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The p-values of the hypothesis testing about relative risks

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Abstract

Logistic regression analysis can provide an estimate of the odds ratio (OR), adjusted for a number of confounders. It is known that it is approximately equal to the associated adjusted relative risk (RR) if the incidence of an outcome of interest is rare in a cohort study or a clinical trial study. In this paper, we consider the incidence of an outcome that is relatively common in a study population, and investigate the relationship between the two null hypotheses that an OR and the associated RR are equal to unity. It is shown that the p-values associated with the two null hypotheses are asymptotically equivalent. This complements the existing formula for converting an adjusted estimate of the OR and the associated confidence interval to their counterparts of the RR.

Keywords: logistic regression; odds ratio; p-value; relative risk.

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1. Introduction

Logistic regression analysis is widely applied in cohort studies and clinical trials. It can provide an estimate of the odds ratio (OR) which is a measure of association between a dichotomous response (disease) and an explanatory factor (exposure) after being adjusted for some confounders (Hosmer and Lemeshow, 1989).

In many cohort studies and clinical trials, however, it is the relative risk (RR), rather than the OR, that is of particular research interest. In the case of the rare incidence of an outcome, an estimate of the OR is a useful approximation to the RR. When the incidence of an outcome is relatively common (say, greater than ten percent), however, using an adjusted estimate of the OR to approximate the RR is not accurate enough, and thus other approaches are required. One important special case is when the confounders in a study are all categorical. In such a case the Mantel-Haenszel method can be applied to derive an adjusted estimate of the RR (Mantel and Haenszel 1959). For the general situation where there are both continuous and categorical confounders, a modified logistic regression approach was proposed by Wacholder (1986) but it is not widely used in practice due to its mathematical complexity. Zhang and Yu (1998) suggested an approximate method via a simple conversion formula, converting an estimate of the OR to the associated estimate of the RR, once the former is obtained through, say, logistic regression analysis. The confidence intervals for the adjusted RR can be calculated similarly. However, the calculation of p-values was not considered by Zhang and Yu (1998).

The p-value of a null hypothesis is the probability of having observed or more extreme data if the null hypothesis were true. It is useful to interpret results of hypothesis testing in many applications. In this paper, the p-values of testing null hypothesis for adjusted estimates of the RR will be investigated.

2. Main result

2.1 Notation

Consider a cohort study or a clinical trial study. Denote the incidences of an outcome of interest in the nonexposed and exposed groups as P_0 and P_1 respectively. Let $Q_1 = 1 - P_1$. The OR and RR are defined to be (see, e.g. Kahn and Sempos, 1989):

$$OR = \frac{P_1 / (1 - P_1)}{P_0 / (1 - P_0)} = \frac{P_1 (1 - P_0)}{P_0 (1 - P_1)} \quad \text{and} \quad RR = \frac{P_1}{P_0}$$

respectively. Let $\beta = \log(OR)$ and $\gamma = \log(RR)$.

Denote estimates of OR , RR , and Q_1 as $\hat{OR}$, $\hat{RR}$, and $\hat{Q}_1$ respectively, and let $\hat{\beta} = \log(\hat{OR})$ and $\hat{\gamma} = \log(\hat{RR})$, where an estimate $\hat{\beta} = \log(\hat{OR})$ may be derived from logistic regression analysis, for instance.

In most of applications, the following null hypotheses are of particular interest:

$$H_{01}: OR=1, \tag{1}$$

and

$$H_{02}: RR=1. \tag{2}$$

2.2 The asymptotic equivalence of the p-values

We shall investigate the relationship of the calculated p-values when testing the two null hypotheses (1) and (2). First, from the definitions of the OR and RR, we may obtain by some algebra

$$RR - 1 = Q_1 (OR - 1). \tag{3}$$

For most of the commonly used estimates of $\hat{\beta}$, $\hat{\gamma}$ and $\hat{Q}_1$ obtained from a sample of size n , their variances have an order of $O(n^{-1})$. In such a case, $\hat{\gamma}$ may be approximately expressed as a function of the random variables $\hat{\beta}$ and $\hat{Q}_1$ via equation (3):

$$\hat{RR}-1 = \hat{Q}_1(\hat{OR}-1) + O_p(n^{-1/2}), \quad (4)$$

where $O_p(n^{-1/2})$ denotes a random variable, U_n , satisfying $U_n/n^{-1/2}$ being bounded in probability. Now denote $g(x_1, x_2) = \log[1 + x_2\{\exp(x_1) - 1\}]$ and let $g_i'(\beta, Q_1)$ be $\partial g(x_1, x_2) / \partial x_i$ ($i=1,2$) evaluated at (β, Q_1) . From equation (4) and Taylor expansion (see for instance, Kendall and Stuart, 1976, p.246) we obtain

$$\hat{\gamma} = g(\beta, Q_1) + g_1'(\beta, Q_1)(\hat{\beta} - \beta) + g_2'(\beta, Q_1)(\hat{Q}_1 - Q_1) + O_p(n^{-1/2}),$$

which, under the null hypothesis H_{01} , reduces to

$$\hat{\gamma} = Q_1 \hat{\beta} + O_p(n^{-1/2}).$$

Correspondingly, the associated variance of $\hat{\gamma}$, $\text{var}(\hat{\gamma})$, satisfies

$$\text{var}(\hat{\gamma}) = Q_1^2 \text{var}(\hat{\beta}) + o(n^{-1/2}).$$

This leads to

$$\hat{\gamma} / \sqrt{\text{var}(\hat{\gamma})} = \hat{\beta} / \sqrt{\text{var}(\hat{\beta})} + O_p(n^{-1/2}). \quad (5)$$

Equation (5) implies that when $\text{var}(\hat{\beta})$ and $\text{var}(\hat{\gamma})$ are available, the two test statistics for testing the null hypotheses (1) and (2), $\hat{\gamma} / \sqrt{\text{var}(\hat{\gamma})}$ and $\hat{\beta} / \sqrt{\text{var}(\hat{\beta})}$, are asymptotically equivalent.

In practice, however, the variances of $\hat{\beta}$ and $\hat{\gamma}$ in equation (5) are usually unknown.

Consequently commonly-used test statistics rely on some estimated variances, $\hat{\text{var}}(\hat{\beta})$ and $\hat{\text{var}}(\hat{\gamma})$, leading to the following test statistics:

$$z_{OR} = \hat{\beta} / \sqrt{\hat{\text{var}}(\hat{\beta})} \quad \text{and} \quad z_{RR} = \hat{\gamma} / \sqrt{\hat{\text{var}}(\hat{\gamma})}, \quad (6)$$

for testing the null hypotheses (1) and (2) respectively. It is clear from equation (5) that the two test statistics in (6) are still asymptotically equivalent when $\lim_{n \rightarrow \infty} \Pr \left\{ \hat{\text{var}}(\hat{\beta}) = \text{var}(\hat{\beta}) \right\} = 1$ and $\lim_{n \rightarrow \infty} \Pr \left\{ \hat{\text{var}}(\hat{\gamma}) = \text{var}(\hat{\gamma}) \right\} = 1$. Note that this is a very weak condition and is satisfied by most of the commonly used estimates of the variances, for instance, the estimates of the variances by the Woolf's method and Katz's method (Kahn and Sempos, 1989).

Finally, we note that for most of the commonly-used methods under some mild regular conditions, say logistic regression analysis, $z_{OR} = \hat{\beta} / \sqrt{\hat{\text{var}}(\hat{\beta})}$ asymptotically has the standard normal distribution under the null hypothesis H_{01} . On the basis of the above analysis, $z_{RR} = \hat{\gamma} / \sqrt{\hat{\text{var}}(\hat{\gamma})}$ also has the same asymptotic distribution, the standard normal distribution. Hence, the corresponding p-values for testing the null hypotheses (1) and (2) are asymptotically equivalent.

3. Numerical examples

In this section, the theoretical analysis in the previous section is illustrated through numerical examples.

First we consider a simulation study, where a number of random samples of sizes $n = 2m$ were generated using the binominal distributions with parameters (P_1, m) and (P_0, m) for exposed and nonexposed groups respectively. The sample sizes, $n = 2m$, were taken from 50 to 1000 with an increment of 10, and both probabilities, P_1 and P_0 , were set to be 0.15. For each of the simulated samples, the estimated variances, $\hat{\text{var}}(\hat{\beta})$ and $\hat{\text{var}}(\hat{\gamma})$, were calculated using the Woolf's method and Katz's method respectively. The test statistics, z_{OR} and z_{RR}

given in equation (6), and their associated p-values, P_{OR} and P_{RR} , were then computed; see Kahn and Sempos, 1989, pp45-63.

Figure 1 displays the difference of the p-values, $d = P_{OR} - P_{RR}$, versus sample size. It can be seen that the difference converges to zero rapidly as the sample size becomes large.

(Figure 1)

Next, to have a close look at the obtained theoretical result, we examine an artificial numerical example. We deliberately consider here a categorical confounder in order to use the Mantel-Haenszel method to verify the result.

Consider a clinical trial carried out to investigate the improvement of a new treatment on a certain disease, say respiratory illness. The experiment was organized in two centers. In each of the centers, two groups of patients having the same symptoms were selected through simple random sampling, one group being treated with a new treatment, and another with a placebo. It is interested in the association between treatment and respiratory outcome, after adjusting for the effect of center. The data are displayed in Table 1.

Table 1. An artificial example

Center	Treatment	Favorable	Unfavorable	Total
1	New treatment	12	6	18
1	Placebo	10	8	18
2	New treatment	14	10	24
2	Placebo	9	24	33

Logistic regression analysis was performed for this data set, giving an estimate of the OR 2.672, adjusted for the confounder ‘center’, with a 95% confidence interval, (1.133, 6.305). The p-value for testing the null hypothesis (1) is 0.0248 from the logistic regression. When converting the estimate of the OR to an estimate of the RR using the Zhang and Yu’s formula (1998), the p-value for testing the null hypothesis (2) is approximately 0.0248 according to the theoretical result in the previous section.

Since the only confounder is categorical for this particular example, we can verify the result using the Mantel-Haenszel method. The result of analysis for the above data using the Mantel-Haenszel method is displayed in Table 2. It can be seen that the resulting p-value for RR, 0.0256, is close to 0.0248, the value derived from logistic regression analysis and used to approximate the p-value for testing the hypothesis (2).

Table 2. Results using the Mantel-Haenszel method

	Estimate	95% confidence interval	Test statistic	p-value
OR	2.638	(1.124, 6.189)	2.229	0.0258
RR	1.605	(1.060, 2.431)	2.233	0.0256

In practice, whenever there are considerable continuous confounders such that the Mantel-Haenszel method is not applicable, the p-values for testing the null hypothesis (1), calculated from logistic regression analysis, can be used as approximate p-values for hypothesis testing (2).

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Figure 1. The difference of the p-values for testing the null hypotheses about the OR and RR
versus sample size