A new measure of between-studies heterogeneity in meta-analysis

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Acknowledgements

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Heterogeneity in meta-analysis

- Clinical vs statistical heterogeneity

- Excess of between-studies variation in the effect estimates above that expected by chance

- Important to decide the appropriateness of combining results
Notation

Meta-analysis based on $K$ studies

$$\hat{\beta}_i \sim N\left( \bar{\beta}, \tau^2 + v_i \right) \tag{1}$$

$\tau^2$ is the common between-study variation ($\tau^2 = 0$ in a fixed-effects model)

$v_i$ is the study-specific within (error) variation

$$\bar{\beta} = \frac{\sum_{i=1}^{K} \hat{\beta}_i w_i}{\sum_{i=1}^{K} w_i}$$

$$\text{Var}\left( \beta \right) = \left( \sum_{i=1}^{K} w_i \right)^{-1} \tag{2}$$

$$w_i = \left( \tau^2 + v_i \right)^{-1}$$
How to detect heterogeneity

▶ Estimate of $\tau^2$
  May be difficult to interpret and compare

▶ Cochran’s $\chi^2$ test or the $Q$-test
  May have poor/excessive power

▶ Measures of heterogeneity: $R_I^1$ and $I^2^2$
  Defined as $\frac{\tau^2}{\tau^2+\sigma^2}$
  $\sigma^2$ is a summary measure of the observed within-study variance, $\nu_i$

\[
1\sigma^2 = (K - 1) \frac{\sum_{i=1}^{K} w_i}{\left((\sum_{i=1}^{K} w_i)^2 - \sum_{i=1}^{K} w_i^2\right)}
\]

\[
2\sigma^2 = \frac{K}{(\sum_{i=1}^{K} w_i)}
\]
Aims

Homogeneity of within-studies variances is unlikely to hold

<table>
<thead>
<tr>
<th>Analysis</th>
<th>within-study variances</th>
<th>$\sigma^2(I^2)$</th>
<th>$\sigma^2(R_I)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>[6, 6.1, 6.2, 5.9, 6, 5.9, 6.1, 5.8, 6, 6.2]</td>
<td>6.018</td>
<td>6.017</td>
</tr>
<tr>
<td>B</td>
<td>[5, 19, 3, 15, 6, 23, 4, 17, 2, 8.8]</td>
<td>6.017</td>
<td>5.602</td>
</tr>
</tbody>
</table>

- To propose a new measure of heterogeneity that relaxes this assumption
- Compare the performances of the new estimator through simulations studies
$R_b$ a new measure of heterogeneity

The new measure quantifies the contribution of $\tau^2$ relative to the variance of the pooled random effects estimate.

If $v_i = 0, \forall i$, $\text{Var}(\beta) = \tau^2/K$

$$R_b = \frac{\tau^2}{K \text{Var} \left( \hat{\beta}_{re} \right)} = \frac{1}{K} \sum_{i=1}^{K} \frac{\tau^2}{v_i + \tau^2}$$ (3)

It can be expressed as percentage
\( R_b \) a new measure of heterogeneity (2)

It is a function of \( \tau^2, K, \) and \( v_i \)

\( R_b \) satisfied the properties for a measure of heterogeneity

As the other measures, it depends on the precision of \( \beta_i (v_i) \)

\( R_b \) is a consistent and asymptotically normal distributed estimator
(Wald-type confidence intervals)
Compared to $I^2$ and $R_I$

It can be expressed as the average of the proportions of $\tau^2$ to individual overall variances

$$R_b < R_I \text{ and } I^2 < R_I$$

Differences between $I^2$ and $R_b$ depend upon distribution for $\nu_i$

It coincides with $I^2$ and $R_I$ when $\nu_i = \sigma^2 \forall i = 1, \ldots, K$
Simulation study

- Different scenario simulations ($R_b = 0.1, 0.5, 0.7$; $CV_{V_i} = 0.5, 1, 2$; $CV_B = 0.5, 1, 3$; $K = 5, 20, 50, 100$)
- Percent relative bias and coverage
- [https://alecri.shinyapps.io/bias/](https://alecri.shinyapps.io/bias/)
Simulation results: $R_b$

- Invariant to the magnitude of $\bar{\beta}$
- Bias for small $K$ (also for $I^2$ and $R_I$)
- It decreased as $K$ increased
- Positive bias for low $R_b$
- No specific pattern according to $CV_{v_i}$ and $CV_B$
- Good coverage across simulation scenarios
Simulation results: comparison

- $I^2$ and $R_I$ overestimated the impact of heterogeneity
- Bias and coverage for $I^2$ and $R_I$ worsened as $CV_{Vi}$ increased
## Illustrative examples

<table>
<thead>
<tr>
<th>1st author</th>
<th>K</th>
<th>Effect size</th>
<th>$\beta$ (95% CI)</th>
<th>$p$</th>
<th>Q-test</th>
<th>$CV_{vi}$</th>
<th>$R_b$ (95% CI)</th>
<th>$I^2$ (95% CI)</th>
<th>$R_I$ (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gibson</td>
<td>13</td>
<td>Std. Mean Diff.</td>
<td>-0.19 (-0.35, -0.04)</td>
<td>0.008</td>
<td>0.67</td>
<td>51 (17, 85)</td>
<td>55 (11, 85)</td>
<td>56 (19, 94)</td>
<td></td>
</tr>
<tr>
<td>Colditz</td>
<td>13</td>
<td>Log RR</td>
<td>-0.71 (-1.06, -0.36)</td>
<td>&lt;0.001</td>
<td>1.14</td>
<td>74 (53, 96)</td>
<td>92 (82, 98)</td>
<td>94 (85, 100)</td>
<td></td>
</tr>
<tr>
<td>Millet</td>
<td>15</td>
<td>Log OR</td>
<td>-0.05 (-0.20, -0.11)</td>
<td>0.53</td>
<td>1.78</td>
<td>39 (9, 68)</td>
<td>61 (16, 100)</td>
<td>77 (44, 100)</td>
<td></td>
</tr>
</tbody>
</table>

- $R_b$ was similar to $I^2$ and $R_I$ in case of homogenous $v_i$.
- Differences increased as $CV_{vi}$ increased.
Conclusions

- $R_b$ is easy to interpret as the proportion of the variance of the pooled estimate due to heterogeneity
- It does not make any assumption about the distribution of $v_i$
- It is easy to compute (implemented in hetmeta R package and %metaanal SAS macro)
- We recommend $R_b$ as preferred measure of heterogeneity
References I


- http://alecri.github.io/software/hetmeta

- http://www.hsph.harvard.edu/donna-spiegelman/software/metaanal
Simulation study: details

True $R_b$: 0.1, 0.5, 0.7

$\bar{\beta} = \log(\text{RR}) = 1, 1.5, 2, 4$

$CV_B = \tau/\bar{\beta} = 0.5, 1, 3$

$K = 5, 20, 50, 100$

$v_i \sim \logN(\text{E}[v_i], \text{Var}[v_i])$

$\text{E}[v_i] = (\tau^2/R_b) - \tau^2$ and $\text{Var}[v_i] = (CV_{v_i} \text{E}[v_i])^2$

$CV_{v_i} = \sqrt{\text{Var}[v_i]/\text{E}[v_i]} = 0.5, 1, 2$

$\beta_i \sim N(\beta, \tau^2 + v_i)$

each scenario replicated $N = 10,000$