Journal of Clinical Epidemiology 105 (2019) 19−26

Journal of Clinical Epidemiology

ORIGINAL ARTICLE

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

Loukia M. Spineli*

Institut für Biometrie, Medizinische Hochschule Hannover, Hannover, Germany

Accepted 10 September 2018; Published online 14 September 2018

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,

Conflict of interest: The author declares no conflict of interest.

* Corresponding author: Institut für Biometrie (OE 8410), Medizinische Hochschule Hannover, Carl-Neuberg-Straße 1, 30625, Hannover, Germany. Tel.: +49 0 511 532 4377; fax: +49 0 511 532 4295.

E-mail address: Spineli.Loukia@mh-hannover.de.

https://doi.org/10.1016/j.jclinepi.2018.09.002

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 of handling MOD conventionally through exclusion or imputation, rather than modeling on the NMA findings.

2. Materials and methods

2.1. Motivating example

We used the published NMA of Baker et al. on seven pharmacologic treatments for chronic obstructive pulmonary disease (COPD) [14]. The primary outcome was COPD exacerbations. Twenty-six randomized controlled trials (18 two-arm, 2 three-arm, and 6 four-arm) with 20,939 patients (median: 546; IQR: 279–794) contributed to the analysis of COPD exacerbations and provided also information on patient withdrawals. In five trials (2 two-arm and 3 four-arm), we calculated negative nonevents in at least one arm, after subtracting the reported number of events and number of MOD from the number randomized, and hence, we decided to exclude these trials. The reviewers "lumped" the interventions in four distinct classes, but we considered the interventions as reported in the trials (Table S1 in Appendix 1 illustrates the analyzed data set).

2.2. Transitivity assumption in the presence of missing outcome data

To elaborate on the notion of transitivity assumption in the context of MOD, we considered the interpretation of transitivity as described in the study by Salanti [15]:

a) Missing participants in intervention A have been subject to similar missingness mechanisms in BA and CA trials. If intervention A is claimed to be similar in BA and CA trials (transitivity interpretation 1 in the study by Salanti [15]), then it can also be claimed that the mechanisms led to premature discontinuation of participants who received intervention A are similar in BA and CA trials (Fig. 1A). However, if A is not systematically comparable in BA and CA trials (eg, different administration in BA and CA trials), then it is reasonable to assume that missingness mechanisms in A might be different in BA and CA trials (Fig. 1B). In this case, transitivity assumption is violated.
b) Missing interventions (T*) in each trial are assumed to be missing for reasons irrelevant to trialists' expectations about possible missingness mechanisms (resemblance of transitivity interpretation 2 in the study by Salanti [15]). In that case, missing interventions are assumed to be MAR (Fig. 1C). However, if an active intervention (T*) is systematically avoided to be compared with another active (newer) intervention because, for instance, it is believed that patients randomized in the former may fail to experience immediate improvement in their outcome (O) and hence, dropout early (the distribution of the outcome will differ between completers and missing participants), then transitivity assumption is violated as the missingness of this intervention is associated with

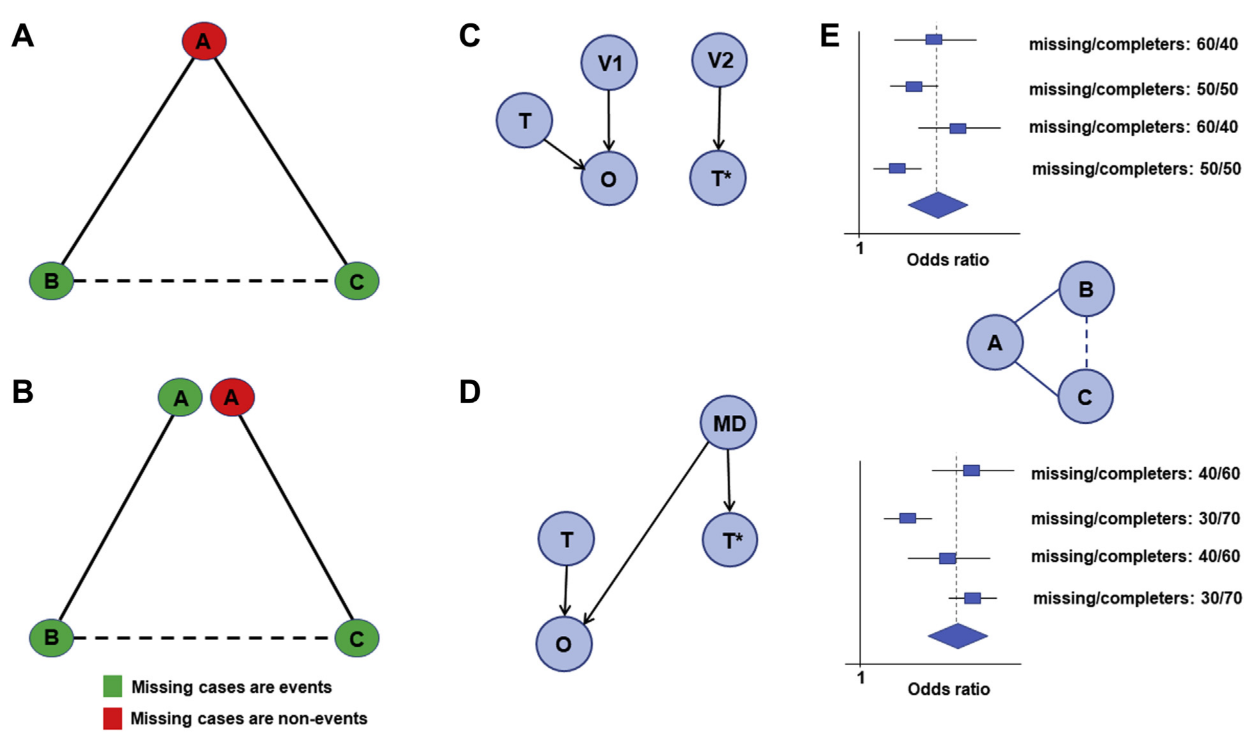

Fig. 1. Interpretations of transitivity assumption in the context of missing binary outcome data: transitivity assumption holds in (A) and (C), but it is violated in (B), (D) and (E). MD, missing outcome data; O, investigated outcome; T, observed treatments; T*, missing treatments; V1, V2, measured and unmeasured variables.

the expectations for premature discontinuation (MD) (Fig. 1D).

c) There are no differences in missingness mechanisms between observed and unobserved interventions (resemblance of transitivity interpretation 3 in the study by Salanti [15]). If we denote with y_C^m, a measure of informative missingness (eg, odds ratio of event between missing and completers in the logarithmic scale [5,9]) in intervention C of CB trial and with $y_C^{'m}$, the latent measure of informative missingness in unobserved intervention C of BA trial, then y_C^m and $y_C^{'m}$ are perceived as exchangeable under the transitivity assumption, namely, being sampled from the same distribution. If exchangeability is not deemed feasible, missingness mechanisms in C might be different in CB and BA trials and it is further implicated that C might operate differently in these trials. Consequently, transitivity assumption is violated.

d) The extent of MOD constitutes important effect modifier [16]. When the distribution of MOD differs systematically across comparisons, it signifies different risk of bias due to MOD (i.e., low, moderate, or high) and by extension, may implicate the validity of transitivity assumption (resemblance of transitivity interpretation 4 in the study by Salanti [15]). For instance, in BA and CA trials, if patients randomized in A tend to leave massively due to health deterioration (MOD are not MAR), followed by patients randomized in B but less frequently in C, then the ratio of missing to completers will be distributed differently between these comparisons raising concerns for intransitivity (Fig. 1E). Addressing MOD via exclusion or imputation will lead to biased indirect estimate for BC. Specifically, the resulting population after exclusion might not reflect the population originally randomized which may further implicate the distribution of other important effect modifiers in BA and CA trials, whereas imputation fails to adjust for bias due to missingness.

2.3. Modifying arm-specific scenarios for non–star-shaped networks

In a star-shaped network, where all experimental interventions are compared with a single control, both common and arm-specific scenarios can be safely applied without compromising transitivity assumption. However, in non–star-shaped networks, where an intervention might be the experimental in one trial but the control in another trial, arm-specific scenarios require modification in their application, otherwise we risk violating transitivity.

To ensure that transitivity assumption holds in non–star-shaped networks when arm-specific scenarios are considered, we introduce a simple yet necessary modification of their application. Initially, the reference intervention of the network is selected based on a priori decision on what constitutes the ‘‘decision comparator set’’ [17]. Then, we may assume the same scenario about MOD for all nonreference interventions but a different scenario for the reference intervention. This is a reference-specific scenario. With this modification, transitivity in missingness mechanisms is preserved across the network because all nonreference interventions are assigned the same missingness scenario irrespective of the comparator in each trial.

This modification is immediately applicable in networks with both placebo and active comparisons, where placebo is usually selected as the reference intervention (eg, Cipriani et al. [18]). In networks with many inactive interventions, such as placebo, no treatment, and usual care (eg, Corbett et al. [19]), the reference-specific approach can be ‘‘relaxed’’, and scenarios about MOD can be tailored to intervention (in)activity; for example, all inactive interventions may receive the same scenario, whereas all active interventions may be assigned another scenario. Alternatively, one may tailor the missingness scenarios to the state of interventions being recent or old, which is a reasonable consideration in a network of solely active interventions (eg, Cipriani et al. [20]). In this case, newer-generation interventions may receive the same scenario, whereas older-generation interventions may be assigned another scenario.

2.4. Implications for consistency assumption

Conventional arm-specific and reference-specific scenarios have different implications for the validity of consistency assumption. For example, in a triangle network of BA, CA. and CB trials, the conventional best-case scenario (commonly implemented through imputation) will consider all MOD to be events in arms B and C for trials BA and CA, respectively, and in arm C for trials CB, whereas all MOD will be considered to be nonevents in arm A for trials BA and CA and in arm B for CB trials. It is obvious that A and C satisfy transitivity in missingness mechanisms but not B, which has different missingness mechanisms in BA and CB trials. While the indirect estimate of CB is valid under the conventional best-case scenario (and assuming that missingness is low), it is not consistent with the direct estimate of CB and hence, the mixed estimate for CB will be irrelevant. Subsequently, consistency assumption is compromised, hindering the mixture of the direct and indirect estimate of CB to obtain a solid mixed effect for CB. Suppose now that multiarm trials are also included in that loop and all MOD are treated as nonevents only in arm A of ABC trials. Transitivity is still compromised in that loop due to the different missingness mechanisms considered in arm B, namely, all MOD are nonevents in CB trials but events in ABC and BA trials.

Contrariwise, the respective reference-specific scenario ensures transitivity in the missingness mechanisms across the network because missing participants in nonreference interventions (here, B and C) are assumed to be more likely to have experienced the event as opposed to missing participants in reference intervention (here, A). Therefore, consistency assumption is applicable and can provide valid mixed effect for CB.

2.5. *Setup of the empirical evaluation*

We compared the conventional with the reference-specific best- and worst-case scenario in terms of basic parameters (i.e., all comparisons with the reference intervention), common between-trial variance (τ^2) and ranking probabilities using Bayesian random-effects NMA model with consistency equations and accountability of multi-arm trials [21,22]. Placebo was the reference of the network. We used odds ratio in the logarithmic scale (log OR) as effect measure.

Conventional MAR was applied by excluding MOD before meta-analysis, whereas conventional best- and worst-case scenarios were performed by imputing all MOD as having the harmful event and not, respectively, in the first arm, which we considered to be the control in each trial. For the reference-specific scenarios and on average MAR, we extended the NMA model to incorporate the pattern-mixture informative missingness odds ratio (IMOR) parameter in order to account for the uncertainty about the studied scenarios [5,23]. We considered on average MAR (i.e., log IMORs are centered on zero with some uncertainty) as primary analysis. Details on the model specification and the Bayesian analyses are found in Appendix 2.

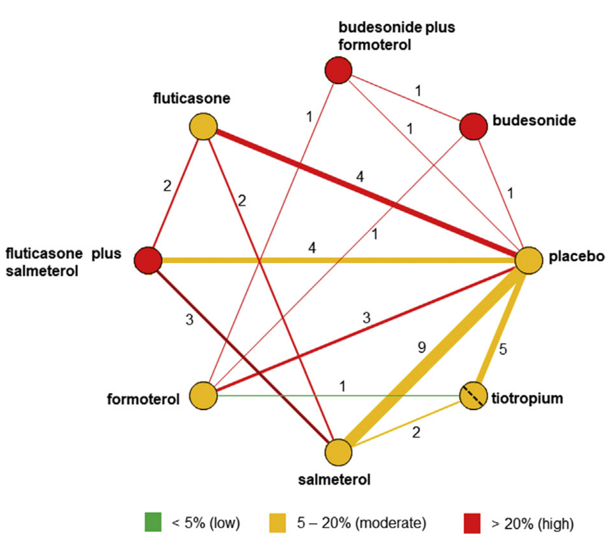

Fig. 2. Network of seven pharmacologic interventions and placebo for chronic obstructive pulmonary disease. The thickness of lines reflects the number of trials observed. Green, orange, and red reflects low, moderate, and high missingness, respectively. The dotted line on tiotropium indicates risk of intransitivity in missingness mechanisms for the loops that include tiotropium versus placebo, if arm-specific scenarios are to be considered. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

3. Results

Following the "five-and-twenty" rule at which a trial is judged to have a low risk of attrition bias for MOD less than 5%, high attrition bias for MOD above 20%, and moderate bias otherwise [24], missingness was judged to be high in three interventions (Fig. 2) and in 67% of the observed comparisons, while moderate in five interventions and four comparisons (Table 1). Violation in transitivity assumption was possible in two loops that included tiotropium versus placebo, if arm-specific scenarios were applied, because tiotropium was the experimental arm when compared with placebo, but the control when compared with salmeterol or formoterol (Fig. 2).

3.1. *Implications for basic parameters and* τ^2

Conventional best- and worst-case scenarios led to different conclusions as they yielded posterior mean of log ORs below and above zero, respectively, with smaller posterior variance overall compared with the corresponding reference-specific scenarios (Fig. 3). Conventional best-

Table 1. Distribution of percentage missing outcome data per trial

Intervention	Trials	Min.	1st qrtl.	Median	3rd qrtl.	Max.
PBO	19	5%	13%	18%	22%	44%
BUD	1	31%	31%	31%	31%	31%
BUD+	1	28%	28%	28%	28%	28%
FLU	4	0%	10%	20%	30%	40%
FLU+	4	5%	10%	21%	30%	31%
FOR	4	1%	11%	18%	24%	32%
SAL	10	2%	9%	14%	18%	32%
TIO	7	1%	4%	8%	9%	12%
Comparison						
BUD vs. PBO	1	38%	38%	38%	38%	38%
BUD + vs. PBO	1	36%	36%	36%	36%	36%
FLU vs. PBO	4	6%	14%	23%	32%	39%
FLU + vs. PBO	4	6%	8%	20%	32%	35%
FOR vs. PBO	3	16%	20%	23%	31%	38%
SAL vs. PBO	9	5%	12%	15%	20%	33%
TIO vs. PBO	5	6%	10%	11%	13%	15%
FOR vs. BUD	1	32%	32%	32%	32%	32%
BUD + vs. BUD	1	30%	30%	30%	30%	30%
SAL vs. FLU	2	29%	31%	32%	33%	34%
FLU + vs. FLU	2	28%	30%	32%	34%	36%
BUD + vs. FOR	1	30%	30%	30%	30%	30%
SAL vs. TIO	2	7%	8%	9%	10%	11%
FLU + vs. SAL	3	3%	17%	30%	30%	31%
FOR vs. TIO	1	1%	1%	1%	1%	1%

Abbreviations: BUD, budesonide; BUD+, budesonide plus formoterol; FLU, fluticasone; FLU+, fluticasone plus salmeterol; FOR, formoterol; Max, maximum; Min, minimum; PBO, placebo; SAL, salmeterol; qrtl, quartile; TIO, tiotropium.

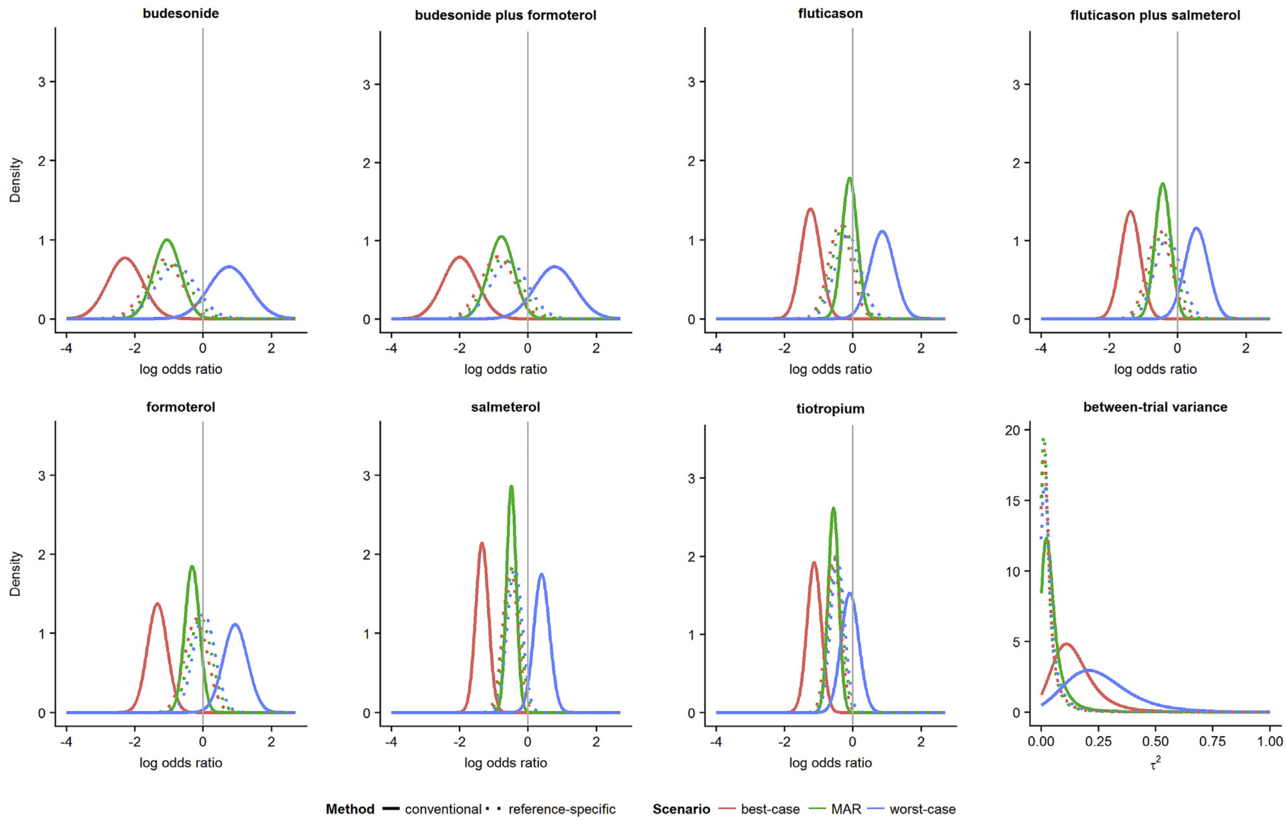

Fig. 3. A series of density plots on log odds ratio of basic parameters and between-trial variance using conventional (via imputation as commonly applied in meta-analysis) and reference-specific (via pattern-mixture model) best- and worst-case scenarios. Results after excluding (conventional MAR) and modeling missing outcome data to approximate MAR (on average MAR) are also presented. MAR: missing at random.

case scenario tended to favor the active interventions as opposed to worst-case scenario. Contrariwise, conventional MAR yielded similar results with on average MAR and reference-specific scenarios but with comparatively smaller posterior variance. The posterior median of τ^2 was larger and with substantial posterior variance under conventional best- and worst-case scenario. Contrariwise, conventional MAR, on average MAR and reference-specific scenarios led to very low and more precise τ^2 (particularly, under the latter three).

3.2. Implications for ranking probabilities

Overall, conventional best- and worst-case scenarios led to different intervention hierarchies as the former awarded larger probability on higher rankings for the active interventions as opposed to the latter (Fig. 4 and Table S2 in Appendix 1). By contrast, reference-specific scenarios provided similar ranking probabilities that were relatively lower than those obtained under the respective conventional scenarios. Consequently, the posterior variance of rankings was greater under on average MAR and reference-specific scenarios (Table S2 in Appendix 1). Conventional MAR agreed more or less with on average MAR and the reference-specific scenarios.

4. Discussion

Using a conceptual discussion on the role of transitivity assumption in the context of binary MOD, we demonstrated that in non–star-shaped networks, application of arm-specific scenarios for MOD, as commonly used in conventional meta-analysis, may compromise the validity of transitivity assumption, and by extent, the credibility of NMA results. To allow for transitivity in the missingness mechanisms across the network, arm-specific scenarios must be applied to the appointed reference and nonreference interventions rather than to the arms compared in each trial. Intransitivity in the missingness mechanisms may compromise the validity of indirect estimate and/or may manifest as inconsistency between the indirect and direct evidence in the ‘‘affected’’ loop leading to invalid mixed estimate for the comparison of interest.

Then, using a motivating example, we showed that conventional application of best- and worst-case scenario within each trial led to different conclusions and intervention hierarchies and, in addition, increased τ^2. Our findings confirmed the observations of relevant literature that fixing observations before analysis either with exclusion or imputation of MOD led to more precise overall treatment effects [5,6,9,23], while modeling MOD

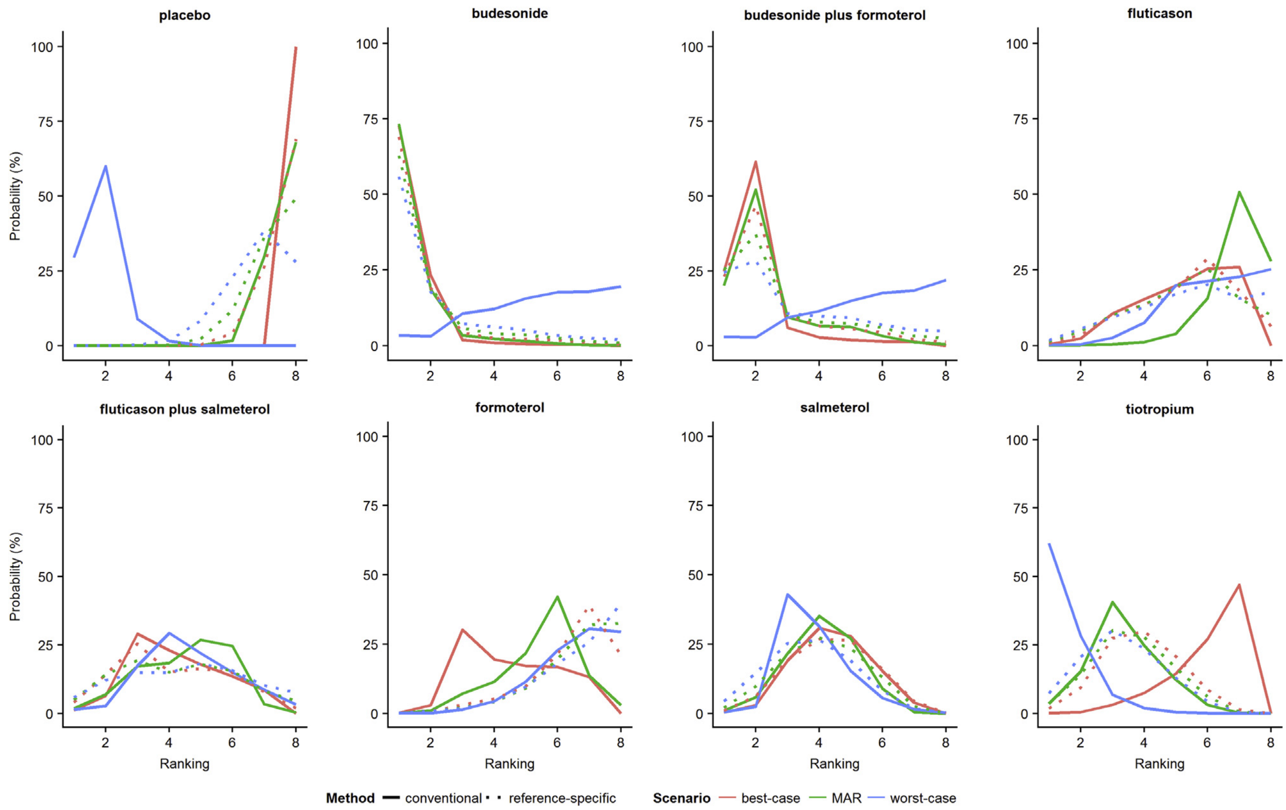

Fig. 4. Rankograms using conventional (via imputation as commonly applied in meta-analysis) and reference-specific (via pattern-mixture model) best- and worst-case scenarios. Results after excluding (conventional MAR) and modeling missing outcome data to approximate MAR (on average MAR) are also presented. MAR, missing at random.

naturally increased uncertainty around the treatment effects, which by extension, lowered τ^2 substantially (also observed in [5,9,23]). Reduction in the estimation of τ^2 is also an indication that large part of τ^2 has been explained after adjusting for MOD. In addition, by modeling MOD, we were able to learn about the missingness mechanisms in each intervention (Fig. S1 in Appendix 1). Nevertheless, we did not consult expert opinion to decide on the priors for log IMOR that best fit the condition and interventions studied; instead, we applied the priors we considered in a previous study [23].

To illustrate the benefits of modeling MOD, we used identical log IMORs with intervention-specific normal prior distribution. Turner et al. [5] discussed the possibility to use alternative missingness parameters in conjunction with various prior structures. Using different prior structures, we are able to learn about the missingness mechanism in each trial, intervention, and trial-arm and, in addition, to investigate the extent to which NMA findings are implicated by these structures. Further researcher is needed to investigate the extent to which different prior structures for the missingness parameter might impact on NMA estimates. Nevertheless, plausibility of transitivity assumption, as described in Section 2.2, remains necessary for the successful application of any prior structure. Finally, extending the pattern-mixture model with different prior structures for log IMOR to a multivariate meta-analysis and NMA of multiple endpoints can provide a more thorough investigation of the missingness mechanisms. This is an interesting yet unexplored area for further work.

5. Conclusions

Affirmation of transitivity assumption is necessary also in the context of MOD, especially, when arm-specific scenarios are applied in complex networks. Analysts should model, rather than exclude or impute MOD, while considering plausible scenarios, to provide bias-adjusted results.

Acknowledgments

The author would like to thank Konstantinos Pateras and Chrysostomos Kalyvas for commenting on earlier versions of the article. The author is also thankful to three anonymous reviewers for their comments and suggestions that really improved the article.

This work was supported by the German Research Foundation (Deutsche Forschungsgemeinschaft under grant number SP 1664/1-1). The funder had no involvement in study design; in the collection, analysis, and interpretation

of data; in the writing of the report; and in the decision to submit the article for publication.

Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jclinepi.2018.09.002.

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