Implementation of Miettinen-Nurminen score method with or without stratification in R

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ABSTRACT

Analysis of a 2 × 2 table for clinical data involves computing the point estimate and confidence interval for risk difference, relative risk, or odds ratio. While point estimates of these comparative parameters are uniquely defined, several statistical methods have been proposed to estimate the confidence interval for each parameter. The Miettinen-Nurminen (MN) score method is expected to be used increasingly over traditional interval estimation methods. The MN score method has not been previously implemented in R software for data with stratification. There is a need for a comprehensive software implementation of the MN score method. This article describes the implementation of the MN score method in the sasLM R software package. To demonstrate the usage of the sasLM functions introduced, recently published clinical data are provided as examples.

Keywords: Confidence Intervals; Odds Ratio; Risk

INTRODUCTION

A 2 × 2 table is constructed with clinical data to compare the effect of a novel treatment to that of a reference treatment. The structure of a typical 2 × 2 table for clinical data is shown in Table 1. The total number of subjects who received novel or reference treatment is denoted as \(n_1\) and \(n_2\), respectively. The number of subjects who had pre-defined events after receiving the novel or reference treatment is denoted as \(y_1\) and \(y_2\), respectively.

The risk of an event in each population receiving novel or reference treatment can be estimated using the following equations:

\[
R_1 = \frac{y_1}{n_1} \\
R_2 = \frac{y_2}{n_2}
\]

Table 1: Structure of a 2 × 2 table

| Treatment      | Event | Yes | No  | Total |
|----------------|-------|-----|-----|-------|
| Novel          |       |     |     |       |
| Reference      |       |     |     |       |

\[\begin{array}{ccc}
\text{Novel} & y_1 & n_1 - y_1 & n_1 \\
\text{Reference} & y_2 & n_2 - y_2 & n_2 \\
\end{array}\]
The risk difference (RD) is a direct comparison of the two risks, for which the point estimate and standard error (SE) are defined as follows.

Risk difference (RD) = \( R_1 - R_2 \)

SE(RD) = \( \sqrt{\frac{R_1(1 - R_1)}{n_1} + \frac{R_2(1 - R_2)}{n_2}} \)

The ratio of the risks gives relative risk (RR), for which the point estimate and SE are defined as follows.

Relative risk (RR) = \( \frac{R_1}{R_2} \)

SE(log RR) = \( \sqrt{\frac{1}{y_1 - 1} + \frac{1}{y_2 - 1}} \)

The odds of an event are defined by the number of events divided by the number of non-events.

\( O_1 = \frac{y_1}{n_1 - y_1} = \frac{R_1}{1 - R_1} \)

\( O_2 = \frac{y_2}{n_2 - y_2} = \frac{R_2}{1 - R_2} \)

The ratio of the odds gives odds ratio (OR), for which the point estimate and SE are defined as follows.

Odds ratio (OR) = \( \frac{O_1}{O_2} = \frac{\frac{R_1}{1 - R_1}}{\frac{R_2}{1 - R_2}} \)

SE(log OR) = \( \sqrt{\frac{1}{y_1} + \frac{1}{n_1 - y_1} + \frac{1}{y_2} + \frac{1}{n_2 - y_2}} \)

Analysis of a 2 × 2 table involves computing the point estimate and confidence interval (CI) for RD, RR, or OR. All three comparative parameters (RD, RR, and OR) can be determined in a prospective randomized trial. However, RD and RR cannot be determined in a case-control study, and OR serves as the sole comparative parameter.

While point estimates of these comparative parameters are uniquely defined, several statistical methods have been proposed to estimate the CI for each parameter [1]. The following equation shows the classical method of interval estimation that yields Wald CI.

\[ CI = \text{point estimate} \pm z_{\alpha/2} \cdot \text{SE} \]

Here, \( \alpha \) is the confidence level, and \( z_{\alpha/2} \) is the number corresponding to the \((0.5 + \alpha/2) \times 100\) percentile from the standard normal distribution. The limitation of Wald CI is that it is unreliable when the sample size is small or the point estimate approaches the value of 0 or 1.

In a dissertation thesis published in 1985, Miettinen and Nurminen delineated a new method that uses restricted estimation of variance in the chi-square function for interval estimation.
This Miettinen-Nurminen (MN) score method is theoretically more appropriate than traditional ones. It is recommended in one of the most preferred textbooks on categorical data analysis, which was written by Alan Agresti [3]. It was also the method of choice in analyzing phase 3 trial data of molnupiravir for the treatment of coronavirus disease 2019 (COVID-19) [4]. For these reasons, authors expect this method to become increasingly popular in the near future. This article describes the implementation of the MN score method in the sasLM R software package.

METHODS

Two different sets of functions were necessary to implement the MN score method because the method uses weight when the data has stratification. A set of three functions (RDmn1, RRmn1, and ORmn1) was designed to estimate the MN CI of RD, RR, and OR for data without stratification. Another set of three functions (RDmn, RRmn, and ORmn) was designed for data with stratification. Analysis of stratified data is methodologically similar to meta-analysis. These functions were packaged into a pre-existing R package, sasLM, which contained a set of three functions (RD, RR, and OR) for Wald CI estimation [5,6]. The functions were encoded by Kyun-Seop Bae, based on the procedures described in the original article by Miettinen and Nurminen [2]. R version 4.2.1, PropCIs version 0.3-0, and sasLM version 0.9.2 were used for the implementation and analyses presented in the results section.

RESULTS

The sasLM package contains a comprehensive set of functions for estimating the MN score CI of a 2 × 2 table. In addition, the package also has functions for traditional methods. The 2 × 2 table analysis functions in the sasLM package can be divided into four groups: 1. Wald CI for data without stratification; 2. MN score CI for data without stratification; 3. Cochran-Mantel-Haenszel CI for data with stratification; 4. MN score CI for data with stratification. The list of implemented functions and the source codes can be found on the Comprehensive R Archive Network (CRAN) at https://CRAN.R-project.org/package=sasLM.

Wald CI for data without stratification - sasLM::RD, RR, OR

Before we discuss the MN score functions, it is worthwhile to mention that the sasLM package also provides functions of interval estimation by the classical method. CIs estimated by the classical method can be compared with those estimated by the MN method. For data without stratification, Wald CIs for RD, RR, and OR can be computed by sasLM functions RD, RR, and OR, respectively.

As an example, interim analysis data from a recently published study on molnupiravir for the treatment of COVID-19 is presented in Table 2 [4]. In this phase 3 clinical trial, efficacy was assessed by the number of events, defined as the incidence of hospitalization or death for 29 days after randomization.

| Table 2. Example 1  |
|----------------------|
| Treatment           | Number of events | Number of participants |
| Molnupiravir         | 28               | 385                     |
| Placebo             | 53               | 377                     |

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Wald CIs for Table 2 data are obtained by the following script (Fig. 1).

```
install.packages("sasLM")
library(sasLM)
RD(y1=28, n1=385, y2=53, n2=377)
p1 p2 RD SE lower upper
1 0.07272727 0.1405836 -0.06785628 0.02226299 -0.1114909 -0.02422163

RR(y1=28, n1=385, y2=53, n2=377)
p1 p2 RR SELog lower upper
1 0.07272727 0.1405836 0.5173242 0.2221087 0.3347368 0.7995866

OR(y1=28, n1=385, y2=53, n2=377)
odd1 odd2 OR SELog lower upper
1 0.07843137 0.16358025 0.47946726 0.29705752 0.2961034 0.7763803
```

Figure 1. R script and result for Wald confidence interval – sasLM::RD, RR, OR.

The confidence level can be specified, and if not specified, as in this script, the default level of 0.95 is used. Each function returns values for the point estimate and lower and upper confidence limits.

**MN score CI for data without stratification - sasLM::RDmn1, RRmn1, ORmn1**

The MN score CIs for RD, RR, and OR are computed by functions RDmn1, RRmn1, and ORmn1 of the sasLM package, respectively. The MN score CIs for Table 2 data are obtained by the following script (Fig. 2).

```
RDmn1(y1=28, n1=385, y2=53, n2=377)
p1 p2 RD lower upper
1 0.07272727 0.14058355 -0.06785628 -0.11285540 -0.02445596

RRmn1(y1=28, n1=385, y2=53, n2=377)
p1 p2 RR lower upper
1 0.07272727 0.14058355 0.51732419 0.33217812 0.80313200

ORmn1(y1=28, n1=385, y2=53, n2=377)
odd1 odd2 OR lower upper
1 0.07843137 0.16358025 0.47946726 0.29705752 0.29705752 0.7763803
```

Figure 2. R script and result for Miettinen-Nurminen score confidence interval – sasLM::RDmn1, RRmn1, ORmn1.

The point estimate of a parameter (RD, RR, or OR) remains the same for both methods. However, the CI changes slightly depending on the method of estimation.

For units of percentage, multiply the results by 100 and round it to the desired decimal point. For RD, the point estimate (−6.8 percentage point) and the 95% MN score CI (−11.3 to −2.4) are the same as those reported in the original article, which were obtained using SAS® version 9.4.

For confirmation of calculation correctness, the source codes for RDmn1, RRmn1, and ORmn1 are shown in Fig. 3.

**Comparison with the PropCIs package – PropCIs::diffscoreci, riskscoreci, orscoreci**

The PropCIs package provides functions for various interval estimation methods for proportions [7]. The MN score method was implemented in the PropCIs R package for
Implementation of MN score method

Figure 3. R script of RDmn1, RRmn1, and ORmn1 functions.
data without stratification but not for data with stratification. The respective functions for estimating MN score CI for RD, RR, and OR are `diffscoreci`, `riskscoreci`, and `orscoreci`.

To compare the results obtained with sasLM functions (Fig. 2), an analysis of the same data by PropCIs functions is shown in Fig. 4.

```r
install.packages("PropCIs")
library(PropCIs)
diffscoreci(x1=28, n1=385, x2=53, n2=377, conf.level=0.95)
data:
  95 percent confidence interval:
  -0.1128553 -0.0244560
riskscoreci(x1=28, n1=385, x2=53, n2=377, conf.level=0.95)
data:
  95 percent confidence interval:
  0.3353390 0.7955456
orscoreci(x1=28, n1=385, x2=53, n2=377, conf.level=0.95)
data:
  95 percent confidence interval:
  0.2969481 0.7741719
```

Figure 4. R script and result for Miettinen-Nurminen score confidence interval – PropCIs::diffscoreci, riskscoreci, orscoreci.

Note that the results are the same for RD (`RDmn1` and `diffscoreci` functions), but they are different for RR (`RRmn1` and `riskscoreci` functions) and OR (`ORmn1` and `orscoreci` functions). The reason for this observation will be addressed in the discussion section.

**Cochran-Mantel-Haenszel CI for data with stratification - sasLM::ORcmh**

The Cochran-Mantel-Haenszel test is used as a classical statistic in the analysis of stratified data. ORcmh is a function in the sasLM package that computes OR and associated CI for two groups with stratification by the Cochran-Mantel-Haenszel method.

As an example of data with stratification, the final data gathered from all randomized participants of the molnupiravir trial is presented in Table 3 [4]. Randomization was stratified according to the time since symptom onset.

Analysis of Table 3 data is demonstrated in Fig. 5.

It returns the same values as `mantelhaen.test` of the stats R package, but the data input formats are different. For `mantelhaen.test`, the data input should be a 3-dimensional array or a factor object with at least two levels. For ORcmh, the data input should be in the simple form of a data frame or matrix, of which each row means a stratum and the four required column names are y1, n1, y2, and n2.

### Table 3. Example 2

| Strata                | Molnupiravir | Placebo |
|-----------------------|--------------|---------|
|                       | Number of events | Number of participants | Number of events | Number of participants |
| ≤ 3 days of symptom onset | 25            | 339       | 28            | 335       |
| > 3 days of symptom onset | 23            | 370       | 40            | 364       |
To estimate MN score CI for data with stratification, weight is given to each stratum in proportion to the amount of comparative information in it. The MN method is implemented in RDmn, RRmn, and ORmn functions of the sasLM package for RD, RR, and OR, respectively. The MN score CI functions for data with stratification in sasLM package can be verified by any reader as the source codes are open on CRAN [5]. The analysis of Table 3 data is demonstrated in Fig. 6.

### Implementation of MN score method

```r
data2 = data.frame(y1=c(25, 23), n1=c(339, 370), y2=c(28, 40), n2=c(335, 364))
data2
y1 n1 y2 n2
1 25 339 28 335
2 23 370 40 364

ORcmh(data2)
$ORs
odd1       odd2        OR     SElog     lower     upper
1 0.07961783 0.09120521 0.8729527 0.2866293 0.4977502 1.5309816
2 0.06628242 0.12345679 0.5368876 0.2728489 0.3145096 0.9165007

$Common
OR     SElog     lower     upper
1 0.6740762 0.196439 0.4586694 0.9906452

RDmn(data2)
$Strata
p1         p2           RD       lower        upper
1 0.07374631 0.08358209 -0.009835777 -0.05174840  0.031572839
2 0.06216216 0.10989011 -0.047727948 -0.08980705 -0.007330023

$Common
p1           p2           RD        lower        upper
0.067708565 0.097294830 -0.029585465 -0.058936760 -0.000855763

RRmn(data2)
$Strata
p1         p2        RR     lower     upper
1 0.07374631 0.08358209 0.8823220 0.5190589 1.4989567
2 0.06216216 0.10989011 0.5656757 0.3421610 0.9326189

$Common
p1         p2         RR      lower      upper
0.06770635 0.09729907 0.71722286 0.50158714 1.02477468

ORmn(data2)
$Strata
odd1       odd2        OR     lower     upper
1 0.07961783 0.09120521 0.8729527 0.5004017 1.5229755
2 0.06628242 0.12345679 0.5368876 0.3160002 0.9124205

$Common
odd1       odd2         OR      lower      upper
0.07239721 0.10866823 0.69098604 0.50158714 1.02477468

round(RDmn(data2)$Strata*100, 1)
p1   p2   RD lower upper
1  7.4  8.4  -1.0  -5.2   3.2
2  6.2 11.0  -4.8  -9.0  -0.7

round(RDmn(data2)$Common*100, 1)
p1   p2   RD lower upper
 6.8  9.7  -3.0  -5.9  -0.1
```

**Figure 5.** R script and result for Cochran-Mantel-Haenszel confidence interval – sasLM::ORcmh.

**Figure 6.** R script and result for Miettinen-Nurminen score confidence interval – sasLM::RDmn, RRmn, ORmn.

**MN score CI for data with stratification - sasLM::RDmn, RRmn, ORmn**

To estimate MN score CI for data with stratification, weight is given to each stratum in proportion to the amount of comparative information in it. The MN method is implemented in RDmn, RRmn, and ORmn functions of the sasLM package for RD, RR, and OR, respectively. The MN score CI functions for data with stratification in sasLM package can be verified by any reader as the source codes are open on CRAN [5]. The analysis of Table 3 data is demonstrated in Fig. 6.
Each function returns the values for each stratum as well as common values. In this example, the difference in risk is −1.0 percentage point with a 95% confidence interval of −5.2 to 3.2 for the first stratum. For the second stratum, the difference is −4.8 percentage points with a 95% confidence interval of −9.0 to −0.7. Overall, the RD is −3.0 percentage points, and the 95% confidence interval is −5.9 to −0.1 for all randomized participants.

DISCUSSION

The MN score method has not been previously implemented in R software for data with stratification. In the PropCIs R package, the MN score method was implemented for data without stratification. In order to provide a comprehensive set of functions for estimating the MN score CI, appropriate functions were implemented in the sasLM package.

The sasLM package allows the estimation of CI by the classical Wald method, Cochran-Mantel-Haenszel method, and MN score method. Functions RD, RR, and OR compute the Wald CIs for data without stratification. Functions RDmn1, RRmn1, and ORmn1 provide the MN score CIs for unstratified data, whereas RDmn, RRmn, and ORmn provide those for stratified data. Functions for stratified data can also be used for meta-analysis of fixed effects.

In comparing sasLM functions (RDmn1, RRmn1, and ORmn1) with their respective PropCIs functions (diffscoreci, riskscoreci, and orscoreci), diffscoreci produces the same results as RDmn1. However, riskscoreci and orscoreci produce values slightly different from those by RRmn1 and ORmn1. This observation is explained by the fact that riskscoreci is based on cubic equation approximation of the objective function, and orscoreci increases or decreases the initial guess by a multiple of 1.001 in search of the solution. These procedures limit the accuracy of results, often to no more than three significant figures. SAS® and the PF R package use the same limited procedures in the MN score CI estimation for RR and OR.

In conclusion, the MN score method was implemented in the R sasLM package for analysis of 2 × 2 tables with and without stratification. This package is expected to serve the scientific community in accurately estimating RD, RR, and OR.

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