Dynamische Unterstützung durch Shrinkage-Schätzung zur Verknüpfung von randomisierten und nicht-randomisierten Studien

Christian Röver

UNIVERSITÄTSMEDIZIN GÖTTINGEN UMG

Department of Medical Statistics,
University Medical Center Göttingen,
Göttingen, Germany

GMDS 2025, Jena
September 9, 2025

Dynamic borrowing through shrinkage estimation to link randomized and non-randomized studies

- **hierarchical models** useful for implementing **similarity** / **correlation**
- **meta-analysis** methods generally aimed at combining **several** ($k > 1$) estimates
- special case: **two** ($k = 2$) estimates
  - any considerations of "similarity" / "correlation" / "heterogeneity" relate to considered **pair**
  - conventions / tools familiar from meta-analysis remain available
  - close links exist to related borrowing approaches

Normal-normal hierarchical model

Introduction

- use of the **normal-normal hierarchical model (NNHM)** common (normal approximation for **uncertainty** and heterogeneity)

$$
\begin{aligned}
y_i|\theta_i &\sim \mathrm{Normal}(\theta_i, s_i^2), \\
\theta_i|\mu,\tau &\sim \mathrm{Normal}(\mu, \tau^2), \quad i \in \{1,\ldots,k\}
\end{aligned}
$$

Normal-normal hierarchical model

- use of the **normal-normal hierarchical model (NNHM)** common (normal approximation for uncertainty and **heterogeneity**)

$$\begin{aligned} y_i|\theta_i &\sim \mathrm{Normal}(\theta_i, s_i^2), \\ \theta_i|\mu,\tau &\sim \mathrm{Normal}(\mu, \tau^2), \qquad i \in \{1, \ldots, k\} \end{aligned}$$

- use of the **normal-normal hierarchical model (NNHM)** common (normal approximation for uncertainty and heterogeneity)

$$
\begin{aligned}
y_i|\theta_i &\sim \mathrm{Normal}(\theta_i, s_i^2), \\
\theta_i|\mu, \tau &\sim \mathrm{Normal}(\mu, \tau^2), \quad i \in \{1, \ldots, k\}
\end{aligned}
$$

Normal-normal hierarchical model

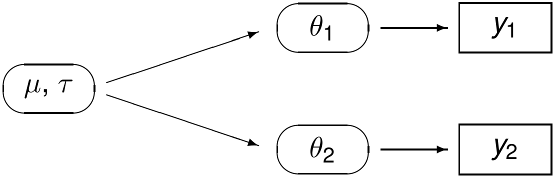
Introduction

- use of the **normal-normal hierarchical model (NNHM)** common (normal approximation for uncertainty and heterogeneity)

$$\begin{aligned} y_i|\theta_i &\sim \mathrm{Normal}(\theta_i, s_i^2), \\ \theta_i|\mu,\tau &\sim \mathrm{Normal}(\mu, \tau^2), \quad i \in \{1,2\} \end{aligned}$$

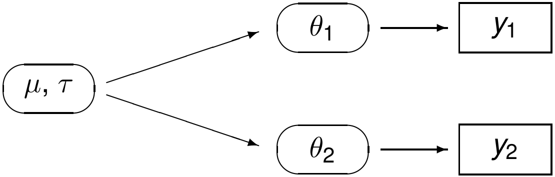
- use of the **normal-normal hierarchical model (NNHM)** common (normal approximation for uncertainty and heterogeneity)

$$\begin{aligned} y_i|\theta_i &\sim \mathrm{Normal}(\theta_i, s_i^2), \\ \theta_i|\mu,\tau &\sim \mathrm{Normal}(\mu, \tau^2), \quad i \in \{1,2\} \end{aligned}$$



- use of the **normal-normal hierarchical model (NNHM)** common (normal approximation for uncertainty and heterogeneity)

$$\begin{aligned} y_i|\theta_i &\sim \mathrm{Normal}(\theta_i, s_i^2), \\ \theta_i|\mu,\tau &\sim \mathrm{Normal}(\mu, \tau^2), \quad i \in \{1,2\} \end{aligned}$$



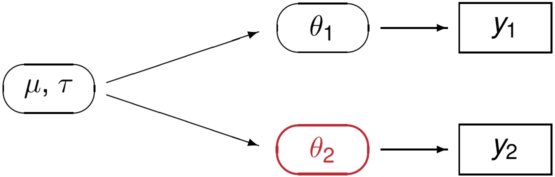
- "source" ($i = 1$) and "target" ($i = 2$) studies

Normal-normal hierarchical model

Introduction

- use of the **normal-normal hierarchical model (NNHM)** common (normal approximation for uncertainty and heterogeneity)

$$
\begin{aligned}
y_i|\theta_i &\sim \text{Normal}(\theta_i, s_i^2), \\
\theta_i|\mu,\tau &\sim \text{Normal}(\mu, \tau^2), \quad i \in \{1,2\}
\end{aligned}
$$



- "source" ($i = 1$) and "target" ($i = 2$) studies
- aim: **shrinkage estimate** (of target θ_2)

Normal-normal hierarchical model

Motivation: the bias allowance connection

- Why use a hierarchical model? Why introduce an "overall mean" μ?

[1] C. Röver, T. Friede. Dynamically borrowing strength from another study through shrinkage estimation. *Statistical Methods in Medical Research*, **29**(1):293–308, 2020.

Normal-normal hierarchical model

Motivation: the bias allowance connection

- Why use a hierarchical model? Why introduce an "overall mean" μ?
- **hierarchical model**

$$\begin{aligned} y_i|\theta_i &\sim \mathrm{Normal}(\theta_i, s_i^2), \\ \theta_i|\mu,\tau &\sim \mathrm{Normal}(\mu,\tau^2), \quad i \in \{1,2\} \end{aligned}$$

[1]

[1] C. Röver, T. Friede. Dynamically borrowing strength from another study through shrinkage estimation. *Statistical Methods in Medical Research*, **29**(1):293–308, 2020.

Normal-normal hierarchical model

Motivation: the bias allowance connection

- Why use a hierarchical model? Why introduce an "overall mean" μ?
- **hierarchical model**

$$\begin{aligned} y_i|\theta_i &\sim \mathrm{Normal}(\theta_i, s_i^2), \\ \theta_i|\mu,\tau &\sim \mathrm{Normal}(\mu, \tau^2), \quad i \in \{1,2\} \end{aligned}$$

is equivalent to a **bias allowance model**:

$$\begin{aligned} y_i|\theta_i &\sim \mathrm{Normal}(\theta_i, s_i^2), \\ \theta_2|\mu,\tau &= \mu \\ \theta_1|\mu,\tau &\sim \mathrm{Normal}(\mu, 2\tau^2) \end{aligned}$$

(as far as shrinkage estimates (θ_i) are concerned)

(and as long as an improper uniform prior is used for μ)[1]

[1] C. Röver, T. Friede. Dynamically borrowing strength from another study through shrinkage estimation. *Statistical Methods in Medical Research*, **29**(1):293–308, 2020.

Normal-normal hierarchical model

Motivation: the power prior connection

- the **power prior** would apply an **exponent** a_0 $(0 \leq a_0 \leq 1)$ to the source study's likelihood contribution [2]
- in the NNHM, this corresponds to setting a (fixed) **heterogeneity** $\left(\tau = \sqrt{\frac{s^2}{2}\left(\frac{1}{a_0} - 1\right)}\right.$ or $\left. a_0 = \left(\frac{\tau^2}{s_1^2} + 1\right)^{-1}\right)$
- one-to-one correspondence $(\tau \leftrightarrow a_0)$ $\rightarrow$ assuming a prior for τ implies a prior for a_0 [3]
- prior specification "as usual" in NNHM [4]

---

[2] J. G. Ibrahim, M.-H. Chen. Power prior distributions for regression models. *Statistical Science*. 2000;**15**(1):46–60.
[3] C. Röver, T. Friede. Meta-analytic-predictive priors based on a single study. `arXiv:2505.15501`, 2025.
[4] C. Röver, R. Bender, S. Dias, C.H. Schmid, H. Schmidli *et al*. On weakly informative prior distributions for the heterogeneity parameter in Bayesian random-effects meta-analysis. *Research Synthesis Methods*, **12**(4):448–474, 2021.

Normal-normal hierarchical model

Motivation: the MAP prior relationship

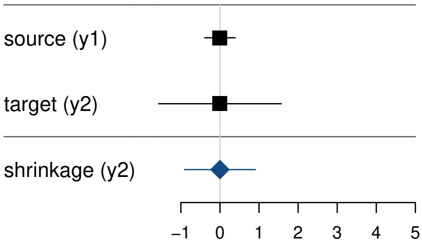
- Schmidli *et al.* (2014)[5] pointed out that for a **shrinkage estimate**, the posterior may be **factored** into contributions by
  - ith study (data y_i likelihood), and
  - $k-1$ remaining studies (meta-analytic-predictive (**MAP**) **prior**)
- idea works also for $k=2$ studies [6]
  (even if the MAP prior then refers to a *meta-analysis of a single study*)
- MAP prior allows to illustrate / communicate / scrutinize / quantify prior information contributed by "source" study.

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

[6] C. Röver, T. Friede. Meta-analytic-predictive priors based on a single study. `arXiv:2505.15501`, 2025.

Shrinkage estimation

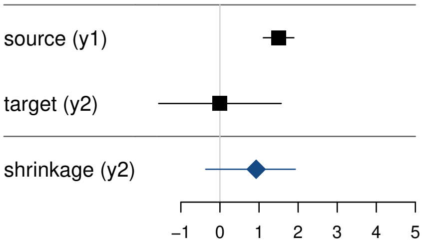
How does it work?



- consider example with "large" source data ($s_1 = 0.2$) and "small" target ($s_2 = 0.8$)
  (motivation: log-OR outcomes, $n_1 = 400$ vs. $n_2 = 25$ patients, $\tau \sim$ half-Normal(0.5) prior)
- precision gain

Shrinkage estimation

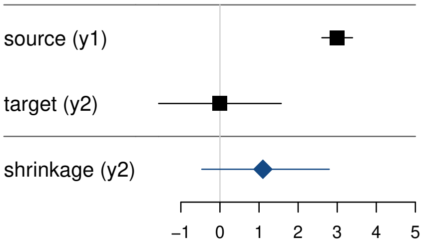
How does it work?



- consider example with "large" source data ($s_1 = 0.2$) and "small" target ($s_2 = 0.8$)
  (motivation: log-OR outcomes, $n_1 = 400$ vs. $n_2 = 25$ patients, $\tau \sim$ half-Normal(0.5) prior)
- precision gain
- **shrinkage estimate** as a "compromise" . . .

Shrinkage estimation

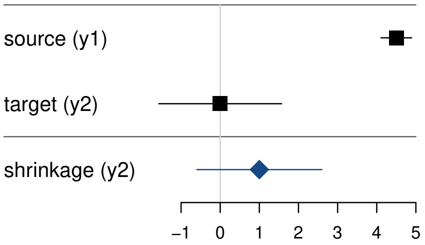
How does it work?



- consider example with "large" source data ($s_1 = 0.2$) and "small" target ($s_2 = 0.8$)
  (motivation: log-OR outcomes, $n_1 = 400$ vs. $n_2 = 25$ patients, $\tau \sim$ half-Normal(0.5) prior)
- precision gain
- **shrinkage estimate** as a "compromise" . . .
  . . . but "source" influence (+precision gain) vanish with increasing discrepancy

Shrinkage estimation

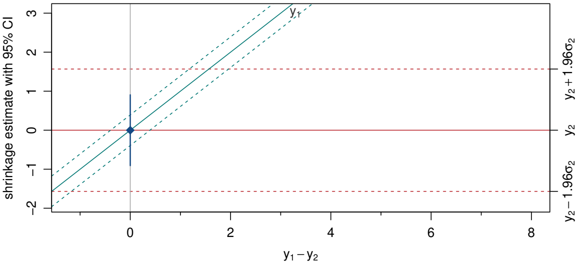
How does it work?



- consider example with "large" source data ($s_1 = 0.2$) and "small" target ($s_2 = 0.8$)
  (motivation: log-OR outcomes, $n_1 = 400$ vs. $n_2 = 25$ patients, $\tau \sim$ half-Normal(0.5) prior)
- precision gain
- **shrinkage estimate** as a "compromise" . . .
  . . . but "source" influence (+precision gain) vanish with increasing discrepancy
- "dynamic" behaviour

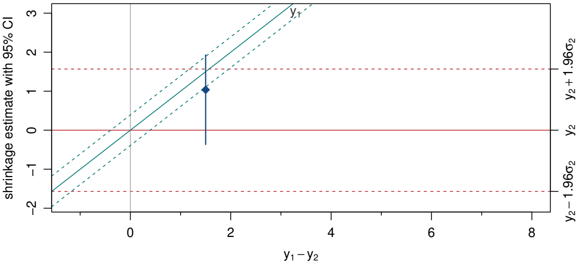
Shrinkage estimation

“Dynamic” borrowing



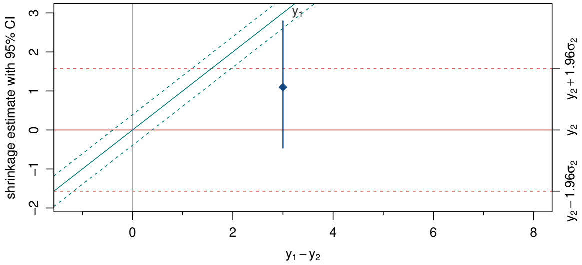
Shrinkage estimation

"Dynamic" borrowing



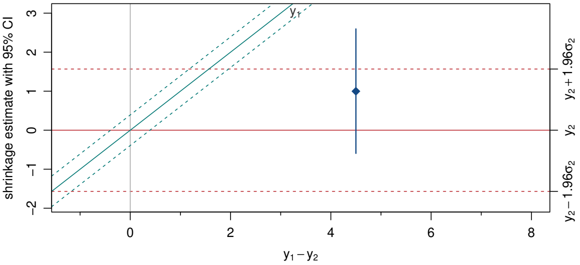
Shrinkage estimation

“Dynamic” borrowing



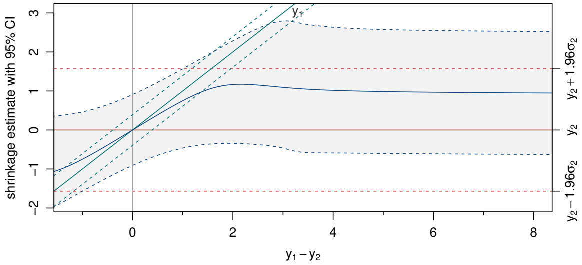
Shrinkage estimation

"Dynamic" borrowing



Shrinkage estimation

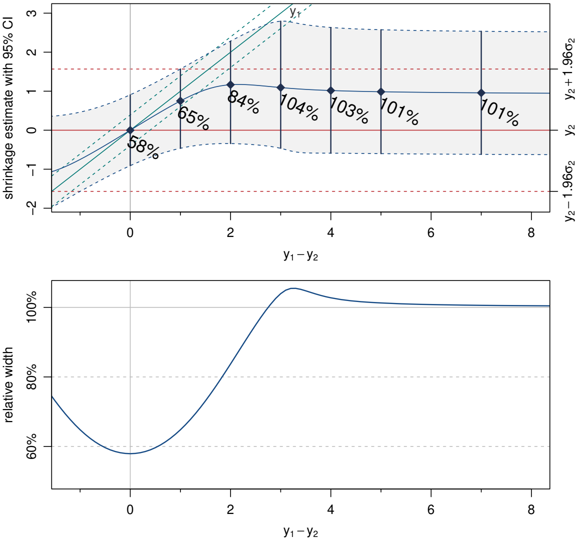
“Dynamic” borrowing



- “dynamic” behaviour

Shrinkage estimation

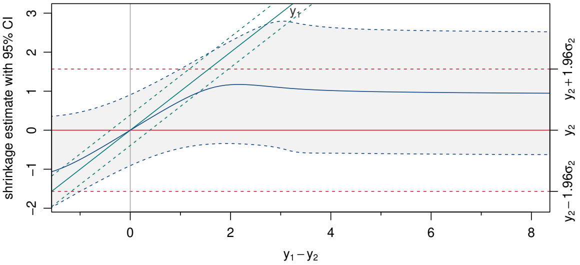
“Dynamic” borrowing

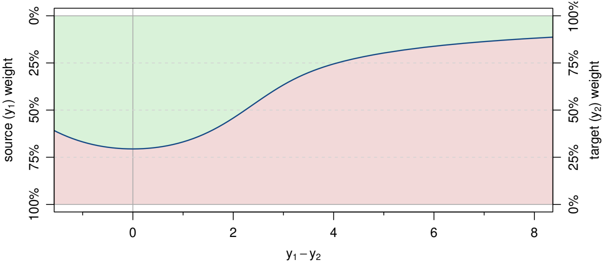


- “dynamic” behaviour
- shrinkage **interval width**: substantial gains

Shrinkage estimation

“Dynamic” borrowing

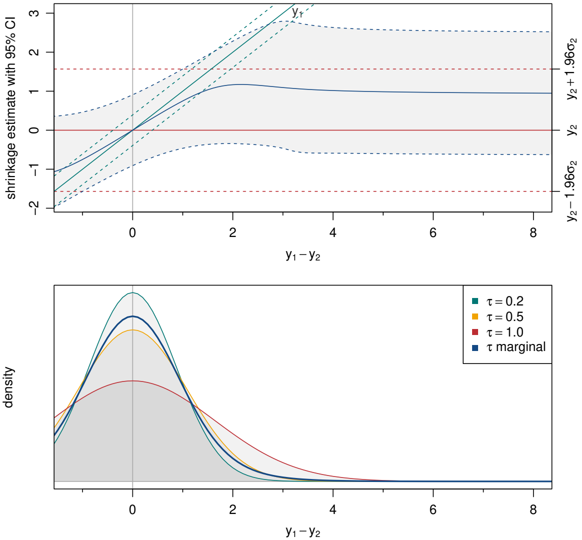




- “dynamic” behaviour
- shrinkage **interval width**: substantial gains
- “**weight**” contribution of source (y_1) to shrinkage estimate (θ_2) depends on discrepancy ($y_1 - y_2$)

Shrinkage estimation

“Dynamic” borrowing

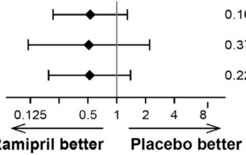


- “dynamic” behaviour
- shrinkage **interval width**: substantial gains
- “**weight**” contribution of source (y_1) to shrinkage estimate (θ_2) depends on discrepancy ($y_1 - y_2$)
- only central region relevant (if prior is taken seriously)

Alport example

Meta-analysis of two HRs, shrinkage estimation

Efficacy	Ramipril		Placebo		Hazard ratio (95% CI)	P
	Events/ N (%)					
Disease progression (Non-RCT)	17/42	(40.5)	12/28	(42.9)	0.53 (0.22, 1.29)	0.16
Disease progression (RCT)	3/11	(27.3)	5/9	(55.6)	0.51 (0.12, 2.20)	0.37
Disease progression (RCT shrinkage estimate)					0.52 (0.19, 1.39)	0.22



- Gross *et al.* (2020)[7] performed a **meta-analysis** of two (*observational* and *RCT*) estimates to derive a **shrinkage estimate** for an RCT in Alport syndrome (endpoint: hazard ratio (HR), *time to disease progression*, using a HN(0.5) prior for τ)

[7] O. Gross B. Tönshoff, L.T. Weber *et al.* A multicenter, randomized, placebo-controlled, double-blind phase 3 trial with open-arm comparison indicates safety and efficacy of nephroprotective therapy with ramipril in children with Alport's syndrome. *Kidney International*, **97**(6):1275–1286, 2020. (Figure 2b).

- Alport example setup:

			hazard ratio		log-HR			
i	estimate	n_i	HR	95% CI	estimate	95% CI	y_i	s_i
1	observational	70	0.53	[0.22, 1.29]	-0.63	[-1.52, 0.25]	-0.635	0.451
2	RCT	20	0.51	[0.12, 2.20]	-0.67	[-2.13, 0.78]	-0.673	0.742
2	shrinkage		0.52	[0.20, 1.39]	-0.65	[-1.63, 0.33]		

Alport example

Setup

- Alport example setup:

			hazard ratio		log-HR			
i	estimate	n_i	HR	95% CI	estimate	95% CI	y_i	s_i
1	observational	70	0.53	[0.22, 1.29]	-0.63	[-1.52, 0.25]	-0.635	0.451
2	RCT	20	0.51	[0.12, 2.20]	-0.67	[-2.13, 0.78]	-0.673	0.742
2	shrinkage		0.52	[0.20, 1.39]	-0.65	[-1.63, 0.33]		

- interval substantially shorter ([-1.63, 0.33] instead of [-2.13, 0.78]):
  $\rightarrow$ width reduced to 67%

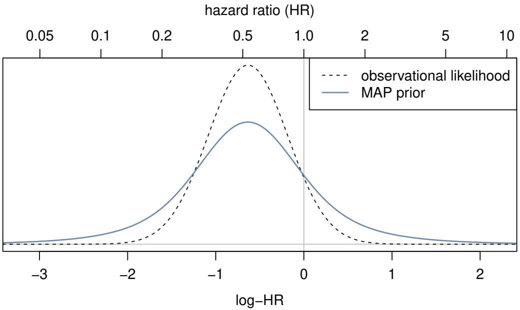
Alport example

Setup

- Alport example setup:

			hazard ratio		log-HR			
i	estimate	n_i	HR	95% CI	estimate	95% CI	y_i	s_i
1	observational	70	0.53	[0.22, 1.29]	-0.63	[-1.52, 0.25]	-0.635	0.451
2	RCT	20	0.51	[0.12, 2.20]	-0.67	[-2.13, 0.78]	-0.673	0.742
2	shrinkage		0.52	[0.20, 1.39]	-0.65	[-1.63, 0.33]		

- interval substantially shorter ([-1.63, 0.33] instead of [-2.13, 0.78]):
  $\rightarrow$ width reduced to 67%
- precision gain corresponds to “effective sample size gain” of $+120\%$
  ($=$ 24 “extra patients”)



- “observational” evidence may be expressed in terms of meta-analytic-predictive (**MAP**) **prior** for RCT effect [8]
- effective sample size ($\mathrm{ESS}_{\mathrm{ELIR}}$): 26 patients

[8] C. Röver, T. Friede. Meta-analytic-predictive priors based on a single study. `arXiv:2505.15501`, 2025.

Alport example
Operating characteristics

- assume $s_1 = 0.451$, $s_2 = 0.742$ (as in Alport application),
- use half-Normal(0.5) heterogeneity prior for analysis (“**analysis prior**”) and data generation (“**design prior**”)

τ prior		coverage	CI width	sample size
analysis	design	(95% CI)	(median)	gain (median)
HN(0.5)	HN(0.5)	94.8%	0.701	103%
HN(0.2)	HN(0.2)	94.9%	0.576	201%
HN(1.0)	HN(1.0)	94.9%	0.818	49%
HN(0.5)	HN(0.2)	97.5%	0.694	107%
HN(0.5)	HN(1.0)	91.1%	0.717	95%

Alport example
Operating characteristics

- assume $s_1 = 0.451$, $s_2 = 0.742$ (as in Alport application),
- use half-Normal(0.5) heterogeneity prior for analysis (“**analysis prior**”) and data generation (“**design prior**”)

τ prior		coverage	CI width	sample size
analysis	design	(95% CI)	(median)	gain (median)
HN(0.5)	HN(0.5)	94.8%	0.701	103%
HN(0.2)	HN(0.2)	94.9%	0.576	201%
HN(1.0)	HN(1.0)	94.9%	0.818	49%
HN(0.5)	HN(0.2)	97.5%	0.694	107%
HN(0.5)	HN(1.0)	91.1%	0.717	95%

- “more borrowing” in case of less heterogeneity
- stochastically larger / smaller analysis priors lead to conservative / anticonservative behaviour

Shrinkage estimation / MAP prior
Robustification

- additional option to implement robust behaviour: two-component mixture likelihood [9]
- explicit consideration of **two hypotheses**: *source* and *target* are related / unrelated
- target **prior** results as **two-component mixture** (informative (MAP) vs. vague)
- need to specify probabilities (“mixture weights”) and uninformative prior component
- prior specification non-trivial (Lindley’s paradoxical effects lurking)

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

Dynamic borrowing via the NNHM

Summary

- special ($k = 2$) case of a meta-analysis applications
  (software, guidance, etc. available)
- connections to **related methods** (bias allowance, power prior, . . .)
- explicit reference to corresponding **MAP prior** possible
- heavy-tailed MAP prior ensures **robust behaviour**
  (current data not "swamped" by historical data)
- option to implement additional scepticism via **robustification**

References

- C. Röver, T. Friede. Dynamically borrowing strength from another study through shrinkage estimation. *Statistical Methods in Medical Research*, **29**(1):293–308, 2020.
- C. Röver, T. Friede. Bounds for the weight of external data in shrinkage estimation. *Biometrical Journal*, **65**(5):1131–1143, 2021.
- C. Röver, R. Bender, S. Dias, C.H. Schmid, H. Schmidli *et al.* On weakly informative prior distributions for the heterogeneity parameter in Bayesian random-effects meta-analysis. *Research Synthesis Methods*, **12**(4):448–474, 2021.
- C. Röver, T. Friede. Meta-analytic-predictive priors based on a single study. `arXiv:2505.15501`, 2025.
- C. Röver. Bayesian random-effects meta-analysis using the `bayesmeta` R package. *Journal of Statistical Software*, **93**(6), 2020.

GMDS Academy 2025

Three parallel workshops, 20 participants each:

Workshop 1:

Meta-analysis

Speaker:
- Wolfgang Viechtbauer (Maastricht University)
- Christian Röver (UMG Göttingen)
- Sebastian Weber (Novartis Basel)

Workshop 2:

Causal inference

Speaker:
- Vanessa Didelez (BIPS Bremen)
- Arthur Allignol (Daiichi Sankyo)
- Oliver Kuß (DDZ Düsseldorf)
- Alexandra Strobel (UMH Halle)

Workshop 3:

Time-to-event analysis

Speaker:
- Hannes Buchner (Staburo München)
- Xiaofei Liu (MHH Hannover)
- Ann-Kathrin Ozga (UKE Hamburg)

+++ additional slides +++

Heterogeneity priors[10]

TABLE 2 Categories of heterogeneity and corresponding τ ranges in the context of log-ORs, according to Spiegelhalter *et al.* (2004).[15] Sec. 5.7

category	range
"reasonable"	$0.1 < \tau < 0.5$
"fairly high"	$0.5 < \tau < 1.0$
"fairly extreme"	$\tau > 1.0$

TABLE 3 Implications of a range of half-normal heterogeneity priors $p(\tau)$ on probable values of heterogeneity τ and predicted effects θ_i (*marginal* prior predictive distributions). The three rightmost columns show the corresponding probabilities for the three categories from Table 2.

	heterogeneity τ			95% predictive interval		category probability (%)		
$p(\tau)$	median	mean	95% quant.	$\theta_i - \mu$	$\exp(\theta_i - \mu)$	reason-able	fairly high	fairly extreme
half-normal(0.1)	0.07	0.08	0.20	[-0.22, 0.22]	[0.80, 1.24]	32	0	0
half-normal(0.2)	0.13	0.16	0.39	[-0.44, 0.44]	[0.65, 1.55]	60	1	0
half-normal(0.5)	0.34	0.40	0.98	[-1.09, 1.09]	[0.34, 2.98]	52	27	5
half-normal(1.0)	0.67	0.80	1.96	[-2.18, 2.18]	[0.11, 8.89]	30	30	32
half-normal(2.0)	1.35	1.60	3.92	[-4.37, 4.37]	[0.013, 79.0]	16	19	62

[10] C. Röver, R. Bender, S. Dias, C.H. Schmid, H. Schmidli *et al.* On weakly informative prior distributions for the heterogeneity parameter in Bayesian random-effects meta-analysis. *Research Synthesis Methods*, **12**(4):448–474, 2021.