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Closed-form fiducial confidence intervals for some functions of independent binomial parameters with comparisons

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Abstract

Approximate closed-form confidence intervals (CIs) for estimating the difference, relative risk, odds ratio, and linear combination of proportions are proposed. These CIs are developed using the fiducial approach and the modified normal-based approximation to the percentiles of a linear combination of independent random variables. These confidence intervals are easy to calculate as the computation requires only the percentiles of beta distributions. The proposed confidence intervals are compared with the popular score confidence intervals with respect to coverage probabilities and expected widths. Comparison studies indicate that the proposed confidence intervals are comparable with the corresponding score confidence intervals, and better in some cases, for all the problems considered. The methods are illustrated using several examples.

Keywords

beta distribution, constrained maximum likelihood estimates, score test, precision, powers, Wald test

1 Introduction

There has been a continuing interest in developing inferential procedures for binomial distributions because of their common occurrences in many applied sciences, especially in medical sciences. Specifically, many summary indices in comparative clinical trials can be expressed as a function of independent binomial success probabilities. For example, odds ratios are most commonly used in case–control studies, and other studies such as cross-sectional and cohort study designs. Relative risk is frequently used in clinical trials to compare the risk of developing a disease for those who are not taking a treatment with those who are undergoing a treatment. The relative risk is also used to compare the risk of developing a side effect in people receiving a drug as compared to the people who are not taking the drug. To define these summary indices formally, let p_e denotes the probability

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of an event (such as death or adverse symptoms) in the exposed group of individuals, and p_c denotes the same in the control group. The ratio p_e/p_c is a measure of relative risk for the exposed group. The ratio of odds is defined by $p_e(1-p_c)/(p_c(1-p_e))$ which represents the relative odds of event in the exposed group compared to that in the control group. Another important problem in clinical studies and meta-analysis is that of estimating a linear combination of binomial proportions. As noted in Andrés and Hernández,[1] the problem of estimating a linear combination of proportions arises, among others, in dose–response studies, public health surveys, and multicenter clinical studies.

Exact conditional methods are available for testing or estimating some of the aforementioned summary indices. For example, Fisher's exact test can be used to test the difference between two proportions, and the exact conditional method by Cornfield[2] can be used to find confidence intervals (CIs) for the odds ratio. However, it is well known that exact conditional methods are in general too conservative yielding CIs that are unnecessarily wide. Some of the unconditional methods proposed in the literature (e.g. Suissa and Shuster[3]) are too complex and numerically involved. As noted by Agresti and Min,[4] a disadvantage of the unconditional approach is that calculations are complex, and in some cases, there is no guarantee that the proposed algorithm produces the intended interval. Several approximate and asymptotic methods have been proposed in the literature for estimating summary indices involving binomial parameters. Among all methods, the score method based on the likelihood approach appears to be the most popular method, producing satisfactory results for moderate to large samples. Miettinen and Nurminen[5] have proposed likelihood-based score methods for finding CIs for the difference between two proportions, the relative risk and for the odds ratio. Bedrick[6] and Bailey[7] compared several methods for estimating the risk ratio and found that the score method by Miettinen and Nurminen[5] is quite satisfactory and comparable with other methods. Newcombe[8] has compared 11 approximate CIs for estimating the difference and concluded that the score CI by Miettinen and Nurminen[5] is comparable to the other satisfactory CIs. Recently, Andrés and Hernández[1] used the score method to find satisfactory CIs for a linear combination of proportions. The simulation studies by Andrés and Hernández[1] indicated that the score CIs have good coverage properties even for small samples.

In general, the score method is satisfactory for many estimation problems involving binomial or Poisson distributions. However, the score method involves finding the constrained maximum likelihood estimates (MLEs), that is the MLEs under the null hypothesis, which cannot be expressed in closed-form for many problems. Some nonlinear root finding methods are necessary to obtain the constrained MLEs numerically. There are some closed-form asymptotic CIs available for some problems, but they are valid only for large samples.

In this article, we propose a simple approach that produces closed-form CIs for estimating various summary indices involving binomial proportions. In fact, our approach can be used to find approximate CIs for any smooth function of binomial parameters and does not require computation of the constrained MLEs. The closed-form approximate CIs that we propose in the sequel are based on the fiducial approach by Krishnamoorthy and Lee[9] and the modified normal-based approximation by Krishnamoorthy[10] to the percentiles of a linear combination of independent continuous random variables. In fact, the estimation problems simplify to finding percentiles of some functions of independent beta random variables. Furthermore, the computation of these approximate CIs requires only beta percentiles, and so they are very simple to use. We also note that the method of variance estimate recovery (MOVER) due to Zou and Donner[11] may be used to find CIs for all problems considered in the sequel. However, as noted by Newcombe,[12] MOVER CIs pose some problems at the boundary of the sample space whereas the CIs that we propose in the sequel do not require special cares at the extreme values.

The rest of the article is organized as follows. In the following section, we describe the fiducial approach and the modified normal-based approximation by Krishnamoorthy[10] and provide some general results that are needed to find closed-form CIs. In Section 3, we develop CIs for the difference of proportions, relative risk, and for the odds ratio and outline the score methods for each problem. In Section 3.4, we compare the new CIs with the score CIs in terms of exact coverage probabilities and expected widths. In Section 4, we describe the new closed-form CI for a linear combination of binomial proportions along with the score method by Andrés and Hernández.[1] These two CIs for a linear combination of proportions are compared with respect to coverage probabilities and expected widths. Our comparison studies indicate that the new CIs are quite comparable for all the problems addressed in this paper. We illustrate the methods using four practical examples in Section 5. Some concluding remarks are given in Section 6.

2 Fiducial approach

The fiducial CIs are determined by the percentiles of fiducial quantities of individual binomial parameters given in Krishnamoorthy and Lee.[9] To describe this procedure, let $X \sim$ binomial(n, p), and let $B_{a,b}$ denote the beta random variable with shape parameters a and b. It is well known that, for an observed value k of X, $P(X \geq k|n, p) = P\big(B_{k,n-k+1} \leq p\big)$ and $P(X \leq k|n, p) = P\big(B_{k+1,n-k} \geq p\big)$. On the basis of this relation, we see that there is a pair of fiducial distributions for p, namely, $B_{k,n-k+1}$ for setting lower limit for p and $B_{k+1,n-k}$ for setting upper limit for p. Indeed, the Clopper–Pearson exact $100(1-2\alpha)\%$ CI for p is given by $\big(B_{k,n-k+1;\alpha},\ B_{k-1,n-k;1-\alpha}\big)$, where $B_{a,b;\alpha}$ denotes the 100α percentile of the beta distribution. Instead of having two fiducial variables, a random quantity that is "stochastically between" $B_{k,n-k+1}$ and $B_{k+1,n-k}$ can be used as a single approximate fiducial variable for p. On the basis of Cai's[13] result, a simple choice is $B_{k+.5,n-k+.5}$. Furthermore, $B_{k+.5,n-k+.5}$ is the posterior distribution with respect to the Jeffreys prior $B_{1/2,1/2}$. Hypothesis test or CI for p can be obtained from the distribution of $B_{k+.5,n-k+.5}$. For example, the $100\frac{\alpha}{2}$ percentile and the $100\big(1-\frac{\alpha}{2}\big)$ percentile of $B_{k+.5,n-k+.5}$ form a $1-\alpha$ CI for p.

Let $X_1, \ldots, X_g$ be independent random variables with $X_i \sim$ binomial(n_i, p_i), $i = 1, \ldots, g$. Let $(k_1, \ldots, k_g)$ be an observed value of $(X_1, \ldots, X_g)$. A fiducial quantity for a real-valued function $h(p_1, \ldots, p_g)$ is given by $h\big(B_{k_1+.5,n_1-k_1+.5}, \ldots, B_{k_g+.5,n_g-k_g+.5}\big)$, and the appropriate percentiles of this fiducial quantity form a CI for $h(p_1, \ldots, p_g)$. For example, the lower 100α percentile and upper 100α percentile of $h\big(B_{k_1+.5,n_1-k_1+.5}, \ldots, B_{k_g+.5,n_g-k_g+.5}\big)$ form a $100(1-2\alpha)\%$ CI for $h(p_1, \ldots, p_g)$. This method may be appropriate as long as the percentiles of h are smooth and monotone. For a given $k_1, \ldots, k_g$, the distribution of $h\big(B_{k_1+.5,n_1-k_1+.5}, \ldots, B_{k_g+.5,n_g-k_g+.5}\big)$ does not depend on any unknown parameters, and so its percentiles can be estimated using Monte Carlo simulation or approximated for some functions as shown in the sequel. Furthermore, we note that the fiducial variable $B_{k_i+.5,n_i-k_i+.5}$ is defined for all possible values of $(k_1, \ldots, k_g)$, and so it does not require any modification to handle zero counts.

Closed-form approximate percentiles of fiducial quantity described in the preceding paragraph can be obtained for some commonly used functions of $(p_1, \ldots, p_g)$ such as the difference, relative risk, odds ratio, product $p_1 \times \cdots \times p_g$, and for a linear combination of $p_1, \ldots, p_g$. To find approximate percentiles, we shall use the modified-normal based approximation (MNA) due to Krishnamoorthy.[10] This MNA approximation is conducive to find percentiles of a linear combination of independent continuous random variables not necessarily from the same family. To outline the approximation, let $X_1, \ldots, X_g$ be independent continuous random variables, and let

$X_{i;\alpha}$ denote the 100α percentile of X_i, $i = 1, \ldots, g$. An approximation to the 100α percentile of a linear function $Q = \sum_{i=1}^{g} w_i X_i$, where w_i's are known constants, is given by

$$Q_\alpha \simeq \sum_{i=1}^{k} w_i E(X_i) - \left[\sum_{i=1}^{k} w_i^2 \left[E(X_i) - X_i^l\right]^2\right]^{\frac{1}{2}}, \quad \text{for } 0 < \alpha \leq .5 \tag{1}$$

where $X_i^l = X_{i;\alpha}$ if $w_i > 0$, and is $X_{i;1-\alpha}$ if $w_i < 0$. The upper percentile

$$Q_{1-\alpha} \simeq \sum_{i=1}^{k} w_i E(X_i) + \left[\sum_{i=1}^{k} w_i^2 [E(X_i) - X_i^u]^2\right]^{\frac{1}{2}}, \quad \text{for } 0 < \alpha \leq .5 \tag{2}$$

where $X_i^u = X_{i;1-\alpha}$ if $w_i > 0$, and is $X_{i;\alpha}$ if $w_i < 0$. The above approximations coincide with the exact ones when X_i's are independent $N(\mu_i, \sigma_i^2)$ random variables, and they can be used as approximations for other independent continuous random variables. Krishnamoorthy[10] showed several applications, including beta distribution, where the MNAs are very satisfactory.

The above approximation can also be used to find approximate percentiles of the ratio $R = X/Y$, where X and Y are independent continuous random variables with Y being positive. Noting that the α quantile c of X/Y is the root of the equation $P(X - cY \leq 0) = \alpha$, the root is approximated by setting the α quantile of $X - cY$ to zero, and solving the resulting equation for c. This approximation yields

$$R_\alpha \simeq \frac{\mu_x\mu_y - \left\{(\mu_x\mu_y)^2 - \left[\mu_y^2 - (Y_{1-\alpha} - \mu_y)^2\right]\left[\mu_x^2 - (\mu_x - X_\alpha)^2\right]\right\}^{\frac{1}{2}}}{\left[\mu_y^2 - (\mu_y - Y_{1-\alpha})^2\right]}, \quad 0 < \alpha \leq .5 \tag{3}$$

where $\mu_x = E(X)$ and $\mu_y = E(Y)$. The upper 100α percentile of X / Y can be obtained similarly and is given by

$$R_{1-\alpha} \simeq \frac{\mu_x\mu_y + \left\{(\mu_x\mu_y)^2 - \left[\mu_x^2 - (X_{1-\alpha} - \mu_x)^2\right]\left[\mu_y^2 - (\mu_y - Y_\alpha)^2\right]\right\}^{\frac{1}{2}}}{\left[\mu_y^2 - (\mu_y - Y_\alpha)^2\right]}, \quad 0 < \alpha \leq .5 \tag{4}$$

In the following sections, we shall apply the above MNA to find approximate percentiles of some functions of independent beta random variables and thereby obtain approximate CIs for various problems involving binomial parameters.

3 CIs

Let $X_1 \sim \text{binomial}(n_1, p_1)$ independently of $X_2 \sim \text{binomial}(n_2, p_2)$. In the following, we shall describe various methods for finding CIs for the difference between two binomial proportions, relative risk, odds ratio, and for a linear combination of proportions.

3.1 Difference

3.1.1 Fiducial CIs

The fiducial quantity for the difference $p_1 - p_2$ is given by $Q_D = B_{k_1+.5, n_1-k_1+.5} - B_{k_2+.5, n_2-k_2+.5}$, where (k_1, k_2) is an observed value of (X_1, X_2). The 100α and $100(1-\alpha)$ percentiles of Q_D form a $100(1 - 2\alpha)\%$ CI for $p_1 - p_2$. The percentiles of Q_D can be estimated using Monte Carlo simulation.

A closed-form approximation for the percentiles of Q_D can be obtained on the basis of MNA in equations (1) and (2) as follows. Let

$$\tilde{p}_i = \frac{k_i + .5}{n_i + 1}, \quad \text{and} \quad B_{i;\alpha} = B_{k_i+.5, n_i - k_i + .5; \alpha}, \quad i = 1, 2 \tag{5}$$

where $B_{a,b;\alpha}$ denotes the 100α percentile of the beta distribution with shape parameters a and b. In terms of these quantities, a lower 100α percentile of Q_D can be obtained from equation (1) as

$$Q_{D;\alpha} \simeq \tilde{p}_1 - \tilde{p}_2 - \left[\left(\tilde{p}_1 - B_{1;\alpha}\right)^2 + \left(\tilde{p}_2 - B_{2;1-\alpha}\right)^2\right]^{\frac{1}{2}}, \quad \text{for } 0 < \alpha \le .5 \tag{6}$$

and an approximate $100(1-\alpha)$ percentile is expressed as

$$Q_{D;1-\alpha} \simeq \tilde{p}_1 - \tilde{p}_2 + \left[\left(\tilde{p}_1 - B_{1;1-\alpha}\right)^2 + \left(\tilde{p}_2 - B_{2;\alpha}\right)^2\right]^{\frac{1}{2}}, \quad \text{for } 0 < \alpha \le .5 \tag{7}$$

The interval $(Q_{D;\alpha}, Q_{D;1-\alpha})$ is an approximate $100(1-2\alpha)\%$ CI for the difference $p_1 - p_2$.

3.1.2 The score CI

The well-known Wald statistic for testing $H_0 : p_1 - p_2 = d$ is given by

$$Z = \frac{\hat{p}_1 - \hat{p}_2 - d}{\sqrt{\frac{\hat{p}_1\hat{q}_1}{n_1} + \frac{\hat{p}_2\hat{q}_2}{n_2}}} \tag{8}$$

where $\hat{q}_i = 1 - \hat{p}_i, \ i = 1, 2$. The above Z statistic has an asymptotic standard normal distribution. The Wald CI is obtained by inverting the test based on Z. Instead of using the usual estimate of variance of $(\hat{p}_1 - \hat{p}_2)$ in equation (8), Miettinen and Nurminen[5] have used the variance estimate based on the MLE under the constraint that $p_1 = p_2 + d$. Specifically, they proposed the following test statistic

$$T_M = \frac{\hat{p}_1 - \hat{p}_2 - d}{[(\tilde{p}_2 + d)(1 - \tilde{p}_2 - d)/n_1 + \tilde{p}_2(1 - \tilde{p}_2)/n_2]^{\frac{1}{2}}\sqrt{R_n}} \tag{9}$$

where $R_n = (n_1 + n_2)/(n_1 + n_2 - 1)$, and $\tilde{p}_2$ is the maximum likelihood estimator under the constraint that $p_1 - p_2 = d$. Even though the constrained likelihood equation (a function of $\tilde{p}_2$) is a polynomial of order three, the likelihood equation has a unique closed-form solution; see Appendix I of Miettinen and Nurminen.[5] Since the constrained MLE is also a function of d, an approximate CI for $p_1 - p_2$ can be obtained by solving the equation $|T_M| = z_{1-\alpha/2}$ for d numerically. The R package "gsDesign" or the recent one "PropCIs" can be used to compute the score CI for $p_1 - p_2$.

3.2 Relative risk

3.2.1 Fiducial CIs

The fiducial variable for $R = p_1/p_2$ is given by $Q_R = B_{k_1+.5,n_1-k_1+.5}/B_{k_2+.5,n_2-k_2+.5}$, where (k_1,k_2) is an observed value of (X_1,X_2). Appropriate percentiles of Q_R form a CI for p_1/p_2. Using the MNA approximations in equations (3) and (4), we find the approximate $1-\alpha$ lower CL for R as

$$R_L = \frac{\tilde{p}_1\tilde{p}_2 - \sqrt{(\tilde{p}_1\tilde{p}_2)^2 - \left[\tilde{p}_2^2 - (u_2 - \tilde{p}_2)^2\right]\left[\tilde{p}_1^2 - (l_1 - \tilde{p}_1)^2\right]}}{\tilde{p}_2^2 - (u_2 - \tilde{p}_2)^2} \tag{10}$$

the approximate $1-\alpha$ upper confidence limit as

$$R_U = \frac{\widetilde{p_1}\widetilde{p_2} + \sqrt{(\widetilde{p_1}\widetilde{p_2})^2 - \left[\widetilde{p_1}^2 - (u_1 - \widetilde{p_1})^2\right]\left[\widetilde{p_2}^2 - (l_2 - \widetilde{p_2})^2\right]}}{\widetilde{p_2}^2 - (l_2 - \widetilde{p_2})^2} \tag{11}$$

where $\tilde{p}_i = \frac{k_i+.5}{n_i+1}$ and

$$(l_i, u_i) = \left(B_{k_i+.5, n_i-k_i+.5; \alpha/2}, B_{k_i+.5, n_i-k_i+.5; 1-\alpha/2}\right), \quad i = 1, 2$$

3.2.2 The score CIs

Miettinen and Nurminen's[5] CI for the relative risk $R = p_1/p_2$ is formed by the roots of the equation

$$\chi_R^2 = \frac{[\hat{p}_1 - R\hat{p}_2]^2}{\tilde{V}_{\hat{p}_1 - R\hat{p}_2}} \tag{12}$$

with

$$\tilde{V}_{\hat{p}_1 - R\hat{p}_2} = \frac{n_1 + n_2}{n_1 + n_2 - 1}\left[\frac{\widetilde{p_1}(1 - \widetilde{p_1})}{n_1} + R^2 \frac{\widetilde{p_2}(1 - \widetilde{p_2})}{n_2}\right] \tag{13}$$

In the above variance estimate, $\tilde{p}_2$ is estimated under the constraint that $\widetilde{p_1} = R\widetilde{p_2}$, and is the root of the equation

$$\widetilde{p_2} = \left[-B - \left(B^2 - 4AC\right)^{1/2}\right]/(2A) \tag{14}$$

with $A = R(n_1 + n_2)$, $B = -[Rn_1 + X_1 + n_2 + RX_2]$ and $C = X_1 + X_2$. The $100(1 - \alpha)\%$ CI is formed by the roots of the equation $\chi_R^2 = \chi_{1;1-\alpha}^2$. The R package "gsDesign" can be used to calculate the Miettinen–Nurminen[5] CI.

3.3 Odds ratio

Recall that (k_1,k_2) is an observed value of (X_1,X_2), where $X_1 \sim \text{binomial}(n_1,p_1)$ independently of $X_2 \sim \text{binomial}(n_2,p_2)$.

3.3.1 Fiducial CIs

Recall that a fiducial variable for p_i is given by $B_{k_i+.5, n_i-k_i+.5}$, where $B_{a,b}$ denotes the beta random variable with the shape parameters a and b. A fiducial quantity for the odds ratio $OR = [p_1/(1 - p_1)]/[p_2/(1 - p_2)]$ can be obtained by substitution and is given by

$$Q_{OR} = \frac{\left[B_{k_1+.5, n_1-k_1+.5}/(1 - B_{k_1+.5, n_1-k_1+.5})\right]}{\left[B_{k_2+.5, n_2-k_2+.5}/(1 - B_{k_2+.5, n_2-k_2+.5})\right]} = \frac{G_1}{G_2}, \text{ say} \tag{15}$$

Percentiles of Q_{OR}, which can be estimated using Monte Carlo simulation, form a CI for the odds ratio. Since Q_{OR} is the ratio of two independent positive random variables, we can approximate the percentiles using equations (3) and (4). However, these approximations are valid only when

$n_i - k_i \geq 1$, because the required expectation for the approximation is $E(B_{a,b}/\ (1 - B_{a,b})) = a/(b-1)$, which exists only when $b > 1$, or in the present context $n_i - k_i \geq 1$. To avoid this restriction, we approximate the percentiles of $\ln G_1 - \ln G_2$ from which percentiles of Q_{OR} can be obtained. Specifically, noting that $\ln Q_{OR} = \ln G_1 - \ln G_2$, we can use equations (1) and (2) to find approximate percentiles of $\ln Q_{OR}$ as follows.

Noting that $E(\ln B_{a,b}) = \psi(a) - \psi(a+b)$, where ψ is the digamma function, we find

$$\mu_{g1} = E\ln(G_1) = \psi(k_1 + .5) - \psi(n_1 + 1) \quad \text{and} \quad \mu_{g2} = E\ln(G_2) = \psi(k_2 + .5) - \psi(n_2 + 1)$$

Furthermore

$$G_{1;\alpha} = \ln\left[\frac{B_{k_1+.5,n_1-k_1+.5;\alpha}}{\left(1 - B_{k_1+.5,n_1-k_1+.5;\alpha}\right)}\right], \quad \text{and} \quad G_{2;\alpha} = \ln\left[\frac{B_{k_2+.5,n_2-k_2+.5;\alpha}}{\left(1 - B_{k_2+.5,n_2-k_2+.5;\alpha}\right)}\right] \tag{16}$$

Using the above expectations and percentiles in equation (1), we find the approximate 100α percentile of $\ln Q_{OR}$ as

$$\ln Q_{OR;\alpha} \simeq \mu_{g1} - \mu_{g2} - \left\{(\mu_{g1} - G_{1;\alpha})^2 + (\mu_{g2} - G_{2;1-\alpha})^2\right\}^{1/2}, \quad 0 < \alpha < .5 \tag{17}$$

and the approximate $100(1-\alpha)$ percentile as

$$\ln Q_{OR;1-\alpha} \simeq \mu_{g1} - \mu_{g2} + \left\{(\mu_{g1} - G_{1;1-\alpha})^2 + (\mu_{g2} - G_{2;\alpha})^2\right\}^{1/2}, \quad 0 < \alpha \leq .5 \tag{18}$$

Exponentiating the above percentiles, we can find approximate percentiles of Q_{OR}. Our preliminary numerical investigation suggested that the above approximation is satisfactory only when $\min\{k_1, n_1 - k_1, k_2, n_2 - k_2\} \geq 2$, equivalently, all cell entries in a 2×2 table are two or more. So we recommend this approximation when this condition is met and to use the simulation for other cases.

3.3.2 Score CIs

Miettinen and Nurminen[5] have proposed a score CI for the ratio of odds, and it is described as follows. Define

$$\chi^2_\xi = [n_1(\hat{p}_1 - \tilde{p}_1)]^2\left[\frac{1}{n_1\tilde{p}_1(1-\tilde{p}_1)} + \frac{1}{n_2\tilde{p}_2(1-\tilde{p}_2)}\right]\left(\frac{n_1 + n_2 - 1}{n_1 + n_2}\right) \tag{19}$$

where

$$\tilde{p}_1 = \tilde{p}_2\xi/[1 + \tilde{p}_2(\xi - 1)] \quad \text{and} \quad \tilde{p}_2 = [-B + (B^2 - 4AC)^{1/2}]/(2A)$$

with $A = n_2(\xi - 1)$, $B = n_1(\xi) + n_2 - (X_1 + X_2)(\xi - 1)$ and $C = -(X_1 + X_2)$. Then the $100(1-\alpha)\%$ CI is formed by the values of ζ that satisfy

$$\chi^2_\zeta = \chi^2_{1-\alpha} \tag{20}$$

The R package "gsDesign" is available to find the roots of the above equation, and these roots form a $1-\alpha$ CI for the odds ratio.

3.4 Coverage and precision studies

To judge the coverage properties of the approximate CIs in the earlier sections and to compare them, we evaluated their exact coverage probabilities using the binomial probabilities for each pair of observed samples. Specifically, for a given (n_1, p_1, n_2, p_2), the exact coverage probability of a $100(1-\alpha)\%$ CI for $(L(X_1, X_2), U(X_1, X_2))$ is given by

$$\sum_{x_1=0}^{n_1}\sum_{x_2=0}^{n_2}\binom{n_1}{x_1}p_1^{x_1}(1-p_1)^{n_1-x_1}\binom{n_2}{x_2}p_2^{x_2}(1-p_2)^{n_2-x_2}I_{[(L(x_1,x_2),U(x_1,x_2))]}(p_1/p_2) \tag{21}$$

where $I_{[A]}(x)$ is the indicator function. For an accurate CI, the above coverage probability should be close to the nominal level $1-\alpha$.

In Table 1, we reported the coverage probabilities of the fiducial CIs (6) and (7) and the score CIs based on equation (9) for the difference of proportions. We chose the sample size and parameter configurations as given in Miettinen and Nurminen.[5] We reported error rates for lower bound (ER_L), upper bounds (ER_U), and the total error rates (ER) along with the expected widths. Examination of table values indicates that both CIs are in general quite comparable with respect to coverage and precision. There are cases where the fiducial CIs are shorter than the corresponding score CIs while maintaining the coverage probabilities close to the nominal level .95. We also plotted the coverage probabilities of these two CIs in Figure 1. The coverage probabilities were computed for moderate to large sample sizes as shown in Figure 1. The plots in Figure 1 clearly indicate that both methods are quite comparable with respect to coverage probabilities in most cases, and the score CIs are more liberal than the fiducial CIs in some cases; see the last two plots in Figure 1.

Table 1. Error rates (%) for 95% confidence intervals for the difference for lower bound (ER_L), upper bound (ER_U), and expected width (EW).

				Score				Fiducial			
p_1	p_2	n_1	n_2	ER_L	ER_U	ER	EW	ER_L	ER_U	ER	EW
0.5	0.5	10	10	2.1	2.1	4.2	.79	2.1	2.1	4.2	.75
		10	50	2.4	2.4	4.8	.60	2.8	2.8	5.6	.59
		25	10	2.5	2.5	5.0	.66	2.6	2.6	5.2	.64
0.2	0.2	25	25	2.7	2.8	5.5	.45	2.7	2.7	5.4	.42
		50	50	2.4	2.4	4.8	.31	2.6	2.6	5.2	.31
		25	125	3.0	1.8	4.8	.34	2.6	2.4	5.0	.33
0.1	0.1	50	50	2.4	2.4	4.8	.25	2.9	2.9	5.8	.23
		50	250	3.1	1.4	4.5	.19	2.7	2.5	5.2	.18
		250	50	1.4	3.2	4.6	.19	2.5	2.7	5.2	.18
0.65	0.35	10	10	1.9	2.2	4.1	.76	1.9	3.2	5.1	.72
		10	50	2.0	2.7	4.7	.57	2.6	2.7	5.3	.57
		50	50	2.1	2.5	4.6	.37	2.1	2.5	4.6	.36
0.35	0.05	50	50	2.4	2.4	4.8	.29	1.7	3.4	5.1	.29
		50	250	2.7	2.3	5.0	.26	2.4	2.6	5.0	.26
		250	50	2.0	3.0	5.0	.18	1.5	3.7	5.2	.17
0.15	0.05	50	50	3.3	1.9	5.2	.25	1.7	3.7	5.4	.23
		50	250	3.1	1.6	4.7	.21	2.4	2.7	5.1	.20
		250	50	1.2	3.1	4.3	.17	2.0	3.3	5.3	.15

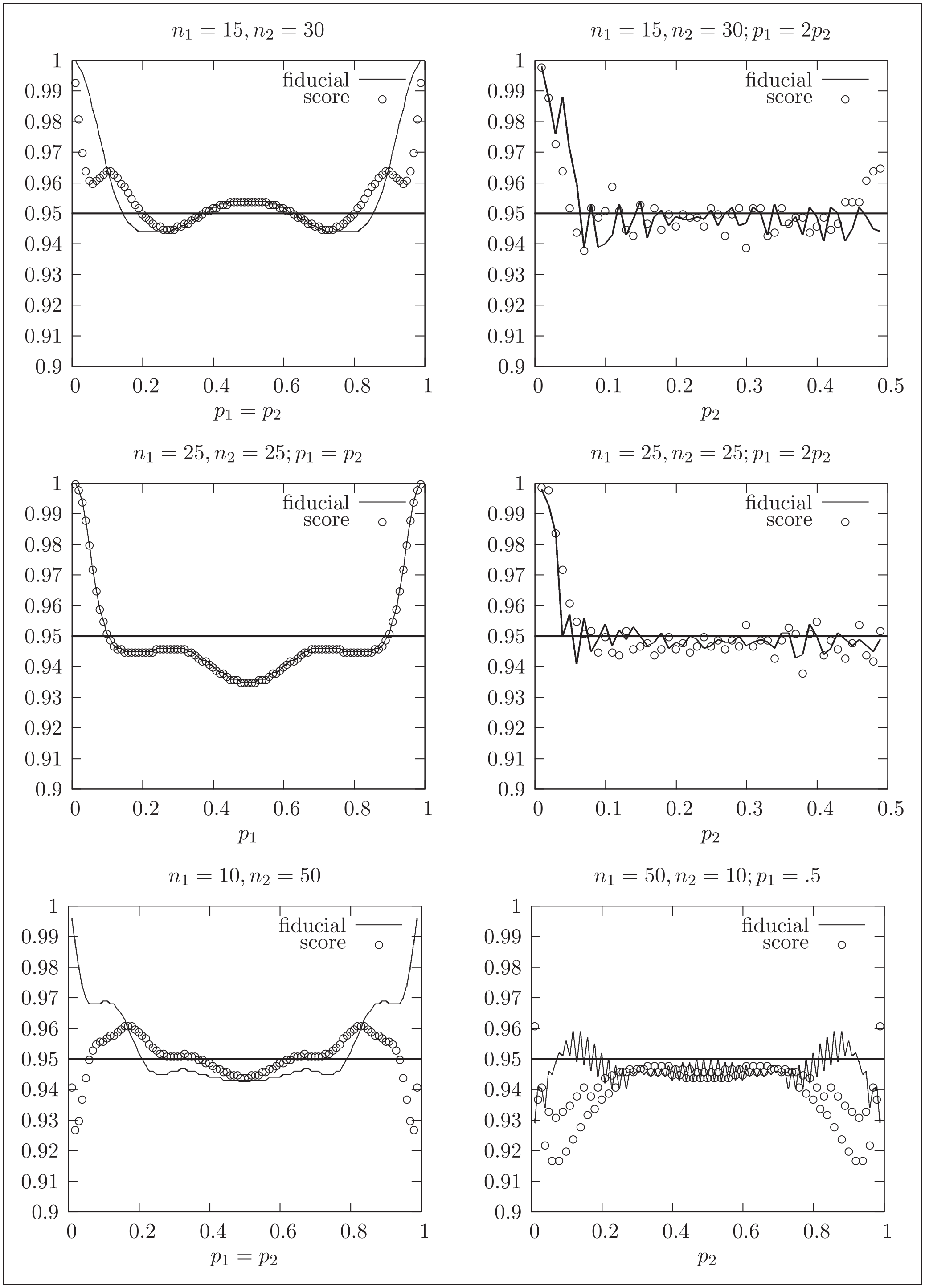

Figure 1. Coverage probabilities of 95% fiducial and score CIs for the difference $p_1 - p_2$.

The coverage probabilities of the fiducial CIs in equations (10) and (11) and the score CIs based on equation (12) for the relative risk are reported in Table 2 for the same sample size and parameter configurations given in Miettinen and Nurminen.[5] The expected width of the score CIs is infinite in most cases because the score CIs are defined to be $(0, \infty) \approx (0, 10^7)$ for sample points (X_1, X_2) at the boundaries. On the other hand, the expected width of the fiducial CIs is always finite because the fiducial CIs are always a finite interval. In cases where the probabilities at the boundaries are very close to zero, the expected widths of the score CIs are finite (at least practically). In those cases, the fiducial CIs and the score CIs have similar expected widths. These findings suggest that the score and fiducial CIs should be similar for nonextreme values. Notice that the coverage probabilities of both CIs are similar for most cases, and the fiducial CIs could be slightly liberal for some cases. We also plotted coverage probabilities of these two CIs in Figure 2. We once again observe that these two CIs perform similar in terms of coverage probabilities. For the parameter values at the boundary, the score CIs could be liberal while the fiducial CIs could be conservative (see the plot for $n_1 = 10$, $n_2 = 50$).

To compare the CIs for the odds ratio, we calculated the exact coverage probabilities and expected widths of CIs for the sample size and parameter configurations given in Miettinen and Nurminen[5] and reported them in Table 3. We here see that the fiducial CIs could be somewhat liberal than the score CIs; however, the coverage probabilities are not far from the nominal level. As the fiducial CIs are finite for all sample points, they have finite expected widths whereas the score CIs have infinite expected width for all the cases considered. This is because the score CIs for the odds ratio are defined as infinite intervals for sample points at the boundaries. In order to compare the CIs over a wide range of parameter space, we plotted the coverage probabilities for various

Table 2. Error rates (%) for 95% confidence intervals for the relative risk for lower bound (ER_L), upper bound (ER_U), and expected width (EW).

				Score				Fiducial			
p_1	p_2	n_1	n_2	ER_L	ER_U	ER	EW	ER_L	ER_U	ER	EW
0.5	0.5	10	10	2.1	2.1	4.2	∞	2.1	2.1	4.2	13.3
		10	50	2.8	2.8	5.6	1.30	2.8	2.8	5.6	1.29
		25	10	2.5	2.5	5.0	∞	2.6	2.6	5.2	13.1
0.2	0.2	25	25	2.7	2.7	5.4	∞	2.7	2.7	5.4	45.91
		50	50	2.6	2.6	5.2	∞	2.6	2.6	5.2	2.43
		25	125	3.2	1.8	5.0	1.80	2.6	2.4	5.0	1.81
0.1	0.1	50	50	2.5	2.5	5.0	∞	3.0	3.0	6.0	62.8
		50	250	3.2	1.5	4.7	2.0	2.7	2.5	5.2	1.99
		250	50	1.5	3.2	4.7	∞	2.5	2.7	5.2	58.1
0.65	0.35	10	10	1.9	2.5	4.4	∞	1.6	3.1	4.7	188
		10	50	2.2	2.8	5.0	∞	1.9	2.9	4.8	2.31
		50	50	2.2	2.8	5.0	∞	2.1	2.8	4.9	1.84
0.35	0.05	50	50	0.0	3.6	3.6	∞	2.9	2.8	5.7	2828
		50	250	2.0	2.8	4.8	∞	2.3	2.7	5.0	12.4
		250	50	0.0	3.7	3.7	∞	4.2	2.7	6.9	2808
0.15	0.05	50	50	1.0	3.2	4.2	∞	2.6	2.8	5.4	1258
		50	250	2.4	2.3	4.7	∞	2.4	2.6	5.0	6.70
		250	50	0.0	3.7	3.7	∞	3.2	2.8	6.0	1213

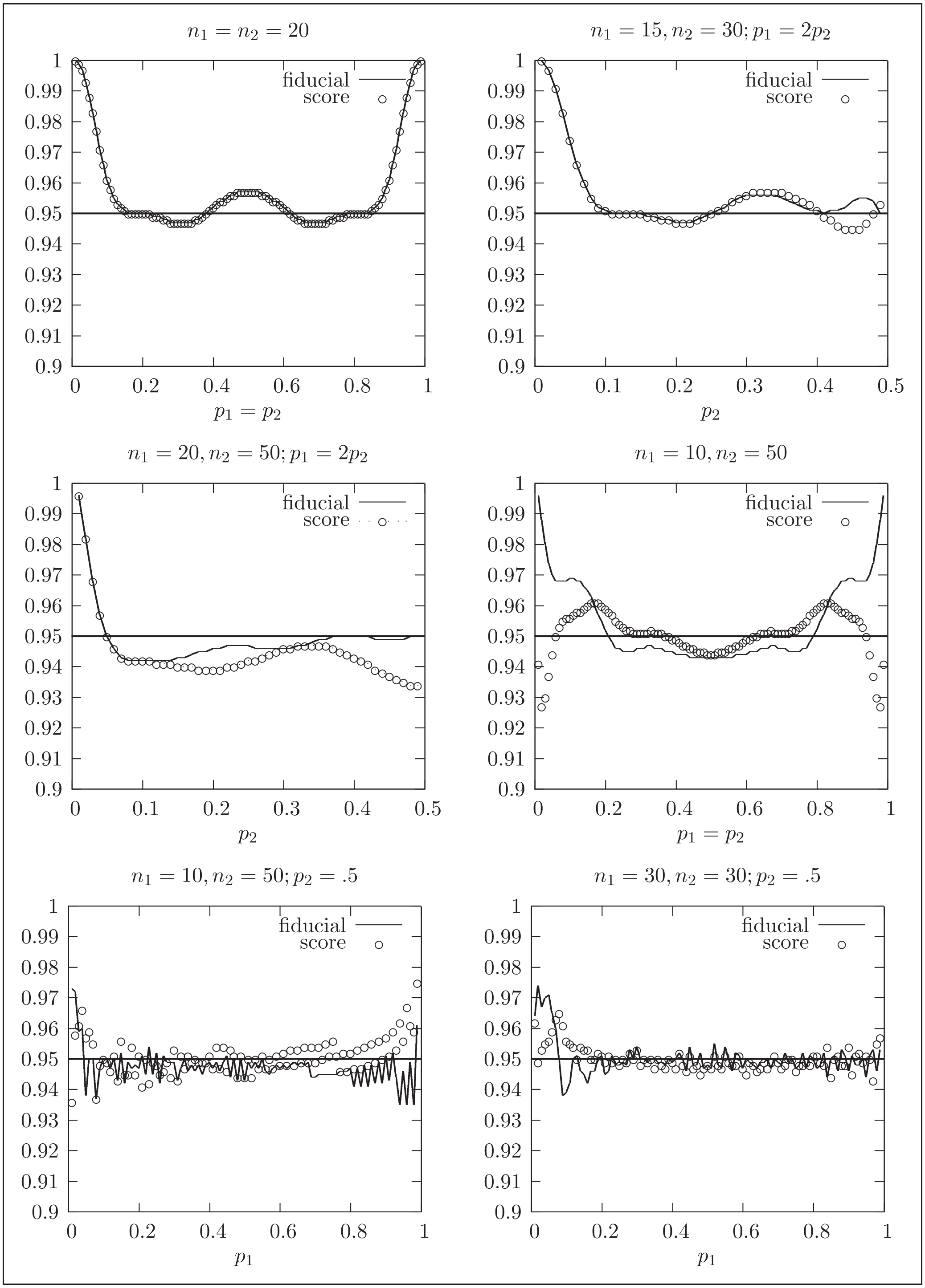

Figure 2. Coverage probabilities of 95% fiducial and score CIs for the relative risk.

parameter values and sample sizes in Figure 3. These plots of coverage probabilities also indicate that the fiducial CIs are slightly more liberal than the score CIs, but the coverage probabilities seldom fall below .94 when the nominal level is .95.

4 CIs for a linear function of proportions

We shall now consider the problem of finding CIs for $W = \sum_{i=1}^{g} w_i p_i$, where $w_1, \ldots, w_g$ are specified values, based on independent random variables $X_1, \ldots, X_g$ with $X_i \sim \text{binomial}(n_i, p_i)$, $i = 1, \ldots, g$.

4.1 Fiducial CIs

A fiducial CI for $\eta = \sum_{i=1}^{g} w_i p_i$ is formed by the percentiles of the fiducial quantity $W = \sum_{i=1}^{g} w_i B_{k_i+.5, n_i-k_i+.5}$, where $(k_1, \ldots, k_g)$ is an observed value of $(X_1, \ldots, X_g)$. The percentiles of this fiducial quantity can be approximated using the MNA in Section 3.2.2. In particular, noting that $E(B_i) = (k_i + .5)/(n_i + 1)$, one can find approximations to the percentiles of W. Our preliminary investigations indicated that a better approximation for the percentiles of W can be obtained by using $E(B_i) \simeq \hat{p}_i = k_i/n_i$, $i = 1, \ldots, g$. Letting $(l_i, u_i) = \left(B_{k_i+.5, n_i-k_i+.5;\alpha}, B_{k_i+.5, n_i-k_i+.5;1-\alpha}\right)$, for $0 < \alpha \leq .5$, we find

$$W_\alpha \simeq \sum_{i=1}^{g} w_i \hat{p}_i - \sqrt{\sum_{i=1}^{g} w_i^2 \left(\hat{p}_i - l_i^*\right)^2}, \quad \text{with} \quad l_i^* = \begin{cases} l_i & \text{if} \quad w_i > 0, \\ u_i & \text{if} \quad w_i < 0 \end{cases} \tag{22}$$

Table 3. Error rates (%) for 95% confidence intervals for the odds ratio for lower bound (ER_L), upper bound (ER_U), and expected width (EW).

				Score				Fiducial			
p_1	p_2	n_1	n_2	ER_L	ER_U	ER	EW	ER_L	ER_U	ER	EW
0.5	0.5	10	10	2.1	2.1	4.2	∞	2.6	2.6	5.2	91.4
		10	50	2.4	2.4	4.8	∞	2.8	2.8	5.6	28.1
		25	10	2.5	2.5	5.0	∞	3.2	3.2	6.4	30.9
0.2	0.2	25	25	2.7	2.7	5.4	∞	2.7	2.7	5.4	62.0
		50	50	2.4	2.4	4.8	∞	2.6	2.6	5.2	3.26
		25	125	3.2	1.8	5.0	∞	2.7	2.9	5.6	2.70
0.1	0.1	50	50	2.4	2.4	4.8	∞	3.0	3.0	6.0	70.2
		50	250	3.2	1.5	4.7	∞	2.5	2.8	5.3	2.37
		250	50	1.9	3.9	5.8	∞	2.8	2.5	5.3	64.8
0.65	0.35	10	10	1.9	2.0	3.9	∞	5.0	2.0	7.0	4734
		10	50	2.1	2.7	4.8	∞	2.8	2.6	5.4	605
		50	50	2.3	2.4	4.7	∞	2.8	2.4	5.2	7.62
0.35	0.05	50	50	2.3	2.4	4.7	∞	3.5	2.7	6.2	4587
		50	250	2.6	2.6	5.2	∞	2.8	2.2	5.0	23.7
		250	50	0.0	3.7	3.7	∞	3.8	2.6	6.4	4366
0.15	0.05	50	50	1.0	3.1	4.1	∞	2.8	2.3	5.1	1519
		50	250	2.8	2.1	4.9	∞	2.7	2.5	5.2	9.0
		250	50	0.0	3.8	3.8	∞	3.2	2.6	5.8	1435

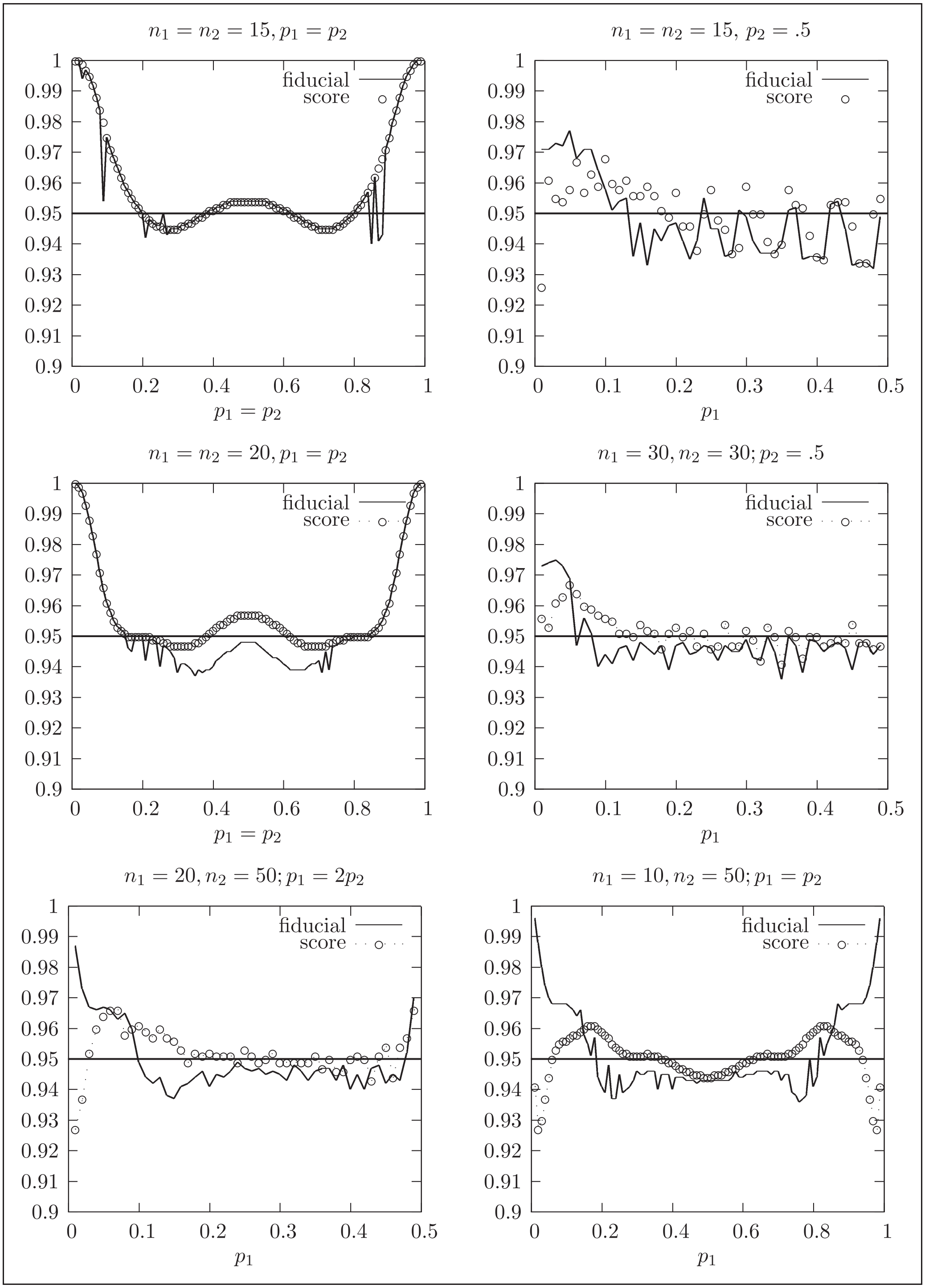

Figure 3. Coverage probabilities of 95% fiducial and score CIs for odds ratio.

and

$$W_{1-\alpha} \simeq \sum_{i=1}^{g} w_i \hat{p}_i + \sqrt{\sum_{i=1}^{g} w_i^2 \left(\hat{p}_i - u_i^*\right)^2}, \quad \text{with} \quad u_i^* = \begin{cases} u_i & \text{if} \quad w_i > 0, \\ l_i & \text{if} \quad w_i < 0 \end{cases} \tag{23}$$

The interval $(W_\alpha, W_{1-\alpha})$ is an approximate $100(1-2\alpha)\%$ two-side CI for $\eta = \sum_{i=1}^{g} w_i p_i$.

4.2 Score CIs

Let $\hat{\eta} = \sum_{i=1}^{g} w_i \hat{p}_i$. Consider testing

$$H_0 : \eta = \eta_0 \text{ vs. } H_1 : \eta \neq \eta_0 \tag{24}$$

where η_0 is a specified value. Let $S = \sum_{i=1}^{g} w_i p_i$. Then

$$z_0 = \frac{\hat{\eta} - \eta_0}{\sqrt{V_0}} \sim N(0, 1) \text{ asymptotically} \tag{25}$$

where $V_0 = \sum_{i=1}^{g} w_i^2 \widetilde{p}_{i0}(1 - \widetilde{p}_{i0})/n_i$, and the $\widetilde{p}_{i0}$ is the MLE of p_i obtained under $H_0 : \sum_{i=1}^{g} w_i p_i = \eta_0$. To calculate z_0, let $S_w = \sum_{i=1}^{g} w_i$ and $N = \sum_{i=1}^{g} n_i$. The value of z_0^2 is determined by

$$y(z_0^2) = N + (S_w - 2\eta)C - \sum_{i=1}^{g} R_i = 0 \tag{26}$$

where $C = z_0^2/(\hat{\eta} - \eta_0)$, $R_i^2 = n_i^2 + 2n_i w_i b_i C + w_i^2 C^2$ and $b_i = 1 - 2\hat{p}_i$ with $\hat{p}_i = k_i/n_i$, $i = 1, \ldots, g$. Andrés and Hernández[1] noted that, in order to carry out a test for equation (24), the value of z_0 is not needed, and the null hypothesis in equation (24) is rejected if $y(z_{1-\alpha/2}^2) \geq 0$, where z_q is the 100 q percentile of the standard normal distribution.

The endpoints of the score CI are determined by the roots (with respect to η) of the equation $y(z_{1-\alpha/2}^2) = 0$. Even though the score test is easy to apply, finding the CI requires a numerical iterative method, and the program Z_LINEAR_K.EXE posted at www.ugr.es/local/bioest can be used.

4.3 Simulation studies for linear function of proportions

We evaluated coverage probabilities of the fiducial CIs in equations (22) and (23) and of the score CIs by Andrés and Hernández[1] for linear combinations of proportions and reported them in Table 4. We chose the same sample size, parameter, and weight configurations as given in Table 4 of Andrés and Hernández[1] for easy comparison purpose. We estimated coverage probabilities at 1000 points (p_1,p_2,p_3) randomly generated from uniform (.001, .999) distributions and reported the mean and the minimum coverage probabilities, and the expected widths for each sample size configuration in Table 4. Examination of table values indicates that the minimum coverage probabilities of the fiducial CIs are closer to the nominal level than those of the score CIs for many cases. These two CIs are quite similar in terms of coverage probabilities and expected widths even though the fiducial CIs are slightly better in some cases. Furthermore, the score test as described in Section 4.2 is easy to apply while finding the score CIs is numerically involved. On the other hand, the fiducial CIs are easy to compute as they require only beta percentage points.

Table 4. Coverage probability (CP) and expected width (EW) of 95% CIs for linear function of proportions.

Model	Methods					
	Score			Fiducial		
(n_1, n_2, n_3)	Mean CP	Min CP	EW	Mean CP	Min CP	EW
$g = 3$						
$w_i = (1/3, 1/3, 1/3)$						
(10,10,10)	.944	.899	.27	.946	.902	.27
(30,30,30)	.948	.929	.16	.949	.936	.16
(30,10,10)	.950	.902	.24	.947	.924	.24
(30,20,10)	.951	.930	.22	.948	.933	.21
$w_i = (1, -1/2, -1/2)$						
(10,10,10)	.951	.924	.58	.949	.920	.56
(30,30,30)	.949	.939	.35	.948	.935	.34
(30,10,10)	.944	.924	.44	.947	.918	.43
(30,20,10)	.947	.929	.41	.947	.930	.40
$w_i = (-1, 1/2, 2)$						
(10,10,10)	.954	.916	1.07	.948	.924	1.05
(30,30,30)	.951	.944	.64	.950	.936	.64
(30,10,10)	.955	.898	.99	.950	.921	.96
(30,20,10)	.955	.889	.97	.951	.919	.95
$w_i = (1, 1, -1)$						
(10,10,10)	.943	.921	.82	.945	.909	.80
(30,30,30)	.948	.924	.49	.947	.930	.49
(30,10,10)	.950	.918	.73	.945	.915	.71
(30,20,10)	.951	.930	.65	.945	.930	.63
$g = 4$						
$w_i = (1/4, 1/4, 1/4, 1/4)$						
(10,10,10,10)	.938	.917	0.24	.945	.926	0.23
(20,20,20,20)	.945	.929	0.17	.947	.937	0.17
(20,20,10,10)	.944	.931	0.21	.946	.935	0.20
(20,15,10,5)	.951	.931	0.24	.948	.929	0.23
$w_i = (-1, 1, -1, 1)$						
(10,10,10,10)	.938	.920	0.94	.946	.920	0.93
(20,20,20,20)	.945	.921	0.69	.947	.936	0.69
(20,20,10,10)	.944	.930	0.83	.947	.934	0.82
(20,15,10,5)	.951	.929	0.96	.947	.931	0.94
$w_i = (1/3, 1/3, 1/3, 1)$						
(10,10,10,10)	.953	.928	0.54	.948	.934	0.52
(20,20,20,20)	.952	.943	0.39	.948	.939	0.39
(20,20,10,10)	.954	.935	0.52	.948	.932	0.50
(20,15,10,5)	.956	.903	0.65	.951	.920	0.64
$w_i = (-3, -1, 1, 3)$						
(10,10,10,10)	.950	.932	2.12	.948	.934	2.09
(20,20,20,20)	.947	.938	1.53	.948	.939	1.52
(20,20,10,10)	.952	.939	1.85	.949	.933	1.78
(20,15,10,5)	.956	.923	2.23	.949	.933	2.18

5 Examples

Example 1: This example along with data is taken from Agresti and Min.[4] The original source of data is Okumura et al.[14] A study of preterm infants who required mechanical ventilation was conducted on infants born between 27 and 32 weeks gestational period. The study compared 26 infants with periventricular leukomalacia and 26 infants with normal development on various characteristics. Results on neonatal adverse event are given in Table 5.

The sample odds ratio is 2.08. The exact conditional approach (Cornfield[2]) produced 95% CI for the odds ratio as (0.1, 127.3). The 95% CI based on the unconditional approach by Agresti and Min[4] is (.2, 29.4). The score method by Miettinen and Nurminen[5] yielded (.25, 17.1). The fiducial approach based on Monte Carlo simulation with 1000,000 runs is (.21, 27.4). To find the approximate fiducial CI, we found

$$\frac{B_{k_1+.5,n_1-k_1+.5;.025}}{1-B_{k_1+.5,n_1-k_1+.5;.025}}=.0166,\ \frac{B_{k_1+.5,n_1-k_1+.5;.975}}{1-B_{k_1+.5,n_1-k_1+.5;.975}}=.2896,\ \frac{B_{k_2+.5,n_2-k_2+.5;.025}}{1-B_{k_2+.5,n_2-k_2+.5;.025}}=.0042,$$

and

$$\frac{B_{k_2+.5,n_2-k_2+.5;.975}}{1-B_{k_2+.5,n_2-k_2+.5;.975}}=.1191.$$

Using these percentiles in equations (17) and (18), we calculated the approximate fiducial CI as (.21, 27.4). Notice that the fiducial CI based on the simulation and the one based on the approximation is the same, and these two CIs are in some agreement with that of Agresti and Min[4] whereas the score CI is not in agreement.

Example 2: To assess the effectiveness of a diagnostic test for detecting a certain disease, Koopman[15] reports that 36 out of 40 diseased persons were correctly diagnosed by the test and 16 out of 80 nondiseased persons were incorrectly diagnosed. These data were used by several authors to illustrate their methods for finding CIs for the ratio of proportions. Let p_t and p_f denote, respectively, the true positive diagnoses and false positive diagnoses. The ratio p_t/p_f is often referred to as the positive likelihood ratio. We shall find 95% CIs for p_t/p_f. Noticing that $\hat{p}_t = 0.9$ and $\hat{p}_f = 0.2$, we get the point estimate for the ratio p_t/p_f as 4.5.

The 95% fiducial CIs are computed by simulating the ratio $B_{36.5,4.5}/B_{16.5,64.5}$ 100,000 times, and using the approximations (10) and (11). To compute the approximate fiducial CI, we note that $\widetilde{p}_1 = .8902$, $\widetilde{p}_2 = .2037$, $l_1 = B_{36.5,4.5,.025} = .8902$, $u_1 = B_{36.5,4.5,.975} = .2037$, $l_2 = B_{16.5,64.5,.025} = .1239$, and $u_2 = B_{16.5,64.5,.975} = .2974$. Substituting these numbers in equations (10) and (11), we found the approximate fiducial CI as (2.94, 7.23). Bedrick[6] calculated several CIs from a family of CIs, and the

Table 5. Responses from two infant groups on neonatal adverse event.

	Response	
Group	Yes	No
PVL	2	24
Control	1	25

shorter ones are reported in the following table. In the following table, we first note that the fiducial CIs based on simulation and the approximation are the same. The CIs by Bedrick,[6] the score method, and the fiducial method are in very close agreement.

95% confidence intervals for p_t/p_f

Method	Confidence intervals
Bailey[7]	(2.95, 7.30)
Bedrick[6]	(2.93, 7.10)
Score	(2.93, 7.17)
Fiducial approach using simulation	(2.92, 7.23)
Approx. fiducial	(2.94, 7.23)

Example 3: Birkefle et al.[16] conducted a study to identify and compare traditional Chinese medicine (TCM) patterns and recommended acupuncture points in infertile and fertile women. A cross-sectional study examined the distribution of TCM patterns and acupuncture points among 24 infertile and 24 fertile women, and the results for TCM patterns are reported in Table 6. The hypothesis of interest here is that fertile and infertile women differ in occurrence of TCM patterns. Birkeflet et al.[16] used the odds ratio as the effective measure.

In Table 6, we reported 95% CIs of the odds ratio using the score, fiducial, and exact methods. Even though there are differences among the CIs by various methods, the conclusion based on all three CIs for each pattern is the same. In most cases, the score CIs are in agreement with the corresponding fiducial CIs. The exact CIs are in general wider than those based on the other two methods.

In order to illustrate the methods for finding CIs for the difference between two proportions, we shall use the data in Table 6. We calculated 95% CIs for the difference of proportions in fertile and

Table 6. The prevalence of traditional Chinese medicine (TCM) patterns on infertile and fertile women with 95% CI for the odds ratio of fertile versus infertile.

TCM	Fertile ($n = 24$)	Infertile ($n = 24$)	OR	Score	Fiducial	Mid-p exact
Liver-Yang rising	12	4	5.00	(1.34, 18.4)	(1.40, 20.5)	(1.30, 20.9)
Liver-Blood deficiency	9	13	0.51	(.16, 1.60)	(.16, 1.58)	(.16, 1.65)
Spleen-Qi deficiency	23	22	2.09	(.25, 17.2)	(.21, 27.3)	(.15, 64.2)
Spleen-Yang deficiency	3	10	0.20	(.05,.82)	(.04,.78)	(.04,.86)
Kidney-Yang deficiency	5	15	0.16	(.04,.56)	(.04,.54)	(.04,.58)
Kidney-Yin deficiency	20	10	7.00	(1.86, 26.0)	(1.96, 29.1)	(1.80, 29.2)
Heat	9	1	13.8	(1.96, 92.4)	(2.16,147.5)	(1.88, 316.7)
Blood stasis	14	15	0.84	(.27, 2.66)	(.26, 2.67)	(.26, 2.74)
Stagnant blood due to cold	2	6	0.27	(.06, 1.38)	(.04, 1.36)	(.04, 1.58)
Qi stagnation and blood	2	9	0.15	(.03,.74)	(.03,.70)	(.02,.77)
Damp	19	10	5.32	(1.50, 18.7)	(1.57, 20.3)	(1.46, 20.1)
Cold	3	11	0.17	(.04,.69)	(.04,.66)	(.03,.72)

infertile women using the score and fiducial methods and reported them in Table 7. All fiducial CIs were calculated using the approximations in equations (1) and (2). We once again observe that these two CIs are in good agreement for all the cases. Furthermore, the conclusions based on the CIs for odds ratios and those based on the CIs for the difference are the same.

Example 4: To compare the methods for situations with zero counts, let us consider the case where $n_1 = 24$, $n_2 = 36$, and the number of successes k_1 and k_2 is as given in Table 8. We computed 95% CIs for the difference, relative risk, and odds ratio using the different methods in the preceding sections and present them in Table 8. From the results in Table 8, we see that the conclusions based on both CIs are the same for estimating the difference, relative risk, and odds ratio. However, the fiducial CIs are always finite whereas the score CIs are not finite for estimating the relative risk and odds ratio. Furthermore, we note that the fiducial CIs are shorter than the corresponding score CIs when $(k_1,k_2) = (0,4)$.

Example 5: In a study by Cohen et al.,[17] 120 rats were randomly assigned to four diets as presented in Table 9. The absence or presence of a tumor was recorded for each rat. The data and the contrast $L_i = (l_{i1}, \ldots, l_{i4})$, $i = 1, 2, 3$ of interest are taken from Andrés and Hernández,[1] and they are

Table 7. The prevalence of traditional Chinese medicine (TCM) patterns on infertile and fertile women with 95% CI for the difference between proportions in fertile and infertile groups.

TCM	Fertile ($n=24$)	Infertile ($n=24$)	Difference	Score	Fiducial
Liver-Yang rising	12	4	.333	(.066, .560)	(.065, .546)
Liver-Blood deficiency	9	13	−.167	(−.425, .116)	(−.416, .113)
Spleen-Qi deficiency	23	22	.042	(−.134, .226)	(−.104, .192)
Spleen-Yang deficiency	3	10	−.292	(−.517, −.040)	(−.500, −.040)
Kidney-Yang deficiency	5	15	−.417	(−.635, −.138)	(−.622, −.137)
Kidney-Yin deficiency	20	10	.417	(.145, .633)	(.143, .618)
Heat	9	1	.333	(.116, .543)	(.108, .522)
Blood stasis	14	15	−.042	(−.309, .232)	(−.302, .226)
Stagnant blood due to cold	2	6	.167	(−.385, .052)	(−.362, .045)
Qi stagnation and blood	2	9	.292	(−.510, −.056)	(−.490, −.055)
Damp	19	10	.375	(.098, .600)	(.097, .587)
Cold	3	11	−.333	(−.556, −.077)	(−.539, −.076)

Table 8. 95% confidence intervals for samples with zero count.

	$k_1 = 4, k_2 = 0$		$k_1 = 0, k_2 = 4$	
	Score	Fiducial	Score	Fiducial
Difference	(.0592, .3603)	(.0342, .3361)	(−.2546, .0352)	(−.2245, .0125)
Relative risk	(1.624, ∞)	(1.824, 13294)	(0, 1.3505)	(.0002, 1.213)
Odds ratio	(1.713, ∞)	(1.973, 17051)	(0, 1.3703)	(.0001, 1.219)

presented in Table 9. These authors have proposed several CIs, and among them the CI based on the score method seems to be the best. Our 95% fiducial CI for $\sum_{j=1}^{4} l_{ij}p_j$ is formed by the lower 2.5th percentile and the upper 2.5th percentile of $\sum_{j=1}^{4} l_{ij}B_{k_j+.5,n_j-k_j+.5}$, and these percentiles can be obtained using equations (1) and (2).

Our fiducial CIs along with the score CIs by Andrés and Hernández[1] are given in Table 9. Examination of the CIs in Table 9 shows that the fiducial CIs are slightly shorter than the corresponding score CIs for all the four cases. Nevertheless, these two CIs are quite close for each contrast.

Tebbs and Roths[18] analyzed the data from a multicenter clinical trial where the objective was to evaluate the efficacy of a reduced-salt regime in treating male infants for acute watery diarrhea. The data, reproduced here in Table 10, were also analyzed by Andrés and Hernández.[1] A variable of interest was the number of infants experiencing fever at admission or during the trial. The chi-square test statistic for equality of proportions in different locations is

$$\chi^2 = \sum_{i=1}^{5} \frac{n_i(\hat{p}_i - \hat{p})^2}{\hat{p}(1-\hat{p})} = 84.02$$

Table 9. Types of diets in tumor study.

	Fiber		No Fiber	
	High fat	Low fat	High fat	Low fat
Sample size, n_i	30	30	30	30
Rats with tumor, k_i	20	14	27	19
$L_1 = \text{Fibre} \times \text{Fat}$	1	−1	−1	1
$L_2 = \text{Fibre}$	1	1	−1	−1
$L_3 = \text{Fat}$	1	−1	1	−1
95% CIs for the contrasts				

	95% CIs for the contrasts		
Method	L_1	L_2	L_3
Score	(−.3883, .2445)	(−.7096, − .0772)	(.1420,.7742)
Fiducial	(−.3812, .2405)	(−.6979, − .0767)	(.1405,.7615)

Table 10. Multicenter clinical trial data.

Location	Sample size (n_i) size (n_i)	Fever cases (k_i)	w_i	$\hat{p}_i$
Bangladesh	158	73	158/675	.4620
Brazil	107	32	107/675	.2991
India	175	44	175/675	.2514
Peru	92	34	92/675	.3696
Vietnam	143	104	143/675	.7273

where $\hat{p} = \sum_{i=1}^{5} k_i / \sum_{i=1}^{5} n_i = 287/675 = 0.4252$. The p-value $P(\chi_4^2 > 84.02) = .0000$ clearly indicates that the proportions in different locations are quite different. As noted in Andrés and Hernández,[1] the pooled proportion $\sum_{i=1}^{5} w_i p_i$, where w_i's are proportional to sample sizes as given in Table 10, could be used as overall proportion of subjects who are experiencing fever at admissions or during the trial. A CI for $\sum_{i=1}^{5} w_i p_i$ is desired to judge the overall proportion in different locations.

Andrés and Hernández[1] calculated the 95% score CI for $\sum_{i=1}^{5} w_i p_i$ as (.3907, .4605), and we calculated the fiducial CI as (.3912, .4605). We once again observe that both the score and fiducial methods produced CIs which are in agreement up to three decimal places.

If we ignore the heterogeneity of the groups, the overall proportion is estimated by $\hat{p} = \sum_{i=1}^{5} k_i / \sum_{i=1}^{5} n_i = 287/675 = 0.4252$. The exact Clopper–Pearson 95% confidence for the overall proportion is (.3875, .4635), and the score CI (see Agresti and Coull[19]) is (.3884, .4628). Thus, ignoring the heterogeneity in this problem leads to wider CIs than those noted in the preceding paragraph.

6 Concluding remarks

Even though, the closed-form asymptotic CIs, such as the logit CIs are valid only for very large samples, most practitioners use them because they are easy to understand and calculate. In this article, we provided closed-form CIs for four well-known problems. Computation of the new CIs requires only beta percentiles, and so they are easy to use. Our comparison studies clearly indicated that the new CIs are satisfactory and are comparable with or better than other well-known CIs. An appealing feature of simple closed-form solutions is that their properties, such as the sample size calculation for a given precision and powers, can be easily studied.

The proposed approximate method can be readily applied for other problems other than those addressed in this article. For example, Fleiss[20] introduced a measure for the relative difference defined by $(p_2 - p_1)/(1 - p_1) = 1 - q_2/q_1$, where p_1 denotes the proportion of patients who "improve" when treatment 1 is administered and p_2 is the corresponding proportion of patients treated with treatment 2, and $q_i = 1 - p_i$, $i = 1, 2$. The proposed fiducial approach can be readily applied to find an approximate CI for this function of parameters. Other problems that received some attention are estimation of product of several binomial proportions or the ratio of products of binomial success probabilities (see Buehler,[21] Madansky,[22] and Harris[23]). For example, the problem of estimating $p_1 p_2$ simplifies to estimating $\ln(p_1) + \ln(p_2)$, and a closed-form CI for the latter expression can be readily obtained using our approximate method along with the required expectation $E(\ln B_{a,b}) = \psi(a) - \psi(a + b)$.

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References

1. Andrés AM and Hernández MA. Inferences about a linear combination of proportions. *Stat Methods Med Res* 2011; **20**: 369–387.
2. Cornfield J. A statistical problem arising from retrospective studies. In: Neyman J (ed.) *Proceedings of the third Berkeley symposium on mathematical statistics and probability*, Vol. 4, 1956, pp.135–148.
3. Suissa S and Shuster JJ. Exact unconditional sample sizes for the 2 by 2 binomial trial. *J R Stat Soc Ser A* 1985; **148**: 317–327.
4. Agresti A and Min Y. Unconditional small-sample confidence intervals for the odds ratio. *Biostatistics* 2002; **3**: 379–386.
5. Miettinen O and Nurminen M. Comparative analysis of two rates. *Stat Med* 1985; **4**: 213–226.
6. Bedrick EJ. A family of confidence intervals for the ratio of two binomial proportions. *Biometrics* 1987; **43**: 993–998.
7. Bailey BJR. Confidence limits to the risk ratio. *Biometrics* 1987; **43**: 201–205.
8. Newcombe RG. Interval estimation for the difference between independent proportions: comparison of eleven methods. *Stat Med* 1998; **17**: 873–890.
9. Krishnamoorthy K and Lee M. Inference for functions of parameters in discrete distributions based on fiducial approach: binomial and Poisson cases. *J Stat Plan Infer* 2010; **140**: 1182–1192.
10. Krishnamoorthy K. Modified normal-based approximation to the percentiles of linear combination of independent random variables with applications. To appear in *Commun Stat Simul Comput*.
11. Zou GY and Donner A. Construction of confidence limits about effect measures: A general approach. *Stat Med* 2008; **27**: 1693–1702.
12. Newcombe RG. MOVER-R confidence intervals for ratios and products of two independently estimated quantities. *Stat Methods Med Res* 2013; **25**: 1774–1778.
13. Cai T. One-sided confidence intervals in discrete distributions. *J Stat Plan Infer* 2005; **131**: 63–88.
14. Okumura A, Hayakawa F, Kato T, et al. Physical condition of preterm infants with periventricular leukomalacia. *Pediatrics* 2001; **107**: 469–475.
15. Koopman AR. Confidence intervals for the ratio of two binomial proportions. *Biometrics* 1984; **40**: 513–517.
16. Birkefle O, Laake P and Vollestad N. Traditional Chinese medicine patterns and recommended acupuncture points in infertile and fertile women. *Acupunct Med* 2012; **30**: 12–16.
17. Cohen LA, Kendall ME, Zang E, et al. Modulation of N-Nitrosomethylurea-Induced mammary tumor promotion by dietary fibre and fat. *J Natl Cancer Inst* 1991; **83**: 496–501.
18. Tebbs JM and Roths SA. New large-sample confidence intervals for a linear combination of binomial proportions. *J Stat Plan Infer* 2008; **138**: 1884–1893.
19. Agresti A and Coull BA. Approximate is better than "exact" for interval estimation of binomial proportion. *Am Statist* 1998; **52**: 119–125.
20. Fleiss JL. *Statistical methods for rates and proportions*. New York: Wiley, 1973.
21. Buehler RJ. Confidence intervals for the product of two binomial parameters. *J Am Stat Assoc* 1957; **52**: 482–493.
22. Madansky A. Approximate confidence limits for the reliability of series and parallel systems. *Technometrics* 1965; **7**: 495–503.
23. Harris B. Hypothesis testing and confidence intervals for products and quotients of Poisson parameters with applications to reliability. *J Am Stat Assoc* 1971; **66**: 609–613.