Multilevel models for network meta-analysis

Ning Li[1], Yaoguang Lao[1] and Siu-wai Leung[1,2]

[1]State Key Laboratory of Quality Research in Chinese Medicine, Institute of
Chinese Medical Sciences, University of Macau, Macao, China
[2]School of Informatics, University of Edinburgh, Edinburgh EH8 9AB,
United Kingdom
Email: liningmacau@gmail.com

Abstract

Background: Network meta-analysis of clinical trials includes direct and indirect comparisons of multiple treatments. This study aims to explore whether and how the multilevel models can be applied to network meta-analysis, particularly in ranking multiple treatments and explaining the heterogeneity.

Methods: A three-level model with design-level (level-3), study-level (level-2) and individual-level (level-1) was formulated for network meta-analysis. A network meta-analysis of multiple monotherapy trials on type 2 diabetes mellitus was conducted with the three-level model, in which the effect sizes of multiple anti-diabetic drugs were compared according to an arm-based approach.

Results: An application example for network meta-analysis correctly ranked the anti-diabetic drugs in controlling HbA1c. It also demonstrated that a level-2 variable (i.e. follow-up) in the multilevel model could explain the between-design heterogeneity.

Conclusion: Multilevel models are applicable to network meta-analysis in not only ranking the effect sizes through direct and indirect multiple treatment comparisons but also explaining the between-design heterogeneity.

Keywords: Multiple treatment comparison; Network meta-analysis; Multilevel models

1. Background

Traditional meta-analysis of controlled trials often performs pairwise comparison and seldom conducts comparison of multiple treatments. Network meta-analysis fills this gap that both direct and indirect multiple comparisons should be conducted to infer the relative effectiveness of multiple treatments upon the basic assumptions (Salanti, 2012) that multiple treatment comparisons are transitive (i.e. indirect comparisons are inferable from actual comparative trials), consistent (i.e. expecting coherence among direct and indirect comparisons) and homogeneous (i.e. assuming different studies to test the same population). Network meta-analysis would be problematic with inconsistency and heterogeneity of the trials for comparisons. The problems would be even worse when the clinical trials have multiple arms, multiple outcomes and missing values.

Traditional meta-analysis can be conceptualized as a special case of multilevel models (Hox, 2010) because meta-analysis is inherently hierarchical (e.g. effect sizes are nested within trials). To extend multilevel models to support network meta-analysis, we may introduce additional levels and features, wherever applicable, into the multilevel models for explaining the heterogeneity and estimating the coefficients and variances in meta-regression.

Although the issue of multiple independent outcomes in the trials could be handled by introducing multivariate methods into the traditional non-multilevel meta-analysis, the issue remains unsettled for handling multiple correlated outcomes. It seemed that multilevel models with additional levels could contain those correlated outcomes (Goldstein, 2003). Multilevel modes could be further extended to handle missing values (i.e. some trials failed to report all outcomes) that occur at random (Hox, 2010).

For the issue of inconsistency among direct and indirect treatment comparisons, there is a design-by-treatment interaction approach to estimating the inconsistency (Higgins et al., 2012). Multivariate meta-regression has been used to estimate the consistency and inconsistency in network meta-analysis (White et al., 2012). Random effects meta-regression was used to adjust for study-level variables and explain the difference in effect sizes between-study in mixed treatment comparisons (Nixon et al., 2007). However, multilevel models have not been used in network meta-analysis to address these issues.

For the reasons described above, multilevel models would be appropriate to use in network meta-analysis. In this study we formulated a multilevel model (Section 2) to accommodate multiple treatments by introducing multiple dummy variables into the multilevel regression equation. We adopted an arm-based method to compare the effect sizes of multiple treatments. A design-level (design refers to the same treatments compared in the pair-wise trials or the multiple-arms trials) (Higgins et al., 2012) was added into our proposed multilevel model to accommodate a three-level structure for multiple treatments comparison. Further variables could be added into different levels of this model to explain the between-design heterogeneity. A network meta-analysis (Section 3) on the real-world data from a conventional network meta-analysis (Lao, 2013) was performed to evaluate the applicability of the proposed multilevel model. Finally, we discussed some issues in our research and future research direction (Section 4).

2. Methods

Treatments were represented as dummy variables (Goldstein et al., 2000). A set of specific treatments compared in a trial was represented at (level-3) design-level (Higgins et al., 2012). Hence, our multilevel model with a three-level structure was specified by the following equations for the effect sizes at the aggregate level:

$$y_{\bullet jk} = \beta_{0jk} + \sum_{p}^{n} \beta_{p,jk} drug_p + \sum_{q}^{m} \beta_{q,jk} X_{q,jk} + v_{0k} + u_{0jk} + e_{\bullet jk} \tag{1}$$

$$v_{0k} \sim N(0, \sigma_{v0}^2) \tag{2}$$

$$u_{0k} \sim N(0, \sigma_{u0}^2) \tag{3}$$

$$e_{\bullet jk} \sim N(0, \sigma_e^2 / n_{jk}) \tag{4}$$

where k refers to the design-level (level 3), j refers to the trial-level (level 2) and

the $\bullet$ at the aggregate level represents the individual-level (level-1). $y_{\bullet jk}$ is the effect

size of the common comparator among the multiple drugs. β_{0jk} is the intercept,

$e_{\bullet jk}$ is the residual error at the individual-level (level-1), u_{0jk} is the residual error at

the trial-level (level-2) and v_{0k} is the residual error at the design-level (level-3). The

terms σ_e^2 / n_{jk}, σ_{u0}^2, σ_{v0}^2 are the residual variances at different levels. $drug_p$ is the

indicator of the multiple drugs, and the coefficient $\beta_{p,jk}$ refers to the relative effect

(positive or negative) with the common comparator of statistical significance. The design-level and trial-level variances for this coefficient respectively refer to the inconsistency and heterogeneity of specific comparisons in the network meta-analysis.

$X_{q,jk}$ is a trial-level (level-2) variable and $\beta_{q,jk}$ is its coefficient. Level-1 variables

can be added to the equation when individual patient data are available. Other level-3 variables can be added into the equation if needed.

Restricted maximum likelihood (REML) was used to estimate the specified parameters including regression coefficients and component variances. Missing outcomes in the trials were assumed to occur at random. Multilevel analysis was run in the professional software MLwiN (Rasbash et al., 2009) with the inverse variance weighting. We set level-1 variance to 1 for precise estimation.

3. Example: multilevel network meta-analysis

Network meta-analysis was performed on a dataset of monotherapy trials for multiple durgs of type 2 diabetes mellitus based on our proposed multilevel model. Efficacy data of the anitdiabetic drugs including pioglitazone, metformin, glimepiride, rosiglitzone, sitagliptin, vildagliptin, acarbose, glyburide and gliclazide were originally collected for a conventional network meta-analysis that included 54 random

controlled trials. Four of these 54 trials were of three-arms design and the rest were of
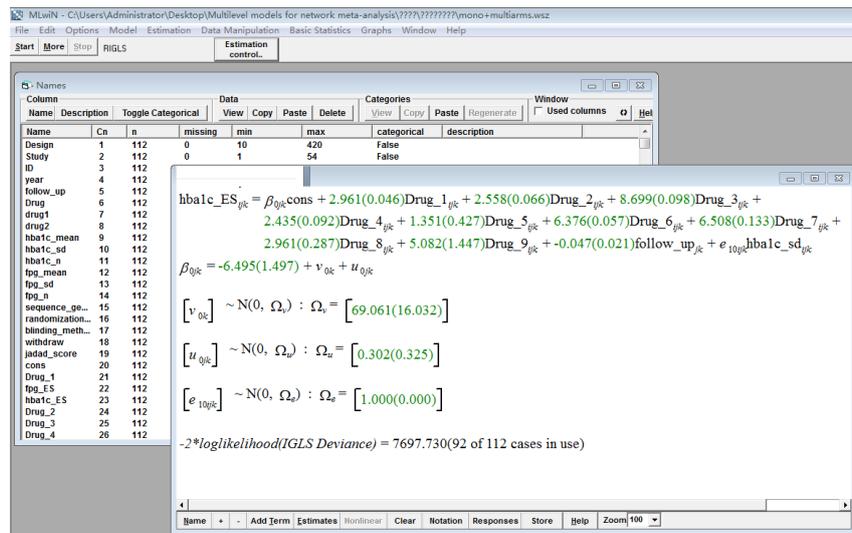

Figure 1. A screenshot of MLwiN running network meta-analysis

two-arms design. The effect sizes were measured as the difference in HbA1c before and after drug treatments. They were represented in standard mean difference (SMD) and 95% confidential intervals (95%CI). An arm-based approach was used to compare the effect sizes. There were also seven variables representing the basic characteristics of the included trials, i.e. publication year, follow-up period, sequence generation, randomization concealment, blinding method, withdrawal and Jaded score.

In our network meta-analysis, all anti-diabetic drugs were more effective than placebo in controlling HbA1c. Between-study variance was small and not statistically significant but the between-design variance was large and statistically significant (P=1.6499e-005). Among the level-2 variables added into the model for explaining the heterogeneity, only the variable *follow-up* was statistically significant (P=0.022316). Its coefficient -0.047 indicated that the follow-up was negatively correlated with the effect size of placebo. The between-design variance σ_{v0}^2 (decreased from 71.892 to 69.601) could be explained 3.19% by level-2 variable *follow-up*. As the between-design variance (P=2.2714e-005) was still statistically significant, more variables from different levels would be needed to explain the between-design variance.

The results from MLwiN are shown in Figure 1. As the result of the network meta-analysis based on multilevel models, the overall ranking of the drugs, i.e. glimepiride, acarbose, vildagliptin, gliclazide, pioglitazone, glyburide, metformin, rosiglitazone and sitagliptin, was consistent with the conventional meta-analysis. Comparison results between any two drugs were given by MLwiN with a dummy variable "drug" valued either 1 or -1. The result of ranking the multiple drugs kept unchanged when the variable "follow-up" was added into the model.

4.   Concluding remarks

Multilevel models are applicable to the network meta-analysis in not only ranking the effect sizes through direct and indirect of multiple treatment comparison but also explaining the between-design heterogeneity.

Our proposed multilevel model provides a generalized framework for conducting both traditional meta-analysis and network meta-analysis, not only comparing treatments but also explaining the between-design heterogeneity. Our preliminary result was consistent with conventional network meta-analysis. A level-2 variable was added into our proposed model but further variables could be included to explain the between-design heterogeneity. However, the proposed model had not addressed the issues of outcome correlations. Further research will address some complicated cases such as outcome correlations, incomplete block structure and missing values in both multiple-arms trials and multiple outcomes. In addition, we will improve the implementation of multilevel models by custom programming in R.

Acknowledgment

Authors' contributions

SL conceived the applicability of multilevel models to network meta-analysis. NL proposed the multilevel model and conducted the multilevel network meta-analysis as reported. YL conducted a conventional network meta-analysis (unpublished) and contributed his raw data for testing the described multilevel model. NL drafted the manuscript and SL revised it for submission. All authors read and approved the final manuscript.

References

Goldstein, H. (2003). Multilevel statistical models (3rd ed.). London: Edward Arnold.

Goldstein, H., Yang, M., Omar R., Turner, R. and Thompson, S. (2000). Meta-analysis using multilevel models with an application to the study of class size effects. Journal of the Royal Statistical Society: Series C (Applied Statistics) 49 (3): 399-412.

Higgins, J.P.T., Jackson, D., Barrett, J.K., Lu, G., Ades, A.E. and White, I.R. (2012). Consistency and inconsistency in network meta-analysis: Concepts and models for multi-arm studies. Research Synthesis Methods 3 (2): 98-110.

Hox, J.J. (2010). Multilevel analysis: Techniques and applications. Routledge Academic.

Nixon, R.M., Bansback, N. and Brennan, A. (2007). Using mixed treatment comparisons and meta-regression to perform indirect comparisons to estimate the efficacy of biologic treatments in rheumatoid arthritis. Statistics in Medicine 26 (6): 1237-54.

Rasbash, J., Charlton, C., Browne, W.J., Healy, M. and Cameron, B. (2009). MLwiN version 2.1. Centre for Multilevel Modelling, University of Bristol.

Salanti, G. (2012). Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: Many names, many benefits, many concerns for the next generation evidence synthesis tool. Research Synthesis Methods 3 (2): 80-97.

White, I.R., Barrett, J.K., Jackson, D. and Higgins, J.P.T. (2012). Consistency and inconsistency in network meta-analysis: Model estimation using multivariate meta-regression. Research Synthesis Methods 3 (2): 111-25.

Lao, Y.G. (2013). Network meta-analysis of anti-diabetic drugs. Unpublished master thesis, University of Macau.