Cochrane Training

A day with... Statistical Methods Group (SMG)

IQWiG

The empirical distribution of τ from IQWiG reports for the application in Bayesian random-effects meta-analyses

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Outline

- Introduction
  - Meta-analysis with very few studies
  - Example
  - Bayesian methods
- Methods
  - Suggestions for prior distributions
  - Meta-analyses from IQWiG reports
- Results
- Interim conclusion
- Outlook
- References

Introduction

Situation

- Fixed-effect (FE) model
  - Assumption: No true heterogeneity
  - Frequently not adequate
- **Random-effects (RE) model**
  - Assumption: True heterogeneity (not too large)
  - Knapp-Hartung (KH) method recommended (Veroniki et al., 2019)
  - Problem: In the case of very few (2-4) studies τ cannot be estimated reliably (Bender et al., 2018)

→ KH method is over-conservative in the case of very few studies

Currently we apply FEM or a qualitative evidence synthesis, but this is circumstantial …

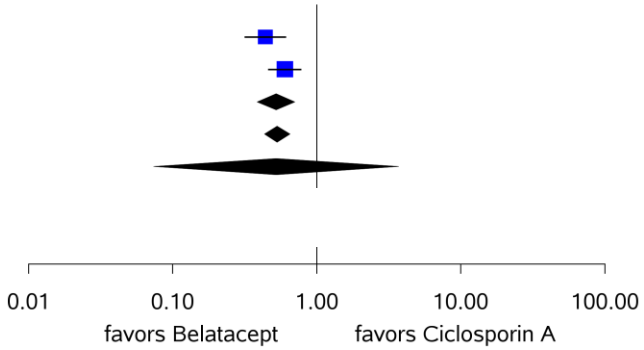
Example

Belatacept after kidney transplant (2 significant studies)

- Belatacept vs Ciclosporin A for prophylaxis of graft rejection in adults receiving a renal transplant (IQWiG report A15-25)
- Endpoint "renal insufficiency in chronic kidney disease stage 4/5"

Figure 1
Belatacept vs. Ciclosporin A
Renal insufficiency in chronic kidney disease

Study	log(HR)	SE	HR (95% CI)	weight (DSL)	HR	95% CI
BENEFIT	-0.82	0.17		44.6	0.44	[0.32, 0.61]
BENEFIT-EXT	-0.51	0.13		55.4	0.60	[0.46, 0.78]
DSL				100.0	0.52	[0.39, 0.71]
CE IV					0.53	[0.43, 0.65]
KH					0.52	[0.07, 3.71]
B-HN(0.5)					0.53	[0.27, 0.98]
B-HN(1.0)					0.52	[0.17, 1.52]



Heterogeneity: Q=2.06, df=1, p=0.151, I^2=51.5%
Overall effect: Z Score=-4.21, p<0.001, Tau=0.157

→ 1) Knapp-Hartung is over-conservative
2) Decision of no significant overall effect is critical

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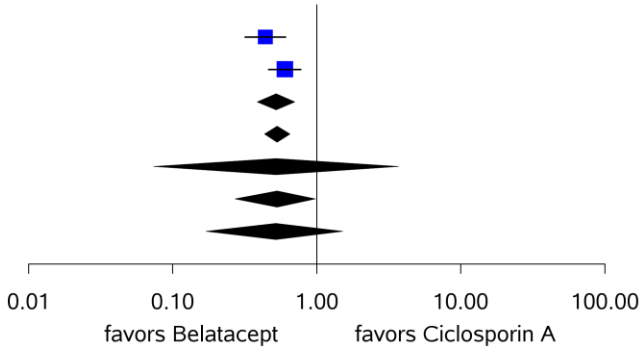

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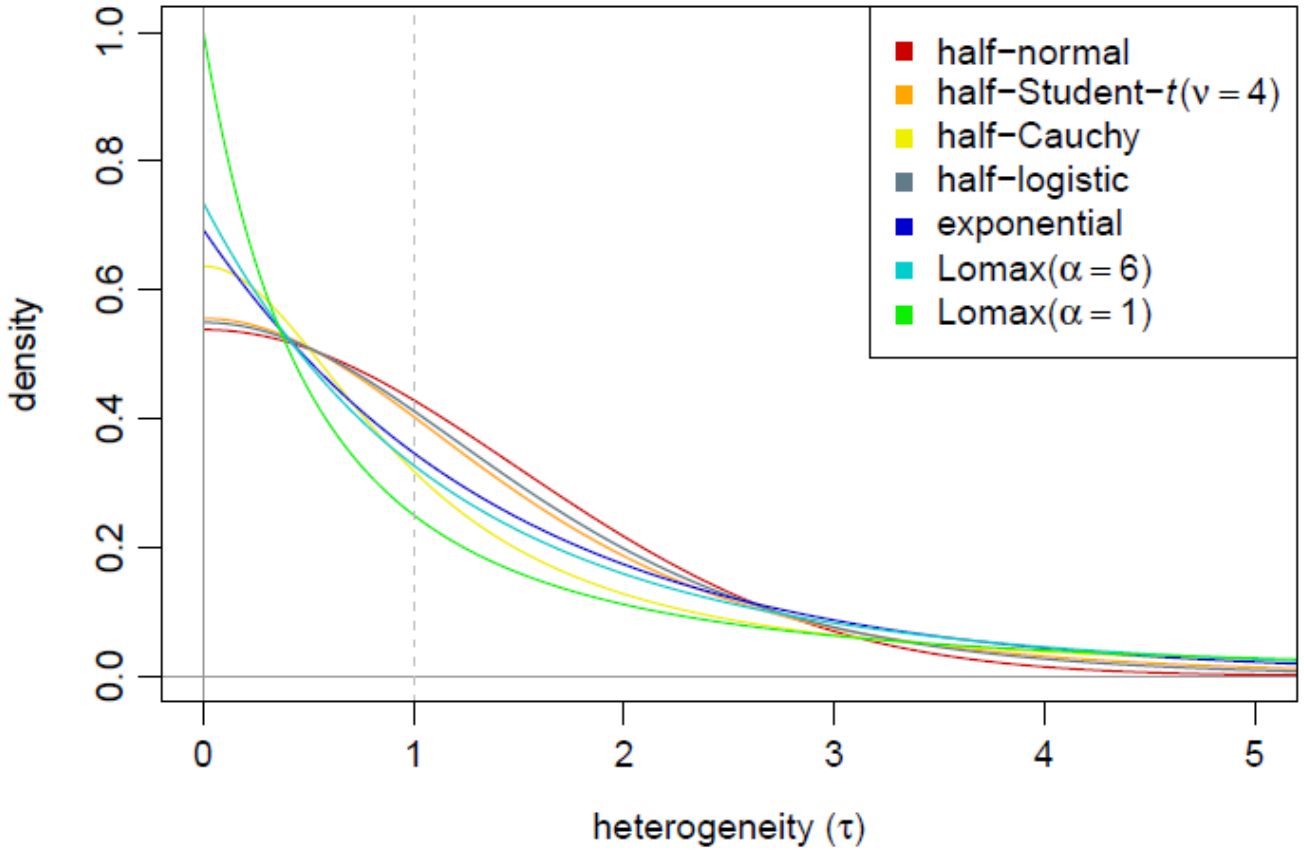
→ 1) Bayesian approach = Compromise between DSL and KH
2) But the final result depends on the prior distribution

Prior distributions

- Bayes: Posterior $\propto$ prior $\times$ likelihood
- Random-effects meta-analysis:
  $y_i = \theta_i + \varepsilon_i, \theta_i = \theta_{RE} + \delta_i$
  $\varepsilon_i \sim N(0, v_i)$, $\delta_i \sim N(0, \tau^2)$, $Var(y_i) = v_i + \tau^2$
- P((θ_{RE}, τ^2)| data) $\propto$ P((θ_{RE}, τ^2)) $\times$ P(data |(θ_{RE}, τ^2))
- For overall mean effect θ_{RE}: Non-informative prior
- For heterogeneity parameter τ: Weakly informative prior to overcome limitations in the case of few studies (Friede et al., 2017; Röver et al., 2021)

Prior distributions

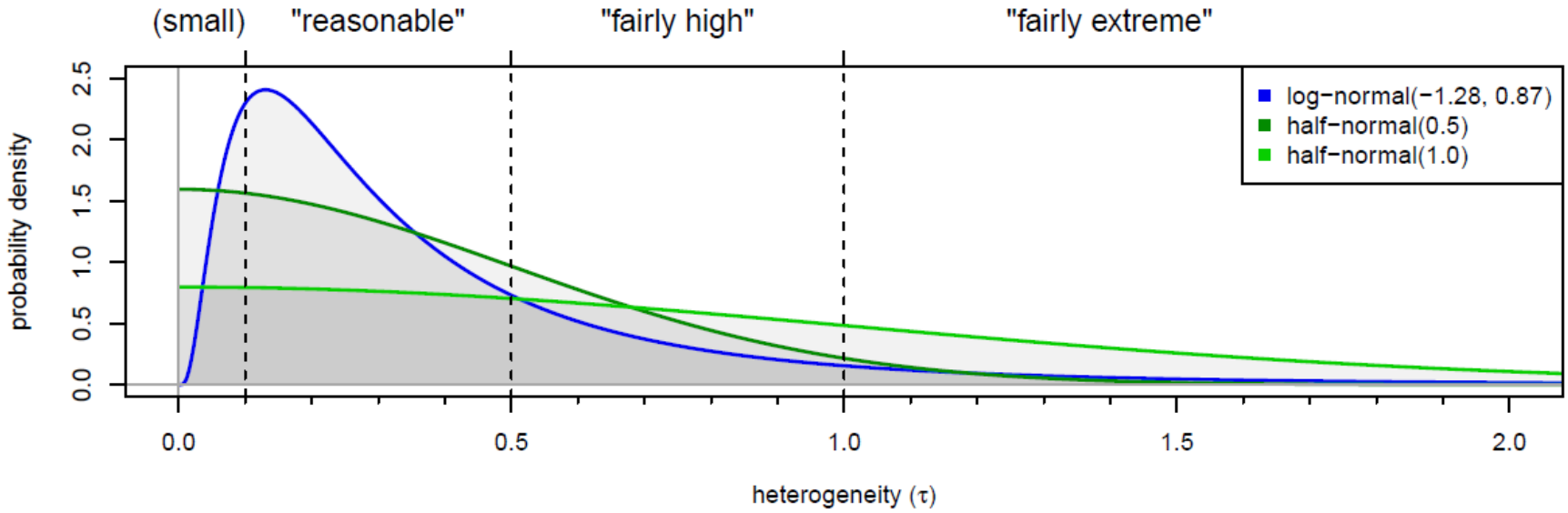
- Potential prior distributions for τ:



See Röver et al. (2021)

Prior distributions

- For pragmatic reasons we concentrate at first on half-normal distribution (Röver et al., 2021)



Comparison of HN(0.5) and HN(1.0) with the lognormal distribution proposed by Turner et al. (2015)

→ Which distribution is suitable in the HTA framework?

Methods

- Collection of all meta-analyses of IQWiG reports from 2005 to June 2020
- Random-effects meta-analysis by means of Knapp-Hartung (IQWiG, 2020)
- Estimation of τ by means of Paule-Mandel
- Conditions:
  - No meta-analyses for sensitivity/specificity
  - No subgroup analyses
  - No sensitivity analyses
  - Fourfold table available: Calculation of OR and RR
- Histograms to illustrate the empirical distribution of τ
- Comparison with HN(0.5) and HN(1.0)

Results

- Data basis:
  - 653 IQWiG reports
  - 118 reports with meta-analyses (forest plot)
  - 1653 meta-analyses
- Effect measures: OR, RR, SMD, (HR)
- In more than 75% of meta-analyses the number of studies is smaller than 5!
- Restrictions:
  - Only estimates of τ larger than zero
  - Only meta-analyses without substantial heterogeneity (Q-test not significant)

Results

Problem:

In about 60% of meta-analyses zero estimates for τ are obtained (similar to others).

Further restriction:

It makes sense to include only meta-analyses where heterogeneity is not too large for a meaningful pooled effect estimation.

Number of meta-analyses with non-zero estimates for τ and no substantial heterogeneity:

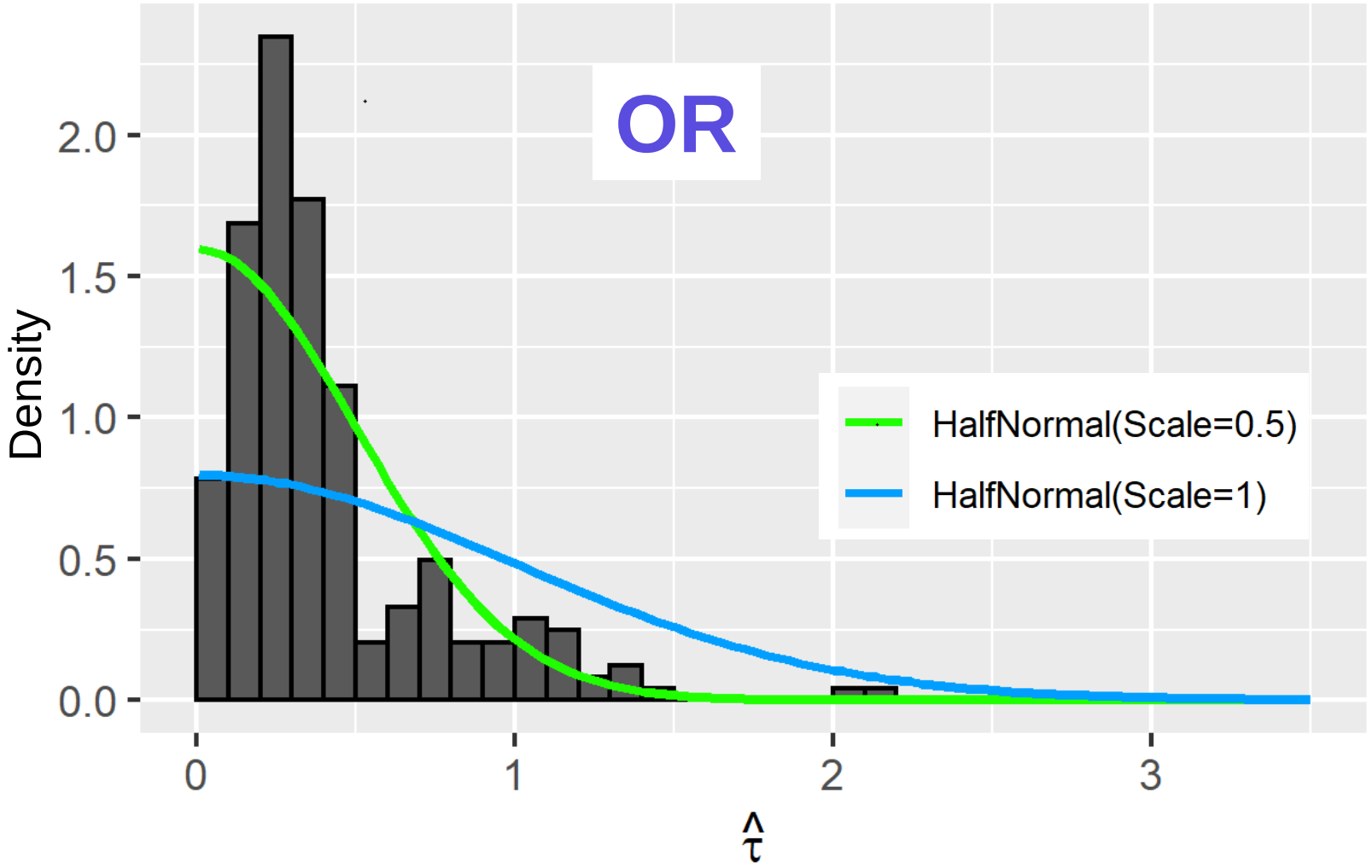
OR: **243** meta-analyses

RR: **260** meta-analyses

SMD: **166** meta-analyses

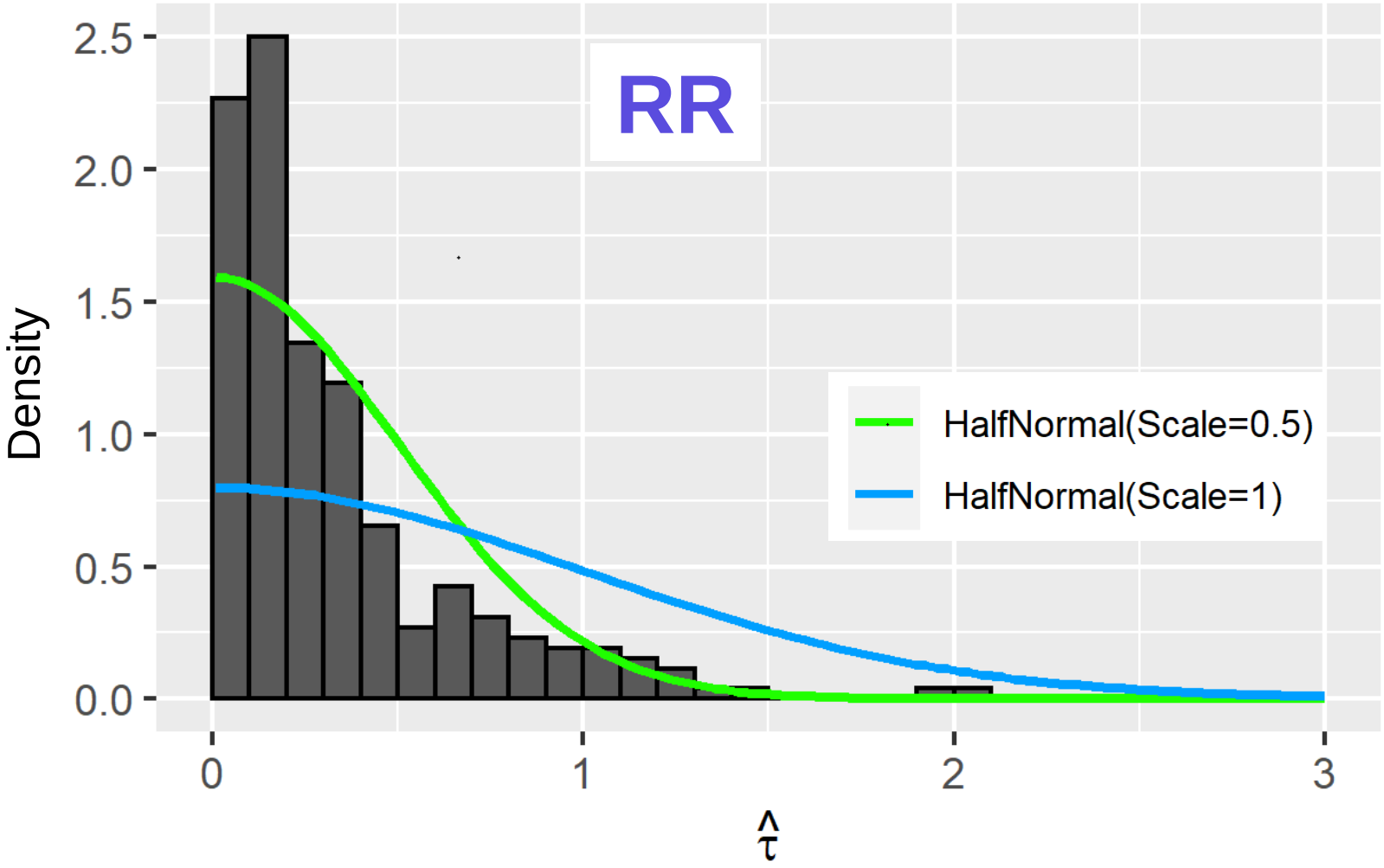
(HR: 21 meta-analyses)

Results



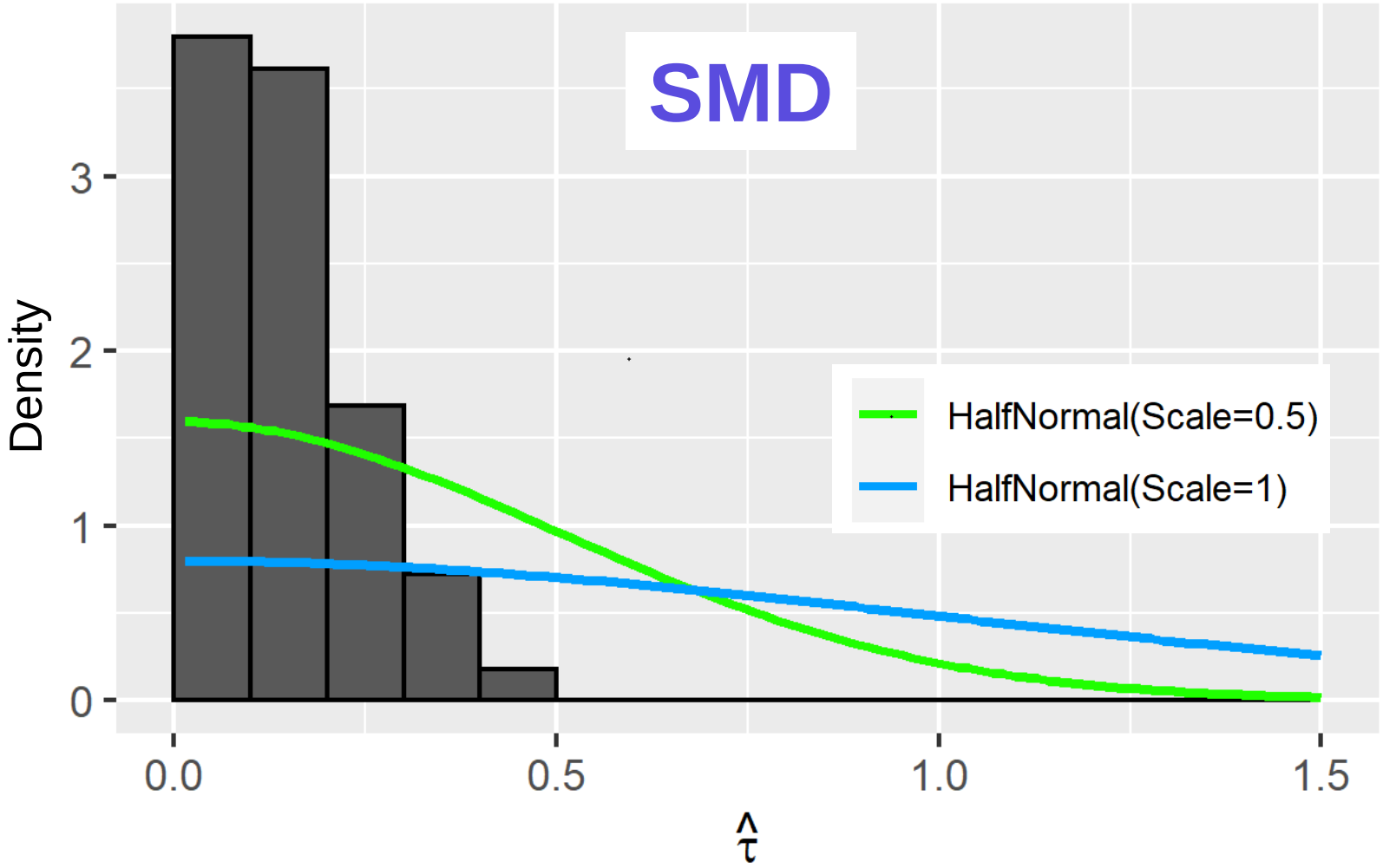
→ **HN(0.5)** distribution seems to be suitable for OR

Results



→ **HN(0.5)** distribution seems to be suitable for RR

Results



→ Distribution with smaller scale than **HN(0.5)** for SMD?

Interim conclusion

- First results are promising
- **HN(0.5)** seems to be suitable for OR and RR (and HR)
- For SMD a distribution with smaller scale parameter seems to be possible
- Pragmatic approach:
  Use of the same prior distribution for all effect measures, e.g., HN(0.5)

Outlook

- Application of various prior distributions (e.g., HN(0.5), HN(1.0), lognormal, Cauchy) to the IQWiG database of meta-analyses
- Key question:
  Can the use of qualitative evidence synthesis be avoided by means of Bayesian meta-analysis?
- **If possible, decision for a suitable standard prior distribution** (together with experts from biometric societies in Germany)
- Application of Bayesian meta-analyses with the chosen standard prior distribution for τ in the case of very few studies in the future

References

- Bender, R. et al. (2018): Methods for evidence synthesis in the case of very few studies. *Res. Syn. Methods* **9**, 382–392.
- Friede, T. et al. (2017): Meta-analysis of few small studies in orphan diseases. *Res. Syn. Methods* **8**, 79-91.
- IQWiG (2020): *General Methods, Version 6.0 of 5 November 2020*. Institute for Quality and Efficiency in Health Care, Cologne.
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- Turner, R.M. et al. (2015): Predictive distributions for between-study heterogeneity and simple methods for their application in Bayesian meta-analysis. *Stat. Med.* **34**, 984-998.
- Veroniki, A.A. et al. (2019): Methods to calculate uncertainty in the estimated overall effect size from a random-effects meta-analysis. *Res. Syn. Methods* **10**, 23-43.