Adjustments for network meta-analysis with a small number of studies by Bartlett-type corrections using an analytical approach

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Abstract Consider network meta-analysis in a small number of studies that cannot hold a nominal confidence level. A bias adjustment method using bootstrap has been proposed by Noma et al. (2018). However, this approach has three problematic aspects: (1) the confidence intervals cannot be expressed in closed form, and one also has to be derived by a numerical approach. (2) Because they did not identify the mechanism of the bias in the confidence intervals, they had to use a computational method such as bootstrap method. Consequently, it remains unclear why the bias occurs and how it should be is adjusted. (3) The bootstrap calculation takes too much time to numerically solve the maximum likelihood estimator or restricted maximum likelihood estimator, as m sets of bootstrap samples need to be generated and m maximum likelihood (ML) or restricted maximum likelihood (REML) estimators need to be calculated.

Our proposed method can analytically derive Bartlett-type corrections for the Wald, Likelihood Ratio, and Score test statistics when nuisance parameters are estimated by not only the ML method but also the REML method. We can derive the explicit confidence intervals for all three test statistics. In addition, by applying the parametric bootstrap to the adjusted test statistics, the higher order correction can be obtained.

Principle findings We propose the three novel achievements that formulate the confidence intervals, identify the bias mechanism, and decrease the calculation time for deriving Bartlett-type adjustment terms. Specifically, we made the the following innovations.

1. We formulate the three explicit confidence intervals of Wald, Likelihood ratio (LR), and Score test statistic using ML and REML estimator for nuisance parameters. This formulation helps to clarify the bias mechanism or derive explicit Bartlett- type correction terms.
2. We derive the explicit Bartlett-type correction terms via the asymptotic expansion. Here, we make improvements on the results of Kojima and Kubokawa (2013). In other words, we also derive the Bartlett-type correction of LR using the REML estimator.
3. We do not have to numerically calculate the Bartlett correction terms, and the calculation time can be reduced to 1 over m relative to the method with m bootstrap samples.

Notations

n : the number of studies
p : the number of treatment effects of interest
p_i: the number of outcomes of the i-th study
N : $\sum_{i=1}^{n} p_i$
$\boldsymbol{\mu}$: p×1 parameter vector of the average treatment effect across all studies
null hypothesis H_0 : $\boldsymbol{r}^T\boldsymbol{\mu} = \boldsymbol{r}^T\boldsymbol{\mu}_0$

$E_{H_0}[X] = E[X|H_0]$,

$$\widehat{\boldsymbol{\mu}}_{(i)}(\boldsymbol{\theta}) = \frac{\partial\left(\widehat{\boldsymbol{\mu}}(\boldsymbol{\theta})\right)}{\partial\theta_i}, \quad \left(h(\boldsymbol{\theta})^2\right)_{(i)} = \frac{\partial\left(h(\boldsymbol{\theta})^2\right)}{\partial\theta_i},$$

$$\boldsymbol{\Sigma}_{(i)}(\boldsymbol{\theta}) = \frac{\partial\left(\boldsymbol{\Sigma}(\boldsymbol{\theta})\right)}{\partial\theta_i}, \quad \boldsymbol{\Sigma}_{(ij)}(\boldsymbol{\theta}) = \frac{\partial\left(\boldsymbol{\Sigma}(\boldsymbol{\theta})\right)}{\partial\theta_i\partial\theta_j},$$

Multivariate random effects meta-analysis model

Consisting of the within-study model and between-studies model,

$$\text{(within-study model)}\ \boldsymbol{y}_i = \boldsymbol{X}_i\boldsymbol{\beta}_i + \boldsymbol{e}_i,$$

$$\text{(between-studies model)}\ \boldsymbol{\beta}_i = \boldsymbol{\mu} + \boldsymbol{v}_i,$$

$\mathbf{y}_i$: p_i×1 vector of a known estimator of a treatment effect within the i-th study
$\boldsymbol{X_i}$: p_i×p_i design matrix in which the element of a treatment corresponding to y_{ij} is 1 and the others are 0
$\boldsymbol{\beta}_i$: p×1 vector of a treatment effect within the i-th study
$\boldsymbol{e}_i$: p_i×1 vector of an error within the i-th study, $\boldsymbol{e}_i \sim N(0, \boldsymbol{R}_i)$
$\boldsymbol{R}_i$: p_i×p_i known covariance matrix of the i-th study
$\boldsymbol{v_i}$: p×1 vector of an error between studies, $\boldsymbol{v}_i \sim N\left(0, \boldsymbol{V}(\boldsymbol{\theta})\right)$
$\boldsymbol{V}(\boldsymbol{\theta})$: p×p covariance matrix, The covariance structure of is known.
$\boldsymbol{\theta}$: q×1 nuisance unknown parameter vector

To easily calculate the asymptotic expansion, we consider the marginal model of the multivariate random effects meta-analysis model as

$$\boldsymbol{y} = \boldsymbol{X}\boldsymbol{\mu} + \boldsymbol{\epsilon}, \quad \boldsymbol{\epsilon} \sim \mathcal{N}(\boldsymbol{0}, \boldsymbol{\Sigma}(\boldsymbol{\theta})), \quad \boldsymbol{\Sigma}(\boldsymbol{\theta}) = \boldsymbol{R} + \boldsymbol{G}(\boldsymbol{\theta}),$$

$\mathbf{y} = (\boldsymbol{y}_1^T, \ldots, \boldsymbol{y}_n^T)^{\mathrm{T}}$ is an N×1 matrix.
$\mathbf{X} = (\boldsymbol{X}_1^T, \ldots, \boldsymbol{X}_n^T)^{\mathrm{T}}$ is an N×p matrix.
$\mathbf{R} = \mathrm{diag}(\boldsymbol{R}_1, \ldots, \boldsymbol{R}_n)$ is an N×N matrix, diag denotes the block diagonal matrix.
$\mathbf{G}(\boldsymbol{\theta}) = \boldsymbol{Z}\mathrm{diag}\left(\boldsymbol{V}(\boldsymbol{\theta}), \ldots, \boldsymbol{V}(\boldsymbol{\theta})\right)\boldsymbol{Z}^T$ is an N×N matrix, $\mathbf{Z} = \mathrm{diag}(\boldsymbol{X}_1, \ldots, \boldsymbol{X}_n)$ is an N×np matrix.

Wald, LR, and Score test statistic & confidence intervals

$l(\widehat{\boldsymbol{\mu}}(\boldsymbol{\theta}), \boldsymbol{\theta})$ is ML or REML function, $\widehat{\boldsymbol{\theta}}$ is an estimator maximizing $l(\widehat{\boldsymbol{\mu}}(\boldsymbol{\theta}), \boldsymbol{\theta})$
$l(\widetilde{\boldsymbol{\mu}}(\boldsymbol{\theta}), \boldsymbol{\theta})$ is ML or REML function under restricted under the null hypothesis,
$\widetilde{\boldsymbol{\theta}}$ is an estimator maximizing $l(\widetilde{\boldsymbol{\mu}}(\boldsymbol{\theta}), \boldsymbol{\theta})$

Wald test statistic

$$W(\widehat{\boldsymbol{\theta}}) = -2\left(l(\widetilde{\boldsymbol{\mu}}(\widehat{\boldsymbol{\theta}}), \widehat{\boldsymbol{\theta}}) - l(\widehat{\boldsymbol{\mu}}(\widehat{\boldsymbol{\theta}}), \widehat{\boldsymbol{\theta}})\right) = \frac{\left(\boldsymbol{r}^T\widehat{\boldsymbol{\mu}}(\widehat{\boldsymbol{\theta}}) - \boldsymbol{r}^T\boldsymbol{\mu}_0\right)^2}{h(\widehat{\boldsymbol{\theta}})^2} \quad \text{where } h(\boldsymbol{\theta}) = \sqrt{\boldsymbol{r}^T(\boldsymbol{X}^T\boldsymbol{\Sigma}(\boldsymbol{\theta})^{-1}\boldsymbol{X})^{-1}\boldsymbol{r}}.$$

LR test statistic

$$LR(\widehat{\boldsymbol{\theta}}, \widetilde{\boldsymbol{\theta}}) = -2\left(l(\widetilde{\boldsymbol{\mu}}(\widetilde{\boldsymbol{\theta}}), \widetilde{\boldsymbol{\theta}}) - l(\widehat{\boldsymbol{\mu}}(\widehat{\boldsymbol{\theta}}), \widehat{\boldsymbol{\theta}})\right) = -2\delta(\widehat{\boldsymbol{\theta}}, \widetilde{\boldsymbol{\theta}}) + W(\widetilde{\boldsymbol{\theta}}),\ \delta(\widehat{\boldsymbol{\theta}}, \widetilde{\boldsymbol{\theta}}) = l(\widehat{\boldsymbol{\mu}}(\widetilde{\boldsymbol{\theta}}), \widetilde{\boldsymbol{\theta}}) - l(\widehat{\boldsymbol{\mu}}(\widehat{\boldsymbol{\theta}}), \widehat{\boldsymbol{\theta}})$$

Score test statistic

$$S(\widetilde{\boldsymbol{\theta}}) = -2\left(l(\widetilde{\boldsymbol{\mu}}(\widetilde{\boldsymbol{\theta}}), \widetilde{\boldsymbol{\theta}}) - l(\widehat{\boldsymbol{\mu}}(\widetilde{\boldsymbol{\theta}}), \widetilde{\boldsymbol{\theta}})\right) = \frac{(\boldsymbol{r}^T\widehat{\boldsymbol{\mu}}(\widetilde{\boldsymbol{\theta}}) - \boldsymbol{r}^T\boldsymbol{\mu}_0)^2}{h(\widetilde{\boldsymbol{\theta}})^2} = W(\widetilde{\boldsymbol{\theta}}).$$

Confidence interval based on the Wald: $\boldsymbol{r}^T\widehat{\boldsymbol{\mu}}(\widehat{\boldsymbol{\theta}}) - z_{\alpha/2}h(\widehat{\boldsymbol{\theta}}) \le \boldsymbol{r}^T\boldsymbol{\mu}_0 \le \boldsymbol{r}^T\widehat{\boldsymbol{\mu}}(\widehat{\boldsymbol{\theta}}) + z_{\alpha/2}h(\widehat{\boldsymbol{\theta}})$.

Confidence interval based on the LR: $\boldsymbol{r}^T\widehat{\boldsymbol{\mu}}(\widetilde{\boldsymbol{\theta}}) - \sqrt{z_{\alpha/2}^2 + 2\delta(\widehat{\boldsymbol{\theta}}, \widetilde{\boldsymbol{\theta}})}h(\widetilde{\boldsymbol{\theta}}) \le \boldsymbol{r}^T\boldsymbol{\mu}_0 \le \boldsymbol{r}^T\widehat{\boldsymbol{\mu}}(\widetilde{\boldsymbol{\theta}}) + \sqrt{z_{\alpha/2}^2 + 2\delta(\widehat{\boldsymbol{\theta}}, \widetilde{\boldsymbol{\theta}})}h(\widetilde{\boldsymbol{\theta}})$.

Confidence interval based on the Score: $\boldsymbol{r}^T\widehat{\boldsymbol{\mu}}(\widetilde{\boldsymbol{\theta}}) - z_{\alpha/2}h(\widetilde{\boldsymbol{\theta}}) \le \boldsymbol{r}^T\boldsymbol{\mu}_0 \le \boldsymbol{r}^T\widehat{\boldsymbol{\mu}}(\widetilde{\boldsymbol{\theta}}) + z_{\alpha/2}h(\widetilde{\boldsymbol{\theta}})$.

$z_{\alpha/2}$ is the upper $\alpha/2$% of the standard normal distribution

Principle findings (Bartlett Adjustment)

Confidence interval of the Wald test statistic with Bartlett-type adjustment.

$$\boldsymbol{r}^T\widehat{\boldsymbol{\mu}}(\widehat{\boldsymbol{\theta}}) - z_{\alpha/2}h(\widehat{\boldsymbol{\theta}})\sqrt{w_{cor}(z_{\alpha/2}^2)} \le \boldsymbol{r}^T\boldsymbol{\mu}_0 \le \boldsymbol{r}^T\widehat{\boldsymbol{\mu}}(\widehat{\boldsymbol{\theta}}) + z_{\alpha/2}h(\widehat{\boldsymbol{\theta}})\sqrt{w_{cor}(z_{\alpha/2}^2)}$$

Confidence interval of the LR test statistic with Bartlett-type adjustment.

$$\boldsymbol{r}^T\widehat{\boldsymbol{\mu}}(\widetilde{\boldsymbol{\theta}}) - \sqrt{LR_{cor}}h(\widetilde{\boldsymbol{\theta}}) \le \boldsymbol{r}^T\boldsymbol{\mu}_0 \le \boldsymbol{r}^T\widehat{\boldsymbol{\mu}}(\widetilde{\boldsymbol{\theta}}) + \sqrt{LR_{cor}}h(\widetilde{\boldsymbol{\theta}}), \text{ where } LR_{cor} = z_{\alpha/2}^2 lr_{cor}(z_{\alpha/2}^2) + 2\delta(\widehat{\boldsymbol{\theta}}, \widetilde{\boldsymbol{\theta}}).$$

Confidence interval of the Score test statistic with Bartlett-type adjustment.

$$\boldsymbol{r}^T\widehat{\boldsymbol{\mu}}(\widetilde{\boldsymbol{\theta}}) - z_{\alpha/2}h(\widetilde{\boldsymbol{\theta}})\sqrt{s_{cor}(z_{\alpha/2}^2)} \le \boldsymbol{r}^T\boldsymbol{\mu}_0 \le \boldsymbol{r}^T\widehat{\boldsymbol{\mu}}(\widetilde{\boldsymbol{\theta}}) + z_{\alpha/2}h(\widetilde{\boldsymbol{\theta}})\sqrt{s_{cor}(z_{\alpha/2}^2)}$$

Because the coverage probabilities of the naïve confidence intervals are $1 - \alpha + O(N^{-1})$, the second-order bias ($O(N^{-1})$) occurs. However, because the coverage probability in the above adjusted confidence intervals is $1 - \alpha + O(N^{-3/2})$, the second-order bias is removed. In addition, by applying the parametric bootstrap to the adjusted test statistics, the higher order correction can be obtained.

Bartlett adjustment equations

$$w_{cor}(x) = 1 + \widehat{E_{H_0}[a_1^2]} + \widehat{E_{H_0}[c_2]} + \frac{1}{4}(1+x)\widehat{E_{H_0}[c_1^2]}.$$

$$lr_{cor}(x) = 1 + \widehat{E_{H_0}[c_2]} + \frac{1}{4}\widehat{E_{H_0}[c_1^2]}.$$

$$s_{cor}(x) = 1 - \widehat{E_{H_0}[a_1^2]} + \widehat{E_{H_0}[c_2]} + \frac{1}{4}(1-x)\widehat{E_{H_0}[c_1^2]}.$$

$$a = \frac{\boldsymbol{r}^T\widehat{\boldsymbol{\mu}}(\widehat{\boldsymbol{\theta}}) - \boldsymbol{r}^T\widehat{\boldsymbol{\mu}}(\boldsymbol{\theta})}{h(\boldsymbol{\theta})},\ b = \frac{\boldsymbol{r}^T\widehat{\boldsymbol{\mu}}(\boldsymbol{\theta}) - \boldsymbol{r}^T\boldsymbol{\mu}_0}{h(\boldsymbol{\theta})},\ c = -\frac{h(\widehat{\boldsymbol{\theta}})^2 - h(\boldsymbol{\theta})^2}{h(\boldsymbol{\theta})^2}.$$

$$a_1 = \sum_{i=1}^{p} \hat{\theta}_{1i}\frac{\boldsymbol{r}^T\widehat{\boldsymbol{\mu}}_{(i)}(\boldsymbol{\theta})}{h(\boldsymbol{\theta})}$$

$$c_1 = -\sum_{i=1}^{p} \hat{\theta}_{1i}\frac{\left(h(\boldsymbol{\theta})^2\right)_{(i)}}{h(\boldsymbol{\theta})^2}$$

$$c_2 = -\sum_{i=1}^{p} \hat{\theta}_{2i}\frac{\left(h(\boldsymbol{\theta})^2\right)_{(i)}}{h(\boldsymbol{\theta})^2} - \frac{1}{2}\sum_{i,j=1}^{p} \hat{\theta}_{1i}\hat{\theta}_{1j}\frac{(h(\boldsymbol{\theta}))_{(ij)}}{h(\boldsymbol{\theta})^2}$$

Simulation results

There are four treatments (A-drug, B-drug, C-drug, and placebo [P]). We are interested in a comparison between the outcome of P and each of the three drugs. We counted the number of the 95% confidence intervals that include the true value.

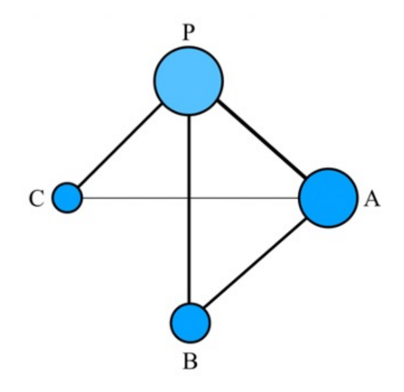

Figure 1: Diagram of simulation study 1

Table 1: Setting of simulation study 1

Design	# of Studies	# of Studies
P vs A	3	9
P vs B	2	6
P vs C	2	6
A vs B	2	6
A vs C	1	3
Total	10	30

N=10

estimator		W	W^{BC}	W_{boot}	W^{BC}_{boot}	LR	LR^{BC}	LR_{boot}	LR^{BC}_{boot}	S	S^{BC}	S_{boot}	S^{BC}_{boot}
MLE	μ_1	86.1	93.6	93.1	92.9	88.9	94.4	94.0	96.8	93.3	95.5	94.8	95.1
MLE	μ_2	86.8	93.8	92.9	92.9	89.2	94.8	93.5	97.6	93.7	96.1	95.1	95.1
MLE	μ_3	86.7	93.9	91.3	91.1	89.5	94.8	92.0	96.8	93.5	95.9	92.9	93.1
REMLE	μ_1	91.3	94.6	96.2	96.2	94.8	95.5	95.8	95.8	98.2	96.3	95.8	95.8
REMLE	μ_2	91.7	94.6	95.9	96.1	95.0	95.9	96.1	96.1	98.5	96.7	95.7	95.5
REMLE	μ_3	91.9	94.6	94.8	94.8	95.1	95.9	95.2	95.0	98.5	96.7	94.8	95.0

N=30

estimator		W	W^{BC}	W_{boot}	W^{BC}_{boot}	LR	LR^{BC}	LR_{boot}	LR^{BC}_{boot}	S	S^{BC}	S_{boot}	S^{BC}_{boot}
MLE	μ_1	92.3	94.6	95.9	95.9	93.2	94.8	95.7	96.8	94.3	94.9	95.5	94.5
MLE	μ_2	92.3	94.6	94.6	94.7	93.1	94.8	94.6	96.3	94.4	95.0	94.5	94.5
MLE	μ_3	92.6	95.0	95.9	95.8	93.6	95.1	95.9	96.8	94.7	95.2	96.1	96.1
REMLE	μ_1	93.8	94.9	95.7	95.7	94.7	94.9	95.4	95.3	95.7	95.0	95.3	95.3
REMLE	μ_2	93.9	94.9	94.5	95.5	94.8	95.0	94.5	94.5	95.6	95.1	94.5	94.5
REMLE	μ_3	94.2	95.1	96.0	95.9	95.0	95.3	95.8	95.8	96.1	95.3	96.0	96.0

Conclusion Through the simulation, we confirmed that the confidence intervals of the three test statistics with Bartlett-type adjustment were improved.
In this research, we derived the three explicit confidence intervals and the explicit Bartlett-type correction terms via the asymptotic expansion, In addition, we do not have to numerically calculate the Bartlett correction terms.

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M. Kojima, T. Kubokawa, Bartlett-type adjustments for hypothesis testing in linear models with general error covariance matrices, Journal of Multivariate Analysis 122 (2013) 162–174.