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Statistical meta-analysis for ordinal categorical data

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ABSTRACT

Traditionally the odds ratio (OR) is used for measuring the extent of association between exposure and its binary outcomes in randomised controlled trials (RCTs) and similar studies. It is inapplicable if the outcomes are on an ordinal scale with more than two categories. In those studies, the generalised odds ratio (GOR) is used for summarising the difference between two stochastically ordered distributions of an ordinal categorical variable. Meta-analysis combines data from various independent trials in estimating the overall effect measure to make the sample size larger so that the inference based on the combined data is more reliable. In this paper we developed a method of meta-analysis using the GOR under independent multinomial sampling scheme for ordinal categorical data.

Keywords: Generalised odds ratio; Ordinal data; Multinomial distribution; Meta-analysis

1 Introduction

The first meta-analysis was performed by Pearson (1904) to overcome the problem of reduced statistical power in studies with small sample sizes; analyzing the results from a group of studies can allow more accurate data analysis [14]. Although meta-analysis is widely used in epidemiology and evidence-based medicine today, a meta-analysis of a medical treatment was not published until 1955. Glass (1976) and Hunter and Schmidt (1990) introduced more sophisticated analytical techniques in educational research in the 1970s. The method for meta-analysis introduced by Peto (1987) was the most widely used technique for adding together homogeneous studies. Then Thompson and Pocock (1987) concluded that meta-analysis provides clear qualitative conclusions but quantitative results have to be interpreted

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carefully as it fails to provide conclusive results for broad treatment policies when there exists heterogeneity among the studies.

It is common to use the relative risk (RR) or odds ration (OR) for measuring effect sizes for binary outcomes in epidemiology. But there are situations in which subjects are classified into several categories of severity of disease and exposures making RR and OR inappropriate. There are some measures proposed for handling outcomes of trials with more than two categories. [4] introduced some odds ratio statistics for the analysis of ordered categorical data assuming a specific model assumption. Later Clayton (1976) generalised the estimators for the case in which some observations are subject to censorship. McCullagh (1977) used paired comparisons on the ordinal variable. Whitehead and Jones (1994) developed stratified proportional odds model for ordinal outcomes transforming the $(j \times l;\ j = 1, 2, \ldots, J;\ l = 1, 2, \ldots, L)$ contingency table for the ith (for $i = 1, 2, \ldots, k$) study into different combinations of 2×2 tables using log odds ratio as the effect measure. Whitehead et al. (2001) also proposed a proportional odds model on individual patient data by the log odds ratio with a general framework for fixed and random effects models. The above studies used either a 2×2 contingency table or a specific model to produce the treatment effect. Edwardes and Baltzan (2000) proposed pooling γ's instead of general odds ratio ($\mathrm{OR}_G = (1+\gamma)/(1-\gamma)$, where γ is known as Goodman and Kruskal's γ) which is the same as Agresti (1980)'s α using sample size weights although weighting by sample size may be misleading when heterogeneity exists among the studies. More importantly a variance estimate is a must for the pooled confidence interval (CI) of the OR_G. Whereas pooling by inverse variance weighted method is more appropriate and makes sense in the presence of heterogeneity.

The generalised odds ratio (GOR) introduced by Agresti (1980) can be easily used as an effect measure for ordinal categorical data for the general $J \times L$ table. This measure is free from any specific model assumption and can be computed directly from the $J \times L$ table. This study attempts to employ GOR to measure the treatment effects for ordered categorical data and then combining the outcome using inverse variance weighted method in meta-analysis without merging the columns of $J \times L$ table. Pooling and using a common study effect for homogeneous studies in meta-analysis has an statistical agreement that in the forest plot the vertical line through the point estimate of the common pooled study effect passes through all the confidence intervals (CIs) of the individual study effects. Unfortunately in many studies there exist statistical disagreement to use the common pooled study effect if the outcome variable is heterogeneous. "Doing a meta-analysis is easy", says Ingram Olkin but "Doing one well is hard" as heterogeneity among studies may lead to incorrect meta-analysis Mann (1990). For discussions on simple pooling and meta-analysis see Bravata and Olkin (2001). Further details on the topic can be found in Emerson (1994) and Egger and Smith (1997).

2 Generalized Odds Ratio

Let J be the number of comparison groups with L ordered outcome categories in each group. Then the $J \times L$ contingency table represents the joint distribution of two ordinal categorical variables. In Table 1, X_{ijl} is the count of the lth category in the jth group for the ith study, $n_{ij.}$ is the total count of jth group for the ith study, $X_{i1L} = n_{i1.} - X_{i11} - X_{i12} - \cdots - X_{i1(L-1)}$, $X_{i2L} = n_{i2.} - X_{i21} - X_{i22} - \cdots - X_{i2(L-1)}$ and $X_{iJL} = n_{iJ.} - X_{iJ1} - X_{iJ2} - \cdots - X_{iJ(L-1)}$.

When both J, $L = 2$, the GOR reduces to the OR for a single 2×2 contingency table. In this study, we refer J=2 comparison groups in RCTs, namely the treatment group and the control group. More details about GOR and its mathematical formulation under independent multinomial sampling for randomized controlled trials are given below.

Table 1: Contingency table for the ith study.

Groups	Category 1	Category 2	$\cdots$	Category L	Sample size
Treatment	X_{i11}	X_{i12}	$\cdots$	X_{i1L}	$n_{i1.}$
Control	X_{i21}	X_{i22}	$\cdots$	X_{i2L}	$n_{i2.}$

The GOR is defined as the ratio of the two proportions of concordant and discordant pairs Agresti (1980, 1990). A pair is said to be concordant if the subject ranked higher on groups/rows also ranks higher on categories/columns. Without loss of generality we assume that the response in category l' is more severe than the response in category l where $l < l'$. Mathematically, the GOR for the ith is defined as

$$\Gamma_i = (\Pi_d)^{-1}\Pi_c, \tag{1}$$

where $\Pi_c = \sum_{r=1}^{L-1}\sum_{s=r+1}^{L}\Pi_{r|1}\Pi_{s|2}$ and $\Pi_d = \sum_{r=2}^{L}\sum_{s=1}^{r-1}\Pi_{r|1}\Pi_{s|2}$. Here, Π_c denotes the probability that the response of a randomly selected subject from group 2 is severer than the response of a randomly selected subject from group 1. Similarly, Π_d denotes the probability that the response of a randomly selected subject from group 1 is severer than the response of a randomly selected subject from group 2. The data with zero cell count is analysed adding $\frac{1}{L}$ to each entry before calculation of the GOR. The value of Γ_i may vary from 0 to ∞. Γ_i =1, represents identical comparison groups as it is in odds ratio.

Suppose an independent random sample of size $n_{ij.}$ are taken from group j (j=1, 2) and X_{ijl} denote the count falling into category l of the ith study. Then the random vector $(X_{ij1}, X_{ij2}, \ldots, X_{ijL})$ follows the multinomial distribution with parameters $n_{ij.}$ and $\pi'_{ij} = (\pi_{i1|j}, \pi_{i2|j}, \ldots, \pi_{iL|j})$, where $\pi_{il|j}$ is the probability of a subject to be in the lth category within the jth comparison group for the ith study.

The maximum likelihood estimator (MLE) of $\pi_{il|j}$ is given by $\hat{\pi}_{il|j} = X_{ijl}/n_{ij.}$ for the ith study. For large $n_{ij.}$, $\sqrt{n_{ij.}}(\hat{\pi}_{ij} - \pi_{ij})$, where $\pi'_{ij} = (\pi_{i1|j}, \pi_{i2|j}, \ldots, \pi_{iL|j})$, asymptotically

follows the L-dimensional multivariate normal distribution with mean vector $\mathbf{0}$ and $L \times L$ covariance matrix with the diagonal entries $\pi_{il|j}(1-\pi_{il|j})$, and off-diagonal entries $-\pi_{il|j}\pi_{il'|j}$ for $l \neq l'$. The MLE of Γ_i, say $\hat{\Gamma}_i$, is defined as

$$\hat{\Gamma}_i = (\hat{\Pi}_d)^{-1}\hat{\Pi}_c \tag{2}$$

where $\hat{\Pi}_c = \sum_{r=1}^{L-1}\sum_{s=r+1}^{L}\hat{\pi}_{r|1}\hat{\pi}_{s|2}$ and $\hat{\Pi}_d = \sum_{r=2}^{L}\sum_{s=1}^{r-1}\hat{\pi}_{r|1}\hat{\pi}_{s|2}$ for the ith study. In addition to the MLE of Γ_i the variance of the MLE is required to construct the CI for Γ_i. Using the delta method [2], the asymptotic variance of $\hat{\Gamma}_i$ becomes

$$\begin{aligned}\text{Asy.Var}(\hat{\Gamma}_i) &= \frac{\sum_{r=1}^{L}[\sum_{s=r+1}^{L}\pi_{s|2} - \Gamma\sum_{s=1}^{r-1}\pi_{s|2}]\pi_{r|1}}{n_1\Pi_d^2} \\ &+ \frac{\sum_{s=1}^{L}[\sum_{r=s-1}^{L}\pi_{r|1} - \Gamma\sum_{r=s+1}^{L}\pi_{r|1}]\pi_{s|2}}{n_2\Pi_d^2}.\end{aligned} \tag{3}$$

Here by convention $\sum_{l=L+1}^{L}\pi_{l|j} = 0$ and $\sum_{l=1}^{0}\pi_{l|j} = 0$ for l=1, 2. To estimate $\text{Var}(\hat{\Gamma}_i)$, say $\widehat{\text{var}}(\hat{\Gamma}_i)$, we substitute $\hat{\pi}_{l|j}$ for $\pi_{l|j}$, $\hat{\Gamma}_i$ for Γ_i, and $\hat{\Pi}_d$ for Π_d in the definition of $\hat{\Gamma}_i$.

For large $n_{ij.}$'s an asymptotic $100(1-\alpha)$ percent confidence interval for the Γ_i is given by

$$\left[\max\left\{\hat{\Gamma}_i - Z_{\alpha/2}\sqrt{\widehat{\text{var}}(\hat{\Gamma}_i)}, 0\right\}, \hat{\Gamma}_i + Z_{\alpha/2}\sqrt{\widehat{\text{var}}(\hat{\Gamma}_i)}\right], \tag{4}$$

where $Z_{\alpha/2}$ is the upper $(100-\frac{\alpha}{2})$th percentile of the standard normal distribution.

2.1 Meta-analysis for fixed effects model

In the fixed effect model the effect the outcome variables are assumed to be drawn from the same population. For $i = 1, 2, \cdots, k$ independent studies if $\hat{\Gamma}_i$ represents logarithm of GOR, the observed effect size with variance v_i, then assuming $\Gamma_1 = \Gamma_2 =, \cdots, \Gamma_k = \Gamma_0$, a pooled estimate of the treatment effect is given by

$$\hat{\Gamma}_0 = \frac{\sum_i \omega_i\hat{\Gamma}_i}{\sum_i \omega_i}. \tag{5}$$

For an arbitrary number of outcome categories (L) in RCTs in which each row is modeled as an independent multinomial distribution, the estimated variance of the ith study is

$$\hat{\omega}_i^{-1} = \sum_{l=1}^{L-1}\sum_{j=1}^{2}\frac{1}{n_{ij.}\hat{\pi}_{ijl}(1-\hat{\pi}_{ijl})} \tag{6}$$

where $n_{ij.}$ is the total count of the jth group for the ith study, $\hat{\pi}_{ijl} = X_{ijl}/n_{ij.}$ is the MLE of π_{ijl} and X_{ijl} is the count of the lth category in the jth group for the ith study.

Assuming $\hat{\Gamma}_i$'s are normally distributed, an approximate $100(1-\alpha)\%$ CI for the ith GOR is given by the formula

$$\exp\left[\hat{\Gamma}_i \pm z_{\alpha/2}\omega_i^{-1/2}\right]. \tag{7}$$

If $\hat{\Gamma}_0$ is assumed to be normally distributed, an approximate $100(1-\alpha)\%$ confidence interval (CI) for the population effect, Γ_0, is given by

$$\exp\left[\hat{\Gamma}_0 \pm z_{\alpha/2}\omega^{-1/2}\right], \tag{8}$$

for the meta analysis where $\hat{\omega}^{-1} = \text{var}(\hat{\Gamma}_0) = 1/\sum_{i=1}^{k}\omega_i$ and $z_{\alpha/2}$ is the $\alpha/2\times 100$ percentage point of a standard normal distribution.

2.2 Meta-analysis for random effects model

In the random effects model the outcome variables are considered to be randomly drawn from different populations. Define $\bar{\omega}$ and s_W^2 to be the mean and variance of the weights from the k studies:

$$\bar{\omega} = \sum_{i=1}^{k}\omega_i/k \text{ and } s_W^2 = \frac{1}{k-1}\left(\sum_{i}^{k}\omega_i^2 - k\bar{\omega}^2\right). \tag{9}$$

Further, define

$$U = (k-1)\left(\bar{\omega} - \frac{s_W^2}{k\bar{\omega}}\right) \text{ and } Q = \sum_{i=*}^{k}\omega_i(\hat{\Gamma}_i - \bar{\Gamma}.)^2, \tag{10}$$

where Q is the heterogeneity test statistic, also known as Cochran's χ^2 statistic [?] for testing the $H_0 = \Gamma_1 = \Gamma_2 = \cdots \Gamma_k = \Gamma_0$. The estimated component of variance due to inter-study variation in effect size, $\hat{\tau}_\Gamma^2$, is calculated as

$$\hat{\tau}_\Gamma^2 = \begin{cases} 0 & \text{if} \quad Q \le k-1 \\ (Q-(k-1))/U & \text{if} \quad Q > k-1. \end{cases} \tag{11}$$

A $100(1-\alpha)\%$ CI for Γ_i is given by

$$\exp\left[\hat{\Gamma}_{iR} \pm z_{\alpha/2}/\sqrt{\omega_i^*}\right], \tag{12}$$

where $\omega_i^* = \frac{1}{[1/\omega_i]+\hat{\tau}_\Gamma^2}$, under the assumption of normality.

The point estimate for the mean treatment effect of all studies, Γ_0, can be computed by

$$\hat{\Gamma}_{0R} = \sum_{i=1}^{k}\omega_i^*\hat{\Gamma}_i/\sum_{i=1}^{k}\omega_i^*. \tag{13}$$

If normality of Γ_{0R} is assumed, a $100(1-\alpha)\%$ CI for Γ_0 is given by

$$\exp\left[\hat{\Gamma}_{0R} \pm z_{\alpha/2}/\sqrt{\sum_{i=1}^{k}\omega_i^*}\right]. \tag{14}$$

3 Conclusions

In this paper, we develop a meta-analysis method using GOR for multi-levels ordinal categorical outcomes. The currently available proportional odds model is restricted to the proportionality assumption and there is no well defined variance estimate of the pooled estimate for the sample size weight method. Use of the LOR or similar effect measures for multi-levels ordinal outcomes by collapsing a $2 \times L$ table into 2×2 tables causes loss of information, inflate the estimate and inappropriately reduce the spread.

The proposed meta-analysis method using GOR is very simple and has straightforward interpretation. It has simple variance estimate for individual study and meta-analysis. It can also be used for binary and latent continuous outcomes. Therefore, GOR is a very useful and superior effect measure in meta-analysis for the ordinal categorical data.

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