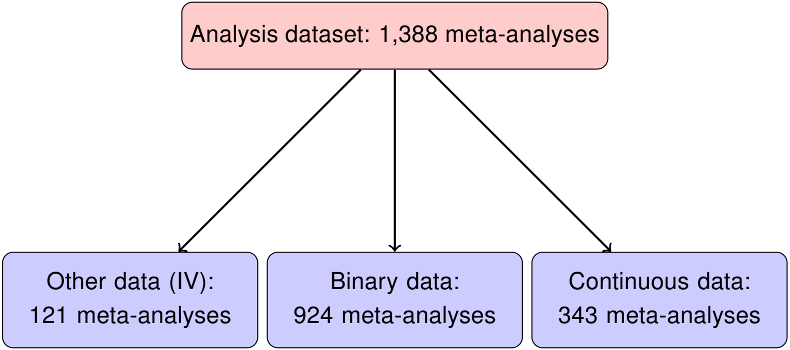
The Cochrane Dataset

Inital dataset: 6,354 reviews, 70,662 studies, 744,720 results

↓ exclusion of unsuitable meta-analyses

Analysis dataset: 738 reviews, 14,320 studies, 22,937 results

The Analysis dataset



Small Study Effect Tests

Weighted linear regression with std. error x_i and effect size y_i:

$$y_i = \beta_0 + \beta_1 x_i + \epsilon_i, \qquad \epsilon_i \sim N(0, x_i \sigma^2)$$

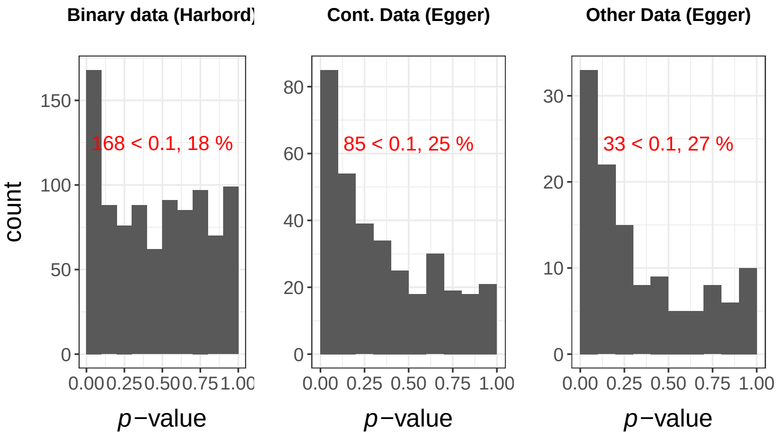
Test for $H0 : \beta_1 = 0$, no funnel plot asymmetry

Adjustments for Binary Data

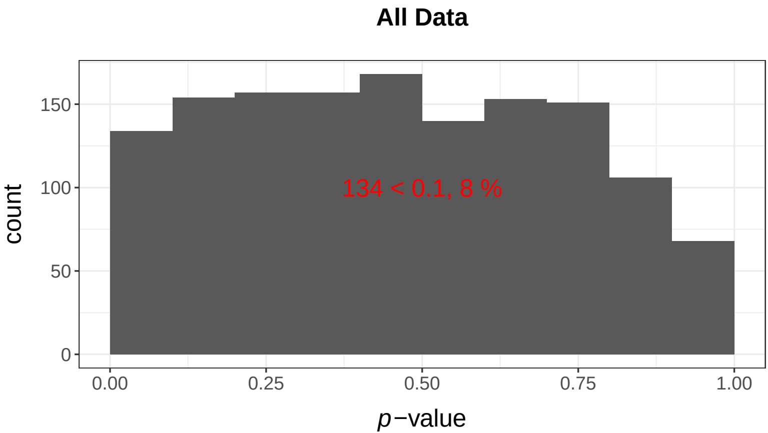
As recommended by Sterne et al. (2001)

- Log odds ratio and risk ratio θ and standard error se_θ are not independent
- Use score of binomial likelihood at log odds ratio $\theta_{\text{H0}} = 0$ instead of log odds ratio, and the inverse Fisher information instead of se_θ

Small Study Effect Tests



Excess Significance Test



Adjustment

Calculate unbiased estimates by

- Sensitivity analysis
- Regression approach

Selection Model

Copas and Shi (2000)

$$\theta_i \sim N(\mu_i, \sigma_i^2) \qquad \mu_i \sim N(\theta, \tau^2)$$

So we have $\theta_i = \mu_i + \sigma_i \epsilon_i$. Introduce

- Baseline study retention rate a
- Std. error dependent retention rate b
- introduces correlation between ϵ_i and selection probability

Sensitivity analysis

To test a pair *a*,*b*, include β:

$$\theta_i = \theta + \beta\,\mathrm{se}_i + \sigma_i \epsilon_i$$

- θ_i is the effect size of study *i* and right-hand side is the fitted value of the model.
- Repeatedly test for $\beta_{\mathrm{H0}} = 0$

Regression

Correct for small study effect (Rücker et al., 2011):

- Use global mean of regression β_0 from $y_i = \beta_0 + \beta_1 x_i + \epsilon_i, \epsilon_i \sim N(0, x_i\sigma^2)$
- Add minimal bias term $\beta_1 \cdot \tau$

$$\theta_{\text{Adj.}} = \beta_0 + \beta_1\tau$$

Adjustment Methods

Differences:

- Regression: uncertainty of bias parameter retained
- Sensitivity analysis: Bias itself is not estimated, but most parsimonious scenario is chosen
- Sensitivity analysis: No adjustment if no evidence for bias

Regression adjustment leads to higher uncertainty of $\theta_{\text{Adj.}}$

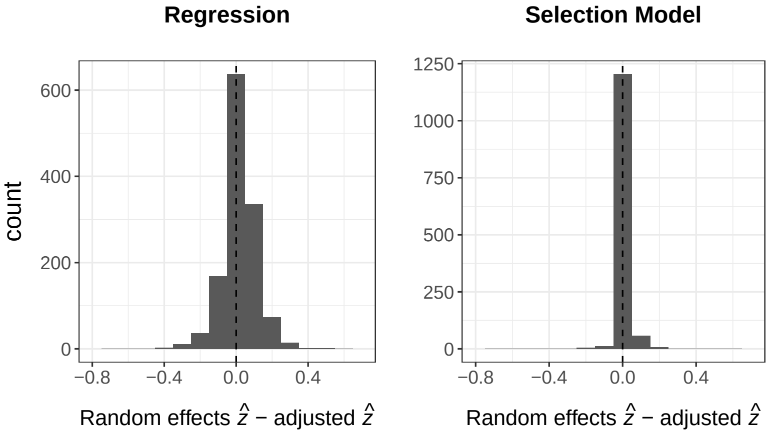
Effect Measure Transformation

$$d = \theta \frac{\sqrt{3}}{\pi} \qquad \mathrm{se}_d^2 = \mathrm{se}^2 \, \frac{\sqrt{3}}{\pi}$$

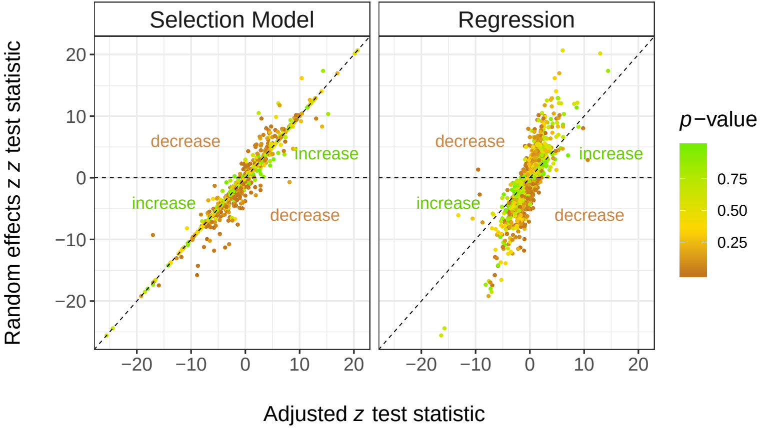
$$r = \frac{d}{\sqrt{d^2 + a}} \qquad a = (n_c + n_t)^2 / n_c n_t$$

$$z = 0.5 \ln \left(\frac{1 + r}{1 - r} \right) \qquad \mathrm{se}_z^2 = \frac{1}{n - 3}$$

Results


Regression
Selection Model
count
600
400
200
0
1250
1000
750
500
250
0
−0.8
−0.4
0.0
0.4
Random effects $\hat{z}$ − adjusted $\hat{z}$
Random effects $\hat{z}$ − adjusted $\hat{z}$

Results


Selection Model
Regression
Random effects z test statistic
Adjusted z test statistic
decrease
increase
increase
decrease
20
10
0
−10
−20
−20
−10
0
10
20
p−value
0.75
0.50
0.25

Missing Study Number

Missing study number according to selection model parameters: 2,618, 11.4%

	= 0	5%	25%	50%	75%	95%	mean
Missing number	226	0	0	1.5	5.9	20.1	4.7
Overall fraction	226	0	0	0.1	0.4	1.0	0.3

Table: Fraction of missing studies and estimates of missing studies with their zero counts (“= 0”), quantiles and means.

Additional Results

Linear mixed model with random effects for meta-analyses and reviews:

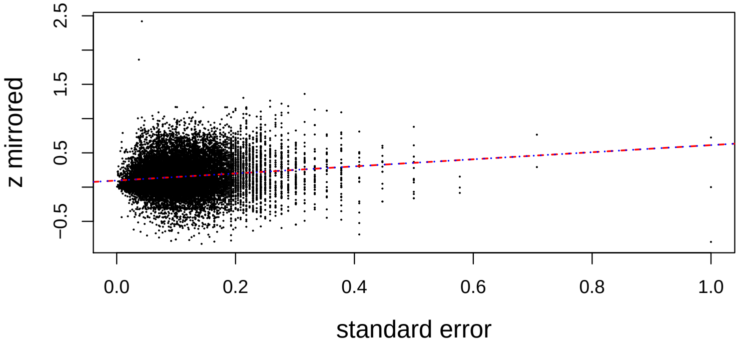
$$\mathbf{y}_i \mid U_j, U_k, \epsilon_i = \beta_0 + x_i\beta_1 + U_j + U_k + \epsilon_i$$

$\rightarrow$ Increased power to estimate β

Mixed Linear Model

AIC improvement to null fit: 1820 to 1306.

Bias parameter β_1 = 0.52 (95%CI: 0.44,0.59)



Limitations

Small study effect $\neq$ publication bias. Also:

- True heterogeneity
- Selective outcome reporting
- Delayed publication
- ...

Small study effect tests do not take into account significance directly.

Limitations

- Unknown amount of secondary outcomes
- Small amount of adverse outcomes
- Publication bias unknown for excluded data
- Exploratory Analysis!

Implications

- Results are largely in line with previous research
- Underline the need for examination of publication and other biases in meta-analyses
- Otherwise, validity of meta-analyses can be contested

References

Copas, J. and Shi, J. Q. (2000). Meta-analysis, funnel plots and sensitivity analysis . *Biostatistics*, 1(3):247–262.

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

Sterne, J. A. C., Egger, M., and Smith, G. D. (2001). Investigating and dealing with publication and other biases in meta-analysis. *BMJ*, 323(7304):101–105.

Backup slides:

Transformation