Exact Confidence Intervals for Small Sample Random Effects Meta-analysis

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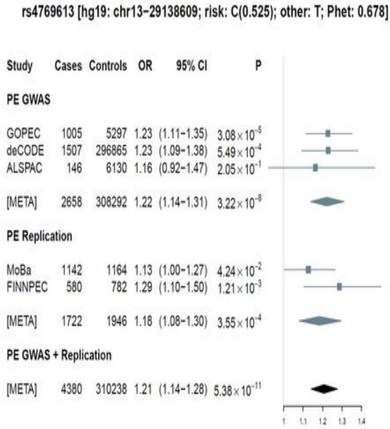
Outline

Meta-analysis is a popular procedure for synthesizing a number of primary studies relating to a single effect into a single summary estimate of size and uncertainty


rs4769613 [hg19: chr13-29138609; risk: C(0.525); other: T; Phet: 0.678]

Study	Cases	Controls	OR	95% CI	P
PE GWAS					
GOPEC	1005	5297	1.23	(1.11-1.35)	3.08×10^{-5}
deCODE	1507	296865	1.23	(1.09-1.38)	5.49×10^{-4}
ALSPAC	146	6130	1.16	(0.92-1.47)	2.05×10^{-1}
[META]	2658	308292	1.22	(1.14-1.31)	3.22×10^{-8}
PE Replication					
MoBa	1142	1164	1.13	(1.00-1.27)	4.24×10^{-2}
FINNPEC	580	782	1.29	(1.10-1.50)	1.21×10^{-3}
[META]	1722	1946	1.18	(1.08-1.30)	3.55×10^{-4}
PE GWAS + Replication					
[META]	4380	310238	1.21	(1.14-1.28)	5.38×10^{-11}

(from “Variants in the fetal genome near FLT1 are associated with risk of preeclampsia,” Nature Genetics, June 2017)

- The most commonly used model is the random effects model:

$$y_k \overset{\text{ind.}}{\sim} \mathcal{N}(\theta_k, \sigma_k^2), k = 1, \dots, K$$
$$\theta_k \overset{\text{iid}}{\sim} \mathcal{N}(\Theta, \tau^2)$$
$$\sigma_k \text{ known}$$

  implying

$$y_k \sim \mathcal{N}(\Theta, \sigma_k^2 + \tau^2)$$

- Goal is inference on Θ
- τ^2, accounting for variability between the primary studies, is a nuisance parameter

- The UMVU estimate of Θ is inverse-variance weighted

$$\frac{\sum_k (\sigma_k^2 + \tau^2)^{-1} y_k}{\sum_k (\sigma_k^2 + \tau^2)^{-1}}$$

with variance

$$(\sum_k (\tau^2 + \sigma_k^2)^{-1})^{-1}$$

- As τ^2 is unknown, typically the DerSimonian-Laird estimator $\hat{\tau}_{DL}^2$ is plugged in

$$\hat{\Theta}_{DL} = \frac{\sum_k (\sigma_k^2 + \hat{\tau}_{DL}^2)^{-1} y_k}{\sum_k (\sigma_k^2 + \hat{\tau}_{DL}^2)^{-1}}$$

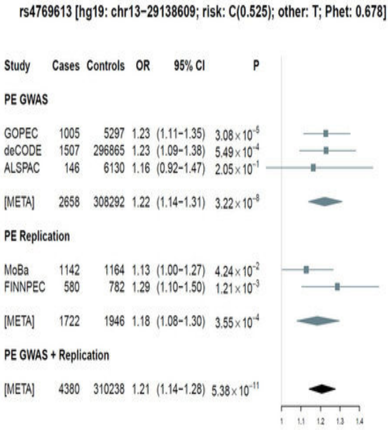
- A confidence interval

$$\left\{ \hat{\Theta}_{DL} - z_{1-\alpha/2}\left(\sum_{k=1}^{K}(\hat{\tau}_{DL}^2 + \sigma_k^2)^{-1}\right)^{-1/2}, \hat{\Theta}_{DL} + z_{1-\alpha/2}\left(\sum_{k=1}^{K}(\hat{\tau}_{DL}^2 + \sigma_k^2)^{-1}\right)^{-1/2} \right\}$$

is obtained from an asymptotic pivot

$$T_0(\Theta; \mathcal{Y}) = (\hat{\Theta}_{DL} - \Theta)^2 \sum_{k=1}^{K}(\hat{\tau}_{DL}^2 + \sigma_k^2)^{-1} \rightsquigarrow \chi_1^2 \quad (K \to \infty)$$

- In many fields, meta-analyses on few (< 6) studies are common
- Even when many primary studies are available, sub-meta-analyses are routinely carried out using few studies



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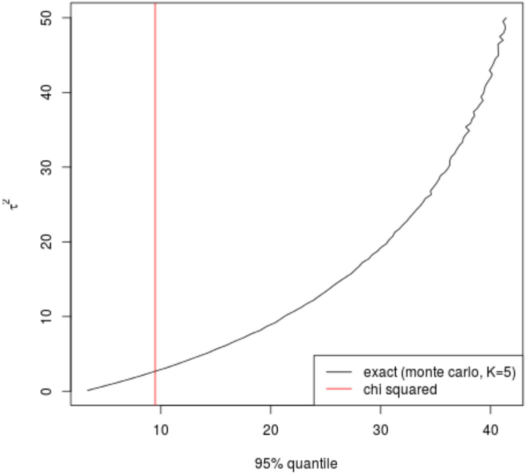
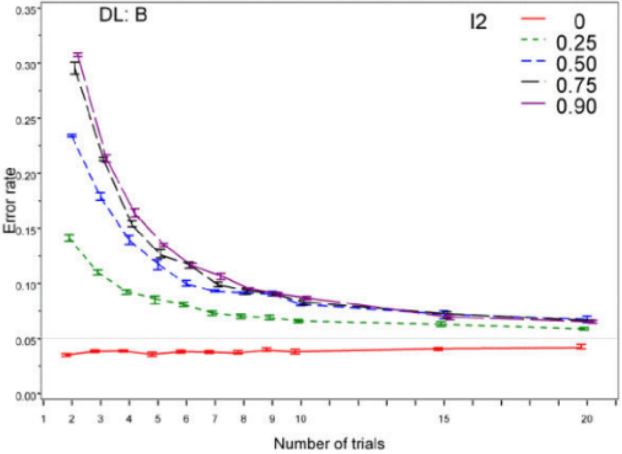
- Problem: when the number of studies is few and heterogeneity is present, the pivot is a poor approximation



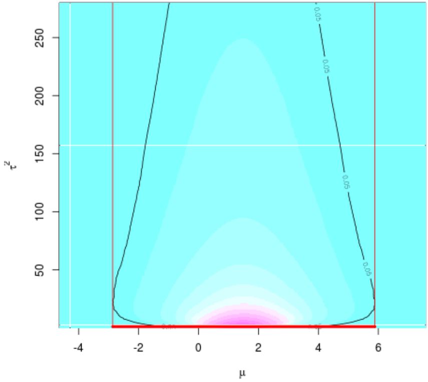
- ...resulting in poor Type I error control



(from IntHout, Ioannidis and Borm '14)

Outline

In the absence of a statistic ancillary to the nuisance parameter, we obtain a CI for Θ at each value of the nuisance parameter and use their union as a conservative CI



Controls the Type I error rate, but at what cost?

- computational?
- power?

Computational costs

- exploit symmetry of the problem
- $y_k \sim \mathcal{N}(\Theta, \sigma^2 + \tau^2)$ means $y_k - \Theta \sim \mathcal{N}(0, \sigma^2 + \tau^2)$
- reasonable to require of our testing procedure that testing $H_0 : \Theta = \Theta_0$ given data $y_1, \ldots, y_K$ be the same as testing $H_0 : \Theta = 0$ given data $y_1 - \Theta, \ldots, y_K - \Theta$
- *Equivariant* test statistics respect the symmetry of the problem: $T(y_1 - \Theta, \ldots, y_K - \Theta) = T(y_1, \ldots, y_K) - \Theta$

- Using an equivariant test statistic we only need to compute the distribution at parameter points $(0, \tau^2)$
    - can't apply this trick again, not a scale family because of σ_k
- So the problem is actually 1-dimensional
- Cost not much of an issue except for statistics that are relatively costly to compute, e.g., MLE
- Easily parallelized (as is the 2-D problem)

- Our proposed statistics for testing the simple null $H_0 : (\Theta, \tau^2) = (\Theta_0, \tau_0^2)$:

$$T\left\{(\Theta_0, \tau_0^2); \mathcal{Y}_0\right\} = T_0(\Theta_0; \mathcal{Y}) + c_0 T_{lik}\left\{(\Theta_0, \tau_0^2); \mathcal{Y}\right\}$$

where

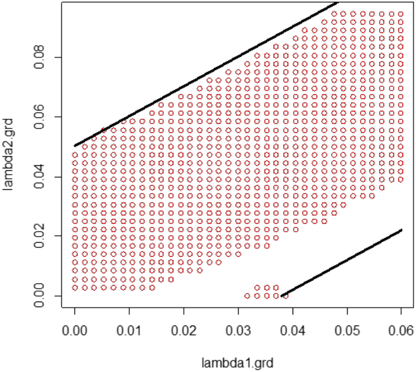
$$T_0(\Theta_0; \mathcal{Y}) = (\hat{\Theta}_{DL} - \Theta_0)^2 \sum_{k=1}^{K} (\hat{\tau}_{DL}^2 + \sigma_k^2)^{-1}$$

$$T_{lik}\left\{(\Theta_0, \tau_0^2); \mathcal{X}\right\} = -\frac{1}{2}\sum_{k=1}^{K}\left[\frac{(Y_k - \hat{\Theta}_{DL})^2}{\hat{\tau}_{DL}^2 + \sigma_k^2} + \log\left\{2\pi(\hat{\tau}_{DL}^2 + \sigma_k^2)\right\}\right] + \sum_{k=1}^{K}\frac{1}{2}\left[\frac{(Y_k - \Theta_0)^2}{\tau_0^2 + \sigma_k^2} + \log\left\{2\pi(\tau_0^2 + \sigma_k^2)\right\}\right]$$

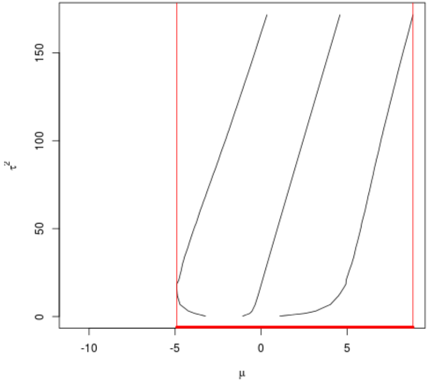
  - Weighted combination of DL statistic and an approximate likelihood ratio statistic
  - Plug DL estimate of Θ into likelihood ratio statistic to avoid computing the MLE
  - These are equivariant

Power, CI length

- Two sources of poor power performance when projecting to form a conservative CI



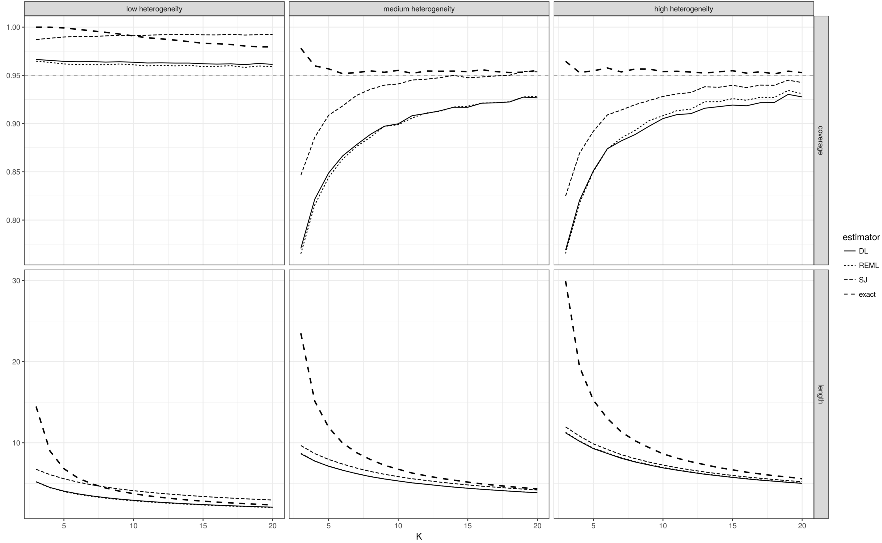
disconnected regions (from related work by L. Tian)



shear (artist's interpretation)

- The proposed estimators are quadratic in Θ, so the region is connected
- The deviation from the vertical of the centers of horizontal sections of the region has variance $O(\tau^{-4})$

Outline


low heterogeneity
medium heterogeneity
high heterogeneity
coverage
length
1.00
0.95
0.90
0.85
0.80
30
20
10
5
10
15
20
K
estimator
DL
REML
SJ
exact

Outline

- look for similar efficiencies with nonnormal primary study effects data, e.g., rare event proportions
- examining robustness against nonnormality