



Shaping the Future of
Drug Development

Comparison of Different Methods of Detecting Publication Bias

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Outline

- Systematic review
- Publication bias
- Bias detection methods
- Comparison of methods
- Conclusion

Systematic Review

- What is Systematic review?

Type of literature review that collects and critically analyses multiple research studies.

- Why to perform it?
 - To plan new studies
 - To introduce new treatment

Steps in Systematic Review

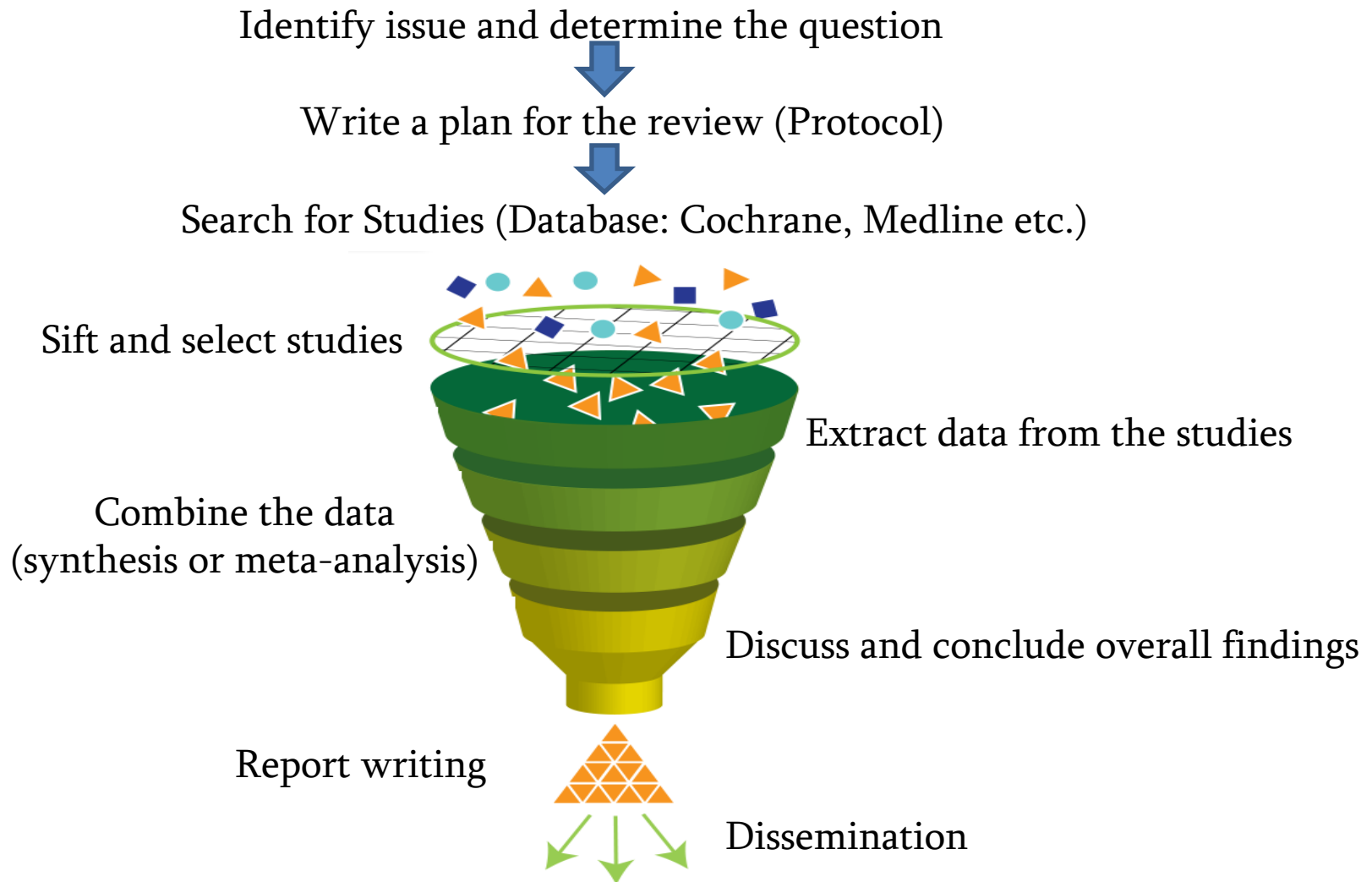


Image source: <http://libguides.utoledo.edu/sysrev/collaboration>

Challenges

- Heterogeneity
 - ✓ Clinical heterogeneity
 - ✓ Statistical heterogeneity
 - Cochrane Q statistic
 - I^2 (Index of Heterogeneity)
- Publication Bias

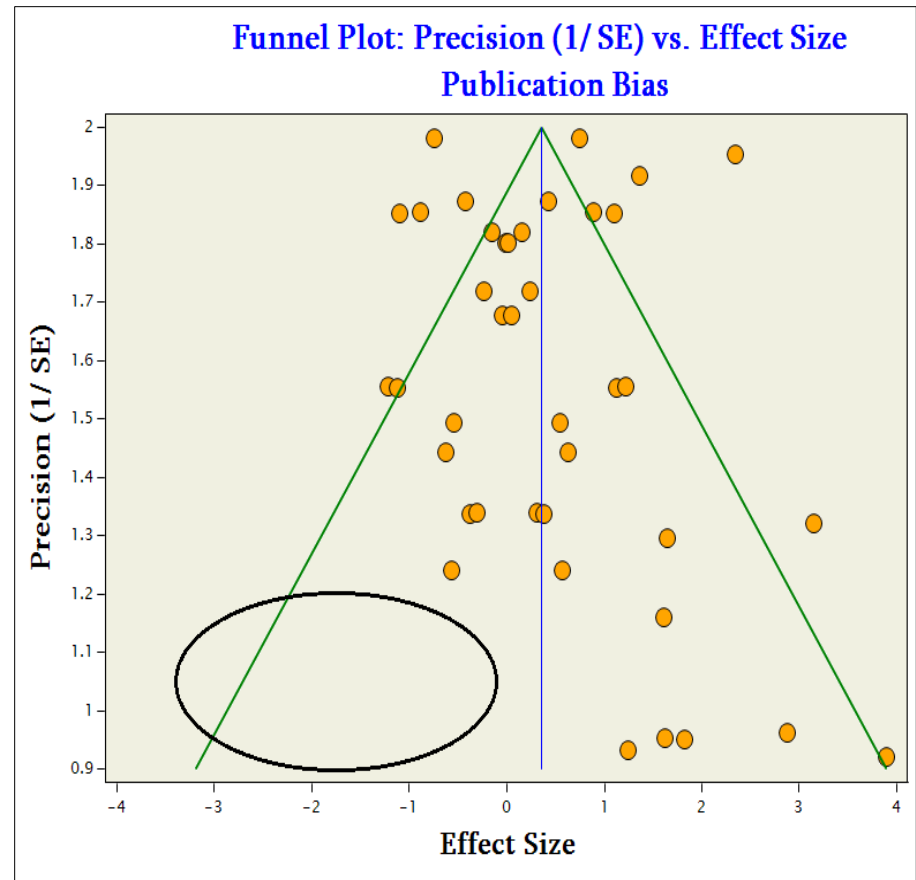
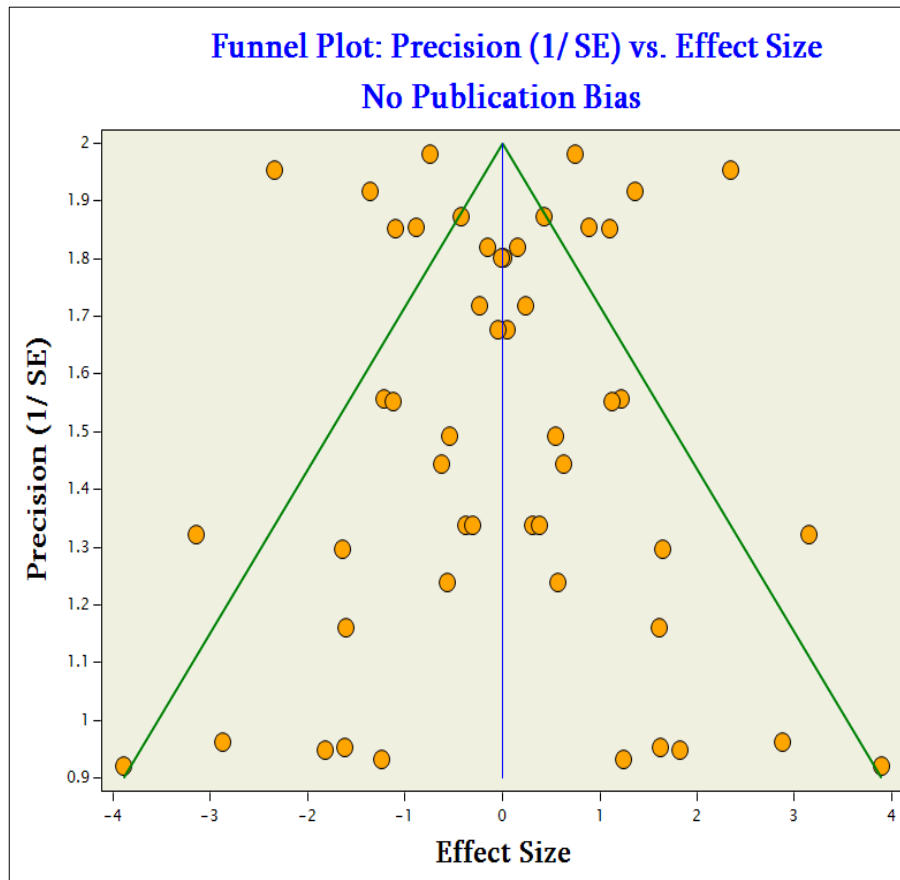
Publication Bias

- What is publication bias?
 - Reasons
 - Mostly studies with significant results
 - Only published studies are included
 - Language bias
- Consequences
- How to assess the bias?

Methods

- Funnel Plot
- Fail-Safe N
- Begg-Mazumdar
- Egger's Regression
- Trim and Fill

Method 1 - Funnel Plot



Source: Meta-Analysis software developed by Cytel

Method 2 - Fail-Safe N

- Estimates the number of non-significant missing studies
- Three approaches:
 - Rosenthal's Fail-Safe N
 - Orwin's Fail-Safe N
 - Rosenberg's Fail-Safe N
- Small value of fail-safe N indicates presence of publication bias

Method 3 - Begg-Mazumdar

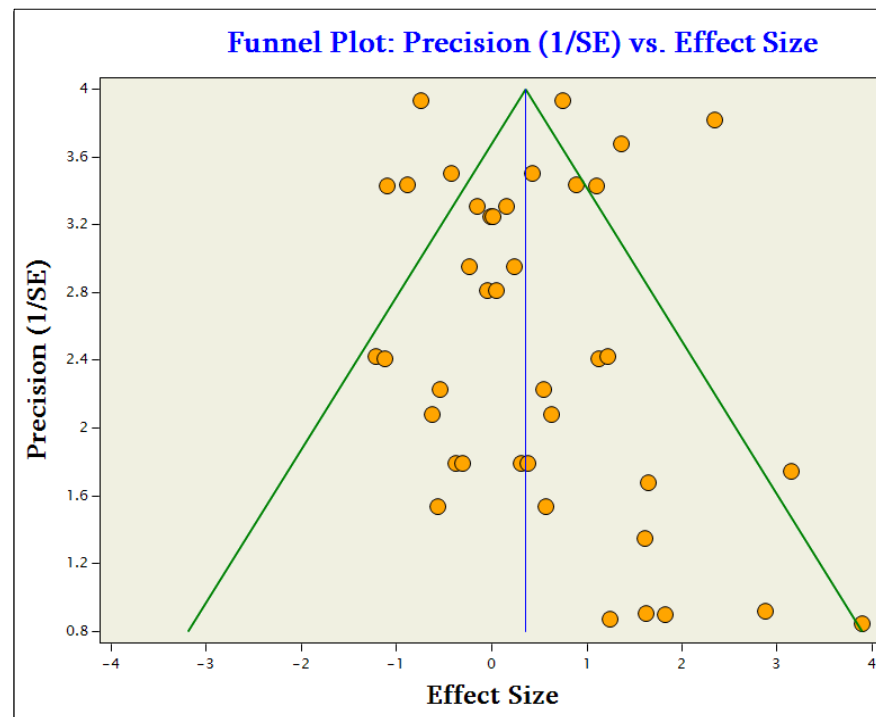
- Uses Kendall's rank correlation test.
- Computes correlation between standardized effect estimates of individual studies and its variance.
- High correlation indicates the presence of publication bias.

Method 4 - Egger's Regression

- Uses linear regression instead of correlation.
- Regression line of (effect size/standard error) on (1/standard error)
- Intercept value close to zero - lesser publication bias.

Method 5 - Trim and Fill

- Two stage iterative procedure
- Gives an approximate number of studies to be imputed to minimize the publication bias



Source: Meta-Analysis software developed by Cytel

Simulation

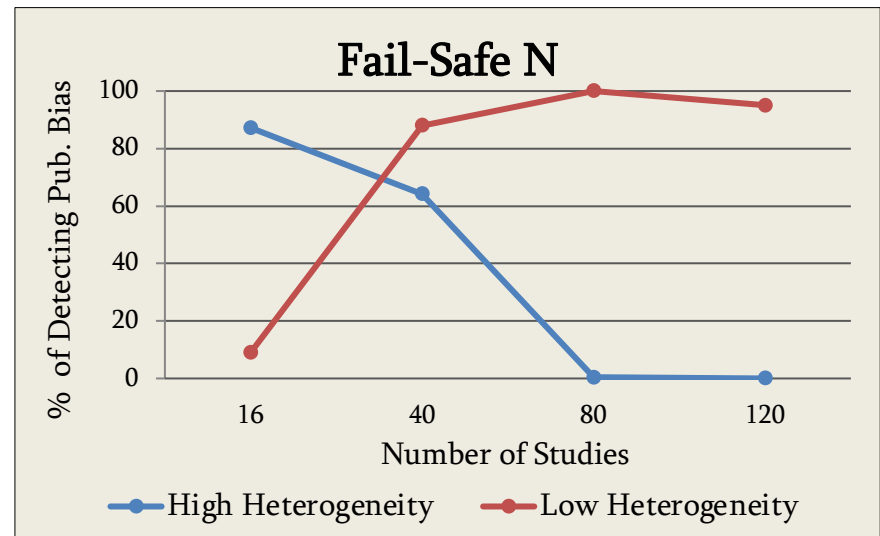
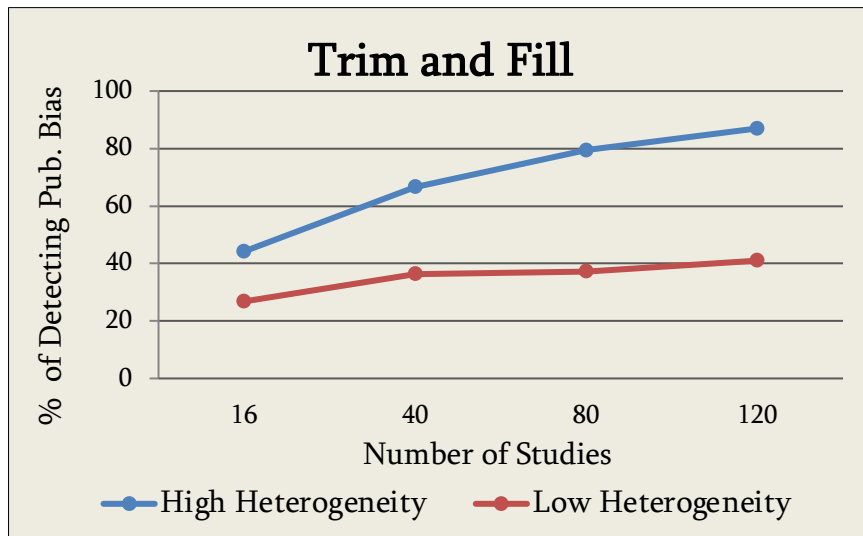
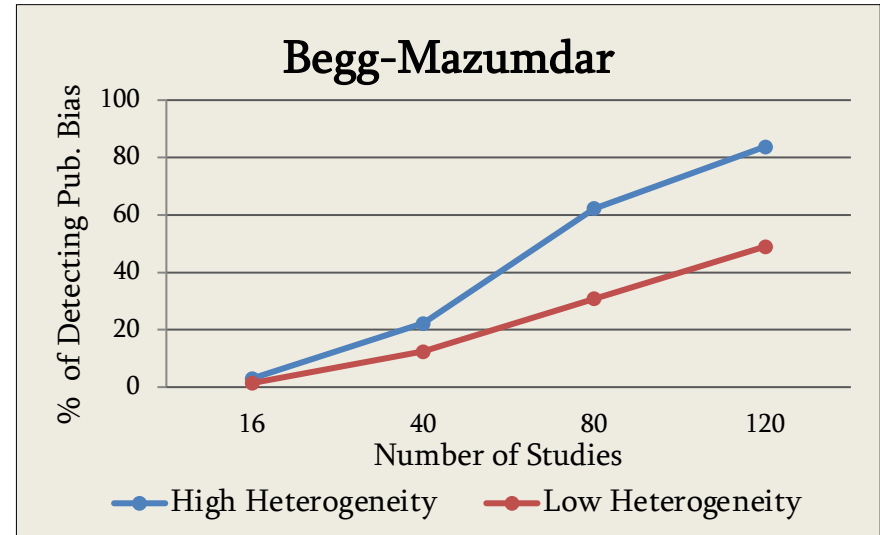
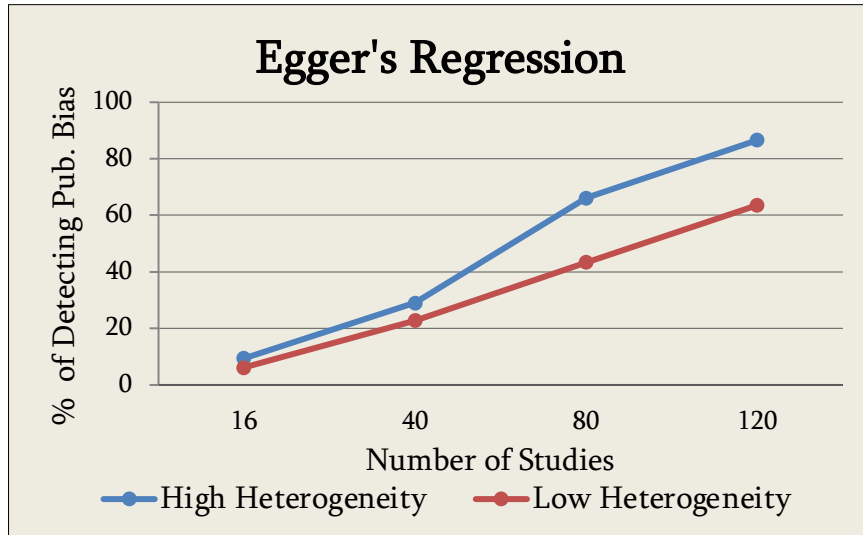
- Four levels of number of studies ($N = 20, 50, 100, 150$)
- Two levels of heterogeneity
 - Low (Index of heterogeneity ≤ 30)
 - High (Index of heterogeneity > 30)
- For each combination,
 - 500 samples
 - From each sample, removed 20% studies
- Effect Size: Log Odds Ratio

Simulation

- E.g. $N = 20$ and low heterogeneity level

StudyID	Events_TreatmentA	Total_TreatmentA	Events_TreatmentB	Total_TreatmentB	LogOddsRatio
13	8	46	1	33	1.907591285
6	5	15	3	41	1.84582669
12	6	43	1	18	1.014054901
9	4	27	4	64	0.958850346
15	6	64	2	45	0.799369394
17	7	52	1	13	0.624154309
14	5	51	2	36	0.61400986
8	3	16	6	51	0.548565952
1	4	24	5	44	0.444685821
20	5	50	3	33	0.105360516
10	3	33	5	50	-0.105360516
11	5	44	4	24	-0.444685821
18	6	51	3	16	-0.548565952
4	2	36	5	51	-0.61400986
7	1	13	7	52	-0.624154309
5	2	45	6	64	-0.799369394
19	4	64	4	27	-0.958850346
2	1	18	6	43	-1.014054901
16	3	41	5	15	-1.84582669
3	1	33	8	46	-1.907591285

Comparison of Methods



Comparison of Methods

Egger's Regression (% of detecting Publication Bias)				
	N = 16	N = 40	N = 80	N = 120
High Heterogeneity	9.4	29	66.2	86.6
Low Heterogeneity	6.2	22.8	43.4	63.6

Begg-Mazumdar (% of detecting Publication Bias)				
	N = 16	N = 40	N = 80	N = 120
High Heterogeneity	3	22.2	62.2	83.8
Low Heterogeneity	1.4	12.4	30.8	49

Trim and Fill (% of detecting Publication Bias)				
	N = 16	N = 40	N = 80	N = 120
High Heterogeneity	44.2	66.6	79.4	87
Low Heterogeneity	26.8	36.4	37.2	41

Fail-Safe N (% of detecting Publication Bias)				
	N = 16	N = 40	N = 80	N = 120
High Heterogeneity	87.2	64.2	0.4	0
Low Heterogeneity	9	88	100	95

Conclusion

- Egger's regression and Begg-Mazumdar
 - Better performance in large number of studies for both high and low heterogeneity
- Trim and Fill
 - Not much impact due to increase in number of studies
 - Performs better in smaller number of studies compared to Egger's regression and Begg-Mazumdar
- Fail-Safe N
 - Trend in performance with respect to increase in number of studies, is in the opposite direction in high and low heterogeneity

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Thank You

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