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A multilevel approach to network meta-analysis within a frequentist framework

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SUMMARY

Meta-analysis is a powerful tool to summarize knowledge. Pairwise or network meta-analysis may be carried out with multivariate models that account for the dependence between treatment estimates and quantify the correlation across studies. From a different perspective, meta-analysis may be viewed as a special case of multilevel analysis having a hierarchical data structure. Hence, we introduce an alternative frequentist approach, called *multilevel network meta-analysis*, which also allows to account for publication bias and the presence of inconsistency. We propose our approach for a three-level data structure set-up: arms within studies at the first level, studies within study designs at the second level and design configuration at the third level. This strategy differs from the traditional frequentist modeling because it works directly on an arm-based data structure. An advantage of using multilevel analysis is its flexibility, since it naturally allows to add further levels to the model and to accommodate for multiple outcome variables. Moreover, multilevel modeling may be carried out with widely available statistical programs.
Finally, we compare the results from our approach with those from a Bayesian network meta-analysis on a binary endpoint which examines the effect on mortality of some anesthetics at the longest follow-up available. In addition, we compare results from the Bayesian and multilevel network meta-analysis approaches on a publicly available "Thrombolytic drugs" database. We also provide the reader with a blueprint of SAS codes for fitting the proposed models, although our approach does not rely on any specific software.

1. Introduction

Meta-analysis [1] is a powerful tool to summarize existing available knowledge in a field of interest in research and to identify global measures of differential treatment effects by combining independent studies that test the same hypotheses. Network meta-analysis (NMA) is applied when pairwise comparisons are either not available in the literature or are inconclusive [2] and it provides a global estimate of efficacy or safety for the multiple treatment network [3–5], see Appendix A in the Supplementary material. Direct meta-analysis is a comparison of the effect sizes of two different treatments (e.g. weighted mean difference, relative risk, odds ratio), say a treatment of

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interest and a reference. In its ability to cope with multiple treatments, NMA provides a natural framework to accommodate for missing comparisons and to deal with correlated data [3–9], where the presence of a correlation structure may derive from multiple endpoints, time-varying responses or clustered observations. On the other hand, multilevel modeling approaches [10–15] offer a valuable framework for carrying out NMA taking advantage of an existing hierarchical data structure.

In this paper, we propose an alternative frequentist approach to NMA via multilevel modeling. This approach differs from the frequentist two-stage modeling by Lumley [16] in that it works directly on the arm-based data structure, where the effects are measured for each arm. Our aim is to take advantage of the wide diffusion of expertise on multilevel modeling among applied researchers and of the related presence of available standard software for multilevel models, to overcome known methodological and practical difficulties in performing NMA. As a by-product, the Supplementary material provides a tutorial on how to use SAS multilevel modeling software to fit a NMA.

The paper is structured in the following way. We firstly introduce multilevel models in the NMA framework. Then, we explain in detail the *multilevel network meta-analysis* approach for a three-level data structure: arms within studies at the first level, studies within study designs at second level and the design configuration at the third level. Finally, we present an application of our novel frequentist approach based on data from a previously published Bayesian NMA on the effect of anesthetic drugs on mortality. In addition, in the Supplementary material we provide the results from an application of the Bayesian and multilevel frequentist approaches on the "Thrombolytics data" presented by Dias et al. [17], a dataset which is not sparse as the "anesthetic drugs" one.

1.1. Background

1.1.1. Network meta-analysis

The pioneering work by Thomas Lumley (2002) [16] proposed the term "network meta-analysis" and introduced the basic tools to perform a meta-analysis including direct and indirect comparisons. In his work, Lumley described the approach referring to very complex networks of treatment comparisons and suggested how to detect inconsistency (or incoherence) between randomized trials, to estimate treatment differences and to assess the related estimates uncertainty. Moreover, Lumley suggested the application of Bayesian approaches to model heterogeneity between treatments together with the underlying inconsistency.

The extension to handle multi-armed trials using non-Bayesian methods was considered by authors such as Salanti et al. (2008) [5], Jackson, Riley and White (2011) [6], White et al. (2012) [8], White (2009) [18] and Higgins et al. (2012) [9]. Salanti et al. [5] described the general set-up of NMA with either arm-based models, where the effect measures are reported for each arm (i.e. odds, absolute risk, hazard or mean), or contrast-based models, where results are presented as a comparison of effects between arms (i.e. odds ratio, risk ratio, hazard ratio or mean difference). However, this paper left some important issues open, such as the quantification of inconsistency, the evaluation of bias and the development of a user-friendly software for NMA models, which are some of the motivations of our contribution. White (2009) [18] updated a Stata (College Station, TX, USA) command, *mvmeta*, to perform a multivariate meta-regression and obtain suitable difference effect estimates. Jackson, Riley and White (2011) [6] explored the potential of the multivariate model for fitting a network data structure adopting a two-stage approach of analysis. The trial-specific parameter of interest and the variance–covariance matrix are obtained at the first stage and then these estimates are combined at the second stage. In this case, the aggregate input data are managed as contrast-level summaries. White et al.(2012) [8] and Higgins et al. (2012) [9] reviewed the concept of inconsistency, here modeled by a treatment-by-design interaction, and the methods to fit consistency and inconsistency models.

On the other hand, Lu and Ades (2004) [19] proposed an alternative Bayesian approach to NMA for multi-arm studies that included both direct and indirect comparisons. Moreover, they explored results from a Markov Chain Monte Carlo (MCMC) algorithm to set up a strategy for selecting the best treatment regimen a posteriori. In a previous work [20] we referred to the Lu and Ades contribution and we outlined the main steps of a Bayesian NMA for binomial models. We adopted a Bayesian hierarchical model implementing a MCMC algorithm in WinBUGS (freely available on the BUGS project website).

In this paper, we propose an alternative frequentist approach to NMA to estimate the consistency and inconsistency models following the Higgins et al. (2012) [9] definition in using *design* to refer to the set of treatments compared in a trial. Our aim is to take advantage of the wide diffusion of expertise on multilevel modeling among applied researchers and of the related presence of available statistical programs for multilevel models to overcome known difficulties in performing NMA.

1.1.2. Multilevel models and meta-analysis

In the last 15–20 years, multilevel methodology has evolved from a specialty area of statistical research into a standard analytical tool used by many applied researchers. Multilevel modeling is now an accepted statistical tool to analyze nested sources of heterogeneity derived from hierarchical data, taking into account the variability associated with each level of the hierarchy. Discussions of methodological and statistical issues including performing a meta-analysis using multilevel model are available from works by Goldstein (2003) [12], van Houwelingen, Arends and Stijnen (2002) [21] and Hox (1995, 2002) [10,14]. These researchers framed the existing methods for meta-analysis of two-arm clinical trials into general multilevel modeling. Flexibility is the major advantage of using these models instead of classical meta-analysis approaches [10,14]: it is natural to include study characteristics as explanatory variables in an attempt to explain existing heterogeneity, and to add additional levels into the model to accommodate for multiple treatment comparisons.

Moreover, in meta-analysis, the question of whether all studies report or not the same outcome is an essential issue. Therefore, it is very important to have models that estimate the contribution of each random effect to the dependent variable variance. Indeed, the standard errors of the coefficients of higher level predictors may be underestimated when a single-level model is used. The fact that multilevel models, also known as variance component models, estimate the variability accounted