Median-unbiased estimators for the amount of heterogeneity in meta-analysis

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Meta-Analysis and the Random-Effects Model

- collect studies that have examined a phenomenon of interest
- quantify the results of each study in terms of an effect size / outcome measure (e.g., standardized mean difference, correlation coefficient, log odds/risk ratio)
- let y_i denote the observed outcome in the ith study ($i = 1, \ldots, k$) and v_i the corresponding sampling variance
- random-effects model:

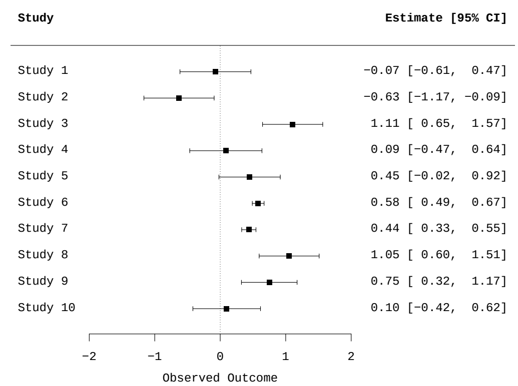
$$y_i = \theta_i + e_i$$

where $\theta_i \sim N(\mu, \tau^2)$ and $e_i \sim N(0, v_i)$
- τ^2 denotes the amount of 'heterogeneity' (i.e., between-study variance) in the underlying true effects/outcomes

Illustrative Example

study	y_i	v_i
1	-0.073	0.0764
2	-0.629	0.0749
3	1.106	0.0550
4	0.086	0.0792
5	0.449	0.0571
6	0.580	0.0021
7	0.437	0.0031
8	1.053	0.0546
9	0.749	0.0470
10	0.099	0.0694

Illustrative Example



Heterogeneity Estimators

- there has been a secret competition in the meta-analytic community to derive ever more estimators for τ^2
  - Hedges/Cochran estimator ([1], same as [2, 3])
  - Hunter-Schmidt estimator ([4, 5])
  - DerSimonian-Laird estimator ([6])
  - maximum-likelihood estimator ([6–8])
  - restricted maximum-likelihood estimator ([6, 9, 10])
  - Paule-Mandel estimator ([11])
  - empirical Bayes estimator ([12, 13])
  - Hartung-Makambi estimator ([14])
  - Sidik-Jonkman estimator ([15])
  - generalized Q-statistic estimator ([16])
  - various Bayesian estimators (e.g., [17–20])
  - ...

DerSimonian-Laird estimator ([6])

- let

$$Q = \sum w_i (y_i - \hat{\theta})^2$$

where

$$\hat{\theta} = \frac{\sum w_i y_i}{\sum w_i} \quad \text{and} \quad w_i = 1/v_i$$

- can show $\text{E}[Q] = c\tau^2 + (k-1)$ where $c = \sum w_i - \frac{\sum w_i^2}{\sum w_i}$
- hence

$$\hat{\tau}^2_{\text{DL}} = \frac{Q - (k-1)}{c}$$

is a method-of-moments estimator of τ^2

Illustrative Example

- $\hat{\theta} = 0.511$
- $Q = 43.665$
- $k = 10$
- $c = 568.562$

$$\hat{\tau}^2_{\text{DL}} = \frac{43.665 - (10 - 1)}{568.562} = 0.061$$

Restricted Maximum-Likelihood Estimator ([6, 9, 10])

- the restricted log likelihood function is given by

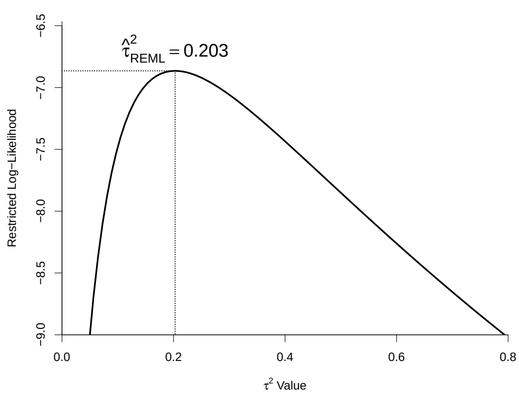
$$ll(\tau^2) = -\frac{1}{2}\sum \ln w_i^{-1} - \frac{1}{2}\ln \sum w_i - \frac{1}{2}\sum w_i (y_i - \hat{\mu})^2$$

where

$$\hat{\mu} = \frac{\sum w_i y_i}{\sum w_i} \quad \text{and} \quad w_i = 1/(v_i + \tau^2)$$

- can easily maximize this over τ^2 with standard algorithms (e.g., Fisher scoring) yielding $\hat{\tau}^2_{\text{REML}}$

Illustrative Example



Paule-Mandel estimator ([11])

- define

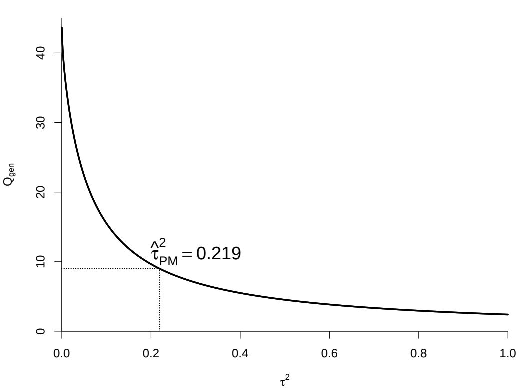
$$Q_{gen} = \sum w_i (y_i - \hat{\mu})^2$$

where

$$\hat{\mu} = \frac{\sum w_i y_i}{\sum w_i} \quad \text{and} \quad w_i = 1/(v_i + \tau^2)$$

- can show $Q_{gen} \sim \chi^2$ with $\text{df} = k - 1$
- hence $\text{E}[Q_{gen}] = k - 1$
- and Q_{gen} is a decreasing function of τ^2
- let $\hat{\tau}^2_{\text{PM}}$ be that value such that $Q_{gen} = k - 1$

Illustrative Example



Confidence Intervals for τ^2

- various methods for constructing confidence intervals for τ^2 have also been proposed
  - Wald-type CIs ([21, 22])
  - profile likelihood CIs ([8, 22])
  - Biggerstaff-Tweedie method ([21])
  - Hartung-Makambi method ([14])
  - Sidik-Jonkman method ([15])
  - bootstrap CIs ([22–24])
  - Q-profile method ([22])
  - generalized Q-statistic CIs ([25])
  - Bayesian credible intervals

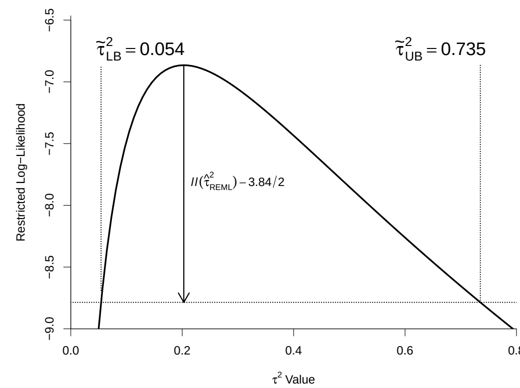
Profile Likelihood CIs ([8, 22])

- a 95% profile likelihood CI for τ^2 is given by the set of $\tilde{\tau}^2$ values satisfying

$$ll(\tilde{\tau}^2) > ll(\hat{\tau}^2_{\text{REML}}) - 3.84/2$$

- all values of $\tilde{\tau}^2$ not rejected by a likelihood ratio test
- bounds can be found via a root finding algorithm

Illustrative Example



Q-Profile Method [22]

- define

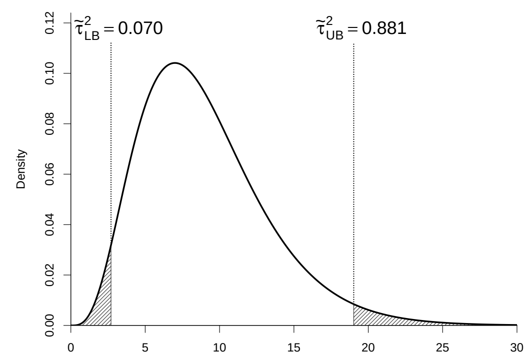
$$Q_{gen} = \sum w_i (y_i - \hat{\mu})^2$$

where

$$\hat{\mu} = \frac{\sum w_i y_i}{\sum w_i} \text{ and } w_i = 1/(v_i + \tau^2)$$

- can show $Q_{gen} \sim \chi^2$ with $\text{df} = k - 1$
- find $\tilde{\tau}^2_{\text{LB}}$ such that $Q_{gen} = \chi^2_{k-1;.975}$
- find $\tilde{\tau}^2_{\text{UB}}$ such that $Q_{gen} = \chi^2_{k-1;.025}$
- then $(\tilde{\tau}^2_{\text{LB}}, \tilde{\tau}^2_{\text{UB}})$ is a 95% CI for τ^2
- the CI is exact (under the assumptions of the model)

Illustrative Example



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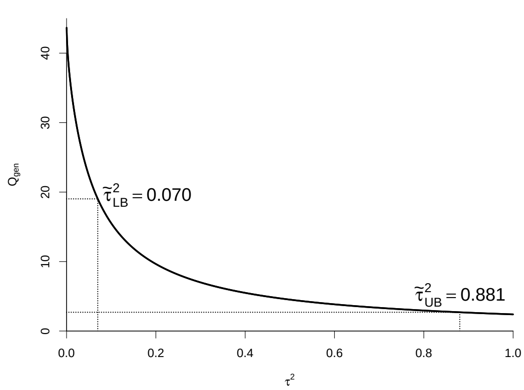

Illustrative Example

Estimator	Value	CI	Bounds
DL	0.061		
REML	0.203	PL	0.054 to 0.735
PM	0.219		
		QP	0.070 to 0.881

When the CI Does not Contain τ^2

- can happen when the method for constructing the CI does not 'match up' with the method for estimating τ^2
- ML/REML estimation matches up with profile likelihood CIs
- clearly, the DL estimator does not match up with the Q-profile method (but what does?)
- does the PM estimator match up with the Q-profile method?

Estimator	Value	CI	Bounds
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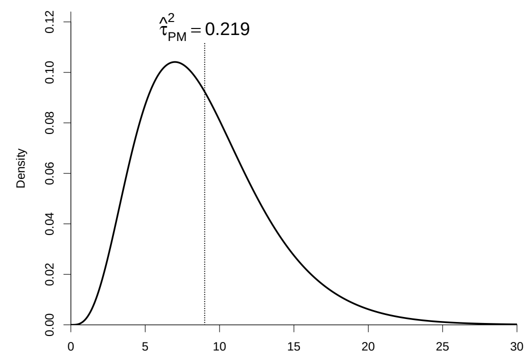
REML	0.203	PL	0.054 to 0.735
PM	0.219		
		QP	0.070 to 0.881

Illustrative Example



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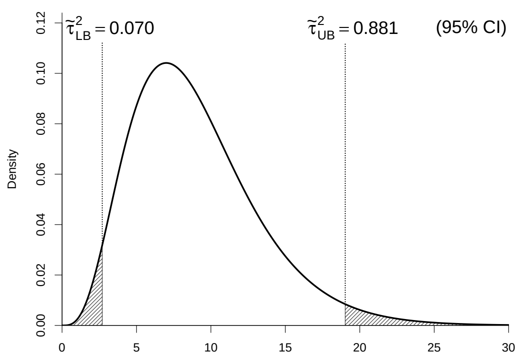

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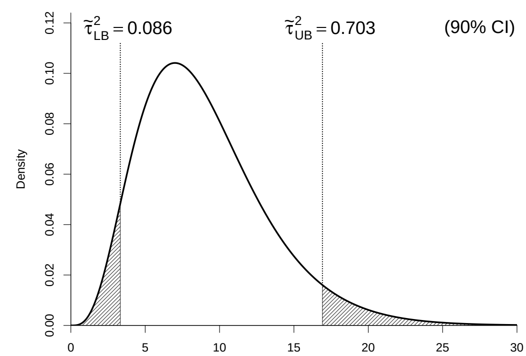

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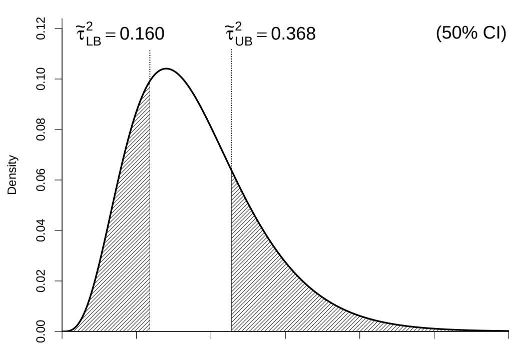

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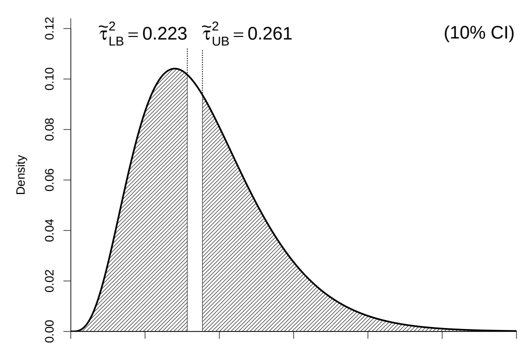

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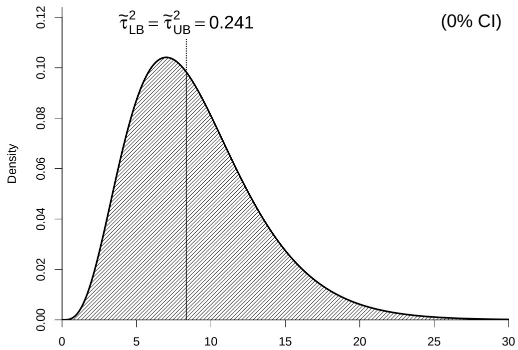

Median Unbiased Estimators

- define

$$Q_{gen} = \sum w_i (y_i - \hat{\mu})^2$$

where

$$\hat{\mu} = \frac{\sum w_i y_i}{\sum w_i} \text{ and } w_i = 1/(v_i + \tau^2)$$

- let $\hat{\tau}^2_{\text{PMM}}$ be that value such that $Q_{gen} = \chi^2_{k-1;.5}$ (i.e., the median of a chi-square distribution with $\mathrm{df} = k - 1$)
- the DL estimator is a special case of the generalized Q-statistic estimator where $w_i = 1/v_i$ ([16])
- can compute a CI based on the exact distribution of Q_{gen} ([25])
- 0% CI gives the respective median unbiased estimator $\hat{\tau}^2_{\text{DLM}}$

Illustrative Example

Estimator	Value	CI	Bounds
DL	0.061		
REML	0.203	PL	0.054 to 0.735
PM	0.219		
PMM	0.241	QP	0.070 to 0.881
DLM	0.090	GENQ	0.014 to 0.499

Final Notes / Conclusions

- median unbiased estimators ([26]) $\hat{\tau}^2_{\text{PMM}}$ and $\hat{\tau}^2_{\text{DLM}}$ are just as likely to overestimate τ^2 as to underestimate it
- median unbiased estimators are invariant under one-to-one transformations, so $\hat{\tau}_{\text{PMM}}$ and $\hat{\tau}_{\text{DLM}}$ are median unbiased for τ
- all estimators require truncation when they are negative which this introduces positive bias into $\hat{\tau}^2_{\text{PM}}$, $\hat{\tau}^2_{\text{DL}}$, and $\hat{\tau}^2_{\text{REML}}$
- $\hat{\tau}^2_{\text{PMM}}$ and $\hat{\tau}^2_{\text{DLM}}$ remain median unbiased even when $\tau^2 = 0$
- but the median unbiased estimators are less efficient
- in practice, a 95% QP CI will always encompass $\hat{\tau}^2_{\text{PM}}$ (and probably a 95% GENQ CI will always encompass $\hat{\tau}^2_{\text{DL}}$)
- more problematic: using $\hat{\tau}^2_{\text{REML}}$ with a QP CI (should use PL CI)
- this work arose from discussions with Theo Stijnen

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Thank You for Your Attention!

Questions, Comments, Suggestions?

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