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An Empirical Bayes Method for Multivariate Meta-analysis with an Application in Clinical Trials

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We propose an empirical Bayes method for evaluating overall and study-specific treatment effects in multivariate meta-analysis with binary outcome. Instead of modeling transformed proportions or risks via commonly used multivariate general or generalized linear models, we directly model the risks without any transformation. The exact posterior distribution of the study-specific relative risk is derived. The hyperparameters in the posterior distribution can be inferred through an empirical Bayes procedure. As our method does not rely on the choice of transformation, it provides a flexible alternative to the existing methods and in addition, the correlation parameter can be intuitively interpreted as the correlation coefficient between risks.

Keywords Bivariate beta-binomial model; Exact method; Hypergeometric function; Meta-analysis; Relative risk; Sarmanov family.

Mathematics Subject Classification 62-07; 62F15; 62E15; 62H10; 62H17; 62H20.

1. Introduction

Meta-analysis is a statistical procedure of combining the evidence from several independent studies concerned with the same scientific question. Recently, the rapid growth of evidence-based medicine has led to a dramatic increasing attention to statistical methods for meta-analysis (Jackson et al., 2011). One of the most important settings considered in meta-analysis is the study of the association between a binary outcome and a binary exposure. Such examples include meta-analysis in clinical trials where subjects are randomized to treatment and placebo groups and the outcome of interest is a certain event. When both

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outcome and exposure are binary variables, the relative risk of an event comparing subjects who received treatment to those who received placebo provides an important measure of treatment effects (Piantadosi, 2005).

Two general statistical approaches can be used to make inference on the relative risk. The first is the univariate analysis which estimates the overall relative risk by the weighted sum of the study-specific relative risks. Under homogeneous treatment effect assumption, the common relative risk can be estimated by a fixed effect model. When homogeneity is in doubts, a random effect model can be adopted (DerSimonian and Laird, 1986). The second approach, which draws lots of attention recently (Chu and Cole, 2006; Hamza et al., 2008; Jackson et al., 2011; Reitsma et al., 2005; Riley et al., 2007; 2008), is the multivariate meta-analysis. This approach accounts for the between-group correlation which is ignored by the univariate analysis. By borrowing strength between multiple groups, the multivariate approach can be more efficient than the univariate analysis in estimating the overall treatment effect (Hamza et al., 2008; Riley et al., 2007a, 2007b). For studies involving binary outcome and exposure, two modeling strategies have been commonly used in the second approach: a bivariate general linear mixed effect model on the transformed proportions (Reitsma et al., 2005) and a bivariate generalized linear mixed effect model on the transformed risks (Chu and Cole, 2006) (e.g., logit or probit transformations). Both models allow for between-group correlation and perform well in most of cases. It is worth pointing out that when the sample sizes for studies are moderate and the event is rare, the latter model can outperform the former (Hamza et al., 2008).

In this paper, we propose an alternative method in the framework of multivariate meta-analysis. Instead of modeling the transformed proportions or risks, we model the risks directly. One advantage of this proposed method is that the inference does not rely on the choice of transformation. As a consequence, the correlation parameter can be intuitively interpreted as the correlation coefficient between risks. Another benefit is that the study-specific relative risk has a posterior distribution with close form expression, which offers computational advantageous when posterior distributions of study-specific treatment effects are also of interest.

This paper is organized as follows. In Sec.2, we state the main results where we describe the proposed model and its inference for multiple 2×2 tables in meta-analysis and its extension for meta-regression analysis. In Sec.3, we conduct simulation studies to evaluate the performance of the proposed method in finite samples. We illustrate our method in Sec.4 with an example of meta-analysis of type 2 diabetes mellitus (T2DM) followed by a brief summary in Sec.5.

2. Main Results

2.1 Notations and Models

For the ith study, let n_{ji}, y_{ji}, and p_{ji} be the number of subjects, the number of subjects experienced a certain event, and the risk of experiencing the event in the jth group, respectively ($j = 1, \ldots, J$). 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. We consider the following random effects model:

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

where $g(p_1, p_2; a_1, b_1, a_2, b_2, \rho)$ is the joint distribution of study-specific random effects p_{1i} and p_{2i} such that the marginal distribution of random effects in jth group p_{ji} is the beta distribution with shape parameters (a_j, b_j) and the correlation coefficient between p_{1i} and p_{2i} is ρ. Similar to a standard random effect model, the model (1) implies that for given study-specific random effects p_{1i} and p_{2i}, y_{1i} and y_{2i} follow independent binomial distributions.

Such a joint distribution of p_{1i} and p_{2i} can be constructed using the procedure proposed by Sarmanov (1966). This procedure has later been studied extensively by Cole et al. (1995), Lee (1996), Shubina and Lee (2004), and Danaher and Hardie (2005). Specifically, let $f_1(p_1)$ and $f_2(p_2)$ be two univariate probability density functions, and $\psi_1(p_1)$ and $\psi_2(p_2)$ be bounded integrable non-constant functions that satisfy $\int \psi_j(p) f_j(p) dt = 0$ for $j = 1, 2$. The function defined by

$$h(p_1, p_2) = f_1(p_1) f_2(p_2)\{1 + \omega \psi_1(p_1)\psi_2(p_2)\}$$

is a bivariate joint density with specified marginals $f_1(p_1)$ and $f_2(p_2)$, provided ω is a number which satisfies the condition that $1 + \omega\psi_1(p_1)\psi_2(p_2) \geq 0$ for all p_1 and p_2.

There are a variety of choices for the functions $\psi_1(p_1)$ and $\psi_2(p_2)$, which lead to different interpretations of the parameter ω. Here we let $f_j(p_j) = \text{beta}(p_j; a_j, b_j) = \{B(a_j, b_j)\}^{-1} p_j^{a_j - 1}(1 - p_j)^{b_j - 1}$ with $B(a, b)$ denotes the beta function, and $\psi_j(p_j) = (p_j - \mu_j)/\delta_j$ with $\mu_j = a_j/(a_j + b_j)$ and $\delta_j^2 = \mu_j(1 - \mu_j)/(a_j + b_j + 1)$ for $j = 1, 2$. One advantage of this choice is that the parameter ω has an intuitive interpretation as the correlation coefficient between p_1 and p_2, i.e., $\omega = \rho$. The joint distribution of p_1 and p_2, referred to as Sarmanov bivariate beta distribution in Danaher and Hardie (2005), is

$$g(p_1, p_2; a_1, b_1, a_2, b_2, \rho) = \text{beta}(p_1; a_1, b_1)\text{beta}(p_2; a_2, b_2)\{1 + \rho\psi_1(p_1)\psi_2(p_2)\}. \quad (2)$$

With the distribution of random effects specified in Eq. (2), the log-likelihood function for the unknown parameters $(a_1, b_1, a_2, b_2, \rho)$ is

$$\begin{aligned}
&\log L(a_1, b_1, a_2, b_2, \rho) \\
&= \sum_{i=1}^{n} \log \int\int \Pr(y_{1i}, y_{2i} | p_{1i}, p_{2i}) g(p_{1i}, p_{2i}; a_1, b_1, a_2, b_2, \rho) dp_{1i} dp_{2i} \\
&= \sum_{i=1}^{n} \log \Bigg[\mathrm{P}_{BB}(y_{1i}; n_{1i}, a_1, b_1)\mathrm{P}_{BB}(y_{2i}; n_{2i}, a_2, b_2) \\
&\quad \times \Bigg\{ 1 + \frac{\rho}{\sqrt{\frac{a_1 b_1}{(a_1+b_1)^2(a_1+b_1+1)}}\sqrt{\frac{a_2 b_2}{(a_2+b_2)^2(a_2+b_2+1)}}} \left(\frac{y_{1i} + a_1}{n_{1i} + a_1 + b_1} - \frac{a_1}{a_1 + b_1} \right) \\
&\quad \times \left(\frac{y_{2i} + a_2}{n_{2i} + a_2 + b_2} - \frac{a_2}{a_2 + b_2} \right) \Bigg\} \Bigg],
\end{aligned} \quad (3)$$

where $P_{BB}(y; n, a, b)$ is the probability mass function of a beta-binomial distribution, i.e.,

$$P_{BB}(y; n, a, b) = \binom{n}{y} \frac{B(y + a, n - y + b)}{B(a, b)}.$$

The last expression in Eq. (3) has been derived by Danaher and Hardie (2005) and an outline of derivation is provided in Appendix Section A. We refer the model (3) as Sarmanov beta-binomial model. Notice that when $\rho = 0$, the Sarmanov beta-binomial model reduces to the independent beta-binomial model, i.e., product of two beta-binomial distributions.

In meta-analysis, the primary quantity of interest is the overall treatment effect, which can be measured by the overall relative risk, defined by $\theta = \mu_2/\mu_1 = \{a_2/(a_2 + b_2)\}/\{a_1/(a_1 + b_1)\}$. In practice, biomedical researchers may be also interested in the statistical evidence on the treatment effects contributed by individual studies. Such quantity can be quantified by the posterior density function of the study-specific relative risk $\theta_i = p_{2i}/p_{1i}$ if we treat $g(p_1, p_2; a_1, b_1, a_2, b_2, \rho)$ as a prior distribution on (p_{1i}, p_{2i}). We next discuss the inference procedures for the overall and the study-specific relative risks.

2.2 Estimation of Overall Relative Risk

At least two methods can be used to make inference on the overall relative risk θ. The first is to introduce another level of hierarchy by imposing prior distributions on the hyperparameters $(a_1, b_1, a_2, b_2, \rho)$. The posterior distribution of θ can be obtained through Monte Carlo simulations. Here we use the second method, which estimates the hyperparameters $(a_1, b_1, a_2, b_2, \rho)$ by maximizing the log-likelihood $\log L(a_1, b_1, a_2, b_2, \rho)$. This can be done by using commonly used statistical software such as *SAS* and *SPLUS/R*. We implement it through *R (R Development Core Team, Version 2.14.1)* with the *optim* function, which uses a quasi-Newton method with box constraints on the ranges of parameters. A SPLUS/R program to fit this model with a working example is attached in Appendix Section B.

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 (3). The variance of the overall relative risk estimate $\hat{\theta}$ 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 relative risk estimate $\hat{\theta}$ is estimated by $\hat{\theta}^2 D^T(-H)^{-1}D$ where $D = (-\hat{b}_1/(\hat{a}_1+\hat{b}_1), \hat{b}_1/(\hat{a}_1+\hat{b}_1), \hat{b}_2/(\hat{a}_2+\hat{b}_2), -\hat{b}_2/(\hat{a}_2+\hat{b}_2), 0)^T$.

2.3 Inference on Study-Specific Relative Risk

The statistical evidence from individual studies can be quantified by the posterior distributions of study-specific relative risks θ_i, namely $\Pr(\theta_i|\text{data}_i, a_1, b_1, a_2, b_2, \rho)$ where $\text{data}_i = (y_{1i}, n_{1i}, y_{2i}, n_{2i})$. Notice that the hyperparameters are unknown. One way to circumvent this problem is to simply replace the hyperparameters by their estimates. Such an approach is called the empirical Bayes method (Carlin and Louis, 2009; Efron and Morris, 1973; 1975; Gelman et al., 2004). The inference based on $\Pr(\theta_i|\text{data}_i, \hat{a}_1, \hat{b}_1, \hat{a}_2, \hat{b}_2, \hat{\rho})$ ignores the uncertainty on the hyperparameter estimates, hence may lead to liberal credible intervals. To obtain credible intervals with coverage probability (CP) close to the nominal level, one can use the bias correction method or the bootstrap method (Carlin and Gelfand, 1991; Deely and Lindley, 1981). In Sec.3, we will investigate the CP of the credible intervals using the empirical Bayes method ignoring the uncertainty on the hyperparameter estimates.

We next derive the posterior distribution of the study-specific relative risk. Note that an important property of Sarmanov beta prior is that it is pseudo-conjugate for binomial distributions (Lee, 1996). Specifically, Sarmanov beta prior can be expressed as a linear combination of products of independent beta distributions. Therefore, the posterior distribution of

the study-specific relative risk can be written as a linear combination of posterior distributions under independent beta priors. In fact, the posterior distribution of relative risk under independent beta priors for a single 2×2 table has been considered by several researchers. Nurminen and Mutanen (1987) and Gupta et al. (1997) derived the posterior distribution under independent beta priors with integer hyperparameters. Hora and Kelley (1983) and Hashemi et al. (1997) extended the previous results to beta priors with any positive hyperparameters. Now we restate their results using expression with hypergeometric functions.

Assume p_{1i} and p_{2i} are independent and follow beta distributions with hyperparameters (a_1, b_1) and (a_2, b_2), respectively. The posterior distributions of p_{1i} and p_{2i} are beta distributions with parameters (α_1, β_1) and (α_2, β_2), respectively, where $\alpha_j = y_j + a_j$ and $\beta_j = n_j - y_j + b_j$ $(j = 1, 2)$. The exact posterior distributions of θ_i can be expressed as

$$f(\theta_i; \alpha_1, \beta_1, \alpha_2, \beta_2) = \begin{cases} \theta_i^{\alpha_2 - 1}\{B(\alpha_1, \beta_1)B(\alpha_2, \beta_2)\}^{-1} B(\alpha_1 + \alpha_2, \beta_1) \\ \times F(1 - \beta_2, \alpha_1 + \alpha_2; \alpha_1 + \alpha_2 + \beta_1; \theta_i) & \text{for } \theta_i \in [0, 1), \\ \theta_i^{-\alpha_1 - 1}\{B(\alpha_1, \beta_1)B(\alpha_2, \beta_2)\}^{-1} B(\alpha_1 + \alpha_2, \beta_2) \\ \times F(1 - \beta_1, \alpha_1 + \alpha_2; \alpha_1 + \alpha_2 + \beta_2; 1/\theta_i) & \text{for } \theta_i \in [1, \infty), \end{cases} \tag{4}$$

where $F(\cdot, \cdot, \cdot, \cdot)$ denotes the hypergeometric function (Gauss, 1813) defined by

$$F(\alpha, \beta; \gamma, z) = \frac{1}{B(\beta, \gamma - \beta)} \int_0^1 t^{\beta - 1}(1 - t)^{\gamma - \beta - 1}(1 - tz)^{-\alpha} dt, \quad \text{for } \gamma > \beta > 0.$$

With the results in (4), the exact posterior distribution of relative risk θ_i under Sarmanov beta prior can be calculated as

$$\begin{aligned} f^*(\theta_i; \alpha_1, \beta_1, \alpha_2, \beta_2, \rho) = {} & \omega_1 f(\theta_i; \alpha_1, \beta_1, \alpha_2, \beta_2) + \omega_2 f(\theta_i; \alpha_1 + 1, \beta_1, \alpha_2, \beta_2) \\ & + \omega_3 f(\theta_i; \alpha_1, \beta_1, \alpha_2 + 1, \beta_2) \\ & + \omega_4 f(\theta_i; \alpha_1 + 1, \beta_1, \alpha_2 + 1, \beta_2), \end{aligned} \tag{5}$$

where $f(\theta_i; \alpha_1, \beta_1, \alpha_2, \beta_2)$ is the posterior density function of relative risk under independent beta priors and is defined in Eq. (4), the weights ω_k $(k = 1, \ldots, 4)$ are functions of a_1, b_1, a_2, b_2, ρ given in Appendix Section A. When the correlation is zero, i.e., $\rho = 0$, in which the weights are $\omega_1 = 1$ and $\omega_2 = \omega_3 = \omega_4 = 0$, Eq. (5) reduces to Eq. (4).

2.4 Extension to Meta-Regression Analysis

When a meta-analysis contains a relatively large number of studies and the study level covariates are available, multivariate meta-regression analysis can assess the impact of study size, trial quality, and other trial characteristics on effect sizes. To account for the heterogeneity between trials and the correlation between treatment groups, models have been proposed in the framework of multivariate generalized linear mixed effect models, such as Van Houwelingen et al. (1993), Smith et al. (1995), Skrondal and Rabe-Hesketh (2004), and Chu and Cole (2006). Now we extend the model (1) to regression setting. Specifically, 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,

$$p_{ji}|(\phi_j, \mu_{ji}) \sim \text{beta}\{p_{ji}; \mu_{ji}/(1/\phi_j - 1), (1 - \mu_{ji})/(1/\phi_j - 1)\} \quad \text{for } j = 1, 2.$$

Then $E[p_{ji}|\phi_j, \mu_{ji}] = \mu_{ji}$ 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

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

where $h(\cdot)$ is a link function and X_i are the study-specific covariates such as the trial quality and race of the study population. To allow for correlation between groups, we assume the paired study-specific risks (p_{1i}, p_{2i}) follow the Sarmanov beta prior distribution, i.e.:

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

This model allows different dispersion parameter ϕ_j across different groups. Similar to the estimation procedure for model (1), this bivariate beta-binomial regression model can be fitted by maximizing the corresponding log-likelihood function.

3. Simulation Studies

In this section, we evaluate the performance of the model (1) through simulation studies. In the first simulation study, we examine the results in Eqs. (4) and (5) empirically via Markov chain Monte Carlo (MCMC) methods. Specifically, the histograms of MCMC samples are overlaid with the corresponding theoretical density functions. The empirical results confirm that the derived density functions are correct. For the interest of space, the details of this simulation are summarized in the Web Supplement.

In the second simulation study, we evaluate the finite sample performance of the maximum likelihood estimator for the overall relative risk. We set the true values as $a_1 = b_1 = a_2 = b_2 = 0.5$, $\rho = 0, 0.2$ and 0.4, and the number of studies $n = 20, 40$, and 60 with the study sample size 50 in each group. Table 1 compares the bias, SE (the standard deviation of the overall log relative risk estimates), SEM (the sampling mean of the standard error estimates), and CP (the CP of Wald-type confidence intervals of the overall log relative risk) estimated from the Sarmanov and independent beta-binomial model. When $\rho = 0$, the independent model gives unbiased estimates, SEM close to SE, and CPs close to nominal level while the Sarmanov model performed equally well in terms of bias, SE, SEM, only with CPs negligibly worse. When ρ increases to 0.2 or 0.4, both models provide unbiased estimates, the SEs of both models decrease due to "borrowing strength" across groups within the same study (Riley et al., 2007). The Sarmanov model provides SEM close to SE and CPs close to 0.95, while the independent model produces unchanged SEMs and over-conservative confidence intervals because it does not account for the between-group correlation. In addition, by "borrowing strength" between multiple groups, the required number of studies to achieve certain efficiency can be significantly reduced, e.g., the SE of log relative risk of the Sarmanov model when $n = 40$ and $\rho = 0.4$ is even smaller than the SE from the independent model when $n = 60$ and $\rho = 0$. These simulation results indicate that Sarmanov model provides valid and efficient inference and is robust to the between-group correlation with moderate number of studies, while the independent model only give valid inference when the between-group correlation is zero.

Table 1

Estimates of the bias, SE (the standard deviation of the estimates), SEM (the sampling mean of the standard error estimate), CP (coverage probability), and RE (relative efficiency) of log relative risk in 5, 000 simulations based on Sarmanov beta-binomial model and independent beta-binomial model, with various numbers of studies n and various between-group correlations ρ. The study sample sizes are 50 in each group. $(a_1, b_1, a_2, b_2) = (0.5, 0.5, 0.5, 0.5)$

		Sarmanov model				Independent model			
n	ρ	Bias	SE	SEM	CP (%)	Bias	SE	SEM	CP (%)
20	0	-0.007	0.229	0.215	93.4	0.001	0.223	0.214	94.4
	0.2	0.001	0.198	0.195	95.2	0.006	0.201	0.214	96.5
	0.4	0.003	0.165	0.172	97.3	0.002	0.183	0.214	97.9
40	0	-0.003	0.156	0.151	93.8	0.003	0.155	0.151	94.7
	0.2	-0.001	0.141	0.137	93.8	-0.002	0.140	0.151	96.7
	0.4	0.001	0.115	0.118	96.5	0.000	0.125	0.151	98.3
60	0	-0.001	0.125	0.123	94.5	0.003	0.123	0.123	95.3
	0.2	-0.001	0.114	0.111	94.3	0.003	0.112	0.123	96.8
	0.4	0.001	0.095	0.096	95.8	0.001	0.101	0.123	98.3

In Sec.2.3, we propose to estimate the study-specific relative risk based on an empirical Bayes method with hyperparameters fixed at their estimates. The corresponding credible interval could be liberal due to the ignored uncertainty on the hyperparameters. In the third simulation study, we investigate the performance of the credible interval based on $\Pr(\theta_i|\text{data}_i, \hat{a}_1, \hat{b}_1, \hat{a}_2, \hat{b}_2, \hat{\rho})$ and compare with the conventional Wald confidence interval which is based on data of the ith study only. The selected parameters are the same as the second simulation study. For each simulated n studies, we obtain the estimates of the hyperparameters by maximizing the log-likelihood in Eq. (3) and then estimate the 95% credible interval from the exact posterior distribution of the first study's relative risk using Eq. (5) (refer to as "Sarmanov CI"). In contrast, we obtain the 95% Wald confidence interval of the first study's relative risk based only on the first study's data (refer to as "Wald CI"). Table 2 compares the CP and the expected length of Sarmanov CI with those of Wald CI. The simulation results suggest that under all settings considered, the CP of Sarmanov CI is close to the nominal level, and so is Wald CI. This indicates that when the number of studies is moderate, Sarmanov CI still performs reasonably well, even without accounting for the uncertainty on the hyperparameters.

4. An Application to a Meta-Analysis of T2DM After Gestational Diabetes

Gestational diabetes mellitus (GDM), affecting around 18% of pregnancies, is a form of diabetes that is diagnosed during pregnancy and increases risk of T2DM (Coustan et al., 2010). Recently, Bellamy et al. (2009) conducted a comprehensive systematic review and meta-analysis to assess the strength of association between GDM and T2DM. Twenty cohort studies conducted from 1991 to 2008 in multiple countries are selected. The data (summarized in Table 1 of the Web Supplement) has 6, 862 and 3, 997 T2DM incidences among 643, 588 and 31, 867 individuals without and with GDM, respectively. We define relative risk as the ratio of risks of T2DM comparing those with GDM to those without.

Table 2
Estimates of the expected length and coverage probability (CP) of 95% Sarmanov CI and Wald CI for the first study's relative risk in 5, 000 simulations with various number of studies n, for various between-group correlations ρ. The study sample sizes are 400 in both groups. $(a_1, b_1, a_2, b_2) = (0.5, 0.5, 0.5, 0.5)$

		Sarmanov CI		Wald CI	
n	ρ	Length	CP (%)	Length	CP (%)
20	0.00	0.885	94.8	0.934	95.3
	0.20	0.868	95.4	0.927	94.9
	0.40	0.983	94.6	1.067	94.6
40	0.00	0.882	94.7	0.904	95.3
	0.20	1.023	94.6	1.097	94.6
	0.40	0.964	94.2	1.022	94.1
60	0.00	0.852	95.0	0.898	95.0
	0.20	0.937	94.5	0.991	95.0
	0.40	0.951	95.0	1.019	94.7

Based on the Sarmanov beta-binomial model, the overall relative risk is estimated as 9.20 (95% CI: 5.17, 16.35), indicating significantly increased risk of developing T2DM for the women with GDM. We note that the study by Feig et al. (2008) has extremely large sample size ($N = 659, 164$) and account for 97.6% of total sample size. To assess the sensitivity of the results to this study, we conduct a sensitivity analysis without this study and the overall relative risk is estimated as 9.11 (95% CI: 4.96, 16.73). These results suggest that our results are not sensitive to this study.

By applying the Sarmanov beta prior distribution with the aforementioned hyperparameters estimates, we obtain each individual study's posterior density distribution. We apply bisection root-finding method to compute the 95% credible intervals. Figure 1 displays the forest plot of the estimates and the 95% CIs of each study-specific relative risk and the overall relative risk. To visually display how each study contributes to the overall relative risk, Fig. 2 plots the posterior density distributions of four randomly selected studies. It shows that while in Gunderson et al. (2007), most of the density of relative risk are between 2 and 5 (mean: 3.91, 95% CI: 2.84, 5.17), the density shifts away from 1 in Lee et al. (2008) with the majority of the density lying between 2 and 7 (mean: 4.81, 95% CI: 3.02, 7.52). In the studies of Benjamin et al. (1993) and O'Sullivan et al. (1989), most of the relative risk density lies in the intervals of Benjamin et al. (1993, DerSimonian and Laird 1986] (mean: 8.81, 95% CI: 2.70, 24.92) and (Chu and Cole, 2006; DerSimonian and Laird 1986] (mean: 7.53, 95% CI: 4.74, 11.77), respectively. Note that the curve of Benjamin et al. (1993) is much more spread out than the other studies because of its relatively small study sample size.

5. Summary

In this paper, we propose an alternative model for multivariate meta-analysis of binary outcomes. In contrast to the commonly used methods which either model the transformed proportions through a general linear model, or model the transformed risks through a generalized linear model, this alternative method directly models the risks without any

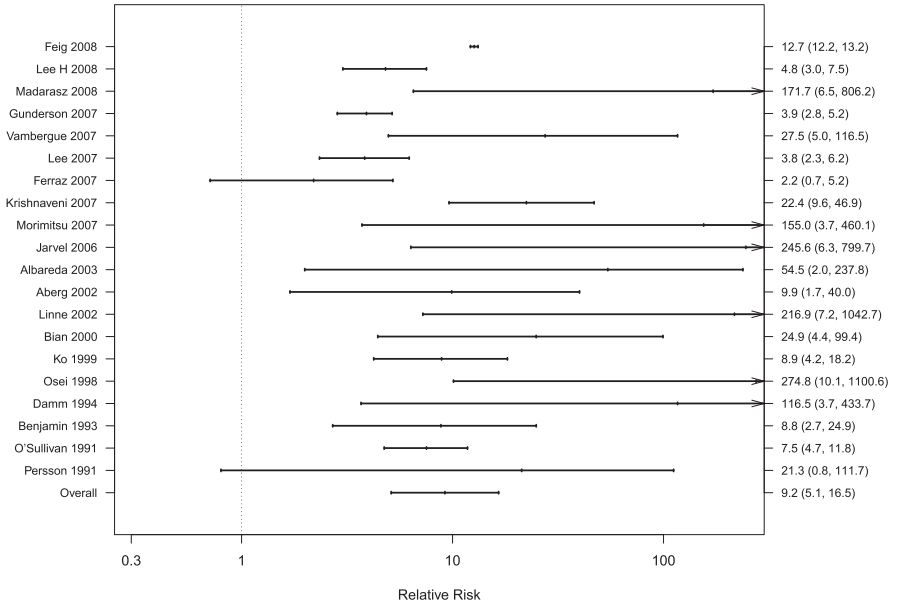

Figure 1. Forest plot of 20 study-specific and the overall relative risk with 95% credible intervals (numbers listed on the right). Relative risk is defined as the ratio of risks of T2DM comparing those with GDM to those without. The numbers on the Y-axis indicate the study years. X-axis is log scale and is truncated at 300.

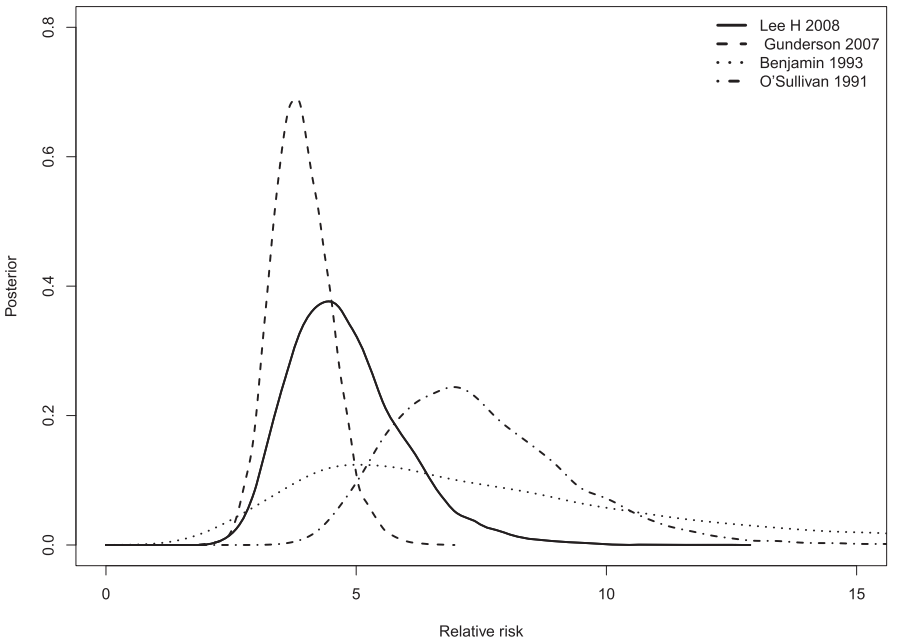

Figure 2. Posterior distributions of study-specific relative risks for four studies: Lee et al. (2008), Gunderson et al. (2007), Benjamin et al. (1993), and O'Sullivan et al. (1989). Relative risk is defined as the ratio of risks of T2DM comparing those with GDM to those without. The numbers in the legend are the study years.

transformation. One advantage of this method is that the inference does not rely on the choice of transformation. The correlation parameter can be intuitively interpreted as the correlation coefficient between risks.

Our contributions in this paper are to propose the use of the Sarmanov beta-binomial model in meta-analysis of clinical trials and to derive the exact posterior distribution function of study-specific treatment effects which enables a simple empirical Bayes inference. With simulation studies, we investigate the efficiency gained by accounting for the between-group correlation in the Sarmanov beta-binomial models and the frequentist performance of the credible intervals based on the empirical Bayes method.

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Supplementary Material

Supplemental data for this article can be accessed at www.tandfonline.com/lsta.

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Appendix

Section A: Some derivations

Derivation of Eq. (3) For simplicity of notation, we suppress the index "i". With some algebra, we can show

$$\int \text{Binomial}(y|n;p)\text{beta}(p;a,b)\{1+c(p-\mu)\}dp = P_{BB}(y|n;a,b) \times \left\{1 + C\left(\frac{y+a}{n+a+b} - \mu\right)\right\}.$$

Denote $\mu_j = a_j/(a_j+b_j)$ and $\sigma_j^2 = \mu_j(1-\mu_j)/(a_j+b_j+1)$ $(j=1,2)$. We have

$$\begin{aligned}
&\int\int \Pr(y_1|n_1;p_1)\Pr(y_2|n_2;p_2)\text{beta}(p_1;a_1,b_1)\text{beta}(p_2;a_2,b_2) \\
&\quad\times\left\{1+\frac{\rho}{\sigma_1\sigma_2}(p_1-\mu_1)(p_2-\mu_2)\right\}dp_1dp_2 \\
&= \int \Pr(y_2|n_2;p_2)\text{beta}(p_2;a_2,b_2)\int \Pr(y_1|n_1;p_1)\text{beta}(p_1;a_1,b_1) \\
&\quad\times\left\{1+\frac{\rho}{\sigma_1\sigma_2}(p_1-\mu_1)(p_2-\mu_2)\right\}dp_1dp_2 \\
&= \int \Pr(y_2|n_2;p_2)\text{beta}(p_2;a_2,b_2)P_{BB}(y_1|n_1;a_1,b_1) \\
&\quad\times\left\{1+\frac{\rho}{\sigma_1\sigma_2}\left(\frac{y_{1i}+a_1}{n_{1i}+a_1+b_1}-\mu_1\right)(p_2-\mu_2)\right\}dp_2 \\
&= \left[\text{P}_{BB}(y_{1i};n_{1i},a_1,b_1)\text{P}_{BB}(y_{2i};n_{2i},a_2,b_2)\right. \\
&\quad\left.\times\left\{1+\frac{\rho}{\sigma_1\sigma_2}\left(\frac{y_{1i}+a_1}{n_{1i}+a_1+b_1}-\mu_1\right)\left(\frac{y_{2i}+a_2}{n_{2i}+a_2+b_2}-\mu_2\right)\right\}\right].
\end{aligned}$$

Derivation of Eq. (5) With beta marginals and mixing functions $\phi_i = (p_i-\mu_i)/\delta_i$, the Sarmanov prior distribution of p_1 and p_2 can be written as linear combination of products

of independent beta distributions as follows:

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

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

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

where the weights ω_k $(k = 1, \ldots, 4)$ are defined by

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

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

and C, the normalizing constant, is calculated as

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

The proof is completed following the derivation of Eq. (4).

Some results on the moments of relative risk Under independent beta priors, the kth posterior moment of relative risk exists for $k < \min(\alpha_1, \beta_2)$ and is given by

$$E[\theta^k; \alpha_1, \beta_1, \alpha_2, \beta_2] = \frac{B(\alpha_1 - k, \beta_1 + k) B(\alpha_2 + k, \beta_2 - k)}{B(\alpha_1, \beta_1) B(\alpha_2, \beta_2)}. \tag{6}$$

Specifically, the mean and variance are given by $E[\theta; \alpha_1, \beta_1, \alpha_2, \beta_2] = \beta_1 \alpha_2 / \{(\alpha_1 - 1)(\beta_2 - 1)\}$ and

$$var(\theta; \alpha_1, \beta_1, \alpha_2, \beta_2) = \frac{\beta_1(\beta_1 + 1)\alpha_2(\alpha_2 + 1)}{(\alpha_1 - 1)(\alpha_1 - 2)(\beta_2 - 1)(\beta_2 - 2)} - \left\{ \frac{\beta_1 \alpha_2}{(\alpha_1 - 1)(\beta_2 - 1)} \right\}^2.$$

Under correlated beta priors, the kth posterior moment of relative risk exists for $k < \min(\alpha_1, \beta_2)$ and is given by

$$E[\theta^k;\alpha_1,\beta_1,\alpha_2,\beta_2,\rho] = \omega_1 E[\theta^k;\alpha_1,\beta_1,\alpha_2,\beta_2] + \omega_2 E[\theta^k;\alpha_1+1,\beta_1,\alpha_2,\beta_2] + \omega_3 E[\theta^k;\alpha_1,\beta_1,\alpha_2+1,\beta_2] + \omega_4 E[\theta^k;\alpha_1+1,\beta_1,\alpha_2+1,\beta_2], \quad (7)$$

where $E[\theta^k;\alpha_1,\beta_1,\alpha_2,\beta_2]$ is the kth posterior moment of relative risk under independent beta priors, defined in Eq. (6).

Some results on correlation coefficients Denote $y_{ji} = \sum_{k=1}^{n_{ji}} Z_{jim}$ where Z_{jim} is the indicator of whether the kth subject in the jth group of ith study experienced an event. Denote the dispersion parameter $\phi_j = 1/(a_j+b_j+1)$. Note that Y_{ji} follows a beta-binomial distribution with parameters (a_j, b_j). Therefore, $\text{corr}(Z_{jik}, Z_{jik'}) = \phi_j$, i.e., the correlation between the outcomes for two subjects from the same study and the same jth group is ϕ_j. Using double expectation technique, we can show that $\text{corr}(Z_{1ik}, Z_{2ik'}) = \rho\sqrt{\phi_1\phi_2}$, i.e., the correlation between the outcomes for two subjects from the same study but different groups is $\rho\sqrt{\phi_1\phi_2}$.

Section B: SPLUS/R program to fit model (1) and a working example

```
# function to compute the log-likelihood in equation (5)
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 (a1,b1,a2,b2,rho) 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 log(RR)
  and use Wald interval on log(RR)
RR.comp.log <- function(par, hessian) {
   a1 <- par[1]; b1 <- par[2]; a2 <- par[3]; b2 <- par[4]
   myRR.overall <- log(a2/(a2+b2)/(a1/(a1+b1)))
   myVar <- solve(-hessian)
   if (flag == 0) myD <- matrix(c(-b1/(a1+b1), b1/(a1+b1),
    b2/(a2+b2), -b2/(a2+b2)), nrow=1)
   if (flag == 1) myD <- matrix(c(-b1/(a1+b1), b1/(a1+b1),
    b2/(a2+b2), -b2/(a2+b2), 0), nrow=1)
   myRR.overall.Var <- as.numeric(myD %*% myVar %*% t(myD))
   myRR.overall.sd <- sqrt(myRR.overall.Var)
   myRR.left.bound <- myRR.overall-1.96*sqrt(myRR.overall
    .Var)
   myRR.right.bound <- myRR.overall+1.96*sqrt(myRR.overall
    .Var)
   return(list(RR=exp(myRR.overall), RR.left=exp(myRR.left
    .bound), RR.right=exp(myRR.right.bound)))
}

# Dataset from Bellamy (2009) Lancet
y1<-c(6628,22,0,150,1,16,7,8,0,0,0,1,0,1,7,0,0,3,18,0)
n1<-c(637341,868,39,2242,111,783,108,489,11,435,70,61,52,
  39,431,35,57,47,328,41)
y2<-c(2874,71,21,43,53,405,6,13,7,23,44,21,10,15,105,10,33,
  14,224,5)
n2<-c(21823,620,68,166,295,5470,70,35,23,435,696,229,28,45,
  801,15,241,47,615,145)

# remove the first study with extremely large sample size
#y1 <- y1[-1]; n1 <- n1[-1]; y2 <- y2[-1]; n2 <- n2[-1]

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))
RR.comp.log(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))
RR.comp.log(par.cal(results$par), results$hessian)
```