Empirical heterogeneity information on subgroup meta analysis

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The Collection of Meta-analyses

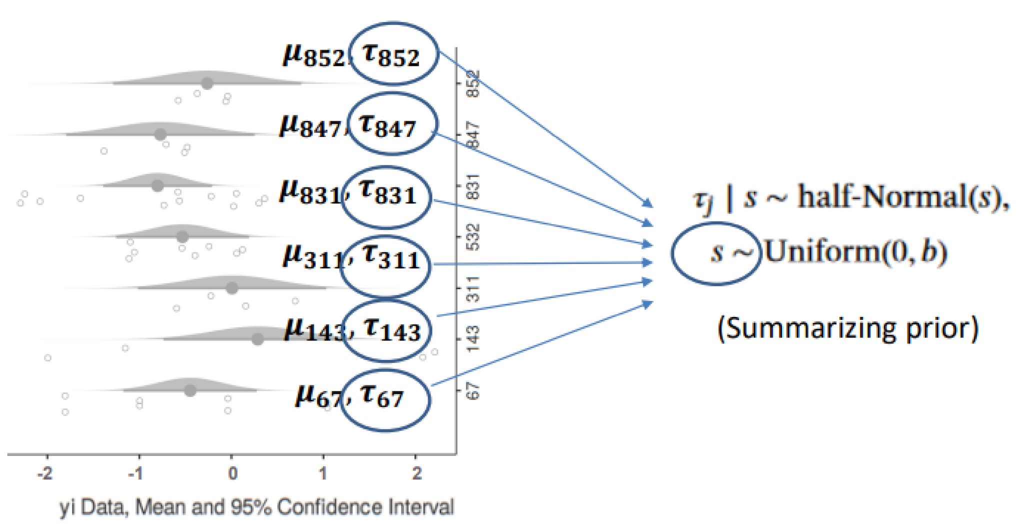
Individual **estimates** y_{ij} (given along with **standard errors** s_{ij}) of study i within meta-analysis j are to be combined in a group of (independently) pooled analyses. The **random-effects model** may be stated as:

$$y_{ij}|\theta_{ij}, \sigma_{ij} \sim \text{Normal}\left(\theta_{ij}, \sigma_{ij}^2\right),$$
$$\theta_{ij}|\mu_j, \tau_j \sim \text{Normal}\left(\mu_j, \tau_j^2\right).$$

for $i = 1, \ldots, k_j$ and , $j = 1, \ldots, n$. Interest usually is in **estimating** μ_j or in **predicting** θ_{k_j+1}. The **heterogeneity** τ_j then constitutes a analysis-specific **nuisance parameter**.

The Summarizing (hyper-)Prior

The **summarizing prior** will detect a suitable scale for **scale-family the heterogeneity priors** $\tau_j \sim \frac{1}{s} p_j(\frac{t}{s})$ in a collection of n meta-analyses [1, 2].

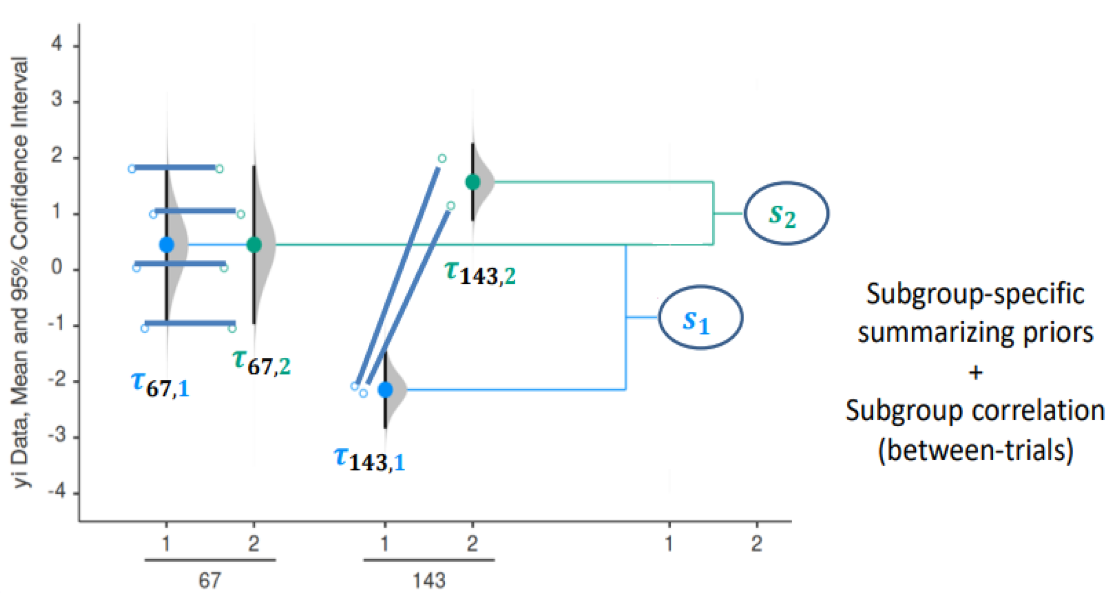


Extension to subgroups

The subgroup version of the random-effects model inherits a heterogeneity matrix structure that allows for the inclusion of **more than one endpoint per trial (subgroups)** in the analysis. The bivariate random effects case includes $g = 1, 2$ subgroups as:

$$\begin{pmatrix} y_{1ij} \\ y_{2ij} \end{pmatrix} \mid \theta, \sigma \sim \text{Normal}\left(\begin{pmatrix} \theta_{1ij} \\ \theta_{2ij} \end{pmatrix}, \begin{pmatrix} \sigma_{1ij}^2 & 0 \\ 0 & \sigma_{2ij}^2 \end{pmatrix}\right),$$
$$\begin{pmatrix} \theta_{1ij} \\ \theta_{2ij} \end{pmatrix} |d \sim \text{Normal}\left(\begin{pmatrix} \beta_{1j} \\ \beta_{2j} \end{pmatrix}, \begin{pmatrix} \tau_{1j}^2 & \rho_j\tau_{1j}\tau_{2j} \\ \rho_j\tau_{1j}\tau_{2j} & \tau_{2j}^2 \end{pmatrix}\right).$$

for a vector of parameters $d = (\beta, \tau, \rho)'$. In contrast to the case of a scalar heterogeneity [3, 4], there is **no widespread consensus** on the prior choices for **heterogeneity matrices**.



The Separation Strategy

The **separation strategy** in Bayesian models allows for flexibility on prior choice as it relies on **separate choices** of scale- and correlation-prior [5].

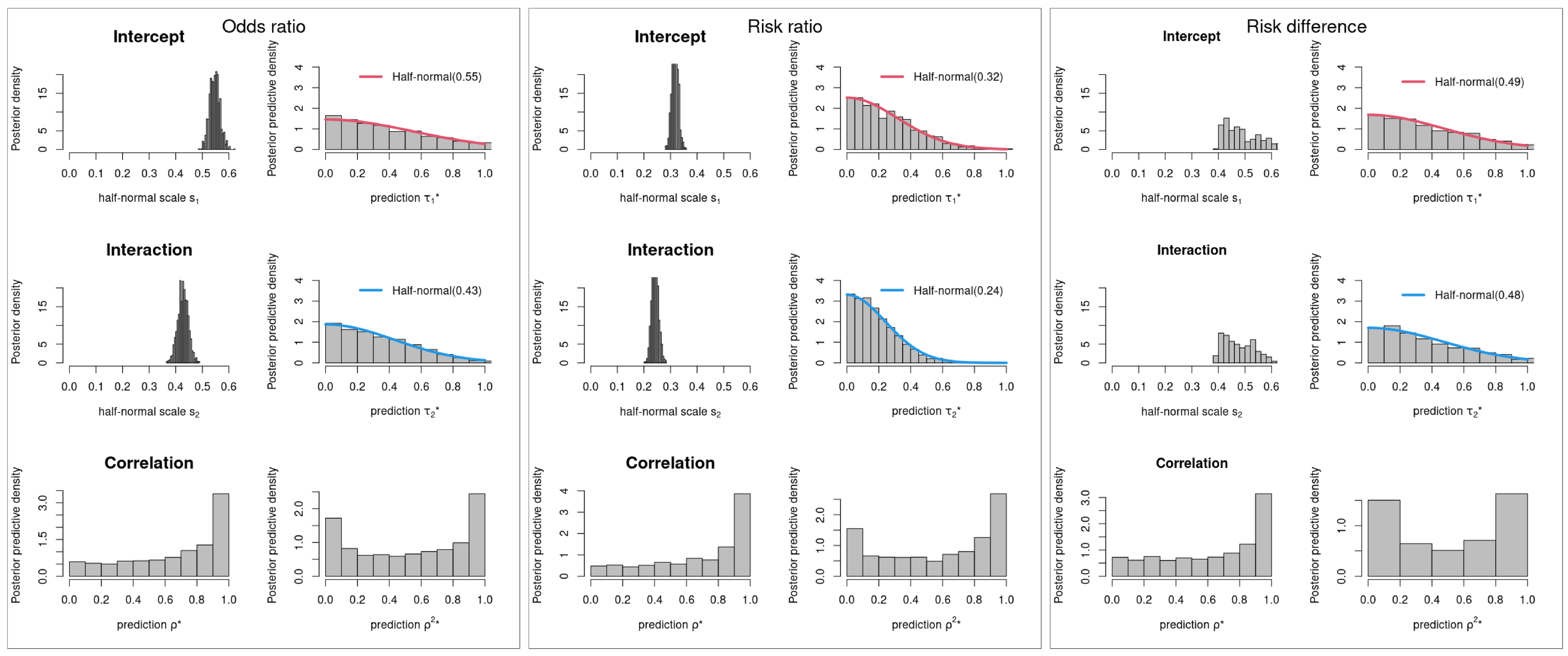
$$\begin{pmatrix} \tau_{1j}^2 & \rho_j\tau_{1j}\tau_{2j} \\ \rho_j\tau_{1j}\tau_{2j} & \tau_{2j}^2 \end{pmatrix} = \begin{pmatrix} \tau_{1j} & 0 \\ 0 & \tau_{2j} \end{pmatrix} \begin{pmatrix} 1 & \rho_j \\ \rho_j & 1 \end{pmatrix} \begin{pmatrix} \tau_{1j} & 0 \\ 0 & \tau_{2j} \end{pmatrix}.$$

For instance, heterogeneity $\tau_{gj} \sim$ half-Normal(s_g) and correlation $(\rho_j + 1)/2 \sim$ Beta(c, c). The heterogeneity here is parameterized in terms of "two effects".

The Cochrane library

...contains data from **many** archived meta-analyses from clinical trials. Question is whether we can utilize this comprehensive data set to find empirical evidence on **heterogeneity priors' scale**.

The investigation includes 14 358 published subgroup meta-analyses with 2 (randomly selected) subgroups. We have assumed the **positive correlation strategy** model instead of the previous **separation strategy**. With that, we may then empirically obtain **informative priors** for the between-trial subgroup-specific and interaction heterogeneities. Here we focus on Bayesian estimates using an **uninformative normal prior** on the **overall values** μ_j such as Normal$(0, 10^2)$ prior.



Empirical information from Cochrane Library data on heterogeneity matrices (subgroup-specific and interaction heterogeneity) in a collection of several bivarite subgroup meta-analysis $g = 1, 2$ of varied sizes sizes k_j).

The Positive Correlation Strategy

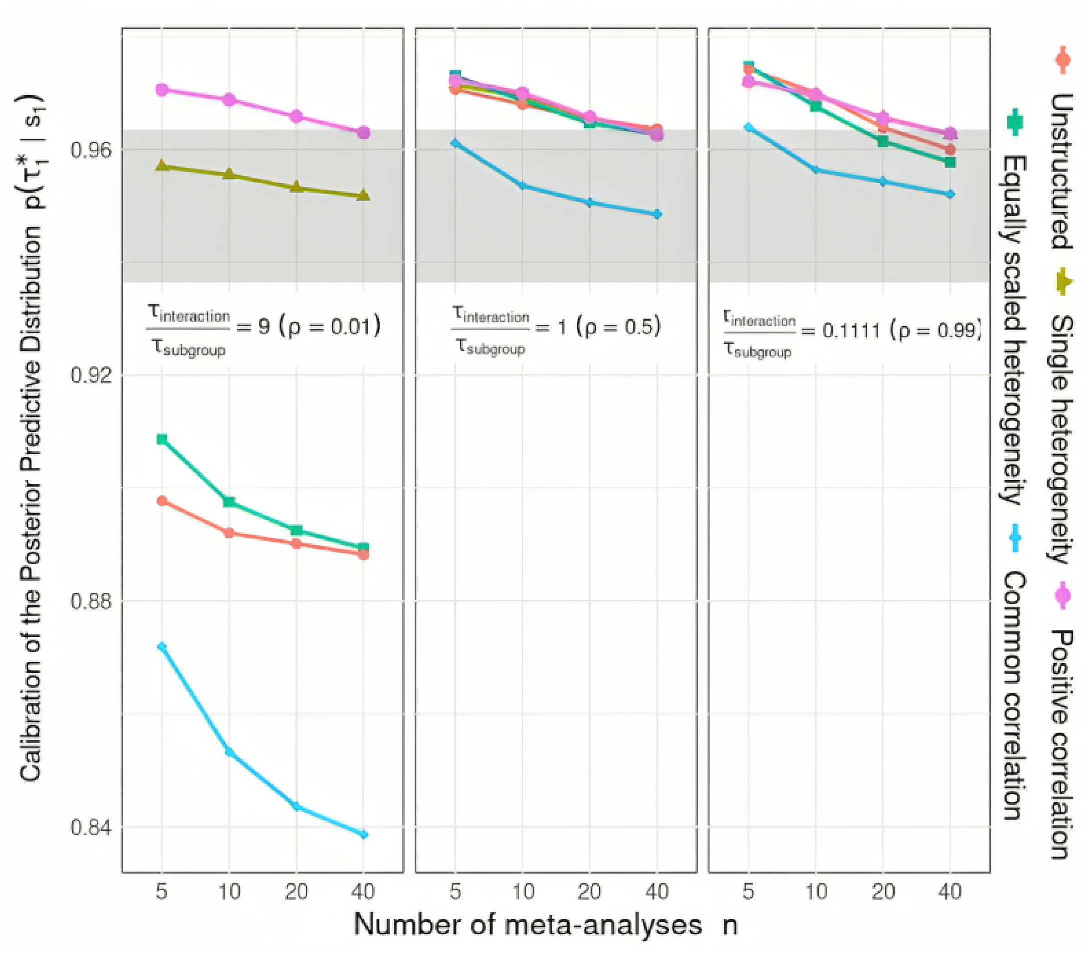
The **positive correlation strategy** in Bayesian models allows for flexibility on scale prior choices but does not allow for negative correlation.

$$\begin{pmatrix} \tau_{1j}^2 & \tau_{1j}^2 \\ \tau_{1j}^2 & \tau_{1j}^2 + \tau_{2j}^2 \end{pmatrix} = \begin{pmatrix} \tau_{1j} & 0 \\ 0 & \tau_{2j} \end{pmatrix} \begin{pmatrix} 1 & \sqrt{\frac{\delta_j}{1+\delta_j}} \\ \sqrt{\frac{\delta_j}{1+\delta_j}} & 1+\delta_j \end{pmatrix} \begin{pmatrix} \tau_{1j} & 0 \\ 0 & \tau_{2j} \end{pmatrix}.$$

where the ratio between heterogeneities is $\sqrt{\delta_j} = \frac{\tau_{1j}}{\tau_{2j}}$. The heterogeneity here is parameterized in terms of "main effect / interaction" (intercept/slope).
For instance, heterogeneity $\tau_{gj} \sim$ half-Normal(s_g).

Simulation Study

The simulation data was generated using an IPD model [6] that yields approximately a **positive correlation structure** $\tau^2_{\text{subgroup}} vv' + \tau^2_{\text{interaction}} uu'$ in the AgD level. The investigation includes 5 alternatives including the correlation strategy and separation strategy alternatives and yields the resulting calibrations for the nominal credible level of **95%** (see figure).



Most of the methods fail to reach nominal coverage when **interaction heterogeneity is large**.

Conclusions

Summarizing priors work well on subgroups as long as the interaction heterogeneity is **small to moderate (moderate to large correlation)** compared to the subgroup-specific heterogeneity, and tend to yield **overly informative** prior recommendations **if subgroups are not correlated**.

In the latter case, the use of a standard weakly informative heterogeneity priors may be more appropriate [7]. For **odds ratios, relative risks and risk differences** in Cochrane database the posterior predictive correlation **was found to be large**, that is $0.77(0.04, 1)$, $0.82(0.05, 1)$ and $0.74(0.04, 1)$ respectively.

References

[1] Turner RM et al. Predictive distributions for between-study heterogeneity and simple methods for their application in bayesian meta-analysis. *Statistics in Medicine*, 34(6):984–998, 2015.

[2] Turner RM 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.

[3] Lilienthal J et al. Bayesian random-effects meta-analysis with empirical heterogeneity priors for application in health technology assessment with very few studies. *Research Synthesis Methods*, 15(2):275–287, 2024.

[4] Röver C et al. Summarizing empirical information on between-study heterogeneity for bayesian random-effects meta-analysis. *Statistics in Medicine*, 42(14):2439–2454, 2023.

[5] Gelman A et al. *Bayesian Data Analysis*. Chapman and Hall/CRC, 1995.

[6] Hua H et al. One-stage individual participant data meta-analysis models: Estimation of treatment-covariate interactions must avoid ecological bias by separating out within-trial and across-trial information. *Statistics in Medicine*, 36(5):772–789, 2017.

[7] Röver C 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.