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Three-dimensional evidence network plot system: covariate imbalances and effects in network meta-analysis explored using a new software tool

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Abstract

Objectives: The aim of the study was to develop the three-dimensional (3D) evidence network plot system—a novel web-based interactive 3D tool to facilitate the visualization and exploration of covariate distributions and imbalances across evidence networks for network meta-analysis (NMA).

Study Design and Setting: We developed the 3D evidence network plot system within an AngularJS environment using a third party JavaScript library (Three.js) to create the 3D element of the application. Data used to enable the creation of the 3D element for a particular topic are inputted via a Microsoft Excel template spreadsheet that has been specifically formatted to hold these data. We display and discuss the findings of applying the tool to two NMA examples considering multiple covariates. These two examples have been previously identified as having potentially important covariate effects and allow us to document the various features of the tool while illustrating how it can be used.

Results: The 3D evidence network plot system provides an immediate, intuitive, and accessible way to assess the similarity and differences between the values of covariates for individual studies within and between each treatment contrast in an evidence network. In this way, differences between the studies, which may invalidate the usual assumptions of an NMA, can be identified for further scrutiny. Hence, the tool facilitates NMA feasibility/validity assessments and aids in the interpretation of NMA results.

Conclusion: The 3D evidence network plot system is the first tool designed specifically to visualize covariate distributions and imbalances across evidence networks in 3D. This will be of primary interest to systematic review and meta-analysis researchers and, more generally, those assessing the validity and robustness of an NMA to inform reimbursement decisions.

Keywords: Covariate; Evidence networks; Heterogeneity; Meta-analysis feasibility; Network meta-analysis; Novel graphical tool; Three dimensional

1. Introduction

Network meta-analysis (NMA) is an increasingly popular statistical method used for estimating the comparative efficacy of all treatments of interest for a given condition, by simultaneously synthesizing data from all relevant randomized controlled trials (RCTs) [1]. Such analyses are commonly used to identify the most effective treatments and inform economic decision models to estimate the relative cost-effectiveness of the treatment options.

Like all statistical modeling, NMA makes a number of assumptions that, if not satisfied by the data being synthesized, can lead to erroneous results and misleading conclusions [2]. The first assumption that needs satisfying is that the network is connected which can be checked by constructing a network diagram [3]. More generally, evidence network diagrams are commonly used for visualizing the available evidence base for the purpose of assessing the feasibility of the meta-analysis and understanding the strength and diversity of the evidence available. A conventional network diagram consists of ‘‘nodes’’ representing the treatments of interest and edges representing available direct comparisons between pairs of interventions and is a key component of global NMA reporting checklists [4]. All nodes should be connected to form a single network via edges and any nodes which are not connected should be excluded. The amount of available evidence can also be presented in network diagrams by ‘‘weighting’’ the nodes and edges using different node sizes and line thicknesses [5].

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What is new?

Key findings

- Visually assimilating, exploring, and interpreting the distribution of covariate values across trials in a network meta-analysis (NMA) is challenging due to the complexities of representing the network structure simultaneously alongside study-level covariate values.
- This article describes a three-dimensional (3D) evidence network plot system—a novel, freely accessible, web-based package to facilitate the exploration of covariate distributions and imbalances across evidence networks in NMA.

What this adds to what was known?

- The primary innovation which allows for the extensions to evidence networks and improvements is the use of a 3D graphical environment, incorporating the graphical representation of covariates on a third ''z''-axis.
- We believe this work to be the first application of a 3D graphical environment to evidence networks in NMA.

What is the implication and what should change now?

- We propose that the 3D evidence network plot system will facilitate the exploration of covariate distributions and imbalances across evidence networks and be of most value in the context of supporting NMA feasibility/validity assessments and to aid in the interpretation of NMA results to a wide audience.

Further assumptions of NMA relate to the comparability of the studies being combined. As for pairwise meta-analysis, differences in the results of studies (beyond that expected by chance) within each (pairwise) treatment comparison are described as between-study heterogeneity. Such variability in study results can lead to inconsistency in treatment estimates across different comparisons in an NMA, where estimates of comparative effectiveness differ between those from direct comparisons and those derived from indirect comparison routes through the network [6]. Although heterogeneity and inconsistency random-effect (RE) terms can be included in NMA models to allow for them [7], results can become increasingly difficult to interpret as the number and magnitude of such terms increase. This can lead to challenging issues, in terms of limiting the ability to generalize from the results [8], for both decision makers [9] and for designers of further studies that are intended to update the evidence base in the future [10,11]. Therefore, it is highly desirable to explain the causes and magnitude of heterogeneity and inconsistency rather than simply accommodate them.

Heterogeneity and inconsistency can frequently be explained by the differences in trial design and the conduct of the individual trials included in the NMA. Assuming summary information from published trial results is being used for the NMA rather than individual patient data [12], it may be possible to identify causes of heterogeneity and inconsistency by extracting information on study- and aggregate patient-level characteristics (e.g., duration of treatment or duration of condition before randomization). Such variables are often described as potential effect modifiers, and if these impact the effectiveness of the interventions of interest, treatment by covariate interactions can be included in the NMA model [7]. Treatment-covariate interactions can be used to explain and reduce heterogeneity and inconsistency in the same way as they are used in meta-regression for pairwise meta-analysis [13]. In addition, when treatment by covariate interactions relating to patient characteristics are identified, it implies that treatment efficacy varies between patients. Therefore, optimal treatment decisions could vary across patient groups depending on their characteristics. In the current paper, we focus on potential effect modifiers which are expressed on a continuous scale (including dichotomous patient-level covariates aggregated at the study level, e.g., % of males), although we note that categorical variables (e.g., individual indicators of study quality) can also be considered using a regression framework and plots including these have been considered elsewhere [14]. Regression modeling is generally superior to subgroup analyses as it allows a holistic analysis, exploring the impact of covariates on all of the data, and allows the simultaneous consideration of multiple (continuous and categorical) covariates [8]. However, it should not be forgotten that regressing study-level summary covariate information on study-level average treatment effects is potentially susceptible to ecological bias.

A recent publication [14], outlining a process for assessing the feasibility of conducting a valid NMA, highlighted the importance of assessing whether there are differences in treatment, patient, and outcome characteristics across comparisons that may affect the summary measures of treatment effects relative to an overall reference treatment. These potential effect modifiers may be known or suspected a priori or identified post hoc. Visually assimilating, exploring, and interpreting the distribution of covariate values across trials in an NMA is challenging due to the complexities of representing the network structure simultaneously alongside study-level covariate values. Although multiple plots could more easily be constructed for individual comparisons within the network, these are of limited use because many will be sparse and uninformative, and each plot only provides a subset of the required information. A holistic approach is required to assess the distribution of covariate values across the whole evidence network.