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ORIGINAL ARTICLE

Modeling missing binary outcome data while preserving transitivity assumption yielded more credible network meta-analysis results

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Abstract

Objectives: The objectives of this study were to elaborate on the conceptual evaluation of transitivity assumption in the context of binary missing participant outcome data (MOD) in network meta-analysis (NMA) and to emphasize on the importance of statistical modeling as a mean to address MOD.

Study Design and Setting: We designate the notion of transitivity assumption in the context of binary MOD and indicate scenarios that compromise transitivity in complex networks. We propose a modification of these scenarios that preserves transitivity assumption. Using a published NMA, we indicate the implications of excluding or imputing, rather than modeling MOD, on NMA findings.

Results: Arm-specific scenarios for MOD, as commonly applied in conventional meta-analysis, compromise the validity of transitivity assumption in complex networks. The motivating example reveals that imputation of those scenarios yields estimates in the opposite direction for the basic parameters with narrower credible intervals and inflates between-trial variance. Contrariwise, modeling MOD after modification of the scenarios yields robust estimates for the basic parameters but wider credible intervals and reduces between-trial variance.

Conclusion: Application of arm-specific scenarios for binary MOD requires modification in complex networks to ensure valid transitivity assumption. Analysts should model, rather than exclude or impute MOD, to provide bias-adjusted results.

Keywords: Network meta-analysis; Transitivity; Consistency; Imputation; Missing outcome data; Systematic review

1. Introduction

Empirical studies on published systematic reviews with pairwise meta-analyses have revealed an inclination of reviewers toward the intention-to-treat (ITT) analysis as the ideal strategy for outcome analysis in the presence of missing participant outcome data (MOD) in a meta-analysis [1–4]. Prominent features of this strategy comprise the ability to maintain the randomized sample in every included trial and, therefore, to preserve power to detect a treatment effect. Furthermore, by analyzing the participants to the intervention originally randomized regardless of protocol deviations or trial completion, we uphold a balance in known and unknown prognostic factors between the compared interventions and hence insulate the trial results from selection bias and cofounding.

However, in an effort to ensure ITT and benefit from the favoring properties of that strategy, reviewers have a preference over scenarios that reflect a rather extreme view over the outcome of missing participants and lack plausibility in practice [1–4]. Such scenarios are either arm-specific or common for both interventions in every trial. For binary outcome, the former includes the best- and worst-case scenario, where all missing participants in the active and control arm of every trial are assumed to have experienced the event, respectively, whereas all missing participants in the opposing arm are assumed not to have experienced the event. Scenarios common in both arms constitute the ‘‘all missing cases are events’’ and ‘‘all missing cases are non-events’’ where all missing participants in both arms of every trial are assumed to have experienced or not the event, respectively. While these scenarios can reveal the extent to which MOD affect the overall treatment effect, they may lead to conflicting conclusions and biased results,

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What is new?

Key findings

- Affirmation of transitivity assumption in the context of missing participant outcome data (MOD) is necessary. Application of scenarios about MOD without any consideration for their transitivity across comparisons within a complex network raises concerns about the validity of transitivity assumption, and by extent, the credibility of network meta-analysis (NMA) results.
- Fixing observations before analysis either with exclusion or imputation of MOD within each trial leads to more precise NMA treatment effects and inflated between-trial variance. Particularly, when extreme scenarios are considered to impute MOD, different conclusions are drawn about the relative effectiveness of the interventions. By contrast, modeling MOD yields more plausible NMA treatment effects with naturally increased uncertainty and, in addition, lowers between-trial variance as a result of inherently adjusting MOD.

What this adds to what was known?

- Opting to model, rather than exclude or impute MOD, while considering clinically plausible scenarios that validate transitivity assumption, constitutes an effective strategy to handle MOD in NMA as it offers bias-adjusted results and inherent accountability of uncertainty due to MOD.

What is the implication and what should change now?

- An attentive analysis plan to handle MOD in NMA should be provided already in the protocol to avoid data-driven decisions. The analysis plan should include and explicitly justify the model for MOD, the missingness parameter, a scenario for primary analysis and clinically plausible scenarios for sensitivity analysis that ensure the validity of transitivity assumption.

especially, when participant loss is substantial across the included trials [2,5].

Because access to individual participant data for an effective management of MOD is rarely the case, an attentive strategy is to use a primary analysis under the missing at random (MAR) assumption [6−8] and then, investigate the degree of deviation from this assumption through a proper statistical model for MOD [5,6,9]. In addition, a series of sensitivity analyses should follow with plausible scenarios of progressive extremity—ideally defined already in the protocol [3]—to investigate the sensitivity of the primary analysis results to these scenarios [1,8]. Nevertheless, the analysts typically exclude MOD from all included trials to perform the primary analysis, whereas they impute MOD in all trials according to a specific scenario to proceed with the sensitivity analysis [1−4]. Despite being easy to implement, these data manipulation does not actually address MOD because the analysis fails to acknowledge not only the scenario about MOD that led to data elimination or augmentation but also the uncertainty around this essentially untestable scenario. Therefore, the manipulated data are treated spuriously as observed.

The analysts should opt primarily for methodologies that attempt to incorporate rather than exclude from or impute MOD in meta-analysis [5,6,9,10]. Pattern-mixture model is the most popular framework to this direction for being intuitive and straightforward to implement, especially in the Bayesian framework [5,9,11]. This model inherently accounts for the bias stemming from MOD and, by extension, accommodates the uncertainty induced by MOD in the trial-specific treatment effects and hence in the overall treatment effect, penalizing trials with larger MOD. In addition, the model fosters thorough investigation of the underlying missingness mechanism in every trial, intervention or trial-arm [5].

Pattern-mixture model has been investigated in conventional meta-analysis [5,9]; however, its utility is also relevant to network meta-analysis (NMA), an extension of conventional meta-analysis that aims to provide internally coherent relative treatment effects for all pairwise comparisons and support outcome-specific hierarchy of the investigated interventions [12,13]. The affirmation of additional necessary assumptions, namely, transitivity and consistency, defines the circumstances that justify the validity of NMA. Addressing MOD in a network of several interventions offers the opportunity to investigate thoroughly the extent of MOD in interventions that have been investigated in different comparisons. Because more than two interventions frame the research question, the scenarios considered to handle missingness in NMA ought to preserve the plausibility of transitivity assumption to secure valid inferences. Particular attention is needed in triangle and more complex structures of networks where some interventions might be the experimental in one trial but the control in another trial. In this case, using scenarios specific to the interventions compared within a trial will result in inconsistent supposition for the missingness mechanisms across the network.

The objectives of this article are to elaborate on the conceptual evaluation of transitivity assumption in the context of binary MOD and to apprize the interested reader of the proper application of arm-specific scenarios, while accounting for the network geometry. Furthermore, we emphasize on the importance of statistical modeling as a mean to address MOD properly. Using a published systematic review with NMA, we illustrate the negative implications