

Contribution to the discussion of “When should meta-analysis avoid making hidden normality assumptions?”: A Bayesian perspective

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We congratulate Drs. Jackson and White on a very interesting paper, providing a comprehensive summary of explicit and implicit normality and independence assumptions commonly being made in random-effects meta-analysis that are easily overlooked and that may deserve more consideration (Jackson and White, 2018). Some of the problems discussed, however, are less of an issue when analyses are done in a Bayesian framework. Normality assumptions are made explicit in the model’s likelihood specification. Any departure from assumptions 1–4 (as listed in Tab. 3) then may cause problems, just as in the frequentist case. Additional assumptions enter the analysis in the form of the prior specification, expressing the information on parameters before taking the data into consideration. These can usually be made reasonably vague, if desired (e.g., a uniform prior for the effect μ , and a weakly informative prior for the heterogeneity τ), and these may also be subjected to sensitivity analyses (Röver, 2017). At the inference or prediction stage, computations are usually carried out *exactly*, following Bayes’ theorem, and, unlike in the frequentist framework, no approximations are necessary at this point (Spiegelhalter et al., 2004, Sec. 3). Normal or other approximations *could* of course also be used in a Bayesian analysis, e.g., when extrapolating around the posterior mode (Gelman et al., 2014, Sec. 13) or when analysis is based on INLA (Rue et al., 2009). Such methods have been proposed for network meta-analysis (Sauter and Held, 2015; Günhan et al., 2018), however, such cases are usually explicitly indicated.

To exemplify the issue, consider the smoking cessation example data (example one). We utilize the `bayesmeta` R package to derive the posterior distribution for the logarithmic odds ratio (log-OR), using an (improper) uniform prior for the effect μ and a half-normal prior with scale 0.5 for the heterogeneity τ (Röver, 2017). For the frequentist analyses, we use the `metafor` package with default settings (Viechtbauer, 2010). Figure 1 illustrates the normal approximation utilized in the construction of the confidence interval along with the effect’s posterior density. The (marginal) posterior distribution is not normal, but rather a *normal mixture* (Röver, 2017), as becomes obvious when comparing to a normal approximation (based on matching mean and variance) that is also shown.

Differences between (frequentist) normal approximation and posterior tend to be particularly large in case of substantial uncertainty in the heterogeneity parameter. While this happens especially in the common case of few studies (Friede et al., 2017a; see also Fig. 1), differences are still noticeable in the present data set consisting of twelve seemingly homogeneous OR estimates, where, due to an estimated heterogeneity of $\hat{\tau} = 0$, effectively one ends up performing a common-effect analysis in the frequentist framework. An value of $\hat{\tau} = 0$ is a “most optimistic” estimate here, in the sense that it will lead to the shortest possible confidence interval for a random-effects analysis.

Although the data seem to “look” homogeneous, and despite the fact that we have a somewhat large sample size of $k = 12$ studies, there is rather little information on the actual heterogeneity level in the data. From the investigation by Turner et al. (2015), we know that for a general Cochrane review, empirically we

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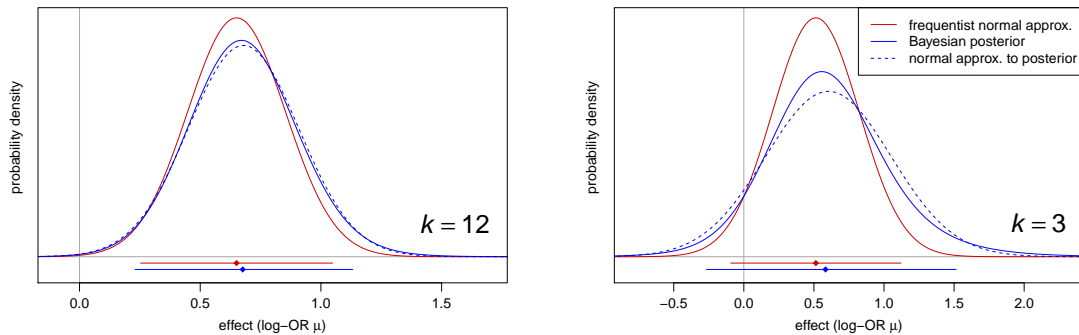


Figure 1 While the frequentist confidence interval is based on a normal approximation (red), the posterior (blue) is not normal. For comparison, a normal approximation to the posterior (with matching mean and variance) is also shown (dashed line). Discrepancies are even more evident when the analysis is based on a smaller subset of only $k = 3$ most recent studies (right panel). Corresponding estimates and 95% confidence/credible intervals are shown at the bottom of the plot.

may expect a heterogeneity level of roughly up to $\tau = 1.16$ with 95% probability. In the present example, the (Q-profile) 95% confidence interval for τ is $[0.00, 0.95]$, so we cannot say that the data provided a substantial constraint on the actual heterogeneity level. Although the τ estimate is zero and the data are compatible with a common-effect model, they are also consistent with even “fairly high” heterogeneity (Spiegelhalter et al., 2004, Sec. 5.7.3).

A Bayesian random-effects analysis is able to consider the range of plausible heterogeneity values via marginalization over the joint posterior distribution and with that leads to slightly more cautious results here. Due to the large standard errors, the relative increase in CI width is not dramatic in this case, but the Bayesian analysis yields an estimated log-OR and 95% CI of 0.68 [0.23, 1.13] compared to 0.65 [0.25, 1.05] from the frequentist analysis. While the half-normal heterogeneity prior with scale 0.5 focuses the analysis a priori on up to *fairly high* heterogeneity values (mostly $\tau \leq 1.0$), a sensitivity analysis using a scale of 1.0 leads to a similar estimate of 0.68 [0.22, 1.16].

Since no large- k - (many-study-) asymptotics are invoked in a Bayesian analysis, the results are valid independent of the number of included studies. This is particularly useful in the case of a meta-analysis of few studies only, which is very common especially in the context of medical applications: a majority of studies published in the *Cochrane Library* are based on as few as 2–3 studies (Davey et al., 2011; Kontopantelis et al., 2013). While small- k adjustments for confidence intervals based on Student- t distributions are available, these only work really well in certain cases (equal standard errors) and tend to lead to unnecessarily wide intervals for few studies (Röver et al., 2015; Friede et al., 2017a,b).

In a Bayesian model, it is generally relatively easy to accommodate model variations that avoid simplifying approximations *at the modeling stage* (such as unknown standard errors, non-normal study-level likelihood, or non-normal heterogeneity), especially when applying MCMC methods (e.g., Stevens, 2011). In the frequentist case, usually dedicated GLMM software is required for this purpose. Incorporation e.g. of standard error uncertainty is less straightforward (Dominguez Islas and Rice, 2018). Quite often, more complex models may also lead to numerical difficulties especially in the common case of a small number of observations (e.g., Jackson et al., 2018; Seide et al., 2018), so that application of certain more sophisticated models may simply not be possible in some instances. Even if more detailed likelihood specifications are used, the inference stage will commonly still rely on approximations (e.g., via Wald-type intervals or likelihood ratio tests), which may in fact be even more questionable in more complex models.

We would like to thank Drs. Jackson and White for an inspiring paper which highlighted some important issues in random-effects meta-analyses. We feel that some of the issues are less problematic in the Bayesian framework and recommend Bayesian random-effects meta-analyses for practical applications.

Conflict of Interest

The authors have declared no conflict of interest.

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