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Exact approaches for testing non-inferiority or superiority of two incidence rates

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ABSTRACT

We studied an unconditional approach based on partial maximization using different penalty values for comparing two incidence rates from Poisson distributions. We also consider a full maximization approach and an approach based on estimation and full maximization. Generally, the third approach has good performance.

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1. Introduction

In clinical trials, it is quite common that the follow-up time for each subject is not exactly the same. In addition, some subjects may experience more than one event during the study. An incidence rate is often the parameter of interest in the study which is defined as the total number of events divided by the total follow-up time. For example, patients in a breast cancer study (Rothman et al., 2012) are being followed for a certain time and the number of breast cancer cases is observed. In a parallel arm clinical trial, incidence rates for each group can be estimated and the comparison of their difference is often of interest in medical research.

A traditional method for testing the difference of incidence rates is an asymptotic approach based on commonly used test statistics (Krishnamoorthy and Thomson, 2004; Liu et al., 2006), such as the likelihood ratio test, the score test, and the Wald test. Asymptotic approaches are often used in large sample settings (Krishnamoorthy and Thomson, 2004; Ng and Tang, 2005). The convergence rate of the sample distribution to the limiting distribution depends on the sample size and the incidence rate for each group. This approach was often shown to be associated with unsatisfactory type I error control in small or medium sample settings (Ng and Tang, 2005).

An alternative to asymptotic approaches is an exact approach. When exact approaches are used, one has to eliminate the nuisance parameter in the null likelihood (Basu, 1977). In the conditional approach (Fisher, 1970), the nuisance parameter is eliminated by fixing the total number of events and the number of subjects in each group. The reference distribution is constructed by enumerating all possible tables for the p-value calculation. The size of the reference distribution is often smaller as compared to other exact testing procedures, which may lead to the conservativeness of the conditional approach. The second method to eliminate the nuisance parameter is the one based on maximization. Due to the nature of Poisson data, it would be easy to apply the partial maximization since the range of the nuisance parameter is not bounded. Because

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the parameter of a Poisson mean parameter is unbounded, it makes sense to consider the approach of Berger and Boos (1994), who maximize the nuisance parameter over a confidence set under the null hypothesis of equal means. Following Lloyd (2008), we call this method "partial maximization" and the associated tuning parameter γ of the $1-\gamma$ confidence interval a "penalty value". The p-value of this approach is calculated by maximizing the null likelihood over a confidence interval (Berger and Boos, 1994). It is well known that the density function of a Poisson distribution is a non-increasing function of the parameter after a large enough threshold. We use this property to propose the full maximization approach for comparing the difference between incidence rates. The third method is an estimated approach (Storer and Kim, 1990), in which the nuisance parameter is replaced by its maximum likelihood estimate (MLE).

A combination of these three methods can also be utilized to eliminate the nuisance parameter for testing non-inferiority or superiority for Poisson data. Han (2008) considered a combination of the conditional approach and partial maximization, and Shan (2013c) considered a combination of estimation and partial maximization. A combination may produce a closer actual type I error rate to the test size and potentially increase the power of the study. In this article, we will consider a combination of estimation and full maximization. This combination was first proposed by Lloyd (2008) for comparing two proportions. Later, it was successfully applied to other important statistical problems, such as trend tests with binary endpoints (Shan et al., 2012, 2013), correlated data (Shan, 2013b,a). In addition, a penalty value is often introduced in the partial maximization approach. We conduct an extensive comparison for the approach based on partial maximization using different penalty values, and the optimal value is recommended in this article.

The rest of this article is organized as follows. In Section 2, we review the existing unconditional test based on partial maximization and propose two new unconditional testing procedures. In Section 3 we compare the performance of the competing tests by studying their actual type I error rates and average power. In Section 4 an example from a breast cancer study is used to illustrate the testing procedures. Section 5 is given to some remarks.

2. Existing and proposed procedures

In a parallel study, suppose that X_{ij} and t_{ij} are the number of event and the follow-up time for the jth subject in the ith group, $i = 1, 2$, and $j = 1, 2, \ldots, n_i$, where n_1 and n_2 are the number of subjects in the first group and the second group, respectively. The total number of events in the ith group is $X_i = \sum_{j=1}^{n_i} X_{ij}$, and the total exposure time for the ith group is $t_i = \sum_{j=1}^{n_i} t_{ij}$. An incidence rate can be computed as the total number of events divided by the sum of follow-up time. Suppose that each subject is allowed to experience more than one event in the study. For example, the number of heart attacks is often more than one for an individual patient. In this article, we are interested in comparing the incidence rate between two groups, λ_1 and λ_2. The hypotheses are given as

$$H_0 : \lambda_1 \geq \lambda_2,$$

versus

$$H_a : \lambda_1 < \lambda_2.$$

Although we consider a one-sided hypotheses in the article, it can be readily and easily extended to general hypotheses. The incidence rate difference $\theta = \lambda_2 - \lambda_1$ is the parameter of interest.

Traditionally, three test statistics are used for testing the superiority of incidence rates. They are the Wald test, the likelihood ratio test, and the score test (Shan, 2013c). These three test statistics have been compared using different exact approaches (Han, 2008; Shan, 2013c), and the score test has been recommended for use due to the good performance. Let (x_1, x_2) be the observed data for (X_1, X_2). The score statistic is given as

$$T = \frac{x_2/t_2 - x_1/t_1}{\sqrt{(x_1 + x_2)/(t_1 t_2)}},$$

where $(x_1 + x_2)/(t_1 t_2)$ is the estimated variance of θ (Ng and Tang, 2005). The null hypothesis will be rejected for large values of the test statistics.

2.1. Partial maximization

Unlike the problem of comparing two proportions, the range of incidence rate difference θ is not bounded with the range from $-\infty$ to $+\infty$. It would be difficult to search for the maximum of the rejection region over an unbounded range. To overcome the computational burden, an unconditional approach based on partial maximization was proposed by Berger and Boos (1994) (referred to as the B approach). In this approach, the p-value is calculated by maximizing the tail probability over a confidence interval instead of the unbounded range. It is computationally easy to find the maximum over a confidence interval. Two-sided confidence intervals of the nuisance parameter are calculated at a fixed level of $1 - \gamma$, where γ is a penalty value which is often chosen to be a very small number, such as 10^{-3}, or 10^{-4}. The $100(1 - \gamma)\%$ confidence interval $C(x_1, x_2)$ for the observed data (x_1, x_2) is calculated from the exact confidence interval of the rate in Poisson distribution (Ulm, 1990), and is given as

$$C(x_1, x_2; \gamma) = \left(\frac{1}{x_1 + x_2} \chi^2_{\{\gamma/2, 2(x_1+x_2)\}}, \frac{1}{x_1 + x_2} \chi^2_{\{(1-\gamma/2), 2(x_1+x_2+1)\}} \right),$$

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