



Shaping the Future of  
Drug Development

# Comparison of Different Methods of Detecting Publication Bias

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# Outline

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

# Systematic Review

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- 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

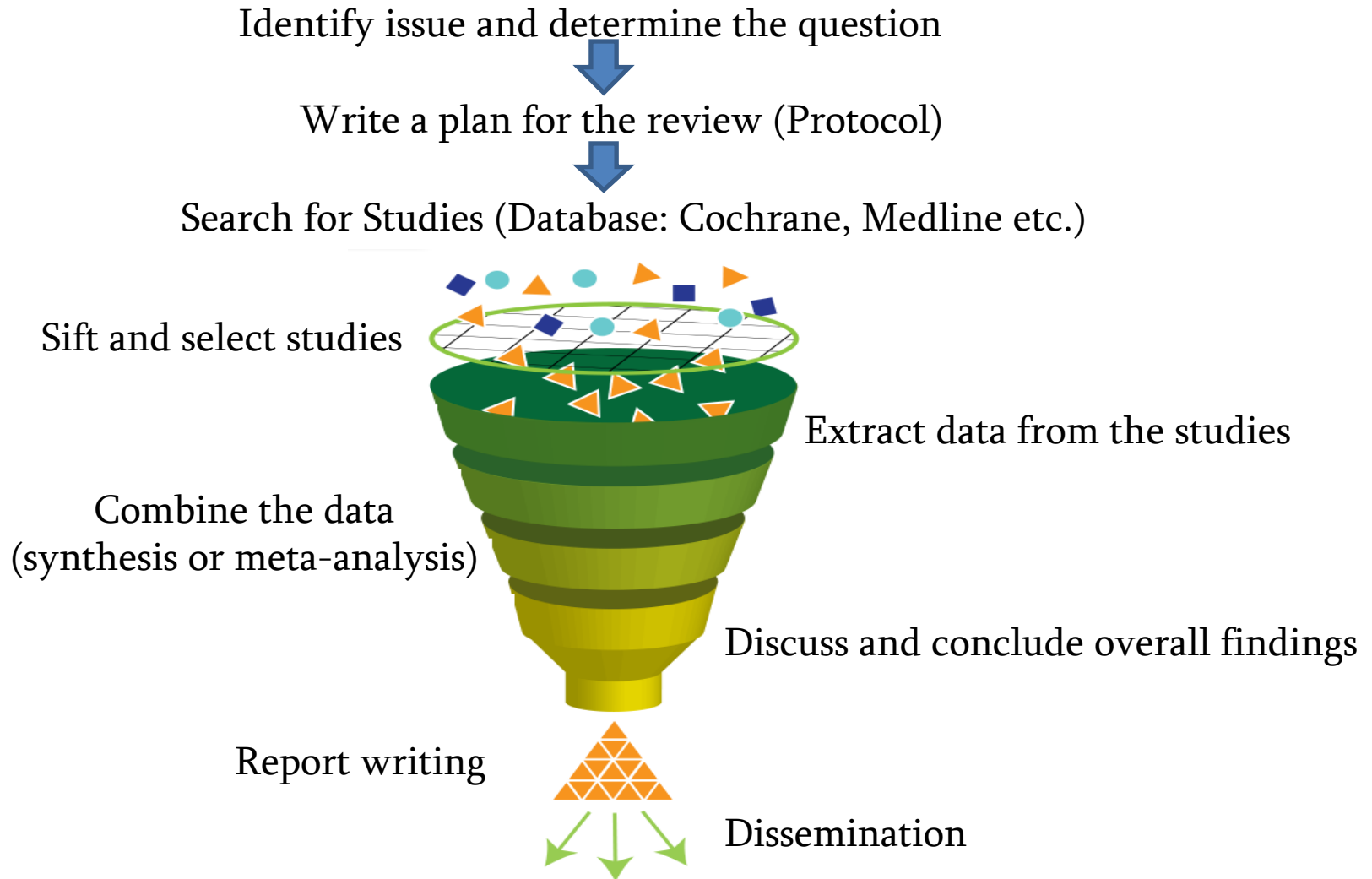


Image source: <http://libguides.utoledo.edu/sysrev/collaboration>

# Challenges

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

# Publication Bias

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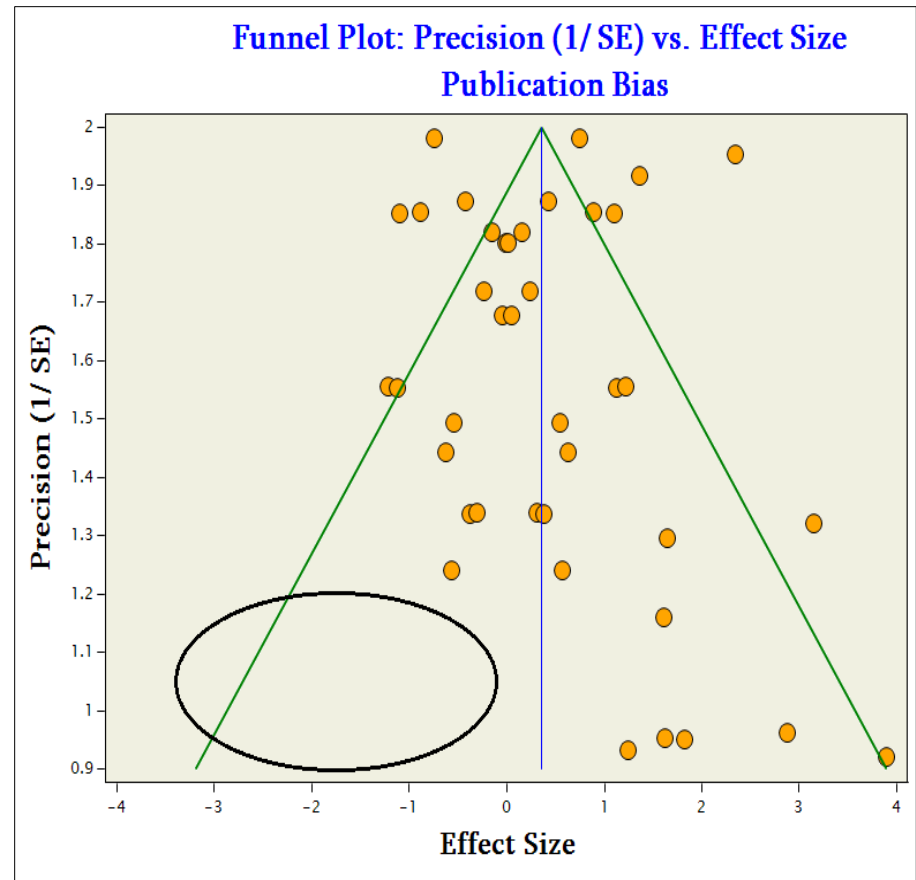
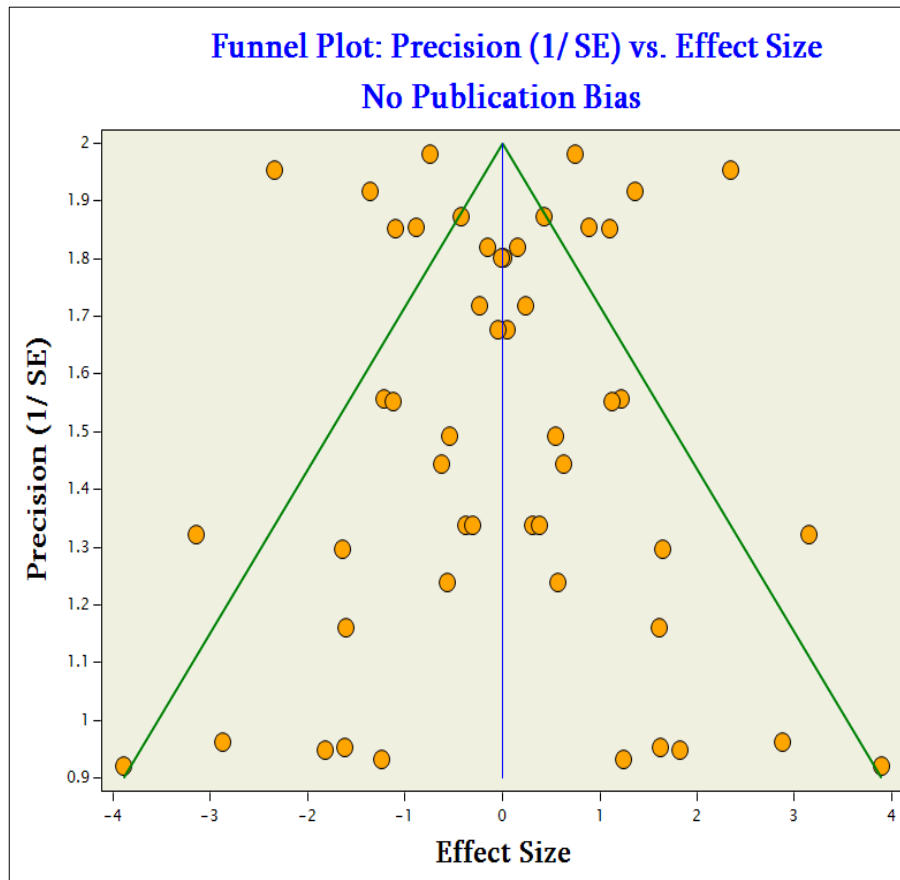
- What is publication bias?
  - Reasons
    - Mostly studies with significant results
    - Only published studies are included
    - Language bias
- Consequences
- How to assess the bias?

# Methods

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- 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

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- 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

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- 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.

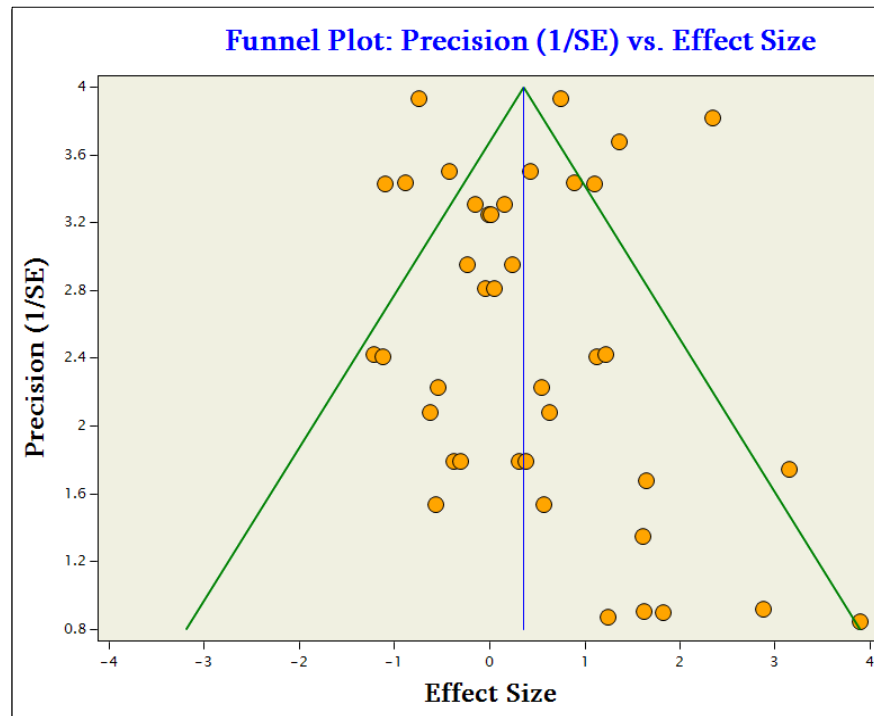
# Method 4 - Egger's Regression

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- 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

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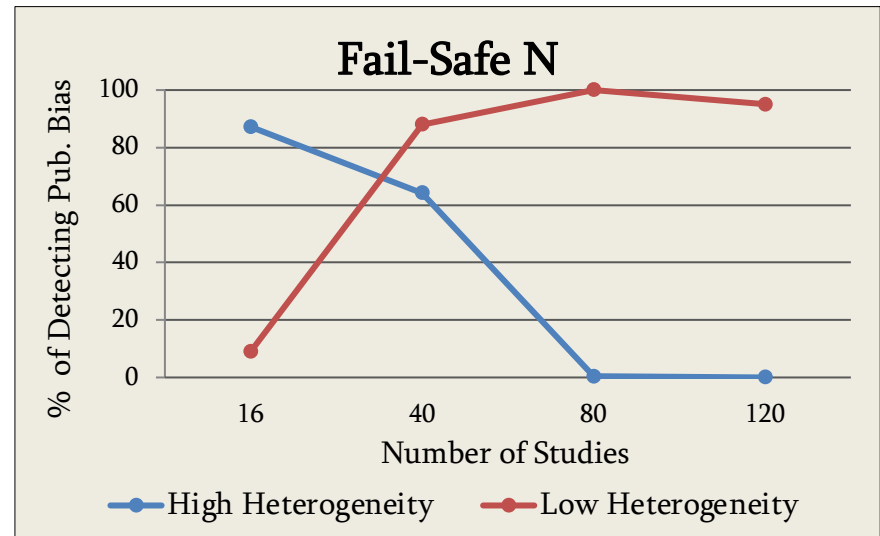
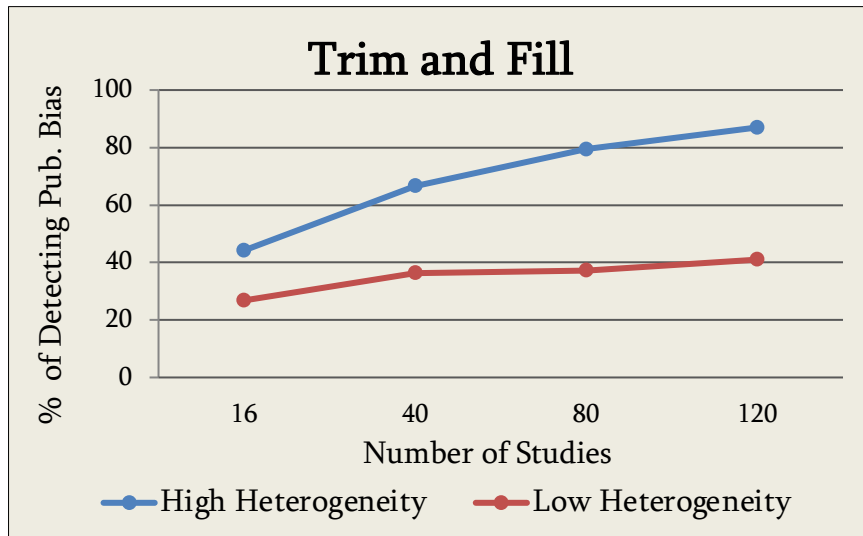
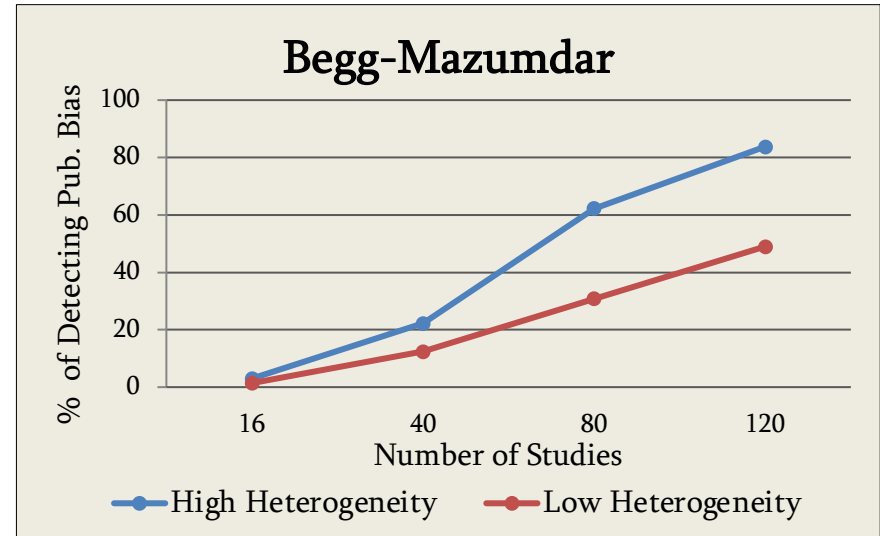
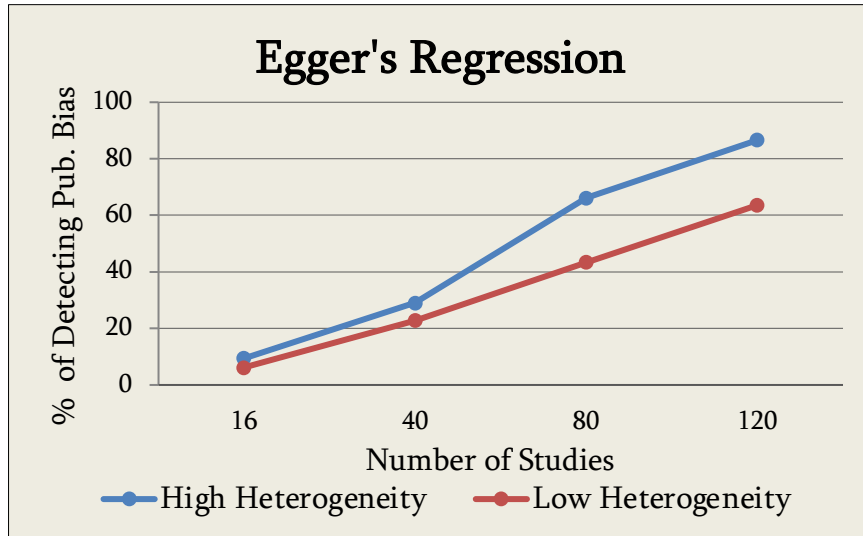
- Four levels of number of studies ( $N = 20, 50, 100, 150$ )
- Two levels of heterogeneity
  - Low (Index of heterogeneity  $\leq 30$ )
  - High (Index of heterogeneity  $> 30$ )
- For each combination,
  - 500 samples
  - From each sample, removed 20% studies
- Effect Size: Log Odds Ratio

# 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   | <b>86.6</b> |
| 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   | <b>83.8</b> |
| 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                              | <b>44.2</b> | 66.6   | 79.4   | 87      |
| Low Heterogeneity                               | <b>26.8</b> | 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        | <b>0</b> |
| Low Heterogeneity                             | 9      | 88     | <b>100</b> | 95       |

# Conclusion

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- 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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