Meta-analysis of two studies in the presence of heterogeneity with applications in rare diseases

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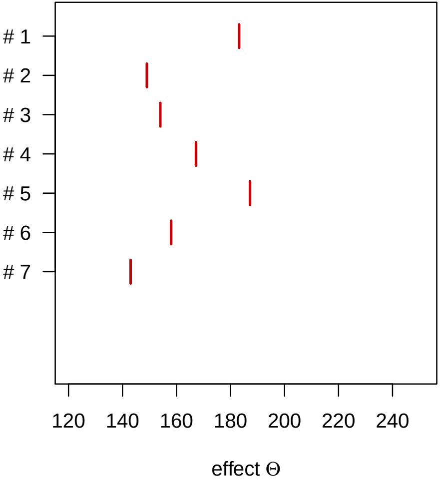
Overview

- meta-analysis
- frequentist and Bayesian approaches
- two-study meta-analysis
- examples
- simulation study
- 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

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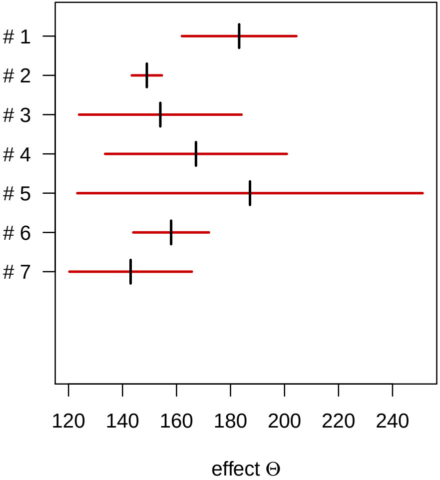

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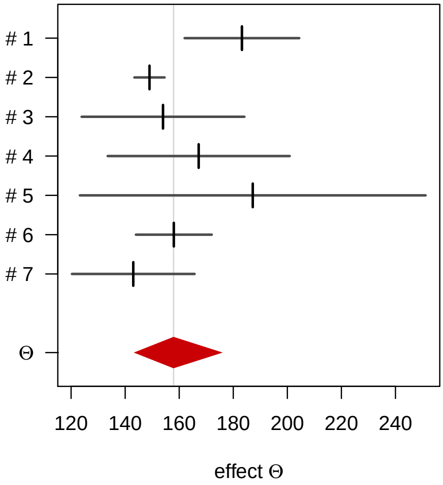

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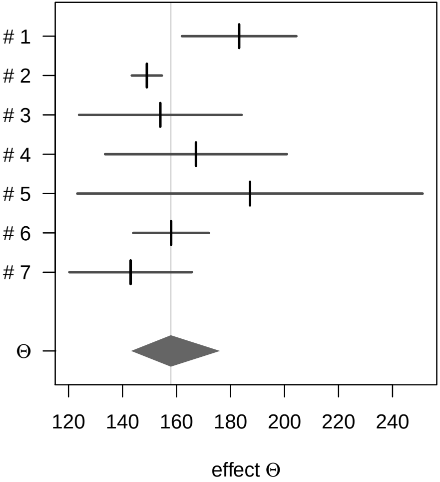

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Meta analysis

The random-effects model

- assume *normal-normal hierarchical model (NNHM)*[1]:

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

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

- model components:

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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(uncertainty in τ not accounted for)

- Hartung-Knapp-Sidik-Jonkman approach (accounting for τ estimation uncertainty)[2]:
  - 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:
$$\hat{\Theta} \;\pm\; \sqrt{q}\,\hat{\sigma}_{\Theta}\; t_{(k-1);(1-\alpha/2)}$$

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

[3] 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.

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$$\hat{\Theta} \;\pm\; \sqrt{q}\,\hat{\sigma}_{\Theta}\; t_{(k-1);(1-\alpha/2)}$$
- *modified* Knapp-Hartung approach[3]:
  - 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 [4]
  - set up model likelihood (same as frequentist)
  - specify prior information about unknowns (Θ, τ)
  - posterior: $\propto$ prior $\times$ likelihood
  - inference requires integrals, e.g. $p(\Theta \,|\, y, \sigma) \;=\; \int p(\Theta, \tau \,|\, y, \sigma)\, \mathrm{d}\tau \ldots$
  - use numerical methods for integration (MCMC, `bayesmeta` R package[5], ...)

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

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

- Frequentist approach:
  - relies on asymptotics (Normal or Student-*t* approximation)
  - normal approximation neglects uncertainty in heterogeneity: too liberal for few studies
  - Student-*t* approximation tends to be conservative for few studies[6]

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[7] T. C. Smith, D. J. Spiegelhalter, A. Thomas. *Bayesian approaches to random-effects meta-analysis: A comparative study*. Statistics in Medicine, 14(24):2685, 1995.

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- Bayesian approach:
  - consideration of prior information
  - propagation of uncertainty
  - straightforward interpretation
  - computationally more expensive, usually done via simulation (MCMC, BUGS)[7]
  - special case of simple random-effects MA may be solved semi-analytically (using `bayesmeta` R package)[8]

[6] 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.

[7] T. C. Smith, D. J. Spiegelhalter, A. Thomas. *Bayesian approaches to random-effects meta-analysis: A comparative study*. Statistics in Medicine, 14(24):2685, 1995.

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- *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[9]
- frequentist methods run into problems for few studies (small k)
- two-study case: no satisfactory frequentist procedure[10]
- despite extreme setting, error control crucial[11]

[9] 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.

[10] 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

[11] 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.

- part of frequentist methods' problem:
  estimation of heterogeneity parameter ($\tau \geq 0$)
  and consideration of its uncertainty
- not a problem for Bayesian methods;
  also: consideration of prior information on plausible τ values
- have: long-run properties of Bayesian methods[12]
- how do methods compare for the extreme (but common) case of $k = 2$?
  $\rightarrow$ investigate corresponding estimates and intervals

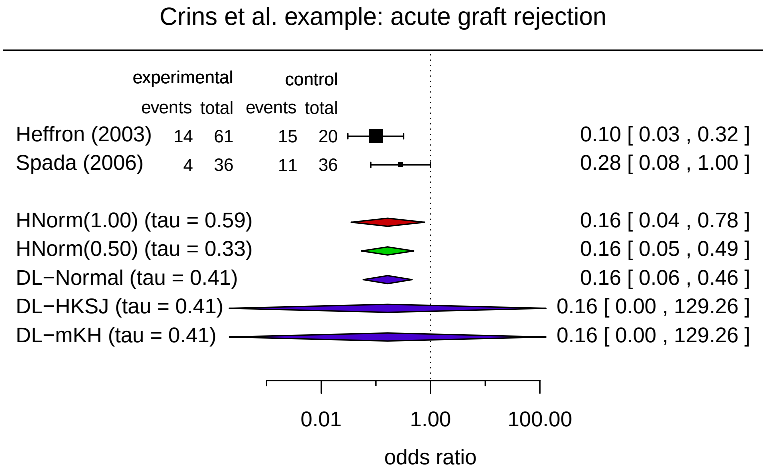
[12] T. Friede, C. Röver, S. Wandel, B. Neuenschwander. Meta-analysis of few small studies in orphan diseases. *Research Synthesis Methods*, (in press), 2016.

- two examples of two-study meta-analyses[13,14]
- 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[15]

[13] 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.

[14] 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).

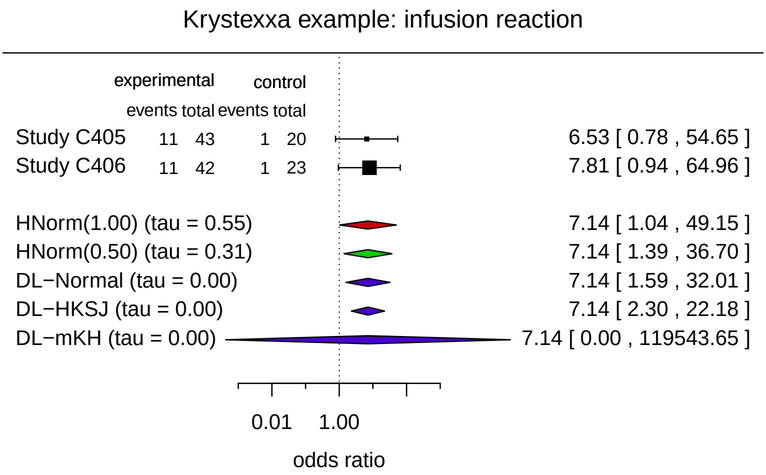
[15] A.L. Rukhin. Estimating common mean and heterogeneity variance in two study case meta-analysis. *Statistics & Probability Letters* 82(7):1318-1325, 2012.



Crins et al. example: acute graft rejection
experimental
control
events total events total
Heffron (2003) 14 61 15 20
Spada (2006) 4 36 11 36
0.10 [0.03 , 0.32]
0.28 [0.08 , 1.00]
HNorm(1.00) (tau = 0.59)
HNorm(0.50) (tau = 0.33)
DL−Normal (tau = 0.41)
DL−HKSJ (tau = 0.41)
DL−mKH (tau = 0.41)
0.16 [0.04 , 0.78]
0.16 [0.05 , 0.49]
0.16 [0.06 , 0.46]
0.16 [0.00 , 129.26]
0.16 [0.00 , 129.26]
0.01
1.00
100.00
odds ratio

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

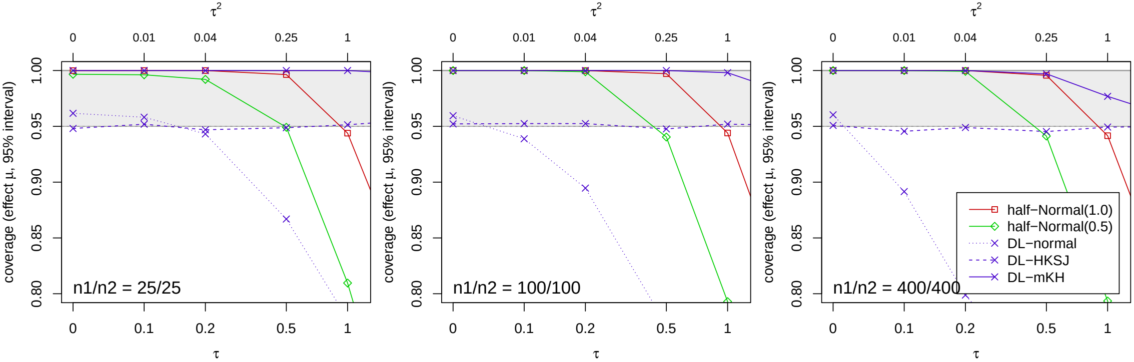
heterogeneity estimation: **zero estimates**

- 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

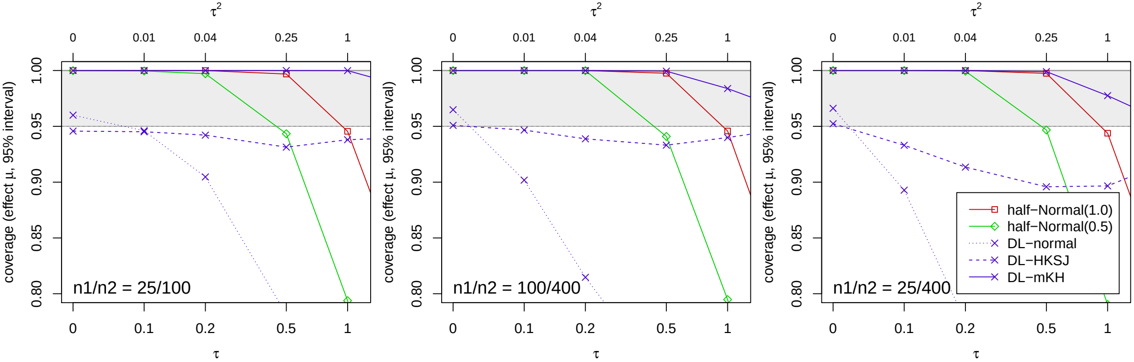
effect CI coverage (two equal-sized studies)



- undercoverage for normal approx.

Simulation study

effect CI coverage (two unequal-sized studies)



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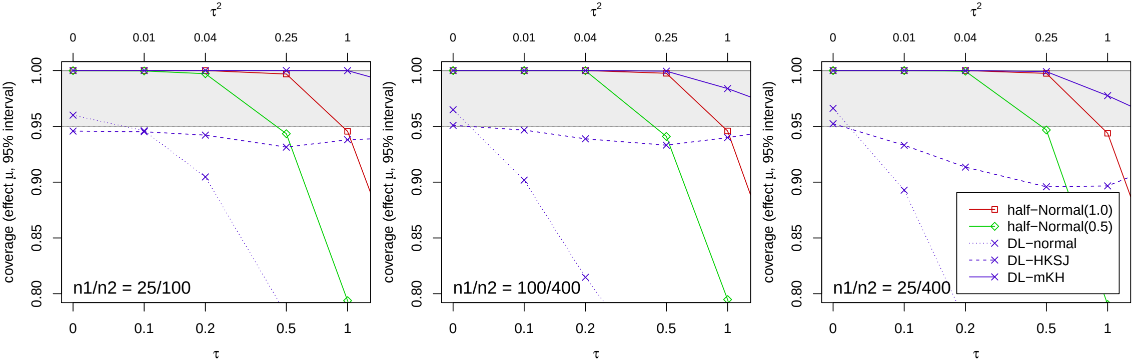
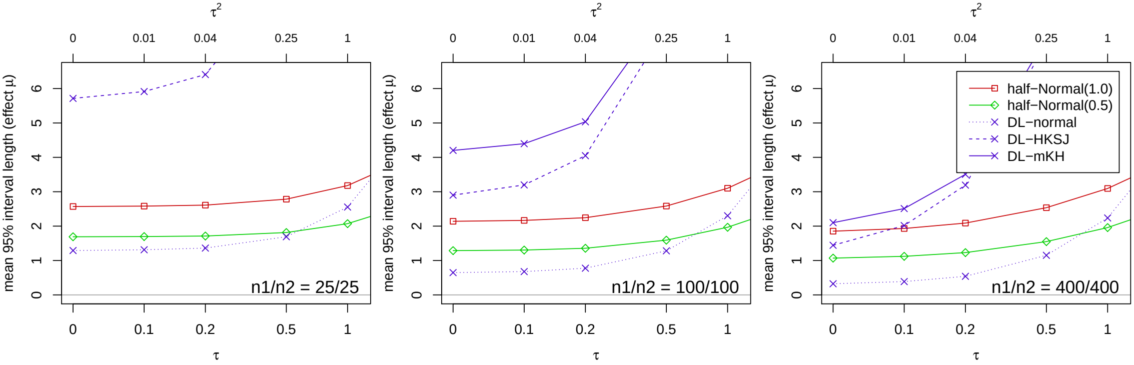


- undercoverage for normal approx.
- undercoverage for HKSJ at unequal sizes
- Bayesian intervals as expected
- mKH very conservative

Simulation study

effect CI length (two equal-sized studies)



Simulation study

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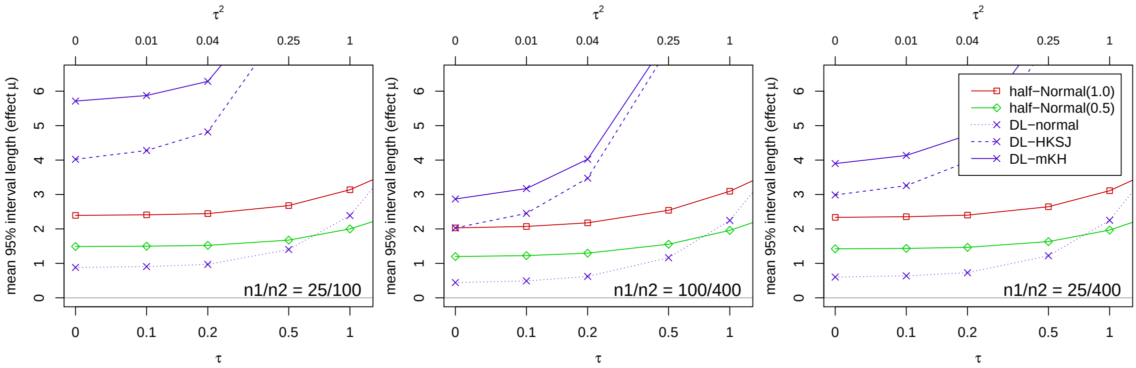

- substantially shorter intervals for Bayesian methods

Conclusions

- 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[16]

[16] 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. Preprint: `http://arxiv.org/abs/1606.04969`.