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

XXVIIIth International Biometric Conference

Alessio Crippa

July 11th 2016

Acknowledgements

My co-authors:

- Polyna Khudyakov
- Molin Wang
- Nicola Orsini
- Donna Spiegelman

Funding organization:

- Karolinska Institutet's funding for doctoral students
- Young Scholar Award from the Karolinska Institutet's Strategic Program in Epidemiology

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

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

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

v_i is the study-specific within (error) variation

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

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

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

How to detect heterogeneity

- Estimate of τ^2
  May be difficult to interpret and compare
- Cochran's χ^2 test or the Q-test
  May have poor/excessive power
- Measures of heterogeneity: R_I[1] and I^2[2]
  Defined as $\frac{\tau^2}{\tau^2+\sigma^2}$
  σ^2 is a summary measure of the observed within-study variance, v_i

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

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

Aims

Homogeneity of within-studies variances is unlikely to hold

Analysis	**within-study variances**	$\sigma^2(I^2)$	$\sigma^2(R_I)$
A	[6, 6.1, 6.2, 5.9, 6, 5.9, 6.1, 5.8, 6, 6.2]	6.018	6.017
B	[5, 19, 3, 15, 6, 23, 4, 17, 2, 8.8]	6.017	5.602

- 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 τ^2 relative to the variance of the pooled random effects estimate

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

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

It can be expressed as percentage

R_b a new measure of heterogeneity (2)

It is a function of τ^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 β_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 τ^2 to individual overall variances

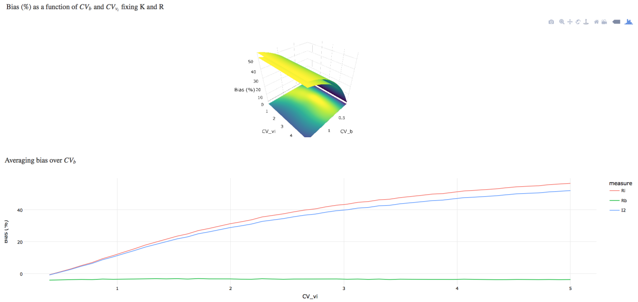
$R_b < R_I$ and $I^2 < R_I$

Diffences between I^2 and R_b depend upon distribution for v_i

It coincides with I^2 and R_I when $v_i = \sigma^2 \; \forall i = 1, \ldots, K$

Simulation study

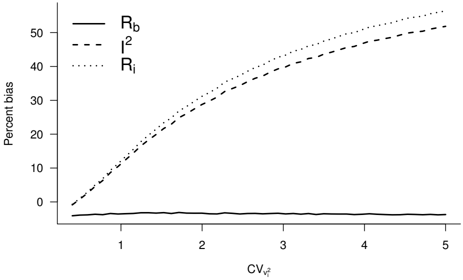
- Different scenario simulations ($R_b = 0.1, 0.5, 0.7$; $CV_{v_i} = 0.5, 1, 2$; $CV_B = 0.5, 1, 3$; $K = 5, 20, 50, 100$)
- Percent relative bias and covarage
- `https://alecri.shinyapps.io/bias/`



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_{v_i} increased

Illustrative examples

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

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

- Crippa A, Khudyakov P, Wang M, Orsini N, Spiegelman D. A new measure of between-studies heterogeneity in meta-analysis. Statistics in medicine. 2016 Jan 1.
- Takkouche B, Cadarso-Suárez C, Spiegelman D. Evaluation of old and new tests of heterogeneity in epidemiologic meta-analysis. American Journal of Epidemiology. 1999 Jul 15;150(2):206-15.
- Higgins J, Thompson SG. Quantifying heterogeneity in a meta-analysis. Statistics in medicine. 2002 Jun 15;21(11):1539-58.
- `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

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

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

$K = 5, 20, 50, 100$

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

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

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

each scenario replicated N = 10,000