Within-study covariance estimators for network meta-analysis with contrast-based approach

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Abstract

The contrast-based approach is one of the primary approaches in network meta-analysis. For statistical modeling in network meta-analysis and meta-regression models, within-study covariance estimates are needed to adequately address the correlations among the multivariate outcomes. In this computational note, we present the formulas of covariance estimators for standard effect measures used in modern meta-analysis practice: risk difference, risk ratio, odds ratio, mean difference, and standardized mean difference (Cohen's *d* and Hedge's *g*).

Key words: network meta-analysis; contrast-based approach; multivariate random-effects model; within-study covariance matrix; network meta-regression.

1. Introduction

Contrast-based network meta-analysis using the multivariate meta-analysis and meta-regression models is one of the primary approaches in network meta-analysis (Nikolakopoulou, White and Salanti, 2021; Salanti et al., 2008; White et al., 2012). For statistical modeling in network meta-analysis, within-study covariance matrices are usually assumed to be known and fixed to their adequate estimates based on study-specific summary statistics, similar to conventional pairwise meta-analyses (DerSimonian and Laird, 1986; Higgins and Thomas, 2019). However, even though the within-study variance estimators are well known, which have been widely adopted in conventional pairwise meta-analyses (Whitehead, 2002), there are no literatures that explicitly present the formulas of within-study covariance estimators. In this computational note, we present the formulas of covariance estimators for standard effect measures used in the practice of modern meta-analysis.

2. Network meta-analysis and meta-regression models

We here discuss the contrast-based network meta-analysis and meta-regression models (White et al., 2012). The former is a special case of the latter; thus, we adopt the notation of the network meta-regression model without loss of generality. Here, we consider that N trials are synthesized and that $p+1$ treatments are compared. Y_{ij} denotes an estimator of a treatment effect in contrast to a reference treatment (e.g., placebo) for the jth treatment in the ith trial ($i = 1, 2, \dots, N; j = 1,2, \dots, p$). Commonly used effect measures are risk difference, risk ratio, odds ratio, mean difference, and standardized mean difference; the ratio measures are usually transformed on a logarithmic scale (Whitehead, 2002). For the network meta-regression model, we assume the following

multivariate random-effects regression model for the outcome variable $\boldsymbol{Y}_i = \left(Y_{i1}, Y_{i2}, \ldots, Y_{ip}\right)^T$:

$$\boldsymbol{Y}_i = \boldsymbol{\theta}_i + \boldsymbol{e}_i \tag{1}$$

$$\boldsymbol{\theta}_i = \boldsymbol{X}_i^T \boldsymbol{\beta} + \boldsymbol{\varepsilon}_i$$

where $\boldsymbol{\theta}_i = \left(\theta_{i1}, \theta_{i2}, \ldots, \theta_{ip}\right)^T$ and $\boldsymbol{\beta} = \left(\boldsymbol{\beta}_1^T, \ldots, \boldsymbol{\beta}_p^T\right)^T$. The regression function model $\boldsymbol{X}_i^T \boldsymbol{\beta}$ involves a design matrix:

$$\boldsymbol{X}_i = \begin{pmatrix} \boldsymbol{x}_{i1} & \mathbf{0} & \cdots & \mathbf{0} \\ \mathbf{0} & \boldsymbol{x}_{i2} & \ldots & \mathbf{0} \\ \vdots & \vdots & \ddots & \vdots \\ \mathbf{0} & \mathbf{0} & \cdots & \boldsymbol{x}_{ip} \end{pmatrix}$$

where $\boldsymbol{x}_{ij}$ is a $q_j \times 1$ covaraiate vector for Y_{ij} (q_j is the number of the covariates) and $\boldsymbol{\beta}_j$ is its $q_j \times 1$ regression coefficient vector. In addition, $\boldsymbol{e}_i$ and $\boldsymbol{\varepsilon}_i$ are independent random variation terms within and across studies ($p \times 1$ random vectors), assumed to be distributed as $\boldsymbol{e}_i \sim \mathrm{MVN}(\mathbf{0}, \boldsymbol{S}_i)$ and $\boldsymbol{\varepsilon}_i \sim \mathrm{MVN}(\mathbf{0}, \boldsymbol{\Sigma})$. Also, $\boldsymbol{S}_i$ (a $p \times p$ matrix) is the within-study covariance matrix,

$$\boldsymbol{S}_i = \begin{pmatrix} s_{i11}^2 & s_{i12} & \cdots & s_{i1p} \\ s_{i21} & s_{i2}^2 & \ldots & s_{i2p} \\ \vdots & \vdots & \ddots & \vdots \\ s_{ip1} & s_{ip2} & \cdots & s_{ip}^2 \end{pmatrix}$$

which is usually assumed to be known and fixed to its valid estimate, as noted above. In addition, $\boldsymbol{\Sigma}$ is the between-studies covariance matrix. For studies that do not include a reference treatment, the data augmentation approach of White et al. (2012) can be adopted, where a quasi-small dataset is added into the reference arm (e.g., 0.0001 events for 0.001 patients for a binary outcome). Under these assumptions, we estimate the model parameters $\{\boldsymbol{\beta}, \boldsymbol{\Sigma}\}$ using valid estimating methods (e.g., the restricted maximum likelihood estimation; Noma et al., 2023a; White et al., 2012). Notably, most individual

clinical trials typically involve only two, three, or four arms; we therefore formally replace $\boldsymbol{Y}_i$, $\boldsymbol{X}_i$, and $\boldsymbol{S}_i$ with their subvectors and submatrices in the estimating functions.

3. Estimating the within-study covariances

3.1 General results

In this computational note, we discuss the estimators of the within-study covariances s_{ijk}'s ($i = 1, 2, \dots, N; j, k = 1,2, \dots, p$). These quantities are defined as

$$s_{ijk} = \mathrm{Cov}(Y_{ij}, Y_{ik})$$

and indicate that the outcome variables Y_{ij} and Y_{ik} are defined as contrast measures compared with a common reference treatment. Thus, these variables are correlated. For all possible effect measures discussed below, these quantities are expressed as differences of arm-specific outcome measures (e.g., the difference of log odds of the binomial probabilities for odds ratio). Without loss of generality, we denote these arm-specific outcome measures as Z_{ij} ($j = 0,1,2, \dots, p$) (i.e., $Y_{ij} = Z_{ij} - Z_{i0}$, where Z_{i0} is the outcome measure of the reference treatment group). The covariance is then expressed as

$$\mathrm{Cov}\left(Y_{ij}, Y_{ik}\right) = \mathrm{Cov}\left(Z_{ij} - Z_{i0}, Z_{ik} - Z_{i0}\right) = \mathrm{Var}(Z_{i0})$$

because Z_{ij} and Z_{ik} are independent ($j \neq k$). Therefore, the within-study covariance estimator is provided as the variance estimator of the group-specific outcome variable Z_{i0}. The variance estimator is simply provided by adequate probability models for types of effect measures. In the following sections, we present the concrete formulas.

3.2 Dichotomous outcome

For a dichotomous outcome, the binomial probability model is generally adopted. For simplicity, we adopt a somewhat different notation in Sections 3.2–3.3. Without loss of generality, we consider a three-arm trial in which the outcome variable follows

$$X_i \sim Binomial(N_i, p_i)$$

where i indicates the group ($i = 0, 1, 2$). We formally regard group 0 as the reference group. For trials with more than three arms, the same formulas can be adapted.

3.2.1 Risk difference

A commonly used effect measure is the risk difference (RD),

$$\mathrm{RD}_i = p_i - p_0$$

and the empirical estimator is $\widehat{\mathrm{RD}}_i = X_i/N_i - X_0/N_0$ $(i = 1, 2)$. Using the results from Section 3.1, we can express the covariance estimator between $\widehat{\mathrm{RD}}_1$ and $\widehat{\mathrm{RD}}_2$ as

$$\mathrm{Cov}\left(\widehat{\mathrm{RD}}_1, \widehat{\mathrm{RD}}_2\right) = \mathrm{Var}\left[\frac{X_0}{N_0}\right] = \frac{X_0(N_0 - X_0)}{N_0^3}$$

Note that this estimator is an exact estimator that does not use large sample approximations.

3.2.2 Risk ratio

The risk ratio (RR) is another representative effect measure that can express a relative risk:

$$\mathrm{RR}_i = p_i/p_0$$

In modeling for the network meta-regression model (1), this measure is usually transformed to a logarithm-scale,

$$\mathrm{LRR}_i = \log(p_i) - \log(p_0)$$

and the empirical estimator is $\widehat{\mathrm{LRR}}_i = \log(X_i/N_i) - \log(X_0/N_0)$ $(i = 1, 2)$. The covariance estimator is then provided as

$$\mathrm{Cov}\left(\widehat{\mathrm{LRR}}_1, \widehat{\mathrm{LRR}}_2\right) = \mathrm{Var}\left[\log\left(\frac{X_0}{N_0}\right)\right] = \frac{1}{X_0} - \frac{1}{N_0}$$

3.2.3 Odds ratio

Another representative measure is the odds ratio (OR), although this measure cannot be directly interpreted as an effect measure except in cases where it becomes a good approximation of the risk ratio under the event frequency (Greenland, 1987; Higgins and Thomas, 2019):

$$\mathrm{OR}_i = p_i(1-p_0)/\{(1-p_i)p_0\}$$

In modeling for the network meta-regression model (1), this measure is also transformed to a logarithm-scale,

$$\mathrm{LOR}_i = \log(p_i) - \log(1-p_i) + \log(1-p_0) - \log(p_0)$$

and the empirical estimator is $\widehat{\mathrm{LOR}}_i = \log(X_i/N_i) - \log\{(N_i - X_i)/N_i\} + \log\{(N_0 - X_0)/N_0\} - \log(X_0/N_0)$ $(i = 1, 2)$. The covariance estimator is given as

$$\mathrm{Cov}\left(\widehat{\mathrm{LOR}}_1, \widehat{\mathrm{LOR}}_2\right) = \mathrm{Var}\left[\log\left(\frac{N_0 - X_0}{N_0}\right) - \log\left(\frac{X_0}{N_0}\right)\right] = \frac{1}{X_0} + \frac{1}{N_0 - X_0}$$

3.3 Continuous outcome

For a continuous outcome, the normal distribution model is generally adopted. In this section, we also consider a three-arm trial without loss of generality, where the outcome variable follows a normal distribution $N(\mu_i, \sigma_i^2)$. We denote the empirical estimators of the means and variances as $\{M_i, S_i^2\}$ reported in the individual studies, where i indicates the group ($i = 0, 1, 2$). Also, we denote the sample size of the group *i* as N_i. We formally regard group 0 as the reference group.

3.3.1 Mean difference

The mean difference (MD) is a commonly used effect measure,

$$\mathrm{MD}_i = \mu_i - \mu_0$$

and the empirical estimator is $\widehat{\mathrm{MD}}_i = M_i - M_0 \ \ (i = 1, 2)$. Using the results from Section 3.1, we express the covariance estimator between $\widehat{\mathrm{MD}}_1$ and $\widehat{\mathrm{MD}}_2$ as

$$\mathrm{Cov}\left(\widehat{\mathrm{MD}}_1, \widehat{\mathrm{MD}}_2\right) = \mathrm{Var}[M_0] = \frac{S_0^2}{N_0}$$

Note that, if S_0^2 is constructed on the basis of the sample unbiased variance estimator, this estimator is an exact estimator that does not use large sample approximations.

3.3.2 Standardized mean difference

The standardized mean difference (SMD) is a standardized measure of MD_i by the common standard deviation between the groups:

$$\mathrm{SMD}_i = \frac{\mu_i - \mu_0}{\sigma^2}$$

When this measure is adopted, we assume equal variances between the corresponding two groups, $\sigma^2 = \sigma_0^2 = \sigma_i^2 \ \ (i = 1, \ 2)$. We denote an empirical estimator of σ as S^2 (the pooled sample variance estimator used in the Student's *t*-test (Student, 1908) is usually adopted). The empirical estimator of SMD_i is $d_i = (M_i - M_0)/S$, which is known as Cohen's *d* (Hedges, 1981; Hedges and Olkins, 1985). Similar to the case of mean difference, a straightforward covariance estimator is given as

$$\mathrm{Cov}(d_i, d_0) = \mathrm{Var}\left[\frac{M_0}{S}\right] = \frac{1}{N_0}$$

In addition, in practice, an alternative adjusted estimator (Hedge's *g*; Hedges, 1981; Hedges and Olkins, 1985) is widely used:

$$g_i = d_i J(\nu_i)$$

where $\nu_i = N_i + N_0 - 2$ and

$$J(\nu) = \frac{\Gamma(\nu/2)}{\sqrt{\nu/2}\,\Gamma((\nu-1)/2)}$$

$\Gamma(.)$ is the gamma function. White (2015) has provided a covariance estimator between g_1 and g_2 using the large sample approximations of White and Thomas (2005),

$$\mathrm{Cov}(g_1, g_2) = J(\nu_{12})^2 \left\{ \frac{\nu}{(\nu - 2)N_0} + g_1 g_2 V(\nu_{12}) \right\}$$

where

$$V(\nu) = \frac{\nu}{\nu - 2} - \frac{1}{J(\nu)^2}$$

In the work of White (2015), ν_{12} is noted as "the degrees of freedom used to estimate the pooled standard deviation." However, there are two degrees of freedom in the quantities used in defining g_1 and g_2. If the sample sizes N_1 and N_2 are similar, the two degrees of freedom are similar and White's estimator can be straightforwardly adopted using an appropriate intermediate value of the two degrees of freedom. Otherwise, because Cohen's *d* and Hedge's *g* are asymptotically equivalent, the asymptotic covariance estimator based on Cohen's *d* could be used as an alternative adequate choice.

4. Concluding remarks

The covariance estimators provided in Section 3 can be directly used in $\boldsymbol{S}_i$ of the network meta-analysis and meta-regression models (1). Existing evidence obtained via simulation studies has shown that the plug-in-type estimating methods provide valid inference and prediction results under various settings (Noma, 2023; Noma et al., 2023ab; Noma, Nagashima and Furukawa, 2020; Noma et al., 2018). These computational notes will be useful in future software development and applications.

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