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Methodology

Using Generalized Linear Mixed Models to Evaluate Inconsistency within a Network Meta-Analysis

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ABSTRACT

Background: Network meta-analysis compares multiple treatments by incorporating direct and indirect evidence into a general statistical framework. One issue with the validity of network meta-analysis is inconsistency between direct and indirect evidence within a loop formed by three treatments. Recently, the inconsistency issue has been explored further and a complex design-by-treatment interaction model proposed. **Objective:** The aim of this article was to show how to evaluate the design-by-treatment interaction model using the generalized linear mixed model. **Methods:** We proposed an arm-based approach to evaluating the design-by-treatment inconsistency, which is flexible in modeling different types of outcome variables. We used the smoking cessation data to compare results from our arm-based approach with those from the standard contrast-based approach. **Results:** Because the contrast-based approach requires transformation of data, our example showed that such a transformation may yield biases in the treatment effect and inconsistency evaluation, when event rates were low in some treatments. We also compared contrast-based and arm-based models in the evaluation of design inconsistency when different heterogeneity variances were estimated, and the arm-based model yielded more accurate results. **Conclusions:** Because some statistical software commands can detect the collinearity among variables and automatically remove the redundant ones, we can use this advantage to help with placing the inconsistency parameters. This could be very useful for a network meta-analysis involving many designs and treatments.
Keywords: generalized linear mixed models, design-by-treatment interaction, network meta-analysis, randomized controlled trials.

Introduction

One recent development in meta-analysis methodology is network meta-analysis for comparisons of multiple treatment groups [1–8]. Network meta-analysis incorporates all available evidence into a general statistical framework to yield consistent results for treatment differences. Network meta-analysis makes a few assumptions: one is homogeneity; that is, the included studies for any pair of comparison are similar in their study characteristics, and this is the same assumption behind the traditional pairwise meta-analysis; the other is similarity; that is, the potential confounders and effect modifier are distributed similarly across different pairwise comparisons across the whole network [9]. When these assumptions are violated, we may observe inconsistency in the results between direct and indirect evidence, posing a potential threat to the validity of network meta-analysis.

The issue of inconsistency within a network meta-analysis has been discussed from several different perspectives, and methods have been proposed to evaluate and detect inconsistency [10–14]. Lu and Ades [13] proposed to assess treatment effect inconsistency within a loop formed by three treatments in a network meta-analysis. For instance, for a loop of treatments A, B, and C, there is potential inconsistency if head-to-head trials comparing A to B, B to C, or A to C are all available. If the loop is formed because of a three-arm trial, however, no inconsistency can be evaluated because the three-arm trial is internally consistent. Dias et al. [14] later proposed a Bayesian node-splitting model to evaluate the inconsistency between the direct and indirect evidence. Higgins et al. [12] and White et al. [15] later proposed a full design-by-treatment model by separating multi-arm trials from two-arm trials. Suppose head-to-head trials comparing A to B, B to C, or A to C are all available. For the Lu and Ades loop inconsistency model, there is only one potential inconsistency factor in the loop of A-B-C even if a three-arm design comparing A, B, and C is also included. In contrast, for the design-by-treatment model, there are three inconsistency factors because there are four "designs" (three two-arm trial designs and one three-arm trial design) involved in the loop. It has been shown that the loop inconsistency model by Lu and Ades can be viewed as a special case of the design-by-treatment

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interaction model in which no difference is assumed for each pairwise comparison between the two-arm and three-arm trials [12].

The original design-by-treatment interaction model is formulated on the basis of treatment contrasts of all pairwise comparisons within a network meta-analysis. The model with treatment contrasts as the unit of observation is known as the contrast-based model or the trial-based model [16–18]. This formulation gives rise to several inconveniences: first, noncontinuous outcome variables need to be transformed into a continuous variable; for example, the log odds ratio and the associated standard error need to be calculated for a binary outcome variable. Second, a multiarm trial has multiple data entries, and the dependency within these correlated data needs to be properly taken into account in the analysis. Third, setting up the potential inconsistency factors within a contrast-based network meta-analysis model that involves many different designs and multiarm trials could be a tedious task and is prone to errors.

An alternative to the contrast-based model for network meta-analysis is to use the treatment arm as the unit of observation, known as the arm-based model [6,17–19]. The aim of this study was therefore to show how the design-by-treatment interaction model can be implemented into an arm-based approach to network meta-analysis within the generalized linear mixed model framework. We first briefly review the design-by-treatment interaction model and show how it can be implemented within generalized linear mixed models using the treatment arm as the unit of observation, instead of using treatment contrasts. We then use an example of binary outcome to demonstrate our approach. Results from our proposed approach are compared with those from the contrast-based model.

Contrast-Based Design-by-Treatment Interaction Model for Network Meta-Analysis

In this section, we briefly review the contrast-based design-by-treatment interaction model, and the details can be found in the two articles by Higgins et al. [12] and White et al. [15]. The "design" of a study is the set of treatments compared within the study, and the design-by-treatment interaction (i.e., design inconsistency) refers to differences in effect sizes between studies involving different sets of treatments [12]. The full design-by-treatment interaction model can be written as follows [12,15]:

$$\mu_{\mathrm{di}}^{\mathrm{AJ}} = \delta^{AJ} + \beta_{\mathrm{di}}^{AJ} + \omega_d^{\mathrm{AJ}}, \qquad \text{Model 1}$$

where $\mu_{\mathrm{di}}^{\mathrm{AJ}}$ is the observed difference in outcome between treatments J and A, such as difference in means for continuous data or log odds ratio for binary data, in study i within design d; δ^{AJ} is the fixed effect of treatment J relative to treatment A; β_{di}^{AJ} is a study-by-treatment interaction term to estimate the standard heterogeneity, that is, variations in the treatment effect for comparison AJ within studies in design d; and ω_d^{AJ} is a design-by-treatment interaction term to reflect inconsistency (variability between designs). In model 1, β_{di}^{AJ} is treated as random effect, and a multivariate distribution is assumed when multiarm trials are involved in the comparisons:

$$\left(\beta_{\mathrm{di}}^{\mathrm{AB}}, \beta_{\mathrm{di}}^{\mathrm{AC}}, \ldots\right)^{\mathrm{T}} \sim N\left(0, \sum\right)$$

The covariance matrix $\sum$ is usually structured by assuming that all treatment contrasts have the same degree of heterogeneity, τ^2, and the correlation between random effects is set at 0.5 [13,20,21]. The inconsistency parameter ω_d^{AJ} is modeled as fixed effect, but its exact number (i.e., its degree of freedom) depends on the nature of multiarm designs in the network. The degree of freedom for inconsistency, df_{inc}, is $df_{\mathrm{inc}} = \sum_d (T_d - 1) - (T - 1)$, where T_d is the number of treatments in a design d and T is the total number of treatments in the network [15]. For example, suppose a network meta-analysis consists of two designs with three arms and six with two arms and compares a total of four treatments; its df_{inc} is 10 − (4 − 1) = 7. For a network meta-analysis with many different designs and multiarm trials, however, any parameterization requires a very careful tabulation of designs and treatments to locate those identifiable ω_d^{AJ} in the network [12,15].

Arm-Based Design-by-Treatment Interaction Model for Network Meta-Analysis

In our previous studies, we proposed an arm-based generalized linear mixed model to implement the Lu and Ades Bayesian model for network meta-analysis [17,18]. In this section, we extend our model by incorporating the full design-by-treatment interaction. In a network with study 1, 2, …, to p, and treatments A, B, …, K, the generalized linear mixed model with treatment arms as the unit of observation can be written as follows:

$$g\left(\hat{y}_{ij}\right) = \sum_{j=1}^{p} b_j \mathrm{study}_j + \sum_{k=B}^{K} d_{Ak} t_k + \sum_{k=A}^{K} \gamma_{kj} t_k, \qquad \text{Model 2}$$

where $g(.)$ is the link function in the model, $\hat{y}_{ij}$ is the estimated outcome for each arm i in study j, and b_1 to b_p are regression coefficients for dummy variables study_1 to study_p, respectively. Variables t_k, $k = A$ to K, are dummy variables where treatment k is coded 1 and the other treatments are coded 0. We use treatment A as the reference group for the whole network, and t_A is therefore excluded from model 2; consequently, d_{Ak}, the regression coefficient for t_k , is the estimated average difference between treatment A and k. In model 2, γ_{Aj} to γ_{Kj} are random effects for treatment A to K, respectively, and these random effects (i.e., heterogeneities in treatment effects across studies) follow a multivariate normal distribution:

$$\begin{pmatrix} \gamma_{Aj} \\ \gamma_{Bj} \\ \vdots \\ \gamma_{Kj} \end{pmatrix} \sim \left(0, \begin{pmatrix} \sigma^2 & 0 & \ldots & 0 \\ 0 & \sigma^2 & \ldots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \ldots & \sigma^2 \end{pmatrix} \right)$$

Our previous study [17] shows that to estimate the variance σ^2 correctly, dummy variables t_k need to be centered; otherwise, σ^2 tends to be underestimated.

Suppose there are q designs within our network meta-analysis, resulting in $(q-1) \times (K-1)$ interaction terms that are introduced to model 2 to obtain the full design-by-treatment model:

$$g\left(\hat{y}_{ij}\right) = \sum_{j=1}^{p} b_j \mathrm{study}_j + \sum_{k=B}^{K} d_{Ak} t_k + \sum_{k=A}^{K} \gamma_{kj} t_k + \sum_{i=1}^{q-1} \sum_{k=B}^{K} \omega_{ik} \mathrm{design}_i \times t_k,, \qquad \text{Model 3}$$

where $\mathrm{design}_i \times t_k$, $i = 1$ to $q - 1$ and $k = B$ to K, are the product interaction terms between design_i (dummy variable in which studies within the same design i are coded 1 and those of different designs coded 0) and t_k, and ω_{ik} is the estimated design-by-treatment inconsistency. Note that not all the interaction terms in model 3 can be estimated, and the number of estimable interactions is the degree of freedom for inconsistency, df_{inc}, discussed in the previous section.

Example Data

The example data set contains results of 24 trials investigating treatments to help with smoking cessation. This data set has previously been investigated by Higgins et al. [12], Lu and Ades [13], and Hasselblad [22]. Table 1 shows how data are organized for the arm-based analysis. Note that there are some small