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Interval estimation of diagnostic odds ratio in meta-analysis by means of profile likelihoods

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Abstract

The objectives of this paper are to (1) derive the profile maximum likelihood estimator $(PMLE)$ for a true diagnostic odds ratio over across k studies in meta-analysis, (2) build the confidence intervals by replacing $PMLE$ into the variance of logarithm of each diagnostic odds ratio, leading to two profile likelihood intervals ($WPLF$, $WPLR$), (3) create bootstrapping confidence interval ($BOOT$) from $PMLE$ distribution by using the percentile, (4) compare the interval performance between all profile intervals with the conventional intervals, such as Mantel-Haenszel method (MH) and Weighted least squares method (WLS) in terms of the coverage probability and the width of interval. The results under a simulation plan indicated that for moderated study size (k = 8, 16) and small sample size ($n_i^D, n_i^H \leq 50$), there were only three proposed interval estimates ($WPLF$, $WPLR$, and $BOOT$) that could be calibrated the coverage probability at 95% and the interval widths of $WPLF$ and $WPLR$ are narrower than the $BOOT$. Hence, we recommend to use $WPLF$ and $WPLR$ rather than the conventional intervals in such situations.

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1. Introduction

Meta-analysis is the statistical procedure to integrate all various results of several studies into one true result. Conventionally, the weighted average estimators such as Mantel-Haenszel method and Weighted Least Square

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method are used to estimate the effect size. According to the book of Böhning et al. [1], the profile maximum likelihood estimator $(PMLE)$ under effect homogeneity of relative risks (RR) performs better than the Mantel-Haenszel estimator with the smaller bias and smaller variance when RR ranged between 0.0001 to 0.3333. Conversely, information of the $PMLE$ for the diagnostic odds ratio (DOR) as the effect of interest is limited. A gap of study is based on the insufficient knowledge of the $PMLE$ on the DOR.

2. Deriving the profile likelihood under effect homogeneity

Suppose that the diagnostic odds ratio is defined by the ratio of the odds of positivity in disease relative to the odds of positivity in the non-diseased group. The diagnostic odds ratio estimator is $\widehat{DOR} = (TP/FN)/(FP/TN) = \left[(1-\hat{p}^D)/\hat{p}^D\right]/\left[\hat{p}^H/(1-\hat{p}^H)\right]$, where the false negative rate $\left(\hat{p}^D = x^D/n^D\right)$ is the probability that the test is negative among diseased persons and the false positive rate $\left(p^H = x^H/n^H\right)$ is the probability that the test is positive among healthy persons. After maximizing the binomial log-likelihood with respect to the nuisance parameter p_i^D for the $i-th$ study $(i=1,2,...,k)$, the solution is as

$$p_i^D = f_i\left(DOR_i\right) = -\left(\frac{n_i + X_i - X_i \cdot DOR_i - p_i\left(DOR_i\right)}{2\left(DOR_i - 1\right)\left(n_i^D\right)}\right)$$

where $X_i = x_i^D - x_i^H$, $n_i = n_i^D + n_i^H$, $p_i\left(DOR_i\right) = \sqrt{\left(n_i + X_i - X_i \cdot DOR_i\right)^2 + 4\left(DOR_i - 1\right)\left(n_i^D\right)\left(X_i + n_i^H\right)}$. Under homogeneity of $DOR_1 = ... = DOR_k = DOR$, the solution of the pooled diagnostic odds ratio of profile likelihood is

$$DOR_{PMLE} = \frac{\sum_{i=1}^{k}\left(n_i^H - x_i^H\right)}{\sum_{i=1}^{k}\left(\frac{\left(n_i^D - X_i\right) f_i'\left(DOR\right)}{1 - f_i\left(DOR\right)} + \frac{n_i^H\left(\left(DOR \cdot f_i'\left(DOR\right) + f_i\left(DOR\right)\right) - f_i'\left(DOR\right)\right)}{1 - f_i\left(DOR\right) + DOR \cdot f_i\left(DOR\right)} - \frac{\left(n_i^H + X_i\right) f_i'\left(DOR\right)}{f_i\left(DOR\right)}\right)}.$$

3. Recalling the conventional inverse-variance weighted estimator

Under effect homogeneity for estimating $T = log(DOR)$ over all k studies, the conventional weighted least squares estimator [1, 2] is of the form $\hat{T}_{WLS} = \sum_{i=1}^{k} w_i \hat{T}_i \Big/ \sum_{i=1}^{k} w_i$ where $\hat{T}_i = log\left(\widehat{DOR_i}\right)$, $w_i = 1/V(\hat{T}_i)$, and the variance of $\hat{T}_i$ is estimated by $\hat{V}(\hat{T}_i) = \frac{1}{\hat{w}_i} \approx \frac{1}{n_i^D\left(\hat{p}_i^D\right)\left(1-\hat{p}_i^D\right)} + \frac{1}{n_i^H\left(\hat{p}_i^H\right)\left(1-\hat{p}_i^H\right)}$. In addition, the variance estimate of $\hat{T}_{WLS}$ is given as $\hat{V}(\hat{T}_{WLS}) = 1\Big/\sum_{i=1}^{k}\hat{w}_i$. The 95% confidence interval (CI) for population effect of $T = log(DOR)$ under normal approximation is given as $\hat{T}_{WLS} - 1.96\sqrt{\hat{V}(\hat{T}_{WLS})} \le log\left(DOR\right) \le \hat{T}_{WLS} + 1.96\sqrt{\hat{V}(\hat{T}_{WLS})}$, leading to the 95% CI of DOR as $\widehat{DOR}_{WLS} \cdot exp\left(\pm 1.96\sqrt{\hat{V}(\hat{T}_{WLS})}\right)$ where $\widehat{DOR}_{WLS} = exp\left(\hat{T}_{WLS}\right)$.

4. Constructing two confidence intervals of profile likelihood estimator

The idea to create the confidence intervals ($WPLR$, $WPLF$) of the $PMLE$ for estimating a true constant DOR over across k studies is based on the substitution of the $PMLE$ into the variance formula of logarithm of each diagnostic odds ratio. Referring above, the conventional variance of $\hat{T}_i = log\left(\widehat{DOR_i}\right)$ is

$$\hat{V}(\hat{T}_i) = \frac{1}{\hat{w}_i} \approx \frac{1}{n_i^D\left(\hat{p}_i^D\right)\left(1-\hat{p}_i^D\right)} + \frac{1}{n_i^H\left(\hat{p}_i^H\right)\left(1-\hat{p}_i^H\right)} \quad (1)$$