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Dynamically borrowing strength from another study through shrinkage estimation

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Abstract

Meta-analytic methods may be used to combine evidence from different sources of information. Quite commonly, the normal–normal hierarchical model (NNHM) including a random-effect to account for between-study heterogeneity is utilized for such analyses. The same modeling framework may also be used to not only derive a combined estimate, but also to borrow strength for a particular study from another by deriving a *shrinkage estimate*. For instance, a small-scale randomized controlled trial could be supported by a non-randomized study, e.g. a clinical registry. This would be particularly attractive in the context of rare diseases. We demonstrate that a meta-analysis still makes sense in this extreme case, effectively based on a synthesis of only two studies, as illustrated using a recent trial and a clinical registry in Creutzfeld-Jakob disease. Derivation of a shrinkage estimate within a Bayesian random-effects meta-analysis may substantially improve a given estimate even based on only a single additional estimate while accounting for potential effect heterogeneity between the studies. Alternatively, inference may equivalently be motivated via a model specification that does not require a common overall mean parameter but considers the treatment effect in one study, and the difference in effects between the studies. The proposed approach is quite generally applicable to combine different types of evidence originating, e.g. from meta-analyses or individual studies. An application of this more general setup is provided in immunosuppression following liver transplantation in children.

Keywords

Random-effects meta-analysis, Bayesian statistics, between-study heterogeneity, shrinkage estimation, posterior predictive *p*-values

1 Introduction

In clinical research of orphan diseases, one of the major problems is often the recruitment of a sufficient number of subjects to perform a meaningful clinical trial. Examples include neuromyelitis optica,[1] myocarditis,[2] and Creutzfeld-Jakob disease (CJD).[3] In such cases, it may be possible to gain some power by using more sophisticated trial designs, and it is often desirable to be able to formally utilize additional information external to the actual trial, which may be implemented via the use of informative prior distributions in the eventual analysis.[4] The external information could be in the form of related studies or elicited expert opinion.[5] For instance, in the context of a small-scale randomized controlled trial in idiopathic nephrotic syndrome in children, a rare condition, Thall et al.[6] recently proposed the elicitation of expert opinions on response probabilities based on the bins-and-chips approach.[7]

When considering external evidence, the obvious danger is that a too simplistic approach may lead to a ‘‘naïve’’ pooling of initially separate data. For example, while data from non-randomized studies (e.g. clinical registries)

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may undoubtedly contribute complementing information to a randomized clinical trial, one may want to prevent a complete mixing of both types of data, which would in a sense also invalidate the original randomization. Rather it seems desirable to stratify the analysis for the different sources by explicitly allowing for potential heterogeneity between data sets, which then implicitly downweights the impact on one another. Here the weights depend on the observed similarity of estimates, also known as *dynamic borrowing* of information.[8] The eventual analysis then may refer explicitly to the outcome of the randomized trial, and not to some overall average, as generally more weight is placed on evidence from randomized controlled trials.

A simple approach originally proposed by Pocock[9] was recently implemented by Schoenfeld et al.,[10] who investigated the use of adult data to support the analysis of a paediatric trial, and who utilized a variance component of known (elicited) magnitude to account for heterogeneity between the two studies' estimates. A closely related approach is implemented in the normal-normal hierarchical model (NNHM) that is commonly utilized in random-effects meta-analysis; the difference essentially is that heterogeneity is treated as an unknown for which a prior distribution may be specified. Technically, inference on the study of primary interest is done by investigating the corresponding *shrinkage estimate*. The contribution of information from additional studies then may readily be evaluated by considering the corresponding *meta-analytic-predictive (MAP)* prior.[11,12] The NNHM is readily generalized (and in fact most commonly used) for combining more than two studies; such an approach may e.g. be used to extrapolate information from early-phase studies in the approval process.[12] In the case of two studies, the NNHM can also be shown to be to some extent equivalent to a similar, more general model specification as we will explain below.

While the interpretation of parameters within the familiar NNHM context is straightforward and with the inclusion of an unknown heterogeneity parameter it is intended that evidence from separate studies is sufficiently loosely connected to provide a robust estimation framework, it is not obvious to what extent this approach actually improves estimates in the extreme case of only two studies or more generally two data sources. Here we develop a suitable statistical hierarchical model to include two sources of data, e.g. two studies or meta-analyses. Within the proposed model, we describe a shrinkage estimator and inference methods including posterior predictive *p*-values. Furthermore, the value of this approach in the particular case of only two studies is evaluated in simulations.

The manuscript is organized as follows. In the next section, we present the statistical model and, in particular, shrinkage estimation and inference. The following sections are dedicated to a simulation study investigating the operating characteristics of the proposed methodology and an application in CJD. Motivated by a meta-analysis investigating the effect of immunosuppression in paediatric liver transplantation patients, we extend the shrinkage applications to more general settings considering two data sources, e.g. two meta-analyses, rather than two studies. Finally, we close with some conclusions and a brief discussion.

2 Statistical model and shrinkage estimation

2.1 The normal–normal hierarchical model

The most commonly used model for random-effects meta-analysis is the normal-normal hierarchical model (NNHM). This model is applicable for the joint analysis of several (k) real-valued effect measurements y_i that have individual standard errors σ_i associated ($i = 1, \ldots, k$). Here it is assumed that each observation y_i is a noisy measurement of an underlying true value θ_i with a normally distributed offset whose magnitude is given through the (known) standard error σ_i

$$y_i|\theta_i \sim \mathrm{N}(\theta_i, \sigma_i^2) \tag{1}$$

The θ_i then may be more or less similar across measurements; at the study level, a certain amount of *heterogeneity* is anticipated by introducing another variance component τ and assuming

$$\theta_i|\mu, \tau \sim \mathrm{N}(\mu, \tau^2) \tag{2}$$

where the overall effect μ and heterogeneity $\tau \geq 0$ are unknown. If $\tau = 0$, the model simplifies to the *fixed-effect* model, in which $\theta_1 = \cdots = \theta_k = \mu$, but in general this is a *random-effects* model.[13–15] In the following, we will mostly be concerned with the special case of analyzing only $k = 2$ studies. Note that while classically, in the meta-analysis context, the y_i usually originate from different *studies*, more generally these may also be *estimates* of other kinds, e.g. estimates from meta-analyses.

2.2 Shrinkage estimation

Quite commonly, the main interest lies in determining the *overall effect* μ. When the aim of the analysis is to provide a basis for planning a new study, it may also be of interest to *predict* a future outcome θ_{k+1}. In some cases, however, it is of interest to derive an updated estimate for a particular (ith) study effect θ_i, which is informed by the remaining studies under consideration.

If the heterogeneity τ was zero, then the model would reduce to the fixed-effect model, and all estimates y_i would effectively relate to the same parameter ($\theta_i = \mu$), which may then be jointly estimated by simply averaging the estimates y_i (with "inverse variance" weights). If the heterogeneity appears to be close to zero, then the model will behave similarly to the fixed-effect model, and all estimated study effects θ_i will be "shrunk" towards the estimated overall mean μ to some degree. If on the other hand the heterogeneity is large, then there is very little to be learned from one estimate (y_i) about another parameter (θ_j, $j \neq i$), and different estimates only provide very little support to one another. Effectively, this results in more or less *shrinkage* towards the overall mean μ, depending on the apparent heterogeneity in the data.[12,16] This *shrinkage estimation* of study-specific means θ_i, which is also known as *best linear unbiased prediction (BLUP)* in a frequentist framework,[17–19] will be our focus in the following. When the heterogeneity τ is assumed fixed and known (and an improper uniform prior for μ is used), then the frequentist and Bayesian approaches lead to identical mean effect (μ)[20] as well as shrinkage estimates (θ_i)[17,21]; in general, however, these are different.

2.3 The Bayesian approach to meta-analysis

The inference problems within the NNHM may be approached using frequentist or Bayesian methods.[13–15,21,22] A Bayesian approach has proven especially useful in cases where large-sample asymptotics do not apply,[23] e.g. for the analysis of few studies[20] or even only two studies.[24] Here, we will follow a Bayesian approach and investigate its properties in some more detail.

Within the NNHM we have several unknowns; first the study-specific effects θ_i, whose hyperprior is given through Equation (2). For the overall mean effect μ, it is often convenient to use a non-informative (improper) uniform prior. The heterogeneity $\tau \geq 0$ determines the expected variability between individual studies; depending on the measurement scale of the considered effects, in practical applications a plausible upper bound can usually be specified. Half-normal (HN) priors (e.g. with scale parameters 0.5 or 1.0) have proven useful, for example, in the context of logarithmic odds-ratio (log-OR) endpoints.[20,22,25] An analogous reasoning similarly applies for many log-transformed endpoints, like relative risks or hazard ratios; if different studies are considered unlikely to differ by more than a certain *factor*, then one can usually translate this into a prior specification for the heterogeneity τ on the logarithmic scale.[21,22]

The heterogeneity τ is usually considered a nuisance parameter, while the primary interest is in inferring the overall effect (μ), a prediction (θ_{k+1}), or a shrinkage estimate (θ_i). Within the Bayesian framework, shrinkage estimation may be motivated in two different ways; the *meta-analytic-combined (MAC)* approach simply considers the shrinkage estimate as one of the parameters in the NNHM model, where all k studies are analyzed jointly. The *meta-analytic-predictive (MAP)* approach on the other hand considers the same problem sequentially: first, all but the ith study are analyzed, and the derived posterior (predictive) distribution then constitutes the prior for the analysis of the ith study. Both approaches can be shown to be equivalent and lead to identical results,[11] but the MAP approach allows to explicate the information 'borrowed' from the additional estimates via the MAP prior. Technically, inference requires integration over the parameters' posterior distribution,[16,22] for example, to derive the relevant marginal posterior distribution for shrinkage estimation ($p(\theta_i|y_1, y_2, \sigma_1, \sigma_2)$). Computations for inference within the NNHM may be performed in `R` using the `bayesmeta` package.[21,26] In the following, the shown estimates will be posterior medians, and credible intervals are determined as shortest posterior intervals.

2.4 *Posterior predictive p-values*

Posterior predictive p-values are conceptually closely related to "classical" p-values, and were originally developed in the context of model checking.[16,27,28] The definition is relatively straightforward; like a classical p-value, it is based on a null hypothesis H_0 and a pre-specified ("test-") statistic or "discrepancy variable" $T(\cdot)$, which is a function of the data. The statistic T is (as usual) defined so that it is sensitive to deviations from the null hypothesis. The realised statistic value $T(y)$ then is determined for the present data set y. In order to judge whether the statistic value is "sufficiently extreme" to constitute evidence against the null hypothesis, it is compared against its *posterior predictive distribution, conditional on* H_0.

Similarly to the usual p-values, this means a comparison against values of the statistic amongst data sets that might have occurred *conditioning on the observed data as well as the null hypothesis*. Technically, posterior predictive p-values are often easily computed using Monte Carlo sampling, which here means first drawing parameter values from the intersection of the parameters' posterior distribution and null hypothesis, then drawing a data set $y^\star$ from the corresponding predictive distribution, and determining the statistic value $T(y^\star)$. Repeated sampling then allows to explore the relevant distribution of statistic values and eventually compute p-values via the corresponding tail probabilities. While posterior predictive p-values generally do not follow a uniform distribution under the null hypothesis, the deviation is usually on the conservative side.[27,29]

The test statistic to be used needs to be pre-specified. For instance, an obvious choice for the overall effect μ may be the posterior probability of a non-beneficial effect, i.e.

$$T(y) = \mathrm{P}(\mu > 0|y) \tag{3}$$

The null hypothesis then is usually specified for a certain parameter as one- or two-sided. Accordingly, the test statistic's relevant distribution (or the sampling scheme, in case of MCMC computation) as well as the statistic's rejection region is affected. Computation of posterior predictive p-values is also implemented in the `bayesmeta` R package.[21]

2.5 The reference model as an alternative variation of the NNHM

When meta-analyzing a pair of estimates, the common NNHM may sometimes be hard to motivate, as an exchangeable model of both estimates θ_i centered around a common mean value μ may seem inappropriate. Consider for example the joint analysis of randomized and observational data; reference to a common mean parameter μ or identical variances τ^2 may be counterintuitive in such a case. An "asymmetric" treatment of both estimates in terms of a "reference" estimate and a "secondary", related observable with an uncertain amount of offset associated may seem more appealing. It is possible to formulate a slight variation of the NNHM following this second approach, which may seem more realistic, and for which one can then show that both approaches are equivalent *as far as shrinkage estimates are concerned*. In the following, we will refer to this model variation as the *reference model*.

Suppose that the prior for the effect μ in the NNHM is given by an (improper) uniform distribution, and that the heterogeneity prior is defined through a density $p_\star(\tau)$. Then the model variation is defined as follows; for the observables y_i we assume

$$y_i|\vartheta_i \sim \mathrm{N}(\vartheta_i, \sigma_i^2) \tag{4}$$

which so far is analogous to the NNHM setup. At the next hierarchy level, we then specify

$$\vartheta_1|\alpha, \beta \sim \mathrm{N}(\alpha, 0) \quad (\text{i.e., } \vartheta_1{=}\alpha), \tag{5}$$

$$\vartheta_2|\alpha, \beta \sim \mathrm{N}(\alpha, \beta^2) \tag{6}$$

where the "effect" parameter α again has an improper uniform prior and the variance component β now has a prior density given by $\frac{1}{\sqrt{2}}p_\star(\frac{\beta}{\sqrt{2}})$. The parameter β hence has a prior that is scaled by a factor of $\sqrt{2}$ relative to τ, which corresponds to a factor 2 difference for the *squared* parameters (the variances).

The reference model parametrisation of the problem is different here in that the two observables y_i are treated asymmetrically. The first one (y_1) measures the parameter α (the reference) "directly", while the second one (y_2) includes an additional offset with variance β^2. The variance component β again implements the heterogeneity between the first and second observable, but in a slightly different manner than in the original NNHM. While the parameterizations are different, the associated shrinkage estimates (for θ_i or ϑ_i) are identical, as shown in detail in Appendix 1. Since $\vartheta_1 = \alpha$, the shrinkage estimate for ϑ_1 is identical to an estimate of α in this context. The NNHM's heterogeneity (τ) prior needs to be re-scaled by a factor of $\sqrt{2}$ to yield the corresponding β prior. Note, however, that the equivalence only holds for the case of $k = 2$ estimates, and an (improper) uniform effect prior; for other cases, the model would need to be adapted accordingly.

As has been pointed out by Neuenschwander et al.,[30] the model may also be regarded as a special case of Pocock's bias model, or the model underlying the commensurate prior. In both instances, for the case of $k = 2$ studies, the discrepancy between the two underlying parameters (here: ϑ_1 and ϑ_2) is also modeled via a variance parameter analogous to β^2 above. The connection is made somewhat differently in the *power prior* model,[31] where the external data are downweighted via an exponential parameter between 0 and 1 that is applied to part of the likelihood function. For a given τ (or β) value, the approaches are again identical when the exponential parameter is set to be $(2\frac{\tau^2}{\sigma_2^2}+1)^{-1}$ or $\left(\frac{\beta^2}{\sigma_2^2}+1\right)^{-1}$.

3 Dependency of the shrinkage estimate on the observed heterogeneity

In the following, we investigate the effect of varying the input data on the resulting shrinkage estimates. The setup is similar to the one also adopted in the subsequent simulation study; we consider the case of two estimates (y_1 and y_2) with standard errors $\sigma_1 = 0.8$ and $\sigma_2 = 0.2$, and we assume a uniform prior for μ and a half-normal (HN) prior with scale 0.5 for the heterogeneity τ. We set $y_1 = 0$ and then vary the difference between the estimates ($y_2 - y_1$), which is in a sense also the ''observed heterogeneity'' in the data. Then we derive the shrinkage estimate for the first parameter θ_1.

Figure 1 (top panel) illustrates the effect on the shrinkage estimate and the corresponding 95% credible interval. One can see how the estimate (posterior median of θ_1) moves (mostly) in concordance with the second estimate (y_2) and that the resulting interval is narrowest when y_1 and y_2 are in close agreement. For larger differences, the estimated heterogeneity increases, less borrowing of information takes place, the interval widens and the estimate of θ_1 is less attracted towards y_2. Eventually the shrinkage interval exhibits a certain degree of robustness and barely changes with increasing difference. This robustness feature may be explained by the fact that implicitly the meta-analysis is equivalent to an analysis of the first study using the MAP-prior based on the second study.[11] The prior derived via the hierarchical model from the first study then is rather vague and heavy-tailed, leading to the robust behaviour.[32]

The middle panel shows that the shrinkage interval is shorter than the ''plain'' interval ($y_1 \pm 1.96\sigma_1$) when the estimates y_1 and y_2 are similar, that it may also get wider in some cases, but that its width eventually is bounded. The bottom panel shows the probability distribution of the difference $y_2 - y_1$ (which has variance $\sigma_1^2 + \sigma_2^2 + 2\tau^2$) for several selected values of τ. Based on the assumptions, the absolute difference is unlikely to exceed a value of, say, $|y_2 - y_1| = 4$, and so the probable cases essentially are those in the left half of the plot.

The scenario shown here is where we would in fact expect the greatest gain from considering the second estimate (y_2) in estimating θ_1, since the second estimate's error is much smaller than the first ($\sigma_2 \ll \sigma_1$). The figure looks qualitatively similar if we match or reverse the relative magnitudes of the standard errors σ_1 and σ_2, and also if we use a wider heterogeneity prior, but in those cases there is less information to be borrowed and hence less ''shrinkage'' taking place.

4 Simulation study

4.1 Setup

The simulations shown in the following are based on the NNHM, and since binary endpoints are very common in meta-analysis applications,[33] the setup is motivated by a scenario featuring a log-OR endpoint. If a study of size n_i results in a contingency table as an outcome, this may be converted into a log-OR that is associated with an approximate standard error of $\sigma_i = \frac{4}{\sqrt{n_i}}$.[21] A similar formula applies, for example, for logarithmic hazard ratios (log-HRs) from a survival analysis with respect to the event counts.[22] In the following, we will consider combinations of ''small'', ''medium'' and ''large'' studies of sizes $n_i \in \{25, 100, 400\}$, corresponding to standard errors of $\sigma_i \in \{0.8, 0.4, 0.2\}$. The true mean effect μ is (arbitrarily) fixed at zero. Analysis of a pair of studies will be based on a uniform prior for the effect μ, and a half-normal (HN) prior for the heterogeneity τ. Heterogeneity values in the range 0.5–1.0 may be considered as *fairly high* and above 1.0 as *fairly extreme*.[22] A prior scale parameter of 0.5 already is a conservative choice, but in addition we also investigate the use of a HN(1.0) prior.[20,22] The true heterogeneity values in the simulation will be varied among $\tau \in \{0.0, 0.1, 0.2, 0.5, 1.0, 2.0\}$ in order to check performance conditional on particular τ values. Similarly, we investigate the *marginal* performance by drawing τ according to the specified prior distribution. The primary interest will be in the first of the two studies ($i = 1$) and especially the shrinkage estimate of its study-specific effect θ_1. The number of simulations for each scenario is 10,000.

We can compare the resulting precision by comparing the 95% shrinkage interval width δ_i with the original confidence interval width and considering the *relative width* $q_i = \frac{\delta_i}{2\times 1.96\sigma_i}$. Assuming that standard errors scale with $n_i^{-0.5}$, we can then estimate the approximate *gain in effective sample size* as $q_i^{-2} - 1$. For example, if the shrinkage

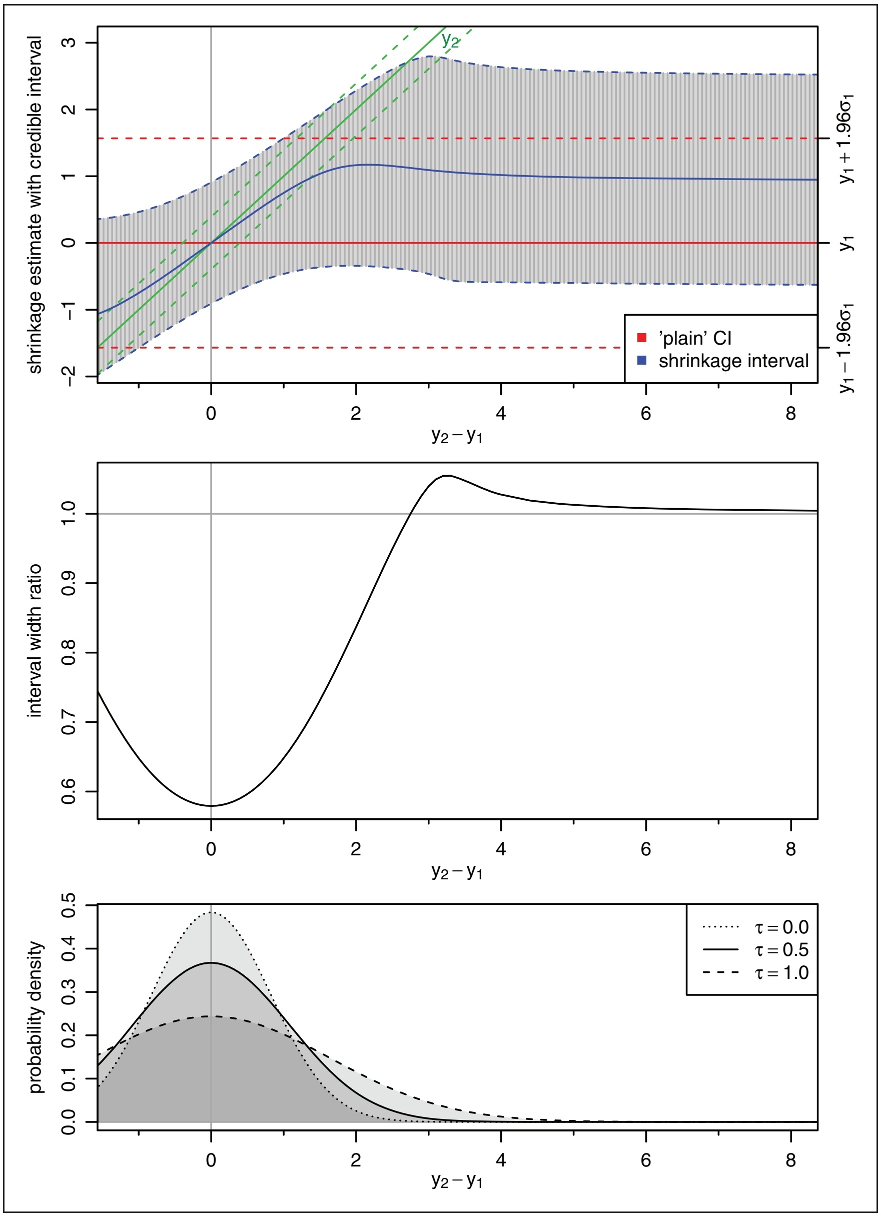


Figure 1. Effect of varying the difference between quoted estimates ($y_2 - y_1$) on the first shrinkage estimate (for θ_1). In the top row, one can see how the interval itself varies relative to the "plain" interval ($y_1 \pm 1.96\sigma_1$, red lines); the second estimate (y_2) and its corresponding CI are shown in green. The second row shows the ratio of interval lengths, and the bottom row shows the probability density of the actualized difference for selected values of τ. The heterogeneity prior used here for the analysis was half-normal (HN) with scale 0.5.

interval is only half as wide as the original interval, this precision gain corresponds to a roughly four-fold (300%) increase in sample size. If the interval is $q_i = 90\%$ as wide, then this corresponds to an approximate $q_i^{-2} - 1 = 23\%$ increase. R code to reproduce the simulations is included in the supplement.

4.2 Coverage

Table 1 illustrates the coverage of shrinkage intervals for the effect θ_1 for different combinations of study sizes (n_1, n_2), heterogeneity values (τ) and heterogeneity priors (scales 0.5 and 1.0). The columns marked by an asterisk (*) correspond to the "marginal" simulations in which heterogeneity τ is not fixed, but varied according to the specified prior distribution. Coverages are close to or above the nominal 95% level, except if heterogeneity

Table 1. Coverage (%) of shrinkage intervals for estimation of the first study's mean parameter (θ_1).

	τ prior:	HN (0.5)							HN (1.0)						
n_1/n_2	τ:	0.0	0.1	0.2	0.5	1.0	2.0	*	0.0	0.1	0.2	0.5	1.0	2.0	*
25/400		99.7	99.6	98.9	93.4	84.0	79.0	94.7	99.3	99.3	99.0	96.7	92.5	90.5	95.1
25/100		98.7	98.7	98.1	93.9	86.1	80.0	95.1	98.4	98.6	98.5	96.5	93.2	90.8	94.4
100/400		98.7	98.2	97.1	93.2	90.9	90.4	94.9	98.1	97.7	97.2	94.8	93.7	93.5	95.3
25/25		96.6	96.7	96.1	94.5	90.5	84.6	95.0	97.0	97.2	96.6	95.7	94.0	92.1	94.9
100/100		96.7	96.5	96.3	94.0	91.1	90.7	95.7	96.7	96.4	96.6	95.3	93.7	93.6	94.9
400/400		96.7	96.6	95.0	94.0	94.0	93.9	95.0	96.4	96.4	95.0	94.9	94.9	94.8	95.0
100/25		96.0	95.6	95.3	94.8	93.8	92.3	94.7	96.0	95.8	95.6	95.2	94.7	94.3	94.8
400/100		95.5	95.6	95.4	94.7	93.7	93.8	95.1	95.6	95.5	95.5	94.9	94.3	94.5	95.1
400/25		95.1	95.1	95.2	94.7	94.9	94.5	95.3	95.0	95.2	95.2	94.8	95.0	95.0	95.2

Note: Sample sizes (n_1 and n_2) as well as settings for the heterogeneity prior ($p(\tau)$) and actual heterogeneity values (τ) are varied. The columns labelled by an asterisk (*) correspond to drawing the heterogeneity from its corresponding prior distribution.

Table 2. Mean width (%) of shrinkage intervals (for θ_1) relative to original "plain" CI based only on y_1 and σ_1.

	τ prior:	HN (0.5)							HN (1.0)						
n_1/n_2	τ:	0.0	0.1	0.2	0.5	1.0	2.0	*	0.0	0.1	0.2	0.5	1.0	2.0	*
25/400		62.4	62.7	63.0	65.6	72.1	82.9	65.1	75.6	75.9	76.2	78.6	83.8	90.8	81.5
25/100		67.5	67.5	67.9	69.9	75.2	84.3	69.5	78.4	78.4	78.8	80.9	85.2	91.4	83.2
100/400		78.5	78.7	79.9	85.2	91.3	95.8	83.4	85.7	85.8	86.8	90.9	95.0	97.7	92.1
25/25		78.9	79.0	79.0	79.7	81.8	86.9	79.7	85.2	85.2	85.3	86.2	88.4	92.4	87.6
100/100		85.1	85.3	85.7	88.4	92.5	96.2	87.5	89.9	90.1	90.4	92.7	95.6	97.9	93.9
400/400		89.9	90.5	91.9	95.5	97.8	99.0	93.7	93.0	93.4	94.5	97.2	98.7	99.5	97.3
100/25		92.9	92.9	93.0	93.4	94.6	96.6	93.3	95.0	95.0	95.1	95.6	96.7	98.1	96.1
400/100		95.0	95.1	95.4	96.6	98.1	99.1	96.2	96.5	96.6	96.9	97.9	98.9	99.5	98.2
400/25		98.0	98.0	98.1	98.2	98.6	99.2	98.2	98.6	98.6	98.6	98.8	99.1	99.5	99.0

approaches a priori improbable large values. For the simulations in which τ is drawn from its prior distribution, we know that *by definition* the coverage would be exactly 95% *if* the effect μ was also drawn from its prior.[34] Since the effect prior is improper and μ was arbitrarily fixed at zero for the simulations, this only holds approximately here.

4.3 Interval length and effective sample size gain

Table 2 shows the mean lengths of shrinkage intervals relative to the original ("plain") confidence interval based on y_1 and σ_1 alone (which has width $2 \times 1.96\sigma_1$). While we have seen in the previous section that intervals may be shorter or longer in certain cases, here we see that on average the shrinkage intervals are always shorter than the plain intervals. As expected, the gain is largest if the study under consideration is small relative to the additional evidence ($n_1 < n_2$, $\sigma_1 > \sigma_2$), and if heterogeneity is low. Assuming a wider heterogeneity prior also reduces the amount of borrowing of information and leads to wider intervals.

The gain in precision may approximately be translated to an equivalent gain in effective sample size (as expressed through the q_i introduced above). The average gain is shown in Table 3. This relative gain in information may be substantial and is most pronounced if n_1 is small relative to n_2. For example, for the HN(0.5) heterogeneity prior and $n_1 = 25$, we can expect a gain of at least one third across all scenarios, and

Table 3. Gain (%) in effective sample size when using the shrinkage estimate, relative to the original CI.

τ prior:	HN (0.5)							HN (1.0)						
n_1/n_2 τ:	0.0	0.1	0.2	0.5	1.0	2.0	*	0.0	0.1	0.2	0.5	1.0	2.0	*
25/400	162.7	160.7	158.9	144.3	113.4	68.8	147.9	77.7	76.5	75.4	67.1	50.5	28.9	58.3
25/100	123.3	123.3	121.3	111.3	89.7	56.2	113.8	64.9	64.9	63.6	56.9	43.6	25.5	50.0
100/400	64.6	64.1	60.1	43.7	25.9	12.8	49.4	37.5	37.2	34.4	23.8	13.4	6.3	20.7
25/25	61.2	60.9	60.8	58.4	51.8	36.9	58.7	38.7	38.5	38.2	35.8	30.0	19.6	32.2
100/100	38.8	38.2	37.1	29.8	19.4	10.0	32.3	24.4	23.8	23.0	17.5	10.7	5.3	14.8
400/400	24.3	22.8	19.5	10.9	5.3	2.5	15.1	16.1	15.0	12.5	6.5	3.0	1.3	6.3
100/25	15.9	16.0	15.8	14.8	11.9	7.6	14.9	10.9	10.9	10.7	9.6	7.2	4.2	8.4
400/100	10.9	10.7	10.0	7.3	4.2	2.0	8.3	7.4	7.2	6.6	4.5	2.5	1.1	3.9
400/25	4.1	4.1	4.0	3.7	2.9	1.7	3.7	2.9	2.8	2.8	2.4	1.8	1.0	2.1

even a gain of more than 100% is well achievable in certain cases. When averaging over the heterogeneity prior, i.e. if we assume the prior to accurately reflect the probability distribution for τ, we can expect a gain of more than 50% for the cases where $n_1 = 25$ and more than 100% when in addition $n_2 > n_1$.

4.4 Fraction of shortened intervals

While there is a gain *on average*, the shrinkage intervals may in some cases also turn out wider than the original interval. Table 4 shows the percentages of intervals showing a smaller width. In a majority of cases, we can expect a shorter interval, the exceptions are again cases where the heterogeneity is large, or the second study is small.

4.5 Implications for practical application

The previous sections illustrate the process of shrinkage estimation within the NNHM framework and investigate the potential benefits. Across a range of realistic settings, the method exhibits sensible and robust behaviour, and despite the seemingly pathological outset of synthesizing only two estimates, the expected information gain may still be substantial. In the following, we will illustrate the approach by applying it in two examplary cases, one based on two *studies* (one randomized, one observational), and one based on two *estimates* from meta-analyses of different types of studies.

5 An application in Creutzfeld-Jakob disease

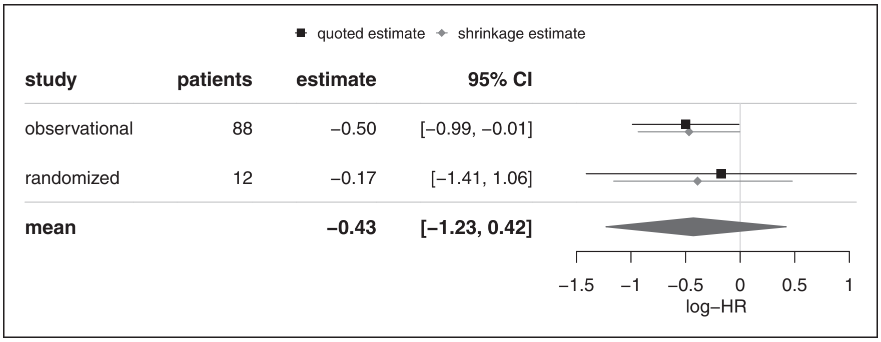
With a prevalence of 1 in 1,000,000[35] and an incidence of 1.5 per million and year,[36] Creutzfeld-Jakob disease (CJD) is clearly a rare disease by any standard. In a recent systematic review, Unkel et al.[37] identified a number of shortcomings in the methodologies applied in clinical studies conducted in CJD and advocated the use of innovative statistical methodology including evidence synthesis approaches.

Varges et al.[3] studied the use of doxycycline, an antiprion agent, in early CJD. They conducted a double-blind randomised placebo-controlled trial that failed to recruit the originally planned number of patients and was terminated prematurely with only $n = 12$ patients (seven on doxycycline and five on placebo). Additionally, data were available from an observational study of $n = 88$ patients including 55 patients who received doxycycline. The primary endpoint was all-cause mortality which was analyzed using Cox proportional hazard regressions. In the case of the randomized controlled trial, the model included only the factor treatment as independent variable whereas the analysis of the observational data in addition was stratified by propensity scores. The observed log hazard ratios (standard errors) were −0.173 (0.631) and −0.499 (0.249) in the randomized controlled trial and the observational study, respectively. Varges et al. performed a random-effects meta-analysis to estimate the overall (pooled) effect μ using standard frequentist methodology. They reported a combined hazard ratio of 0.633 with 95% confidence interval of (0.402; 0.999).

Now suppose primary interest was in the 'randomized' effect, but one is willing to utilize external observational evidence as supporting information. We may now apply the shrinkage estimation approach. Figure 2 shows the

Table 4. Fraction (%) of shrinkage intervals turning out shorter than the original CI. Note the differing ordering of rows compared to Tables 1 to 3.

τ prior:	HN (0.5)							HN (1.0)						
n_1/n_2 τ:	0.0	0.1	0.2	0.5	1.0	2.0	*	0.0	0.1	0.2	0.5	1.0	2.0	*
25/25	100.0	99.9	100.0	99.7	97.4	81.6	99.5	99.4	99.2	99.1	97.8	91.1	68.6	91.4
25/100	99.9	99.9	99.9	99.1	92.3	68.7	98.6	99.2	99.2	98.8	96.1	83.9	57.6	86.9
25/400	99.9	99.9	99.9	98.9	90.7	64.5	98.1	99.3	99.3	99.1	95.8	82.1	54.4	85.8
100/25	99.8	99.8	99.7	98.6	90.0	65.7	98.1	98.3	98.2	97.9	94.5	80.4	54.1	85.2
100/100	99.4	99.0	98.5	91.0	68.8	39.6	91.5	97.6	96.8	95.5	83.8	59.8	33.4	71.3
100/400	99.1	98.7	97.4	84.2	57.0	31.4	87.2	97.4	96.9	94.5	77.0	50.1	27.0	65.4
400/25	99.7	99.8	99.5	97.6	86.9	59.3	96.9	98.1	98.1	97.0	92.8	76.2	48.8	82.3
400/100	98.6	98.1	95.8	80.6	54.4	29.2	84.7	96.1	95.0	91.2	72.8	46.9	24.5	62.3
400/400	97.6	95.6	88.5	60.1	33.7	17.7	72.0	95.0	92.1	83.2	54.1	30.0	15.5	48.6



study	patients	estimate	95% CI
observational	88	−0.50	[−0.99, −0.01]
randomized	12	−0.17	[−1.41, 1.06]
mean		**−0.43**	**[−1.23, 0.42]**

Figure 2. Forest plot for the CJD example (log-HR outcome). The shrinkage interval for the log-HR based on randomized evidence here is $[-1.16, 0.48]$, spanning only two-thirds of the original confidence interval width.

estimated logarithmic hazard ratios based on obervational and randomized data along with the derived mean estimate (μ). The two shrinkage estimates are also shown next to the original (quoted) estimates. For the randomized trial, the updated credible interval covers the range of $[-1.16, 0.48]$ and is only 66% as wide as the original interval. This amount of shrinkage implies a gain in effective sample size of 129%, i.e. this corresponds to more than a doubling of the original sample size from 12 patients to an 'effective number' of some 27 patients. For the randomized patients' shrinkage estimate, we then obtain a posterior probability of a non-beneficial effect of $\mathrm{P}(\theta_{\mathrm{rand.}} > 0|y) = 0.16$. The associated (one-sided) posterior predictive p-value is similar, with $p = 0.13$.

From two studies, there is only very little to be learned about the between-study heterogeneity τ.[24] The prior median heterogeneity was at 0.34, which a posteriori is slightly reduced to 0.28; the posterior 95% quantile is at 0.85 instead of 0.98. Note that while the estimates for the overall mean and the shrinkage estimate do not differ much in this particular case, their interpretations are quite different. The R code to reproduce the calculations for this example is provided in Appendix 1.

6 Beyond two studies: more general shrinkage applications

So far we have described shrinkage estimation mostly in terms of "studies" and corresponding parameter estimates. However, the method may be applied more widely. Estimates do not need to come from *studies*, these could also originate from different types of evidence, for example, from two meta-analyses, or from a meta-analysis and a single study.

If the NNHM is fitted to the results of meta-analyses, then this adds another hierarchical level to the model. In the spirit of a *bias allowance model* framework,[38] in addition to between-study variability, the variability *between study types* is considered as a separate variance component. Especially in the context of normal models[39,40] and when interest is in main effects,[41] application of a one-stage model simultaneously including all hierarchy levels

	study	control	treatment	log–OR	s.e.	95% CI
observational	Gibelli (2004)	19 / 28	16 / 28	−0.460	0.556	[−1.550, 0.631]
	Schuller (2005)	8 / 12	3 / 18	−2.303	0.880	[−4.028, −0.577]
	Ganschow (2005)	29 / 54	9 / 54	−1.758	0.456	[−2.651, −0.864]
	Gras (2008)	3 / 34	0 / 50	−2.418	1.529	[−5.414, 0.579]
	observational combined			**−1.467**	**0.434**	**[−2.336, −0.611]**
randomized	Heffron (2003)	15 / 20	14 / 61	−2.310	0.599	[−3.485, −1.135]
	Spada (2006)	11 / 36	4 / 36	−1.258	0.642	[−2.517, −0.000]
	randomized combined			**−1.810**	**0.556**	**[−2.910, −0.708]**
	randomized shrinkage			**−1.659**	**0.419**	**[−2.494, −0.838]**

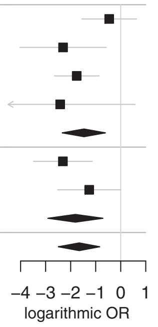


Figure 3. Illustration of a more general shrinkage application. The two sources of evidence themselves here are meta-analyses of observational and randomized studies. The combined randomized estimate may then borrow information from the observational studies' evidence. The two combined estimates are again meta-analysed to yield a shrinkage interval for the randomized effect.

may in many cases not lead to substantially different results from a simpler two-stage approach in which data at the study-level are combined first, and summaries are subsequently combined in a second stage.[42] This way, inference is substantially simplified, and standard meta-analysis software can be used.

Consider the example of a meta-analysis investigating the effect of immunosuppression in paediatric patients, where the outcome of interest is the occurrence of acute rejection (AR) events that the therapy is supposed to prevent.[43] Only two randomized trials are available, but in addition four observational studies reported on the effect. One may not expect to see identical effects in both types of studies, but the discrepancy between them will be limited. A meta-analysis of the two randomized trials may then profit from considering the outcomes of the four observational trials in addition, leading to a particular kind of extrapolation approach.[44]

Figure 3 shows the example data. In both sets of studies we see similar effects, the negative combined estimates of the log-odds-ratio indicate a successful prevention of AR events, and the two associated credible intervals are mostly overlapping. After combining the two sets of studies separately, we may now perform a meta-analysis of the resulting two combined estimates (in all cases using uniform priors for effects and HN(0.5) priors for heterogeneities). The *shrinkage* estimate for the mean effect in the randomized studies then provides an estimate for the randomized effect that is also informed by the observational evidence, while allowing for heterogeneity (at a second level) between both types of estimates. Note that in this context the shrinkage estimate then does not refer to a single study, but to one of the meta-analysis estimates that are combined here. The shrinkage estimate is shown at the very bottom of Figure 3. Compared to the original estimate based only on the two randomized trials, the shrinkage estimate is, in concordance with the observational evidence, slightly more moderate (at a lower absolute log-OR). Consideration of the additional evidence also gains precision: the shrinkage interval is 25% shorter than the original interval.

For the shrinkage estimate, we get a posterior probability of $\mathrm{P}(\theta_{\mathrm{rand.}} > 0|y) = 0.00007$ of a non-beneficial effect. With $p = 0.0002$, the associated posterior predictive p-value again is of a similar magnitude. Compared to the original meta-analysis of two randomized studies only, we can again see the gain in precision; here the evidence for a beneficial effect was not yet quite as pronounced ($\mathrm{P}(\mu > 0|y) = 0.0023$ and $p = 0.0079$). The R code to reproduce the calculations for this example is provided in Appendix 1.

7 Discussion

Use of the NNHM to consider external information via shrinkage estimation provides a transparent procedure based on well-defined parameters and a common model framework. The NNHM may readily be generalized, for example, to more studies, more levels of hierarchy, or the inclusion of regression parameters. The amount of information considered may be explicated by noting that a joint analysis is equivalent to the use of a meta-analytic-predictive (MAP) prior.[11] At the same time, heavy tails of the MAP prior ensure a certain degree of robustness of the shrinkage estimate in case of prior-data conflicts.[32] The simulations demonstrate that the gain in precision may be greater than expected, and substantial especially in cases where the external data are associated with equal or less uncertainty than the data that are of primary interest. The possible precision gain may allow the conduct and evaluation of trials in circumstances where otherwise evidence would be too sparse, or it may generally enable to allocate resources more efficiently.

In the spirit of the *reference model* parametrization outlined above, the institution of an "overall mean" μ is not necessary. In many cases, when the data to be synthesized are of differing natures, the idea of a "central" mean parameter might be hard to motivate; what is relevant here is that the two estimates are modeled as being connected via an uncertain normally distributed offset. Normality here especially implies symmetry, i.e. the displacement between the two does not have a preferred direction; over- or under-estimation of one another are equally likely, so that *a priori* no systematic bias is assumed. Availability of this alternative motivation broadens the range of applicability of meta-analytic methods.

As usual, the user needs to be aware of the limits of the applicability of the model, which here in particular means that the normality assumptions should be plausible.[45] These assumptions might be challenged, for example, when estimates are based on count data suffering from small-sample or rare-event problems, in which case more specific models may be more appropriate.[46] We also make the implicit assumption that patient populations are sufficiently similar to allow for a meaningful comparison. Furthermore, analyses of non-randomized studies may need to be adjusted for confounding,[47,48] as was also done in the CJD example.

Although frequentist analyses still dominate clinical trials, examples of Bayesian analyses are emerging. A recent application is the trial by Laptook et al.[49] in newborns with hypoxic-ischemic encephalopathy, a form of brain damage resulting from an insufficient supply of oxygen to the brain. The authors used the Bayesian framework to interpret their results in the light of different choices of priors that they termed "neutral", "skeptical" and "optimistic".[50] In this regard, it differs from our proposal as we advocate the use of external data to inform the prior. The connection to common meta-analysis methods then helps motivating the choice of model details. Sensitivity analyses could be performed in our setting by varying the prior on the between-trial heterogeneity τ, for example, by varying the scale parameter of the half-normal prior.

Although not assessed in the simulations here, the performance of frequentist shrinkage BLUP estimators is likely to be unsatisfactory when dealing with only two studies. The reason lies in the underestimation of the between-study heterogeneity with a high likelihood of the variance estimate resulting in zero, and the challenge to incorporate the uncertaintly in the estimation of the heterogeneity in the inference.[20,24,51] A Bayesian alternative was described here and shown in simulations to have satisfactory properties under practically relevant scenarios. Therefore, the approach described here adds to the tool box of practicing statisticians. The proposed Bayesian approach can easily be implemented using the R package `bayesmeta`[21,26] and relevant code is provided as appendices for the two-study and the two-meta-analyses cases. The code to reproduce the simulations is also provided in the online supplement. The availability of posterior predictive *p*-values may aid in the interpretation of the findings. Furthermore, the efficient implementation facilitates sensitivity analyses and the assessment of operation characteristics of the procedures through simulations in so-called clinical scenario evaluations.[52]

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Appendices

1. R code for CJD example

```
# specify the data:
cjd <- cbind.data.frame("study" = c("observational", "randomized"),
                        "logHR" = c(-0.49948, -0.17344),
                        "logHR.se" = c(0.2493, 0.6312),
                        stringsAsFactors=FALSE)
# analyze:
require("bayesmeta")
bm <- bayesmeta(y          = cjd$logHR,
                sigma      = cjd$logHR.se,
                labels     = cjd$study,
                tau.prior  = function(t){dhalfnormal(t, scale=0.5)})
# show results:
bm
forestplot(bm)
# show shrinkage estimates:
bm$theta
# interval length ratio (66%);
(q <- diff(bm$theta[7:8,"randomized"])
      / (2*qnorm(0.975)*bm$theta[2,"randomized"]))

# effective sample size gain (129%);
(1/q)^2 - 1
```

```
# heterogeneity prior median and 95% quantile:
qhalfnormal(c(0.50, 0.95), scale=0.5)
# heterogeneity posterior:
bm$summary[,"tau"]

# compute posterior predictive p-value
# (one-sided, for the randomized (shrinkage) effect,
# and using the posterior probability of a beneficial effect
# as the "test statistic"):
p1 <- pppvalue(bm, parameter="randomized", value=0,
               alternative="less", statistic="cdf",
               n=1000, seed=123)
p1

# for comparison, the posterior probability
# of a non-beneficial randomized effect:
1 - bm$pposterior(theta=0, individual="randomized")
```

2 R code for paediatric transplantation example

```
# load packages and data:
require("bayesmeta")
data("CrinsEtAl2014")

# compute effect sizes (log-OR for acute rejection (AR) events)
# using the metafor library's "escalc()" function;
# 4 observational studies:
effsize.obs <- escalc(ai=exp.AR.events, n1i=exp.total,
                      ci=cont.AR.events, n2i=cont.total,
                      slab=publication, measure="OR",
                      subset=(CrinsEtAl2014[,"randomized"]=="no"),
                      data=CrinsEtAl2014)
# 2 randomized studies:
effsize.rand <- escalc(ai=exp.AR.events, n1i=exp.total,
                       ci=cont.AR.events, n2i=cont.total,
                       slab=publication, measure="OR",
                       subset=(CrinsEtAl2014[,"randomized"]=="yes"),
                       data=CrinsEtAl2014)

# perform meta-analysis of 4 observational studies:
bm.obs <- bayesmeta(effsize.obs,
                    tau.prior=function(x){dhalfnormal(x,scale=0.5)})
# perform meta-analysis of 2 randomized studies:
bm.rand <- bayesmeta(effsize.rand,
                     tau.prior=function(x){dhalfnormal(x,scale=0.5)})

# perform 2nd-stage meta-analysis of previous MA results:
bm.combi <- bayesmeta(y      =c(bm.obs$summary["mean","mu"],
                                bm.rand$summary["mean","mu"]),
                      sigma  =c(bm.obs$summary["sd","mu"],
                                bm.rand$summary["sd","mu"]),
                      labels=c("observational", "randomized"),
                      tau.prior=function(x){dhalfnormal(x,scale=0.5)})

# compare "plain" randomized posterior and shrinkage estimate:
```

```
rbind("randomized-only" = bm.rand$summary[,"mu"],
      "shrinkage" = bm.combi$theta[-(1:2),"randomized"])
# interval length ratio (75%):
(q <- diff(bm.combi$theta[7:8,"randomized"])
      / diff(bm.rand$summary[5:6,"mu"]))

# compute posterior predictive p-value:
p1 <- pppvalue(bm.combi, parameter="randomized", value=0,
               alternative="less", statistic="cdf",
               n=1000, seed=123)
p1
# posterior probability of a non-beneficial randomized effect:
1 - bm.combi$pposterior(theta=0, individual="randomized")
# compute posterior predictive p-value
# for initial MA of 2 randomized studies only:
p2 <- pppvalue(bm.rand, parameter="mu", value=0,
               alternative="less", statistic="cdf",
               n=1000, seed=123)
p2
# original posterior probability of non-beneficial effect:
1 - bm.rand$pposterior(mu=0)
```

3 Model equivalence

Shrinkage estimation in the NNHM and in the *reference model* introduced above yield identical results, as long as an improper uniform prior for the effect (μ or α) is used. The heterogeneity prior densities are given by $p_\star(\tau)$ for then NNHM, and by $\frac{1}{\sqrt{2}}p_\star(\frac{\beta}{\sqrt{2}})$ for the reference model. Equivalence of the two models for the shrinkage estimates can be seen by comparing the resulting MAP priors $p(\theta_2|y_1)$ and $p(\vartheta_2|y_1)$. To do so, we first introduce a reparametrisation (re-scaling) of the heterogeneity parameter as $\gamma = \frac{\beta}{\sqrt{2}}$, where the new heterogeneity parameter's prior distribution then simply is given by $p_\star(\gamma)$. The corresponding MAP prior densities then are given by

$$p(\theta_2|y_1) = \iint p(\theta_2|\mu,\tau)p(\mu,\tau|y_1)\,\mathrm{d}\mu\,\mathrm{d}\tau \tag{7}$$

$$\propto \int\left[\int p(\theta_2|\mu,\tau)p(y_1|\mu,\tau)\,\mathrm{d}\mu\right]p_\star(\tau)\,\mathrm{d}\tau \tag{8}$$

and

$$p(\vartheta_2|y_1) = \iint p(\vartheta_2|\alpha,\gamma)p(\alpha,\gamma|y_1)\,\mathrm{d}\alpha\,\mathrm{d}\gamma \tag{9}$$

$$\propto \int\left[\int p(\vartheta_2|\alpha,\gamma)p(y_1|\alpha,\gamma)\,\mathrm{d}\alpha\right]p_\star(\gamma)\,\mathrm{d}\gamma \tag{10}$$

In order to show that the integrals are identical, it now suffices to show that the terms in square brackets (the "conditional MAP priors" $p(\theta_2|y_1,\tau)$ and $p(\vartheta_2|y_1,\gamma)$, respectively) are identical. For the NNHM we have

$$\begin{aligned}&\int p(\theta_2|\mu,\tau)p(y_1|\mu,\tau)\,\mathrm{d}\mu\\ &\quad= \int \frac{1}{\sqrt{2\pi\tau^2}}\exp\left(-\frac{1}{2}\frac{(\theta_2-\mu)^2}{\tau^2}\right)\frac{1}{\sqrt{2\pi(\tau^2+\sigma_1^2)}}\exp\left(-\frac{1}{2}\frac{(y_1-\mu)^2}{\tau^2+\sigma_1^2}\right)\mathrm{d}\mu\end{aligned} \tag{11}$$

$$= \frac{1}{\sqrt{2\pi(2\tau^2 + \sigma_1^2)}} \exp\left(-\frac{1}{2}\frac{(\theta_2 - y_1)^2}{2\tau^2 + \sigma_1^2}\right) \tag{12}$$

where the integral results as a convolution of two normal densities. Analogously, for the second variation we get

$$\begin{aligned} &\int p(\vartheta_2|\alpha,\gamma)p(y_1|\alpha,\gamma)\mathrm{d}\alpha \\ &= \int \frac{1}{\sqrt{2\pi 2\gamma^2}} \exp\left(-\frac{1}{2}\frac{(\alpha - \vartheta_2)^2}{2\gamma^2}\right) \frac{1}{\sqrt{2\pi\sigma_1^2}} \exp\left(-\frac{1}{2}\frac{(\alpha - y_1)^2}{\sigma_1^2}\right) \mathrm{d}\alpha \end{aligned} \tag{13}$$

$$= \frac{1}{\sqrt{2\pi(2\gamma^2 + \sigma_1^2)}} \exp\left(-\frac{1}{2}\frac{(\vartheta_2 - y_1)^2}{2\gamma^2 + \sigma_1^2}\right) \tag{14}$$

With that, the two resulting MAP priors are identical, and the two models will yield the same results as far as the shrinkage estimates are concerned.