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Review article

Network meta-analysis: The way forward for evidence-based decisions

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ABSTRACT

Systematic reviews and meta-analyses play a crucial role in clinical research by providing a means of evaluating the effectiveness of interventions in situations of uncertainty. Pairwise meta-analysis, which is the most widely used method, compares active interventions to placebos or other treatments. However, this approach has limitations in its ability to assess multiple interventions simultaneously, making it less suitable for comprehensive decision-making. This is where Network Meta-analysis (NMA) comes in, which extends pairwise meta-analysis to allow for the assessment of more than two interventions within a single analysis, even when direct head-to-head comparisons are not available. NMA shares similarities with pairwise meta-analysis, including systematic literature searches, bias assessment, data extraction, and statistical pooling. Two critical assumptions underlie NMA: transitivity and consistency. NMA can be performed using frequentist or Bayesian approaches, with both fixed and random effects models. Recent developments such as population adjustment methods and Component NMA have enhanced its utility. The significant advantage of NMA is its ability to generate treatment rankings based on the probability of each treatment being the most effective. Web-based applications such as MetaInsight and NMA Studio simplify the NMA process, making it more accessible without coding skills. NMA is essential in evidence-based decision-making, providing comprehensive comparisons of multiple interventions, overcoming the limitations of pairwise meta-analysis. While challenges persist, transparency is maintained, and decision-making bodies recognize NMA's value. NMA is a powerful tool that defines the future of healthcare decision-making.

1. Network meta-analysis: The way forward for evidence-based decisions

Systematic reviews and meta-analyses are tools to help collate, evaluate and understand the existing evidence, and are often used in the application of evidence into practice.[1] Meta-analysis in clinical effectiveness research is an important tool providing answers to questions about the effectiveness of treatments when surrounded by uncertainties. Pairwise meta-analysis is the most common statistical method used across the scientific world to synthesise evidence on the effectiveness of the two interventions[2,3] Owing to the limitation of not being able to capture a wide array of potential interventions, pairwise meta-analysis is of limited utility in decision-making.[4] In a pairwise meta-analysis, an active intervention was compared to a placebo or another intervention. It is challenging to interpret these findings when there are multiple treatment options that need to be scrutinised for effectiveness.[5] Network meta-analysis can be helpful in making decisions when there are more than two available treatment options. Here we aim to discuss network meta-analysis and its potential as a tool in decision making processes.

1.1. What is a network meta-analysis?

Network meta-analysis (NMA), also called mixed treatment comparison (MTC), has attracted interest over the last decade as an extension of pairwise meta-analysis.[6] It can handle more than two interventions in a single analysis, despite missing head-to-head comparisons between some interventions. It combines both direct and indirect evidence to provide a more precise effect estimate. Similar to a pairwise meta-analysis NMA is a statistical component of systematic literature review and requires assessment of bias amongst included studies, data extraction and statistical pooling and assessment of certainty in the obtained treatment effect. The graphical representation of network meta-analysis as a network of trials provides information about the available treatment options and the most common comparator (anchor) along with the information about available direct comparisons of interventions (Fig. 1). As it is evident from Fig. 1, treatment I is the

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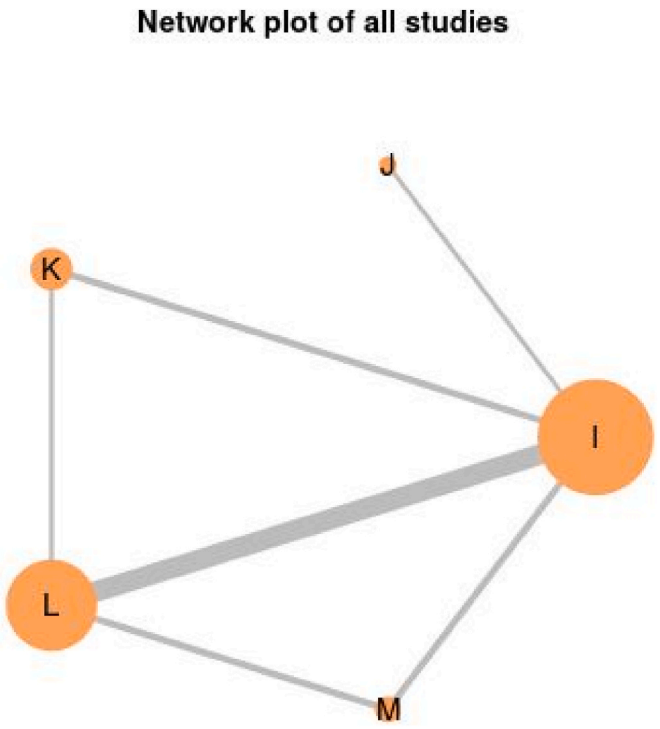

Fig. 1. Network plot: nodes representing the treatments and edges representing the number of studies in each head-to-head comparison.

most common comparator treatment and the head-to head comparisons include I vs J, I vs K, I vs L, I vs M, and L vs M. The nodes represent the treatment and edges represent the number of direct comparisons between the treatments. The size of the node represents the number of participants randomised to the treatment representing the node and the thickness of the edges correspond to the number of trials with head-to-head comparisons.[7]

1.2. Assumptions in NMA

The two key assumptions underlying NMA are transitivity and consistency.[5] The transitivity assumption refers to the similarity of common comparator when it appears in different direct comparisons in the network and all the participants in the network of trials had equal opportunity to be receive any treatment in the network. For example, in Fig. 1 treatment I is the most common comparator in the network of trials. For the network to satisfy assumption of transitivity, treatment I should be similar in terms of dosage, route of administration, duration, and frequency etc, when it appears in various head-to-head comparisons like I vs J, I vs K and so on. Also, the participants randomised to treatment I and J in the trial I vs J has equal chances of getting treatment K if it was an option in the trial. This implies that treatment K is missing at random, and the trials do not differ in terms of effect modifiers/population characteristics. The second assumption in a NMA is that of consistency which is an extension of transitivity and refers to the agreement between the direct and indirect evidence of comparison.[5] Let's consider the loop I-L-M in Fig. 1. For the consistency assumption to hold L vs M direct comparison should agree when L & M are compared via treatment I in the closed loop.

1.3. Statistical methods

Like pairwise meta-analysis, network meta-analysis involves combining individual study results with adjustments for trials with multiple comparison arms (more than 2 treatments). NMA can be performed using either frequentist or bayesian approaches. Bayesian approach differs from frequentist as it relies on probabilistic distribution of all model parameters in relation to observed data and prior assumptions whereas the later uses distributions in relation to the observed data only.

Both frequentist and bayesian approaches for NMA can be modelled using fixed or random effects. When using bayesian approach, best fitting model (fixed or random effects) for the data can be selected based upon deviance information criteria and changes in heterogeneity.[8,9]

The ability of NMA to generate rankings of multiple treatments in comparison is an added advantage (Fig. 2). Though it is not as straight forward and requires a careful interpretation. The rankings generated are always based on one outcome and there are multiple relevant outcomes, leading to situations where a treatment may excel in one aspect, such as a beneficial outcome, while simultaneously performing poorly in another aspect, such as a harmful outcome. Secondly, rankings do not account for degree of differences in treatment effects and ignore the fact that these differences may only be a chance effect. Also, the quality of evidence is often not considered while generating treatment rankings.

The methods used to generate treatment rankings are dependent upon the research question. Therefore, while interpreting the treatment rankings, the research question and ranking metrics used should be considered in addition to magnitude of differences, chance effect, and quality of evidence.[10]

1.4. Newer developments

Ever since Bucher et al.,[11] described the indirect treatment comparisons, the methodology has been evolving. In recent years, there have been developments to overcome many challenges like differences in population characteristics and having a sparse and disconnected network. With the ease of data sharing and availability of individual participant data, the NMA is now better positioned to address population adjustments and provide estimates that are more reliable.[12,13] Disconnected and sparse network is another common challenge especially when the interventions are relatively newer and there are few randomised controlled trials available. Methods are developed and been evolving to address these issues. Disconnected networks arise when there is no possibility of direct or indirect comparisons of interventions. Several approaches like population adjustment methods; propensity score matching; using the non-randomised evidence and component NMA have been used in case of disconnected networks.[14–17]

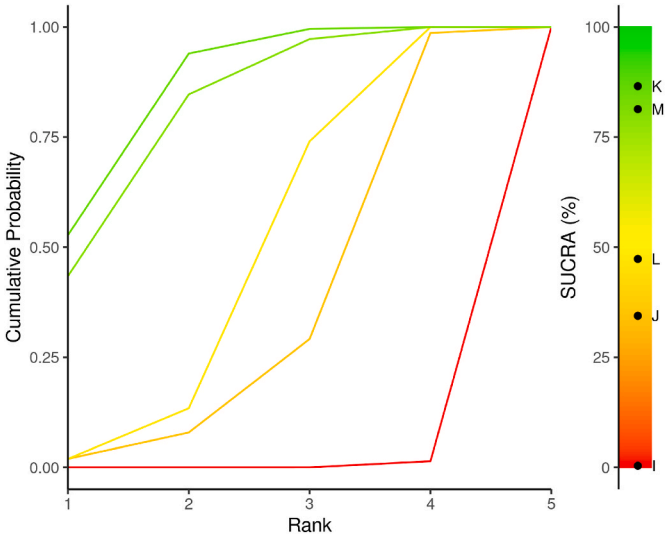

Fig. 2. Litmus Rank-O-Gram showing Cumulative probabilities and SUCRA (surface under the cumulative ranking curve) values for each treatment. Higher SUCRA values and cumulative ranking curves nearer the top left indicate better performance. The plot was created using MetaInsight app.

Component NMA has garnered particular interest due to its ability to disentangle complex interventions into active components and allow comparisons at the component level.[18] Complex interventions are defined as having number of active interacting components.[19] This approach can identify the components or combinations of components that are most likely to be effective, which is an important consideration for public health decision-making.

With a growing interest in real world evidence, methods such as matching adjusted indirect comparisons and propensity score matching have evolved to include both real-world studies and randomised controlled trials in a single statistical model using Bayesian and frequentist methods.[14] These advances have contributed to the growing preference for network meta-analysis among decision-makers and clinicians.

1.5. Simplifying the process of NMA

The process of NMA like a pairwise meta-analysis starts with a literature review most commonly a systematic review, this requires, searching screening an assessing the literature. This can be a time-consuming process, however there are tools to assist in this process. Tools such as Covidence and Rayyan can help to manage and perform systematic reviews more effectively, including features to help searching and screening.[20,21] These types of tools are more increasingly relying on AI and machine learning to help reduce the burden on the reviewers, however this is typically limited to the screening process and puts a lot of trust in these tools to work effectively and correctly.[22]

While most AI/machine learning tools are focussed on searching and screening in more recent years there has been a focus for tools for data extraction, tools such as pitts AI, allow for semi-automated data extraction using large language models such as ChatGPT.[23] However, as with any new tool especially one using AI/machine learning they need to be used with caution and with strict oversight by reviewers.

After data extraction NMA can be fit using many common statistical software such as R, STATA, SAS and WinBugs, using both frequentist and Bayesian approaches.[24–26] While packages within these software's exist, they often require specialist knowledge of the statistical programming languages these software use, adding a layer of difficulty and inaccessibility to NMA models. To overcome these limitations, in more recent years web applications have been developed to allow NMA models to be fit without knowledge of the underlying code. This comes with the caveat that the user of the software should still understand the principle of NMA, and that the applications should effectively communicate its outputs.

Examples of these applications are web apps such as MetaInsight and NMA Studio the former supporting both Bayesian and frequentist and the later only frequentist.[27,28] Both these apps are available and free to use from any modern web browser, allowing for the simplification of the process of NMA and making NMA more accessible.

These applications provide publication ready output such as network diagrams and forest plots. Alongside this MetaInsight offers both a Litmus Rank-O-Gram and Radial SUCRA plot for ranking results, and NMA Studio a p-score heatmap and scatter plot. NMA studio also offers a league table including both risk of bias and certainty of evidence from Confidence in Network Meta-Analysis (CINeMA),[29] CINeMA is its own application to help evaluate the six domains which contribute to bias within NMA (within-study bias, reporting bias, indirectness, imprecision, heterogeneity and incoherence), using The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, producing its own plots including network plots with certainty of evidence incorporated within them.[30–32] Table 1 shows an example of certainty of evidence as generated by the CINeMA app based on the aforementioned six domains.

With all these outputs being easily available, these applications make it easy for users to perform a NMA within a web browser and publish the results easily thus simplifying the process of NMA.

1.6. NMA and decision making

Decision making in medical practise unlike meta-analysis is a complex multidimensional framework that aims to choose the best available treatment option. Evidence-based decision making should be based on comparisons of all available interventions. Evidence from a pragmatic randomised controlled trials is gold standard to obtain comparative effectiveness. On most occasions head-to-head comparisons of all competing interventions are not available in the form of randomised controlled trials. RCTs are expensive, take a long time to complete and cannot always provide relative effectiveness for all competing interventions. Pairwise meta-analysis can point towards the best available treatment if there are only two choices. In real life scenarios, the decision makers have multiple treatment options to choose from. When multiple options are available, it is common to *'lump'* treatments together to justify a pairwise comparison.[33] If sufficient trials are available, multiple pairwise meta-analysis or subgroup analysis within a

Table 1
Illustration of the certainty of evidence for both direct and indirect comparisons as generated by CINeMA. It incorporates the six criteria for each pairwise comparison in a NMA and generates ratings for each pairwise comparison based on the assessments of the six domains.

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating	Reason(s) for downgrading
I:J	5	No concerns	Low risk	No concerns	No concerns	Major concerns	No concerns	Moderate	"Heterogeneity"
I:K	2	No concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low	"Imprecision", "Incoherence"
I:L	4	No concerns	Low risk	No concerns	No concerns	Major concerns	Major concerns	Very low	"Heterogeneity", "Incoherence"
I:M	1	No concerns	Low risk	No concerns	No concerns	Major concerns	Major concerns	Very low	"Heterogeneity", "Incoherence"
K:L	3	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	"Imprecision"
L:M	2	Some concerns	Low risk	No concerns	No concerns	Major concerns	No concerns	Low	"Within-study bias","Heterogeneity"
J:K	0	No concerns	Low risk	No concerns	No concerns	Major concerns	No concerns	Moderate	"Heterogeneity"
J:L	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	"Imprecision"
J:M	0	No concerns	Low risk	No concerns	No concerns	Major concerns	No concerns	Moderate	"Heterogeneity"
K:M	0	No concerns	Low risk	No concerns	No concerns	Major concerns	No concerns	Moderate	"Heterogeneity"

pairwise meta-analysis are conducted. These are difficult to interpret, does not highlight the best treatment option and lack transparency.

Decision makers are usually concerned about internal and external validity of NMA. The internal validity is affected if there are differences in confounders/effect modifiers between the trials. Although NMAs are typically based on RCTs, if the assumption of transitivity is not satisfied, it may very well compromise the internal validity. Such differences can result in misleading results and hence need to be carefully addressed in the statistical model by incorporating the interactions between treatment and covariates.[34] In instances where participants of the trials included in an NMA exhibit variations in disease severity, the resulting relative treatment effects when derived, may fail to portray the true effect, thereby introducing confounding bias. Likewise, if additional treatments received lack sufficient homogeneity, the relative effects obtained will be carry the confounding influence. Therefore, combining such trials without proper adjustments could be detrimental to the internal validity of the NMA results. External validity of NMA is as good as those of included studies and hence need further care while extrapolation. Alternatively, use of population adjustment methods and use of individual participant data can help in overcoming these challenges.[14,35]

Given its ability to compare more than two interventions in a single analysis, network meta-analyses can play a pivotal role in decision making with its ability to provide an elaborate and interpretable comparison of treatments in the network. It is important to note that NMA were designed to optimizes the utilization of both direct and indirect evidence to generate cohesive estimates of intervention effects, enhancing efficiency, precision, and robustness.[36] Though the ability to generate treatment rankings makes the approach attractive, it requires a careful interpretation and is seldom able to predict the single best treatment.

With the advancing methods and ability to incorporate real-world data, the treatment estimates obtained in a NMA can be more realistic. The challenge of being statistically intense remains, with the emergence of web-based applications, it is now getting more user friendly.

Although, the assumptions underlying NMA are discerned barriers to its adoption. It is imperative to note that the element of transparency is maintained, and several decision-making bodies have now adopted and recognised NMA as one of the methods for obtaining comparative effectiveness estimates.

2. Conclusion

The field of network meta-analysis is constantly developing and getting recognition. With the emergence of web applications, the methodology is becoming more accessible. As the approach is attracting interest, it is now a becoming necessity for decision makers to be acquainted with concepts of NMA. It is unquestionably efficient for evaluating several competing interventions and defines the 'next stage' in health care decision making.

Ethical considerations

Not applicable.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Nishant Jaiswal reports a relationship with University of Glasgow that includes: employment. Ryan Field reports a relationship with University of Glasgow that includes: employment. Both authors are affiliated to Evidence Synthesis Group @CRSU at the University of Glasgow. The group is associated with development of applications that support network meta-analysis. The group also conducts and supports complex reviews like network meta-analysis which is the subject matter in this manuscript. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Nishant Jaiswal: Conceptualization, Writing – original draft, Writing – review & editing. **Ryan Field:** Conceptualization, Writing – original draft, Writing – review & editing.

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