Model averaging for robust extrapolation in evidence synthesis

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Basel, Switzerland

December 6, 2018

This project has received funding from the European Union’s Seventh Framework Programme for research, technological development and demonstration under grant agreement number FP HEALTH 2013-602144.
Overview

- meta-analysis & extrapolation
- NNHM, example
- informative priors, mixture priors
- example applications
- conclusions
extrapolation desirable when evidence sparse or relevance unclear: paediatric/adult applications, bridging studies,…

common situation in meta-analysis:

majority of analyses in Cochrane data base include \( \leq 3 \) studies\(^1\), many overall + subgroup analysis results

aims:

- formal utilization of related evidence
- robust procedure (no naïve, over-optimistic pooling)

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Meta-analysis

The common NNHM (random-effects) model

- \( k \) studies
- estimates \( y_i \in \mathbb{R} \) (\( i = 1, \ldots, k \))
- standard errors \( \sigma_i > 0 \)
- **normal-normal hierarchical model (NNHM):**

\[
\begin{align*}
y_i|\theta_i, \sigma_i &\sim N(\theta_i, \sigma_i^2), \quad \theta_i|\mu, \tau \sim N(\mu, \tau^2) \\
\Rightarrow y_i|\mu, \sigma_i, \tau &\sim N(\mu, \sigma_i^2 + \tau^2)
\end{align*}
\]

- data: \( y_i \) (and \( \sigma_i \))
- two unknowns:
  - “effect” \( \mu \in \mathbb{R} \) (of primary interest)
  - “heterogeneity” \( \tau \geq 0 \) (between-study variance component)
investigation of efficacy of migraine treatments in children (OR > 1 indicates benefit)

desirable: RCTs with placebo control

paediatric patients: ethical concerns / feasibility

<table>
<thead>
<tr>
<th>publication</th>
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<th>triptan</th>
<th>placebo</th>
<th>log–OR</th>
<th>CI</th>
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<tbody>
<tr>
<td>Ueberall (1999)</td>
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3 paediatric studies (<12yr)
Migraine example data

Triptans for headache relief in children (and adolescents)

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<tr>
<td>Hämäläinen (1997b)</td>
<td>adolescents</td>
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<td>[−0.876, 1.785]</td>
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<td>Rothner (1997)</td>
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<td>113 / 226</td>
<td>46 / 74</td>
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<td>[−1.034, 0.041]</td>
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<td>Winner (1997)</td>
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<td>111 / 222</td>
<td>32 / 76</td>
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<td>[−0.207, 0.844]</td>
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<td>Rothner (1999a)</td>
<td>adolescents</td>
<td>96 / 186</td>
<td>20 / 34</td>
<td>−0.292</td>
<td>[−1.033, 0.449]</td>
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<td>Rothner (1999b)</td>
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<td>17 / 62</td>
<td>7 / 30</td>
<td>0.216</td>
<td>[−0.797, 1.230]</td>
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<td>Rothner (1999c)</td>
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<td>23 / 66</td>
<td>14 / 36</td>
<td>−0.174</td>
<td>[−1.014, 0.666]</td>
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<td>1.035</td>
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<td>Visser (2004a)</td>
<td>adolescents</td>
<td>159 / 233</td>
<td>165 / 240</td>
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<td>[−0.412, 0.364]</td>
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<td>Ahonen (2006)</td>
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<td>71 / 96</td>
<td>35 / 96</td>
<td>1.599</td>
<td>[0.982, 2.216]</td>
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<td>Evers (2006)</td>
<td>adolescents</td>
<td>18 / 29</td>
<td>8 / 29</td>
<td>1.458</td>
<td>[0.350, 2.565]</td>
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<td>262 / 480</td>
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<td>141 / 242</td>
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<td>[−0.013, 0.621]</td>
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<td>Callenbach (2007)</td>
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<td>19 / 46</td>
<td>15 / 46</td>
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<td>Lewis (2007)</td>
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<td>97 / 148</td>
<td>67 / 127</td>
<td>0.533</td>
<td>[0.046, 1.019]</td>
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<td>82 / 144</td>
<td>79 / 133</td>
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<td>Linder (2008)</td>
<td>adolescents</td>
<td>383 / 544</td>
<td>94 / 170</td>
<td>0.654</td>
<td>[0.300, 1.008]</td>
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<td>Ho (2012)</td>
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<td>167 / 284</td>
<td>147 / 286</td>
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<td>Fujita (2014)</td>
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<td>23 / 74</td>
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3 paediatric studies (<12yr) + 20 adolescent studies (12–17yr)\(^2\)

Extrapolation
Bayesian framework

- extrapolation:
  - Bayesian methods commonly **suggested**\(^3\)
  - Bayesian methods predominant approach **in practice**\(^4\)

- obvious approaches:
  - via hierarchical models
  - via **informative prior** distribution

- here: Bayesian meta-analysis via **bayesmeta** R package\(^5\)

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\(^3\) e.g.: European Medicines Agency (EMEA). Guideline on clinical trials in small populations, July 2006.
Food and Drug Administration (FDA). Leveraging existing clinical data for extrapolation to pediatric uses of medical devices - guidance for industry and food and drug administration staff. Draft guidance, June 2016.


\(^5\) [http://cran.r-project.org/package=bayesmeta](http://cran.r-project.org/package=bayesmeta)
Informative priors & robustness

- **danger**: posterior as simplistic prior / data “compromise”
- **desirable**: sensible behaviour in case of prior / data conflict;
in case of doubt, data should overrule prior
- **approach**: robustness via heavy-tailed mixture priors\(^6\)

- here: two parameters–
  - informative priors for effect and/or heterogeneity?
  - include further external information?\(^7\)

- in following (for simplicity):
  informative joint effect / heterogeneity prior

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Robust mixture priors

Setup

- idea: prior $p(\theta)$ for children’s data as a mixture:

$$p(\theta) = (1 - w) \times p_1(\theta) + w \times p_2(\theta)$$

where

- $p_1(\theta)$ is uninformative / vague
- $p_2(\theta)$ is informative (based on adolescent data + prior $p_1$)
- $w \in [0, 1]$ expresses certainty about external data’s relevance

- interpretation: e.g., $w = 50%$ - -
  - same effect with probability $w = 50%$
  - separate effects with probability $(1 - w) = 50%$

- mixture setup should lead to robust behaviour in case of prior/data conflict

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Robust mixture priors

Inference

- technically: **mixture prior** implies **mixture posterior**
  \( \rightarrow \) model averaging

- **posterior** again is a **mixture** of (conditional) posteriors under priors \( p_1 \) and \( p_2 \)

- **weighting** of posteriors is given through **marginal likelihoods** (Bayes factor) and weight \( w \)

- only need to determine two posteriors and Bayes factor, then re-weight

- equivalence of **meta-analytic-predictive (MAP)** and **meta-analytic-combined (MAC)** approaches simplifies computations\(^9\)

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Example: children’s effect prior setup

- **vague prior** $p_1$:
  - effect: $\mu \sim N(0, 2^2)$
  - heterogeneity: $\tau \sim \text{halfNormal}(0.5)$
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- **informative prior** $p_2$
  (posterior from adolescent studies):
  - effect: $\mu = 0.30$ [0.07, 0.54]
  - heterogeneity: $\tau = 0.41$ [0.21, 0.65]
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(1 – $w = 50\%$)

(w = 50\%)

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Example: children’s effect posterior

- based on **vague** prior $p_1$ (only children’s data):
  - effect: $\mu = 0.55 \ [−0.24, 1.50]$
  - heterogeneity: $\tau = 0.49 \ [0.00, 1.04]$
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  - effect: \( \mu = 0.33 \ [0.10, 0.56] \)
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- Bayes factor: 5.12

**Weight**
- weight: 16.3%
- weight: 83.7%
## Example: estimates

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<td>0.554</td>
<td><strong>[-0.240, 1.495]</strong></td>
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<tr>
<td><strong>children combined</strong></td>
<td></td>
<td>0.338</td>
<td><strong>[0.003, 0.875]</strong></td>
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</table>

### Log–OR Distribution

-1 0 1 2 3

log–OR
Example: sensitivity check

- what role does the specification of **prior weight** \( w \) play?
- \( w = 0 \) \( \Rightarrow \) ignorance of adolescent data
- \( w = 1 \) \( \Rightarrow \) complete pooling

**Graph:**
- standalone analysis
- complete pooling
- effect \( \mu \) (posterior median and 95% CI)
- \( p(M_1) \)
2nd example: paediatric transplantation

- effect of Interleukin-2 receptor antagonists (IL-2RA) on acute rejection reaction after liver transplantation (OR < 1 indicates benefit)
- 2 RCTs in children\(^\text{10}\), 14 in adults\(^\text{11}\). In conflict?

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<td>0.000</td>
<td>[−2.869, 2.869]</td>
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<td>Neuhaus (2002)</td>
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<td>Yan (2004)</td>
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<td>−1.435</td>
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<td>Boillot (2005)</td>
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<td>[−0.399, 0.278]</td>
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<td>Fasola (2005)</td>
<td>adults</td>
<td>−0.765</td>
<td>[−1.792, 0.263]</td>
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<td>Yoshida (2005)</td>
<td>adults</td>
<td>−0.211</td>
<td>[−0.952, 0.529]</td>
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<tr>
<td>de Simone (2007)</td>
<td>adults</td>
<td>−0.264</td>
<td>[−0.978, 0.450]</td>
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<td>Kato, cohort 1 (2007)</td>
<td>adults</td>
<td>−0.385</td>
<td>[−1.801, 1.031]</td>
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<td>Kato, cohort 2 (2007)</td>
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<td>Klintmalm (2007)</td>
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<td>Calmus (2010)</td>
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<td>[−0.671, 0.638]</td>
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<td>−0.263</td>
<td>[−0.482, −0.053]</td>
</tr>
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<td>Spada (2006)</td>
<td>children</td>
<td>−1.258</td>
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<td><strong>children only</strong></td>
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<td>−1.693</td>
<td>[−2.735, −0.620]</td>
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2nd example: children’s effect prior setup

- **vague prior** \( p_1 \):
  - effect: \( \mu \sim N(0, 2^2) \)
  - heterogeneity: \( \tau \sim \text{halfNormal}(0.5) \)

- **informative prior** \( p_2 \)
  - (posterior from adult studies):
    - effect: \( \mu = -0.26 \ [ -0.48, 0.05 ] \)
    - heterogeneity: \( \tau = 0.11 \ [ 0.00, 0.34 ] \)

\[
(1 - w = 50\%)
\]

\[
(w = 50\%)
\]
2nd example: children’s effect posterior

- based on **vague** prior $p_1$ (only children’s data):
  - effect: $\mu = -1.71$ [−2.73, −0.62]
  - heterogeneity: $\tau = 0.33$ [0.00, 0.94]

- based on **informative** prior $p_2$
  (adolescents’ + children’s data):
  - effect: $\mu = -0.37$ [−0.66, −0.13]
  - heterogeneity: $\tau = 0.22$ [0.00, 0.55]

- **Bayes factor**: 0.032
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2nd example: estimates

<table>
<thead>
<tr>
<th>publication</th>
<th>subjects</th>
<th>log–OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Washburn (2001)</td>
<td>adults</td>
<td>0.000</td>
<td>[−2.869, 2.869]</td>
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<tr>
<td>Neuhaus (2002)</td>
<td>adults</td>
<td>−0.256</td>
<td>[−0.663, 0.152]</td>
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<tr>
<td>Yan (2004)</td>
<td>adults</td>
<td>−1.435</td>
<td>[−2.900, 0.030]</td>
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<tr>
<td>Boillot (2005)</td>
<td>adults</td>
<td>−0.060</td>
<td>[−0.399, 0.278]</td>
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<tr>
<td>Fasola (2005)</td>
<td>adults</td>
<td>−0.765</td>
<td>[−1.792, 0.263]</td>
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<td>Yoshida (2005)</td>
<td>adults</td>
<td>−0.211</td>
<td>[−0.952, 0.529]</td>
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<tr>
<td>de Simone (2007)</td>
<td>adults</td>
<td>−0.264</td>
<td>[−0.978, 0.450]</td>
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<tr>
<td>Kato, cohort 1 (2007)</td>
<td>adults</td>
<td>−0.385</td>
<td>[−1.801, 1.031]</td>
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<tr>
<td>Kato, cohort 2 (2007)</td>
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<td>[−2.358, 0.683]</td>
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<tr>
<td>Klintmalm (2007)</td>
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<td>[−0.789, 0.308]</td>
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<td>Schmeding (2007)</td>
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<tr>
<td>Lupo (2008)</td>
<td>adults</td>
<td>−0.788</td>
<td>[−2.214, 0.637]</td>
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<tr>
<td>Neuberger (2009)</td>
<td>adults</td>
<td>−0.604</td>
<td>[−1.134, −0.074]</td>
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<tr>
<td>Calmus (2010)</td>
<td>adults</td>
<td>−0.016</td>
<td>[−0.671, 0.638]</td>
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<td><strong>adults only</strong></td>
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<td>[<strong>−0.482, −0.053</strong>]</td>
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<tr>
<td>Spada (2006)</td>
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<td>[−2.517, −0.000]</td>
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<tr>
<td><strong>children only</strong></td>
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<td><strong>−1.693</strong></td>
<td>[<strong>−2.735, −0.620</strong>]</td>
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<tr>
<td><strong>children combined</strong></td>
<td></td>
<td><strong>−1.673</strong></td>
<td>[<strong>−2.648, −0.309</strong>]</td>
</tr>
</tbody>
</table>

prior/data conflict reflected in results
2nd example: sensitivity check

- check: effect of **prior weight** \( w \)
- \( w = 0 \)  \( \Rightarrow \) ignorance of adolescent data
- \( w = 1 \)  \( \Rightarrow \) complete pooling

\[
\begin{align*}
\mu & \text{(posterior median and 95\% CI)} \\
\end{align*}
\]
Variations / extensions
More than two prior components

- choice of “vague” standard deviation (here: $\sigma = 2$) is relevant (affects Bayes factor: *Lindley’s paradox*)
- may consider more than 2 prior components, e.g.:
  - common effect $\mu$ and heterogeneity $\tau$ (“complete pooling”)
  - common heterogeneity $\tau$ only (“heterogeneity pooling”)
  - common effect $\mu$ only (“effect pooling”)
  - no common parameters (“standalone analyses”)
- plausible?
- complex models may be barely distinguishable based on little data
- sparser models may be more desirable (*Ockham’s razor*)
Conclusions

- meta analyses often based on few studies (especially subgroup analyses)
- Bayesian approach formalizes otherwise often informal extrapolation / model choice; incorporates uncertainty
- transparent information flow (prior distribution, Bayes factor, ...)
- computations relatively easy using bayesmeta R package
- prior settings need to be chosen carefully
- may check sensitivity to model specifications
- model variations: mixtures of $\geq 2$ components
- many generalizations possible
  (other sources of external information, “main” analysis not a meta-analysis, ...)

C. Röver, S. Wandel, T. Friede.
Model averaging for robust extrapolation in evidence synthesis.
+++ additional slides +++
Example R code

Three meta analyses

```
# main MA computations:

require("bayesmeta")
vaguepriorsd <- 2

# meta analysis for adolescents only:
bma.adol <- bayesmeta(y=logOR.adol, sigma=stdErr.adol,
                      mu.prior.mean=0, mu.prior.sd=vaguepriorsd,
                      tau.prior=function(t){dhalfnormal(t,scale=0.5)})

# meta analysis for children only:
bma.child <- bayesmeta(y=logOR.children, sigma=stdErr.children,
                       mu.prior.mean=0, mu.prior.sd=vaguepriorsd,
                       tau.prior=function(t){dhalfnormal(t,scale=0.5)})

# joint meta analysis for all patients:
bma.joint <- bayesmeta(y=c(logOR.adol, logOR.children),
                      sigma=c(stdErr.adol, stdErr.children),
                      mu.prior.mean=0, mu.prior.sd=vaguepriorsd,
                      tau.prior=function(t){dhalfnormal(t,scale=0.5)})
```
```
bayesfactor <- bma.joint$marginal / (bma.adol$marginal * bma.child$marginal)

prior.odds <- 0.5 / (1 - 0.5)

# determine posterior:
prior.odds <- prior.odds * bayesfactor
post.odds <- post.odds / (post.odds + 1)
post.prob <- post.odds / (post.odds + 1)
print(post.prob)  # =0.837

# plot posterior density:
x <- seq(-0.5, 1.0, le=200)
plot(x, (1-post.prob) * bma.child$dposterior(mu=x)
     + post.prob * bma.joint$dposterior(mu=x),
     type="l", xlab="log-OR", ylab="posterior density")

# (...)
## Simulations

Coverage, CI width; homogeneous and heterogeneous scenarios

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<th># studies</th>
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