Complementing evidence from a small scale RCT by registry data in a rare disease setting

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Creutzfeld-Jakob disease (CJD): a (very) rare disease

A small randomized trial (N=12) on the use of Doxycycline was conducted (endpoint: survival), registry data (N=88) was considered in addition (analysis stratified by propensity scores)

heterogeneity anticipated
both estimates were combined (using standard random-effects meta-analysis)¹

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<th>95% CI</th>
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normal-normal hierarchical model (NNHM):

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y_i | \theta_i \sim \text{Normal}(\theta_i, \sigma_i^2), \\
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- study-specific effects \( \theta_i \)
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(Bayesian approach: prior specification for \( \mu \) and \( \tau \))
Random-effects meta-analysis

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HR

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**Introduction**

Random-effects meta-analysis

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Complementing evidence from an RCT...
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Introduction
Shrinkage estimation

commonly:
- main interest in overall effect $\mu$

shrinkage estimation:
- (updated) estimate of study’s specific effect $\theta_i$
- based on all estimates $(y_1, \ldots, y_k, \sigma_1, \ldots, \sigma_k)$
- more or less “shrunk” towards the overall mean $\mu$, (depending on heterogeneity)
- a.k.a. best linear unbiased prediction (BLUP) \(^2\)

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Why shrinkage?

- often of primary interest: a particular study (-outcome)
- here:
  - randomized study
  - additional data
- aim: to infer the randomized study’s outcome
  (a shrinkage estimate, not an overall mean\(^3\))
- NNHM (meta-analysis) model provides framework
- useful when data are sparse (e.g., rare diseases)

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Shrinkage estimation
The MAP / MAC connection

- Two ways to analyze $i$th estimate:
  - **Meta-analytic-combined (MAC)** approach: perform joint meta-analysis of all studies, determine $i$th shrinkage estimate
  - **Meta-analytic-predictive (MAP)** approach: meta-analyze all but $i$th study; resulting posterior yields *meta-analytic predictive (MAP)* prior, use MAP prior and data $y_i$ to infer $\theta_i$

- Both approaches yield identical results

**MAP approach**
  - Additional motivation
  - Quantification of information contributed by additional studies

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consider: primary interest in randomized trial outcome (no “breaking of randomization” by pooled analysis)

does it make sense to consider shrinkage estimates from a 2-study meta-analysis?

how do shrinkage estimates behave in general?
Shrinkage estimation

Two-study scenario

- consider: primary interest in randomized trial outcome (no “breaking of randomization” by pooled analysis)
- does it make sense to consider shrinkage estimates from a 2-study meta-analysis?
- how do shrinkage estimates behave in general?

- investigate example cases

- consider pair of studies, binary endpoint (log-OR);
  $n_1 = 25, n_2 = 400 \rightarrow$ approx. $\sigma_1 = 0.8, \sigma_2 = 0.2$
- effect prior: $p(\mu) = \text{uniform}$
- heterogeneity prior: $p(\tau) = \text{half-Normal}(0.5)$
\[ \sigma_1 = 0.8, \quad \sigma_2 = 0.2, \text{ interested in } \theta_1 \]
Shrinkage estimation

Two-study scenario

\[ y_2 - y_1 \]

\[ \text{shrinkage interval} \]

\[ y_1 - 1.96 \sigma_1 \]
\[ y_1 + 1.96 \sigma_1 \]

\( \sigma_1 = 0.8, \quad \sigma_2 = 0.2, \) interested in \( \theta_1 \)
Shrinkage estimation
Two-study scenario

\[ y_2 - y_1 \]

shrinkage interval

\[ y_1 - 1.96 \sigma_1, y_1 + 1.96 \sigma_1 \]

\[ y_1, y_1 + 1.96 \sigma_1 \]

\[ y_1 - 1.96 \sigma_1 \]

\[ y_2 \]

\[ \sigma_1 = 0.8, \sigma_2 = 0.2, \text{interested in } \theta_1 \]
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\[ y_1 \pm 1.96 \sigma_1 \]

\[ y_1 - 1.96 \sigma_1 \]

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Two-study scenario

\[ y_2 - y_1 \]

shrinkage interval

'yplain' CI

\[ y_1 - 1.96\sigma_1 \]

\[ y_1 \]

\[ y_1 + 1.96\sigma_1 \]

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robust behaviour
Shrinkage estimation

Two-study scenario

\[ y_2 - y_1 \]

- Shrinkage interval
- 58% 65% 84% 104% 103% 101% 101%

'plain' CI

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robust behaviour

relative shrinkage interval width: may be substantially shorter
Shrinkage estimation

Two-study simulations

- how do shrinkage intervals behave on average?
- what gain can we expect (if any)?

- investigate:
  - coverage
  - interval width

- consider again pairs of studies (binary endpoint);
  \( n_1, n_2 \in \{25, 100, 400\} \),
  \( \sigma_1, \sigma_2 \in \{0.8, 0.4, 0.2\} \)

- prior: uniform prior for \( \mu \), half-Normal(0.5) for heterogeneity \( \tau \)
  (sensitivity analysis with half-Normal(1.0))

- derive estimate for \( \theta_1 \)
## Shrinkage estimation

### Two-study simulations: **coverage (%)**

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## Shrinkage estimation

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**good coverage** for non-extreme heterogeneity
## Shrinkage estimation

**Two-study simulations: relative interval width (%)**

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<td>98.1</td>
<td>98.2</td>
<td>98.6</td>
<td>99.2</td>
</tr>
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*: heterogeneity $\tau$ drawn from prior distribution

- substantial precision gain possible
Shrinkage estimation
The Creutzfeld-Jakob disease (CJD) example

<table>
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<tr>
<th>study</th>
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<th>95% CI</th>
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</thead>
<tbody>
<tr>
<td>observational</td>
<td>0.61</td>
<td>[0.37, 0.99]</td>
</tr>
<tr>
<td>randomized</td>
<td>0.84</td>
<td>[0.24, 2.90]</td>
</tr>
<tr>
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<td><strong>0.65</strong></td>
<td><strong>[0.29, 1.53]</strong></td>
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- shrinkage interval width: 66%
- 129% sample size gain (12 → ≈27 patients)
- results not dominated by external data (only ≈15 of 88 pts. contributed)
Shrinkage estimation
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- quoted estimate • shrinkage estimate

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- shrinkage interval width: 66%
- 129% sample size gain (12 → ≈27 patients)
- results not dominated by external data (only ≈15 of 88 pts. contributed)

```r
> require("bayesmeta")
> # perform analysis:
> bm <- bayesmeta(y = cjd$logHR, sigma = cjd$logHR.se,
+                  labels = cjd$study,
+                  tau.prior = function(t){dhalfnormal(t, scale=0.5)})
> # show shrinkage estimates:
> print(exp(bm$theta[c(7,4,8),"randomized"]))
95% lower    median 95% upper
0.3142006 0.6767489 1.6112718
```
Conclusions
Shrinkage estimation for 2 studies

- readily motivated, transparent
- valid (coverage close to nominal level)
- robust behaviour
- potentially substantial gain despite ‘pathological’ setting ($k = 2$)
- especially if external data come with great precision ($\sigma_2 \leq \sigma_1$)
- special “$k = 2$”-case: alternative parametrisation possible (reference to “overall mean” $\mu$ not necessary)
- article under review\(^5\)
- computations quick & easy using \texttt{bayesmeta} R package\(^6\)


\(^6\)http://cran.r-project.org/package=bayesmeta
+++ additional slides +++
CJD example

R code

cjd <- cbind.data.frame("study" = c("observational", "randomized"),
                      "logHR"  = c(-0.49948, -0.17344),
                      "logHR.se" = c(0.2493, 0.6312))

# analyze:
require("bayesmeta")
bm <- bayesmeta(y = cjd$logHR,
                sigma = cjd$logHR.se,
                labels = cjd$study,
                tau.prior = function(t){dhalfnormal(t, scale=0.5)})

# show results:
print(bm)

# show forest plot:
forestplot(bm, xlab="log-HR")

# show shrinkage estimates:
print(bm$theta)
print(exp(bm$theta[c(7,4,8), "randomized"]))
the normal-normal hierarchical model (NNHM):

\[ y_i | \theta_i \sim \text{Normal}(\theta_i, \sigma_i^2), \]
\[ \theta_i | \mu, \tau \sim \text{Normal}(\mu, \tau^2) \quad (\text{for } i = 1, \ldots, k) \]

the alternative reference model:

\[ y_i | \vartheta_i \sim \text{Normal}(\vartheta_i, \sigma_i^2), \]
\[ \vartheta_1 | \alpha, \beta \sim \text{Normal}(\alpha, 0) \quad (\text{i.e., } \vartheta_1 = \alpha), \]
\[ \vartheta_2 | \alpha, \beta \sim \text{Normal}(\alpha, \beta^2) \]

both models yield identical shrinkage estimates\(^7\) for \(k = 2\) and

- (improper) uniform priors for \(\mu\) and \(\alpha\)
- (any) heterogeneity prior with density \(p(\tau) = f_*(\tau)\),
  and matching prior with density \(p(\beta) = \frac{1}{\sqrt{2}} f_*(\frac{\beta}{\sqrt{2}})\) for \(\beta\)

Heterogeneity ($\tau$)

Half-Normal prior: motivation (1)

- **recommended family**: half-$t$, half-Normal, half-Cauchy
  (*not* recommended: inverse-Gamma)

- effect measure here: logarithmic **ratio** (odds ratio, hazard ratio,...)

- heterogeneity $\tau$ may be translated into implied **spread of effects** $\theta_i$ and $\exp(\theta_i)$

- Spiegelhalter et al. (2004)\(^9\) proposed **categories**
  - “reasonable”: $0.1 < \tau < 0.5$
  - “fairly high”: $0.5 < \tau < 1.0$
  - “fairly extreme”: $\tau > 1.0$

- Turner & al. (2015)\(^{10}\) empirically investigated heterogeneity in meta-analyses archived in the Cochrane Library

---


Heterogeneity ($\tau$)
Half-Normal prior: motivation (2)

- **proposed categories:**
  - “reasonable”: $0.1 < \tau < 0.5$
  - “fairly high”: $0.5 < \tau < 1.0$
  - “fairly extreme”: $\tau > 1.0$

- **Implications** of certain $\tau$ values:
  *95% range of effects* $\exp(\theta_i)$
  *spans a range of* $\exp(3.92\tau)$
  *(ratio largest / smallest)*

<table>
<thead>
<tr>
<th>$\tau$</th>
<th>$\exp(3.92\tau)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>1.00</td>
</tr>
<tr>
<td>0.1</td>
<td>1.48</td>
</tr>
<tr>
<td>0.2</td>
<td>2.19</td>
</tr>
<tr>
<td>0.5</td>
<td>7.10</td>
</tr>
<tr>
<td>1.0</td>
<td>50.4</td>
</tr>
<tr>
<td>2.0</td>
<td>2540</td>
</tr>
</tbody>
</table>
Heterogeneity ($\tau$)

Half-Normal prior: motivation (3)

- Small: "reasonable"
- Fairly high: "fairly high"
- Fairly extreme: "fairly extreme"

Turner et al. (2015)

- Half-Normal(0.5)
- Half-Normal(1.0)
Standard errors and sample sizes

Heuristics

- assume: standard errors scale with $\frac{1}{\sqrt{N}}$
- doubling the sample size ($N = 2 \times N_0$) means a shorter s.e., shorter by a factor of $\frac{1}{\sqrt{2}} = 71\%$

<table>
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<tr>
<th>$N$</th>
<th>$\frac{1}{\sqrt{N/N_0}}$</th>
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<tbody>
<tr>
<td>$N_0$</td>
<td>100 %</td>
</tr>
<tr>
<td>$2N_0$</td>
<td>71 %</td>
</tr>
<tr>
<td>$3N_0$</td>
<td>58 %</td>
</tr>
<tr>
<td>$4N_0$</td>
<td>50 %</td>
</tr>
<tr>
<td>...</td>
<td>...</td>
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</tr>
<tr>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>$\sigma/\sigma_0$</th>
<th>gain</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 %</td>
<td>0 %</td>
</tr>
<tr>
<td>90 %</td>
<td>23 %</td>
</tr>
<tr>
<td>80 %</td>
<td>56 %</td>
</tr>
<tr>
<td>70 %</td>
<td>104 %</td>
</tr>
<tr>
<td>50 %</td>
<td>300 %</td>
</tr>
<tr>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

- inversely: a SE only $\frac{\sigma}{\sigma_0} = 71\%$ as wide
  implies a 100% gain in sample size
- generally:
  effective sample size gain $(\frac{\sigma}{\sigma_0})^{-2} - 1$
Shrinkage estimation

Two-study simulations: **relative sample size gain (%)**

| $n_1/n_2$ | $\tau$ | 0.0 | 0.1 | 0.2 | 0.5 | 1.0 | 2.0 | *
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
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<th></th>
<th></th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>25/400</td>
<td></td>
<td>162</td>
<td>160</td>
<td>158</td>
<td>144</td>
<td>113</td>
<td>68.4</td>
<td>147</td>
</tr>
<tr>
<td>25/100</td>
<td></td>
<td>123</td>
<td>123</td>
<td>121</td>
<td>111</td>
<td>89.6</td>
<td>56.3</td>
<td>113</td>
</tr>
<tr>
<td>100/400</td>
<td></td>
<td>64.5</td>
<td>64.0</td>
<td>60.0</td>
<td>43.8</td>
<td>25.7</td>
<td>12.7</td>
<td>49.4</td>
</tr>
<tr>
<td>25/25</td>
<td></td>
<td>61.2</td>
<td>60.9</td>
<td>60.7</td>
<td>58.4</td>
<td>51.8</td>
<td>36.9</td>
<td>58.7</td>
</tr>
<tr>
<td>100/100</td>
<td></td>
<td>38.8</td>
<td>38.1</td>
<td>37.1</td>
<td>29.6</td>
<td>19.4</td>
<td>10.1</td>
<td>32.3</td>
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<tr>
<td>400/400</td>
<td></td>
<td>24.2</td>
<td>22.9</td>
<td>19.4</td>
<td>11.0</td>
<td>5.5</td>
<td>2.4</td>
<td>15.1</td>
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<tr>
<td>100/25</td>
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<td>15.9</td>
<td>16.0</td>
<td>15.8</td>
<td>14.8</td>
<td>11.9</td>
<td>7.5</td>
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<td>10.7</td>
<td>10.0</td>
<td>7.3</td>
<td>4.2</td>
<td>2.0</td>
<td>8.3</td>
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<tr>
<td>400/25</td>
<td></td>
<td>4.1</td>
<td>4.1</td>
<td>4.0</td>
<td>3.7</td>
<td>2.9</td>
<td>1.7</td>
<td>3.7</td>
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*: heterogeneity $\tau$ drawn from prior distribution