



Shaping the Future of
Drug Development

Comparison of Different Methods of Detecting Publication Bias

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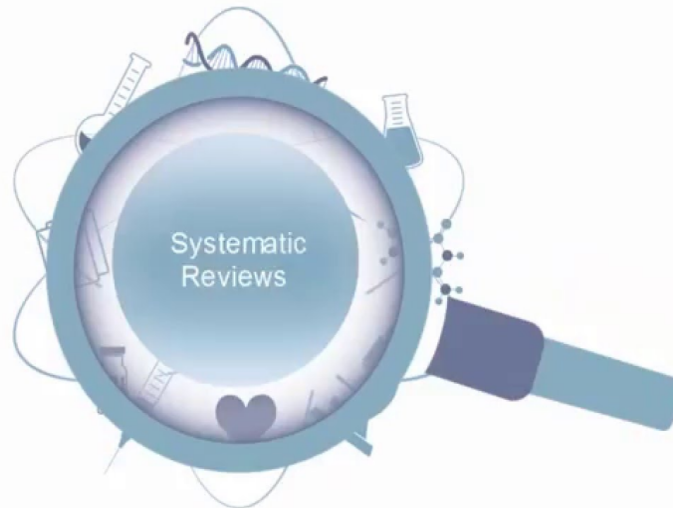
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Outline

- Systematic review and Meta-analysis
- Publication bias
- Bias detection methods
- Comparison of methods
- Conclusion

Systematic review

Type of literature review that collects and critically analyses multiple research studies about a particular question in standardized and systematic way.



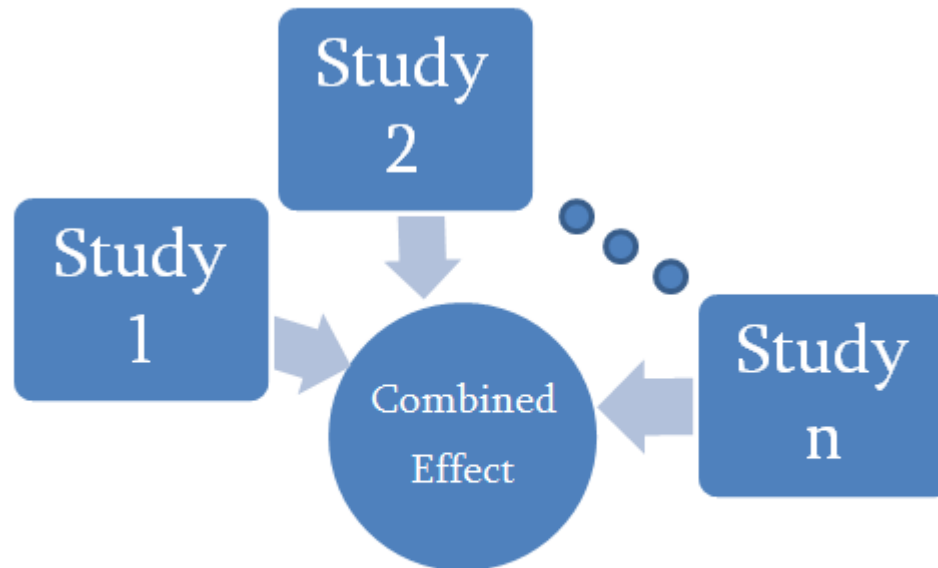
Source: <http://cccr.org/cochrane.org/animated-storyboard-what-are-systematic-reviews>

Steps in systematic review

- Define a research problem
- Search and identify the relevant work
- Define study selection criteria i.e. inclusion and exclusion criteria
- Meta-analysis
- Interpret the findings from meta-analysis

Meta-analysis

A statistical analysis that combines the results of multiple scientific studies.



Steps in meta-analysis

- Compute combined study effect
- Test the robustness of combined effect
 - Test for Heterogeneity
 - Test for Publication Bias
 - Sensitivity Analysis

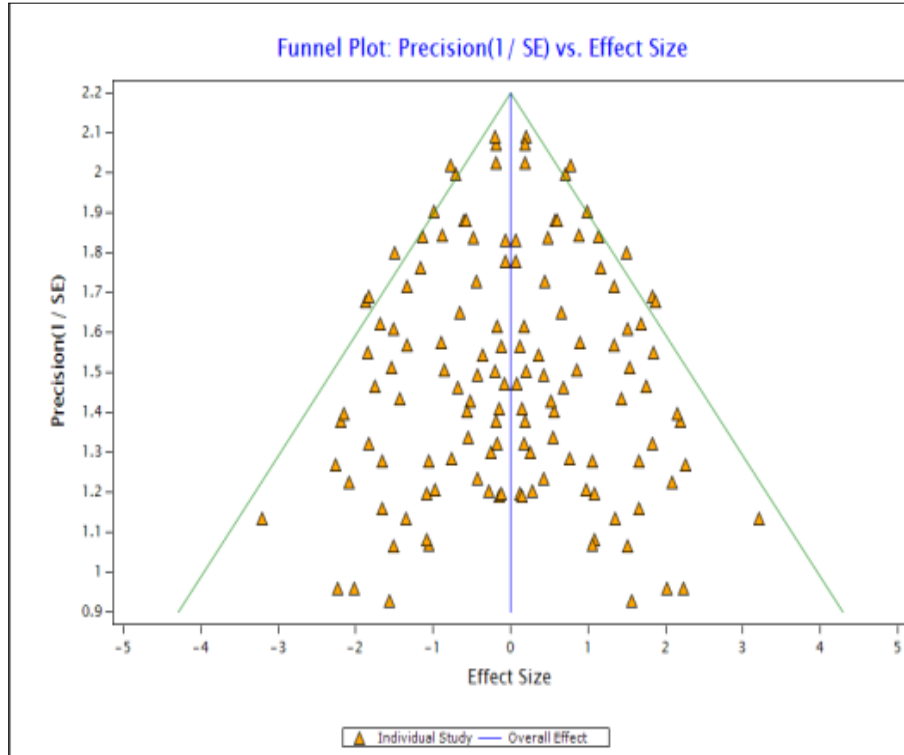
Publication Bias

- What is publication bias?
- Consequences
- How to assess the bias?

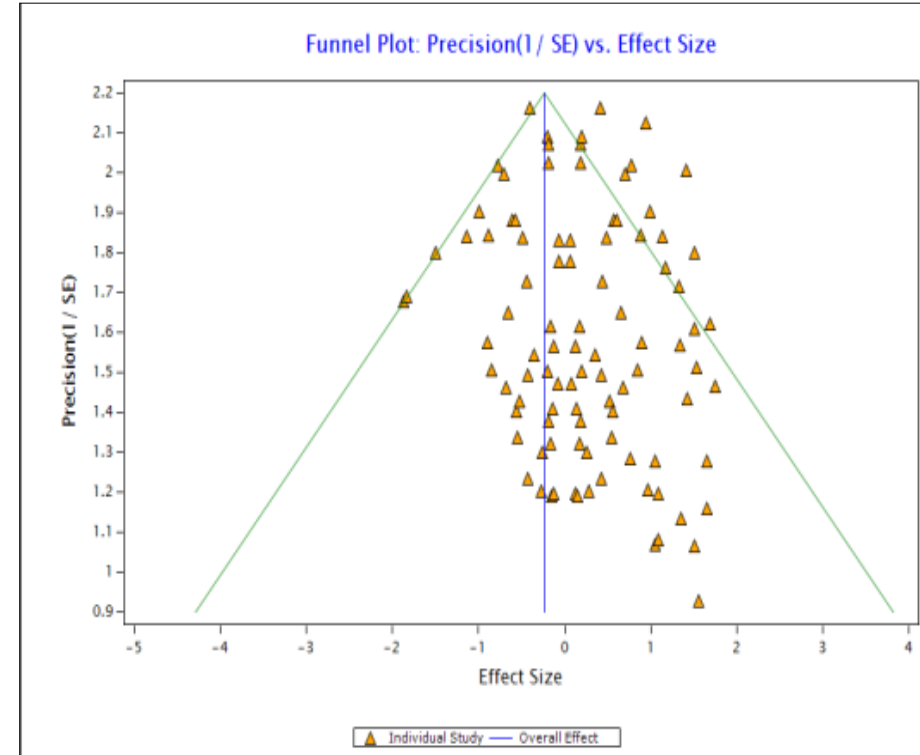
Method 1 - Funnel Plot

Scatter plot of estimates of the treatment effects of each study against the measure of its precision (1/Standard Error)

Funnel Plot: No Publication Bias



Funnel Plot: With Publication Bias



Source: Meta-Analysis software developed in Cytel

Method 2 - Fail-Safe N

- Three approaches:
 - Rosenthal's Fail-Safe N
 - Orwin's Fail-Safe N
 - Rosenberg's Fail-Safe N
- Estimate the No. of missing studies (hypothetical) to make the graph symmetric
- Small value of fail-safe N indicates presence of publication bias

Method 3 - Begg-Mazumdar

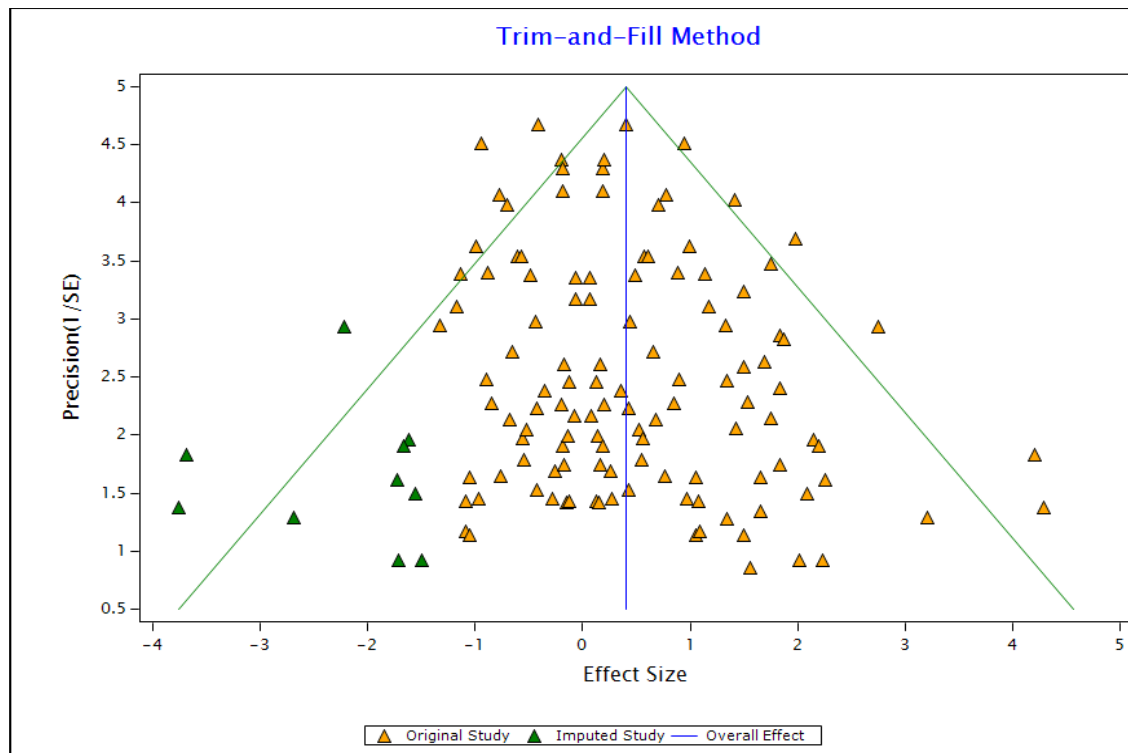
- Uses Kendall's rank correlation test.
- Tests the interdependence of variance and effect size.

Method 4 - Egger's Regression

- Uses the linear regression instead of correlation.
- Regression line of Y (effect size/standard error) on X (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

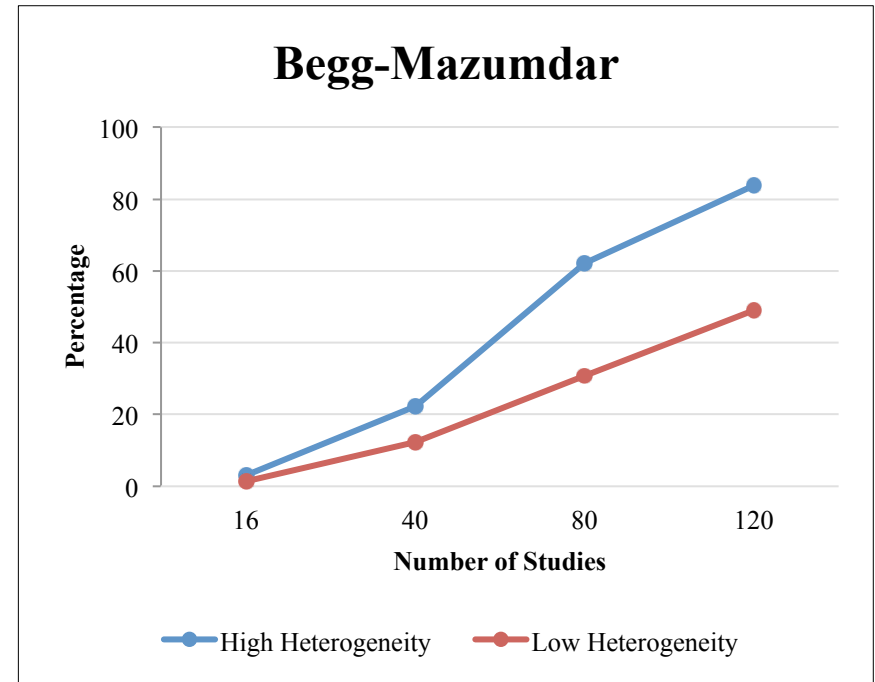
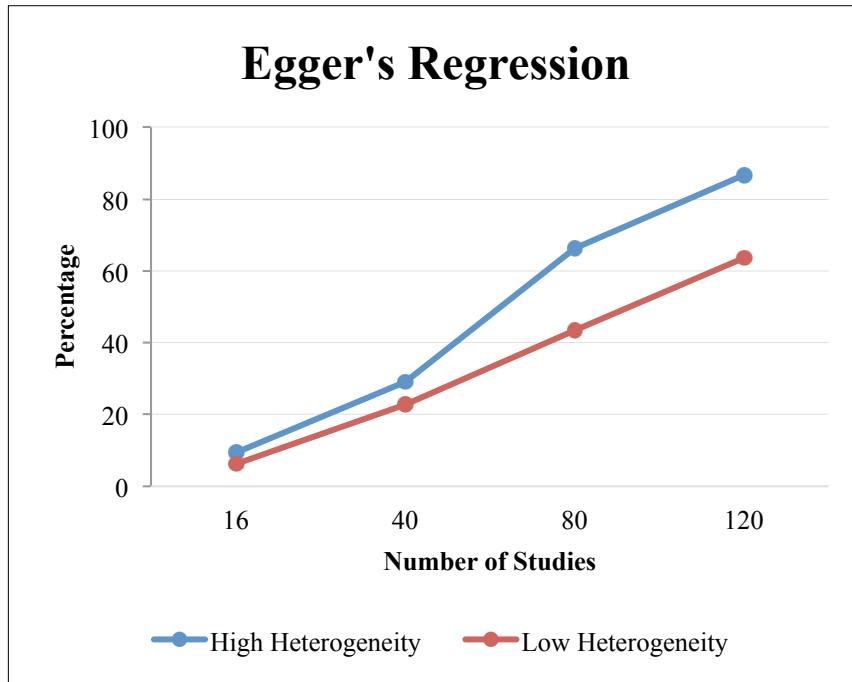


Source: Meta-Analysis software developed in Cytel

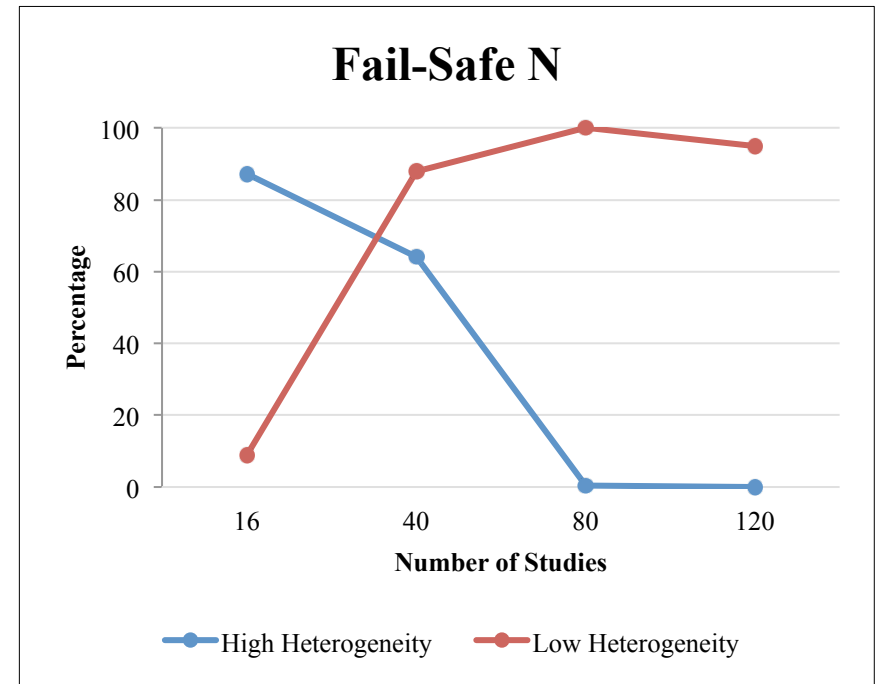
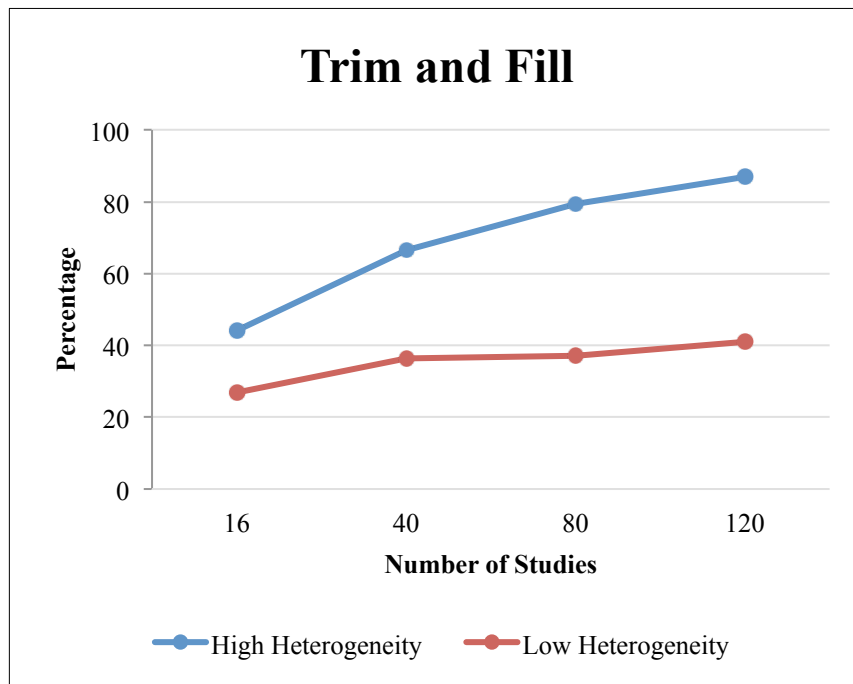
Simulation

- Four levels of No. 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 datasets with no publication bias
 - 500 datasets with 20% bias

Comparison (% studies correctly detected)



Comparison (% studies correctly detected)



Conclusion

- High heterogeneous data:
 - Begg-Mazumdar, Eggers regression and Trim-and-Fill performs better.
 - Fail-Safe N method gives opposite results compared to other three
- Low heterogeneous data:
 - Fail-Safe N works better
- Small number of studies :
 - Fail Safe N and Trim and Fill methods are advisable

Conclusion (Cont...)

- Large number of studies
 - Begg-Mazumdar and Egger's regression methods gives reliable results.
- Begg-Mazumdar and Egger's regression methods perform quite similar.

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Thank You

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