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Interval estimation of odds ratio in a stratified randomized clinical trial with noncompliance

Kung-Jong Lui [a,*], Kuang-Chao Chang [b]

[a] Department of Mathematics and Statistics, College of Sciences, San Diego State University, San Diego, CA 92182-7720, USA
[b] Department of Statistics and Information Science, Fu-Jen Catholic University, Taipei, Taiwan, ROC

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ABSTRACT

It is not uncommon to encounter a randomized clinical trial (RCT), in which we need to account for both the noncompliance of patients to their assigned treatment and confounders to avoid making a misleading inference. In this paper, we focus our attention on estimation of the relative treatment efficacy measured by the odds ratio (OR) in large strata for a stratified RCT with noncompliance. We have developed five asymptotic interval estimators for the *OR*. We employ Monte Carlo simulation to evaluate the finite-sample performance of these interval estimators in a variety of situations. We note that the interval estimator using the weighted least squares (WLS) method may perform well when the number of strata is small, but tend to be liberal when the number of strata is large. We find that the interval estimator using weights which are not functions of unknown parameters required to be estimated from data can improve the accuracy of the interval estimator based on the WLS method, but lose precision. We note that the estimator using the logarithmic transformation of the WLS point estimator and the interval estimator using the logarithmic transformation of the Mantel–Haenszel (MH) type of point estimator can perform well with respect to both the coverage probability and the average length in all the situations considered here. We further note that the interval estimator derived from a quadratic equation using a randomization-based method can be of use as the number of strata is large. Finally, we use the data taken from a multiple risk factor intervention trial to illustrate the use of interval estimators appropriate for being employed when the number of strata is small or moderate.

1. Introduction

The odds ratio (OR) is probably one of the most important indices to measure the strength of association between a risk factor and a binary outcome in epidemiology (Cornfield, 1956). As noted elsewhere (Fleiss, 1981; Tu, 2003; Lui, 2004), the *OR* has many nice numerical properties. These include its value is invariant with respect to various study designs, symmetric when success and failure are interchanged, and can be stable when the underlying probability of response for the standard treatment varies between trials and be expressed as the model parameter under the log-linear or logistic regression model. Thus, the *OR* has been recommended to measure the relative treatment effect in therapeutic equivalence or in meta-analysis (Tu, 1998, 2003; Garrett, 2003; Rousson and Seifert, 2008). Jacobson et al. (1999) also used the *OR* to report the treatment effect of receiving thalidomide on esophageal aphthous ulcers in patients with human immunodeficiency virus infection.

In a randomized clinical trial (RCT), we may encounter the situations in which there are patients not complying with their assigned treatment due to ethical reason or a previously negative experience of taking an assigned treatment (Sato, 2001; Matsuyama, 2002; Matsui, 2005; Lui, 2007a,b). Since noncompliance often occurs non-randomly, analyzing data as

* Corresponding author. Tel.: +1 619 594 6191; fax: +1 619 594 6746.
E-mail address: kjl@rohan.sdsu.edu (K.-J. Lui).

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treated or as per protocol can lead us to obtain a biased estimate of a treatment effect (Sommer and Zeger, 1991). A quite common and popular approach to analyze data with noncompliance is the intention-to-treat (ITT) analysis, in which one compares patients according to the treatment to which they are originally assigned despite what treatment they actually receive. When using the ITT analysis, we may apply all commonly-used interval estimators of the *OR* for stratified analysis (Lui, 2004, pp. 94–98) not accounting for noncompliance to obtain a confidence interval for the *OR*. However, note that the "treatment efficacy" is defined as the effect of a treatment relative to a control on those patients who would fully comply with their treatment regimen (Last, 1988). The ITT analysis using interval estimators (Lui, 2004) without accounting for noncompliance would estimate the "programmatic effectiveness" rather than the "treatment efficacy" when there are patients not complying with their assigned treatment (Sommer and Zeger, 1991). When the extent of noncompliance varies between different studied populations, the former may even change regardless of a fixed value of the latter. In fact, the ITT analysis generally tends to underestimate the treatment efficacy (Schwartz and Lellouch, 1967; Sheiner and Rubin, 1995; Piantadosi, 1997; Lui, 2007a). Thus, the development in estimation of the treatment efficacy in the presence of noncompliance becomes essentially important and useful. Here, we focus our attention on estimation of treatment efficacy measured by the *OR* in stratified data with noncompliance. Note that the treatment efficacy considered here is similar to the complier average causal effect discussed elsewhere (Angrist et al., 1996; Little and Rubin, 2000; Zhou and Li, 2006). Recently, Lui (2008a) has considered estimation of the *OR* for a RCT with both noncompliance and missing outcomes, but restricted the discussion on the simplest case of a single 2×2 table. These results and findings are inapplicable to the situations considered here when there are confounders needed to take into account. For example, in a multi-centre trial, patients who attend various centers may possess different characteristics and thereby, the probability of patient response can vary between centers. To account for the centre effects on the probability of patient response, we may wish to employ stratified analysis with strata formed by centers. Some recent discussions on estimation of other important measure, including risk difference (RD) or risk ratio (RR), for a RCT with noncompliance under various situations also appear elsewhere (Frangakis and Rubin, 1999; Zhou and Li, 2006; Lui, 2007a,b,c, 2008b; Lui and Chang, 2007; Lui and Cumberland, 2008). None of these papers discusses, however, estimation of the *OR* under a stratified RCT with noncompliance as focused here. Note that the probability of response is often not extremely small in a RCT, the RR and *OR* cannot be regarded as similar measures as commonly done for rare diseases in epidemiology. Thus, the results about estimation of the RR in stratified analysis (Lui and Chang, 2007) cannot be applied here.

In this paper, we consider estimation of the *OR* in large strata under a stratified RCT with noncompliance. We have developed five asymptotic interval estimators for the *OR*. We employ Monte Carlo simulation to evaluate the finite-sample performance of these interval estimators in a variety of situations. We use the data taken from a multiple risk factor intervention trial (MRFIT) (Multiple Risk Factor Intervention Trial Research Group, 1982) to illustrate the use of interval estimators appropriate for being employed when the number of strata is small or moderate.

2. Notations and methods

Consider comparing an experimental treatment ($G = 1$ for experimental) with a standard treatment ($G = 0$ for standard) in data with K strata formed by centers in a multi-centre study or by the combined levels of several confounders in a RCT. Suppose that for each stratum k ($k = 1, 2, \ldots, K$), we randomly assign patients to either of these two treatments, but there are some patients not complying with their assigned treatment. Following Angrist et al. (1996), we define for each patient the function $D(G)$ as the status of his/her received treatment: $D(G) = 1$ if the patient assigned to treatment G actually receives the experimental treatment, and $D(G) = 0$ otherwise. Thus, we may divide our population into four subpopulations. These include compliers ($D(1) = 1$ and $D(0) = 0$), never-takers ($D(1) = D(0) = 0$), always-takers ($D(1) = D(0) = 1$), and defiers ($D(1) = 0$ and $D(0) = 1$). As commonly assumed for a RCT with noncompliance (Zhou and Li, 2006; Li and Frangakis, 2005), we also assume monotonicity ($D(1) \geq D(0)$) (i.e., no defiers). Thus, if a patient assigned to the experimental treatment ($G = 1$) receives the standard treatment ($G = 0$), he/she must be a never-taker. Similarly, if a patient assigned to the standard treatment receives the experimental treatment, he/she must be an always-taker. However, if a patient assigned to the experimental treatment receives his/her assigned (experimental) treatment, he/she can be either a complier or an always-taker. Also, if a patient assigned to the standard treatment receives his/her assigned (standard) treatment, he/she can be either a complier or a never-taker. For each given stratum k ($k = 1, 2, \ldots, K$), we let $\pi_{1J|k}^{(G)}$ denote the cell probability for a randomly selected patient assigned to treatment G ($G = 1, 0$) who has a positive response and falls in category J: $J = C$ for compliers, $=$A for always-takers, and $=N$ for never-takers. We further let $\pi_{2J|k}^{(G)}$ denote the corresponding cell probability of a negative response for a randomly selected patient assigned to treatment G in stratum k. To conveniently represent summation over a given subscript, we use "+" notation to designate summation of cell probabilities over that particular subscript. For example, we let $\pi_{+J|k}^{(1)}$ represent $\pi_{1J|k}^{(1)} + \pi_{2J|k}^{(1)}$. Note that because we randomly assign patients to one of the two treatments, we have $\pi_{+J|k}^{(1)} = \pi_{+J|k}^{(0)} = \pi_{+J|k}$ for $J = C, A, N$, where $\pi_{+J|k}$ denotes the distribution of subpopulations in the sampling population. We define $\pi_{1|Jk}^{(G)} = \pi_{1J|k}^{(G)}/\pi_{+J|k}$ ($G = 1, 0, J = C, A, N$), the conditional probability of a positive response for patients assigned to treatment G ($G = 1, 0$) among subpopulation J in stratum k. Since randomized patients, who are always-takers (or never-takers), will take the same experimental (or standard) treatment regardless of their assigned treatments within each stratum, the exclusion restriction assumption (Angrist et al., 1996) for always-takers