Bayesian Inference on Risk Differences: An Application to Multivariate Meta-Analysis of Adverse Events in Clinical Trials

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Multivariate meta-analysis is useful in combining evidence from independent studies that involve several comparisons among groups based on a single outcome. For binary outcomes, the commonly used statistical models for multivariate meta-analysis are multivariate generalized linear mixed effects models which assume risks, after some transformation, follow a multivariate normal distribution with possible correlations. In this article, we consider an alternative model for multivariate meta-analysis where the risks are modeled by the multivariate beta distribution proposed by Sarmanov. This model has several attractive features compared to the conventional multivariate generalized linear mixed effects models, including simplicity of likelihood function, no need to specify a link function, and a closed-form expression of distribution functions for study-specific risk differences. We investigate the finite sample performance of this model through simulation studies and illustrate its use with an application to multivariate meta-analysis of adverse events of tricyclic antidepressant treatment in clinical trials.

Key Words: Bivariate beta-binomial model; Exact method; Hypergeometric function; Relative risk; Sarmanov family.

1. Introduction

Differences between two proportions are commonly used as an important comparative measure in biomedical research. In epidemiology, the difference in rate of a condition between an exposed population and an unexposed population is called attributable risk (Rothman, Greenland, and Lash 2008), which is used to describe the reduction in incidence that would be observed if the population were entirely unexposed, compared with its current exposure pattern. It is an important measure for policymakers in planning public health interventions (Northridge 1995). In clinical trials with a binary outcome, the difference in proportion of risk comparing subjects who receive treatment to those who receive placebo or standard treatment provides an important measure of drug efficacy (Piantadosi 2005). In addition, the difference in proportions of withdrawal due to adverse effects between treatment groups provides an important measure of drug safety. In drug safety studies, the difference in proportions of withdrawal can be evaluated by meta-analysis of adverse events in clinical trials.

Multivariate data arise in meta-analysis when each study involves more than one group. The commonly used

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statistical models for multivariate meta-analysis with binary outcomes are multivariate generalized linear mixed effects models (Van Houwelingen, Zwinderman, and Stijnen 1993; Smith, Spiegelhalter, and Thomas 1995; Skrondal and Rabe-Hesketh 2004; Chu and Cole 2006), which assume risks, after some transformation, follow a multivariate normal distribution with possible correlations. For an excellent review of statistical methods for multivariate meta-analysis, we refer to the papers by Van Houwelingen, Zwinderman, and Stijnen (1993) and Jackson, Riley, and White (2011), the books by Hartung, Knapp, Sinha (2011) and Stangl and Berry (2000), and the references therein. In this article, we consider an alternative model for multivariate meta-analysis where the risks are modeled by the multivariate beta distribution proposed by Sarmanov (1966), referred to as Sarmanov beta distribution. This model has the following major attractive features: first, marginally, the risks follow beta distributions which are flexible distributions to model risks; second, the risks are modeled without any transformation, which avoids the need to specify a link function for risks as we know misspecification of link functions may have a noticeable impact of the inference (Chu, Guo, and Zhou 2010). Furthermore, due to the simplicity of Sarmanov beta distribution, the marginalized likelihood function has a closed-form expression, which can greatly simplify the likelihood-based inference. Furthermore, Sarmanov beta distribution is pseudoconjugate to the binomial distributions. We will show later in this article that this pseudoconjugation property leads to a closed-form expression of distribution functions for study-specific risk differences.

The family of multivariate distributions proposed by Sarmanov (1966) is a flexible family of distributions. This Sarmanov family has been studied extensively by Lee (1996) and Shubina and Lee (2004) and has been applied to areas such as Markov chain models for longitudinal data analysis by Cole et al. (1995) and prediction models for efficient business decisions in marketing sciences by Park and Fader (2004) and Danaher and Hardie (2005). In this article, we apply Sarmanov beta distributions to multivariate meta-analysis with special focus on risk differences. The performance of the model, relative to others, on bias, coverage probability and efficiency, is assessed through simulation studies. In meta-analysis of clinical trials, researchers may be also interested in the statistical evidence on risk difference contributed by individual studies. Such evidence can be quantified by the posterior distribution of study-specific risk difference. To this end, we derive a closed-form expression of the posterior density functions of the study-specific risk differences when the risks are correlated. The main results are provided in Section 2, followed by simulation studies in Section 3. An example of investigation for adverse events of tricyclic antidepressant treatment is provided for illustration in Section 4, followed by a brief discussion in Section 5.

2. Main Results

For the jth group under comparison, let n_j, y_j, and p_j be the number of subjects, number of subjects experiencing event of interest, and risk of experiencing that event ($j = 1, \ldots, J$). For simplicity, we consider the cases with two groups under comparison (i.e., $J = 2$) and the extension to cases with more than two groups is straightforward. Assume that the prior distributions of risks p_1 and p_2 are beta random variables with hyperparameters (a_1, b_1) and (a_2, b_2), respectively, where $a_j, b_j > 0$. The posterior distributions of p_1 and p_2 are beta distributions with parameters (α_1, β_1) and (α_2, β_2), respectively, where $\alpha_j = y_j + a_j$ and $\beta_j = n_j - y_j + b_j$ $(j = 1, 2)$.

We first restate the main results in Chen and Luo (2011) on the exact posterior distribution of risk difference $D = p_1 - p_2$ under independent beta prior distributions. Suppose p_1 and p_2 are independent beta random variables with densities defined by

$$\text{beta}(p_1; \alpha_1, \beta_1) = \{B(\alpha_1, \beta_1)\}^{-1} p_1^{\alpha_1 - 1}(1 - p_1)^{\beta_1 - 1},$$

and

$$\text{beta}(p_2; \alpha_2, \beta_2) = \{B(\alpha_2, \beta_2)\}^{-1} p_2^{\alpha_2 - 1}(1 - p_2)^{\beta_2 - 1},$$

where $B(\alpha, \beta)$ is the beta function defined by

$$B(\alpha, \beta) = \int_0^1 w^{\alpha - 1}(1 - w)^{\beta - 1} dw.$$

The probability density function of the risk difference D is expressed as

$$f_D(d) = \Gamma(\alpha_1 + \beta_1)\Gamma(\alpha_2 + \beta_2) \times \begin{cases} \dfrac{(-d)^{\beta_1 + \beta_2 - 1}(1 + d)^{\alpha_1 + \beta_2 - 1}}{\Gamma(\beta_1)\Gamma(\alpha_2)\Gamma(\alpha_1 + \beta_2)} \\ \times F_1(\beta_2, \alpha_1 + \alpha_2 + \beta_1 + \beta_2 - 2, \\ \quad 1 - \alpha_2, \alpha_1 + \beta_2; 1 + d, 1 - d^2) \\ \qquad \text{if } -1 \le d \le 0, \\ \dfrac{d^{\beta_1 + \beta_2 - 1}(1 - d)^{\alpha_2 + \beta_1 - 1}}{\Gamma(\beta_2)\Gamma(\alpha_1)\Gamma(\alpha_2 + \beta_1)} \\ \times F_1(\beta_1, \alpha_1 + \alpha_2 + \beta_1 + \beta_2 - 2, \\ \quad 1 - \alpha_1, \alpha_2 + \beta_1; 1 - d, 1 - d^2) \\ \qquad \text{if } 0 < d \le 1, \end{cases} \tag{1}$$

where F_1 denotes the Appell function of the first kind defined by

$$F_1(a, b, b', c; x, y) = \sum_{m=0}^{\infty} \sum_{n=0}^{\infty} \frac{(a)_{m+n}(b)_m(b')_n x^m y^n}{(c)_{m+n} m! n!}, \quad \text{for } |x| < 1, |y| < 1,$$

and $(c)_k = c(c+1)\cdots(c+k-1)$ denotes the ascending factorial.

In practice, independence between risks can be an oversimplification of reality because two groups under comparison can share some common yet possibly unobserved factors. In this regard, Kass and Raftery (1995) and Howard (1998) suggested a family of correlated prior distributions defined by

$$\pi(p_1, p_2) = K e^{-u^2/2} p_1^{\alpha_1-1}(1-p_1)^{\beta_1-1} p_2^{\alpha_2-1}(1-p_2)^{\beta_2-1}, \tag{2}$$

where $u = \sigma^{-1}\log[\{p_1/(1-p_1)\}/\{p_2/(1-p_2)\}]$, K is the normalizing constant, the parameter $\sigma > 0$ is introduced to account for the correlation between p_1 and p_2. Specifically, the larger σ is, the smaller the correlation is. Note that this family of correlated prior distributions can only account for positive correlation between proportions (Kass and Raftery 1995).

Alternatively, a family of bivariate distributions constructed from marginal distributions were proposed by Sarmanov (1966) and later studied by Lee (1996) and Shubina and Lee (2004). This family of distributions allows for both positive and negative correlations. With prespecified marginal beta distributions $\text{beta}(p_1; a_1, b_1)$ and $\text{beta}(p_2; a_2, b_2)$ for p_1 and p_2, respectively, Sarmanov (1966) proposed the bivariate distribution of the form

$$\begin{aligned} &g(p_1, p_2; a_1, b_1, a_2, b_2, \rho) \\ &\quad = \text{beta}(p_1; a_1, b_1)\text{beta}(p_2; a_2, b_2)\{1 + \rho\psi_1(p_1)\psi_2(p_2)\}, \end{aligned} \tag{3}$$

where $\psi_j(\cdot)$ are bounded integrable nonconstant functions that satisfy $\int \psi_j(t)\text{beta}(p_j; a_j - 1, b_j - 1)dt = 0$ for $j = 1, 2$, and $1 + \rho\psi_1(p_1)\psi_2(p_2) \geq 0$ to ensure a nonnegative distribution (Lee 1996). One choice of function $\psi_j(p_j)$ can be $\psi_j(p_j) = (p_j - \mu_j)/\delta_j$, where $\mu_j = a_j/(a_j + b_j)$ is the mean of p_j and $\delta_j = \sqrt{\mu_j(1-\mu_j)/(a_j + b_j + 1)}$ is the standard deviation of p_j $(j = 1, 2)$. This function $\psi_j(p_j)$ leads to the parameter ρ with an intuitive interpretation of correlation coefficient, that is, $\rho = \text{corr}(p_1, p_2)$ when $\psi_j(p_j) = (p_j - \mu_j)/\delta_j$. Note that when $\rho = 0$, Equation (3) reduces to independent bivariate beta distribution, that is, the product of two independent beta distributions.

One advantage of the bivariate distributions proposed by Sarmanov (referred to as Sarmanov beta priors) is their simplicity in modeling because they only requires specification of marginal distributions and correlation. This is important in Bayesian inference because it is often easier to specify and interpret univariate priors compared to bivariate priors. Sarmanov beta priors also have the mathematical property for being pseudoconjugate for binomial distributions; that is, Equation (3) can be expressed as a linear combination of independent bivariate beta distributions (Lee 1996). Here we derive the exact posterior distribution of risk difference under Sarmanov beta priors based on this property.

With beta marginals and functions $\psi_j = (p_j - \mu_j)/\delta_j$, the Sarmanov prior distribution of p_1 and p_2 can be written as linear combination of independent bivariate beta distributions (Lee 1996),

$$\begin{aligned} &g(p_1, p_2; a_1, b_1, a_2, b_2, \rho) \\ &\quad = v_1\text{beta}(p_1; a_1, b_1)\text{beta}(p_2; a_2, b_2) \\ &\qquad + v_2\text{beta}(p_1; a_1 + 1, b_1)\text{beta}(p_2; a_2, b_2) \\ &\qquad + v_3\text{beta}(p_1; a_1, b_1)\text{beta}(p_2; a + 1, b_2) \\ &\qquad + v_4\text{beta}(p_1; a_1 + 1, b_1)\text{beta}(p_2; a_2 + 1, b_2), \end{aligned}$$

where v_k $(k = 1, \ldots, 4)$ are weights defined by $v_1 = 1 + \rho\gamma, v_2 = v_3 = -\rho\gamma, v_4 = \rho\gamma, \gamma = (\mu_1\mu_2)/(\delta_1\delta_2)$. After some algebra, the posterior distribution of p_1 and p_2 given data is also a linear combination of independent bivariate beta distributions,

$$\begin{aligned} &\Pr(p_1, p_2|y_1, y_2, a_1, b_1, a_2, b_2, \rho) \\ &\quad = \omega_1\text{beta}(p_1; \alpha_1, \beta_1)\text{beta}(p_2; \alpha_2, \beta_2) \\ &\qquad + \omega_2\text{beta}(p_1; \alpha_1 + 1, \beta_1)\text{beta}(p_2; \alpha_2, \beta_2) \\ &\qquad + \omega_3\text{beta}(p_1; \alpha_1, \beta_1)\text{beta}(p_2; \alpha_2 + 1, \beta_2) \\ &\qquad + \omega_4\text{beta}(p_1; \alpha_1 + 1, \beta_1)\text{beta}(p_2; \alpha_2 + 1, \beta_2), \end{aligned}$$

where $\alpha_j = y_j + a_j$, $\beta_j = n_j - y_j + b_j$ $(j = 1, 2)$ and the weights ω_k $(k = 1, \ldots, 4)$ are defined by,

$$\omega_1 = \frac{v_1 B(\alpha_1, \beta_1)B(\alpha_2, \beta_2)}{CB(a_1, b_1)B(a_2, b_2)},$$
$$\omega_2 = \frac{v_2 B(\alpha_1 + 1, \beta_1)B(\alpha_2, \beta_2)}{CB(a_1 + 1, b_1)B(a_2, b_2)},$$

$$\omega_3 = \frac{v_3 B(\alpha_1, \beta_1)B(\alpha_2 + 1, \beta_2)}{CB(a_1, b_1)B(a_2 + 1, b_2)}, \quad \text{and}$$
$$\omega_4 = \frac{v_4 B(\alpha_1 + 1, \beta_1)B(\alpha_2 + 1, \beta_2)}{CB(a_1 + 1, b_1)B(a_2 + 1, b_2)},$$

and C, the normalizing constant, is calculated as

$$\begin{aligned} C = &\frac{v_1 B(\alpha_1, \beta_1)B(\alpha_2, \beta_2)}{B(a_1, b_1)B(a_2, b_2)} + \frac{v_2 B(\alpha_1 + 1, \beta_1)B(\alpha_2, \beta_2)}{B(a_1 + 1, b_1)B(a_2, b_2)} \\ &+ \frac{v_3 B(\alpha_1, \beta_1)B(\alpha_2 + 1, \beta_2)}{B(a_1, b_1)B(a_2 + 1, b_2)} \\ &+ \frac{v_1 B(\alpha_1 + 1, \beta_1)B(\alpha_2 + 1, \beta_2)}{B(a_1 + 1, b_1)B(a_2 + 1, b_2)}. \end{aligned}$$

After some algebra, the exact posterior distribution of risk difference under Sarmanov beta prior is calculated as

$$\begin{aligned} &f_D^*(d; \alpha_1, \beta_1, \alpha_2, \beta_2, \rho) \\ &\quad = \omega_1 f_D(d; \alpha_1, \beta_1, \alpha_2, \beta_2) + \omega_2 f_D(d; \alpha_1 + 1, \beta_1, \alpha_2, \beta_2) \\ &\qquad + \omega_3 f_D(d; \alpha_1, \beta_1, \alpha_2 + 1, \beta_2) \\ &\qquad + \omega_4 f_D(d; \alpha_1 + 1, \beta_1, \alpha_2 + 1, \beta_2), \end{aligned} \tag{4}$$

where $f_D(d;\alpha_1,\beta_1,\alpha_2,\beta_2)$ is the posterior density function of risk difference under independent beta prior, defined in Equation (1). Notice that when the correlation ρ is zero, in which the weights are $\omega_1 = 1$ and $\omega_2 = \omega_3 = \omega_4 = 0$, the result in Equation (4) reduces to Equation (1), the main results in Pham-Gia and Turkkan (1993), Nadarajah and Kotz (2007) and Chen and Luo (2011). When the correlation ρ is nonzero, the prior correlation is introduced to the posterior distribution of risk difference through the weights ω_k $(k = 1,\ldots,4)$.

With a single 2×2 table, the correlation parameter ρ is not identifiable and, hence, cannot be estimated from the data. Instead, sensitivity analysis can be conducted to investigate the robustness of the inference of risk difference under various prior distributions. In biomedical studies, data from multiple studies are often available. One such example is in meta-analysis where the goal is to combine statistical evidence from multiple studies to resolve questions that cannot be answered by a single study alone. When data from multiple studies are available, the hyperparameters $(a_1, b_1, a_2, b_2, \rho)$ may be estimated from the data through a random effect model in an empirical Bayes framework. We now consider a random effect model for multiple studies and a possible extension to multiple studies with study level covariates. In both cases, the hyperparameters can be estimated by maximizing the log marginalized likelihood function.

For the ith study, let n_{ji}, y_{ji} and p_{ji} $(j = 1, 2$ for groups 1 and 2, respectively) be the number of subjects, number of subjects experiencing event of interest, and probability of experiencing that event in the jth group, respectively. The study-specific risks, or the random effects, (p_{1i}, p_{2i}) are often assumed to be independent across studies, following a common distribution. Given study-specific risks (p_{1i}, p_{2i}), the numbers of subjects experiencing event of interest, (y_{1i}, y_{2i}), are assumed to be independent. This assumption is commonly made in random effects models such as the multivariate models by Reitsma et al. (2005) and Chu and Cole (2006). A random effect model can be specified as follows:

$$\begin{aligned}&(p_{1i}, p_{2i})|(a_1, b_1, a_2, b_2, \rho) \overset{\text{iid}}{\sim} g(p_1, p_2; a_1, b_1, a_2, b_2, \rho),\\ &(y_{1i}, y_{2i})|(n_{1i}, n_{2i}, p_{1i}, p_{2i}) \overset{\text{ind}}{\sim} \text{Binomial}(y_{1i}|n_{1i}, p_{1i})\\ &\quad \times \text{Binomial}(y_{2i}|n_{2i}, p_{2i}).\end{aligned} \tag{5}$$

The hyperparameters can be obtained by maximizing the log-marginalized likelihood combining all studies,

$$\begin{aligned}&\log L(a_1, b_1, a_2, b_2, \rho)\\ &= \sum_{i=1}^{n} \log \iint \Pr(y_{1i}, y_{2i}|p_{1i}, p_{2i}) g(p_{1i}, p_{2i}; a_1, b_1, a_2,\\ &\quad \times b_2, \rho) dp_{1i} dp_{2i}\\ &= \sum_{i=1}^{n} \log \Bigg[\mathrm{P}_{BB}(y_{1i}; n_{1i}, a_1, b_1) \mathrm{P}_{BB}(y_{2i}; n_{2i}, a_2, b_2)\\ &\quad \Bigg\{ 1 + \frac{\rho}{\sqrt{\frac{a_1 b_1}{(a_1+b_1)^2(a_1+b_1+1)}}\sqrt{\frac{a_2 b_2}{(a_2+b_2)^2(a_2+b_2+1)}}}\\ &\quad \left(\frac{y_{1i}+a_1}{n_{1i}+a_1+b_1} - \frac{a_1}{a_1+b_1} \right)\\ &\quad \times \left(\frac{y_{2i}+a_2}{n_{2i}+a_2+b_2} - \frac{a_2}{a_2+b_2} \right) \Bigg\} \Bigg],\end{aligned} \tag{6}$$

where $\mathrm{P}_{BB}(y_{ji}; n_{ji}, a_j, b_j)$ is the probability mass function of beta-binomial distribution. The last expression in Equation (6) was derived by Danaher and Hardie (2005). We refer to Equation (6) as Sarmanov beta-binomial model. It is worth pointing out that as one benefit of using Sarmanov bivariate beta distribution, the log-marginalized likelihood function has a closed-form expression, which avoids numerical approximation of integrals.

Denote $(\hat{a}_1, \hat{b}_1, \hat{a}_2, \hat{b}_2, \hat{\rho})$ the maximum likelihood estimates based on the log-likelihood function (6). The quantity of primary interest, overall risk difference, defined by $D_{\text{overall}} = \mu_1 - \mu_2$ can be estimated by $\hat{D}_{\text{overall}} = \hat{a}_1/(\hat{a}_1 + \hat{b}_1) - \hat{a}_2/(\hat{a}_2 + \hat{b}_2)$. The variance of the overall risk difference estimate $\hat{D}_{\text{overall}}$ can be estimated by the delta method. Specifically, to avoid computational problems, we reparameterize the parameters (a_1, b_1, a_2, b_2) in their log scale and denote H the corresponding Hessian matrix of the log-likelihood function. The variance of the overall risk difference estimate $\hat{D}_{\text{overall}}$ is estimated by $A^T(-H)^{-1}A$ where $A = (-\hat{a}_1\hat{b}_1/(\hat{a}_1 + \hat{b}_1)^2, \hat{a}_1\hat{b}_1/(\hat{a}_1 + \hat{b}_1)^2, \hat{a}_2\hat{b}_2/(\hat{a}_2 + \hat{b}_2)^2, -\hat{a}_2\hat{b}_2/(\hat{a}_2 + \hat{b}_2)^2, 0)^T$.

On the other hand, the study-specific risk difference in the ith study, D^i_{specific}, has posterior distribution $f^*_D(d; y_{1i} + a_1, n_{1i} - y_{1i} + b_1, y_{2i} + a_2, n_{2i} - y_{2i} + b_2, \rho)$ if the hyperparameters were known. In practice, we can use a naive empirical Bayes method by simply replacing the hyperparameters by their estimates. Note that the inference based on $f^*_D(d; y_{1i} + \hat{a}_1, n_{1i} - y_{1i} + \hat{b}_1, y_{2i} + \hat{a}_2, n_{2i} - y_{2i} + \hat{b}_2, \hat{\rho})$ ignores the uncertainty in the hyperparameter estimates, and hence may lead to credible intervals that are liberal. To improve the coverage performance of the credible intervals, bias correction or bootstrap methods proposed by Deely and Lindley (1981) and Carlin and Gelfand (1991) can be used.

To adjust for study level covariates, model (5) can be extended to regression setting. A possible extension is specified as follows. We assume that the study-specific risk p_{ji} for $j = 1, 2$ have beta distributions with mean parameters μ_{ji} and dispersion parameters ϕ_j, respectively,

$$p_{ji}|(\phi_j, \mu_{ji}) \propto p^{\mu_{ji}/(1/\phi_j - 1) - 1}(1-p)^{(1-\mu_{ji})/(1/\phi_j - 1) - 1} \quad \text{for } j = 1, 2,$$

where $\mathrm{E}[p_{ji}|\phi_j, \mu_{ji}] = \mu_{ji}$ and $\mathrm{var}(p_{ji}|\phi_j, \mu_{ji}) = \delta_{ji}^2 = \phi_j \mu_{ji}(1-\mu_{ji})$. The mean of each beta distribution is a function of covariates

$$\mu_{ji} = h^{-1}(X_i \eta_j) \text{ for } j = 1, 2,$$

where $h(\cdot)$ is some link function and X_i are the study-specific covariates related to study-specific risks. To allow for the correlation between risks, we assume the paired study-specific risks (p_{1i}, p_{2i}) follow the Sarmanov beta distribution; that is,

$$\begin{aligned}(p_{1i}, p_{2i})|(\phi_1, \mu_{1i}, \phi_2, \mu_{2i}) &\propto p_{1i}^{\mu_{1i}/(1/\phi_1-1)-1}(1-p_{1i})^{(1-\mu_{1i})/(1/\phi_1-1)-1} \\ &\times p_{2i}^{\mu_{2i}/(1/\phi_2-1)-1}(1-p_{2i})^{(1-\mu_{2i})/(1/\phi_2-1)-1} \\ &\times \left\{1 + \rho \frac{(p_{1i}-\mu_{1i})}{\delta_{1i}} \frac{(p_{2i}-\mu_{2i})}{\delta_{2i}}\right\}.\end{aligned}$$

This model allows different dispersion parameters ϕ_j across different groups. Similar to the estimation procedure for model (5), this bivariate beta-binomial regression model can be fitted by maximizing the log-marginalized likelihood function.

3. Simulation Studies

In this section, we verify the results in Equations (1) and (4) and evaluate the finite sample performance of the Sarmanov beta-binomial model (6) through simulation studies. In the first set of simulation, we verify the results in (1) and (4) empirically using Markov chain Monte Carlo (MCMC) methods. We consider one study investigated by Vernon et al. (2009) (details in Section 4) with $y_1 = 0$, $n_1 = 5$, $y_2 = 2$, and $n_2 = 7$. We impose three different prior distributions on p_1 and p_2, that is, independent Jeffreys' prior distribution ($a_1 = b_1 = a_2 = b_2 = 0.5$), Sarmanov prior distributions with strong positive and negative correlation ($a_1 = b_1 = a_2 = b_2 = 0.5$, $\rho = 0.5$ and -0.5). Using the "zero trick" in WinBUGS (Page 36 in WinBUGS User Manual, Version 1.4, January 2003), we draw 10^6 samples of p_1 and p_2 from the prior and the posterior distributions, compute the risk difference, and plot the histograms. We then overlay the density function calculated from (1) for independent prior distribution or (4) for Sarmanov prior distributions. The empirical results in Figure 1 indicate that the density functions of risk difference are correct. The posterior distribution under the Sarmanov prior distribution with negative correlation has larger standard deviation (sd = 0.204) than that under the independent prior distribution (sd = 0.167) and the Sarmanov prior distribution with

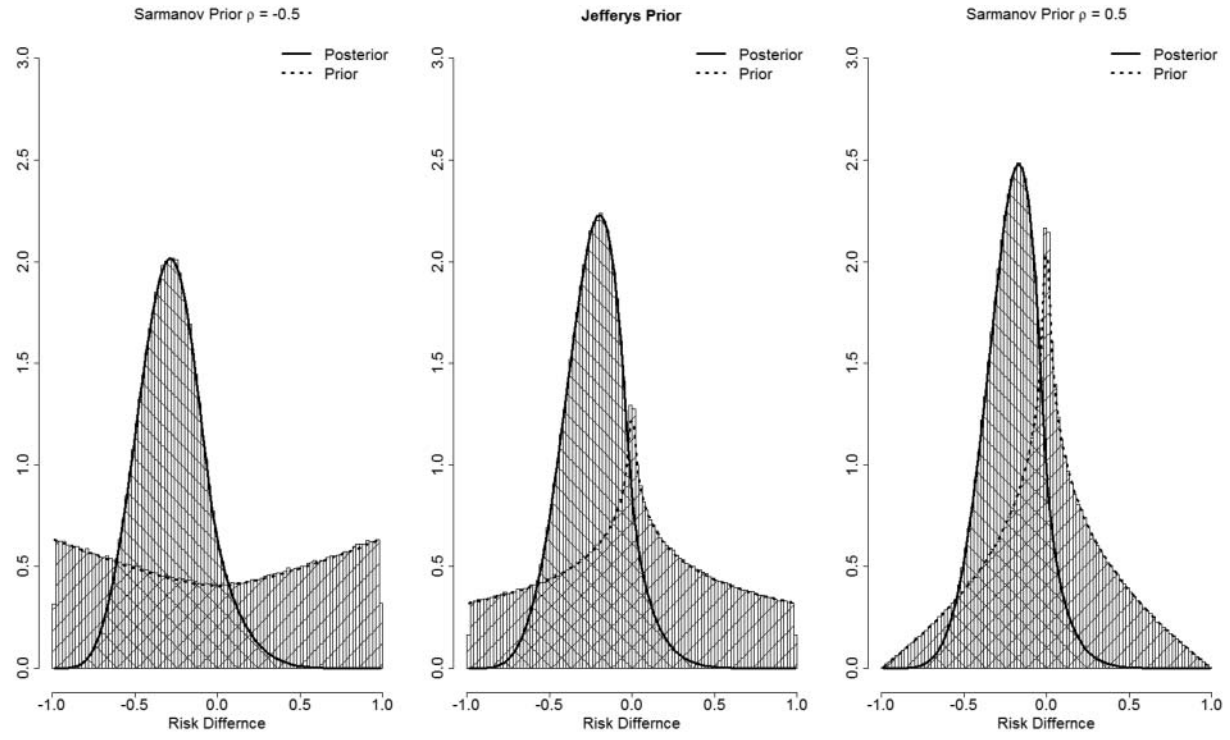

Figure 1. Histograms of 10^6 risk difference samples overlaid with density functions calculated by formulas (1) and (4) under Sarmanov prior with negative correlation (left panel), independent prior (middle panel), and Sarmanov prior with positive correlation (right panel).

Table 1. Estimates of the bias, true standard error (SE), model-based standard error (MBSE), coverage probability (CP), and relative efficiency (RE) of risk difference in 5000 simulations based on Sarmanov beta-binomial model and independent beta-binomial model, with different number of studies n, for different between risks correlations ρ. $(a_1, b_1, a_2, b_2) = (0.5, 0.5, 0.5, 0.5)$

		Sarmanov model					Independent model				
n	ρ	Bias	SE	MBSE	CP (%)	RE	Bias	SE	MBSE	CP (%)	RE
8	0	−0.003	0.178	0.159	89.7	1.000	−0.003	0.178	0.159	90.0	1.00
	0.2	0.002	0.155	0.148	92.7	1.000	0.002	0.160	0.158	92.9	0.938
	0.4	−0.003	0.133	0.135	95.2	1.000	−0.003	0.145	0.159	95.2	0.841
16	0	−0.001	0.126	0.116	91.3	1.000	−0.001	0.126	0.116	92.1	1.00
	0.2	0.001	0.109	0.107	94.2	1.000	0.001	0.111	0.117	95.4	0.964
	0.4	0.001	0.091	0.095	96.5	1.000	0.002	0.099	0.117	97.4	0.845
32	0	0.000	0.088	0.084	92.9	1.000	0.000	0.088	0.084	93.5	1.000
	0.2	0.001	0.076	0.076	94.4	1.000	0.001	0.077	0.084	96.3	0.974
	0.4	0.001	0.065	0.067	95.9	1.000	0.002	0.070	0.084	98.0	0.862
48	0	−0.001	0.071	0.069	93.9	1.000	−0.001	0.070	0.069	94.4	1.029
	0.2	0.001	0.063	0.062	94.3	1.000	0.001	0.063	0.069	96.4	1.000
	0.4	0.001	0.053	0.054	95.9	1.000	0.001	0.057	0.069	98.1	0.865

positive correlation (sd = 0.120). The similar shapes of the posterior distributions of risk difference under different prior distributions suggests that the posterior inference on risk difference is relatively robust to the prior distribution assumptions.

In the second set of simulation, we evaluate the finite sample performance of the maximum likelihood estimate of the overall risk difference. To cover a spectrum of settings in practice and to evaluate the impact of correlation on the inference of overall risk difference, we let the number of studies and correlation between risks vary. Specifically, the number of studies $n = 8$, 16, 32, and 48 and the correlation $\rho = 0$, 0.2, and 0.4. The size of each study in the meta-analysis is randomly sampled from the study sizes in a meta-analysis real study listed in Appendix Table A.1. The hyperparameters (a_1, b_1, a_2, b_2) is set as (0.5, 0.5, 0.5, 0.5). We simulate 5000 datasets in each setting and each dataset is fitted by the Sarmanov and independent models. We use the `optim` function in R (R Development Core Team, Version 2.14.1), which implements a quasi-Newton method with box constraints on the ranges of parameters. An R program to fit both the Sarmanov and independent models is attached in Appendix Section A. Table 1 compares the bias, true standard error (the standard deviation of the overall risk difference estimates and labeled as "SE"), model-based standard error (the square root of the average of the overall risk difference variance estimated via Delta method, labeled as "MBSE"), coverage probability (labeled as "CP"), and relative efficiency (defined as the ratio of the empirical variance of estimates based on Sarmanov model to that of estimates based on independent model, labeled as "RE") of the risk difference estimated from the Sarmanov and independent beta-binomial model. When $\rho = 0$, the independent model is the true model and it has good performance in bias and CP. The CP for the confidence intervals of overall risk difference using the independent model is lower than the nominal level of 95% when $n = 8$, 16, and becomes closer to the nominal level as the number of studies increases. This can be explained by the fact that the empirical standard error is underestimated by the model-based standard error when the sample size is relatively small. Similarly, when $\rho = 0$, Sarmanov model has small bias and satisfactory CP. The CP from Sarmanov model is lower than the nominal level when the number of studies is relatively small (e.g., $n = 8$, 16) and becomes closer to the nominal level when number of studies increases. This is also due to the underestimated standard error in small samples. When the correlation ρ becomes 0.2 or 0.4, both models provide unbiased estimates. Although both models produce smaller SEs as compared with those when $\rho = 0$ due to "borrowing strength" across groups within the same study Riley et al. (2007), the SEs from the Sarmanov model are still smaller than those from the independent model. While the Sarmanov model still has MBSE close to SE and CP close to 0.95, the SEs from the independent model remain unchanged because this model fails to account for the correlation. Therefore, the confidence intervals from the independent model are over-conservative and the CPs deviate upward from the nominal value. When ρ increases, the efficiency gain by using the Sarmanov model can be as large as 15.5%. In conclusion, these simulation results indicate that Sarmanov model provides valid and efficient inference and is robust to the correlation with moderate number of studies, while the independent model only gives valid inference when the correlation is zero. In practice, we recommend to conduct a likelihood ratio test for $\rho = 0$ to select the independent or Sarmanov model. Alternatively, investigators can use the Sarmanov model regardless of the significance level of the test for $\rho = 0$ because the Sarmanov model is a more general model. The

price to pay when using this strategy is to have one more parameter to estimate, that is, ρ, and can slightly lose some statistical efficiency if the independent model is the true model.

4. Multivariate Meta-Analysis of Adverse Events of Tricyclic Antidepressant Treatment

Tricyclic antidepressants are effective in preventing headaches and have become a standard modality in headache prevention. To investigate the efficacy and related adverse effects of tricyclic antidepressants in the treatment of headaches, Jackson et al. (2010) reported a meta-analysis based on multiple clinical trials from year 1964 to year 2009. Among several outcomes of interest, proportion of withdrawal during a trial is paid special attention because it is a very important measure of adverse event, and plays a critical role in drug safety assessment. One question of interest is whether the likelihood of withdrawing due to adverse effects is increased by tricyclic treatment compared to placebo. This can be measured by risk difference (defined as the difference of risks of withdrawal comparing those in tricyclic treatment group to those in placebo group). The numbers of withdrawals due to adverse effects in 16 clinical trials are summarized in Appendix Table A.1. In summary, 16 studies were included in the meta-analysis with 1012 participants in amitriptyline treatment group and 720 participants in control group, among which 375 and 151 participants withdrew due to adverse effects, respectively. Preliminary data analysis finds that the proportion of withdrawal is higher in the tricyclic treatment group than in the placebo group in 11 out of 16 studies, which indicates some potential association between tricyclic treatment and withdrawal.

One caveat here is that the proportions of withdrawal within the same study are expected to be correlated because of study-specific factors, such as location, and the ability of the study coordinators to recruit and retain study participants, etc. To rigorously address this drug-safety question, the correlation

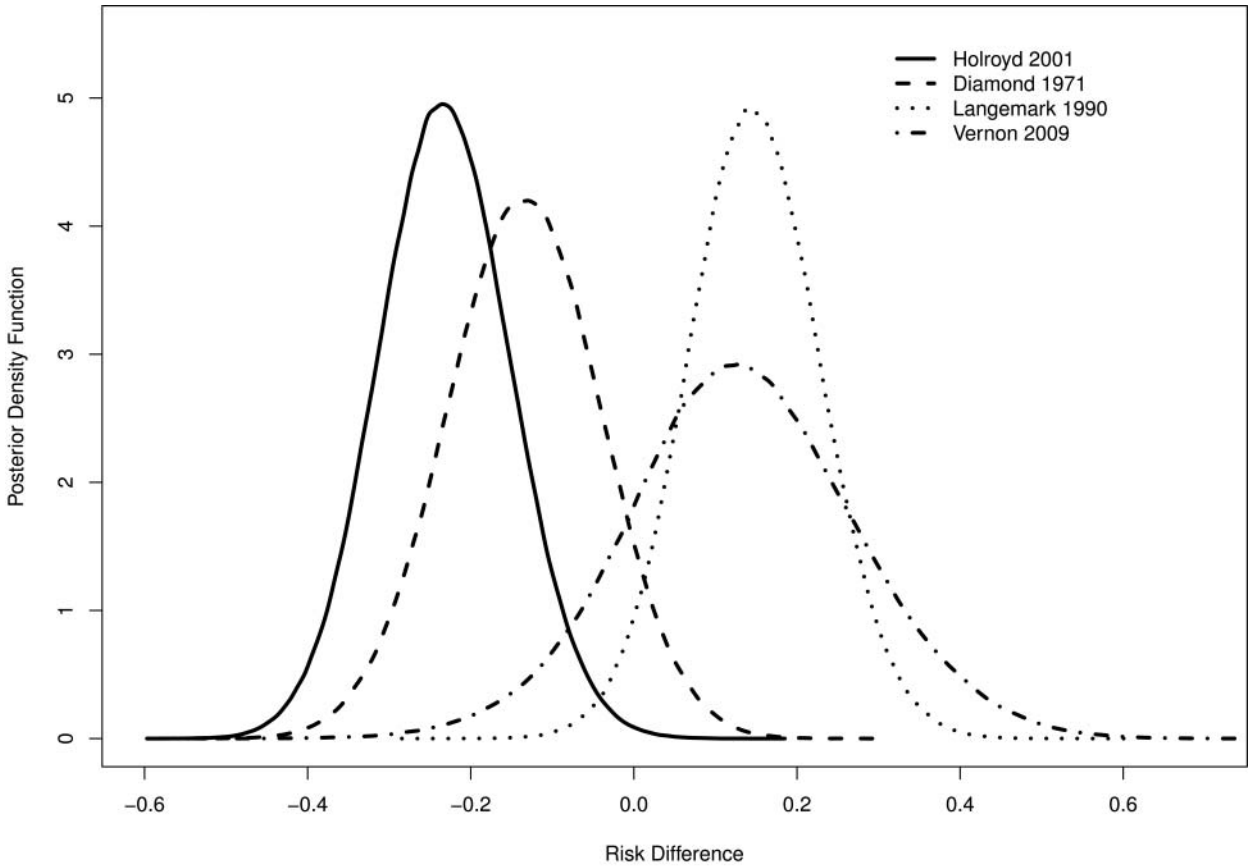

Figure 2. Posterior distributions of risk difference for four studies: Holroyd et al. (2001), Diamond and Baltes (1971), Langemark et al. (1990), and Vernon et al. (2009). Risk difference is defined as difference of risks of withdrawal comparing those in treatment group to those in placebo group.

between two proportions needs to be accounted for. Thus, the random effect model (5) is fitted and the hyperparameters are estimated as $(\hat{a}_1, \hat{b}_1, \hat{a}_2, \hat{b}_2, \hat{\rho}) = (2.042, 7.408, 1.943, 5.179, 0.093)$. Positive correlation between risks of withdrawal is found $\hat{\rho} = 0.093$. The likelihood ratio test for the significance of correlation is conducted by comparing the model (5) with the independent beta-binomial model and yields a p-value of 0.65. The overall risk difference estimate is 0.057 (95% CI: $[-0.049, 0.162]$), suggesting no significant evidence of higher probability of withdrawal in the treated group compared to the placebo group. By applying bisection root-finding method to compute the 2.5% and 97.5% quantiles of posterior distributions for the study-specific risk differences, we construct the 95% credible intervals of study-specific risk difference. To visualize the statistical evidence on risk difference contributed by each study, we plot the posterior density functions of four study-specific risk differences in Figure 2. This suggests that while in Holroyd et al. (2001) most of the density of risk difference lies between -0.5 and 0 (mean: -0.232, 95% CI: $[-0.389, -0.072]$), the density shifts toward zero in Diamond and Baltes (1971) (mean: -0.136, 95% CI: $[-0.321, 0.048]$). In the studies of Langemark et al. (1990) and Vernon et al. (2009), the majority of risk difference density lies in the intervals of $[0, 0.4]$ (mean: 0.148, 95% CI: $[-0.011, 0.310]$) and $[-0.2, 0.5]$ (mean: 0.133, 95% CI: $[-0.145, 0.415]$), respectively. The posterior distribution based on the study of Vernon et al. (2009) is relatively flat due to its small sample size. The left panel of Figure 3 displays the forest plot with 95% credible intervals of study-specific risk differences and 95% confidence interval of overall risk difference based on all 16 studies. Notice that the study of Ladero et al. (1991) can be influential on the analysis results because the estimated risk difference (mean: 0.591, 95% CI: [0.507, 0.666]) is much larger than those in other studies. To evaluate the sensitivity of the inference on this study, we removed

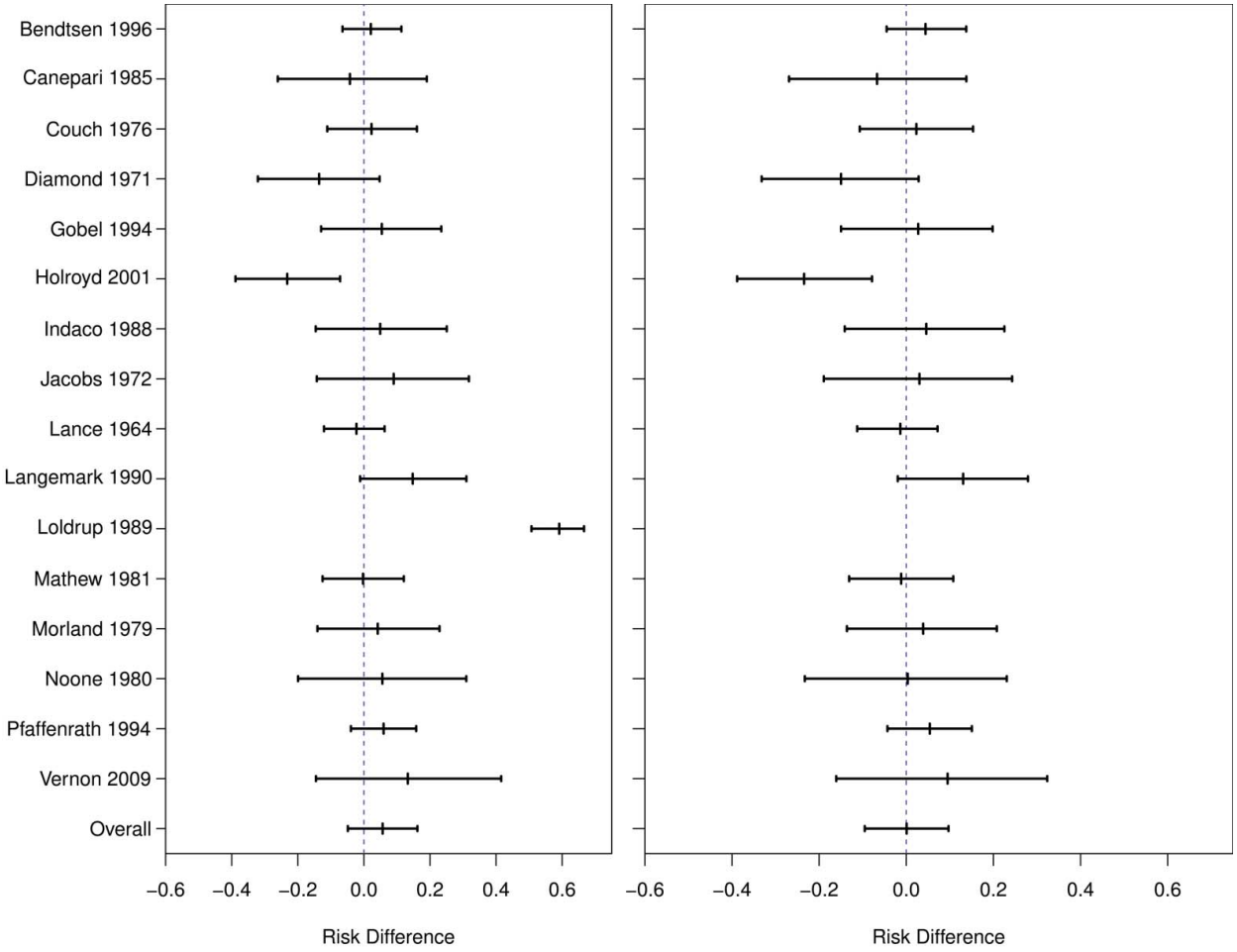

Figure 3. Forest plot of study-specific and overall risk difference with 95% credible/confidence intervals based on 16 studies (left panel) and 15 studies (right panel) after removing the potential outlying study of Ladero et al. (1991). Risk difference is defined as difference of risks of withdrawal comparing those in treatment group to those in placebo group.

it and reanalyzed the dataset. The likelihood ratio test of zero correlation coefficient results in p-value of 0.40. The study of Loldrup is somewhat influential because it lowers the overall risk difference estimate from 0.057 (95% CI: [−0.049, 0.162]) to 0.001 (95% CI: [−0.095, 0.097]) and changes the inference on all the study-specific risk differences, for example, the risk difference estimate of the study Bendtsen, Jensen, and Olesen (1996) is changed from 0.021 (95% CI: [−0.064, 0.113]) to 0.045 (95% CI: [−0.043, 0.139]). The influence of the study of Loldrup can be visualized by comparing the left panel to the right panel (forest plot based on 15 studies with the study of Loldrup removed) of Figure 3.

5. Conclusions

In this article, we extend the current work on Bayesian inference of risk difference under independent prior distributions to correlated prior distributions. In addition to the mathematical value of closed-form formula, one practical advantage is that the formula can greatly reduce the computational cost in estimating a smooth posterior density for risk difference. The results are verified through simulation studies and extensions to multiple studies with study level covariates are discussed. An example in meta-analysis for adverse events of tricyclic antidepressant treatment is illustrated. A limitation of this illustrative case study is that the correlation between risks of withdrawal in treatment and control groups is relatively small $\hat{\rho} = 0.093$ (p-value $= 0.65$). We want to point out that the goal of the method considered in this article is to compare the event rates of events, such as withdrawal or dropout during a trial, between two groups, rather than for safety events detection such as bioterrorism. In addition, the method discussed in this article can be applied to other key safety evaluation such as adverse events of interest in addition to withdrawal during a trial.

Recently, the rapid growth of evidence-based medicine has led to a great deal of attention to multivariate meta-analysis (Jackson, Riley, and White 2011). There is an increasing need for models that can account for heterogeneity between studies and correlation between groups (Jackson, Riley, and White 2011). The Sarmanov models considered in this article offer an alternative to traditional bivariate generalized linear mixed effect model (BGLMM) such as in Skrondal and Rabe-Hesketh (2004) and Chu and Cole (2006). It would be of interest to compare the Sarmanov model to the BGLMM. In addition to the different distributional assumption on the random effects, there are two major differences. First, the BGLMM implicitly assumes that the conditional expectation of transformed study-specific risk $h(p_{2i})$ given the transformed study-specific risk $h(p_{1i})$ is a linear function of $h(p_{1i})$, where $h(\cdot)$ is some link function. The Sarmanov beta-binomial model assumes that the conditional expectation of p_{2i} given p_{1i} is a linear function of p_{1i}. Such conditional expectation relationship may be used empirically to provide guidance in model selection. Second, the BGLMM models the correlation between $h(p_{1i})$ and $h(p_{2i})$, that is, correlation between risks in a transformed scale; hence, the interpretation of such correlation is transformation-dependent and is less intuitive. In contrast, the Sarmanov model directly models the correlation between p_1 and p_2, which has a straightforward interpretation. In practice, information criterions, such as Akaike information criterion (AIC) and Bayesian information criterion (BIC), can also be used for model selection. Although Sarmanov bivariate beta distributions are flexible in modeling and can model both positive and negative correlations, they do not come without a price. One limitation is the natural constraints of correlation coefficient; that is, the correlation coefficient ρ must be subject to the constraints $-c/\max(a_1a_2, b_1b_2) \le \rho \le c/\max(a_1b_2, a_2b_1)$, where $c = \sqrt{a_1a_2b_1b_2}/\sqrt{(a_1+b_1+1)(a_2+b_2+1)}$. It is easy to see that the range is narrower than $[-1, 1]$, which is a common problem for nonnormal bivariate distributions such as the Farlie-Gumbel-Morgenstern distribution (Farlie 1960). A difficulty induced by the constraints is in maximizing log marginalized likelihood functions, for example, Equation (6). To account for the fact that the range of correlation coefficients ρ depends on other parameters, we can reparameterize ρ to ω as $\rho = -c/[\max(a_1a_2, b_1b_2)\{1+\exp(\omega)\}] + c\exp(\omega)/[\max(a_1b_2, a_2b_1)\{1+\exp(\omega)\}]$ where $\omega \in (-\infty, +\infty)$. However, the parameters (a_1, b_1, a_2, b_2) and ω are still highly correlated, which can lead to unstable estimates. One possible solution is to adopt a two-stage estimation procedure and base the inference on the pseudolikelihood (Gong and Samaniego 1981). Another possible solution is to consider an estimating equation approach (Liang and Zeger 1995). Both methods are under investigation. The credible intervals for study-specific risk difference are based on a naive empirical Bayes method, which is known to be liberal due to the ignored uncertainty of the hyperparameters. Intuitively, if the meta-analysis consists of a relatively large number of studies where the hyperparameters are well-estimated, the inference, including coverage probability of the credible interval, using naive empirical Bayes method may be satisfactory. If the meta-analysis consists of relatively small number of studies, the hyperparameters may be estimated with substantial uncertainty and adjustment of the naive empirical Bayes method is needed. In this case, bias correction or bootstrap methods proposed by Deely and Lindley (1981) and Carlin and Gelfand (1991) can be

used. The frequentist properties of the naive empirical Bayes credible intervals, comparing to the bias corrected credible intervals, are to be investigated in our future research. As a final note, in a recent article by Chu et al. (2012), a similar Sarmanov bivariate Beta-binomial model is applied to metaanalyses in making inference on the overall risk difference, whereas our article considers the overall risk difference and provides exact posterior distributions of study-specific risk differences.

APPENDIX

Section A: SPLUS/R program to fit model (5) and a working example

```
#### inference for overall risk difference
  ###
# Compute the log-likelihood function to be
  maximized
myLik <- function(mypar, mydat) {
par <- par.cal(mypar); a1 <- par[1]; b1
  <- par[2]; a2 <- par[3]; b2 <- par[4]
temp1 <- (lgamma(a1+mydat$y1) + lgamma
  (b1+mydat$n1-mydat$y1) + lgamma(a2+
  mydat$y2) + lgamma(b2+mydat$n2-mydat$y2)
  + lgamma(a1+b1) + lgamma(a2+b2))
temp2 <-(lgamma(a1) + lgamma(b1)
  + lgamma(a2) + lgamma(b2) + lgamma(a1+b1
  +mydat$n1) + lgamma(a2+b2+mydat$n2))
if (flag == 0)myLogLik<-sum(temp1-temp2) #
  # if independent beta-binomial model
if (flag == 1) {# if Sarmanov beta-binomial
  model
rho <- par[5]
mu1 <- a1/(a1+b1); mu2 <- a2/(a2+b2)
delta1 <- sqrt(mu1*(1-mu1)/(a1+b1+1));
  delta2 <- sqrt(mu2*(1-mu2)/(a2+b2+1))
temp3 <- (log(1+rho/delta1/delta2*(mydat$
  y1-mydat$n1*mu1)*(mydat$y2-mydat$n2*mu2)
/(a1+b1+mydat$n1)/(a2+b2+mydat$n2)))
myLogLik <- sum(temp1 - temp2 + temp3)}
return(myLogLik)
}

# Back-transform the parameters to original
  scale
par.cal <- function(mypar) {
a1 <- exp(mypar[1]); b1 <- exp(mypar[2]);
  a2 <- exp(mypar[3]); b2 <- exp(mypar[4])
if (flag == 0) return(c(a1,b1,a2,b2))
if (flag == 1) {
eta <- mypar[5]; cc <- sqrt(a1*a2*b1*b2)/
  sqrt((a1+b1+1)*(a2+b2+1))
upper.bound <- cc/max(a1*b2, a2*b1);
  lower.bound <- -cc/max(a1*a2, b1*b2)
rho <- (upper.bound-lower.bound)*exp(eta)/
  (1+exp(eta)) + lower.bound
return(c(a1,b1,a2,b2,rho))}
}

# note: we use Delta method to get the
  variance of RD and use Wald interval on
  RD
RD.comp <- function(par, hessian) {
a1 <- par[1]; b1 <- par[2]; a2 <- par[3];
  b2 <- par[4]
myRD.overall <- a2/(a2+b2) - a1/(a1+b1)
myVar <- solve(-hessian)
if (flag == 0) myD <- matrix
  (c(-a1*b1/(a1+b1)^2, a1*b1/(a1+b1)^2,
  a2*b2/(a2+b2)^2, -a2*b2/(a2+b2)^2),
  nrow=1)
if (flag == 1) myD <- matrix
  (c(-a1*b1/(a1+b1)^2, a1*b1/(a1+b1)^2,
  a2*b2/(a2+b2)^2, -a2*b2/(a2+b2)^2, 0),
  nrow=1)
myRD.overall.Var <- as.numeric(myD
myRD.overall.sd <- sqrt(myRD.overall.Var)
myRD.left.bound <- max(myRD.overall
  -1.96*sqrt(myRD.overall. Var), -1)
myRD.right.bound <- min(myRD.overall
  +1.96*sqrt(myRD.overall. Var), 1)
return(list(RD=myRD.overall,
  RD.left=myRD.left.bound,
RD.right=myRD.right.bound))
}

# Dataset from Jackson et al (2010) BMJ
y2<-c(1,4,8,14,15,9,3,12,7,10,222,23,4,6,
  35,2)
n2<-c(40,16,47,56,44,53,18,26,105,36,306,
  86,23,16,133,7)
y1<-c(0,9,8,13,10,22,2,8,4,4,11,26,
  3,5,26,0)
n1<-c(40,27,53,29,34,48,18,21,49,38,98,94,
  23,15,128,5)

# remove one study with extremely large
  withdrawl probability in the treatment
  group
#y1 <- y1[-11]; n1 <- n1[-11]; y2 <-
  y2[-11]; n2 <- n2[-11]

init.val <- rep(0, 5)

# maximization of the likelihood of
  independent beta-binomial model
```

```
flag <- 0 # flag = 0: independent
  beta-binomial model
results.indep <- optim(init.val[1:4],
  myLik, method = "L-BFGS-B,"
lower=rep(-20,4), upper=rep(20,4), control
  = list(fnscale=-1,maxit=1000),
hessian = T, mydat=list(y1=y1,n1=n1,y2=y2,
  n2=n2))
RD.comp(par.cal(results.indep$par),
  results.indep$hessian)

# maximization of the likelhood of Sarmanov
  beta-binomial model
flag <- 1 # flag = 1: Sarmanov
  beta-binomial model
results <- optim(init.val, myLik, method =
  "L-BFGS-B,"
lower=rep(-20,5), upper=rep(20,5), control
  = list(fnscale=-1,maxit=1000),
hessian=T, mydat=list(y1=y1,n1=n1,y2=y2,
  n2=n2))
RD.comp(par.cal(results$par),
  results$hessian)

# Likelihood ratio test for correlation
pchisq(q=-2*(results.indep$
  value-results$value), df=1, ncp=0,
  lower.tail = FALSE, log.p = FALSE)

#### exact inference for study-specific
  risk difference ###
# Call Appell function to compute the
  density
AppellFun <- function(ca, cb, cbp, cc, x,
  y) {
dyn.load('../appell.so')
returned_data = .Fortran('f1bnl_r_wrapper',
ca=as.complex(ca), cb=as.complex(cb),
  cbp=as.complex(cbp), cc=as.complex(cc),
x=as.complex(x), y=as.complex(y),
  result=complex(1))
return(returned_data$result)
}

# The density function of RD from Eq(1)
risk.diff.dens.func <- function(alpha1,
  beta1, alpha2, beta2, theta){
if(theta<0 & theta>-1){
mylog <- ((beta1+beta2-1)*log(-theta)
  + (alpha2+beta1-1)*log(1+theta)
  -(lgamma(alpha1)+lgamma(beta2)+lgamma
  (alpha2+beta1))
  +(lgamma(alpha1+beta1)+lgamma(alpha2
  +beta2))+log(as.numeric(AppellFun(beta1,
  alpha1+alpha2+beta1+beta2-2,
  1-alpha1,alpha2+beta1,1+theta,
  1-theta^2))))
result <- exp(mylog)
}

if(theta>=0 & theta<1){
mylog <- ((beta1+beta2-1)*log(theta)
  +(alpha1+beta2-1)*log(1-theta)
  -(lgamma(alpha2)+lgamma(beta1)
  +lgamma (alpha1+beta2))
  +(lgamma(alpha1+beta1)+lgamma(alpha2
  +beta2))+log(as.numeric(AppellFun(beta2,
  alpha1+alpha2+beta1+beta2-2, 1-alpha2,
  alpha1+beta2,1-theta,1-theta^2))))
result <- exp(mylog)
}
return(result)
}

# This function is to compute RD under
  correlated prior from Eq(4)
corr.dens.func <- function(alpha1,beta1,
  alpha2,beta2,theta,
omega1,omega2,omega3,omega4) {
results <- (omega1*risk.diff.dens.func
  (alpha1,beta1,alpha2,beta2,theta)
  +omega2*risk.diff.dens.func(alpha1+1,
  beta1,alpha2,beta2,theta)
  +omega3*risk.diff.dens.func(alpha1,beta1,
  alpha2+1,beta2,theta)
  +omega4*risk.diff.dens.func(alpha1+1,
  beta1,alpha2+1,beta2,theta))
return(results)
}

# This function is to compute the weights.
omega.computation <- function(y1, n1, y2,
  n2, a1, b1, a2, b2, rho) {
alpha1 <- y1+a1; beta1 <- n1-y1+b1
alpha2 <- y2+a2; beta2 <- n2-y2+b2

# mu1, mu2: marginal means of p1 and p2
mu1 <- a1/(a1+b1); mu1.1 <- 1-mu1
mu2 <- a2/(a2+b2); mu2.1 <- 1-mu2

# delta1, delta2: marginal sd of p1 and p2
delta1 <- sqrt(mu1*mu1.1/(a1+b1+1))
delta2 <- sqrt(mu2*mu2.1/(a2+b2+1))

# myd: d=(mu1*mu2)/(delta1*delta2)
myd <- (mu1*mu2)/(delta1*delta2)
```

```
## v1-v4 are weights
v2 <- v3 <- -rho*myd
v1 <- 1 - v2
v4 <- -v2

temp1 <- (lgamma(alpha1)+lgamma(beta1)
 +lgamma(alpha2)+lgamma(beta2)
 +lgamma(a1+b1)+lgamma(a2+b2)
 -(lgamma(a1)+lgamma(b1)+lgamma(a2)
 +lgamma(b2)+lgamma(alpha1+beta1)+lgamma
 (alpha2+beta2)))
temp2 <- (lgamma(alpha1+1)+lgamma(beta1)
 +lgamma(alpha2)+lgamma(beta2)
 +lgamma(a1+b1+1)+lgamma(a2+b2)
 -(lgamma(a1+1)+lgamma(b1)+lgamma(a2)
 +lgamma(b2)+lgamma(alpha1+beta1+1)
 +lgamma(alpha2+beta2)))
temp3 <- (lgamma(alpha1)+lgamma(beta1)
 +lgamma(alpha2+1)+lgamma(beta2)
 +lgamma(a1+b1)+lgamma(a2+b2+1)
 -(lgamma(a1)+lgamma(b1)+lgamma(a2+1)
 +lgamma(b2)+lgamma(alpha1+beta1)
 +lgamma(alpha2+beta2+1)))
temp4 <- (lgamma(alpha1+1)+lgamma(beta1)
 +lgamma(alpha2+1)+lgamma(beta2)
 +lgamma(a1+b1+1)+lgamma(a2+b2+1)
 -(lgamma(a1+1)+lgamma(b1)+lgamma(a2+1)
 +lgamma(b2)+lgamma(alpha1+beta1+1)
 +lgamma(alpha2+beta2+1)))

eps <- 1e-30
if (abs(v1) < eps) {
omega1 <- 0
} else {
omega1 <- 1/(1 + v2/v1*exp(temp2-temp1)
 + v3/v1*exp(temp3-temp1)
 + v4/v1*exp(temp4-temp1))
}
if (abs(v2) < eps) {
omega2 <- 0
} else {
omega2 <- 1/(v1/v2*exp(temp1-temp2)
 + 1 + v3/v2*exp(temp3-temp2) +
 v4/v2*exp(temp4-temp2))
}
if (abs(v3) < eps) {
omega3 <- 0
} else {
omega3 <- 1/(v1/v3*exp(temp1-temp3)
 + v2/v3*exp(temp2-temp3) + 1 +
 v4/v3*exp(temp4-temp3))
}
if (abs(v4) < eps) {
omega4 <- 0
} else {
omega4 <- 1/(v1/v4*exp(temp1-temp4)
 + v2/v4*exp(temp2-temp4)
 + v3/v4*exp(temp3-temp4) + 1)
}

return(list(omega1=omega1, omega2=omega2,
 omega3=omega3, omega4=omega4))
}

# Compute the posterior density function
 under correlated prior
post.dens <- function(y1, n1, y2, n2, a1,
 b1, a2, b2, rho,
grid.start, grid.end, grid.num) {

alpha1 <- y1+a1; beta1 <- n1-y1+b1
alpha2 <- y2+a2; beta2 <- n2-y2+b2
temp <- c(alpha1, beta1, alpha2, beta2)
if (max(temp) > 1e5) warning("Large cell
 count! The program may not work or give
 incorrect results!")

myOmega <- omega.computation(y1, n1, y2,
 n2, a1, b1, a2, b2, rho)
theta.grid <- seq(grid.start, grid.end,
 length=grid.num)
theta.dens <- rep(NA,
 length=length(theta.grid))

for(i in 1:length(theta.grid)){
theta.dens[i] <- corr.dens.func(alpha1,
 beta1,alpha2,beta2,theta.grid[i],
myOmega$omega1,myOmega$omega2,
myOmega$omega3,myOmega$omega4)
}
theta.dens <- as.numeric(theta.dens)

return(list(theta.dens=theta.dens,
 theta.grid=theta.grid))
}

# For RD, specify the starting and end
 points of the density range under
 consideration
grid.start <- 0.11; grid.end <- 0.4
grid.num <- 50 # number of grid points

# The study Couch (1976) in Appendix
 Table 1
y1 <- 8; n1 <- 53; y2 <- 8; n2 <- 47
# The hyperparameters obtained from
 maximizing the log marginalized
 likelihood from Eq(6)
```

Table A.1. Data from a meta-analysis of 16 studies on the association between withdrawal due to adverse effects and tricyclic treatment in Jackson et al. (2010). No. withdraws: number of individuals who withdrew from the study. No. individuals: number of individuals who started the study

	Treatment		Control	
Author	No. withdraws	No. individuals	No. withdraws	No. individuals
Bendtsen 1996	1	40	0	40
Canepari 1985	4	16	9	27
Couch 1976	8	47	8	53
Diamond 1971	14	56	13	29
Gobel 1994	15	44	10	34
Holroyd 2001	9	53	22	48
Indaco 1988	3	18	2	18
Jacobs 1972	12	26	8	21
Lance 1964	7	105	4	49
Langemark 1990	10	36	4	38
Loldrup 1989	222	306	11	98
Mathew 1981	23	86	26	94
Morland 1979	4	23	3	23
Noone 1980	6	16	5	15
Pfaffenrath 1994	35	133	26	128
Vernon 2009	2	7	0	5

```
a1 <- 2.04191387; b1 <- 7.40756047; a2
  <- 1.94332271; b2 <- 5.17945361; rho
  <- 0.09303324
myRD <- post.dens(y1, n1, y2, n2, a1, b1,
  a2, b2, rho,
grid.start, grid.end, grid.num)
plot(myRD$theta.grid, myRD$theta.dens,
  type="l")
```


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References

Bendtsen, L., Jensen, R., and Olesen, J. (1991), "A Non-Selective (Amitriptyline), But Not a Selective (Citalopram), Serotonin Reuptake Inhibitor is Effective in the Prophylactic Treatment of Chronic Tension-Type Headache," *Journal of Neurology, Neurosurgery & Psychiatry*, 61, 285–290. [150]

Carlin, B. P., and Gelfand, A. E. (1991), "A Sample Reuse Method for Accurate Parametric Empirical Bayes Confidence Intervals," *Journal of the Royal Statistical Society,* Series B, 53, 189–200. [145,150]

Chen, Y., and Luo, S. (2011), A Few Remarks on "Statistical Distribution of the Difference of Two Proportions," *Statistics in Medicine*, 30, 1913–1915. [143,145]

Chu, H., and Cole, S. R. (2006), "Bivariate Meta-Analysis of Sensitivity and Specificity With Sparse Data: A Generalized Linear Mixed Model Approach," *Journal of Clinical Epidemiology*, 59, 1331. [143,145,150]

Chu, H., Guo, H., and Zhou, Y. (2010), "Bivariate Random Effects Meta-Analysis of Diagnostic Studies Using Generalized Linear Mixed Models," *Medical Decision Making*, 30, 499–508. [143]

Chu, H., Nie, L., Chen, Y., Huang, Y., and Sun, W. (2012), "Bivariate Random Effects Models for Meta-Analysis of Comparative Studies With Binary Outcomes: Methods for the Absolute Risk Difference and Relative Risk," *Statistical Methods in Medical Research*, 21, 621–633. [151]

Cole, B. F., Lee, M. L. T., Whitmore, G. A., and Zaslavsky, A. M. (1995), "An Empirical Bayes Model for Markov-Dependent Binary Sequences With Randomly Missing Observations," *Journal of the American Statistical Association*, 90, 1364–1372. [143]

Danaher, P. J., and Hardie, B. G. S. (2005), "Bacon With Your Eggs? Applications of a New Bivariate Beta-Binomial Distribution," *The American Statistician*, 59, 282–286. [143,145]

Deely, J., and Lindley, D. (1981), "Bayes Empirical Bayes," *Journal of the American Statistical Association*, 76, 833–841. [145,150]

Diamond, S., and Baltes, B. J. (1971), "Chronic Tension Headache-Treated With Amitriptyline-a Double-Blind Study," *Headache: The Journal of Head and Face Pain*, 11, 110–116. [149]

Farlie, D. (1960), "The Performance of Some Correlation Coefficients for a General Bivariate Distribution," *Biometrika*, 47, 307. [150]

Gong, G., and Samaniego, F. J. (1981), "Pseudo Maximum Likelihood Estimation: Theory and Applications," *The Annals of Statistics*, 9, 861–869. [150]

Hartung, J., Knapp, G., and Sinha, B. K. (2001), *Statistical Meta-Analysis With Applications*, Hoboken, NJ: Wiley-Interscience. [143]

Holroyd, K. A., O'Donnell, F. J., Stensland, M., Lipchik, G. L., Cordingley, G. E., and Carlson, B. W. (2001), "Management of Chronic Tension-Type Headache With Tricyclic Antidepressant Medication, Stress Management Therapy, and Their Combination," *The Journal of the American Medical Association*, 285, 2208. [149]

Howard, J. (1998), "The 2 × 2 Table: A Discussion From a Bayesian Viewpoint," *Statistical Science*, 13, 351–367. [144]

Jackson, D., Riley, R., and White, I. R. (2011), "Multivariate Meta-Analysis: Potential and Promise," *Statistics in Medicine*, 30, 2481–2498. [143,150]

Jackson, J. L., Shimeall, W., Sessums, L., DeZee, K. J., Becher, D., Diemer, M., et al. (2010), "Tricyclic Antidepressants and Headaches: Systematic Review and Meta-Analysis," *BMJ*, 341, c5222. [148]

Kass, R. E., and Raftery, A. E. (1995), "Bayes Factors," *Journal of the American Statistical Association*, 90, 773–795. [144]

Ladero, J. M., González, J. F., Benítez, J., Vargas, E., Fernández, M. J., Baki, W., et al. (1991), "Acetylator Polymorphism in Human Colorectal Carcinoma," *Cancer Research*, 51, 2098. [149]

Langemark, M., Loldrup, D., Bech, P., and Olesen, J. (1990), "Clomipramine and Mianserin in the Treatment of Chronic Tension Headache," *A Double-Blind, Controlled Study. Headache: The Journal of Head and Face Pain*, 30, 118–121. [149]

Lee, M. L. T. (1966), "Properties and Applications of the Sarmanov Family of Bivariate Distributions," *Communications in Statistics—Theory and Methods*, 25, 1207–1222. [143,144]

Liang, K. Y., and Zeger, S. L. (1995), "Inference Based on Estimating Functions in the Presence of Nuisance Parameters," *Statistical Science*, 158–173. [150]

Nadarajah, S., and Kotz, S. (2007), "Statistical Distribution of the Difference of Two Proportions," *Statistics in Medicine*, 26, 3518–3523. [145]

Northridge, M. (1995), "Public Health Methods—Attributable Risk as a Link Between Causality and Public Health Action," *American Journal of Public Health*, 85, 1202. [142]

Park, Y. H., and Fader, P. S. (2004), "Modeling Browsing Behavior at Multiple Websites," *Marketing Science*, 280–303. [143]

Pham-Gia, T., and Turkkan, N. (1993), "Bayesian Analysis of the Difference of Two Proportions," *Communications in Statistics Theory and Methods*, 22, 1755–1771. [145]

Piantadosi, S. (2005), *Clinical Trials: A Methodologic Perspective*, Hoboken, NJ: Wiley. [142]

Reitsma, J. B., Glas, A. S., Rutjes, A. W. S., Scholten, R. J. P. M., Bossuyt, P. M., and Zwinderman, A. H. (2005), "Bivariate Analysis of Sensitivity and Specificity Produces Informative Summary Measures in Diagnostic Reviews," *Journal of Clinical Epidemiology*, 58, 982–990. [145]

Riley, R., Abrams, K., Lambert, P., Sutton, A., and Thompson, J. (2007), "An Evaluation of Bivariate Random-Effects Meta-Analysis for the Joint Synthesis of Two Correlated Outcomes," *Statistics in Medicine*, 26, 78–97. [147]

Rothman, K., Greenland, S., and Lash, T. (2008), *Modern Epidemiology* (3rd. ed.), Philadelphia: Lippincott Williams & Wilkins. [142]

Sarmanov, O. (1966), "Generalized Normal Correlation and Two-Dimensional Fréchet Classes," *Soviet Mathematics Doklady*, 7, 596–599. [143,143,144]

Shubina, M., and Lee, M. L. T. (2004), "On Maximum Attainable Correlation and Other Measures of Dependence for the Sarmanov Family of Bivariate Distributions," *Communications in Statistics—Theory and Methods*, 33, 1031–1052. [143,144]

Skrondal, A., and Rabe-Hesketh, S. (2004), *Generalized Latent Variable Modeling: Multilevel, Longitudinal, and Structural Equation Models*, Boca Raton: CRC Press. [143,150]

Smith, T. C., Spiegelhalter, D. J., and Thomas, A. (1995), "Bayesian Approaches to Random-Effects Meta-Analysis: A Comparative Study," *Statistics in Medicine*, 14, 2685–2699. [143]

Stangl, D., and Berry, D. A. (2000), *Meta-Analysis in Medicine and Health Policy* (vol. 4.), Boca Raton: CRC Press. [143]

Van Houwelingen, H. C., Zwinderman, K. H., and Stijnen, T. (1993), "A Bivariate Approach to Meta-Analysis," *Statistics in Medicine*, 12, 2273–2284. [143]

Vernon, H., Jansz, G., Goldsmith, C. H., and McDermaid, C. (2009), "A Randomized, Placebo-Controlled Clinical Trial of Chiropractic and Medical Prophylactic Treatment of Adults With Tension-Type Headache: Results From a Stopped Trial," *Journal of Manipulative and Physiological Therapeutics*, 32, 344–351. [146,149]

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