Vignettes for the R-package BMA: https://github.com/nomahi/BMA

Bartlett-type corrections for improved confidence intervals in random-effects meta-analysis

Hisashi Noma*
Department of Interdisciplinary Statistical Mathematics
The Institute of Statistical Mathematics
10-3 Midori-cho, Tachikawa, Tokyo 190-8562, Japan
*e-mail: noma@ism.ac.jp

In medical meta-analysis, the DerSimonian–Laird and restricted maximum likelihood (REML) confidence intervals for the average treatment effect have been widely used in practice. However, it is well recognized that their coverage probabilities, that is, the probabilities that the intervals contain the true value, can fall substantially below the nominal level. One important reason is that the validity of these confidence intervals relies on the assumption that the number of studies included in the synthesis is sufficiently large. In most medical meta-analyses, however, the number of studies is fewer than 20. Noma (2011) developed three alternative confidence intervals to improve coverage performance, based on (i) the Bartlett-corrected likelihood ratio statistic, (ii) the efficient score statistic, and (iii) the Bartlett-type adjusted efficient score statistic. The Bartlett and Bartlett-type corrections enhance the large-sample approximations for the likelihood ratio and efficient score statistics, and markedly improve coverage performance.

The BMA package and an example code is available at <https://github.com/nomahi/BMA>. The BMA function in this package computes the estimates and confidence intervals of fixed-effects and random-effects meta-analyses. It covers the following methods:

(1) Fixed-effects model: Inverse variance weighted average (point estimate and confidence interval)
(2) Random-effects model:
—Point estimates by DerSimonian and Laird (1986) [method-of-moment] and the maximum likelihood estimate
—Confidence intervals by
(a) The DerSimonian and Laird (1986) method
(b) The likelihood ratio statistic (Hardy and Thompson, 1996)
(c) The Bartlett corrected likelihood ratio statistic (Noma, 2011)

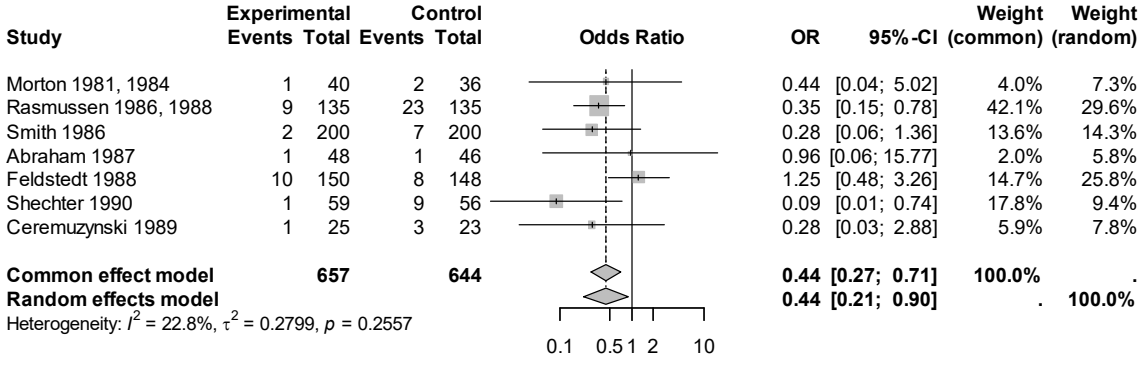
(d) The efficient score statistic (Noma, 2011)

(e) The Bartlett-type adjusted efficient score statistic (Noma, 2011)

where (c), (d) and (e) are the confidence intervals developed by the methods in this article. The BMA package also includes an example dataset by Teo et al. (1991) in Section 5 of Noma (2011).

```
> library("BMA")
>
> data(magnesium)
> print(magnesium)
  id               study d1  n1 d0  n0
1  1    Morton 1981, 1984  1  40  2  36
2  2 Rasmussen 1986, 1988  9 135 23 135
3  3           Smith 1986  2 200  7 200
4  4         Abraham 1987  1  48  1  46
5  5       Feldstedt 1988 10 150  8 148
6  6        Shechter 1990  1  59  9  56
7  7    Ceremuzynski 1989  1  25  3  23
>
> rem1 <- metabin(d1, n1, d0, n0, sm="OR", studlab=study,
data=magnesium)
> summary(rem1)      # Standard random-effects model analysis by "meta"
package

                        OR           95%-CI %W(common) %W(random)
Morton 1981, 1984    0.4359 [0.0378;  5.0217]       4.0        7.3
Rasmussen 1986, 1988 0.3478 [0.1545;  0.7831]      42.1       29.6
Smith 1986           0.2785 [0.0571;  1.3574]      13.6       14.3
Abraham 1987         0.9574 [0.0581; 15.7731]       2.0        5.8
Feldstedt 1988       1.2500 [0.4792;  3.2606]      14.7       25.8
Shechter 1990        0.0900 [0.0110;  0.7364]      17.8        9.4
Ceremuzynski 1989    0.2778 [0.0268;  2.8827]       5.9        7.8

Number of studies: k = 7
Number of observations: o = 1301 (o.e = 657, o.c = 644)
Number of events: e = 78
```

```
                        OR          95%-CI     z p-value
Common effect model  0.4368 [0.2673; 0.7136] -3.31  0.0009
Random effects model 0.4371 [0.2134; 0.8951] -2.26  0.0236

Quantifying heterogeneity (with 95%-CIs):
 tau^2 = 0.2799 [0.0000; 2.7617]; tau = 0.5290 [0.0000; 1.6618]
 I^2 = 22.8% [0.0%; 65.6%]; H = 1.14 [1.00; 1.71]

Test of heterogeneity:
    Q d.f. p-value
 7.77    6  0.2557

Details of meta-analysis methods:
- Mantel-Haenszel method (common effect model)
- Inverse variance method (random effects model)
- Restricted maximum-likelihood estimator for tau^2
- Q-Profile method for confidence interval of tau^2 and tau
- Calculation of I^2 based on Q
>
> plot(rem1)# Forest plot
```



For implementing the BMA function, there are five arguments:

y: Outcome statistics of individual studies: log odds-ratio, log hazard-ratio, standardized mean difference, etc.

V: Estimated variances of these statistics.
data: A data frame containing the variables in the model.
alpha: The confidence level (default is 0.95).
efrom: A logical argument. If it is TRUE (e.g., y is inputted by log scale), the estimates are outputted by the transformed exponential. Default is FALSE.

For example, the result of Table 1 of Noma (2011) (except for Peto's method) is obtained by:

```
> edit_Mg <- escalc(measure="OR", ai=d1, n1i=n1, ci=d0, n2i=n0, data=magnesium)
> # Calculating the summary statistics of individual studies
>
> BMA(yi, vi, data=edit_Mg, eform=TRUE)          # The Bartlett-type corrections for random-effects meta-analysis

 Fixed-effects & random-effects meta-analysis

 Point estimates:
  Fixed-effects model: 0.471
  DerSimonian-Laird (method-of-moment): 0.448
  Maximum likelihood: 0.449

 Variance component estimates:
  DerSimonian-Laird (method-of-moment): 0.171
  Maximum likelihood: 0.162

 Confidence intervals:
  Fixed-effects model: 0.28 0.791
  DerSimonian-Laird (method-of-moment): 0.233 0.861
  Likelihood ratio (LR): 0.192 0.903
  Bartlett corrected LR: 0.158 1.066
  Efficient score: 0.137 1.005
  Bartlett-type adjusted score: 0.145 0.963

 Confidence level:  0.95
```

References

DerSimonian R, Larid NM. Meta-analysis in clinical trials. *Controlled Clinical Trials* 1986; 7: 177-188.

Hardy RJ, Thompson SG. A likelihood approach to meta-analysis with random effects. *Statistics in Medicine* 1996; 15: 619-629.

Noma, H. Confidence intervals for a random-effects meta-analysis based on Bartlett-type corrections. *Statistics in Medicine* 2011; 30: 3304-3312.

Teo KK, Yusuf S, Collins R, Held PH, Peto R. Effects of intravenous magnesium in suspected acute myocardial infarction: overview of randomized trials. *BMJ* 1991; 303: 1499-1503.