Effect and shrinkage estimation in meta-analyses of two studies

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InSPiRe
Innovative methodology for small populations research

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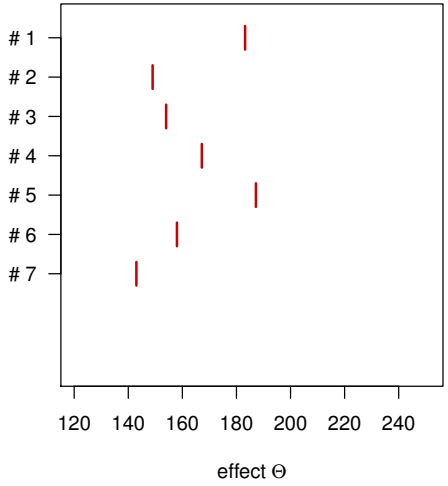
Overview

- meta-analysis
- frequentist and Bayesian approaches
- two-study meta-analysis
- examples + simulations
- shrinkage estimation
- examples + simulations
- conclusions

Meta analysis

The random-effects model



- have:
  - estimates y_i
  - standard errors σ_i
- want:
  - combined estimate $\hat{\Theta}$
- nuisance parameter:
  - between-trial heterogeneity τ

Meta analysis

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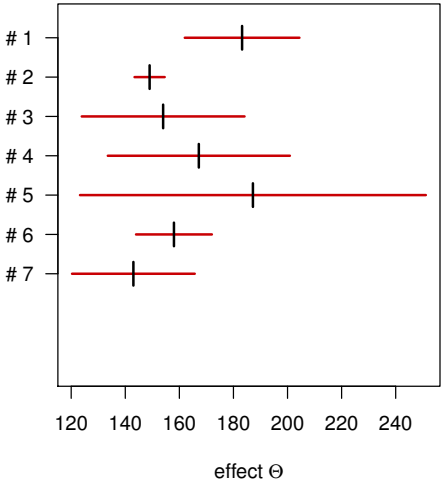

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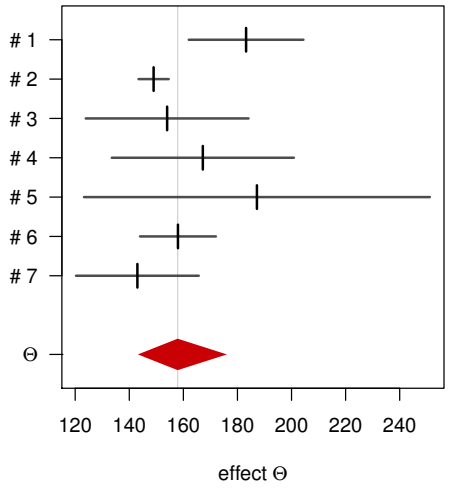

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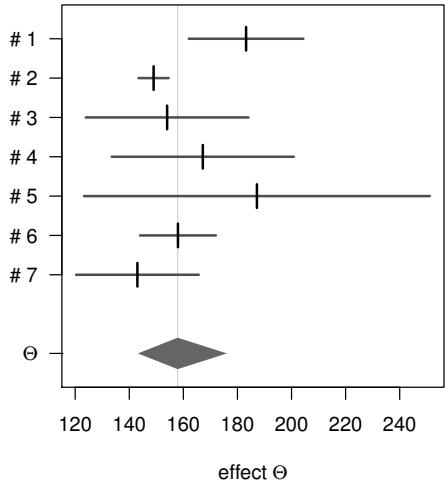

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- assume *normal-normal hierarchical model (NNHM)*

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

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

- model components:

  Data:
  - estimates y_i
  - standard errors s_i

  Parameters:
  - effect Θ
  - heterogeneity τ
  - (study-specific effects θ_i)

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  - (study-specific effects θ_i)

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

Meta analysis

Frequentist approaches

- usual frequentist procedure:
  (1) derive heterogeneity estimate $\hat{\tau}$
  (2) conditional on $\tau = \hat{\tau}$, derive
    - estimate $\hat{\Theta}$
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(uncertainty in τ not accounted for)

Meta analysis

Frequentist approaches

- Hartung-Knapp-Sidik-Jonkman approach (accounting for τ estimation uncertainty)[1]:
  - 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:

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

[1] G. Knapp, J. Hartung. Improved tests for a random effects meta-regression with a single covariate. *Statistics in Medicine* 22(17):2693–2710, 2003.

[2] C. Röver, G. Knapp, T. Friede. Hartung-Knapp-Sidik-Jonkman approach and its modification for random-effects meta-analysis with few studies. *BMC Medical Research Methodology* 15:99, 2015.

Meta analysis

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  - confidence interval via Student-t approximation:

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

- *modified* Knapp-Hartung approach[2]:
  - quadratic form q may turn out < 1, confidence intervals may get shorter
  - truncate q to get more conservative interval:

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

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- Bayesian approach [3]
  - set up model likelihood (same as frequentist)
  - specify prior information about unknowns (Θ, τ)
  - posterior: $\propto$ prior $\times$ likelihood
  - inference requires integrals, e.g. $p(\Theta \mid y, \sigma) = \int p(\Theta, \tau \mid y, \sigma)\, \mathrm{d}\tau \ldots$
  - use numerical methods for integration (MCMC, `bayesmeta` R package[4], ...)
  - straightforward interpretation, no reliance on asymptotics, consideration of prior information, ...

[3] A. J. Sutton, K. R. Abrams. *Bayesian methods in meta-analysis and evidence synthesis*. Statistical Methods in Medical Research, 10(4):277, 2001.

[4] `http://cran.r-project.org/package=bayesmeta`

- *normal-normal hierarchical model (NNHM)* applicable for many endpoints: only need estimates and std. errors of some *effect measure*
- $k = 2$ to 3 studies is a common scenario: *majority* of meta analyses in Cochrane Database[5]
- frequentist methods run into problems for few studies (small k)
- two-study case: no satisfactory frequentist procedure[6]
- despite extreme setting, error control crucial[7]

[5] R.M. Turner et al. Predicting the extent of heterogeneity in meta-analysis, using empirical data from the Cochrane Database of Systematic Reviews. *International Journal of Epidemiology* 41(3):818–827, 2012.
E. Kontopantelis et al. A re-analysis of the Cochrane Library data: The dangers of unobserved heterogeneity in meta-analyses. *PLoS ONE* 8(7):e69930, 2013.

[6] A. Gonnermann et al. No solution yet for combining two independent studies in the presence of heterogeneity. *Statistics in Medicine* 34(16):2476–2480, 2015

[7] European Medicines Agency (EMEA). Guideline on clinical trials in small populations. CHMP/EWP/83561/2005, `http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003615.pdf`, 2006.

Examples

2-study meta analyses

- two examples of two-study meta-analyses[8,9]
- binary endpoints (log-ORs)
- Bayesian analyses:
  - uniform effect (Θ) prior
  - half-normal heterogeneity (τ) priors with scales 0.5 and 1.0
- frequentist analyses:
  - normal approximation
  - Hartung-Knapp-Sidik-Jonkman (HKSJ) interval
  - modified Knapp-Hartung (mKH) interval
  - for $k = 2$ studies *DerSimonian-Laird*, *ML*, *REML* and *Paule-Mandel* heterogeneity estimates coincide[10]

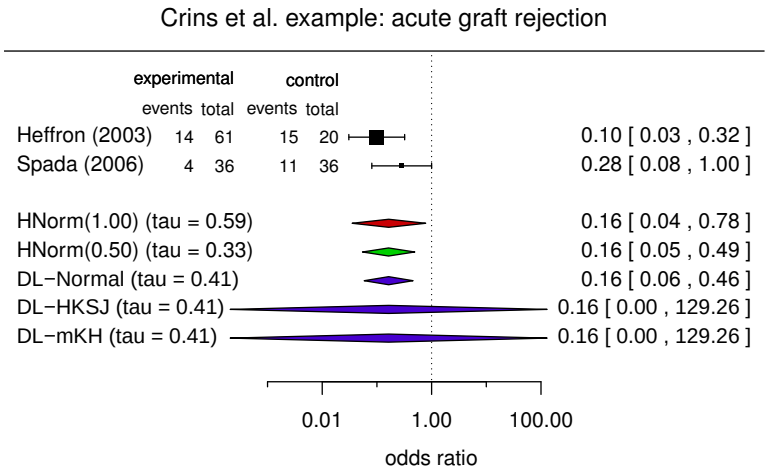
[8] N.D. Crins et al. Interleukin-2 receptor antagonists for pediatric liver transplant recipients: A systematic review and meta-analysis of controlled studies. *Pediatric Transplantation* 18(8):839–850, 2014.

[9] R.C. Davi et al. Krystexxa™ (Pegloticase, PEG-uricase and puricase). Statistical Review and Evaluation STN 125293-0037, U.S. Department of Health and Human Services, Food and Drug Administration (FDA).

[10] A.L. Rukhin. Estimating common mean and heterogeneity variance in two study case meta-analysis. *Statistics & Probability Letters* 82(7):1318-1325, 2012.

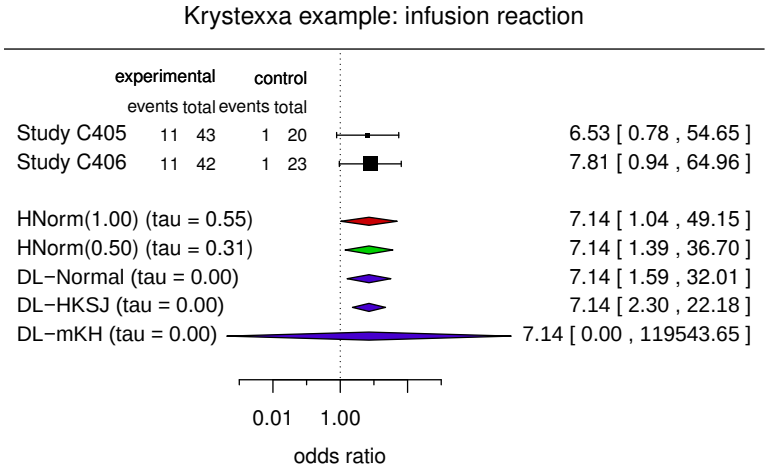
Examples

2-study meta analyses



Examples

2-study meta analyses



Simulation study

Setup

- How do methods compare in general?

- motivation: log-OR endpoint
- simulate data (according to NNHM) on log-OR scale
- consider combinations of studies of sizes $n_1, n_2 \in \{25, 100, 400\}$ (standard errors $\sigma_i = \frac{2}{\sqrt{n_i}}$)
- heterogeneity $\tau \in \{0.0, 0.1, 0.2, 0.5, 1.0\}$

Simulation study

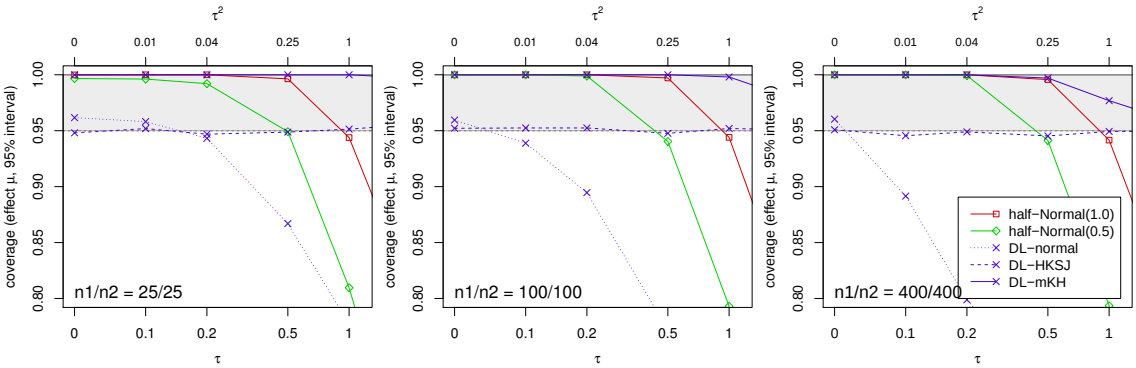
heterogeneity estimation: **zero estimates**

- Percentages of zero heterogeneity estimates (effectively *fixed-effect* analyses):

	true heterogeneity τ				
n_1 / n_2	0.0	0.1	0.2	0.5	1.0
25 / 25	68	67	62	47	29
100 / 100	68	63	52	29	15
400 / 400	68	53	34	16	8
25 / 100	68	65	60	41	23
100 / 400	68	61	46	24	13
25 / 400	68	65	59	39	22

Simulation study

effect CI coverage (two equal-sized studies)



- undercoverage for normal approx.

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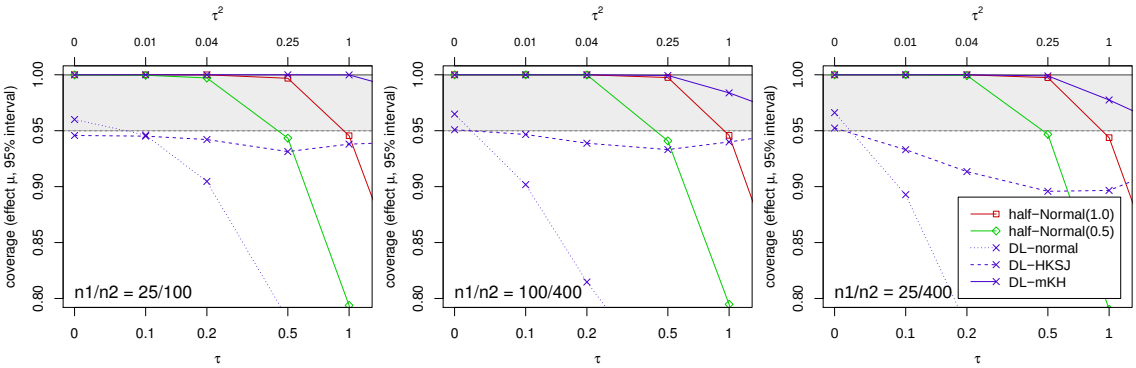

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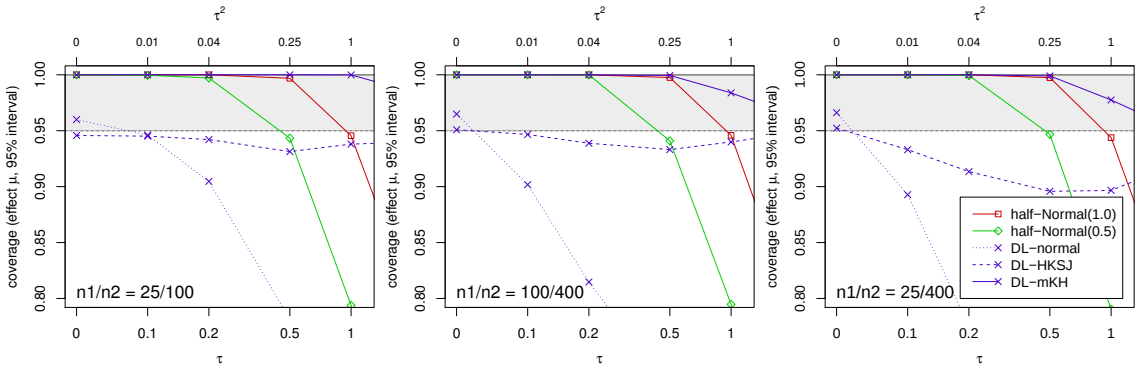
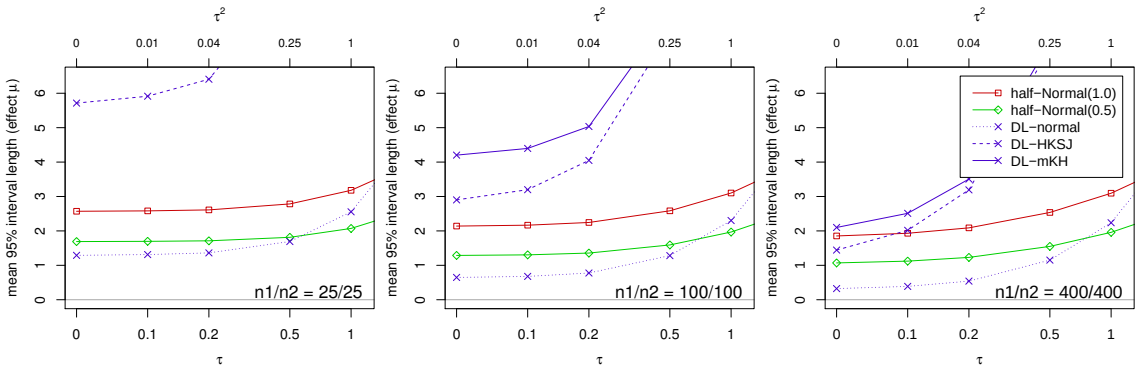


- undercoverage for normal approx.
- undercoverage for HKSJ at unequal sizes
- Bayesian intervals as expected
- mKH very conservative

Simulation study

effect CI length (two equal-sized studies)



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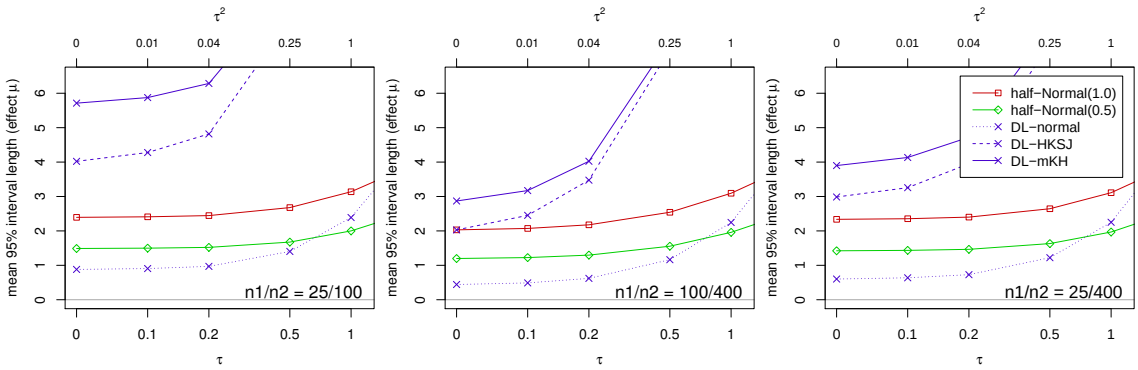


- substantially shorter intervals for Bayesian methods

Conclusions I

Meta-analysis of 2 studies

- two-study meta-analysis is a common scenario
- common frequentist methods tend to be either very conservative or too liberal
- small k technically not a problem for Bayesian approach
  (no reliance on asymptotics)
- w.r.t. long-run performance, Bayesian meta-analysis provides a middle ground
- interpretation is straightforward

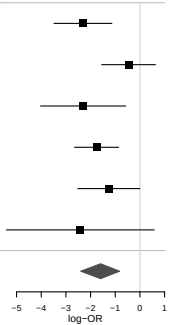
- paper to appear[11]

[11] T. Friede, C. Röver, S. Wandel, B. Neuenschwander. Meta-analysis of two studies in the presence of heterogeneity with applications in rare diseases. *Biometrical Journal*, (in press), 2016. URL: `http://dx.doi.org/10.1002/bimj.201500236`.

Shrinkage estimation

Introduction

study	estimate	95% CI
Heffron (2003)	−2.31	[−3.48, −1.13]
Gibelli (2004)	−0.46	[−1.55, 0.63]
Schuller (2005)	−2.30	[−4.03, −0.58]
Ganschow (2005)	−1.76	[−2.65, −0.86]
Spada (2006)	−1.26	[−2.52, −0.00]
Gras (2008)	−2.42	[−5.41, 0.58]
mean	**−1.59**	**[−2.40, −0.82]**



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- overall mean of studies?
  $\rightarrow$ **effect estimation** (Θ)

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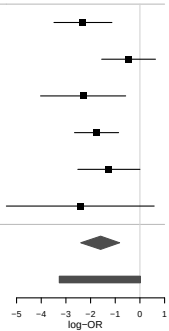

different aims of meta analysis:

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- future studies?
  $\rightarrow$ **prediction** (θ_{k+1})

Shrinkage estimation

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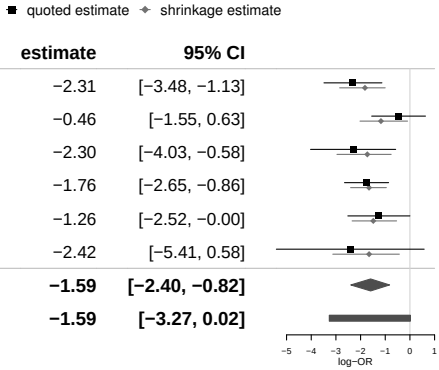


different aims of meta analysis:

- overall mean of studies?
  $\rightarrow$ **effect estimation** (Θ)
- future studies?
  $\rightarrow$ **prediction** (θ_{k+1})
- individual studies?
  $\rightarrow$ **shrinkage estimation** (θ_i)

Shrinkage estimation

Introduction

shrinkage estimation:

- specific for the ith study
- estimate of study's specific mean θ_i
- based on all estimates $(y_1, \ldots, y_k, \sigma_1, \ldots, \sigma_k)$
- (more or less) "shrunk" towards the overall mean Θ

- joint analysis informs hyperprior $p(\Theta, \tau)$ and prior $p(\theta_i|\Theta, \tau)$
  $\rightarrow$ more informative posterior based on data y_i.

Shrinkage estimation

The MAP / MAC connection

- two ways to analyze *i*th estimate:
  - **Meta-analytic-combined (MAC)** approach:
    perform joint meta-analyis of all studies,
    determine *i*th shrinkage estimate
  - **Meta-analytic-predictive (MAP)** approach:
    meta-analyze all but *i*th study;
    resulting posterior yields *meta-analytic predictive (MAP)* prior,
    use MAP prior and data y_i to infer θ_i
- both approaches yield identical results[12]

[12] H. Schmidli, et al. Robust meta-analytic-predictive priors in clinical trials with historical control information. *Biometrics* 70(4):1023–1032, 2014.

Shrinkage estimation

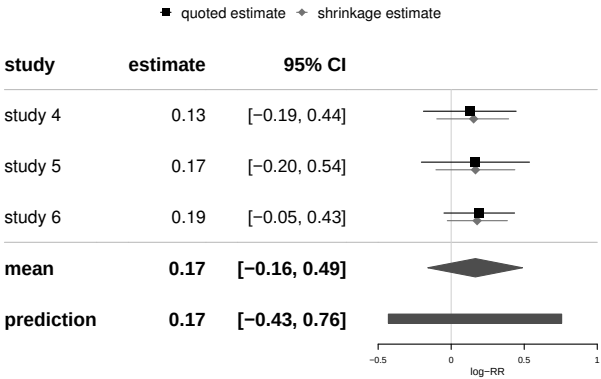
Inference for single trials

- often of primary interest: a particular study (-outcome)
  (**not** a more general evidence synthesis)
- example:
  phase III studies
  additional information: studies from earlier phases
- aim is not a synthesis of all available data,
  but use of MAP prior may be readily motivated[13]
- separate consideration of *(MAP) prior* and *data* yields a transparent analysis
- allows to consider external information when data are sparse
  (e.g. rare diseases)

[13] S. Wandel, B. Neuenschwander, C. Röver, T. Friede. Using phase II data for the analysis of phase III studies: an application in rare diseases. *(submitted for publication)*, 2016. Preprint: `http://arxiv.org/abs/1609.03367`.

Shrinkage estimation

The HSV example



HSV example
(cure rate endpoint, non-inferiority)[a]:

- end of phase II:
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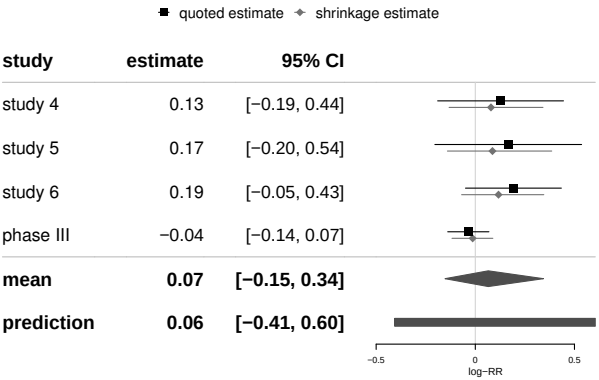

HSV example
(cure rate endpoint, non-inferiority)[a]:

- end of phase II:
  3 studies available,
  prediction interval constitutes prior for planned phase III study
- phase III:
  new trial's **shrinkage interval** summarizes trial considering informative "phase II" prior

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Shrinkage estimation

in 2-study meta-analysis

- common case:
  inference on a **single** study
- consideration of external information / data (**single** estimate)
- consideration of potential heterogeneity
- $\rightarrow$ use NNHM framework and shrinkage estimate

Shrinkage estimation

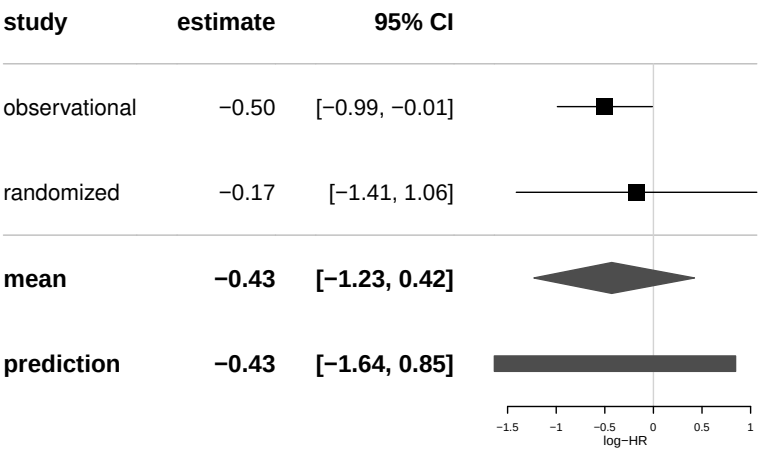
The Creutzfeld-Jakob disease (CJD) example

- Creutzfeld-Jakob disease (CJD) is a **rare disease**
- A small **randomized trial** on the use of Doxycycline was conducted, external **registry data** was considered in addition[14]
- heterogeneity suspected between randomized and observational evidence
- both (randomized and observational) estimates were meta-analyzed using NNHM
- originally, interest was in overall effect (Θ)

[14] D. Varges et al. Doxycycline in early CJD – a double-blinded randomized phase II and observational study. *General Neurology* (accepted for publication).

Shrinkage estimation

The Creutzfeld-Jakob disease (CJD) example



Shrinkage estimation

two-study scenario

- consider: primary interest in randomized trial outcome
  (no “breaking of randomization” by pooled analysis)
- does it make sense to consider shrinkage estimates from a 2-study meta-analysis?
- how do shrinkage estimates behave in general?

Shrinkage estimation

two-study scenario

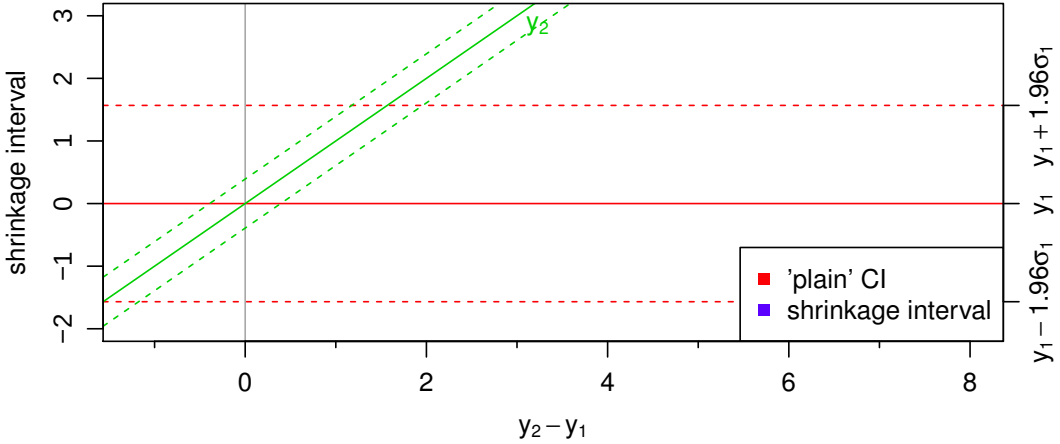
- consider: primary interest in randomized trial outcome
  (no “breaking of randomization” by pooled analysis)
- does it make sense to consider shrinkage estimates from a 2-study meta-analysis?
- how do shrinkage estimates behave in general?

- investigate example cases
- investigate long-run behaviour

- consider again pairs of studies
  $(n_1, n_2 \in \{25, 100, 400\},\ p(\tau) = \text{HN}(0.5), \ldots)$

Shrinkage estimation

two-study scenario



- $n_1 = 25,\ n_2 = 400,\ p(\tau) = \text{HN}(0.5)$, interested in θ_1

Shrinkage estimation

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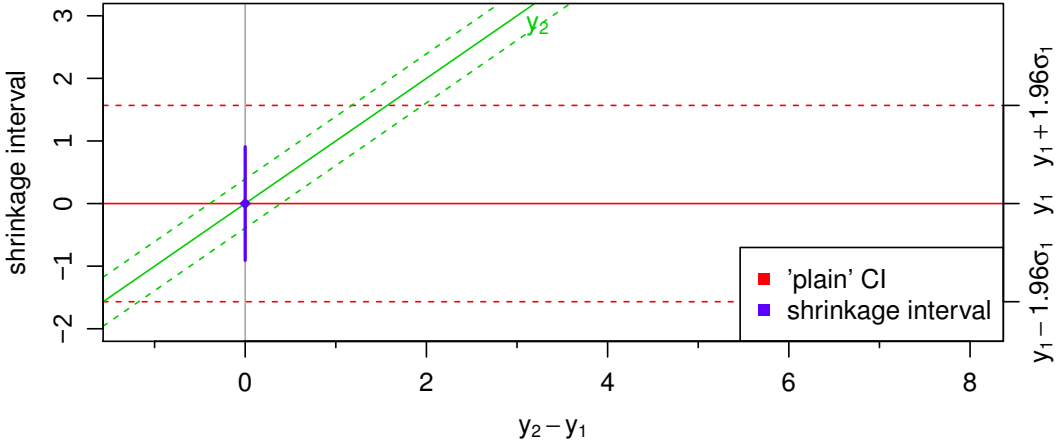

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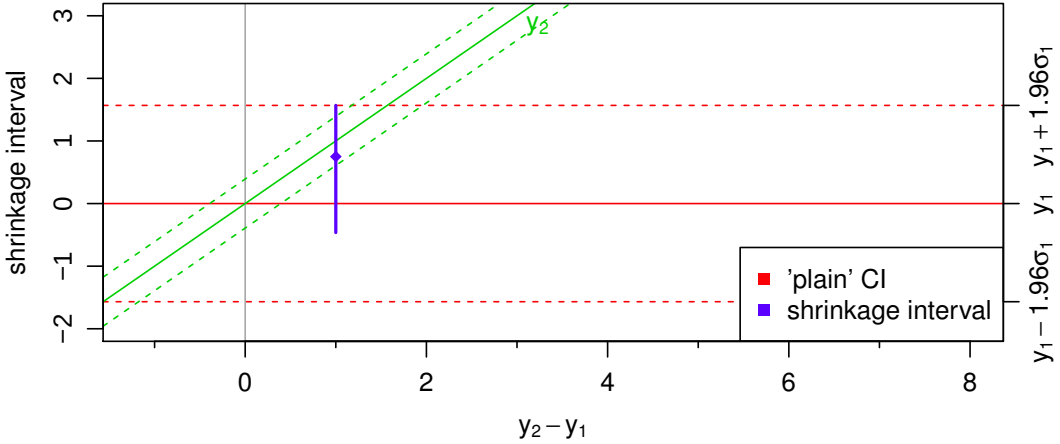

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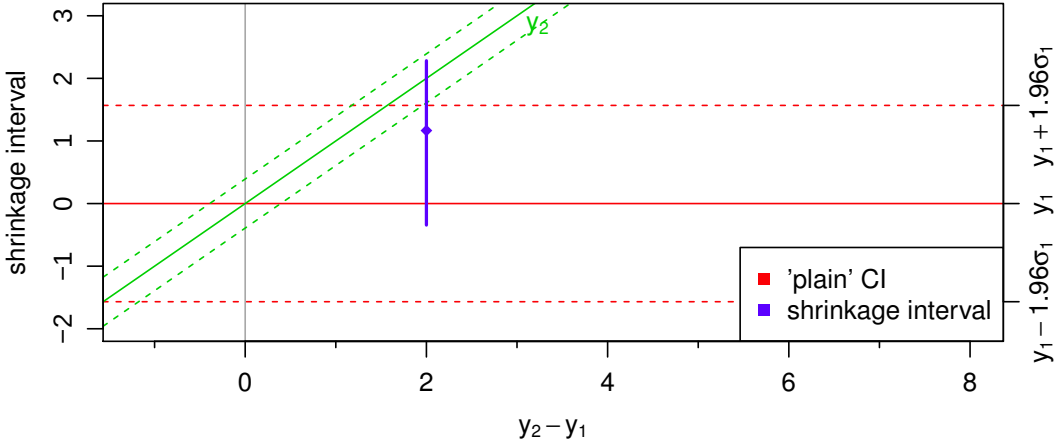

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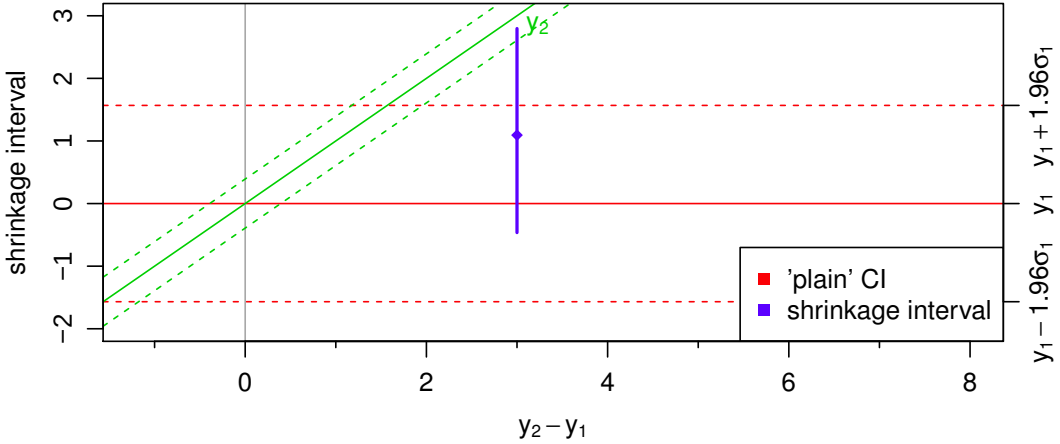

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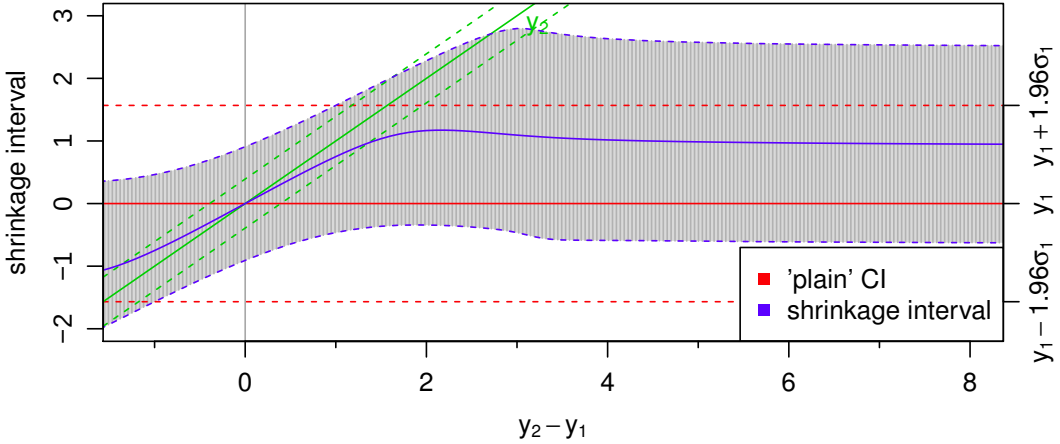
Shrinkage estimation

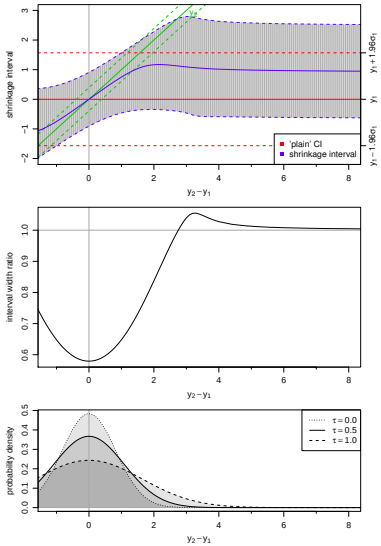
two-study scenario



- $n_1 = 25,\ n_2 = 400,\ p(\tau) = \text{HN}(0.5)$, interested in θ_1

Shrinkage estimation

two-study scenario



- 'robust' behaviour
- ratio of CI widths:
  gain may be substantial
- probability density of $(y_2 - y_1)$:
  unlikely to exceed $|y_2 - y_1| = 5$

Shrinkage estimation

two-study simulations

- how do shrinkage intervals behave *on average*?
- what gain can we expect (if any)?
- investigate:
  - coverage
  - interval width
- may translate shortened intervals into *sample size gain*
  (assuming standard errors scale approximately with $\frac{1}{\sqrt{n}}$), e.g.:
  relative interval with of 90% corresponds to a $(0.90^{-2} - 1) = 26\%$ gain in sample size

Shrinkage estimation

two-study simulations: coverage (%)

τ prior:		HN(0.5)							HN(1.0)						
n_1/n_2	τ:	0.0	0.1	0.2	0.5	1.0	2.0	$*$	0.0	0.1	0.2	0.5	1.0	2.0	$*$
25/400		99.8	99.5	99.0	93.4	84.1	79.4	94.7	99.4	99.2	99.1	96.6	92.6	90.8	95.1
25/100		98.7	98.8	98.3	93.6	86.1	79.9	95.1	98.3	98.7	98.5	96.3	93.2	90.4	94.4
100/400		98.5	98.1	97.2	93.3	90.7	90.6	94.9	98.0	97.6	97.3	95.1	93.5	93.6	95.3
25/25		96.7	96.8	96.1	94.6	90.4	84.5	95.0	97.1	97.1	96.6	95.8	94.1	92.1	94.9
100/100		96.8	96.7	96.4	94.0	91.3	91.0	95.7	96.7	96.6	96.8	95.3	93.8	93.8	94.9
400/400		96.9	96.7	95.0	93.9	93.9	94.1	95.0	96.6	96.6	95.0	94.7	94.9	95.0	95.0
100/25		96.0	95.8	95.1	94.8	93.9	92.6	94.7	96.0	95.9	95.4	95.2	94.8	94.4	94.8
400/100		95.2	95.8	95.2	94.8	93.7	93.8	95.1	95.4	95.7	95.3	95.1	94.4	94.6	95.1
400/25		95.2	94.9	95.3	94.7	94.8	94.5	95.3	95.1	94.9	95.3	94.8	94.9	95.2	95.2

$*$: heterogeneity τ drawn from prior distribution

Shrinkage estimation

two-study simulations: relative interval width (%)

τ prior:		HN(0.5)							HN(1.0)						
n_1/n_2	τ:	0.0	0.1	0.2	0.5	1.0	2.0	$*$	0.0	0.1	0.2	0.5	1.0	2.0	$*$
25/400		62.3	62.7	63.0	65.6	72.1	83.1	65.1	75.6	75.9	76.2	78.6	83.8	90.9	81.5
25/100		67.5	67.4	67.9	69.8	75.2	84.2	69.5	78.5	78.4	78.8	80.8	85.2	91.4	83.2
100/400		78.5	78.7	79.9	85.2	91.4	95.9	83.4	85.7	85.9	86.9	90.9	95.1	97.8	92.1
25/25		78.9	79.0	79.0	79.7	81.8	86.8	79.7	85.2	85.2	85.3	86.2	88.3	92.4	87.6
100/100		85.1	85.4	85.7	88.5	92.5	96.2	87.5	89.9	90.1	90.4	92.7	95.6	97.9	93.9
400/400		89.9	90.5	91.9	95.5	97.8	99.0	93.7	93.0	93.4	94.5	97.2	98.7	99.5	97.3
100/25		92.9	92.9	93.0	93.4	94.6	96.6	93.3	95.0	95.0	95.1	95.6	96.7	98.1	96.1
400/100		95.0	95.1	95.4	96.7	98.1	99.1	96.2	96.5	96.6	96.9	97.9	98.9	99.5	98.2
400/25		98.0	98.0	98.1	98.2	98.6	99.2	98.2	98.6	98.6	98.6	98.8	99.1	99.5	99.0

$*$: heterogeneity τ drawn from prior distribution

Shrinkage estimation

two-study simulations: relative sample size gain (%)

τ prior:		HN(0.5)							HN(1.0)						
n_1/n_2	τ:	0.0	0.1	0.2	0.5	1.0	2.0	$*$	0.0	0.1	0.2	0.5	1.0	2.0	$*$
25/400		162	160	158	144	113	68.4	147	77.8	76.5	75.4	67.1	50.5	28.8	58.3
25/100		123	123	121	111	89.6	56.3	113	64.8	65.0	63.6	57.1	43.5	25.6	50.0
100/400		64.5	64.0	60.0	43.8	25.7	12.7	49.4	37.4	37.1	34.3	23.9	13.3	6.2	20.7
25/25		61.2	60.9	60.7	58.4	51.8	36.9	58.7	38.7	38.5	38.1	35.8	30.0	19.6	32.2
100/100		38.8	38.1	37.1	29.6	19.4	10.1	32.3	24.4	23.8	23.0	17.4	10.7	5.3	14.8
400/400		24.2	22.9	19.4	11.0	5.5	2.4	15.1	16.1	15.1	12.5	6.6	3.1	1.3	6.3
100/25		15.9	16.0	15.8	14.8	11.9	7.5	14.9	10.9	10.9	10.7	9.6	7.2	4.2	8.4
400/100		11.0	10.7	10.0	7.3	4.2	2.0	8.3	7.4	7.2	6.6	4.5	2.5	1.1	3.9
400/25		4.1	4.1	4.0	3.7	2.9	1.7	3.7	2.9	2.8	2.8	2.5	1.8	1.0	2.1

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Shrinkage estimation

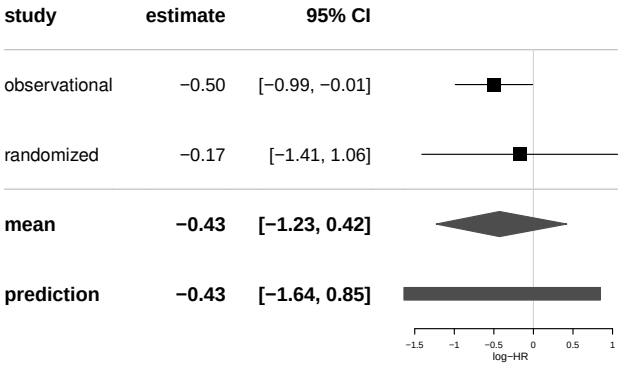
two-study simulations: fraction of shortened intervals (%)

τ prior:		HN(0.5)							HN(1.0)						
n_1/n_2	τ:	0.0	0.1	0.2	0.5	1.0	2.0	$*$	0.0	0.1	0.2	0.5	1.0	2.0	$*$
25/25		100.0	99.9	100.0	99.7	97.4	81.9	99.5	99.4	99.1	99.1	97.7	91.1	68.8	91.4
25/100		99.9	99.9	99.9	99.1	92.3	68.6	98.6	99.2	99.3	98.9	96.4	83.9	57.4	86.9
25/400		99.9	99.9	99.9	98.8	90.7	64.0	98.1	99.3	99.3	99.1	95.8	82.3	53.9	85.8
100/25		99.7	99.8	99.7	98.7	89.9	65.3	98.1	98.2	98.1	97.9	94.6	80.3	53.8	85.2
100/100		99.3	98.9	98.5	90.9	68.6	39.7	91.5	97.6	96.6	95.6	83.7	59.8	33.5	71.3
100/400		99.2	98.7	97.3	84.2	56.9	31.1	87.2	97.5	96.8	94.5	77.0	50.1	26.9	65.4
400/25		99.6	99.8	99.5	97.6	86.7	58.9	96.9	98.1	98.1	97.1	93.0	76.3	48.7	82.3
400/100		98.7	98.2	95.8	80.4	54.4	29.5	84.7	96.1	95.1	91.6	72.4	47.0	24.9	62.3
400/400		97.6	96.0	88.5	60.3	34.1	17.7	72.0	95.1	92.6	83.0	54.2	30.4	15.5	48.6

$*$: heterogeneity τ drawn from prior distribution

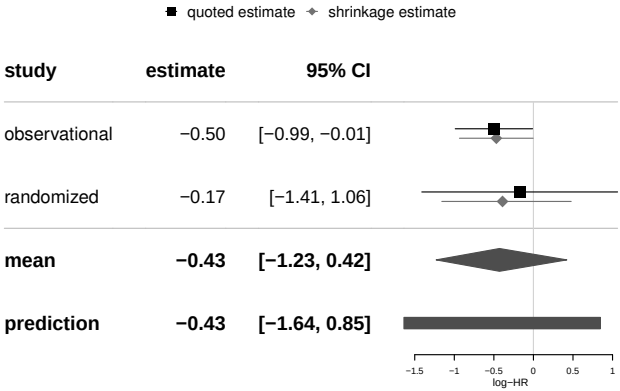
Shrinkage estimation

The Creutzfeld-Jakob disease (CJD) example



Shrinkage estimation

The Creutzfeld-Jakob disease (CJD) example



- shrinkage interval width: 66%, 129% gain in sample size (≈27 instead of 12 patients)

Conclusions II

Shrinkage estimates for 2 studies

- readily motivated
- robust behaviour
- potentially substantial gain despite 'pathological' setting ($k = 2$)
- especially if $\sigma_2 \leq \sigma_1$
- good coverage

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- ```
  install.packages("bayesmeta")
  library("bayesmeta")
  ```
  ```

+++ additional slides +++

CJD example

R code

```
cjd <- cbind.data.frame("study"    = c("observational", "randomized"),
                        "logHR"    = c(-0.49948, -0.17344),
                        "logHR.se" = c(0.2493, 0.6312), stringsAsFactors=FALSE)

# analyze:
require("bayesmeta")
bm <- bayesmeta(y         = cjd$logHR,
                sigma     = cjd$logHR.se,
                labels    = cjd$study,
                tau.prior = function(t){dhalfnormal(t, scale=0.5)})

# show results:
print(bm)

# show forest plot:
forestplot(bm, xlab="log-HR")
forestplot(bm, exponentiate=TRUE, xlog=TRUE, xlab="hazard ratio")

# show shrinkage estimates:
print(bm$theta)
```