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Efficient interval estimation of a ratio of marginal probabilities in matched-pair data: Non-iterative method

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SUMMARY

Matched pair designs have been commonly employed in diagnostic, epidemiologic and laboratory studies. For estimation of a ratio of two marginal probabilities in matched-pair data, a Wald-type logarithmic method is computationally simple but an actual coverage rate is known to be smaller than a nominal one and a length of the confidence interval is shorter than it should be. The Fieller-type method based on constrained maximum likelihood (CML) estimators possesses asymptotically optimum statistical properties and a coverage rate is close to a nominal one. However, hitherto the limits have been obtained by numerical iterations. In this paper, we derive the efficient confidence limits based on CML as analytical solutions of a quartic equation and present the confidence limits in a closed form.

Keywords

Constrained maximum likelihood estimators; Fieller-type method; Interval estimation of a ratio of marginal probabilities; Matched-pair data; Wald-type log method; Wilson interval

1. INTRODUCTION

Matched-pair designs have been widely used to eliminate extraneous factors due to study subject when comparing new and standard procedures. One of the basic statistical analyses on matched-pair data is interval estimation of the ratio of two marginal probabilities. A statistical inference on the ratio can be more interesting or sensible than the difference between two probabilities particularly when the probabilities are near to zero or close to one [1,2,3]. A confidence interval for a ratio based on a Wald-type logarithmic method [4,5] is simple but has an actual coverage rate for the ratio that is too small compared to the nominal coverage rate especially for a small sample size. Nam and Blackwelder [6] developed a Fieller-type method based on constrained maximum likelihood (CML) estimators of nuisance parameters that is asymptotically efficient and provides an accurate coverage rate. The confidence limits are found by using an iterative procedure. Newcombe [7,8] combined two Wilson confidence intervals [9] to obtain a confidence interval for the difference between two independent binomial probabilities. Using a similar approach, Bonett and Price [10] combined two Wilson confidence intervals for the ratio of two marginal probabilities which are correlated. This method performs much better than the Wald-type one in coverage. However, the algebraic derivation provides no reassurance that combining two Wilson $1-\alpha$ intervals will necessarily result in a coverage probability aligned with $1-\alpha$. The Fieller-type method based on CML estimators is asymptotically efficient and it is consistent with a chi-square test, i.e., the interval estimation of a ratio of two marginal probabilities excludes unity when the chi-square test rejects the unity of the ratio or vice-versa. Numerical methods have been used to obtain the confidence limits of the efficient method based on CML estimators. In this note, we derive the analytical solution to the efficient interval estimation of the ratio of two marginal probabilities.

2. INTERVAL ESTIMATION OF THE RATIO OF TWO MARGINAL PROBABILITIES

Consider n pairs of matched observations on a dichotomous variable, with one observation of the pair resulting from a new procedure and the other observation from the standard procedure. Denote x_{ij} 's as the number of observations with response i for the new procedure and response j for the standard one, where i and $j = 1$ or 0 for positive or negative response, respectively. The x_{ij} 's follow a multinomial distribution with probabilities p_{ij} 's, where the p_{ij} 's sum to one. Define $P_1 = p_{11} + p_{10}$ and $P_0 = p_{01} + p_{00}$. The P_1 and P_0 are the probabilities of a positive response with the new and standard procedures, respectively. The observations and probabilities in a matched-pair study are summarized in Table 1.

We are interested in interval estimation of the ratio of two marginal probabilities $\phi = P_1 / P_0$. Since p_{11} and p_{00} can be reparameterized as $p_{11} = (p_{10} - \phi p_{01}) / (\phi - 1)$ and $p_{00} = \{\phi(1 - p_{10}) + p_{01} - 1\} / (\phi - 1)$ for $\phi \neq 1$, the multinomial probabilities, p_{ij} 's, can be expressed in ϕ , p_{10} and p_{01} . The log-likelihood function is written as

$$\ln L = x_{11} \bullet \ln(p_{10} - \phi p_{01}) - (x_{11} + x_{00}) \bullet \ln(\phi - 1) + x_{10} \bullet \ln p_{10} + x_{01} \bullet \ln p_{01} + x_{00} \bullet \ln\{\phi(1 - p_{10}) + p_{01} - 1\}$$

where ϕ is the parameter of interest and p_{10} and p_{01} are nuisance parameters. The constrained maximum likelihood (CML) estimators of p_{10} and p_{01} for a given value of ϕ are obtained by solving two equations, $\partial \ln L / \partial p_{10} = 0$ and $\partial \ln L / \partial p_{01} = 0$. Denoting the solution by $\tilde{p}_{10}$ and $\tilde{p}_{01}$, we have

$$\tilde{p}_{10} = \left[-\widehat{P}_1 + \phi^2 (\widehat{P}_0 + 2\widehat{p}_{10}) + \left\{ (\widehat{P}_1 - \phi^2 \widehat{P}_0)^2 + 4\phi^2 \widehat{p}_{10} \widehat{p}_{01} \right\}^{1/2} \right] / \{2\phi(\phi + 1)\} \quad (1)$$

and $\tilde{p}_{01} = \phi \tilde{p}_{10} - (\phi - 1)(1 - \widehat{p}_{00})$ where $\widehat{p}_1 = x_{1\bullet}/n$, $\widehat{p}_0 = x_{0\bullet}/n$, $\widehat{p}_{10} = x_{10}/n$, and $\widehat{p}_{01} = x_{01}/n$ ([6], APPENDIX A). From the relation, $P_1 - \phi P_0 = 0$, we consider a Fieller-type statistic,

$T(\phi) = \widehat{P}_1 - \phi \widehat{P}_0$ which is asymptotically normally distributed with expectation zero and variance, $\phi(p_{10} + p_{01})/n$ ([6], APPENDIX C). Letting $z_{\alpha/2}$ be the $100 \times \alpha/2$ percentile point of the standard normal distribution, the $100 \times (1 - \alpha)$ confidence interval for ϕ using the CML estimators, $\tilde{p}_{10}$ and $\tilde{p}_{01}$, is obtained by solving two equations,

$$z(\phi)^2 = n(\widehat{P}_1 - \phi \widehat{P}_0)^2 / \left\{ \phi (\tilde{p}_{10} + \tilde{p}_{01}) \right\} = z_{\alpha/2}^2 \quad (2)$$

and (1), simultaneously with respect to ϕ . The lower and upper limits of the confidence interval, ϕ_l and ϕ_u , can be found numerically by an iterative method, e.g., the Newton-Raphson algorithm or the bisection method. Confidence limits obtained by the Wald-type logarithmic method [4],

$$\widehat{\phi} \exp \left[\pm z_{\alpha/2} \{ (x_{10} + x_{01}) / (x_{1\bullet} x_{0\bullet}) \}^{1/2} \right]$$

where $\widehat{\phi} = \widehat{p}_1 / \widehat{p}_0$, can be used as an initial set of values for iterations. Alternatively, we seek the confidence limits for ϕ as analytical solutions which satisfy both (1) and (2). Denote

$$\widehat{q}_{00} = 1 - \widehat{p}_{00}, \quad g_1 = (n\widehat{P}_0 + z_{\alpha/2}^2/2) \widehat{P}_0, \quad g_2 = -(2n\widehat{P}_1 \widehat{P}_0 + z_{\alpha/2}^2 \bullet \widehat{q}_{00}) \text{ and } g_3 = (n\widehat{P}_1 + z_{\alpha/2}^2/2) \widehat{P}_1. \text{ A}$$

series of intensive algebra after substituting (1) in (2) results a fourth order polynomial equation of ϕ and the $100\% \times (1-\alpha)$ confidence limits can be obtained by solving the equation:

$a_0\phi^4 + a_1\phi^3 + a_2\phi^2 + a_3\phi + a_4 = 0$ where $a_0 = g_1^2 - (z_{\alpha/2}^2 \bullet \widehat{P}_0/2)^2$, $a_1 = 2g_1g_2$, $a_2 = g_2^2 + 2g_1g_3 + z_{\alpha/2}^4 (\widehat{P}_1\widehat{P}_0 - 2\widehat{p}_{10}\widehat{p}_{01})/2$, $a_3 = 2g_2g_3$ and $a_4 = g_3^2 - (z_{\alpha/2}^2 \bullet \widehat{P}_1/2)^2$. This equation is rewritten as

$$\phi^4 + b_1\phi^3 + b_2\phi^2 + b_3\phi + b_4 = 0 \quad (3)$$

where $b_i = a_i / a_0$ for $i=1,2,\dots,4$. Denote y_1 as an appropriate real root of the cubic equation (A4) in the Appendix A. The four real roots of the quartic equation (3) are

$$\begin{aligned} \phi = & \left[-(b_1/2 + h_1) \pm \left\{ (b_1/2 + h_1)^2 - 4(y_1/2 + h_2) \right\}^{1/2} \right] / 2 \\ & \text{and} \\ \phi = & \left[(h_1 - b_1/2) \pm \left\{ (h_1 - b_1/2)^2 - 4(y_1/2 - h_2) \right\}^{1/2} \right] / 2 \end{aligned} \quad (4)$$

where $h_1 = (b_1^2/4 - b_2 + y_1)^{1/2}$ and $h_2 = (b_1y_1/2 - b_3)/(2h_1)$. The smallest and largest real roots are the lower and upper limits for ϕ , i.e., ϕ_l and ϕ_u . For an exceptional case of $x_{11} = x_{00} = 0$, confidence limits by CML method (4) and those by combining Wilson methods [10] are identical in Appendix B. Although the exceptional case is unlikely to occur in practice, it is still interesting from a computational or theoretical point of view.

3. AN EXAMPLE

Blake et al [2] sought to determine whether highly sensitive urine-based nucleic acid amplification tests can adequately diagnose vaginal infections without using a speculum. The presenting complaints of 686 patients entered into the study. Ninety-nine patients were positive for trichomonas by one of the two study methods or by culture. Of these 99, 67 were positive by both methods, 9 were positive only when the speculum was not used, 7 were positive only when the speculum was used, and 16 were negative by both methods, i.e., $x_{11} = 67$, $x_{10} = 9$, $x_{01} = 7$, $x_{00} = 16$, $\widehat{P}_1 = 76/99 = 0.77$ and $\widehat{P}_0 = 74/99 = 0.75$. Marginal proportions, $\widehat{P}_1$ and $\widehat{P}_0$, are sensitivities of diagnosis without and with the speculum. An point estimate of a ratio is $\widehat{\phi} = 76/74 = 1.0270$. We are interested in interval estimation of a ratio of two sensitivities. The coefficients of (3) are $b_1 = -4.1203$, $b_2 = 6.3523$, $b_3 = -4.3431$ and $b_4 = 1.1111$, and those of (A4) are $c_1 = -6.3523$, $c_2 = 13.4507$ and $c_3 = -9.4936$. Since $d_1 = -0.000064$ and $d_2 = 1.9 \times 10^{-7}$ we have $\Delta = (d_1/3)^3 + (d_2/2)^2 = 0$. Applying Cardan's method (A6), we obtain $A=B=0$ and $x_1 = 0$ which corresponds to $y_1 = 2.1174$ from $y = x - c_1/3$. The 95% confidence limits which are the smallest and largest roots of (4) are (0.9198, 1.1529). The quartic equation (3) is plotted in Figure 1. The smallest and largest roots of $F(\phi) = 0$ correspond to the lower and upper limits for ϕ . The 95% confidence interval by the Wald-type log method [4] and that by the combined Wilson method [10] are (0.9251, 1.1402) and (0.9224, 1.1436), and they are similar. Since the Wald-type method is anti-conservative, we expect that the interval is shorter and its actual coverage rate is smaller than a nominal 95% coverage rate. All three confidence intervals indicate that the diagnostic method without the use of the speculum is as effective as the method with use of it.

4. FINAL REMARKS

For interval estimation of a ratio of two marginal probabilities in matched pair data, Bonett and Price [10] presented quotients of a Wilson confidence interval for P_1 to that for P_0 . Nam and Blackwelder [6] presented an asymptotically efficient confidence interval directly for the ratio of two probabilities, ϕ , by reparameterization. The direct approach can be theoretically more preferable than the combining two confidence intervals for the ratio. For interval estimation of a ratio of two independent binomial parameters, a preference of the likelihood score method [11] over the crude method [12], the logarithmic method [13] and Bailey's modification [14] has been demonstrated. Nam [15] provided confidence limits by the likelihood method in a closed form. It is interestingly to note that the Wilson interval for a binomial probability, the likelihood score method for a ratio of two independent binomial probabilities and the Fieller-type method based on CML for a ratio of marginal probabilities in matched-pair data are obtained by solving relevant quadratic, cubic and quartic equations regarding to respective parameters. Finally, for a case of the matched-pair 2×2 table where one of the diagonal cells is unidentifiable, Wald-type method, combining Wilson intervals and Fieller-type method based on CML are also applicable for estimation of a ratio of marginal probabilities [16,17]. Unlike in a ratio, a difference between two marginal probabilities is not estimable for this kind of imperfect data.

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APPENDIX A: EFFICIENT INTERVAL ESTIMATION BASED ON CML METHOD IN CLOSED FORM

From (3), we have the 4th order polynomial equation

$$\phi^4 + b_1\phi^3 + b_2\phi^2 + b_3\phi + b_4 = 0 \quad (\text{A1})$$

where $b_j = a_j / a_0$ for $j = 1, 2, \dots, 4$. Using Ferrari's formulation [18], the (A1) can be rewritten as

$$\left(\phi^2 + \frac{1}{2}b_1\phi\right)^2 = \left(\frac{1}{4}b_1^2 - b_2\right)\phi^2 - b_3\phi - b_4 \quad (\text{A2})$$

When $y\left(\phi^2 + \frac{1}{2}b_1\phi\right) + \frac{1}{4}y^2$ is added to both sides of (A2), we have

$$\left(\phi^2 + \frac{1}{2}b_1\phi + \frac{1}{2}y\right)^2 = \left(\frac{1}{4}b_1^2 - b_2 + y\right)\phi^2 + \left(\frac{1}{2}b_1y - b_3\right)\phi + \left(\frac{1}{4}y^2 - b_4\right). \quad (\text{A3})$$

The right-hand side of (A3) will be a perfect square if its discriminant is zero, i.e.,

$(b_1y/2 - b_3)^2 - 4\left(\frac{1}{4}b_1^2 - b_2 + y\right)\left(\frac{1}{4}y^2 - b_4\right) = 0$ which is expressed as a cubic equation of y ,

$$y^3 + c_1y^2 + c_2y + c_3 = 0 \quad (\text{A4})$$

where $c_1 = -b_2$, $c_2 = b_1b_3 - 4b_4$ and $c_3 = -(b_3^2 + b_1^2b_4 - 4b_2b_4)$. The cubic equation (A4) is the resolvent for the quartic equation (A1). Following a standard method, we can find an appropriate root of (A4) so that the right-hand side of (A3) is expressed as a square of a linear function of ϕ . By a substitution of $y = x - c_1/3$, the equation (A4) can be reduced as

$$f(x) = x^3 + d_1x + d_2 = 0 \quad (\text{A5})$$

where $d_1 = c_2 - c_1^2/3$ and $d_2 = 2c_1^3/27 - c_1c_2/3 + c_3$. Define $\Delta = (d_1/3)^3 + (d_2/2)^2$ and $i = \sqrt{-1}$. Cardan's solution of the cubic equation (A5) can be expressed as

$$x_1 = A^{1/3} + B^{1/3}, x_2 = \omega \cdot A^{1/3} + \omega^2 \cdot B^{1/3} \quad \text{and} \quad x_3 = \omega^2 \cdot A^{1/3} + \omega \cdot B^{1/3} \quad (\text{A6})$$

where $A = -d_2/2 + \Delta$, $B = -d_2/2 - \Delta$, $\omega = (-1 + i\sqrt{3})/2$ and $\omega^2 = (-1 - i\sqrt{3})/2$. Roots are also found by using trigonometric method: $x_1 = 2(-d_2/3)^{1/2} \cos(\alpha/3)$ and $x_{2,3} = -2(-d_2/3)^{1/2} \cos(\alpha/3 \pm \pi/3)$ where $\cos(\alpha) = -d_2/3 \left[2 \left\{ -(d_1/3)^3 \right\}^{1/2} \right]$. Any real root of (A5) can be used for solving the quartic equation (A1). If x_1 as a positive real root of (A5), then the corresponding $y_1 = x_1 - c_1/3$ is the resolvent of the quartic equation. By substitution of y_1 in (A3) gives

$$(\phi^2 + b_1\phi/2 + y_1/2)^2 = (h_1\phi + h_2)^2$$

where $h_1 = (b_1^2/4 - b_2 + y_1)^{1/2}$ and $h_2 = (b_1y_1/2 - b_3)/(2h_1)$. The four roots of (A1) are

$$\phi = \left[-(b_1/2 + h_1) \pm \left\{ (b_1/2 + h_1)^2 - 4(y_1/2 + h_2) \right\}^{1/2} \right] / 2$$

and

$$\phi = \left[(h_1 - b_1/2) \pm \left\{ (h_1 - b_1/2)^2 - 4(y_1/2 - h_2) \right\}^{1/2} \right] / 2$$

where h_1 is a real number. The smallest and largest roots are corresponding to the lower and upper limits of the $100\% \times (1 - \alpha)$ confidence interval for ϕ . For $d_1 < 0$ and $d_2 = 0$ which are typical in matched pair data, we have $f(x) = x^3 + d_1x = 0$ which leads to $x_1 = 0$ and $y_1 = b_2/3$. However, it should be noted that d_2 is not always zero.

APPENDIX B: EQUALITY OF CONFIDENCE INTERVALS BY CML AND COMBINING WILSON METHODS WHEN $x_{11} = x_{00} = 0$

For the exceptional case of $x_{11} = x_{00} = 0$, the CML estimators of p_{10} and p_{01} for a given value of ϕ are expressed as

$$\tilde{p}_{10} = \phi / (\phi + 1) \quad \text{and} \quad \tilde{p}_{01} = 1 / (\phi + 1), \quad (\text{B1})$$

respectively, from (1). Thus, the asymptotically efficient interval estimation of a ratio of two marginal probabilities based on the CML estimators is obtained by solving a quadratic equation, $x_{01}^2 \cdot \phi^2 - (2x_{10}x_{01} + n \cdot z_{\alpha/2}^2) \phi + x_{10}^2 = 0$, from (2) with (B1). The two limits of a 100% x (1- α) confidence interval for ϕ are followed as

$$\phi = \left[2x_{10}x_{01} + n \cdot z_{\alpha/2}^2 \pm z_{\alpha/2} \left\{ n(4x_{10}x_{01}) + n^2 \cdot z_{\alpha/2}^2 \right\}^{1/2} \right] / (2x_{01}^2) \quad (\text{B2})$$

where signs + or - are for upper or lower limits, respectively. Wilson's 100% x (1- α) confidence limits of a binomial probability is expressed as

$$P_i = \left[2n\widehat{P}_i + z_{\alpha/2}^2 \pm z_{\alpha/2} \left\{ z_{\alpha/2}^2 + 4n\widehat{P}_i(1 - \widehat{P}_i) \right\}^{1/2} \right] / \left\{ 2(n + z_{\alpha/2}^2) \right\}$$

for $i = 0$ and 1 . Bonett and Price [10] presented confidence limits for a ratio (P_1 / P_0) as

$$l_1 / u_0 < P_1 / P_0 < u_1 / l_0. \quad (\text{B3})$$

The lower limit for a ratio can be written as

$$l_1 / u_0 = \left\{ 2x_{10} + z_{\alpha/2}^2 - z_{\alpha/2} \left(z_{\alpha/2}^2 + 4x_{10}x_{01} / n \right)^{1/2} \right\} / \left\{ 2x_{01} + z_{\alpha/2}^2 + z_{\alpha/2} \left(z_{\alpha/2}^2 + 4x_{10}x_{01} / n \right)^{1/2} \right\}. \quad (\text{B4})$$

Multiply both numerator and denominator of (B4) by $\left\{ 2x_{01} + z_{\alpha/2}^2 - z_{\alpha/2} \left(z_{\alpha/2}^2 + 4x_{10}x_{01} / n \right)^{1/2} \right\}$ and simplify the result as $l_1 / u_0 = \left[2x_{10}x_{01} + n \cdot z_{\alpha/2}^2 - z_{\alpha/2} \left\{ (4x_{10}x_{01} + n \cdot z_{\alpha/2}^2) n \right\}^{1/2} \right] / (2x_{01}^2)$ which is the same to the lower limit of (B2). That is a special case of Nam and Blackwelder [6] for $x_{11} = x_{00} = 0$. Similarly, we can show that the upper limit of (B3) is equivalent to the upper limit of (B2).

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Fig. 1. A curve of $F(\phi) = \phi^4 - (4.1203)\phi^3 + (6.3525)\phi^2 - (4.3431)\phi + 1.1111$: Roots of a quartic equation and confidence limits.

Table 1

Observations and probabilities in a matched-pair study

New procedure	Standard procedures		Sum	New Procedure	Standard procedure		Sum
	Positive	Negative			Positive	Negative	
Positive	x_{11}	x_{10}	$x_{1\bullet}$	Positive	p_{11}	p_{10}	P_1
Negative	x_{01}	x_{00}	$x_{0\bullet}$	Negative	p_{01}	p_{00}	$1 - P_1$
Sum	$x_{\bullet 1}$	$x_{\bullet 0}$	n	Sum	P_0	$1 - P_0$	1

Nam