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Comments

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Abstract

This paper describes the core features of the R package **mmeta**, which implements the exact posterior inference of odds ratio, relative risk, and risk difference given either a single 2×2 table or multiple 2×2 tables when the risks within the same study are independent or correlated.

Keywords: Appell function, Bayesian inference, bivariate beta-binomial, exact distribution, hypergeometric function, Sarmanov family.

1. Introduction

Epidemiological studies often involve comparisons between two populations with binary outcomes. Data from these studies are usually summarized by a single or multiple 2×2 tables. To quantify the association between an exposure and a certain disease, comparative measures between two risks, e.g., odds ratio (OR), relative risk (RR), and risk difference (RD), are frequently used. A Bayesian approach has been widely applied to obtain the posterior distributions of these comparative measures that reflect evidence from the data and available prior knowledge. Bayesian inference on a single study based on a 2×2 table has been investigated by several researchers. Specifically, Nurminen and Mutanen (1987) derived the exact posterior distributions of OR, RR, and RD under independent beta prior distributions with integer hyperparameters. Marshall (1988) extended the results of OR by using hypergeometric func-

tions (Gauss 1812) to allow the hyperparameters being any positive numbers. Nadarajah and Kotz (2007) gave a formula for RD using the Appell hypergeometric function. Chen and Luo (2011) corrected the formula by Nadarajah and Kotz (2007) and further simplified the formula to avoid divergence of the Appell hypergeometric function. Hora and Kelley (1983) and Hashemi, Nandram, and Goldberg (1997) extended the results of Nurminen and Mutanen (1987) on RR to beta prior distributions with any positive hyperparameters.

Multiple 2×2 tables often arise in meta-analysis which combines statistical evidence from multiple studies. Two risks within the same study are possibly correlated because they share some common factors such as environment and population structure. For example, in genetic association studies, people in the same study are likely to live in the same community sharing similar environmental factors or similar ancestors (Lee 1996). Riley (2009) has showed via simulation studies that separate meta-analysis of correlated outcomes can lead to biased estimates of variances of the summary effect sizes. In contrast, multivariate meta-analysis summarizes simultaneously all outcomes of interest instead of conducting many separate univariate meta-analysis. Multivariate meta-analysis has recently received lots of attention (e.g., Reitsma, Glas, Rutjes, Scholten, Bossuyt, and Zwinderman 2005; Chu and Cole 2006; Riley, Abrams, Sutton, Lambert, and Thompson 2007; Riley, Thompson, and Abrams 2008; Hamza, Reitsma, and Stijnen 2008). An excellent overview of multivariate meta-analysis can be found in Jackson, Riley, and White (2011) and Mavridis and Salanti (2012). In the multivariate meta-analysis with a binary outcome and a categorical exposure, two modeling strategies have been commonly used: A bivariate general linear mixed-effects model on the transformed proportions (Reitsma *et al.* 2005; Arends, Hamza, Houwelingen, Heijenbrok-Kal, Hunink, and Stijnen 2008) and a bivariate generalized linear mixed-effects model on the transformed risks (e.g., logit or probit transformations; Houwelingen, Zwinderman, and Stijnen 1993; Houwelingen, Arends, and Stijnen 2002; Chu and Cole 2006; Chu, Guo, and Zhou 2010). However, these two methods are based on the transformed proportions or the transformed risks and thus the interpretation is transformation dependent. Multivariate meta-analysis can be conducted using various software packages including Stata (StataCorp. 2011), SAS (SAS Institute Inc. 2011), R (R Core Team 2013). Specifically, the `mvmeta` command in Stata performs fixed- and random-effects multivariate meta-regression analysis. The SAS `PROC MIXED` routine was the first that popularized multivariate meta-analysis (Houwelingen *et al.* 2002). More recently, the SAS macro `METADAS` was made available to fit bivariate meta-analysis models for diagnostic test accuracy studies (Takwoingi, Guo, and Deeks 2008). R package **metaSEM** (Cheung 2012) can be used to conduct univariate and multivariate meta-analysis using structural equation modeling (SEM) via the **OpenMx** package. In addition, a new R package **mvmeta** (Gasparrini 2012) can perform fixed- and random-effects multivariate meta-analysis and meta-regression.

Instead of modeling the transformed proportions or transformed risks, we use a Sarmanov family of correlated beta prior distributions (referred to as Sarmanov beta prior distributions; Sarmanov 1966) to model the risks directly; see for example, Chen, Chu, Luo, Nie, and Chen (2014a). The correlation parameter can be intuitively interpreted as the correlation coefficient between risks. In addition, the Sarmanov beta prior distribution has the following advantages in modeling. Firstly, it allows for both positive and negative correlations; secondly, it only needs specification of marginal distributions and the correlation parameter, which has important advantages in Bayesian inference because it is often easier to specify and interpret an univariate prior than a bivariate prior; thirdly, it is pseudo-conjugate to binomial distributions, i.e., the Sarmanov beta prior distribution can be expressed as a linear combination

of independent bivariate beta distributions (Lee 1996), which enables us to derive closed-form expressions of the exact posterior distributions for study-specific comparative measures. Such closed-form expressions offer computational convenience when the exact posterior distributions of the study-specific comparative measures are also of interest. We have used the Sarmanov beta prior distribution to make exact posterior inference of some comparative measures (e.g., OR, RR, and RD; Chen *et al.* 2014a; Chen, Luo, Chu, Su, and Nie 2014b; Chen, Luo, Chu, and Wei 2013). This paper describes the **mmeta** package as a collection of a new family of models different from those in the aforementioned packages. Specifically, the inference of the overall and study-specific comparative measures (i.e., OR, RR, and RD) are inferred under the Sarmanov beta prior distributions. The functions of the **mmeta** package have been written in the R language, with some Fortran 77 and C routines which are interfaced through R. The package is built following the S3 formulation of R methods with dependencies on R packages **HI** (Petris, Tardella, and Gilks 2013) and **aod** (Lesnoff and Lancelot 2012). The **mmeta** package (currently version 2.2) is available from the Comprehensive R Archive Network (CRAN) at `http://CRAN.R-project.org/package=mmeta`.

The paper is organized as follows. In Section 2 we outline the exact Bayesian posterior inference approach. We describe the features of two main functions in the **mmeta** package and the analysis of two real datasets in Section 3. In Section 4, we provide a brief discussion.

2. Theory of exact distributions

2.1. Models and inference on overall comparative measures

For the ith study ($i = 1, \ldots, I$; I is the number of studies), let n_{ji}, y_{ji} and p_{ji} be the number of subjects, number of subjects experienced a certain event, and the risk of experiencing the event in the jth group ($j = 1, \ldots, J$; J is the number of groups), respectively. For simplicity, we consider only the settings with two groups under comparison (i.e., $J = 2$) and the extension to cases with more than 2 groups is straightforward. We assume the following Bayesian hierarchical model. At the first stage, we assume that given the study-specific risks (p_{1i}, p_{2i}), y_{1i} and y_{2i} are independently distributed binomial variables, i.e.,

$$(y_{1i}, y_{2i})|(n_{1i}, n_{2i}, p_{1i}, p_{2i}) \sim \text{Binomial}(y_{1i}|n_{1i}, p_{1i}) \times \text{Binomial}(y_{2i}|n_{2i}, p_{2i}). \quad (1)$$

This conditional independence assumption is reasonable because y_{1i} and y_{2i} are calculated using subjects from different groups. To complete the Bayesian hierarchical model, we need to impose a parametric prior distribution on the study-specific risks (p_{1i}, p_{2i}). Here we consider a family of distributions first proposed by Sarmanov (1966), and later studied extensively by Cole, Lee, Whitmore, and Zaslavsky (1995), Lee (1996), Shubina and Lee (2004), Danaher and Hardie (2005), and Chen *et al.* (2014a). The Sarmanov beta prior distribution is constructed such that the marginal distribution of the random-effects in the jth group p_{ji} is equal to a beta distribution with shape parameters (a_j, b_j) and the correlation coefficient between p_{1i} and p_{2i} is ρ (Sarmanov 1966; Lee 1996). Specifically, we denote $\text{beta}(p; a, b) = \{B(a, b)\}^{-1} p^{a-1}(1 - p)^{b-1}$ where $B(a, b)$ is the beta function defined by $\int_0^1 t^{a-1}(1-t)^{b-1}dt$, $\mu_j = a_j/(a_j + b_j)$, and $\delta_j^2 = \mu_j(1-\mu_j)/(a_j + b_j + 1)$. The joint prior distribution of the study-specific risks (p_{1i}, p_{2i}), referred to as Sarmanov beta prior distribution, is

$$(p_{1i}, p_{2i})|(a_1, b_1, a_2, b_2, \rho) \sim g(p_1, p_2; a_1, b_1, a_2, b_2, \rho), \quad (2)$$

where $g(p_1, p_2; a_1, b_1, a_2, b_2, \rho) = \text{beta}(p_1; a_1, b_1)\text{beta}(p_2; a_2, b_2)\{1 + \rho\frac{(p_1-\mu_1)(p_2-\mu_2)}{\delta_1\delta_2}\}$.
With the Bayesian hierarchical model specified in equations (1) and (2), the log marginalized likelihood function for the unknown hyperparameters $(a_1, b_1, a_2, b_2, \rho)$ is

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

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 equation (3) has been derived by Danaher and Hardie (2005) and an outline of its derivation is provided in the Appendix for interested readers. We refer to equation (3) as Sarmanov beta-binomial model. As a benefit of using Sarmanov beta prior distributions, the log marginalized likelihood function has a closed-form expression, which avoids numerical approximation of integrals. Hence the Bayesian hierarchical model specified in equations (1) and (2) has great computational advantage over commonly used multivariate generalized linear mixed-effects models. When $\rho = 0$, the Sarmanov beta-binomial model reduces to the independent beta-binomial model, i.e., the product of two beta-binomial distributions.

The hyperparameters $(a_1, b_1, a_2, b_2, \rho)$ can be estimated by maximizing the log likelihood $\log L(a_1, b_1, a_2, b_2, \rho)$. We implement it through R (R Core Team 2013) with the `optim` function, which uses a quasi-Newton method with box constraints on the ranges of parameters. 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 in equation (3). We use the delta method to obtain the variance of the overall comparative measures, namely the overall odds ratio estimate,

$$\widehat{\text{OR}} = \frac{\hat{\mu}_2/(1 - \hat{\mu}_2)}{\hat{\mu}_1/(1 - \hat{\mu}_1)} = \frac{\hat{a}_2\hat{b}_1}{\hat{a}_1\hat{b}_2},$$

the overall relative risk estimate,

$$\widehat{\text{RR}} = \frac{\hat{\mu}_2}{\hat{\mu}_1} = \frac{\hat{a}_2/(\hat{a}_2 + \hat{b}_2)}{\hat{a}_1/(\hat{a}_1 + \hat{b}_1)},$$

and the overall risk difference estimate,

$$\widehat{\text{RD}} = \hat{\mu}_2 - \hat{\mu}_1 = \frac{\hat{a}_2}{(\hat{a}_2 + \hat{b}_2)} - \frac{\hat{a}_1}{(\hat{a}_1 + \hat{b}_1)}.$$

2.2. Inference on study-specific comparative measures

Denote the study-specific comparative measures $\text{OR}_i = \{p_{2i}/(1-p_{2i})\}/\{p_{1i}/(1-p_{1i})\}$, $\text{RR}_i = p_{2i}/p_{1i}$, and $\text{RD}_i = p_{2i} - p_{1i}$. The statistical evidence of these comparative measures from the ith study can be quantified by the posterior distributions, i.e., $\Pr(\theta_i|\text{data}_i, a_1, b_1, a_2, b_2, \rho)$ where $\theta_i = \text{OR}_i$, RR_i, or RD_i and $\text{data}_i = (y_{1i}, n_{1i}, y_{2i}, n_{2i})$. Note that the true values of the hyperparameters $(a_1, b_1, a_2, b_2, \rho)$ are often unknown. One solution is to simply replace the hyperparameters by their estimates. Such an approach is called empirical Bayes method (Efron and Morris 1973, 1975; Gelman, Carlin, Stern, and Rubin 2004; Carlin and Louis 2009). The coverage property of the credible intervals using the empirical Bayes method has been investigated via simulation studies in Chen *et al.* (2014b). The conclusion is that the credible interval without accounting for the uncertainty on the hyperparameters still performs reasonably well, when the number of studies is moderate (Chen *et al.* 2014b).

An important property of the Sarmanov beta prior distribution for p_1 and p_2 is that it can be written as a linear combination of independent bivariate beta distributions (Lee 1996),

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

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,

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

where $\alpha_j = a_j + y_{ji}$, $\beta_j = b_j + n_{ji} - y_{ji}$ $(j = 1, 2)$ and the weights ω_k $(k = 1, \ldots, 4)$ are defined as

$$\omega_1 = \frac{v_1 B(\alpha_1, \beta_1)B(\alpha_2, \beta_2)}{CB(a_1, b_1)B(a_2, b_2)}, \qquad \omega_2 = \frac{v_2 B(\alpha_1+1, \beta_1)B(\alpha_2, \beta_2)}{CB(a_1+1, b_1)B(a_2, b_2)},$$
$$\omega_3 = \frac{v_3 B(\alpha_1, \beta_1)B(\alpha_2+1, \beta_2)}{CB(a_1, b_1)B(a_2+1, b_2)}, \qquad \omega_4 = \frac{v_4 B(\alpha_1+1, \beta_1)B(\alpha_2+1, \beta_2)}{CB(a_1+1, b_1)B(a_2+1, b_2)},$$

and the normalizing constant C is calculated as

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

The exact posterior distributions of the comparative measures (i.e., OR, RR, and RD) under the Sarmanov beta prior distribution take the following generic form

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

If $\theta_i = \mathrm{OR}_i$, we have for $\theta_i > 0$

$$\begin{aligned} f(\theta_i;\alpha_1,\beta_1,\alpha_2,\beta_2) &= \theta_i^{-1-\beta_2}\Big\{B(\alpha_1,\beta_1)B(\alpha_2,\beta_2)\Big\}^{-1}B(\alpha_1+\alpha_2,\beta_1+\beta_2) \\ &\times \quad F(\alpha_2+\beta_2,\beta_1+\beta_2;\alpha_1+\alpha_2+\beta_1+\beta_2;1-\frac{1}{\theta_i}), \end{aligned} \tag{5}$$

where $F(\cdot,\cdot;\cdot;\cdot)$ denotes the hypergeometric function Gauss (1812) defined by

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

If $\theta_i = \mathrm{RR}_i$, we have

$$\begin{aligned} & f(\theta_i;\alpha_1,\beta_1,\alpha_2,\beta_2) = \Big\{B(\alpha_1,\beta_1)B(\alpha_2,\beta_2)\Big\}^{-1} \\ \times & \begin{cases} \theta_i^{\alpha_2-1}B(\alpha_1+\alpha_2,\beta_1)F(1-\beta_2,\alpha_1+\alpha_2;\alpha_1+\alpha_2+\beta_1;\theta_i) & \text{for } \theta_i \in [0,1), \\ \theta_i^{-\alpha_1-1}B(\alpha_1+\alpha_2,\beta_2)F(1-\beta_1,\alpha_1+\alpha_2;\alpha_1+\alpha_2+\beta_2;1/\theta_i) & \text{for } \theta_i \in [1,\infty), \end{cases} \end{aligned} \tag{6}$$

If $\theta_i = \mathrm{RD}_i$, we have

$$\begin{aligned} & f(\theta_i) = \Gamma(\alpha_1+\beta_1)\Gamma(\alpha_2+\beta_2)(|\theta_i|)^{\beta_1+\beta_2-1} \\ \times & \begin{cases} \frac{(1+\theta_i)^{\alpha_1+\beta_2-1}}{\Gamma(\beta_1)\Gamma(\alpha_2)\Gamma(\alpha_1+\beta_2)}F_1(\beta_2,\zeta,1-\alpha_2,\alpha_1+\beta_2;1+\theta_i,1-\theta_i^2) & \text{if } \theta_i \in [-1,0], \\ \frac{(1-\theta_i)^{\alpha_2+\beta_1-1}}{\Gamma(\beta_2)\Gamma(\alpha_1)\Gamma(\alpha_2+\beta_1)}F_1(\beta_1,\zeta,1-\alpha_1,\alpha_2+\beta_1;1-\theta_i,1-\theta_i^2) & \text{if } \theta_i \in (0,1]. \end{cases} \end{aligned} \tag{7}$$

where $\zeta = \alpha_1+\alpha_2+\beta_1+\beta_2-2$ and $F_1(\cdot,\cdot,\cdot,\cdot;\cdot,\cdot)$ 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.

3. Using package mmeta

3.1. Package overview

The **mmeta** package has two major functions, i.e., `multipletables()` and `singletable()`. The function `multipletables()` is to conduct inference based on multiple 2×2 tables. Specifically, the hyperparameters' maximum likelihood estimates $(\widehat{a}_1,\widehat{b}_1,\widehat{a}_2,\widehat{b}_2,\widehat{\rho})$ and the inference on the overall comparative measures are obtained as described in Section 2.1. The posterior distributions of the study-specific comparative measures can be obtained either by the exact method as stated in Section 2.2 or by the samples obtained from adaptive rejection Metropolis sampling (ARMS, Gilks, Best, and Tan 1995) implemented in the R package **HI**, which is an interface to the C code originally developed by Wally Gilks. The argument `method` can

be either "exact" or "sampling" to control if either the exact posterior distributions or the ARMS samples of the posterior distributions are used. The sampling method is set as default in this package because the current version of Gauss hypergeometric and Appell functions may diverge for some studies with extremely large numbers of subjects. The posterior means of the study-specific comparative measures, the corresponding 95% equal tail credible intervals (the interval between the 2.5% and 97.5% quantiles, referred to as 95% ET CI), and the 95% highest posterior density regions (referred to as 95% HDR) are obtained based on ARMS samples of the posterior distribution. To ensure reproducibility when the sampling method is used, a random seed can be set (using `set.seed` command) before calling `multipletables()` and `singletable()` functions. Various plots can be generated by `multipletables()`, which will be illustrated in the rest of this section. In contrast, the function `singletable()` is to conduct exact posterior inference based on a single 2×2 table for the given prior distributions of risks. This function can be used as a sensitivity analysis tool to investigate the posterior distributions of the comparative measures under various pre-specified prior distributions. The details of the function `singletable()` will be given in Section 3.5.

The arguments used in a call to the function `multipletables()` are

```
multipletables(data = NULL, measure = NULL, model = "Sarmanov",
  method = "sampling", nsam = 10000, alpha = 0.05)
```

In the following we summarize the main arguments of `multipletables()`.

`data`: A data frame that contains `y1`, `n1`, `y2`, `n2`, and `studynames`. The details of the data structure is described in Section 3.2.

`measure`: A character string specifying a comparative measure. Options are `"OR"` (odds ratio), `"RR"` (relative risk), and `"RD"` (risk difference).

`model`: A character string specifying the model. Options are `"Independent"` and `"Sarmanov"` (default). `"Independent"` is the independent beta-binomial model; `"Sarmanov"` is the Sarmanov beta-binomial model.

`method`: A character string specifying the method. Options are `"exact"` and `"sampling"`. `"exact"` denotes the exact method; `"sampling"` (default) is the method based on ARMS samples of the posterior distribution obtained with the R package **HI**.

`alpha`: A numeric value specifying the significance level. Default value is set to 0.05.

`nsam`: A numeric value specifying the number of samples if `method = "sampling"`. Default value is set to `10000`.

3.2. Data structure

The structure of `data` in `multipletables()` requires the input of a data frame with five columns, `y1`, `n1`, `y2`, `n2`, and `studynames`. The meanings of `y1`, `n1`, `y2`, and `n2` can vary for different study designs. Users can define their own data frame to be used in `multipletables()`. For example, a data frame named `Bellamy` based on a meta-analysis of the association between gestational diabetes mellitus and type 2 diabetes mellitus (Bellamy, Casas, Hingorani, and Williams 2009) can be defined as follows.

```
R> y1 <- c(6628, 22, 0, 150, 1, 16, 7, 8, 0, 0, 0, 1, 0, 1, 7, 0, 0, 3,
+    18, 0)
R> n1 <- c(637341, 868, 39, 2242, 111, 783, 108, 489, 11, 435, 70, 61,
+    52, 39, 431, 35, 57, 47, 328, 41)
R> y2 <- c(2874, 71, 21, 43, 53, 405, 6, 13, 7, 23, 44, 21, 10, 15, 105,
+    10, 33, 14, 224, 5)
R> n2 <- c(21823, 620, 68, 166, 295, 5470, 70, 35, 23, 435, 696, 229, 28,
+    45, 801, 15, 241, 47, 615, 145)
R> studynames <- c("Feig 2008", "Lee H 2008", "Madarasz 2008",
+    "Gunderson 2007", "Vambergue 2008", "Lee 2007","Ferraz",
+    "Krishnaveni 2007", "Morimitsu 2007", "Jarvel 2006", "Albareda 2003",
+    "Aberg 2002", "Linne 2002", "Bian 2000", "Ko 1999", "Osei 1998",
+    "Damm 1994", "Benjamin 1993", "O'Sullivan 1964 and 1984",
+    "Persson 1991")
R> Bellamy <- data.frame(y1, n1, y2, n2, studynames = studynames,
+    stringsAsFactors = FALSE)
```

There are two kinds of study designs, i.e., retrospective (or case-control) studies and prospective studies (or clinical trials). In a case-control study, `n1` and `n2` are the numbers of subjects in the control and case groups, respectively, while `y1` and `y2` are the numbers of subjects with exposure in the control and case groups, respectively. `measure = "OR"`, `measure = "RR"`, and `measure = "RD"` correspond to the odds ratio, relative risk, and risk difference of exposure comparing the case group with the control group, respectively. In a prospective study, `n1` and `n2` are the numbers of subjects in the unexposed and exposed groups, respectively, while `y1` and `y2` are the numbers of subjects who experienced a certain event in the unexposed and exposed groups, respectively. `measure = "OR"`, `measure = "RR"`, and `measure = "RD"` correspond to the odds ratio, relative risk, and risk difference of events comparing the exposed group with the unexposed group, respectively.

We have provided two example datasets, i.e., `colorectal` based on a meta-analysis of case-control studies and `withdrawal` based on a meta-analysis of clinical trials. In Sections 3.3 and 3.4, we illustrate the working of the package with the help of these two example datasets.

3.3. Example: `colorectal` dataset

The dataset `colorectal` consists of data from twenty published case-control studies of the N-acetyltransferase 2 (NAT2) acetylation status and colorectal cancer risk. NAT2 is a low-penetrance gene that regulates metabolizing enzymes. The activity of the enzymes is classified as rapid and slow acetylators. Ye and Parry (2002) investigated the association between rapid NAT2 acetylator status (event) and colorectal cancer (case) by conducting a meta-analysis based on twenty published case-control studies from January 1985 to October 2001. The data are summarized in Table 1. We define the odds ratio as the ratio of odds of having rapid NAT2 acetylator status comparing those with colorectal cancer to those without. The `colorectal` dataset example takes around 3 minutes and 1 minute to run using `"exact"` and `"sampling"` methods (10,000 samples), respectively.

To start analyzing the dataset, we first load the **mmeta** package and the `colorectal` dataset.

```
R> library("mmeta")
```

Author	Cases		Controls	
	No. events	No. individuals	No. events	No. individuals
Ilett	27	49	10	41
Ilett	27	49	19	45
Wohlleb	23	43	13	41
Ladero	49	109	40	96
Rodriguez	20	44	13	28
Lang	14	34	92	205
Oda	33	36	33	36
Shibuta	112	234	151	329
Bell	96	202	50	112
Spurr	32	103	34	96
Hubbard	100	275	140	343
Welfare	73	174	74	174
Gil	44	114	68	201
Chen	81	212	96	221
Lee	156	216	134	187
Yoshika	99	106	95	100
Potter	228	527	88	200
Slattery	931	1624	807	1963
Agundez	60	120	119	258
Butler	156	200	162	209

Table 1: Data from a meta-analysis (Ye and Parry 2002) of case-control studies on the association between rapid N-acetyltransferase 2 (NAT2) acetylator status (event) and colorectal cancer risk (cases).

```
R> data("colorectal", package = "mmeta")
```

The `colorectal` dataset has the following structure:

```
R> str(colorectal)
```

```
'data.frame':        20 obs. of  5 variables:
 $ y1        : num  10 19 13 40 13 92 33 151 50 34 ...
 $ y2        : num  27 27 23 49 20 14 33 112 96 32 ...
 $ n1        : num  41 45 41 96 28 205 36 329 112 96 ...
 $ n2        : num  49 49 43 109 44 34 36 234 202 103 ...
 $ studynames: chr  "Ilett" "Ilett1" "Wohlleb" "Ladero" ...
```

The function `multipletables()` is called to conduct exact posterior inference of the odds ratios.

```
R> set.seed(1234)
R> multiple.OR <- multipletables(data = colorectal, measure = "OR",
+    model = "Sarmanov", method = "exact")
R> summary(multiple.OR)
```

```
Model: Sarmanov Beta-Binomial Model
Overall Odds ratio
Estimate: 1.1
95% CI:[0.704,1.718]

Maximum likelihood estimates of hyperparameters:
a1 =3.108, b1 =2.914, a2 =3.942, b2 =3.361, rho =0.125
Likelihood ratio test for within-group correlation (H0: rho=0):
chi2: 3.152; p-value: 0.08
Study-SpecifcOdds ratio:
           Mean Lower Bound Upper Bound
Ilett     3.555       1.417       7.585
Ilett1    1.730       0.748       3.408
Wohlleb   2.429       0.993       5.152
Ladero    1.186       0.674       1.925
Rodriguez 1.074       0.387       2.376
Lang      0.990       0.474       1.791
Oda       1.166       0.274       3.285
Shibuta   1.105       0.790       1.501
Bell      1.141       0.708       1.723
Spurr     0.884       0.477       1.492
Hubbard   0.845       0.597       1.150
Welfare   1.008       0.641       1.515
Gil       1.279       0.779       1.968
Chen      0.827       0.556       1.189
Lee       1.048       0.662       1.562
Yoshika   0.884       0.287       2.061
Potter    0.983       0.704       1.345
Slattery  1.923       1.674       2.185
Agundez   1.201       0.767       1.788
Butler    1.054       0.649       1.627
Overall   1.100       0.704       1.718
```

The likelihood ratio test of $H_0 : \rho = 0$ yields a p value of 0.08 with χ^2 test statistic being 3.152. The estimates of the hyperparameters, the estimated mean and the 95% confidence interval (CI) of the overall odds ratio are provided. In addition, the posterior means and the 95% credible intervals (CI) of all study-specific odds ratios are given. If the argument `model = "Independent"`, the independent Beta-Binomial model is fitted to the dataset. If the argument `method = "sampling"`, adaptive rejection Metropolis sampling implemented in R package **HI** is used to obtain the posterior inference.

The forest plot with the 95% CI of the overall odds ratio and the 95% CIs of the study-specific odds ratios as shown in Figure 1 can be obtained using the `plot` function with the argument `type = "forest"`.

```
R> plot(multiple.OR, type = "forest", addline = 1, xlabel=c(0.3,0.5,2,4))
```

The argument `addline` is to add a blue dotted reference line to the plot. If the argument `file` is specified, (e.g., `file = "multiple_OR_forest"`), the plot will be saved as

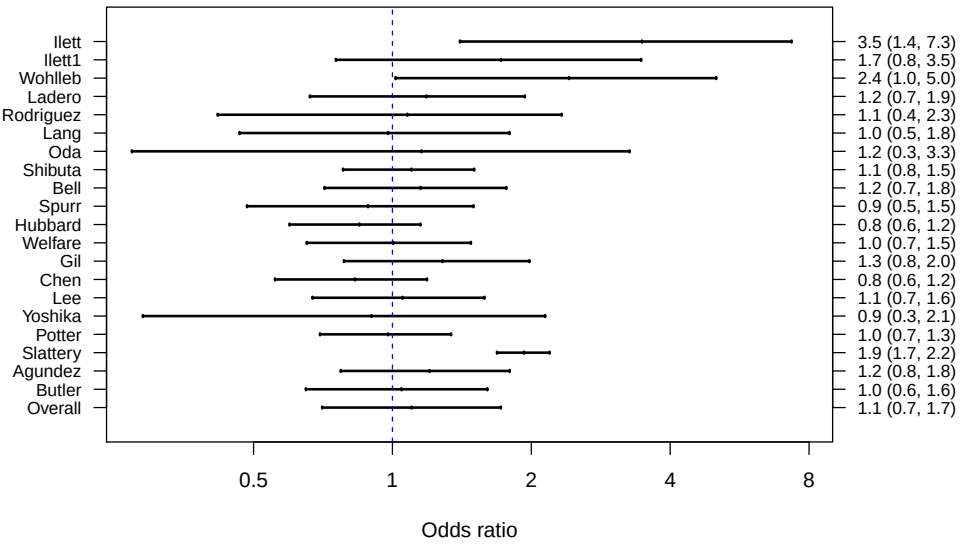

Figure 1: Forest plot of 20 study-specific and the overall odds ratios with 95% CIs.

`"./mmeta/multiple_OR_forest.eps"`, where `"./"` denotes the current working directory and the directory `mmeta` is created automatically if it does not exist. The argument `select` (e.g., `select = 1:4`) can be set to select multiple target studies to be displayed. If the argument `ciShow = TRUE` (by default), the numbers of the posterior means and the CIs will be displayed at the right side of the forest plot. Many standard R plotting arguments (e.g., `xlabel, ylabel, ylim, xlim`) can be set in the `plot` function. See the help file for more details.

The posterior density functions of some target studies can be overlaid as shown in Figure 2 with the argument `type = "overlap"`.

```
R> plot(multiple.OR, type = "overlap", select = c(4, 14, 16, 20))
```

Figure 2 displays the overlaid posterior density functions of odds ratios for four selected studies, i.e., studies 4 (Ladero *et al.* 1991), 14 (Chen *et al.* 1998), 16 (Yoshioka, Katoh, Nakano, Takasawa, Nagata, and Itoh 1999), and 20 (Butler, Ryan, and Roberts-Thomson 2001). Such a plot provides a useful visualization of statistical evidence on association contributed from individual studies. Figure 2 shows that while in Chen *et al.* (1998), most of the density of the odds ratio is between 0.5 and 1.2 (mean: 0.827, 95% CI: [0.556, 1.189]), the density shifts to the right in Butler *et al.* (2001) with the majority of the density laying between 0.6 and 1.5 (mean: 1.054, 95% CI: [0.649, 1.627]). In the studies of Ladero *et al.* (1991) and Yoshioka *et al.* (1999), the density curves are more spread out because of their relatively smaller study sample sizes (mean: 1.186, 95% CI: [0.674, 1.925], and mean: 0.884, 95% CI: [0.287, 2.061], respectively).

The posterior density functions of these target studies can be viewed in a side-by-side manner as in Figure 3 if the argument `type = "sidebyside"`, where both the prior and posterior distributions are displayed.

```
R> plot(multiple.OR, type = "sidebyside", select = c(4, 14, 16, 20),
+    ylim = c(0, 2.7), xlim = c(0.5, 1.5))
```

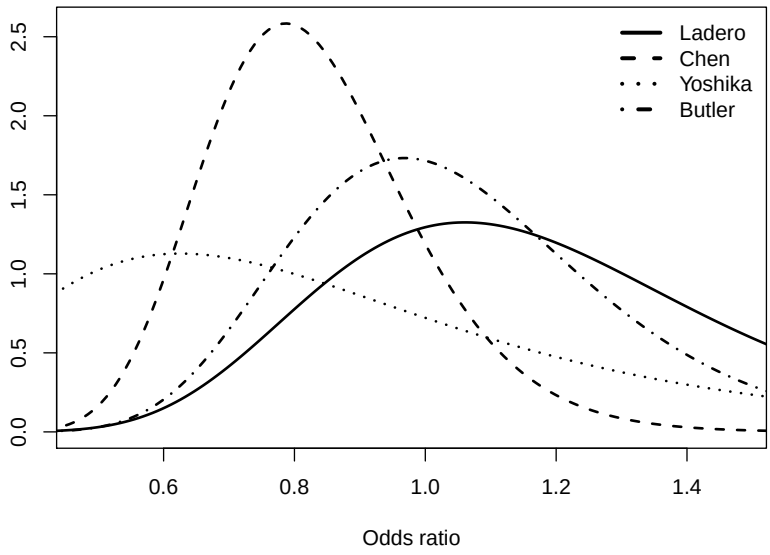

Figure 2: Posterior distributions of study-specific odds ratios for four selected studies in one plot.

Figure 3 displays the prior and posterior distributions of the study-specific odds ratios for these four target studies. Such a plot is useful to investigate the difference between the prior and posterior distributions, hence the strength of contribution from individual studies.

3.4. Example: `withdrawal` dataset

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 effects and it plays a critical role in drug safety. One question of interest is whether the probability of withdrawing due to adverse effects is increased by the tricyclic treatment compared with the placebo. This can be measured by relative risk (defined as the ratio of risks of withdrawal comparing those in the tricyclic treatment group to those in the placebo group). The numbers of withdrawals due to adverse effects in sixteen clinical trials are summarized in Table 2. The `withdrawal` dataset example takes around 2 minutes and 1 minute to run using the `"exact"` and the `"sampling"` method (with 10,000 samples), respectively.

To start analyzing the dataset, we first load the `withdrawal` dataset.

```
R> data("withdrawal", package = "mmeta")
```

The available data have the following structure

```
R> str(withdrawal)
```

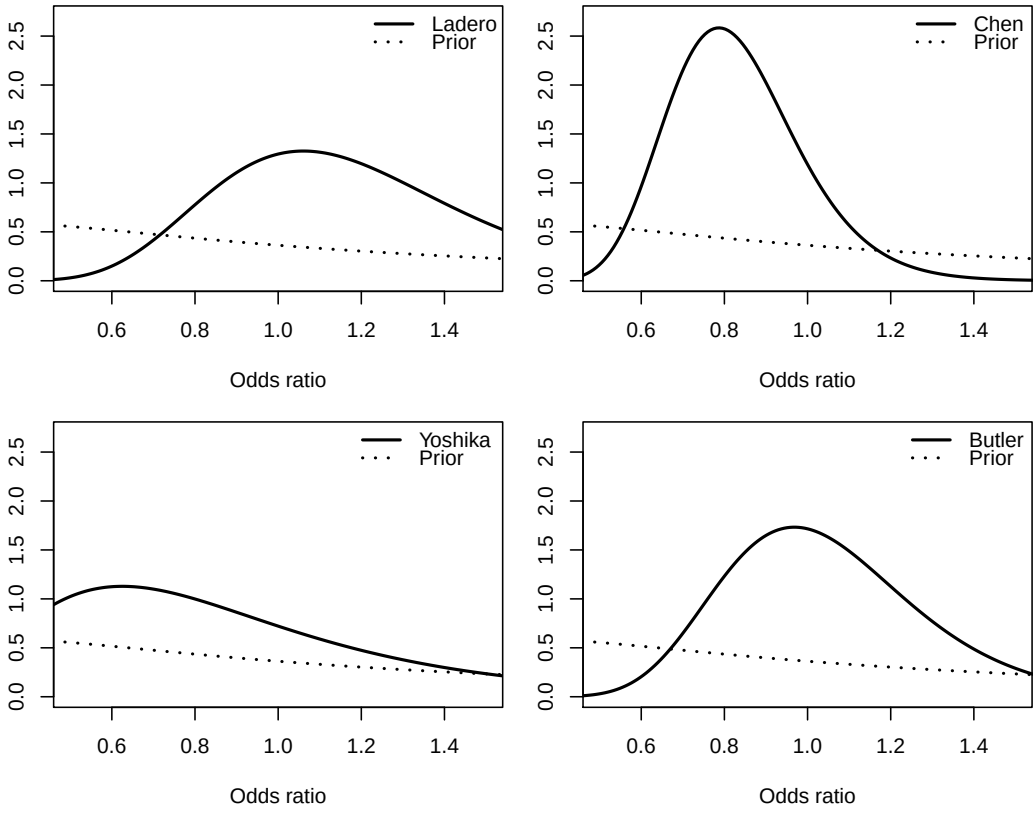

Figure 3: Posterior distributions of study-specific odds ratios for four studies in four separate plots.

```
'data.frame':        16 obs. of  5 variables:
$ y1         : num  0 9 8 13 10 22 2 8 4 4 ...
$ n1         : num  40 27 53 29 34 48 18 21 49 38 ...
$ y2         : num  1 4 8 14 15 9 3 12 7 10 ...
$ n2         : num  40 16 47 56 44 53 18 26 105 36 ...
$ studynames: chr  "Bendtsen 1996" "Canepari 1985" "Couch 1976"
+    "Diamond 1971" ...
```

The function `multipletables()` is called to conduct exact posterior inference of relative risks.

```
R> set.seed(1234)
R> multiple.RR <- multipletables(data = withdrawal, measure = "RR",
+    model = "Sarmanov", method = "exact")
R> summary(multiple.RR)

Model: Sarmanov Beta-Binomial Model
Overall Relative risk
Estimate: 1.263
95% CI:[0.82,1.943]
```

Author	Treatment		Control	
	No. events	No. individuals	No. events	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

Table 2: Data from a meta-analysis of sixteen studies on the association between withdrawal due to the adverse effects and the tricyclic treatment in Jackson *et al.* (2010). No. events: Number of individuals who withdrew from the study. No. individuals: Number of individuals who started the study.

```
Maximum likelihood estimates of hyperparameters:
a1 =2.042, b1 =7.408, a2 =1.943, b2 =5.179, rho =0.093
Likelihood ratio test for within-group correlation (H0: rho=0):
chi2: 0.207; p-value: 0.65
Study-SpecifcRelative risk:
                  Mean Lower Bound Upper Bound
Bendtsen 1996    2.976       0.247      14.039
Canepari 1985    0.906       0.318       1.897
Couch 1976       1.235       0.503       2.570
Diamond 1971     0.673       0.356       1.139
Gobel 1994       1.275       0.653       2.289
Holroyd 2001     0.446       0.217       0.755
Indaco 1988      1.671       0.393       4.975
Jacobs 1972      1.365       0.683       2.558
Lance 1964       0.913       0.294       2.249
Landemark 1990   2.555       0.979       6.069
Loldrup 1989     6.325       3.749      10.782
Mathew 1981      1.016       0.619       1.579
Morland 1979     1.548       0.414       4.270
Noone 1980       1.348       0.510       2.991
Pfaffenrath 1994 1.326       0.838       2.022
Vernon 2009      3.448       0.473      15.038
Overall          1.263       0.820       1.943
```

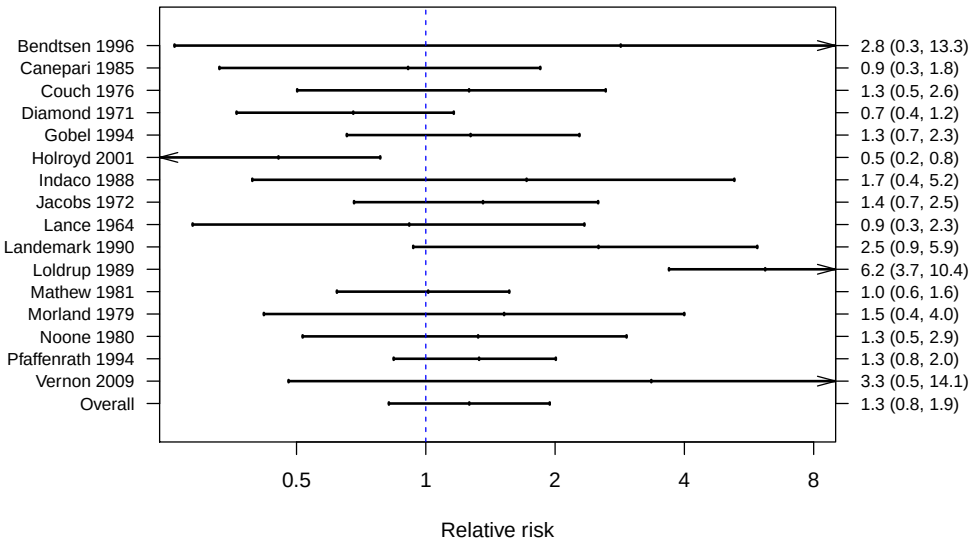

Figure 4: Forest plot of 16 study-specific and the overall relative risks with 95% CIs.

The likelihood ratio test of $H_0 : \rho = 0$ yields a p value of 0.65 with χ^2 test statistic being 0.207. The estimates of the hyperparameters, the estimated mean and the 95% CI of the overall relative risk are provided. In addition, the posterior mean and 95% CI of each study-specific relative risk are given. The forest plot with the confidence interval of the overall relative risk and the credible intervals of the study-specific relative risks as shown in Figure 4 can be obtained using the `plot` function with the argument `type = "forest"`.

```
R> plot(multiple.RR, type = "forest", addline = 1, mar=c(4, 7, 3, 6),
+       xlabel=c(0.2,0.5,3,6.5))
```

The posterior density functions of some target studies can be overlaid as shown in Figure 5 with the argument `type = "overlap"`.

```
R> plot(multiple.RR, type = "overlap", select = c(3, 8, 14, 16))
```

Figure 5 shows that while Couch, Ziegler, and Hassanein (1976) and Noone (1980) have most of the mass of the density of relative risk for values less than 3 (mean: 1.235, 95% CI: [0.503, 2.570], and mean: 1.348, 95% CI: [0.510, 2.991], respectively), the density shifts to the right in Jacobs (1972) (mean: 1.365, 95% CI: [0.683, 2.558]). The density curve of the study of Vernon, Jansz, Goldsmith, and McDermaid (2009) (mean: 3.448, 95% CI: [0.473, 15.038]) is more spread out because of the relatively small study sample size.

Moreover, the posterior density function of each target study can be viewed in a side-by-side manner as in Figure 6 if the argument `type = "sidebyside"`, where both the prior and posterior distributions are displayed.

```
R> plot(multiple.RR, type = "sidebyside", select = c(3, 8, 14, 16),
+    ylim = c(0, 1.2), xlim = c(0.4, 3))
```

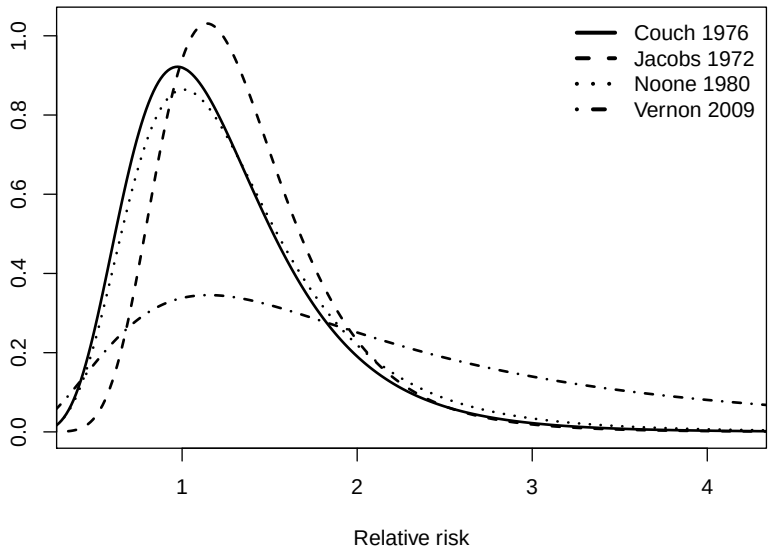

Figure 5: Posterior distributions of study-specific relative risk for four studies in one plot.

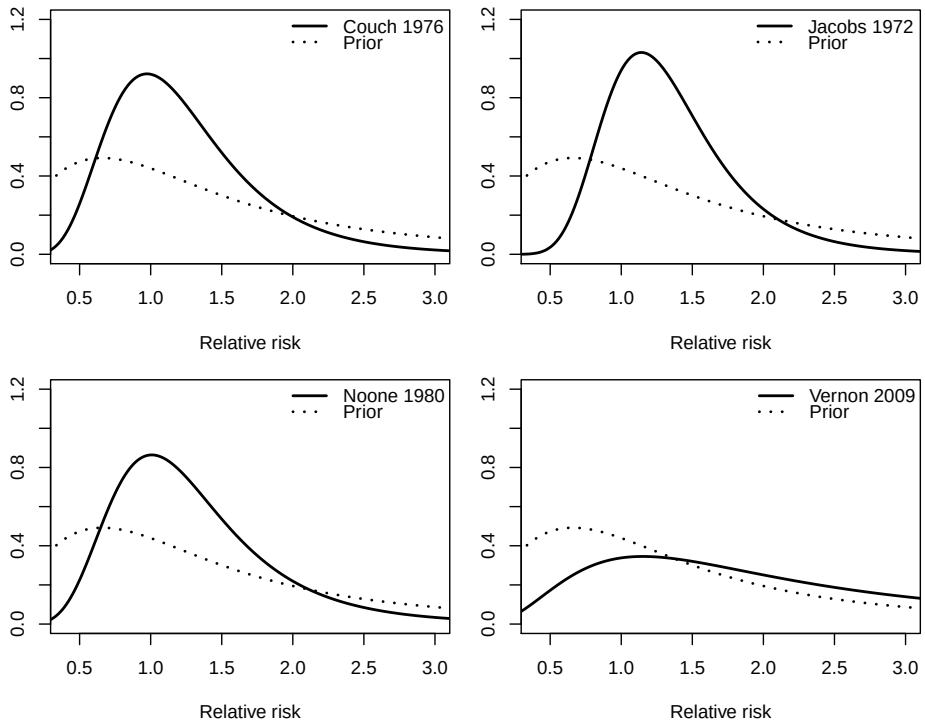

Figure 6: Posterior distributions of study-specific relative risks for four studies in four separate plots.

Figure 6 displays that the study specific odds ratios have very different posterior distributions under the same prior distributions.

Because the estimated relative risk for the study of Loldrup, Langemark, Hansen, Olesen, and

Bech (1989) (mean: 6.325, 95% CI: [3.749, 10.782]) is much larger than those for the other studies, it can be potentially influential to the analysis results. To evaluate the influence of this study, we remove it and reanalyze the dataset by calling the function `multipletables()`. The results can be investigated using `summary()` (not shown).

```
R> multiple.RR.sens <- multipletables(data = withdrawal[-11, ],
+    measure = "RR", model = "Sarmanov")
R> summary(multiple.RR.sens)
```

The likelihood ratio test of zero correlation coefficient results in a p value of 0.40 with the χ^2 test statistics being equal to 0.707. Although the study of Loldrup *et al.* (1989) slightly changes the overall and study-specific relative risk estimates, it is not influential because the overall relative risk estimates are not significant regardless of it being included or not.

If the risk difference is of interest, we define it as the difference of risks of withdrawal comparing those in the treatment group to those in the placebo group. The function `multipletables()` is called to conduct posterior inference of the risk differences.

```
R> set.seed(1234)
R> multiple.RD <- multipletables(data = withdrawal, measure = "RD",
+    model = "Sarmanov")
R> summary(multiple.RD)

Model: Sarmanov Beta-Binomial Model
Overall Risk difference
Estimate: 0.057
95% CI:[-0.049,0.162]

Maximum likelihood estimates of hyperparameters:
a1 =2.042, b1 =7.408, a2 =1.943, b2 =5.179, rho =0.093
Likelihood ratio test for within-group correlation (H0: rho=0):
chi2: 0.207; p-value: 0.65
Study-SpecifcRisk difference:
                  Mean Lower Bound Upper Bound
Bendtsen 1996    0.022      -0.065       0.119
Canepari 1985   -0.046      -0.270       0.187
Couch 1976       0.021      -0.114       0.162
Diamond 1971    -0.138      -0.327       0.040
Gobel 1994       0.055      -0.127       0.230
Holroyd 2001    -0.236      -0.395      -0.082
Indaco 1988      0.047      -0.149       0.253
Jacobs 1972      0.090      -0.143       0.323
Lance 1964      -0.023      -0.124       0.063
Landemark 1990   0.151      -0.004       0.313
Loldrup 1989     0.593       0.509       0.668
Mathew 1981     -0.003      -0.124       0.121
Morland 1979     0.043      -0.143       0.237
Noone 1980       0.059      -0.205       0.311
```

```
Pfaffenrath 1994  0.059      -0.042       0.159
Vernon 2009       0.138      -0.139       0.433
Overall           0.057      -0.049       0.162
```

The forest plot, the overlaid, and side-by-side plots of the posterior density functions for risk difference can also be obtained by using the `plot` function with the argument `type = "forest"`, `type = "overlap"`, and `type = "sidebyside"`, respectively.

Note that the study of Loldrup *et al.* (1989) can be influential on the analysis results because the estimated risk difference (mean: 0.593, 95% CI: [0.509, 0.668]) 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 by calling the function `multipletables()`. The results can be investigated using `summary()` (not shown).

```
R> multiple.RD.sens <- multipletables(data = withdrawal[-11, ],
+    measure = "RD", model = "Sarmanov")
R> summary(multiple.RD.sens)
```

The likelihood ratio test of zero correlation coefficient results in a p value of 0.40. Although the study of Loldrup *et al.* (1989) slightly changes the overall and study-specific risk difference estimates, it is not influential because the overall risk difference estimates are not significant regardless of it being included or not.

3.5. Using the `singletable()` function

When the inference on a specific study based on a single 2×2 table is of interest, the function `singletable()` can be used as a sensitivity analysis tool to conduct the exact posterior inference on comparative measures under various prior distributions. The arguments used in a call to the function `singletable()` are

```
singletable <- function(y1, n1, y2, n2, measure, model = "Sarmanov",
  method = "sampling", alpha = 0.05, nsam = 10000)
```

In the following we summarize the main arguments of `singletable()`.

`y1, n1`: Integers indicating the number of events and the total number of subjects in group 1.

`y2, n2`: Integers indicating the number of events and the total number of subjects in group 2.

`measure`: A character string specifying a comparative measure. Options are `"OR"` (odds ratio), `"RR"` (relative risk), and `"RD"` (risk difference).

`model`: A character string specifying the model. Options are `"Independent"` and `"Sarmanov"` (default). `"Independent"` is the independent beta-binomial model; `"Sarmanov"` is the Sarmanov beta-binomial model.

`method`: A character string specifying the method. Options are `"exact"` and `"sampling"`. `"exact"` denotes the exact method; `"sampling"` (default) is the method based on ARMS samples of the posterior distribution obtained with the R package **HI**.

`a1, b1, a2, b2`: Numeric values specifying the hyperparameters of the beta prior distributions for groups 1 and 2.

`rho`: A numeric value specifying the correlation coefficient for the Sarmanov beta prior distribution. Default value is set to 0.

`alpha`: A numeric value specifying the significance level. Default value is set to 0.05.

`nsam`: A numeric value specifying the number of samples if method is `sampling`. Default value is set to `10,000`.

To illustrate the use of the function `singletable()`, we consider the study by Ladero *et al.* (1991) in the `colorectal` dataset with $y_1 = 40$, $n_1 = 96$, $y_2 = 49$, and $n_2 = 109$. The function `singletable()` is called to conduct exact posterior inference of the odds ratio under four different prior distributions, i.e., Jeffreys prior distribution ($a_1 = b_1 = a_2 = b_2 = 0.5$), Laplace prior distribution ($a_1 = b_1 = a_2 = b_2 = 1$), and two Sarmanov correlated prior distributions with strong positive and negative prior correlations ($a_1 = b_1 = a_2 = b_2 = 0.5$, $\rho = 0.5, -0.5$). The results are listed below.

```
R> set.seed(1234)
R> single.OR.Jeffreys <- singletable(a1 = 0.5, b1 = 0.5, a2 = 0.5,
+    b2 = 0.5, y1 = 40, n1 = 96, y2 = 49, n2 = 109, model = "Independent",
+    measure = "OR", method = "exact")
R> summary(single.OR.Jeffreys)

Measure: Odds ratio
Model: Independent Beta-Binomial Model
Mean: 1.183
Median: 1.134
95% ET CI: [0.659,1.967]
95% HDR CI: [0.603,1.862]

R> set.seed(1234)
R> single.OR.Laplace <- singletable(a1 = 1, b1 = 1, a2 = 1, b2 = 1, y1 = 40,
+    n1 = 96, y2 = 49, n2 = 109, model = "Independent", measure = "OR",
+    method = "exact")
R> summary(single.OR.Laplace)

Measure: Odds ratio
Model: Independent Beta-Binomial Model
Mean: 1.18
Median: 1.133
95% ET CI: [0.66,1.957]
95% HDR CI: [0.586,1.85]

R> set.seed(1234)
R> single.OR.Sar1 <- singletable(a1 = 0.5, b1 = 0.5, a2 = 0.5, b2 = 0.5,
+    rho = 0.5, y1 = 40, n1 = 96, y2 = 49, n2 = 109, model = "Sarmanov",
+    measure = "OR", method = "exact")
R> summary(single.OR.Sar1)
```

```
Measure: Odds ratio
Model: Sarmanov Beta-Binomial Model
Prior: Sarmanov
Mean: 1.187
Median: 1.145
95% ET CI: [0.668,1.968]
95% HDR CI: [0.604,1.845]
```

```
R> set.seed(1234)
R> single.OR.Sar2 <- singletable(a1 = 0.5, b1 = 0.5, a2 = 0.5, b2 = 0.5,
+    rho = -0.5, y1 = 40, n1 = 96, y2 = 49, n2 = 109, model = "Sarmanov",
+    measure = "OR", method = "exact")
R> summary(single.OR.Sar2)
```

```
Measure: Odds ratio
Model: Sarmanov Beta-Binomial Model
Prior: Sarmanov
Mean: 1.187
Median: 1.145
95% ET CI: [0.668,1.968]
95% HDR CI: [0.604,1.845]
```

The corresponding prior and posterior distributions of the odds ratio under four prior distributions are shown in Figure 7 using the `plot` function with the argument `type = "overlap"`.

```
R> par(mfrow = c(2,2))
R> plot(single.OR.Jeffreys, type = "overlap", xlim = c(0.04, 0.3),
+    ylim = c(0, 15), main = "Jeffreys Prior")
R> plot(single.OR.Laplace, type = "overlap", xlim = c(0.04, 0.3),
+    ylim = c(0, 15), main = "Laplace Prior")
R> plot(single.OR.Sar1, type = "overlap", xlim = c(0.04, 0.3),
+    ylim = c(0, 15),
+    main = expression(paste("Sarmanov Prior ", rho, " = 0.5")))
R> plot(single.OR.Sar2, type = "overlap", xlim = c(0.04, 0.3),
+    ylim = c(0, 15),
+    main = expression(paste("Sarmanov Prior ", rho, " = -0.5")))
```

As shown in Figure 7, the posterior distributions under all prior distributions share the similar pattern of having most of their weight on odds ratios between 0.5 and 2. This leads to similar credible intervals under all prior distributions although the Sarmanov beta prior distributions impose relatively strong prior correlations between p_1 and p_2 ($\rho = -0.5$ or 0.5).

4. Conclusion

In this paper, we present an overview of the **mmeta** package to conduct exact posterior inference of the odds ratio, relative risk, and risk difference based on multiple studies or a

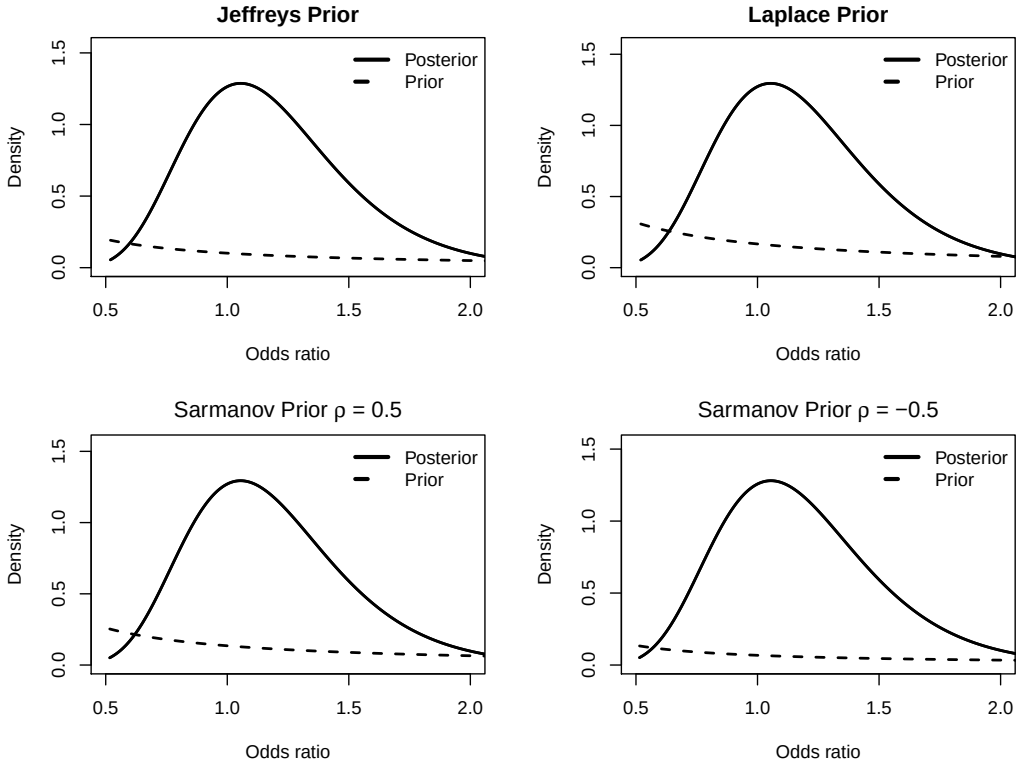

Figure 7: Prior and posterior distributions of odds ratio under Jeffreys prior distribution, Laplace prior distribution, and Sarmanov prior distributions ($\rho = 0.5$ and $\rho = -0.5$).

single study of two populations with binary outcomes. The theory used for model fitting is summarized briefly, and the two major functions (`multipletables()` and `singletable()`) of the package are described in details. Practical use of the **mmeta** package is illustrated with two examples of meta-analysis based on multiple 2×2 tables and one example of a single 2×2 table. As a future research direction, we would like to expand the functionality of this package to conduct meta-regression analysis using the Sarmanov beta prior distributions as illustrated in Chen *et al.* (2014a) and Chen *et al.* (2014b). Moreover, we have investigated many available non-commercial algorithms and software packages to compute the hypergeometric function and the Appell function. To the best of our knowledge, we cannot find one that provides stable computation for studies with extremely large numbers of subjects. Developing a robust algorithm for computation of these two functions are also part of our future research.

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A. Derivation of Equation 3

For simplicity of notation, we suppress the index i. After some algebra, we can show

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

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

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

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