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Can advancement in artificial intelligence improve transitivity assessment in network meta-analysis for clinical decision support?

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Abbreviations: AI = artificial intelligence, EM = effect modifier, GDC = Gower's Dissimilarity Coefficient, NMA = Network Meta-Analysis.

Multiple competing interventions often exist for a given health condition, and many of these are never directly compared in randomized controlled trials. Approximately 30 years ago, methodological approaches were proposed to enable indirect comparisons of alternative treatments, and advances in methodological research have subsequently facilitated the widespread application of network meta-analysis (NMA).[1] Evidence from network meta-analyses has increasingly contributed to the development of clinical practice guidelines.

For decades, it has been recognized that the validity of network meta-analyses relies on 3 assumptions: homogeneity assumption for direct treatment comparisons, transitivity (similarity) assumption for indirect treatment comparisons, and coherence assumption for mixed treatment comparisons.[2] Nonetheless, transitivity assessment remains a challenge, and was not appropriately considered in nearly half of published network meta-analyses.[3] The Grading of Recommendations Assessment, Development, and Evaluation working group has recently acknowledged that "the assessment of intransitivity remains a challenge and the Grading of Recommendations Assessment, Development, and Evaluation working group has not yet provided official detailed guidance on how to deal with this domain."[4]

Artificial intelligence (AI) technologies have been increasingly adopted in evidence-based medicine, with applications covering evidence generation, evidence synthesis, and clinical guideline development and implementation. While the automation or semi-automation of network meta-analyses has been demonstrated to be feasible,[5] no studies known to date have explored AI-driven approaches for transitivity assessment. The potential roles of AI in addressing the challenges associated with transitivity assessment in network meta-analyses are discussed herein.

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1. Effect modification in NMA and AI potentials

The challenge in transitivity assessment is mainly due to difficulties in identifying potential effect modifiers (EMs) and evaluating whether the distribution of EMs is balanced across included trials. Effect modification, also termed effect moderation or subgroup effect, describes the phenomenon whereby the relative treatment effect (e.g., measured using odds ratio or mean difference) differs meaningfully across patient subgroups. A patient or study characteristic that alters the relative treatment effect is defined as an EM (or effect moderator). While any baseline characteristic that varies among patients has the potential to be an EM, only those that alter the relative effect are true EMs. Misclassifying a prognostic factor that does not modify relative treatment effect as an EM can lead to misleading inferences regarding the validity of a NMA.

EMs are traditionally identified through subgroup or meta-regression analyses. However, these approaches suffer from limitations, including an inflated risk of false positives when multiple variables are tested concurrently and diminished statistical power resulting from subgroup stratification of study participants. Machine-learning techniques, such as causal forest methods, have been increasingly applied in a data-driven way to detect EMs from research and real-world data by addressing challenges associated with high-dimensional data, nonlinear relationships, and model overfitting.[6] Advances in AI have facilitated the discovery of new insights and expanded the evidence base regarding EMs, which will facilitate the transitivity assessment in network meta-analyses, as well as the development of personalized medicine in general.

Current approaches to dealing with effect modification in network meta-analyses and the prospective role of AI technologies are briefly outlined below. More information regarding these approaches, including their limitations and potential AI-driven applications, is provided in the Supplementary Table, Supplemental Digital Content, https://links.lww.com/AIEBM/A1.

1.1. Minimizing heterogeneity in network meta-analyses

Strict inclusion and exclusion criteria can be applied to select trials with comparable participants, interventions, and outcomes. Trials exhibiting EMs that differ substantially from those of other studies may be excluded to mitigate heterogeneity. A trial network with reduced heterogeneity may feature more balanced distributions of EMs within and between treatment comparisons. AI technologies can help mitigate heterogeneity by optimizing review questions, extracting trial data automatically, aligning extracted data with predefined

eligibility criteria, and supporting the automated cross-trial comparison of EMs.

1.2. Systematically identifying EMs

There is a methodological gap in guidance on how to systematically identify Ems in network meta-analyses.[3] Relevant EMs may be ideally prespecified in review protocols or detected during the conduct of network meta-analyses. A crucial contribution of AI lies in the boosted discovery of novel Ems.[6] AI tools can also be deployed to automatically search and extract EMs pertinent to a given NMA from dispersed and heterogeneous sources. Furthermore, large language model techniques can be utilized to automatically evaluate the credibility of identified Ems.[7]

1.3. Visualizing and statistical testing

Tables and plots can be used to present data on interventions, outcomes, study, and participant characteristics extracted from trials included in a network meta-analysis. Box plots enable visual comparison of the distribution of EMs within comparisons, whereas violin plots can illustrate the distribution of EMs across treatment comparisons. To statistically test imbalances in potential EMs, analysis of variance or the Kruskal–Wallis test can be employed for numerical variables, and the chi-square test for categorical variables. Large language models can be adopted to automate data extraction, including the retrieval of potential EMs. With the assistance of AI, extracted data regarding potential EMs can be automatically compiled into tabular summaries and graphically visualized. AI tools may also be developed to automatically test statistical differences in EM distributions across trials.

1.4. Gower's dissimilarity coefficients (GDC)

A recent advance in transitivity assessment is the proposed GDC for quantifying the degree of dissimilarity between pairs of trials based on a set of study-level variables.[8] For 2 trials with multiple aggregate characteristics, the dissimilarity score ranges from 0 (perfect similarity) to 1 (maximum dissimilarity), and a dissimilarity matrix enables the systematic storage of dissimilarity values for all pairwise trials. Then summary values are computed to indicate the overall within-comparison dissimilarity and tween-comparison dissimilarity. Using the resulting dissimilarity matrix alongside a linkage method, hierarchical clustering (an unsupervised learning method) can be applied to group similar comparisons.[8] AI approaches can be adopted to automatically extract data on potential EMs, calculate GDC, and cluster similar comparisons for transitivity assessment in a network meta-analysis.

1.5. Network meta-regression analysis

Meta-regression can be employed to explore treatment-covariate interactions in network meta-analyses, particularly when individual patient data from trials are available. The broader uptake of meta-regression methods remains limited due to their technical complexity and data requirements. The recent improvement in MetaInsight, an R Shiny web application, enables researchers to perform network meta-regression via a point-and-click interface, eliminating the need for special software and statistical programming.[9] Further AI-enabled methods could be developed to support automated or semi-automated meta-regression or meta-interpolation analyses.

1.6. Assessing quality of evidence from network meta-analyses

Although detailed guidance for assessing intransitivity is still lacking,[4] methods are available for assessing heterogeneity and incoherence in network meta-analyses, including well-tested quantitative techniques. Given that imbalanced distributions of EMs across trials are common underlying drivers of heterogeneity, intransitivity, and incoherence, any observed heterogeneity or incoherence may indicate the existence of potential intransitivity. Assessing the quality of evidence from network meta-analyses is typically a tedious and time-consuming process, and it is increasingly sophisticated. As such, AI tools could be developed to automatically evaluate the quality or certainty of evidence from network meta-analyses.

2. Summary and recommendations

Although the importance of effect modification has been recognized for decades, it remains largely unresolved in evidence-based medicine practice. This challenge arises mainly from difficulties in identifying EMs and distinguishing them from prognostic factors. Credible evidence on EMs remains scarce, necessitating further progress in clinical research on effect modification and stratified medicine. AI techniques are being increasingly used to generate novel insights into EMs, which will support both personalized medicine and improved assessment of heterogeneity, intransitivity, and incoherence in network meta-analyses. However, concerns have been raised about AI-assisted identification of EMs, including inadequate performance of predictive models and insufficient validation.[10] Additional challenges include inconsistent results by applying different AI tools to the same datasets, the inability of many machine-learning prediction models to estimate causal effects, and the difficulty in interpreting outputs from "black box" systems.[6]

Current approaches to addressing effect modification in network meta-analyses include selecting trials that are as homogeneous as feasible, defining potential EMs a priori, and evaluating the distribution of EMs both within and between treatment comparisons. AI technologies can be leveraged to automate the process of identifying and evaluating potential EMs. There are efforts in evidence-based medicine to develop a "credible AI decision support system." While automated network meta-analyses have been conducted by using generative AI, none of these available applications have included an assessment of intransitivity. If the transitivity assumption is violated, the recommendations generated by the AI system will be invalid. Therefore, it is essential to strengthen quality control checkpoints for AI-driven clinical decision support systems.

In summary, assessing transitivity in network meta-analyses remains a persistent challenge. While existing methods should be applied more explicitly during the conduct and appraisal of network meta-analyses, advances in AI technologies present new opportunities to enhance the assessment of effect modification in clinical research. Automating the conduct of network meta-analyses and transitivity assessment through AI has shown promise, but such applications must remain evidence-based and safeguard the validity of generated results. Ultimately, improvement in transitivity assessment relies on the progress in personalized medicine, an area that stands to benefit greatly from further advancement in AI.

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During the preparation of this work the author(s) used Doubao to refine languages used. After using this tool/service, the author(s) reviewed and edited the contact as needed and take(s) full responsibility for the content of the publication.

References

[1] Ades AE, Welton NJ, Dias S, Phillippo DM, Caldwell DM. Twenty years of network meta-analysis: continuing controversies and recent developments. *Res Synth Methods*. 2024;15:702–27.
[2] Song F, Loke YK, Walsh T, Glenny A-M, Eastwood AJ, Altman DG. Methodological problems in the use of indirect comparisons for evaluating healthcare interventions: survey of published systematic reviews. *BMJ*. 2009;338:b1147.
[3] Wang Y, Xia R, Pericic TP, et al. How do network meta-analyses address intransitivity when assessing certainty of evidence: a systematic survey. *BMJ Open*. 2023;13:e075212.
[4] Izcovich A, Chu DK, Mustafa RA, Guyatt G, Brignardello-Petersen R. A guide and pragmatic considerations for applying GRADE to network meta-analysis. *BMJ*. 2023;381:e074495.
[5] Livieratos A, Kudela M, Zhao Y, et al. MetaMind: a multi-agent transformer-driven framework for automated network meta-analyses. *PLoS One*. 2026;21:e0342895.
[6] Lipkovich I, Svensson D, Ratitch B, Dmitrienko A. Overview of modern approaches for identifying and evaluating heterogeneous treatment effects from clinical data. *Clin Trials*. 2023;20:380–93.
[7] Schandelmaier S, Briel M, Varadhan R, et al. Development of the Instrument to assess the Credibility of Effect Modification Analyses (ICEMAN) in randomized controlled trials and meta-analyses. *CMAJ*. 2020;192:E901–6.
[8] Spineli LM, Papadimitropoulou K, Kalyvas C. Exploring the transitivity assumption in network meta-analysis: a novel approach and its implications. *Stat Med*. 2025;44:e70068.
[9] Morris T, Nevill J, Nevill C, et al. Network meta-regression including baseline risk analysis and interactive visualizations as implemented by the MetaInsight web application. *J Clin Epidemiol*. 2025;184:111839.
[10] Fröhlich H, Balling R, Beerenwinkel N, et al. From hype to reality: data science enabling personalized medicine. *BMC Med*. 2018;16:150.