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Bayesian inference on risk differences: an application to multivariate meta-analysis of adverse events in clinical trials

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Abstract

Multivariate meta-analysis is useful in combining evidence from independent studies which 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 (1966). This model have 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 has a closed-form expression of distribution functions for study-specific risk differences. We investigate the finite sample performance of this model by simulation studies and illustrate its use with an application to multivariate meta-analysis of adverse events of tricyclic antidepressants treatment in clinical trials.

Keywords

Bivariate beta-binomial model; Exact method; Hypergeometric function; Meta-analysis; 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 risk¹, 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 interventions². 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 efficacy³. 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 arises in meta-analysis when each study involves more than one group. The commonly used statistical models for multivariate meta-analysis with binary outcomes are multivariate generalized linear mixed effects models^{4,5,6,7}, which assume risks, after

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some transformation, follow a multivariate normal distribution with possible correlations. For excellent review of statistical methods for multivariate meta-analysis, we refer to the excellent review papers by Van Houwelingen *et al.* (1993)⁴ and Jackson (2011) *et al.*⁸, the books by Hartung *et al.* (2011)⁹ and Stangl and Berry (2000)¹⁰, 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)¹¹, 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; secondly, 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 inference¹². 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 pseudo-conjugate to the binomial distributions. We will show later in this article that this pseudo-conjugation property leads to a closed-form expression of distribution functions for study-specific risk differences.

The family of multivariate distributions proposed by Sarmanov (1966)¹¹ is a flexible family of distributions. This Sarmanov family has been studied extensively by Lee (1996)¹³ and Shubina and Lee (2004)¹⁴ and has been applied to areas such as Markov chain models for longitudinal data analysis by Cole *et al.* (1995)¹⁵ and prediction models for efficient business decisions in marketing sciences by Park and Fader (2004)¹⁶ and Danaher and Hardie (2005)¹⁷. 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 antidepressants treatment is provided for illustration in Section 4 followed by a brief discussion in Section 5.

2 Main Results

For the j -th 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 ($j = 1, \dots, J$). For simplicity, we consider the cases with two groups under comparison (i.e., $J = 2$) and the extension to cases with more than 2 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)¹⁸ 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

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

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

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

and $(c)_k = c(c+1) \dots (c+k-1)$ 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)¹⁹ and Howard (1998)²⁰ suggested a family of correlated prior distributions defined by

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

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 proportions¹⁹.

Alternatively, a family of bivariate distributions constructed from marginal distributions are proposed by Sarmanov (1966)¹¹ and later studied by Lee (1996)¹³ and Shubina and Lee (2004)¹⁴. This family of distributions allows for both positive and negative correlations. With pre-specified 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)¹¹ proposed the bivariate distribution of the form

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

where $\psi_j(\cdot)$ are bounded integrable non-constant 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 distribution¹³.

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, i.e.,

$\rho = \text{corr}(p_1, p_2)$ when $\psi_j(p_j) = (p_j - \mu_j)/\delta_j$. Note that when $\rho = 0$, equation (3) reduces to independent bivariate beta distribution, i.e., the product of two independent beta distributions.

One advantage of the bivariate distributions proposed by Sarmanov (referred to as Sarmanov beta priors) is its simplicity in modeling because it 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 pseudo-conjugate for binomial distributions, i.e., equation (3) can be expressed as a linear combination of independent bivariate beta distributions¹³. 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 distributions¹³,

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

where v_k ($k = 1, \dots, 4$) 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,

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

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

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

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

and C , the normalizing constant, is calculated as

$$\begin{aligned} C = & \frac{v_1 B(\alpha_1, \beta_1) B(\alpha_2, \beta_2)}{B(a_1, b_1) B(a_2, b_2)} + \frac{v_2 B(\alpha_1+1, \beta_1) B(\alpha_2, \beta_2)}{B(a_1+1, b_1) B(a_2, b_2)} \\ & + \frac{v_3 B(\alpha_1, \beta_1) B(\alpha_2+1, \beta_2)}{B(a_1, b_1) B(a_2+1, b_2)} + \frac{v_4 B(\alpha_1+1, \beta_1) B(\alpha_2+1, \beta_2)}{B(a_1+1, b_1) B(a_2+1, b_2)}. \end{aligned}$$

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

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

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)²¹, Nadarajah and Kotz (2007)²² and Chen and Luo (2011)¹⁸. When the correlation ρ is nonzero, the prior correlation is introduced to the posterior distribution of risk difference through the weights ω_k ($k = 1, \dots, 4$).

With a single 2x2 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, ρ) 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 i -th 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 j th 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 Reitma et al. (2005)²³ and Chu and Cole (2006)⁷. A random effect model can be specified as follows,

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

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

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

where $P_{BB}(y_{ji}; n_{ji}, a_j, b_j)$ is the probability mass function of beta-binomial distribution. The last expression in equation (6) is derived by Danaher and Hardie¹⁷. We refer the 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 $(\widehat{a}_1, \widehat{b}_1, \widehat{a}_2, \widehat{b}_2, \widehat{\rho})$ 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 $\widehat{D}_{\text{overall}} = \widehat{a}_1 / (\widehat{a}_1 + \widehat{b}_1) - \widehat{a}_2 / (\widehat{a}_2 + \widehat{b}_2)$. The variance of the overall risk difference estimate $\widehat{D}_{\text{overall}}$ can be estimated by the delta method. Specifically, to avoid computational problems, we reparametrize 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 $\widehat{D}_{\text{overall}}$ is estimated by $A^T (-H)^{-1} A$ where $A = \left(-\widehat{a}_1 \widehat{b}_1 / (\widehat{a}_1 + \widehat{b}_1)^2, \widehat{a}_1 \widehat{b}_1 / (\widehat{a}_1 + \widehat{b}_1)^2, \widehat{a}_2 \widehat{b}_2 / (\widehat{a}_2 + \widehat{b}_2)^2, -\widehat{a}_2 \widehat{b}_2 / (\widehat{a}_2 + \widehat{b}_2)^2, 0 \right)^T$.

On the other hand, the study-specific risk difference in the i th study, D_{specific}^i , 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

$f_D^*(d; y_{1i} + \widehat{a}_1, n_{1i} - y_{1i} + \widehat{b}_1, y_{2i} + \widehat{a}_2, n_{2i} - y_{2i} + \widehat{b}_2, \widehat{\rho})$ ignores the uncertainty in the hyperparameter estimates, hence may lead to credible intervals that are liberal. To improve the coverage performance of the credible intervals, bias correction or boot-strap methods proposed by Deely and Lindley (1981)²⁴ and Carlin and Gelfand (1991)²⁵ 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,

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

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

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

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, i.e.,

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

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)²⁶ (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 , i.e., 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 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 1. The hyperparameters (a_1, b_1, a_2, b_2) is set as $(0.5, 0.5, 0.5, 0.5)$. We simulate 5,000 dataset 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 the 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 study²⁷, 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 give 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 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, i.e., 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 antidepressants 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)²⁸ 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 that 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 sixteen clinical trials are summarized in Appendix Table 1. In summary, sixteen studies were included in the meta-analysis with 1,012 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 between two proportions needs to be accounted for. Thus, the random effect model (5) is fitted and the hyperparameters are estimated as

$(\widehat{a}_1, \widehat{b}_1, \widehat{a}_2, \widehat{b}_2, \widehat{\rho}) = (2.042, 7.408, 1.943, 5.179, 0.093)$. Positive correlation between risks of withdrawal is found $\widehat{\rho}=0.093$. The likelihood ratio test for the significance of correlation is conducted by comparing the model (5) with the independent betabinomial 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)²⁹, 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)³⁰ (mean: -0.136 , 95% CI: $[-0.321, 0.048]$). In the studies of Langemark *et al.* (1990)³¹ and Vernon *et al.* (2009)²⁶, 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)²⁶ 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 Loldrup³² can be influential on the analysis results because of 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 remove it and reanalyze 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 change the inference on all the study-specific risk differences, e.g., the risk difference estimate of the study Bendtsen³³ 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 own 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 antidepressants 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 $\widehat{\rho}=0.093$ (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-analysis⁸. There is an increasing need for models that can account for heterogeneity between studies and correlation between groups⁸. The Sarmanov models considered in this article offer an alternative to traditional bivariate generalized linear mixed effect model (BGLMM) such as in Skrandal and Rabe-Hesketh (2004)⁶ and Chu and Cole

(2006)⁷. 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. Secondly, the BGLMM models the correlation between $h(p_{1i})$ and $h(p_{2i})$, i.e., 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 criteria 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, it does not come without a price. One limitation is its natural constraints of correlation coefficient, i.e., the correlation coefficient ρ must be subject to the constraints $-c/\max(a_1a_2, b_1b_2) \leq \rho \leq c/\max(a_1b_2, a_2b_1)$, 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 non-normal bivariate distributions such as the Farlie-Gumbel-Morgenstern distribution³⁵. A difficulty induced by the constraints is in maximizing log marginalized likelihood functions, e.g. equation (6). To account for the fact that the range of correlation coefficients ρ depends on other parameters, we can reparametrize 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 pseudolikelihood³⁶. Another possible solution is to consider an estimating equation approach³⁷. 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)^{24,25} 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 paper by Chu et al (2012)³⁸, a similar Sarmanov bivariate Beta-binomial model is applied to meta-analyses in making inference on the overall risk difference, whereas our paper considers the overall risk difference and provides exact posterior distributions of study-specific risk differences.

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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 %*% myVar %*% t(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 withdrawal 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 likelihood 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('fibal_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); mu2.1 <- 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)
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")

```

Appendix Table 1

Data from a meta-analysis of sixteen studies on the association between with-drawal due to adverse effects and tricyclic treatment in Jackson *et al.* (2010)²⁸. no. withdraws: number of individuals who withdrew from the study. no. individuals: number of individuals who started the study.

Author	Treatment		Control	
	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

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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)

Figure 2.

Posterior distributions of risk difference for four studies: Holroyd *et al.* (2001)³⁴, Diamond and Baltes (1971)³⁰, Langemark *et al.* (1990)³¹ and Vernon *et al.* (2009)²⁶. Risk difference is defined as difference of risks of withdrawal comparing those in treatment group to those in placebo group.

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 Loldrup³². Risk difference is defined as difference of risks of withdrawal comparing those in treatment group to those in placebo group.

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).

n	ρ	Sarmanov model					Independent model				
		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