Bartlett-type corrections for the confidence interval of a treatment effect of the multivariate random effects meta-analysis model via analytical approach

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Over the past few decades, many researchers have shown an interest in meta-analysis which has been active in various fields: ecology, economics, medical science, medicine, and so on. As Gurevitch *et al.* (2018) indicates, the research with meta-analysis began to be published in 1970s, its number rapidly has increased in recent years, and has exceeded 200,000 papers. As far as the clinical trial is concerned, the number of study has risen to start to be conducted in some countries year by year, the research with meta-analysis seems likely to expand further in the future.

Meta-analysis is to synthesize the measured effect of treatments or correlated outcomes (ex. overall and disease-free survival) of high quality studies via the systematic reviews. It should be noted that there is heterogeneity between studies, assuming that each study has true results, respectively. In order to address this problem, we consider the random effect model. The random effect has the advantage of expressing the difference between studies as its distribution. Thus, this research involves the multivariate random effects meta-analysis model.

In the context of meta-analysis, the treatment effect size of each study have been already known, and average treatment effect size of interest is estimated by summarizing studies. Therefore, the accuracy of overall mean estimator depends the number of study. As Noma *et al.* (2018) points out, the number of study is small in the case conducted subgroup analysis, the study of the orphan disease is few to rare disease[3]. So as to more increase the accuracy in this situation, Noma *et al.* (2018) proposed the bartlett correction via bootstrap. However, the problem seems to lie in the two facts: (1) bootstrap calculation takes much time to numerically solve maximum likelihood (ML) estimator or restricted maximum likelihood (REML) estimator, (2) the confidence interval cannot be expressed in closed form, and has to be derived by numerical approach, it also takes time. In order to search several treatment effects including exploratory analyses, it is important that reducing of the calculation time is discussed. Kojima *et al.* (2013) derives the bartlett correction for hypothesis testing in linear models with general error covariance matrices based on the general consistent estimators of the nuisance parameters. However, likelihood ratio(LR) test statistic need to be modified as a result of using the general consistent estimators, and the confidence interval of LR cannot be derived by explicit. Furthermore, for LR and Score test statistic, REML function under null hypothesis is required, but it was not proposed.

In our research, we show the bartlett correction for the multivariate random effects meta-analysis model via analytical approach and the explicit confidence interval of Wald, LR, Score test statistic based on the ML and REML of nuisance parameters. Welham *et al.* (1997) shows the REML function under the null hypothesis by using submodel, we propose novel REML function for the our research.

Reference

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