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Priors on between-study heterogeneity in Bayesian meta-analysis models: A simulation study using Hamiltonian Monte Carlo sampling

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INTRODUCTION & OBJECTIVE

- Meta-analysis (MA) plays a crucial role in health economic and outcomes research. Random effects (RE) models in MA allow for heterogeneity in treatment effects between studies.
- In a Bayesian framework, prior beliefs are assigned to model parameters, including the between-study heterogeneity, often using non-informative priors.[1]
- Previous research[2] explored the use of different priors for the heterogeneity parameter on MA results using WinBUGS[3] (Gibbs sampling).
- Hamiltonian Monte Carlo (HMC) sampling, implemented in Stan[4], is used increasingly more often in recent years and should be more efficient than Gibbs sampling.[5]

OBJECTIVES

- The aim of this study was to replicate Lambert et al. (2005)[2] instead using HMC sampling.
- Further, the study aimed to expand previous research by investigating performance of additional priors on the between-study heterogeneity parameter (i.e., an informative prior and improper flat prior), and the use of non-centred model parameterization.
- Finally, the study sought to explore model fit under RE models (for each prior investigated) and compare with that for fixed effect (FE) models.

METHODS

Model

- Three meta-analysis models were fitted:
  - **An RE model with centred parameterization**, as used for example in NICE technical support documents:[1]

$$y_i \sim N(\mu_i, s_i^2) \qquad \mu_i \sim N(\theta, \tau^2)$$

    where y_i and s_i are the observed log-odds ratio and its standard error for study i, μ_i is the modelled log-odds ratio, τ is the between-study standard deviation (SD) and θ is the pooled log-odds ratio.
  - **An RE model with non-centred parameterization**:[5]

$$y_i \sim N(\theta + \tau\mu_i, s_i^2) \qquad \mu_i \sim N(0,1)$$

  - **An FE model**:

$$y_i \sim N(\theta, s_i^2)$$

- Models were implemented in Stan.[4] Four chains with 2000 iterations (1000 warmup) each were sampled, with the target average acceptance probability set to 0.98.
- An uninformative prior was placed on the pooled log-odds ratio: $\theta \sim N(0,100)$.
- Fourteen priors for the between-study SD, varying in distribution and level of information, were tested (Table 1).
  - Prior 0 is an improper flat prior.
  - Prior 13 is the empirical Bayes[6] prior.
  - Prior 14 is the informative prior suggested by Turner et al.[7] for a pharmacological vs placebo comparison and a subjective outcome.

Table 1. Between-study SD priors

0.	$\boldsymbol{\tau \sim \text{Uniform}(0, \infty)}$	8.	$\frac{1}{\tau^2} \sim \text{Pareto}(1, 0.25)$
1.	$\boldsymbol{\frac{1}{\tau^2} \sim \text{Gamma}(0.001, 0.001)}$	9.	$\boldsymbol{\tau \sim \text{Uniform}(0, 100)}$
2.	$\boldsymbol{\frac{1}{\tau^2} \sim \text{Gamma}(0.1, 0.1)}$	10	$\tau \sim \text{Uniform}(0, 2)$
3.	$\log \tau^2 \sim \text{Uniform}(-10, 10)$	11.	$\boldsymbol{\tau \sim N(0, 100); \quad \tau > 0}$
4.	$\log \tau^2 \sim \text{Uniform}(-10, 1.386)$	12.	$\boldsymbol{\tau \sim N(0, 1); \quad \tau > 0}$
5.	$\boldsymbol{\tau^2 \sim \text{Uniform}(1/1000, 1000)}$	13.	$\boldsymbol{\tau \sim \text{LogLogistic}(S_0); \quad S_0 = \sqrt{K/\sum s_i^{-2}}}$
6.	$\tau^2 \sim \text{Uniform}(1/1000, 4)$	14.	$\boldsymbol{\tau^2 \sim \text{LogNormal}(-2.13, 1.58); \quad \tau > 0}$
7.	$\boldsymbol{\frac{1}{\tau^2} \sim \text{Pareto}(1, 0.001)}$		

Note: Lambert et al. (2005) used priors 1 to 13.[2] K is the number of studies.

The same case study and simulation study setup as in Lambert et al. (2005) were used.[2]

Case study

- Models were first fitted on data from five studies comparing the effects of short course versus long course antibiotics for acute otitis media.[8]

Simulation study

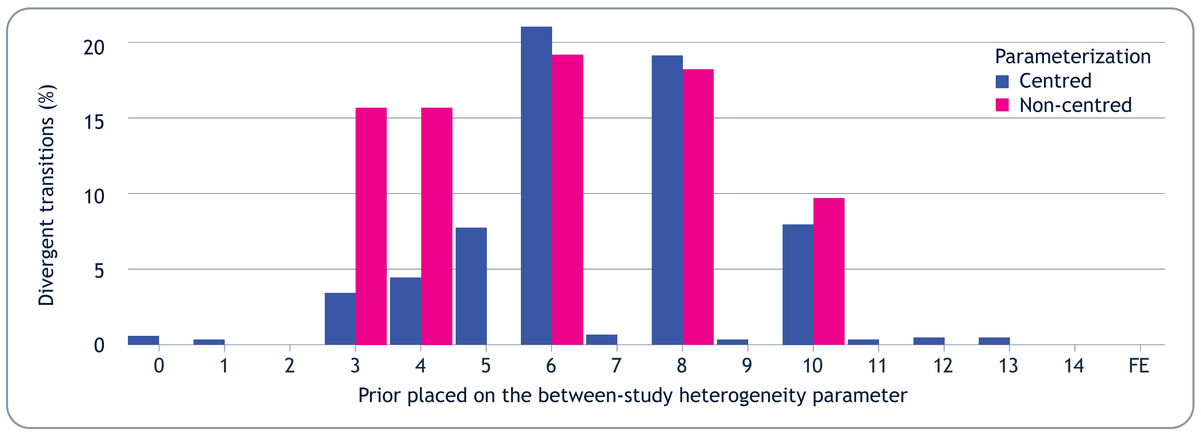
- One thousand simulated dichotomous outcome datasets, with differing true between-study SD and number of studies, were evaluated.
  - A random study effect was drawn from a normal distribution with mean zero, and a varied SD across three scenarios (0.001, 0.3, or 0.8).
  - The placebo log-odds, log-odds ratio and the random study effect were summed to obtain the odds ratio of the treatment arm, and the number of events is drawn from a binomial distribution. Scenarios with 5, 10 and 30 studies were evaluated, with 100 to 500 patients in each of the two study arms.
- Results were compared by assessing the bias, coverage, deviance information criterion (DIC), convergence (based on R-hats and Monte Carlo standard errors) and divergent transitions (an HMC diagnostic indicating Markov chain Monte Carlo estimators may be invalid and biased[8]).

RESULTS

Case study

- The case study demonstrated that priors with zero density at plausible values results in divergent transitions (Figure 1) and may therefore lead to biased results.[9]
- For most priors, the non-centred parametrization decreased the number of divergent transitions.

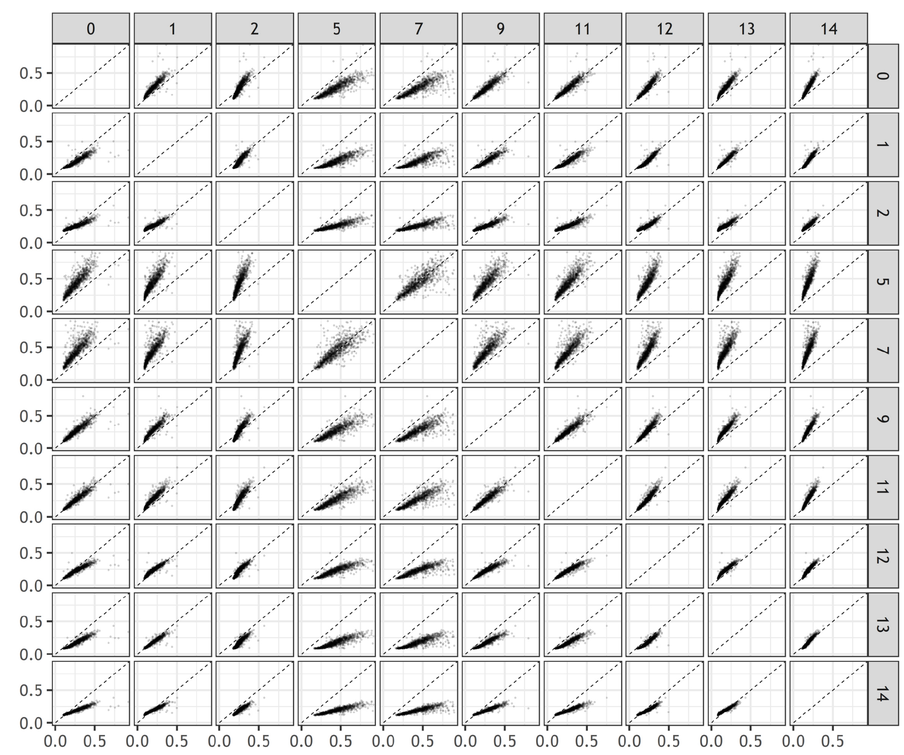
Figure 1. Divergent transitions as percentage of samples per prior and parameterization.



Simulation study

- Based on the observations in the case study, the non-centred parametrization and priors with no or very few divergent transitions were used in the simulation study.
- Figure 2 presents pairwise comparisons of between-study heterogeneity priors for the five-study scenario, illustrating the impact on the SD of the pooled log-odds ratio.
  - Within each pairwise comparison, dots (replications) which lie around the diagonal indicate similar results for the two priors being compared.
  - Conversely, dots which are consistently above (or below) the diagonal indicate a higher (or lower) SD of the pooled log-odds ratio for the row prior versus column prior in the comparison, i.e., more (or less) uncertainty in the treatment effect estimate under the row prior.
  - For example, in the pairwise comparison of informative prior 14 versus flat prior 0 (upper right subplot), there is decreased uncertainty in the treatment effect for prior 14 (dots are consistently above the diagonal).
- Among simulation scenarios, RE models with a gamma prior on precision (1), an empirical Bayes prior (13) and an informative prior on variance (14) were most likely to be favoured over FE models (lowest DIC).
- Convergence issues were more prominent when using the improper flat prior (0), the non-informative normal prior on SD (11), the non-informative priors on SD and variance (5, 9) and the non-informative Pareto prior on precision (7), especially in scenarios with fewer studies and higher true SD.
- The non-informative uniform prior on variance (5) still resulted in many divergent transitions, especially in scenarios with a true SD of 0.001.

Figure 2. Scatter plot matrix comparing all selected between-study SD prior distributions for the five-study scenario with a between-study SD of 0.3, displaying the posterior SD of the pooled log-odds ratio. Each point represents a simulation replication.



CONCLUSIONS

- Findings are very similar to results presented by Lambert et al. (2005)[2], despite the different parameterization and (more efficient[5]) sampling method.
- Selection of an appropriate between-study heterogeneity prior is crucial as it impacts the posterior treatment effect, particularly when dealing with a low number of studies.
- Caution must be exercised to avoid bias when using informative priors.
- In future studies, adopting non-centred model parameterization as standard practice is advisable over centred parameterization.
- HMC diagnostics, such as divergent transitions, are helpful and show that priors with zero density at plausible values should be avoided.

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