Meta-analysis of few small studies in small populations and rare diseases

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June 17, 2015

This project has received funding from the European Union's Seventh Framework Programme for research, technological development and demonstration under grant agreement number FP HEALTH 2013-602144.

InSPiRe
Innovative methodology for small populations research

Overview

- Meta analysis
  - the random-effects model
  - frequentist approaches
  - the Bayesian approach
  - example
- Simulation study
  - heterogeneity estimation
  - effect estimation
- Conclusions

Meta analysis

The random effects model

- assume[1,2]:

$$y_i \sim \text{Normal}(\theta_i, s_i^2), \qquad \theta_i \sim \text{Normal}(\Theta, \tau^2)$$

$$\Rightarrow \quad y_i \sim \text{Normal}(\Theta, {s_i}^2 + \tau^2)$$

- ingredients:

Data:

- estimates y_i
- standard errors s_i

Parameters:

- true parameter value Θ
- heterogeneity τ

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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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Frequentist approaches

- usual frequentist procedure:
  (1) derive heterogeneity estimate $\hat{\tau}$
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      - estimate $\hat{\Theta}$
      - standard error $\hat{\sigma}_{\Theta}$

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- uncertainty in τ not accounted for
- Knapp-Hartung approach[3]:
  - compute

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

  - confidence interval via Student-t approximation:

$$\hat{\Theta} \pm \max\{\sqrt{q}, 1\} \, \hat{\sigma}_\Theta \, t_{(k-1);(1-\alpha/2)}$$

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Meta analysis

Bayesian approach

- Bayesian approach [4]
  - set up model likelihood
  - specify prior information about unknowns (Θ, τ)
  - posterior results as $\propto$ prior $\times$ likelihood
  - marginal posterior $p(\Theta \,|\, \vec{y}, \vec{\sigma}) \;=\; \int p(\Theta, \tau \,|\, \vec{y}, \vec{\sigma})\, \mathrm{d}\tau \;\ldots$

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- Comments:
  - consideration of prior information
  - propagation of uncertainty
  - straightforward interpretation
  - computationally more expensive, usually done via stochastic integration (MCMC, BUGS)[5]
  - special case of simple random-effects MA may be solved semi-analytically (using `bmeta` R package)

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Meta analysis

Frequentist and Bayesian approaches

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

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[7] A.L. Rukhin, B.J. Biggerstaff, M.G. Vangel. Restricted maximum-likelihood estimation of a common mean and the Mandel-Paule algorithm. *Journal of Statistical Planning and Inference* 83(2):319–330, 2000.

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- estimators for τ considered in the following:
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- priors for τ considered in the following (where $\Theta = \log(\text{OR})$):
  - half-Normal ($\sigma = 0.5$)
  - half-Normal ($\sigma = 1.0$)
  - Uniform (0.0, 4.0)

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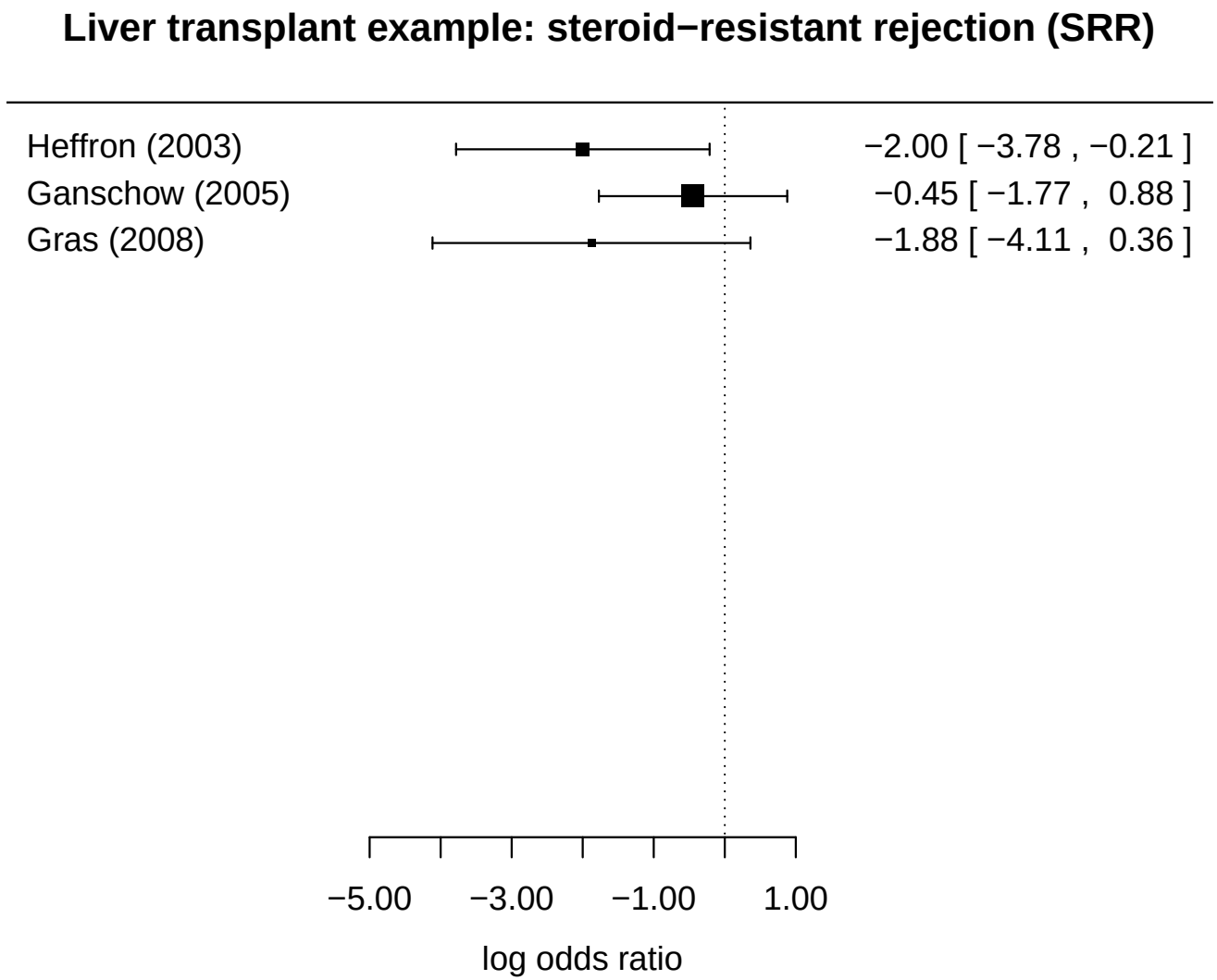
Example

Crins et al. (2014) data[9]



data: 3 estimates
(log ORs)
and standard errors

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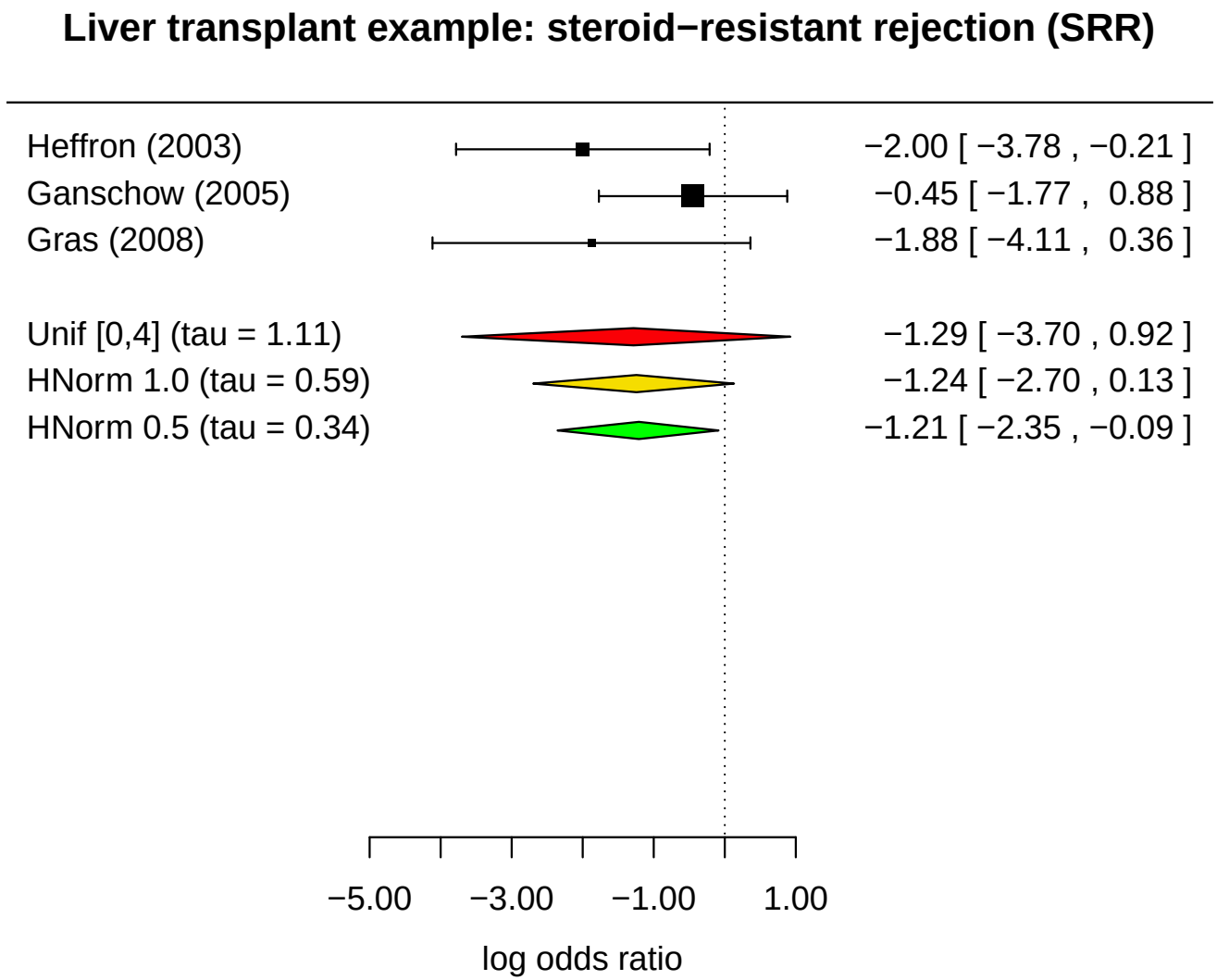

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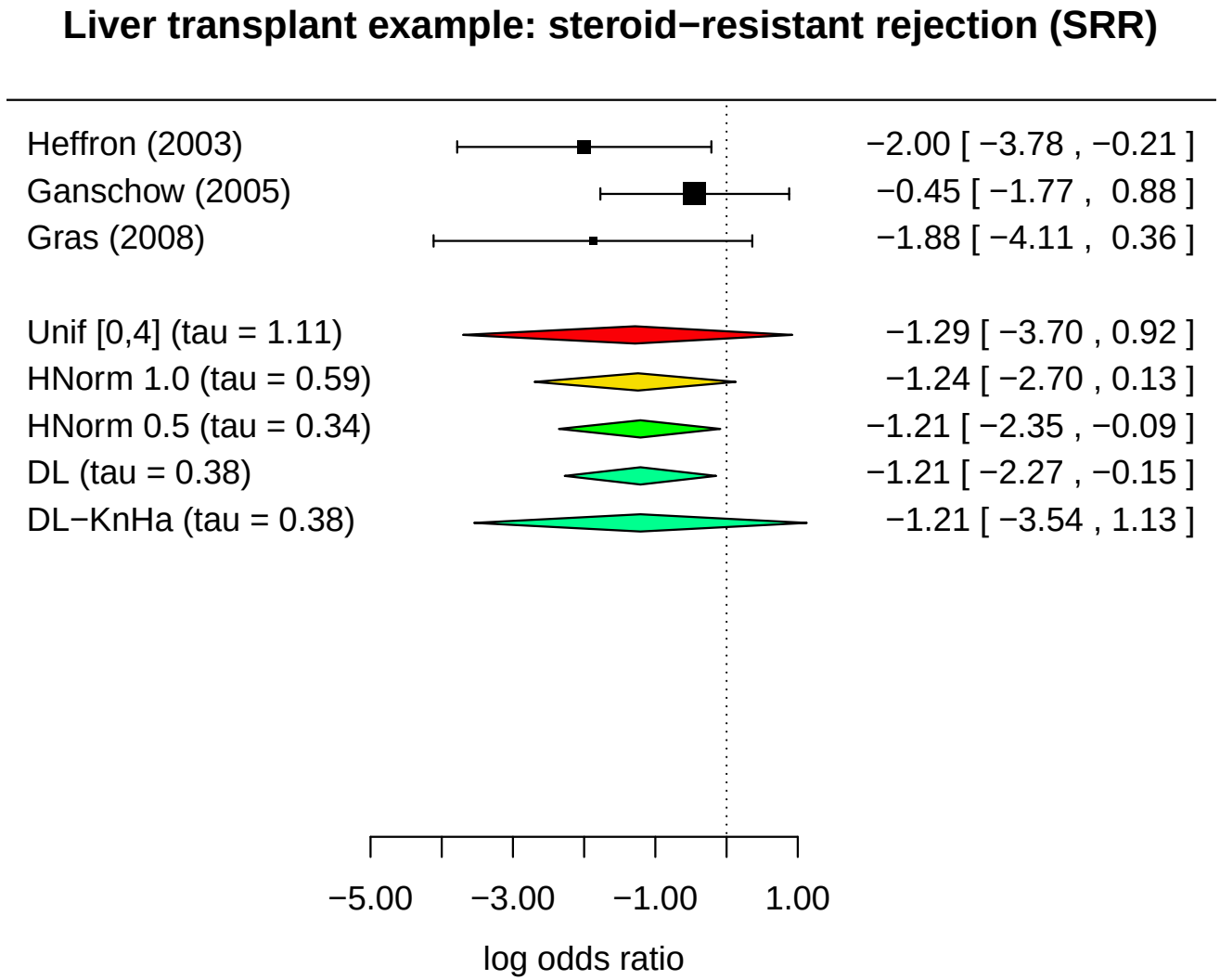

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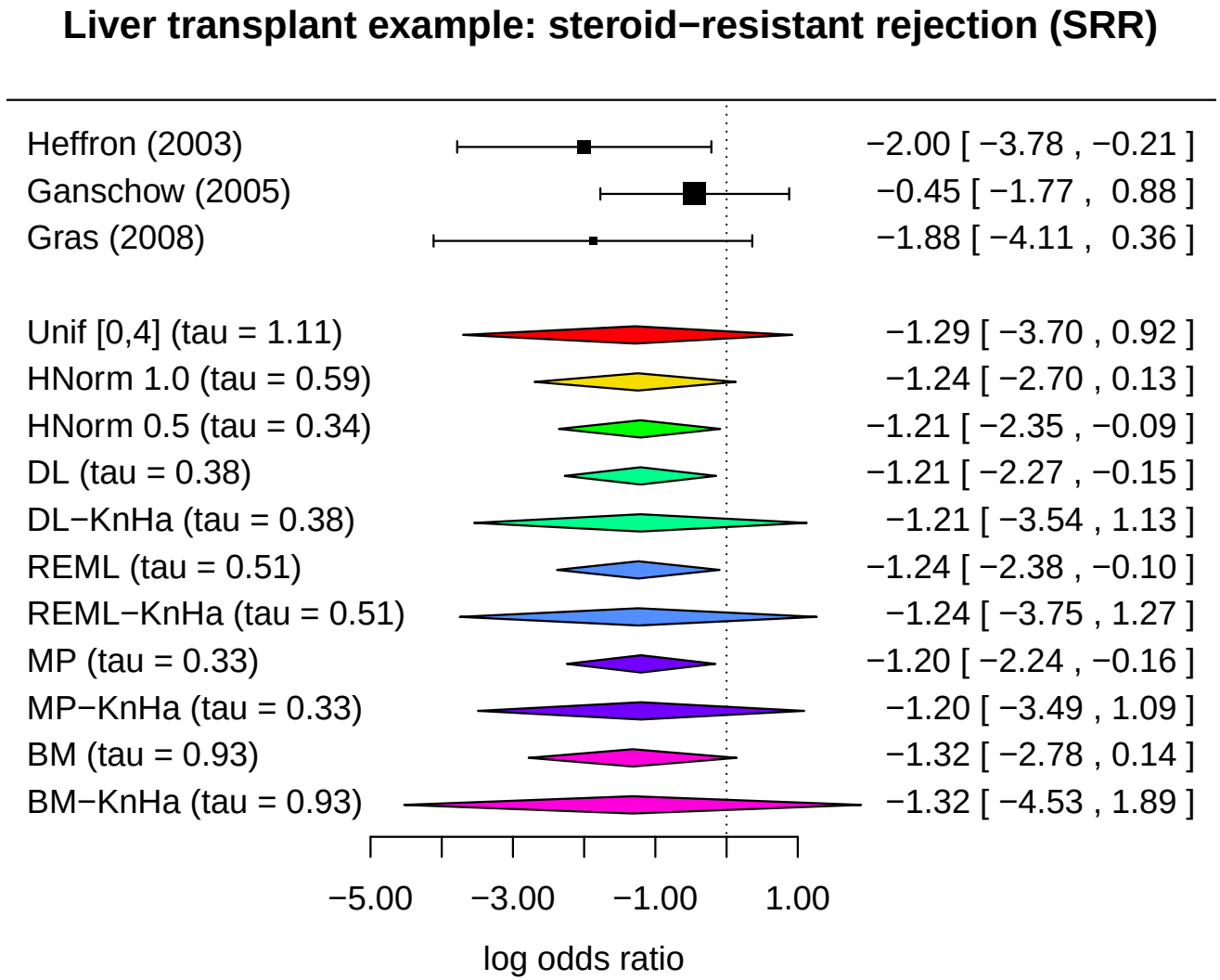

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Crins et al. (2014) data

- 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[10])

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- different analyses yield different answers
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- $k = 2$ to 3 studies is a common scenario
  (*majority* of meta analyses in Cochrane Database[10])
- 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 s_i: truncated χ^2-distribution[11]
- 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)

[11] 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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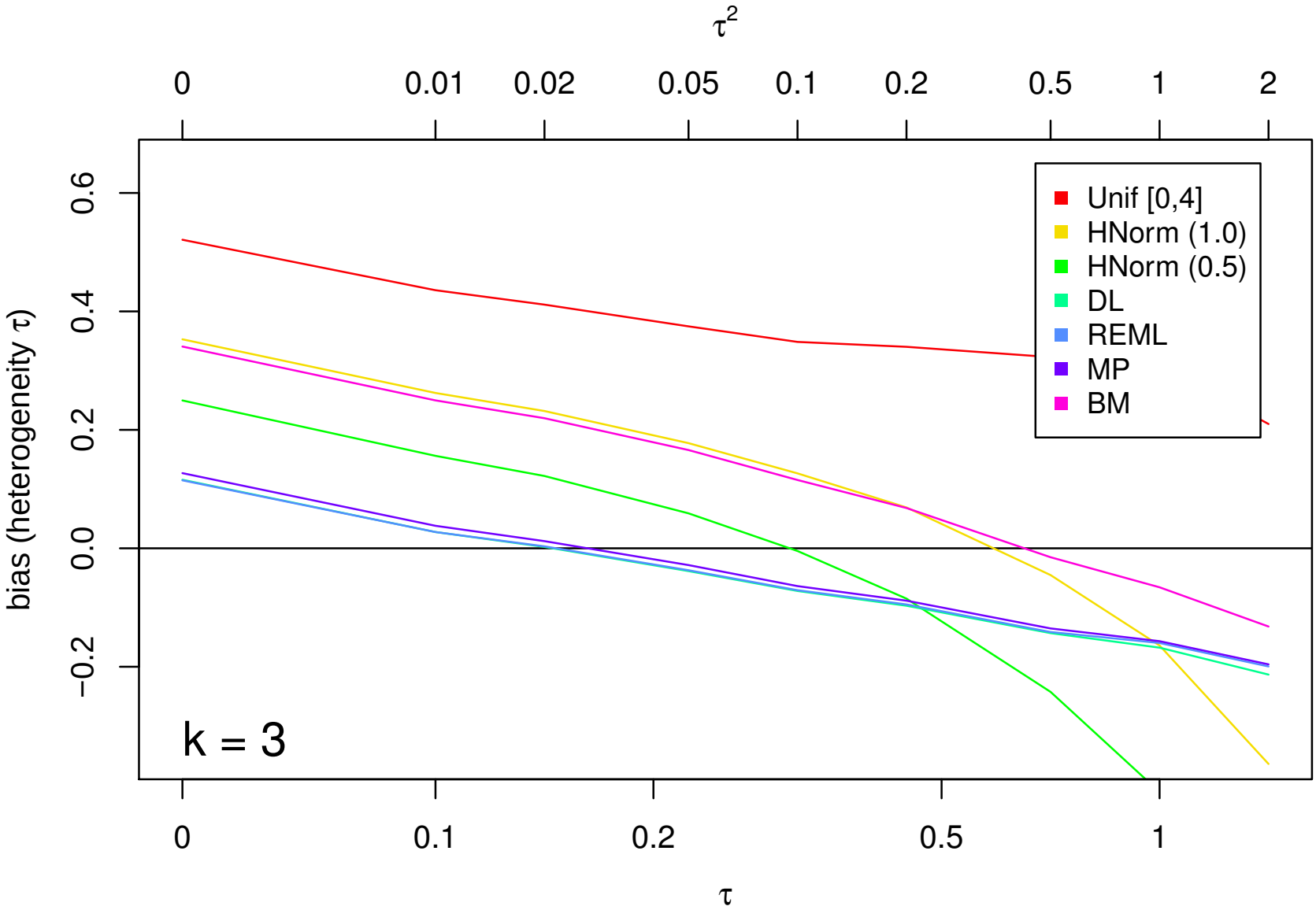
Simulation study

heterogeneity estimation: **bias**



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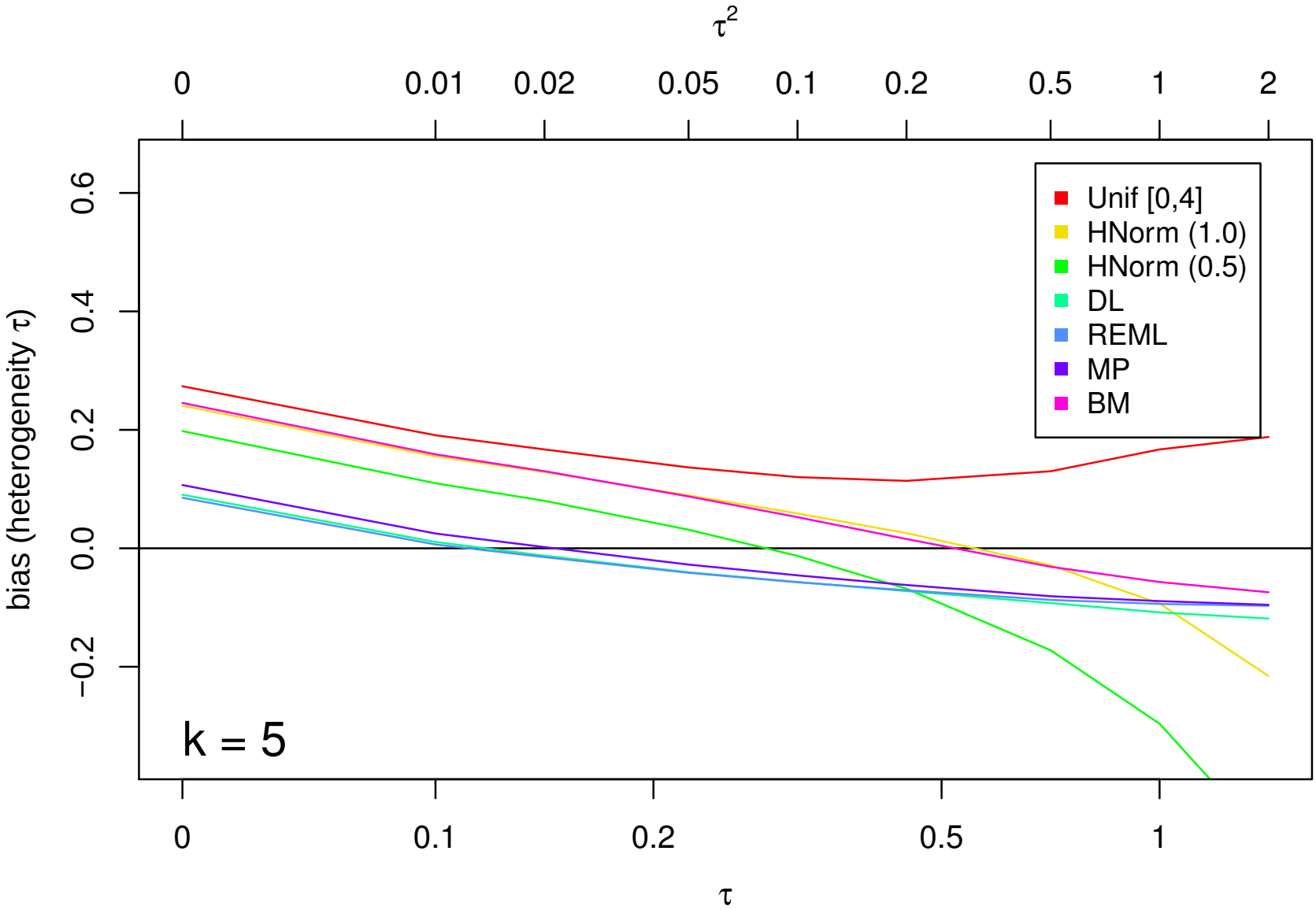

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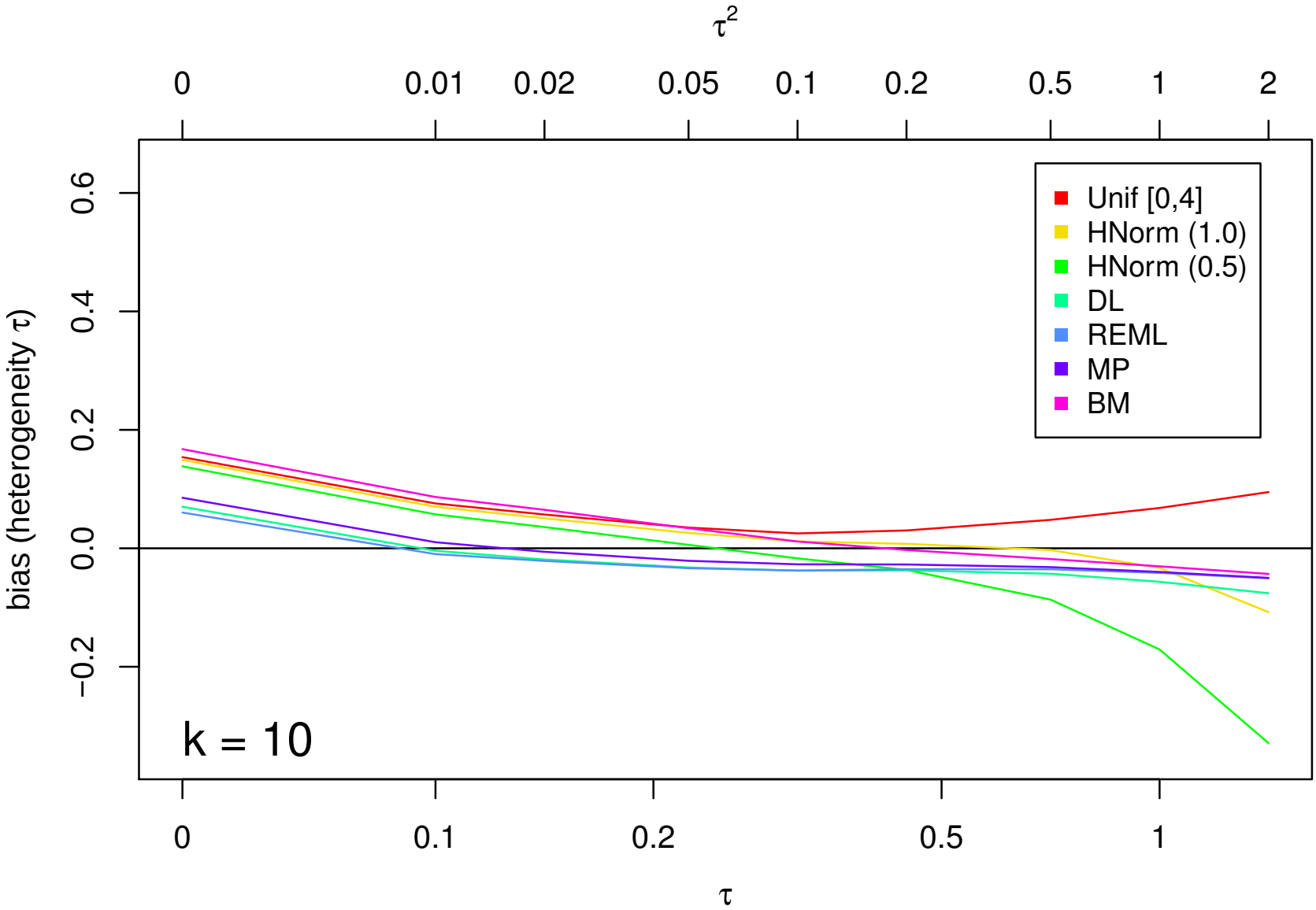

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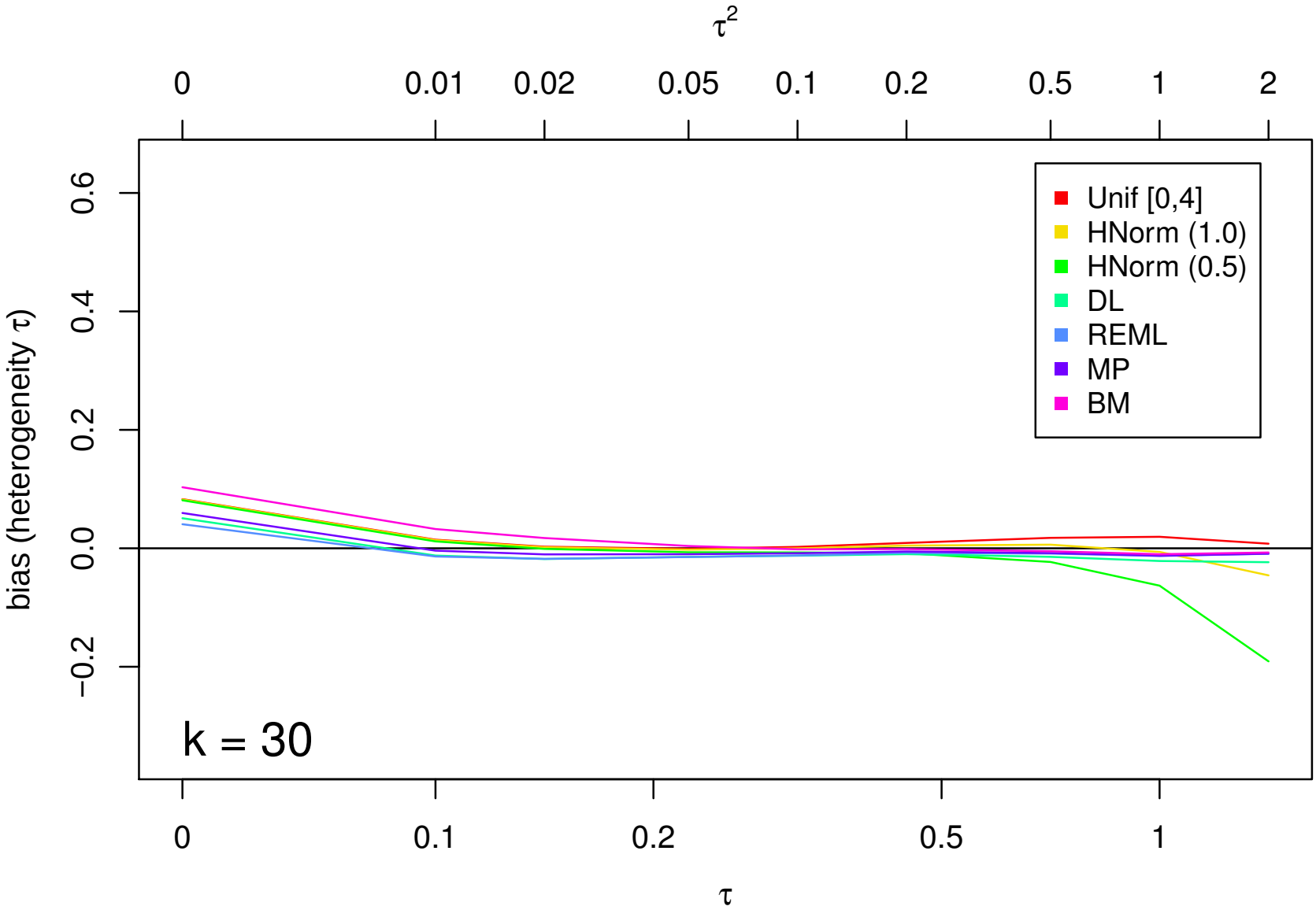


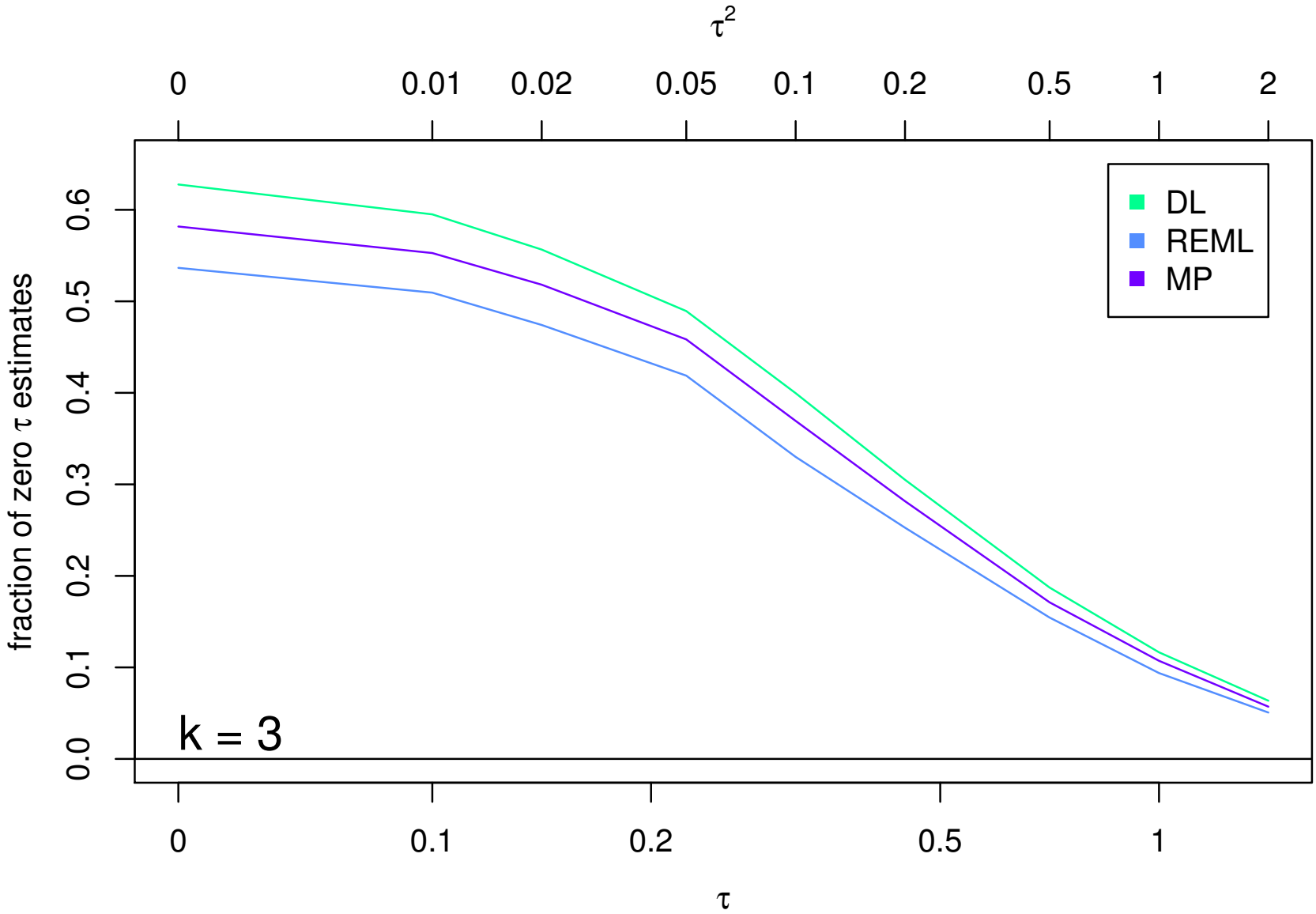
Simulation study

heterogeneity estimation: **bias**

- frequentist estimators similar
- Bayes estimators: positive/negative bias (“shrinkage”), depending on prior
- *Bayes Modal* (penalized likelihood) estimator in between

Simulation study

heterogeneity estimation: **zero estimates**



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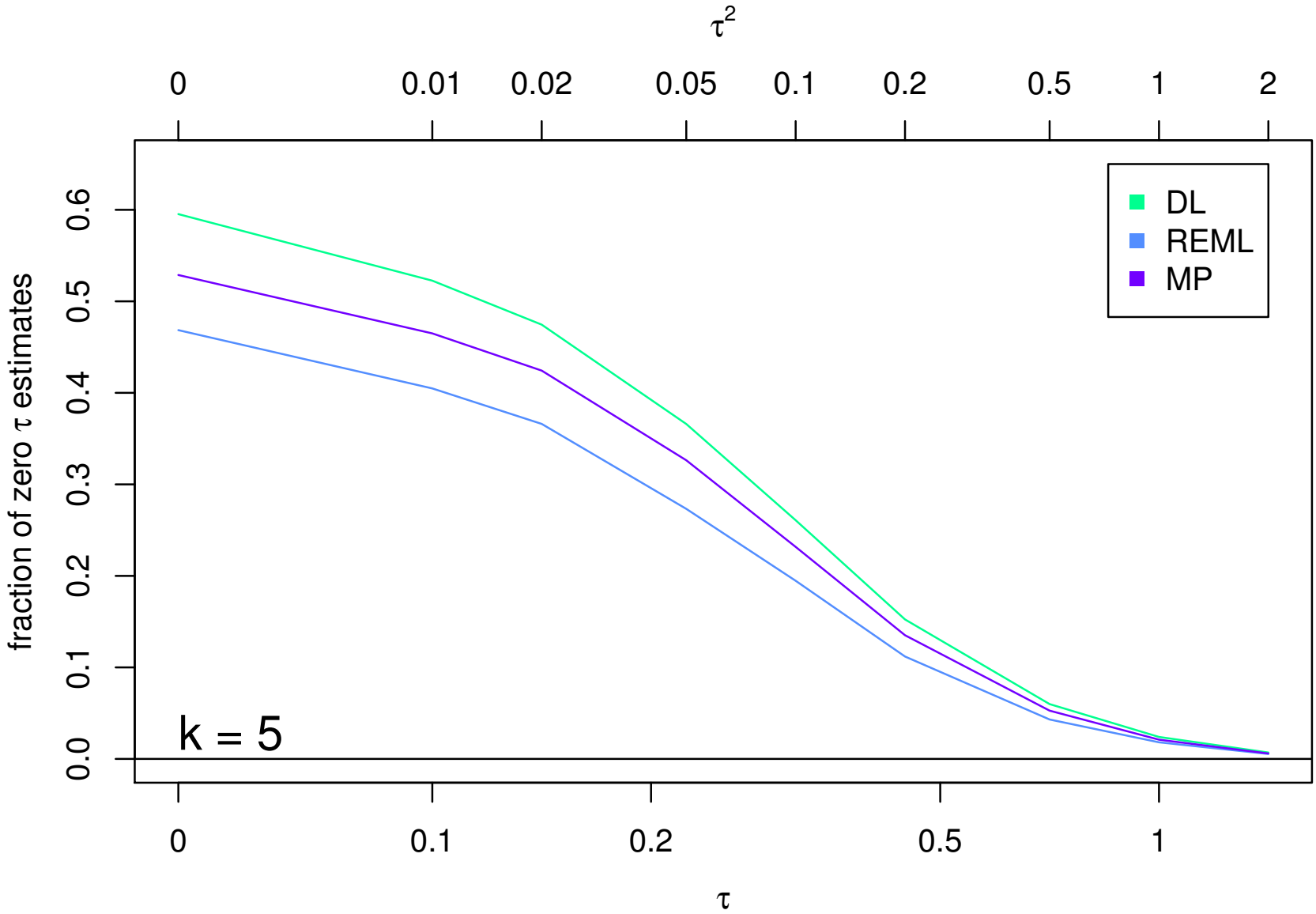

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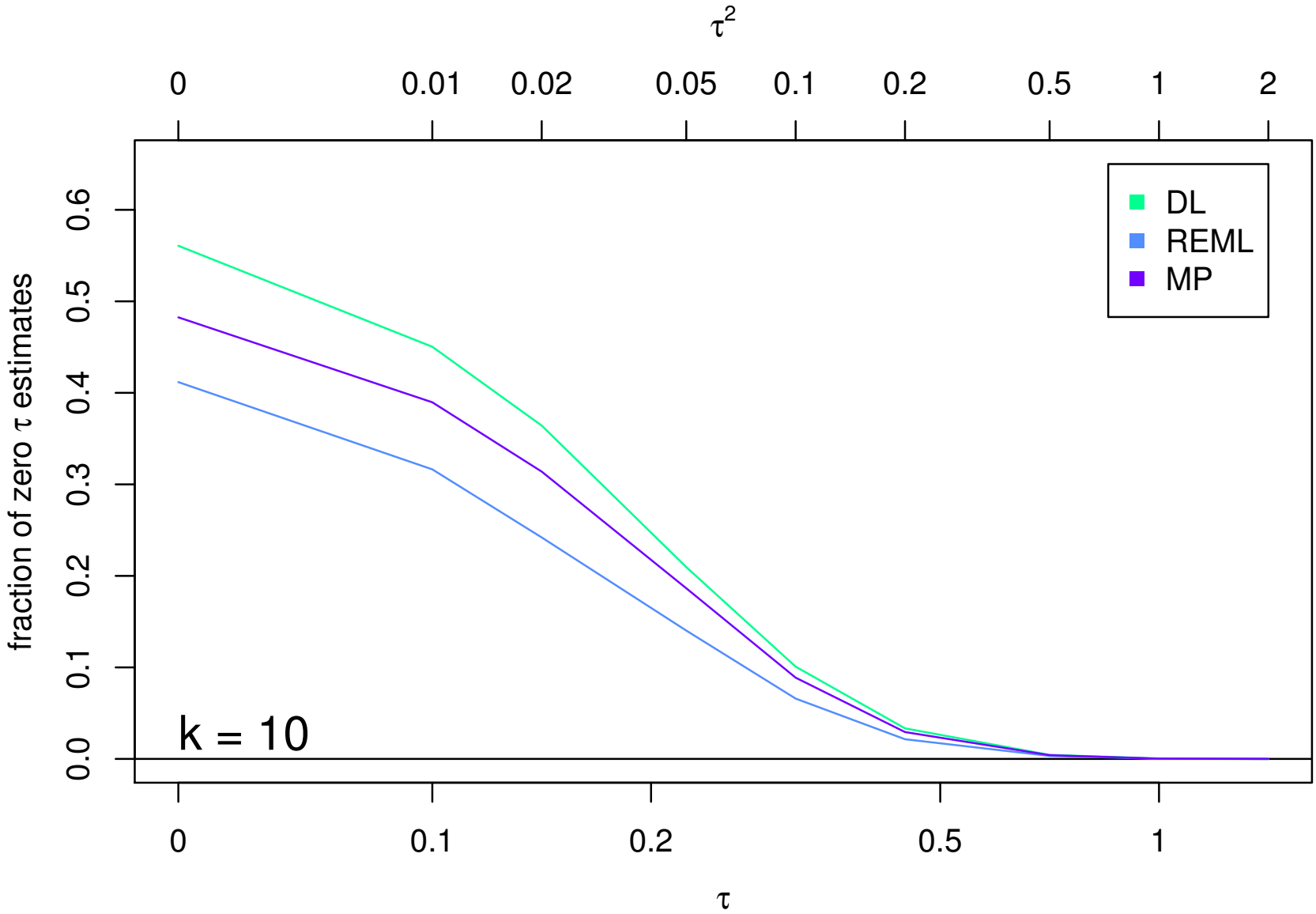

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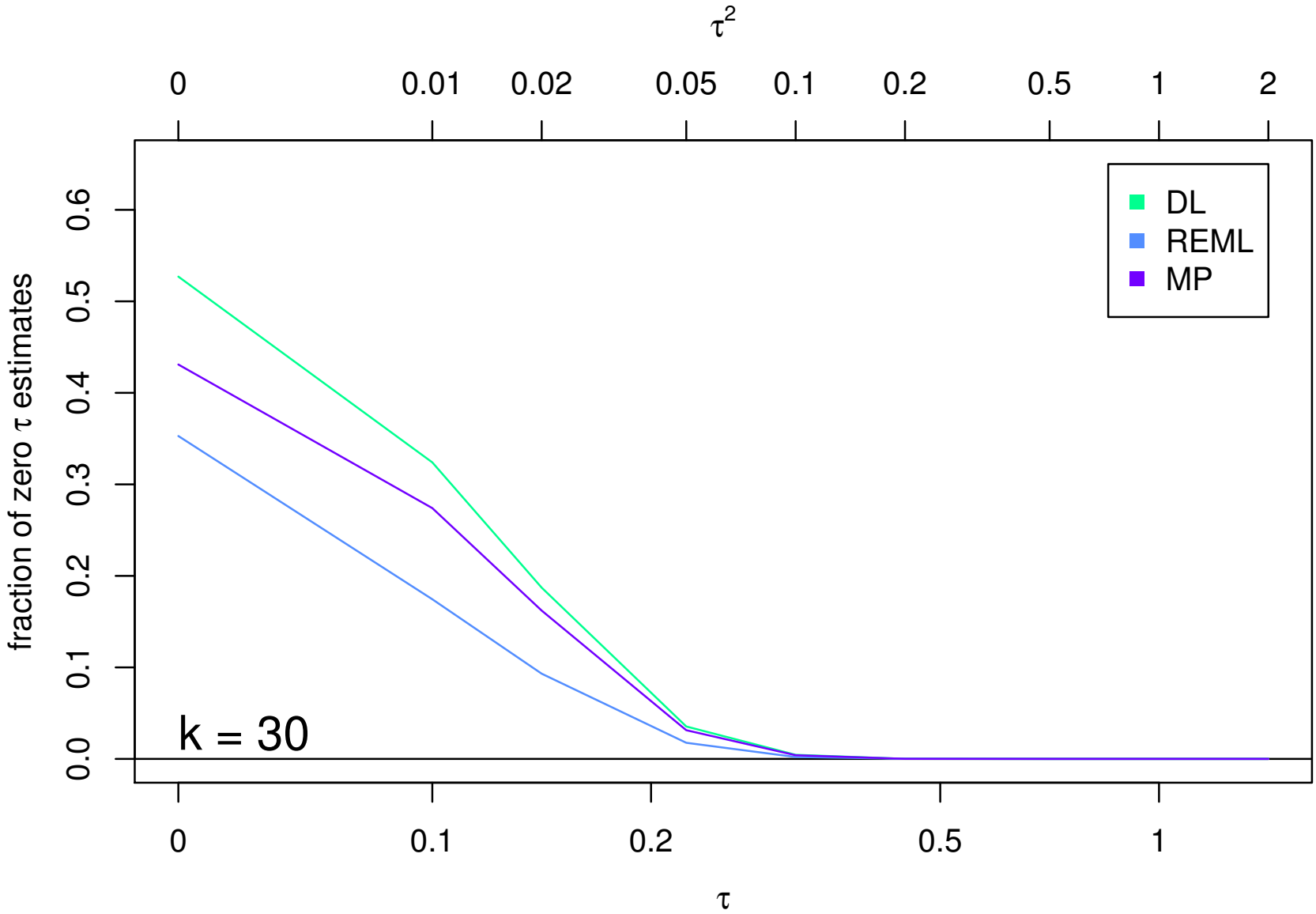


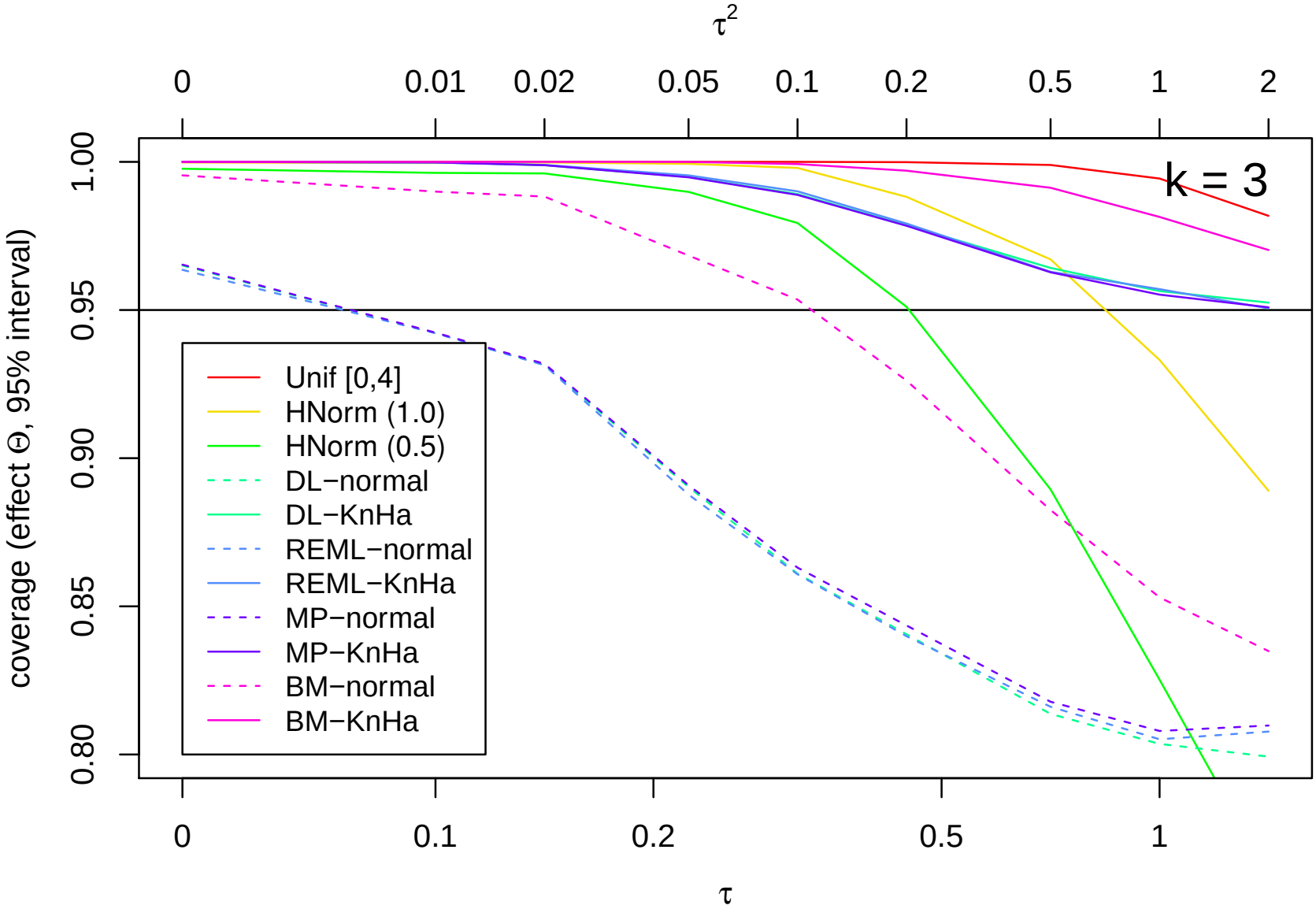
Simulation study

heterogeneity estimation: **zero estimates**

- surprisingly large fraction of zero estimates,
  even for 'large' true τ values
  (leading to *fixed effects* model)

Simulation study

effect estimation: **95% CI coverage**



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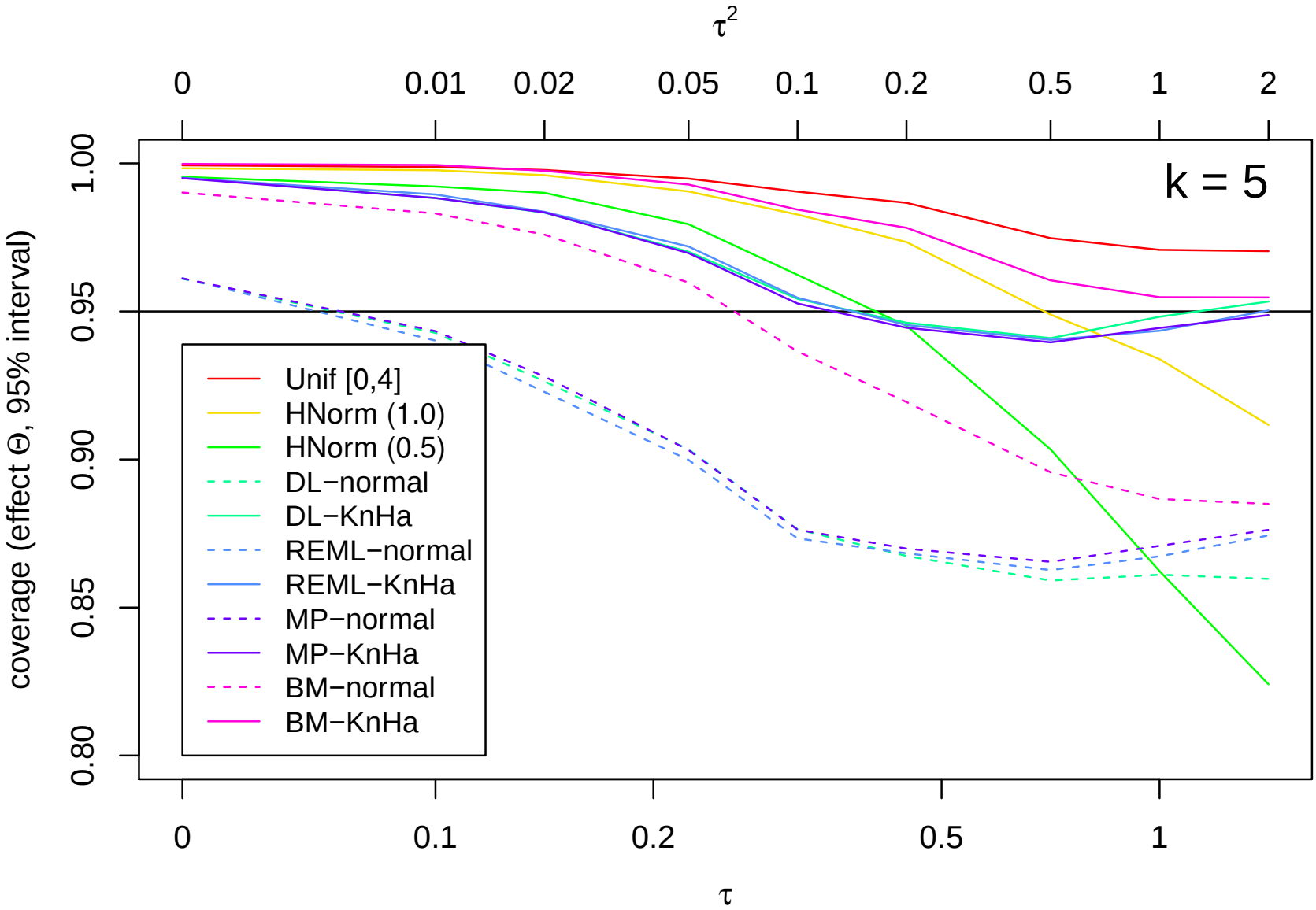

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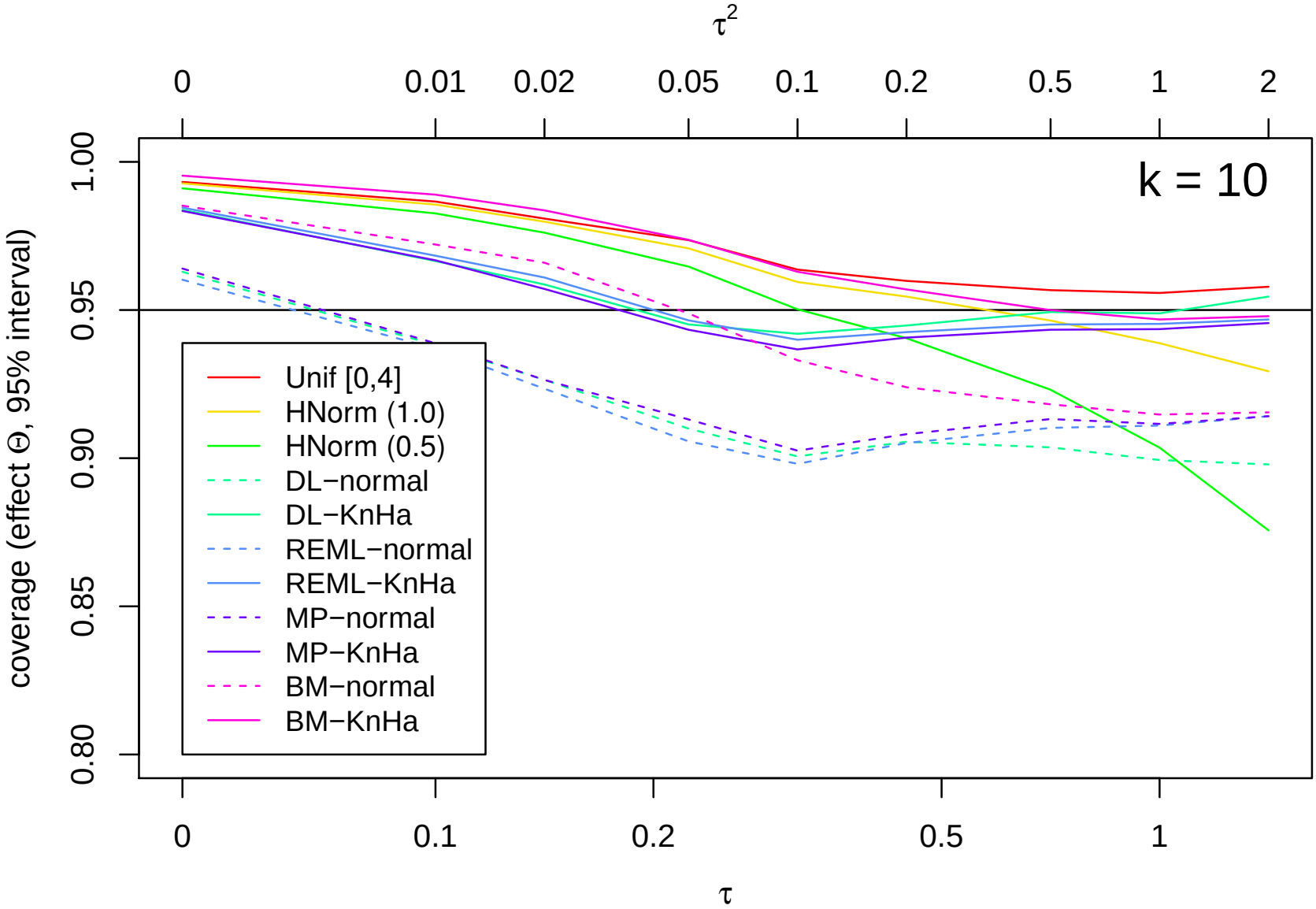

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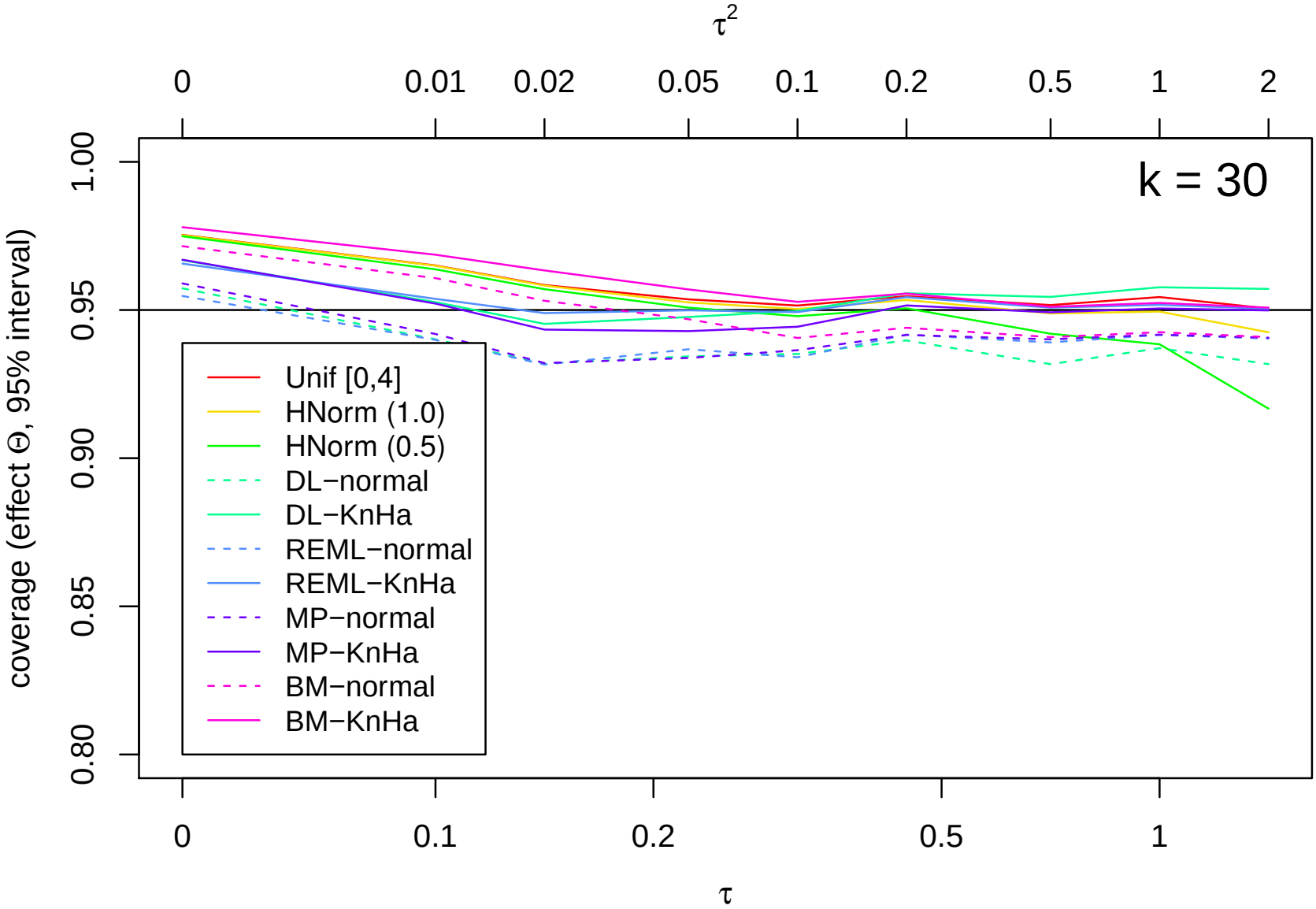


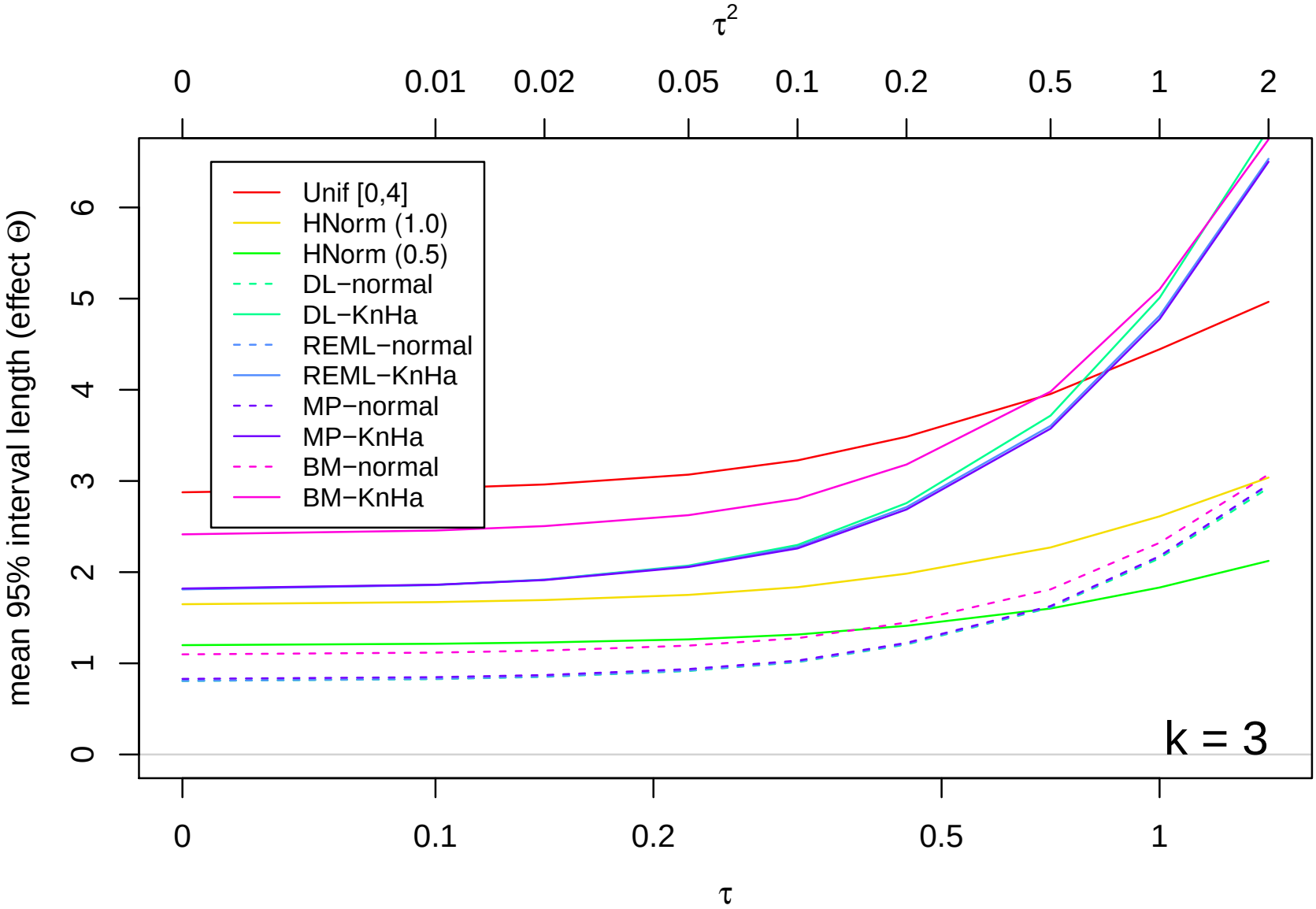
Simulation study

effect estimation: **95% CI coverage**

- poor coverage using normal approximation, Knapp-Hartung adjustment crucial
- little difference between different frequentist methods

Simulation study

effect estimation: **95% CI length**



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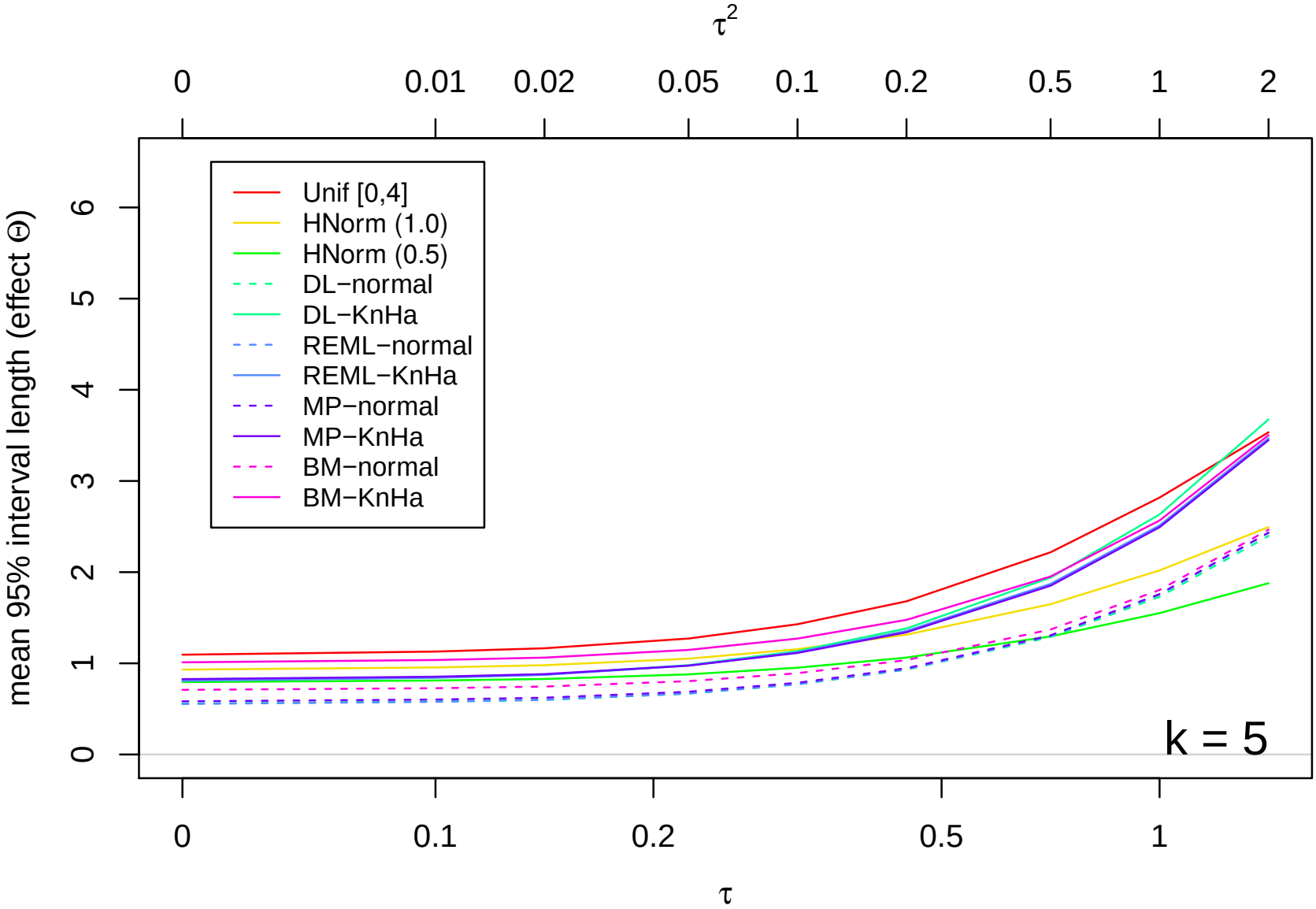

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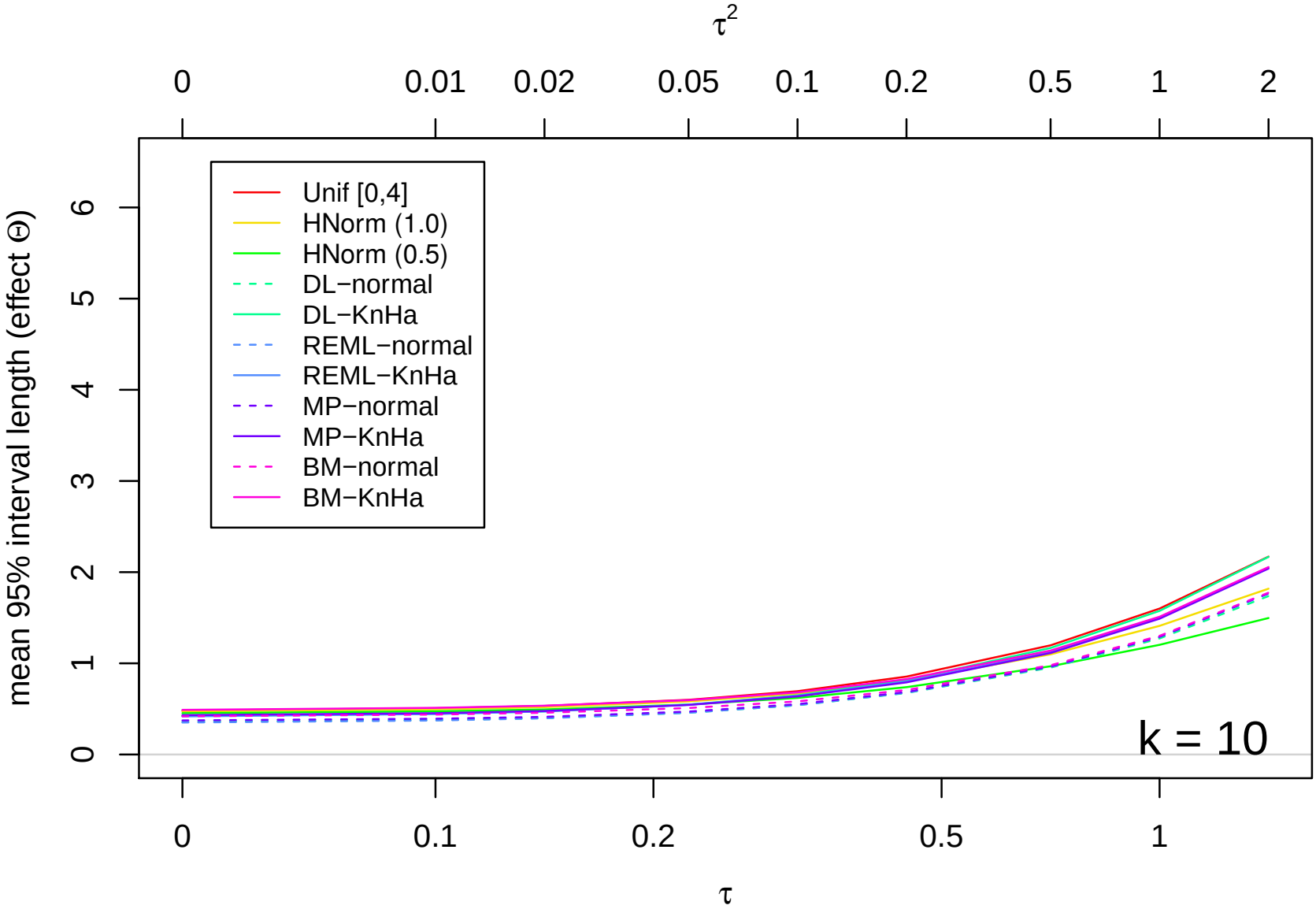

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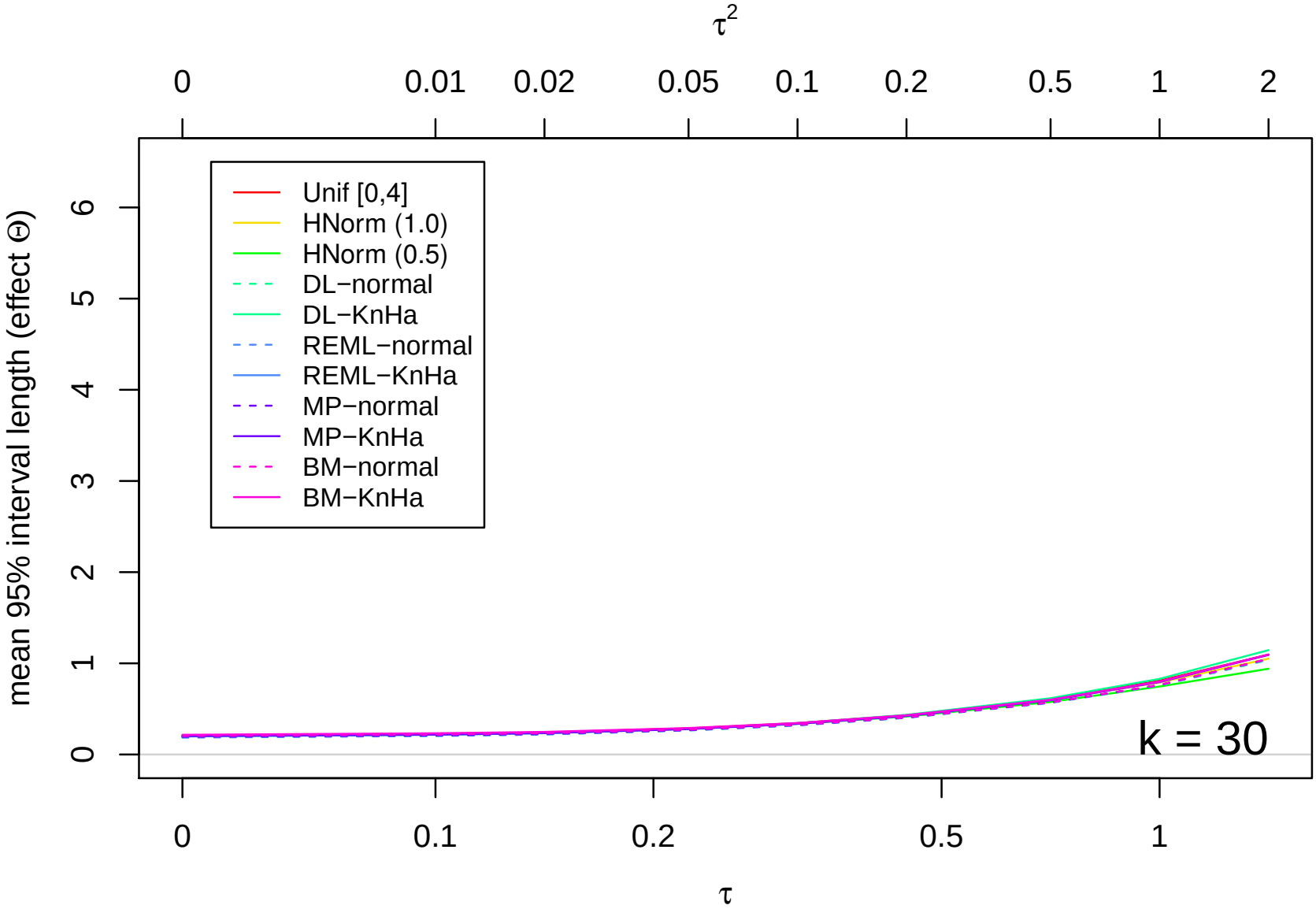

Simulation study

effect estimation: **95% CI length**

- Knapp-Hartung CIs substantially longer than normal CIs, especially for small k
- Bayesian intervals (with realistic priors) shorter

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.[12])
- `bmeta` R package to appear on CRAN soon

- ACKNOWLEDGMENT:
  funded by the EU through InSPiRe (FP HEALTH 2013 - 602144)

[12] 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))
```