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HIERARCHICAL MODELS

A framework for evidence synthesis

Innovative Methodology for Small Populations Research (InSPiRe), WP4 “Evidence synthesis”

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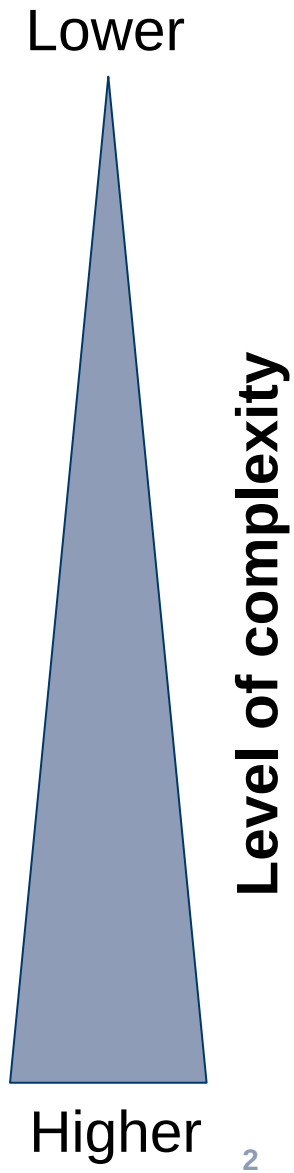
InSPiRe
Innovative methodology for small populations research

EVIDENCE SYNTHESIS

- **Pairwise meta-analysis**
  - comparing two treatments
- **Meta-regression**
  - including study-level covariates
- **Network meta-analysis**
  - comparing multiple treatments indirectly
- **RCT with historical controls**
  - integrating control group data from previous trials
- **Generalized (or cross design) synthesis**
  - combining data from different types of studies

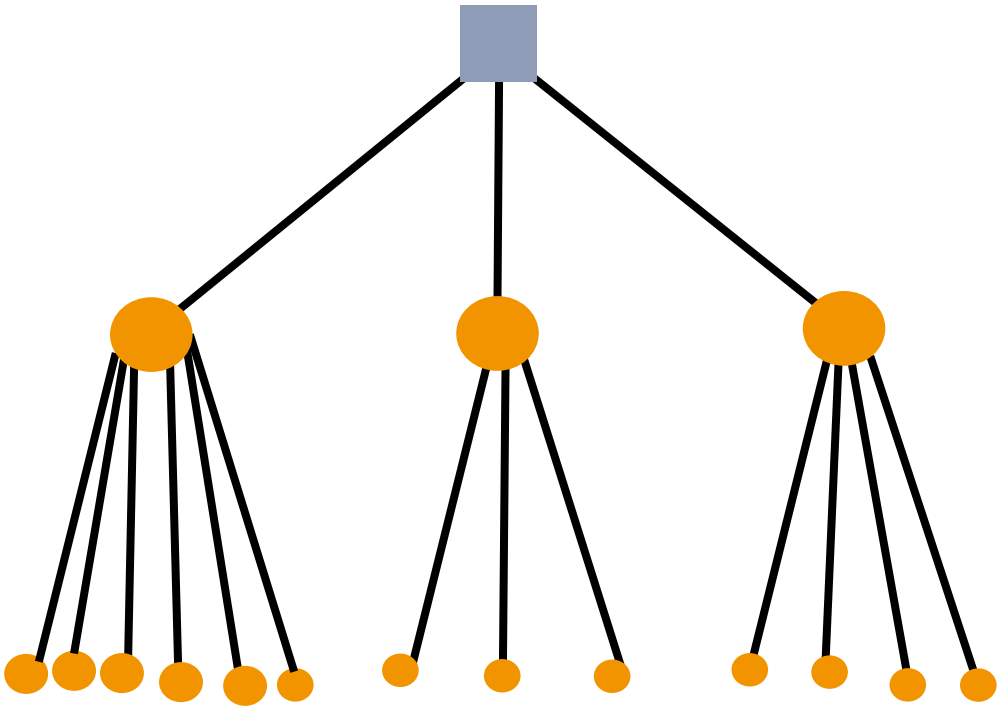


HIERARCHICAL MODELS

Meta-analysis

Studies

Patients



Example: **Normal-normal hierarchical model (NNHM)** for random-effects meta-analysis

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

EMPIRICAL STUDIES

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Empirical studies scraping large databases of meta-analyses (e.g. Cochrane Library) show

- Meta-analyses of (very) **few studies** common
- **Extent of between-trial heterogeneity**

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METHODOLOGY

Predicting the extent of heterogeneity in meta-analysis, using empirical data from the *Cochrane Database of Systematic Reviews*

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STANDARD METHOD FAILS

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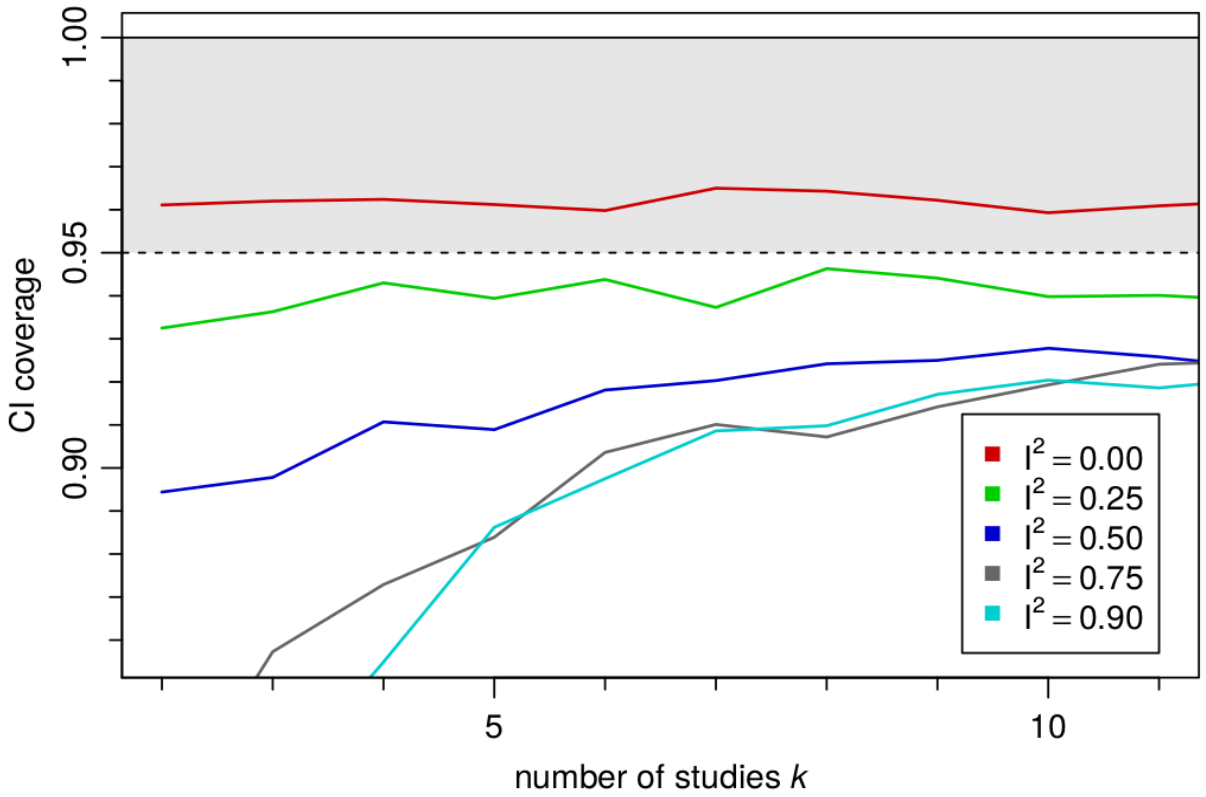
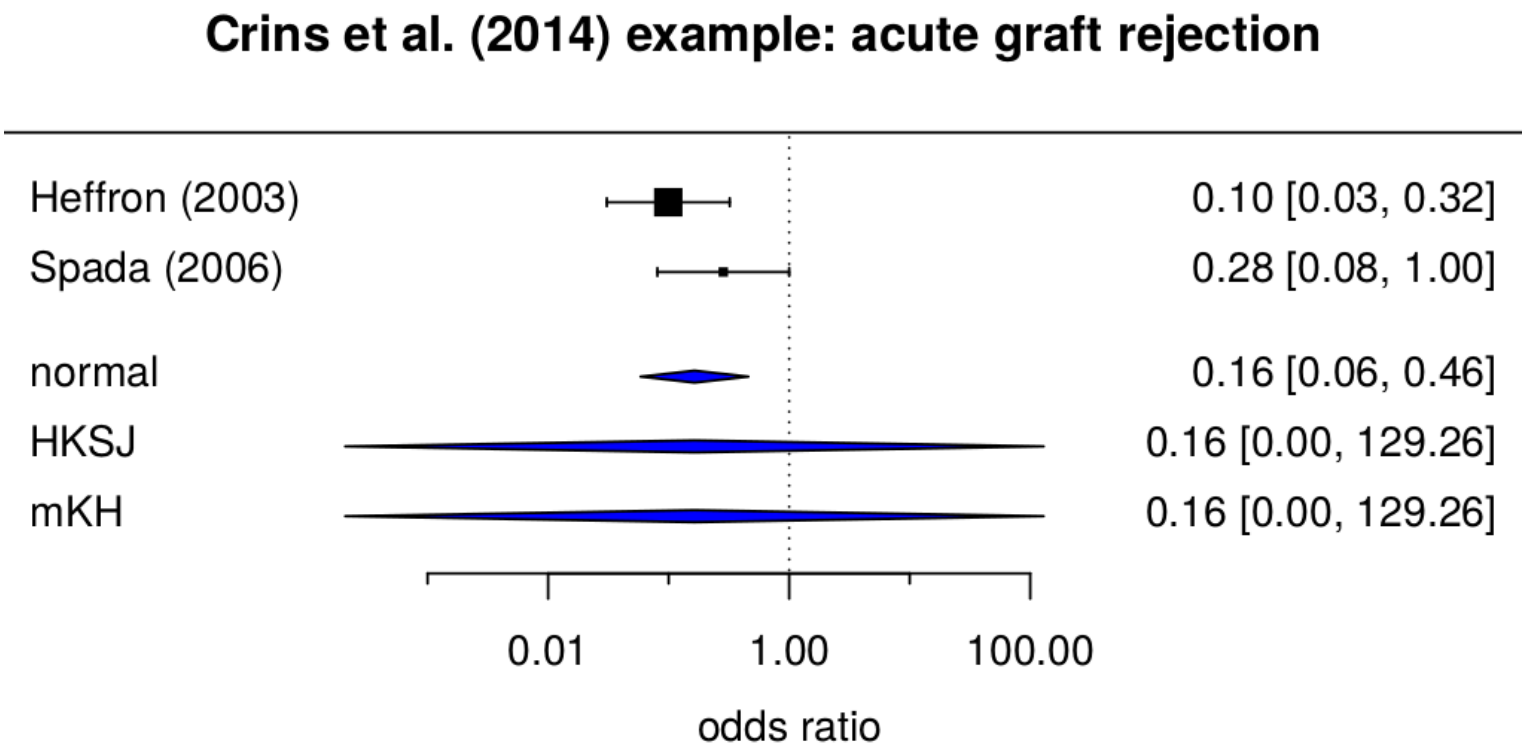
- Standard method (DerSimonian-Laird, DL)
  - Underestimates between-study heterogeneity
  - Fails to account for uncertainty in estimation of heterogeneity



IntHout et al, 2014; Röver et al, 2015

WITH VERY FEW STUDIES: KNAPP-HARTUNG METHOD DOES NOT SOLVE THE PROBLEM

- 97.5% quantile of t-distribution with 1 df = 12.7 !!!
- Example from Friede et al (2017b)



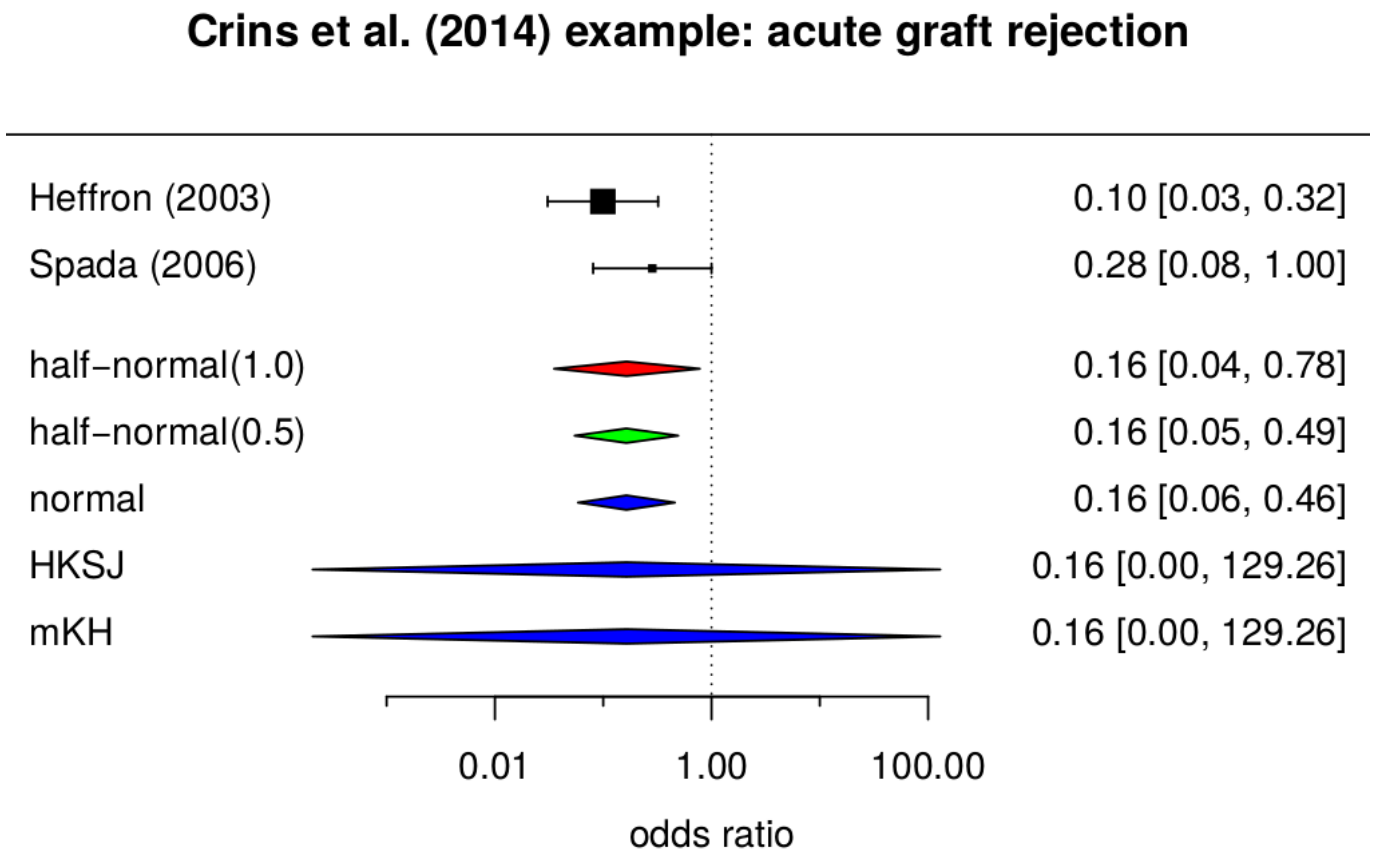
HSJK: Hartung-Knapp-Sidik-Jonkman; mHK: modified Knapp-Hartung; normal: DL

BAYESIAN META-ANALYSIS

- **Idea**: Weakly informative prior on between-trial heterogeneity for meta-analysis with few studies (Spiegelhalter et al, 2004), with uninformative prior on treatment effect
  - Avoids zero estimates of between-trial heterogeneity
  - Accounts for uncertainty in the estimation
- **Easy to compute**
  - Application of DIRECT algorithm (Röver & Friede, 2017a) (which is faster than MCMC sampling and does not require inspection of convergence diagnostics)
  - R package bayesmeta (available from CRAN)

EXAMPLE REVISITED

- **Bayesian intervals** appear to be a reasonable compromise (supported by simulation studies in e.g. Friede et al, 2017a,b)

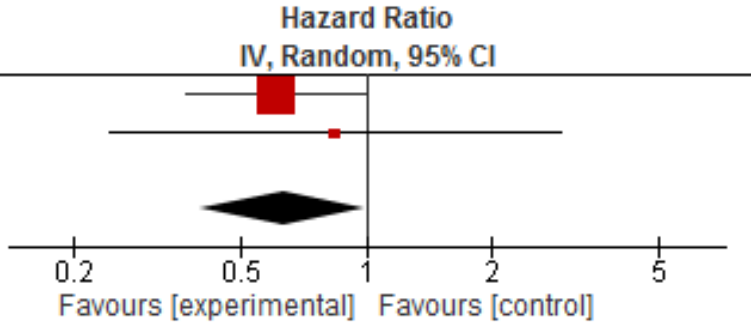


AN EXAMPLE OF CROSS-DESIGN SYNTHESIS

- **Creutzfeldt-Jakob disease (CJD)**
  - prevalence of 1–9 cases per 1,000,000 people
- **Varges et al (2017)** investigated doxycycline in early CJD:
  - double-blinded randomized phase II trial (n=12)
  - observational study (n=88) (Cox regression stratified by terciles of the propensity scores)
  - survival time as primary outcome

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Observational study	-0.49948	0.2493	86.5%	0.61 [0.37, 0.99]
RCT	-0.17344	0.6312	13.5%	0.84 [0.24, 2.90]
Total (95% CI)			**100.0%**	**0.63 [0.40, 1.00]**

Heterogeneity: Tau² = 0.00; Chi² = 0.23, df = 1 (P = 0.63); I² = 0%
Test for overall effect: Z = 1.96 (P = 0.05)

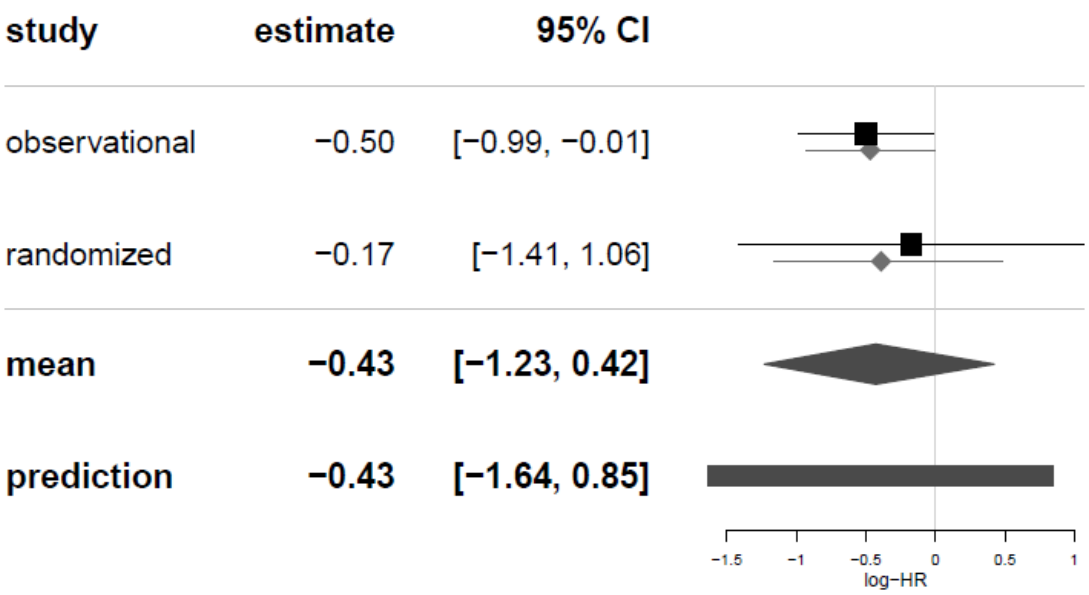


QUANTITIES OF INTEREST

Different **quantities of interest** in a random effects meta-analysis

- average effect (θ) across studies
- effect (θ_{k+1}) of a future study (prediction / extrapolation)
- effect (θ_i) of an individual study in the light of the other studies (shrinkage estimator)

SHRINKAGE ESTIMATOR: EXAMPLE IN CJD



- RCT shrinkage interval width: 66% of original CI width
- Translates into 129% gain in sample size (about 27 instead of 12 patients)

Röver & Friede (2017b) in preparation

ROBUST SHRINKAGE ESTIMATION

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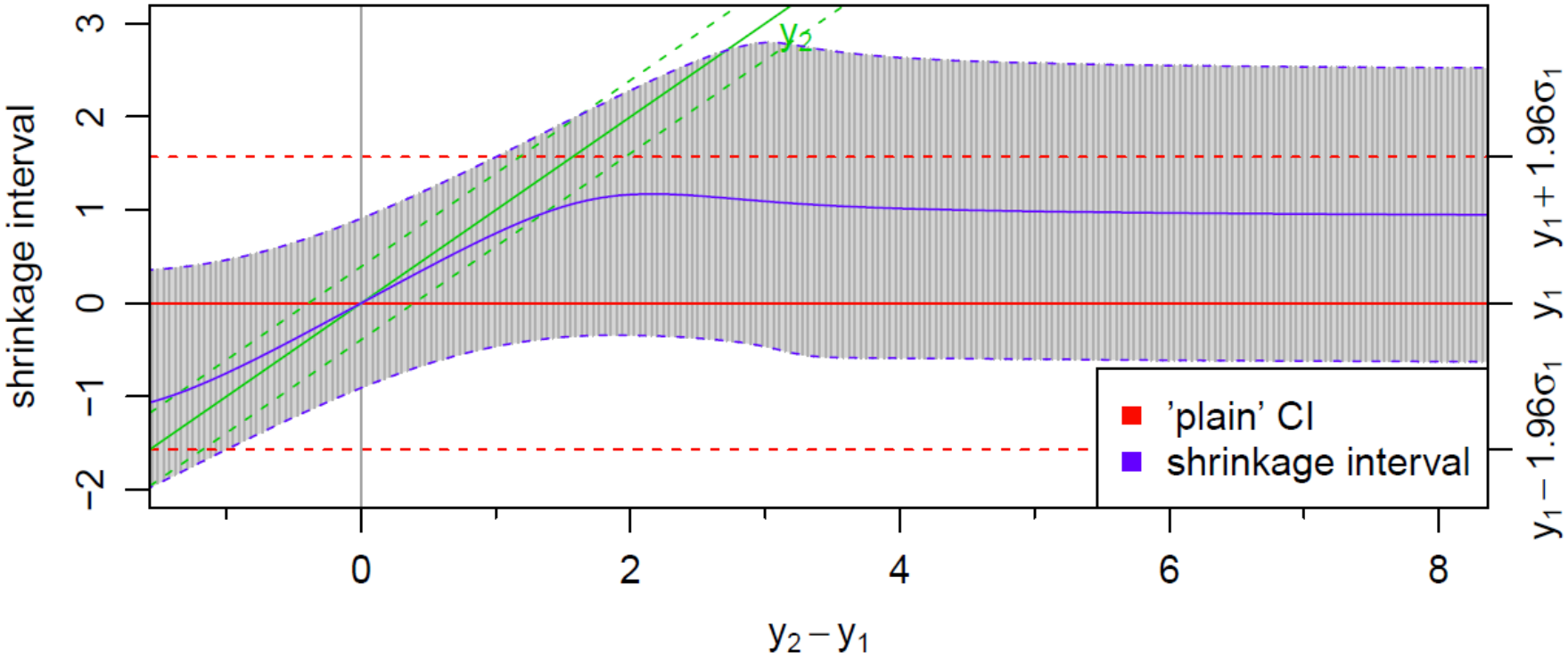
- **Idea**: Use of heavy-tailed meta-analytic predictive (MAP) prior (Schmidli et al, 2014)



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

Röver & Friede (2017b) in preparation

MORE COMPLEX EXAMPLE: EARLY PRO-TECT TRIAL IN ALPORT DISEASE

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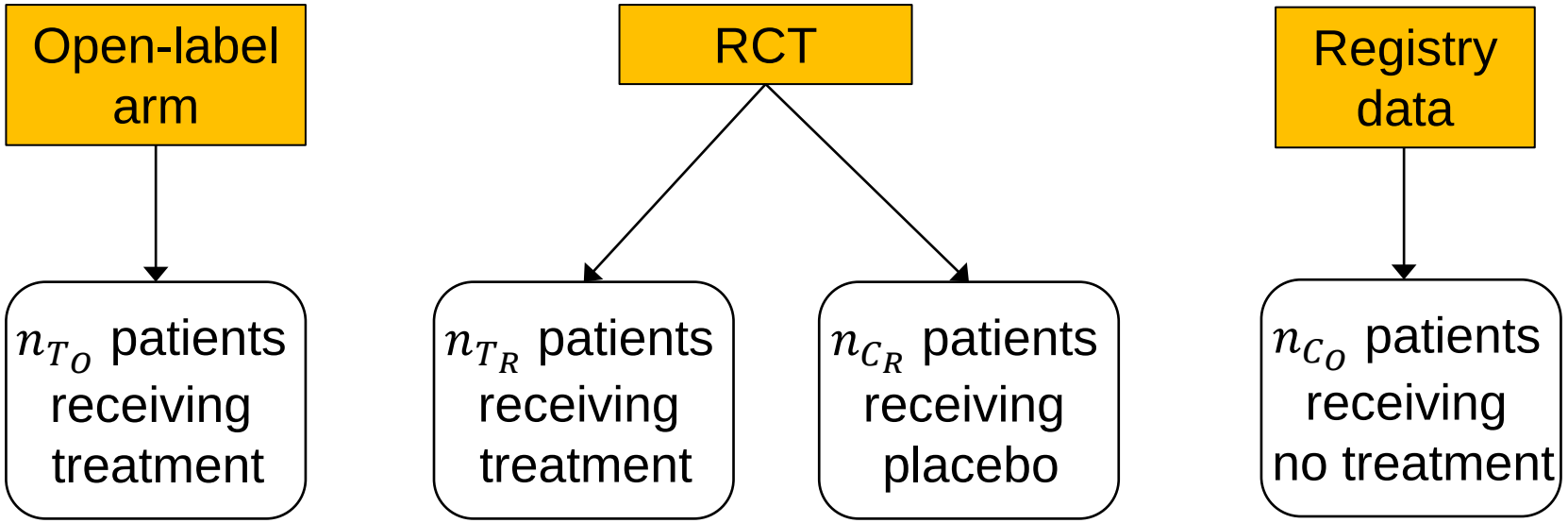
- Alport syndrome is a rare genetic disorder that inevitably leads to end-stage kidney disease.
- Observational data suggest that the ACE inhibitor ramipril delays renal failure and improves life-expectancy in Alport patients.
- Our work (Unkel et al, 2017) is inspired by the ongoing EARLY PRO-TECT Alport trial in paediatric Alport patients (Gross et al. 2012).



CONCLUSIONS AND DISCUSSION

- **Hierarchical models**
  - flexible statistical framework for evidence synthesis
- **Bayesian inference**: advantages over traditional methods in the presence of heterogeneity and only (very) few studies
  - easy to apply using R package `bayesmeta`
- **Cross-design synthesis of available evidence**
  - Promising in rare diseases
  - more practical (and regulatory) experience needed

THE TEAM

The InSPiRe WP4 "Evidence synthesis" team includes

- **University Medical Center Göttingen** (UMG): Tim Friede, Steffen Unkel, Christian Röver, Burak Günhan, Katharina Kramer
- **Medical University Vienna** (MUW): Martin Posch
- **INSERM** (Paris): Sarah Zohar
- **University of Warwick**: Nigel Stallard
- **BfArM**: Norbert Benda
- **Novartis**: Beat Neuenschwander, Simon Wandel

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