Heterogeneity in random-effects meta-analysis

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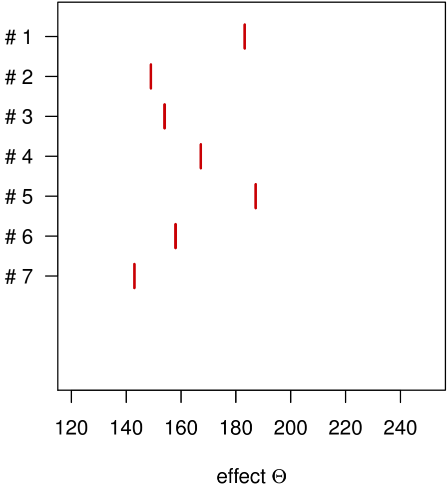
Overview

- Meta analysis
  - the random-effects model
  - frequentist approaches
  - the Bayesian approach
  - example
- Simulation study
  - bias
  - coverage
  - ...
- Conclusions

Meta analysis

Context



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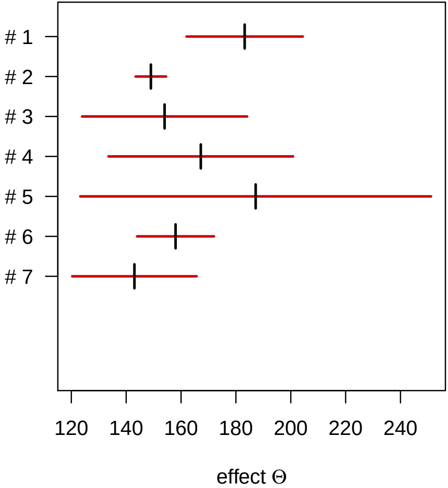
  - standard errors σ_i
- want:
  - combined estimate $\hat{\Theta}$



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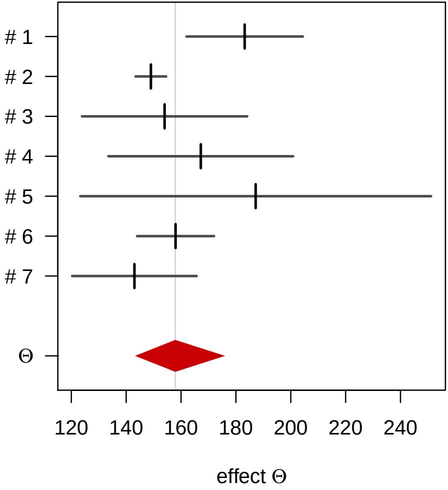

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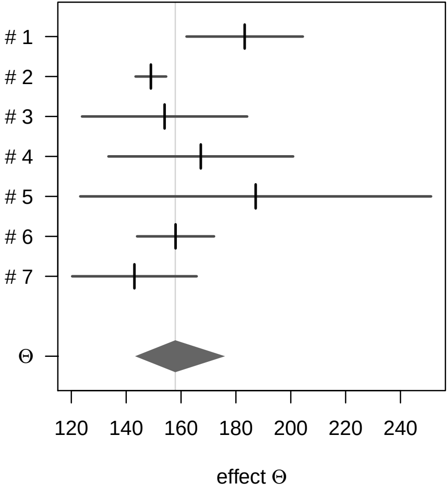

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- $\Theta \in \mathbb{R}$ of primary interest ("effect")
- $\tau \in \mathbb{R}^+$ nuisance parameter ("between-trial heterogeneity")

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- the frequentist approach
  - test for $\tau = 0$ vs. $\tau > 0$ (fixed vs. random effects)
  - derive estimate $\hat{\tau}$
  - derive estimate for Θ *conditional on* $\hat{\tau}$ *being actual heterogeneity* (plug-in estimate)

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Meta analysis
Common approach to inference

- the frequentist approach
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  - derive estimate $\hat{\tau}$
  - derive estimate for Θ *conditional on* $\hat{\tau}$ *being actual heterogeneity* (plug-in estimate)

- Comments:
  - significance tests have low power, $\tau = 0$ hypothesis questionable
  - how to estimate τ? many approaches, questionable properties
  - conditioning on *fixed* τ value only sensible for great accuracy
  - uncertainty in τ often not accounted for
    exception: "Knapp-Hartung" approach[3]
    (leads to Student-t-approximation)
  - usually computationally simple

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Frequentist MA

technically: normal approximation

- usual frequentist procedure:
  - derive heterogeneity estimate $\hat{\tau}$
  - conditional on $\tau = \hat{\tau}$, derive estimate

$$\hat{\Theta} = \frac{1}{\sum w_i} \times \sum w_i \, y_i \qquad \text{where} \quad w_i = \frac{1}{\sigma_i^2 + \hat{\tau}^2}$$

with standard error

$$\mathrm{SE}(\hat{\Theta}) = \sqrt{\frac{1}{\sum w_i}}$$

and use Normal approximation for confidence interval

- "Knapp-Hartung" approach[4] to considering uncertainty in $\hat{\tau}$:
  - compute

$$q \;:=\; \frac{1}{k-1} \sum \frac{(y_i - \hat{\Theta})^2}{\sigma_i^2 + \hat{\tau}^2}$$

  - use Student-t approximation with scale

$$\max\{\sqrt{q}, 1\} \times \textsc{se}(\hat{\Theta})$$

    and $(k-1)$ degrees of freedom to construct confidence interval (instead of Normal approximation)

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- Bayesian approach [5]
  - set up model likelihood
  - specify prior information about unknowns
  - posterior results as $\propto$ prior $\times$ likelihood

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  - set up model likelihood
  - specify prior information about unknowns
  - posterior results as $\propto$ prior $\times$ likelihood
- Comments:
  - consideration of prior information
  - consideration of uncertainty
  - straightforward interpretation
  - computationally more expensive, usually done via stochastic integration (MCMC, BUGS)[6]
  - special case of simple random-effects MA may be solved semi-analytically (using `bmeta` R package)

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- have:
  - likelihood $p(\vec{y}, \vec{\sigma} \,|\, \Theta, \tau)$
  - prior density $p(\Theta, \tau) \;=\; p(\Theta) \times p(\tau)$
- posterior $p(\Theta, \tau \,|\, \vec{y}, \vec{\sigma}) \;\propto\; p(\vec{y}, \vec{\sigma} \,|\, \Theta, \tau) \times p(\Theta, \tau)$
- integrate out marginal posteriors
  - effect $p(\Theta \,|\, \vec{y}, \vec{\sigma}) \;=\; \int p(\Theta, \tau \,|\, \vec{y}, \vec{\sigma}) \, \mathrm{d}\tau$
  - heterogeneity $p(\tau \,|\, \vec{y}, \vec{\sigma}) \;=\; \int p(\Theta, \tau \,|\, \vec{y}, \vec{\sigma}) \, \mathrm{d}\Theta$
- inference: posterior expectations, medians, quantiles,...

- many heterogeneity estimators available
- different prior specifications possible (should depend on context)

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- many heterogeneity estimators available (different answers *to the same question*)
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- estimators for τ considered in the following:
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Frequentist and Bayesian approaches

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  - half-Normal ($\sigma = 0.5$)
  - half-Normal ($\sigma = 1.0$)
  - Uniform (0.0, 4.0)

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Example

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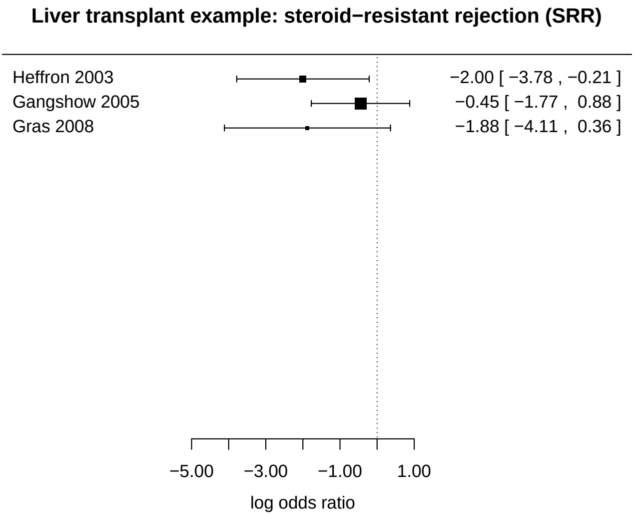

data: 3 estimates
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and standard errors

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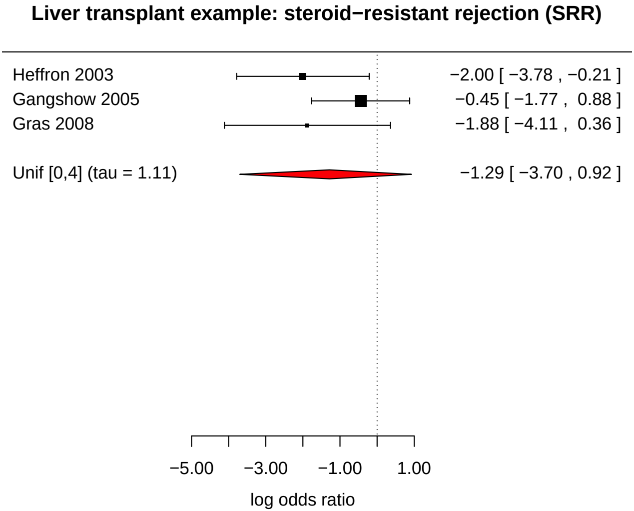

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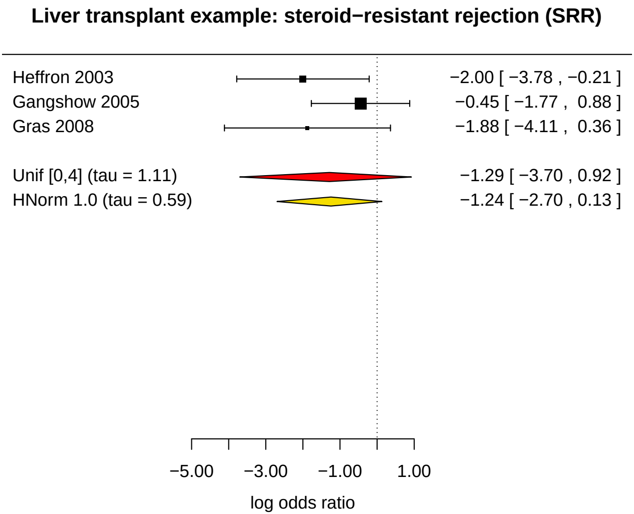

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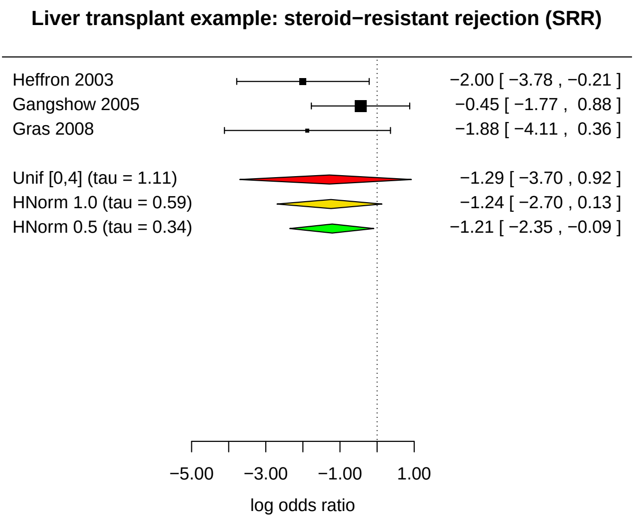

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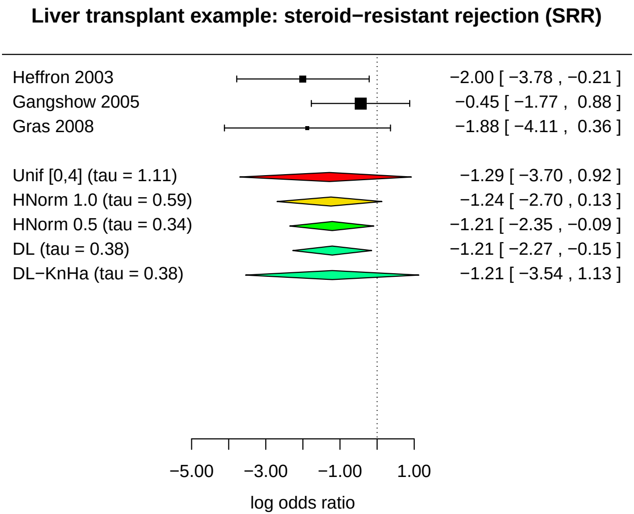

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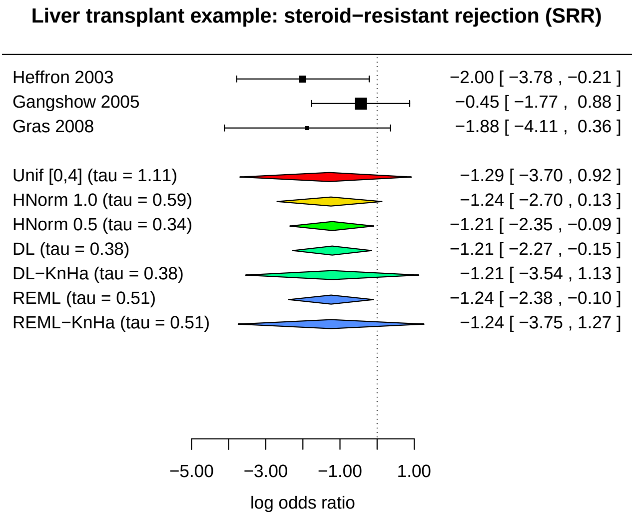

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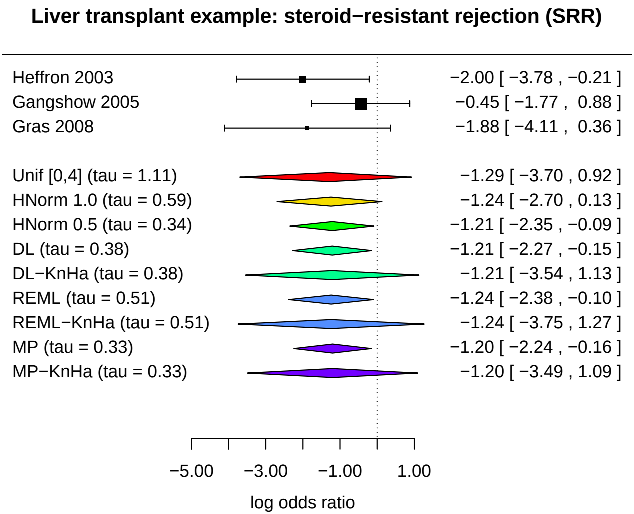

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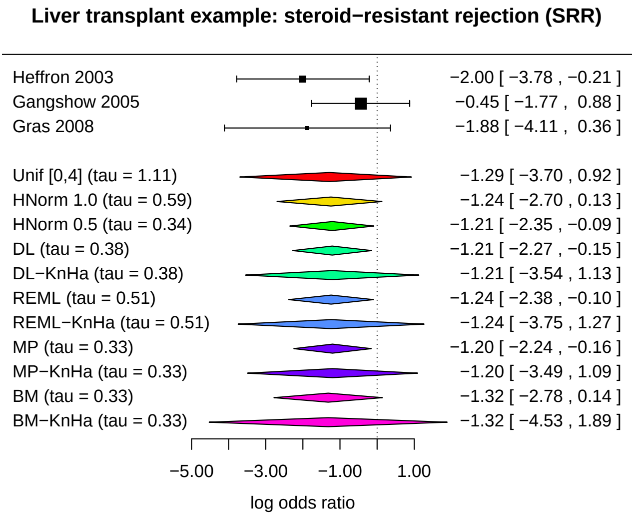

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Example
Crins et al. (2014) data

- different analyses yield different answers
- Bayesian and frequentist analyses answer different questions
- $k = 2$ to 3 studies is a common scenario
  (*majority* of meta analyses in Cochrane Database[11])

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- different analyses yield different answers
- Bayesian and frequentist analyses answer different questions
- $k = 2$ to 3 studies is a common scenario
  (*majority* of meta analyses in Cochrane Database[11])
- how does performance compare **in general**,
  especially for few studies?

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Simulation study
Setup

- number of studies: $k \in \{3, 5, 10, 30\}$
- heterogeneity: $\tau^2 \in \{0.00, 0.01, 0.02, 0.05, 0.1, 0.2, 0.5, 1.0, 2.0\}$ ($I^2 \in \{0.00, 0.06, 0.11, 0.23, 0.37, 0.54, 0.75, 0.85, 0.92\}$)
- standard errors σ_i: truncated χ^2-distribution[12]
- 10'000 repetitions for each combination (k, τ^2)
- compute Bayesian MAs (3 different priors)
- compute frequentist MAs (different τ estimators, Normal and Knapp-Hartung approximation)

[12] S.E. Brockwell, I.R. Gordon. A comparison of statistical methods for meta-analysis. *Statistics in Medicine* 20(6):825–840, 2001.
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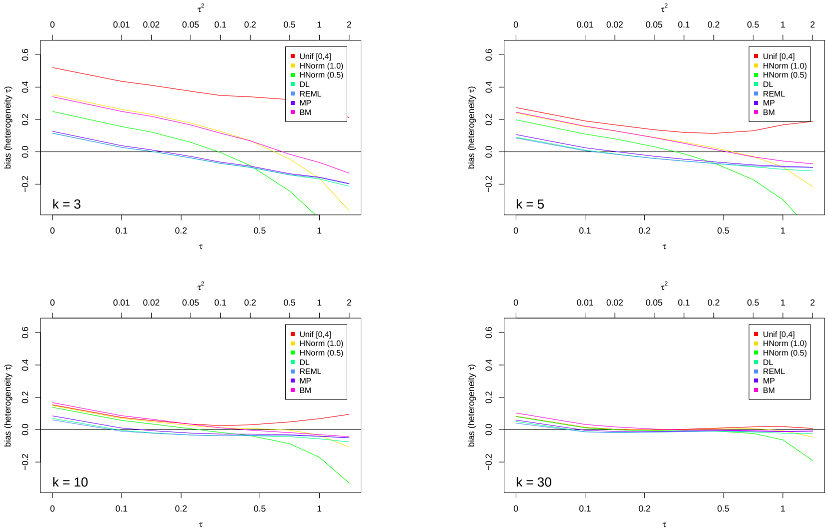
Simulation study

heterogeneity estimation: bias



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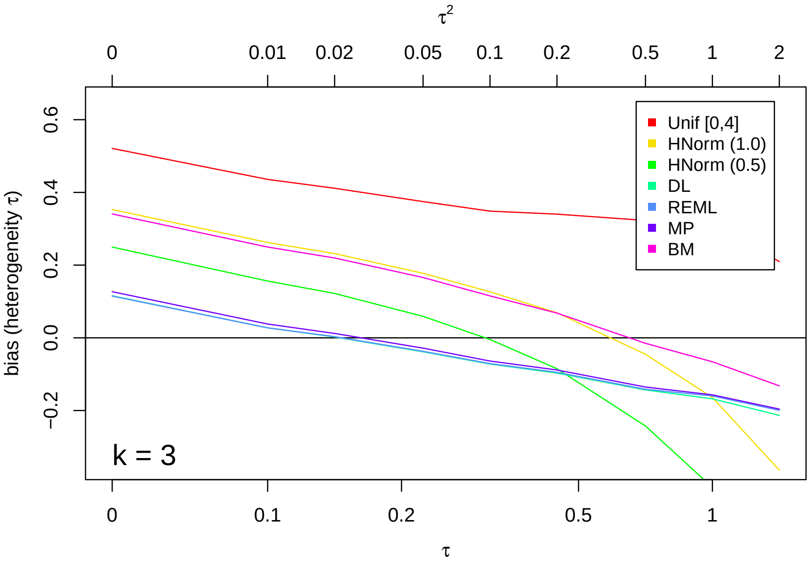

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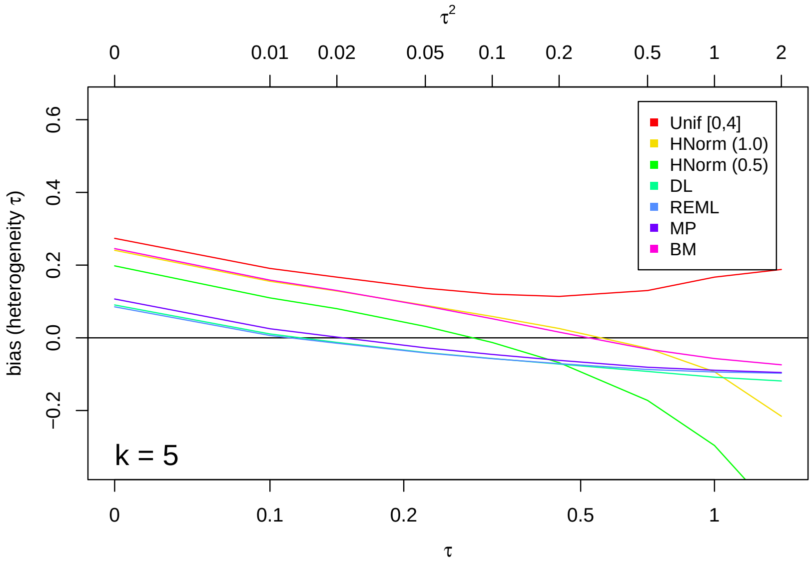

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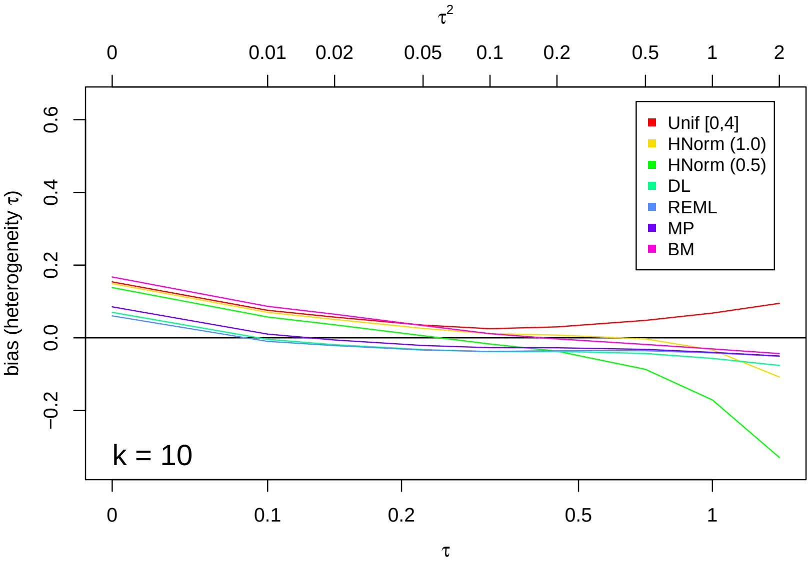

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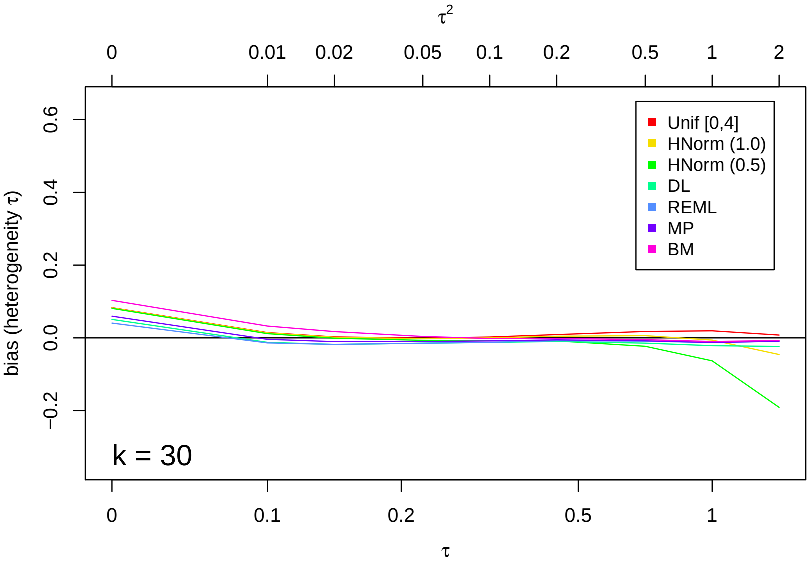

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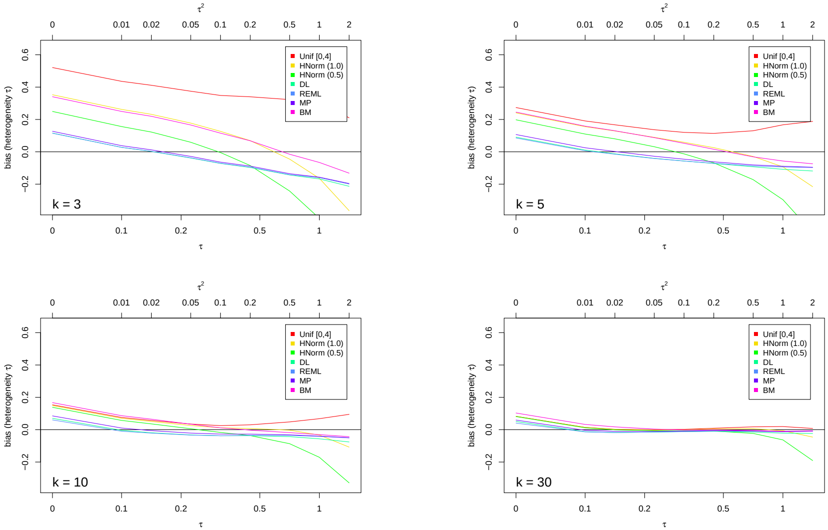

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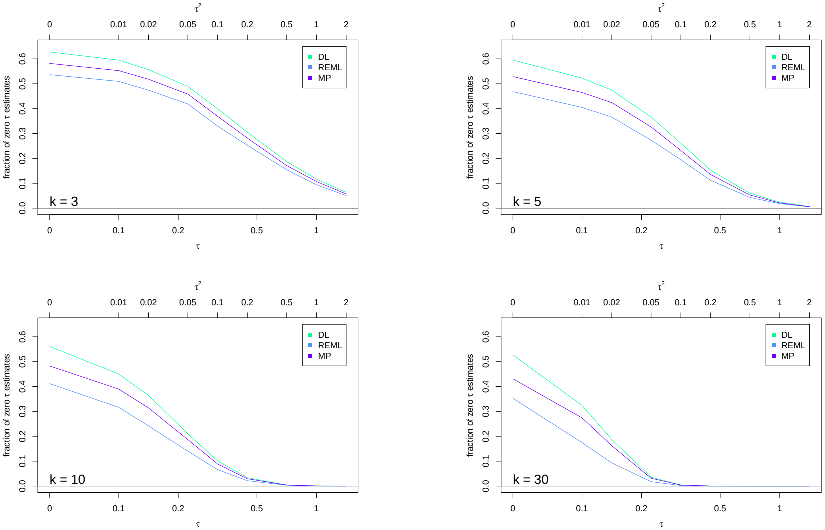
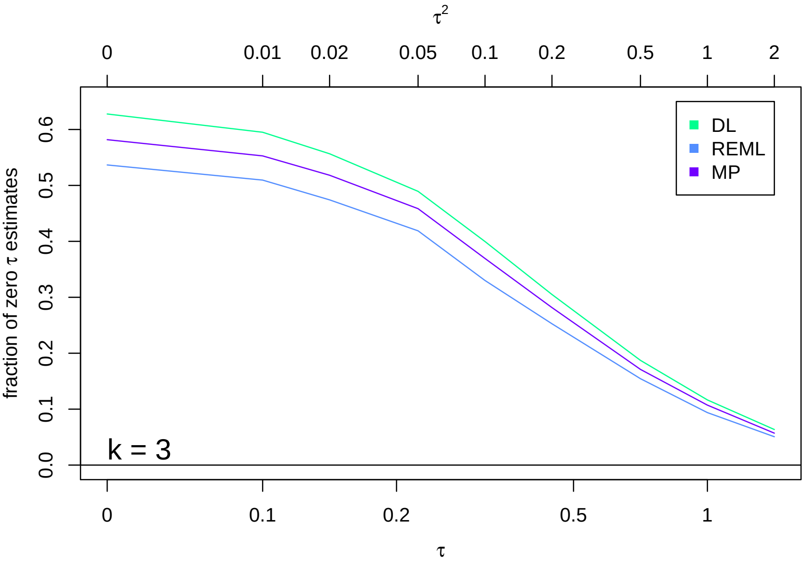
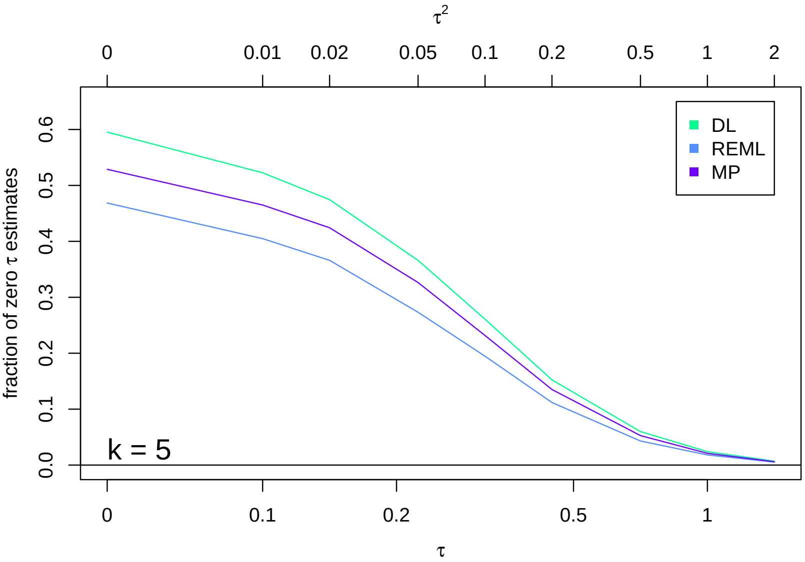
heterogeneity estimation: zero estimates



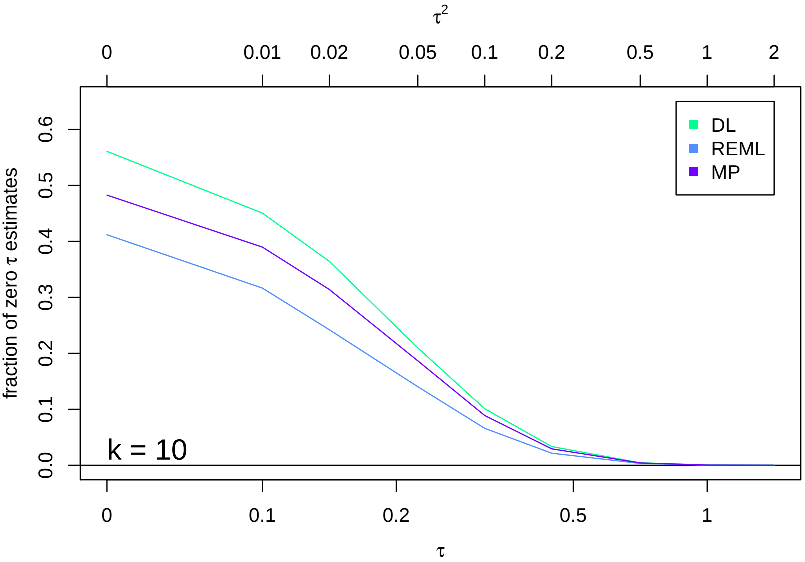
heterogeneity estimation: zero estimates



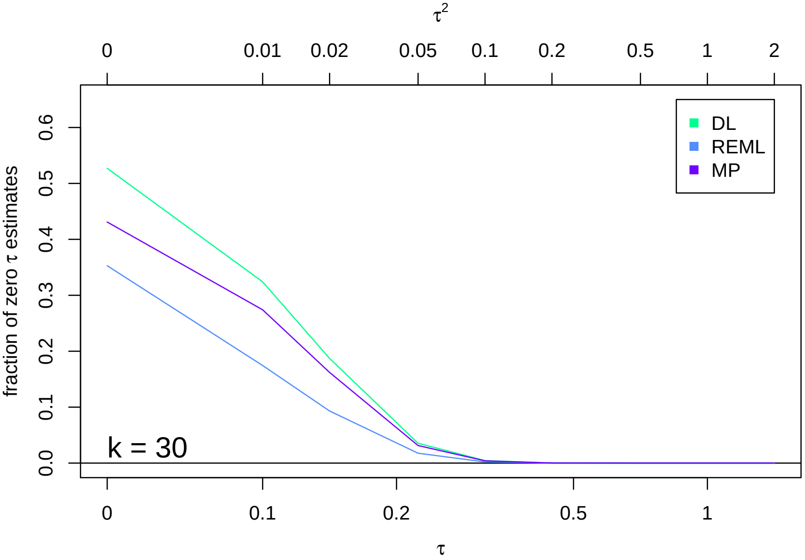
heterogeneity estimation: zero estimates



heterogeneity estimation: zero estimates

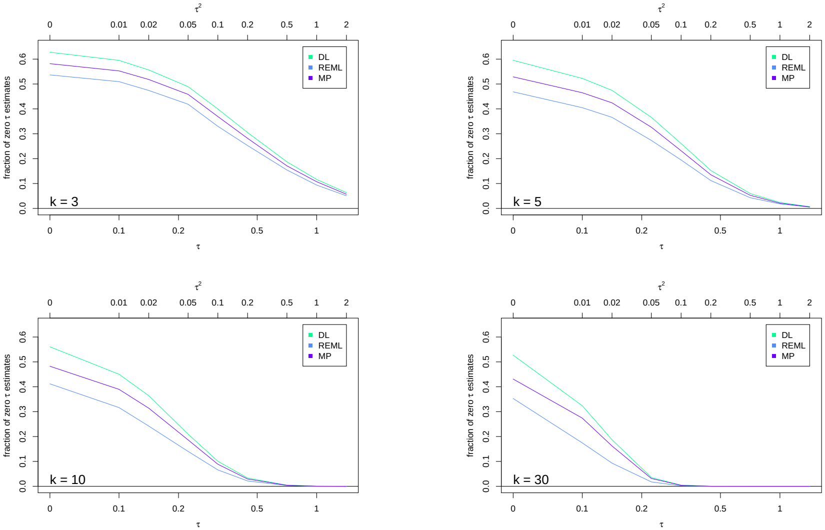


heterogeneity estimation: zero estimates



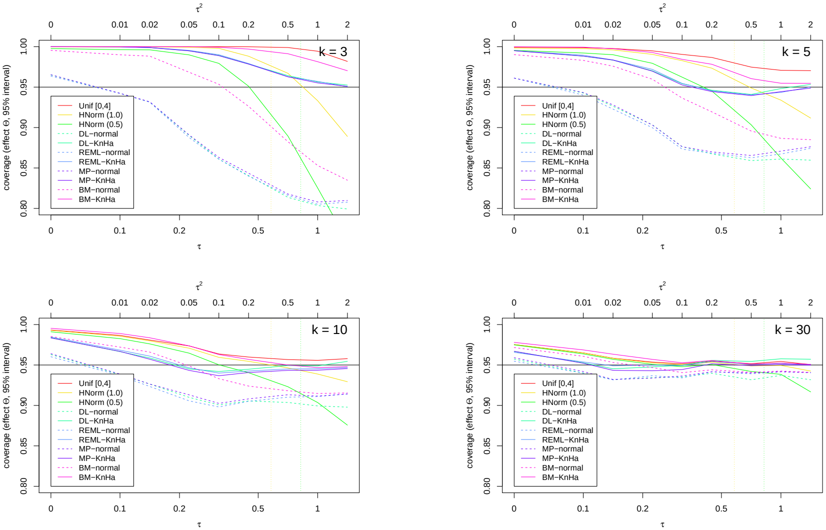
Simulation study

heterogeneity estimation: zero estimates

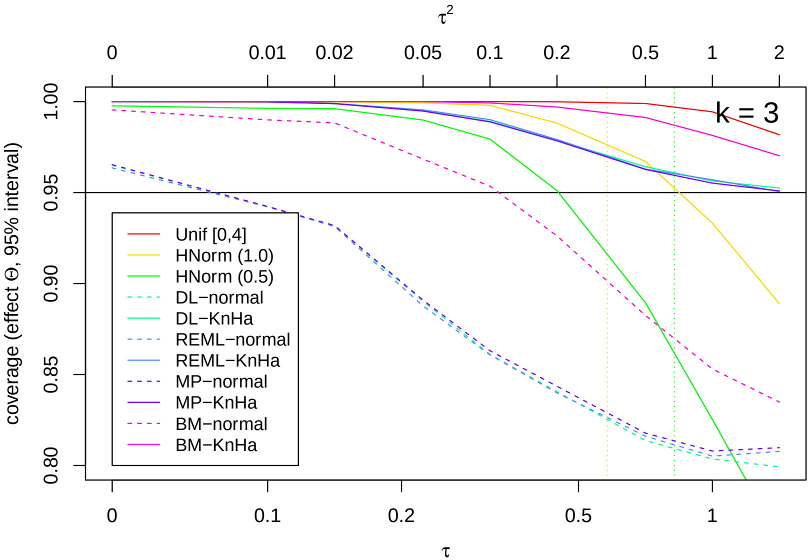


Simulation study

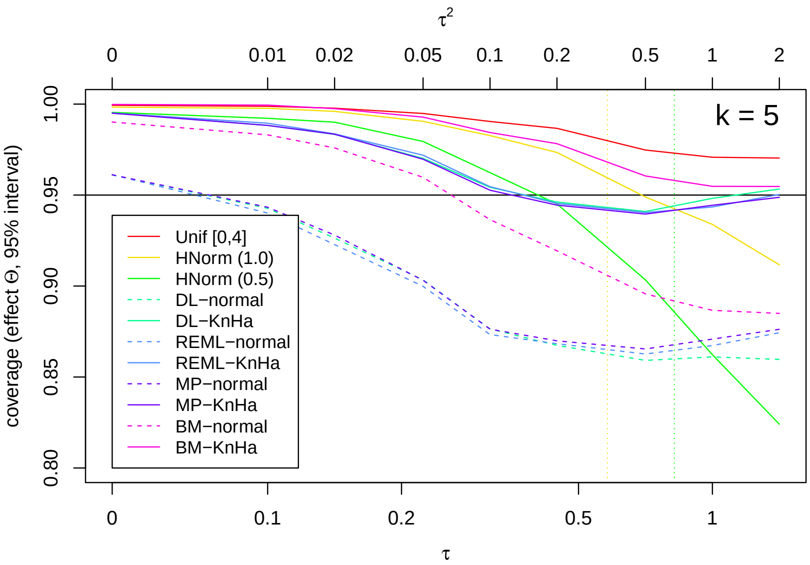
effect estimation: 95% CI coverage



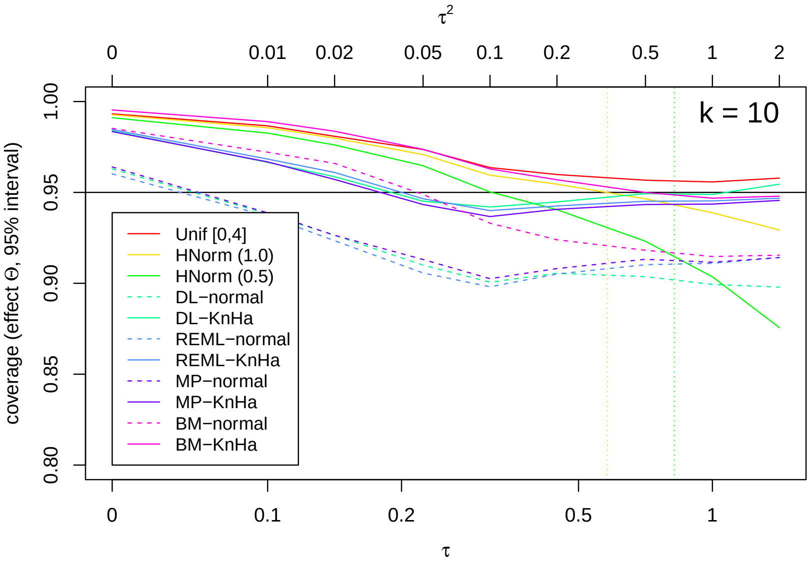
effect estimation: 95% CI coverage



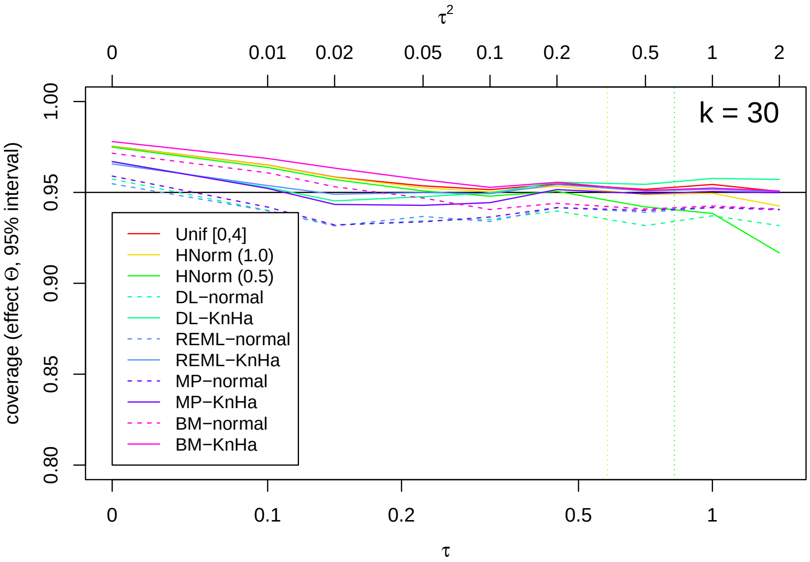
effect estimation: 95% CI coverage



effect estimation: 95% CI coverage

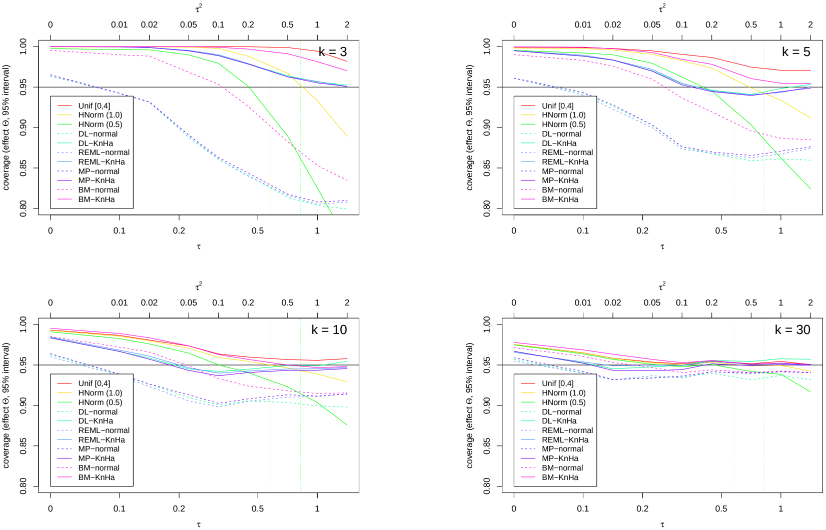


effect estimation: 95% CI coverage



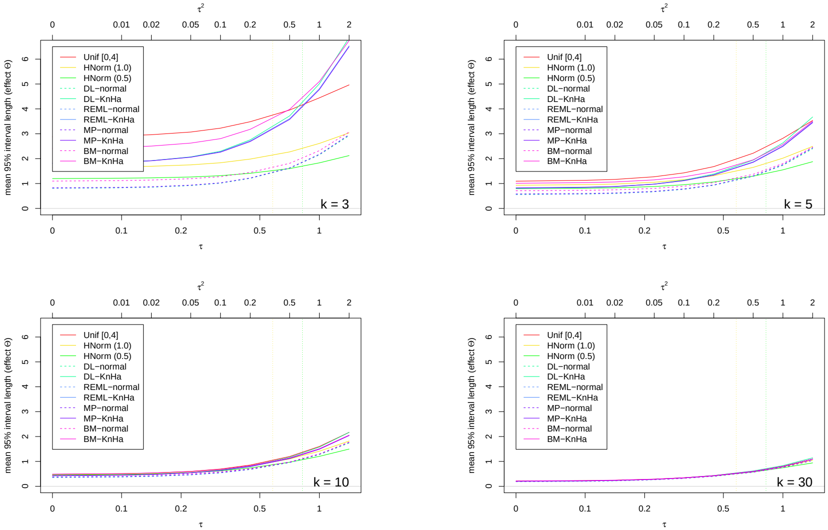
Simulation study

effect estimation: 95% CI coverage

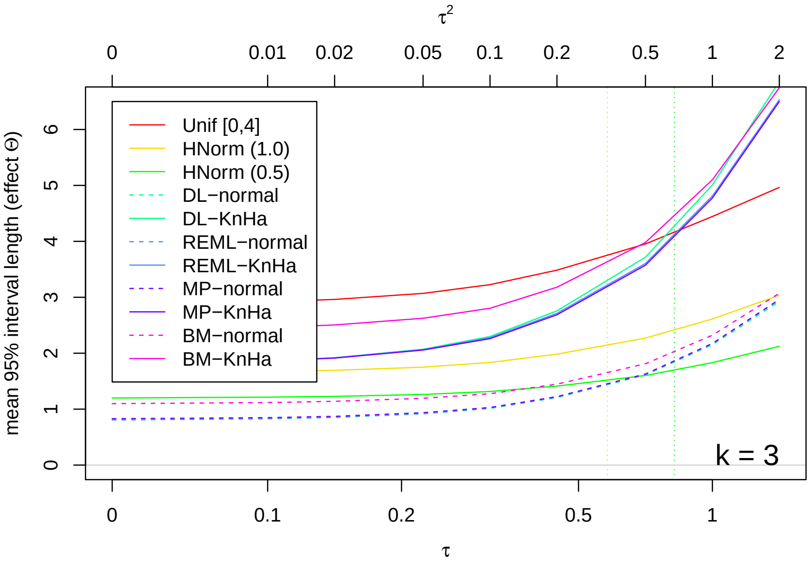


Simulation study

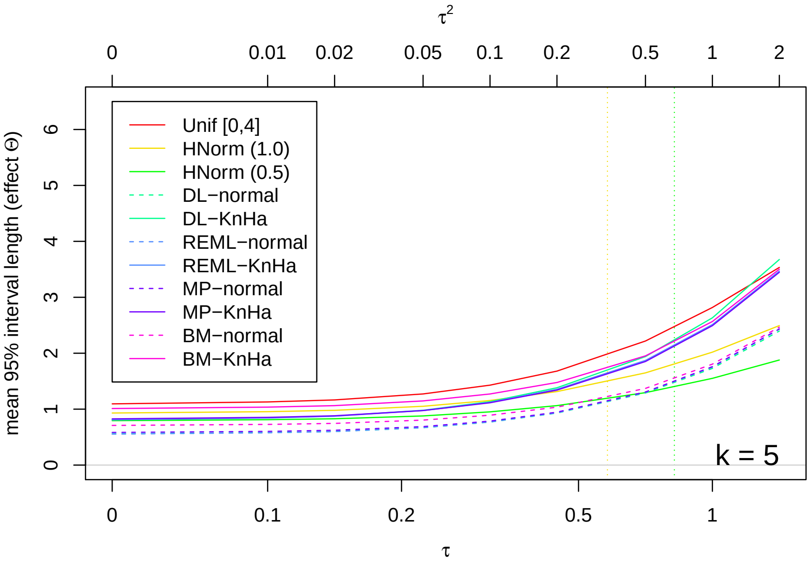
effect estimation: 95% CI length



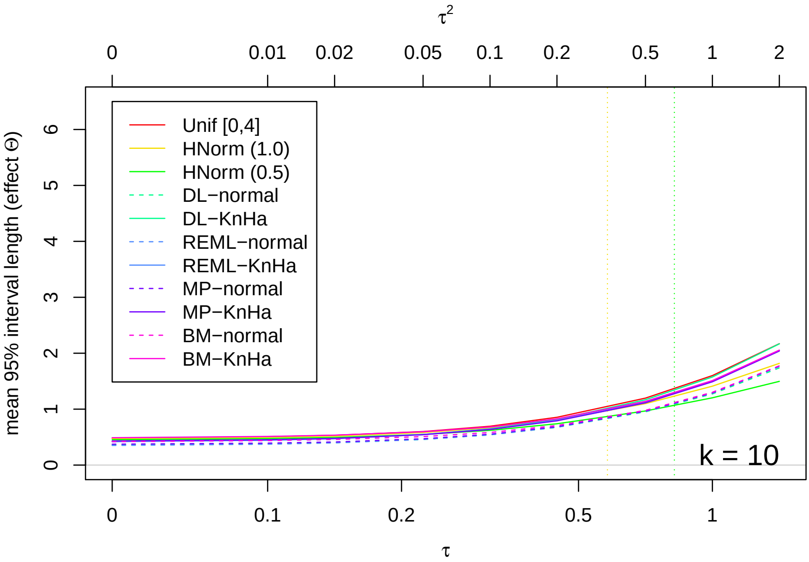
effect estimation: 95% CI length



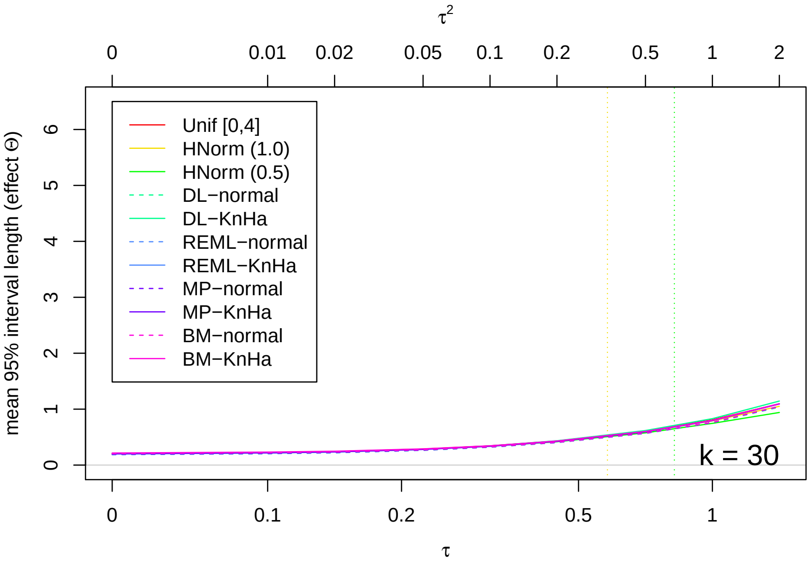
effect estimation: 95% CI length



effect estimation: 95% CI length

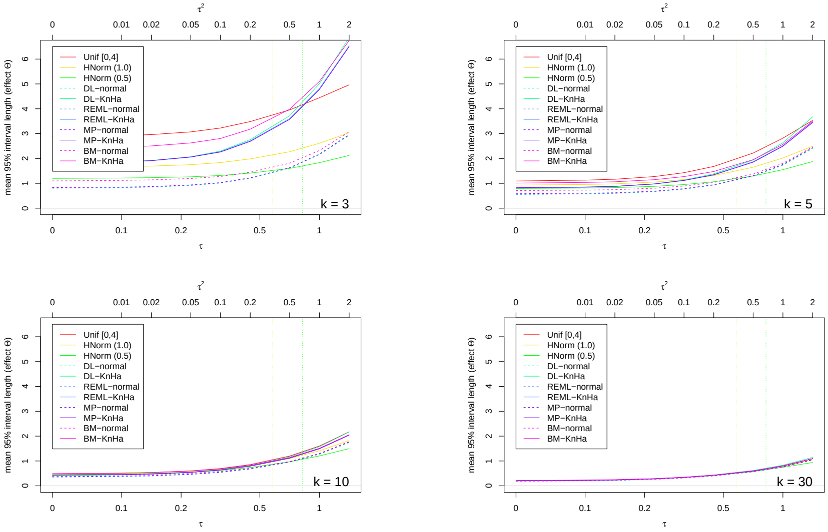


effect estimation: 95% CI length



Simulation study

effect estimation: 95% CI length



Conclusions

- small differences between different frequentist methods
- differences most pronounced in common case of few studies
- consideration of estimation uncertainty:
  undercoverage with normal approximation,
  application of Knapp-Hartung adjustment crucial for nominal level
- surprisingly many zero τ estimates
- Bayesian methods behave as expected:
  conservative / anticonservative for “small” / “large” τ
  (“Mean coverage” (calibration) accurate *by construction*)
- Bayesian methods allow to utilize external information
  (effect and heterogeneity, e.g.[13])
- `bmeta` R package to appear on CRAN soon
- ACKNOWLEDGMENT:
  funded by the EU through InSPiRe (FP HEALTH 2013 - 602144)

[13] R.M. Turner et al. Predictive distributions for between-study heterogeneity and simple methods for their application in Bayesian meta-analysis. *Statistics in Medicine* 34(6):984–998, 2015.

`+++ additional slides +++`

Implementation

bmeta R package under development

```
> cochran01 <- bmeta(Cochran1954[,"mean"], sqrt(Cochran1954[,"se2"]))
> cochran02 <- bmeta(Cochran1954[,"mean"], sqrt(Cochran1954[,"se2"]),
+                    mu.prior.mean=150, mu.prior.sd=100,
+                    tau.prior=function(x){return(dexp(x, rate=0.05))})
>
> cochran01$summary
                tau          mu    mu.pred
mode      10.303255 156.504954 154.16345
median    12.888735 157.896520 157.33321
mean      14.844457 158.547999 158.54800
sd         9.950631   8.358115  19.70028
95% lower  0.000000 143.180913 119.77459
95% upper 32.665117 176.106158 200.12309
>
> # compute posterior quantiles:
> cochran01$qposterior(mu.p=c(0.005, 0.995))
[1] 135.0429 187.3122
>
> # plot posterior density:
> x <- seq(from=130, to=190, length=100)
> plot(x, cochran02$dposterior(mu=x), type="l")
> lines(x, cochran01$dposterior(mu=x))
```