Progress and challenges of network meta-analysis

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Abstract

In the past years, network meta-analysis (NMA) has been widely used among clinicians, guideline makers, and health technology assessment agencies, and has played an important role in clinical decision-making and guideline development. To inform further development of NMAs, we conducted a bibliometric analysis to assess the current status of published NMA methodological studies, summarized the methodological progress of seven types of NMAs, and discussed the current challenges of NMAs.

Keywords: Network meta-analysis, methodological advances, bibliometric analysis, diagnostic test accuracy, individual participant data

1. Introduction

Network meta-analysis (NMA), also known as mixed treatment comparison or multiple treatments comparison meta-analysis, uses statistical methods to allow

the simultaneous synthesis of data from a network of trials about more than two competing healthcare interventions [1-4]. Compared with traditional pairwise meta-analysis, NMA has the major advantages in borrowing strength from indirect evidence to determine the certainty of all treatmentcomparisons, allowing for the evaluation of the comparative effects that have not been investigated head-to-head in randomized clinical trials, and potentially producing more reliable and definitive results [5-9]. Even in the absence of direct evidence, NMA can use indirect treatment comparison analyses to provide useful evidence to inform healthcare decision-making [10-12]. Furthermore, NMA allows for the estimation of the relative effectiveness among all interventions, visualization of a larger amount of evidence, and ranking of the most effective interventions [13-15]. As such NMA has been becoming increasingly used in the medical literature and in the health technology assessment 16-18. In the past few years, several types of NMA with the development of statistical methods have been proposed, such as network meta-analyses of diagnostic test accuracy, network meta-analyses of individual participant data, component network meta- analysis***. In this review, we conducted a bibliometric analysis to assess the current status of published NMA methodological studies, summarized the methodological progress of seven types of NMAs, and discussed the current challenges of NMAs. This review would provide the key points and resources regarding the progress and challenges of NMAs.

2. Status Quo of Methodological Studies of Network Meta-Analyses

We conducted a comprehensive search of PubMed, Embase, Cochrane Library, and Web of Science using search terms of “network meta-analysis”, “mixed treatment comparison meta-analysis”, “mixed treatment meta-analysis”, “multiple treatment comparison meta-analysis” up to October 2020. Two reviewers independently reviewed the titles and abstracts of retrieved records to identify NMA methodological studies and then extracted information on the characteristics of eligible studies. Disagreements were resolved by discussion with a third reviewer. We defined NMA methodological studies as studies that focused on any aspects of NMA, including design, conduct, analysis (eg, including bias, statistical plan and methods) or reporting, as well as statistical studies (eg, studies testing new algorithms or analytical methods, simulation studies)19. Finally, we included 454 NMA methodological studies for the bibliometric analysis. We used VOSviewer 1.6.16 (Leiden University, Leiden, Netherlands) to create visual network maps for countries, and institutions, and produce density map for high-frequency keywords. In the visual network maps, nodes represent the analytical elements, such as countries, institutions, and keywords, and the size of nodes reflects the number of publications or frequency[20-26]. The links between nodes indicate the collaboration or co-occurrence, and different colors of nodes and lines represent different clusters or years [27-29].

2.1 Publication year

Before 2008, there were few NMA methodological publications

each year (Figure 1). The number of publications increased steadily to 12 in 2010. Afterwards the number of studies increased rapidly and reached 63 in 2014, indicating the remarkable development of NMA during this period. Since then, the annual publication number fluctuated between 36 and 67. In summary, NMA has attracted more attention from 2012 to October 2020, when 92.29% (419 studies) of all the included studies were published.

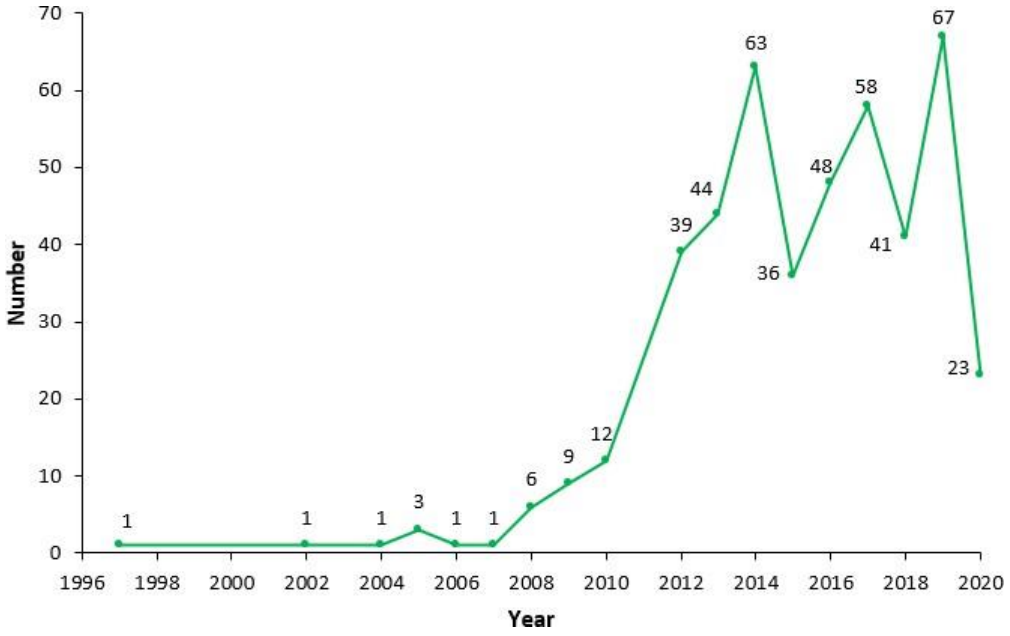


Figure 1. Publication years of NMA methodological studies

2.2 Distribution of Journals

454 NMA methodological studies were published in 118 journals. The journals contributing to more than 3 NMA methodological studies are displayed in

Figure 2. *Value in Health* was the most productive journal with a number of 104 (22.91%) publications, followed by *Research Synthesis Methods* (47, 10.35%), *Journal of Clinical Epidemiology* (36, 7.93%), *Statistics in Medicine* (36, 7.93%), and *BMC Medical Research Methodology* (27, 5.95%). Of the top 10 journals, five were from the United Kingdom (UK), four from the United States (USA), and one from the Netherlands. The top 5 journals published 250 papers, which accounted for 55.07% of the included studies, indicating that these journals have made greater contributions to the development of NMA methodology.

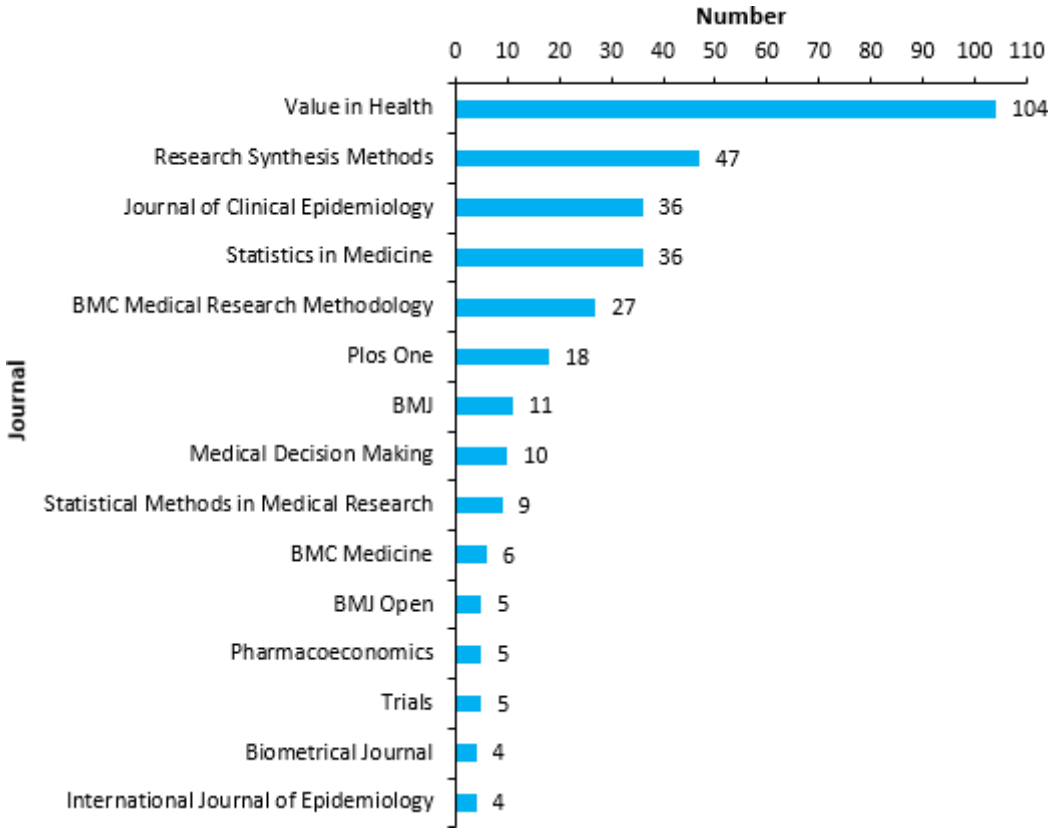


Figure 2. Journals contributing to more than 3 NMA methodological studies

2.3 Distribution of countries

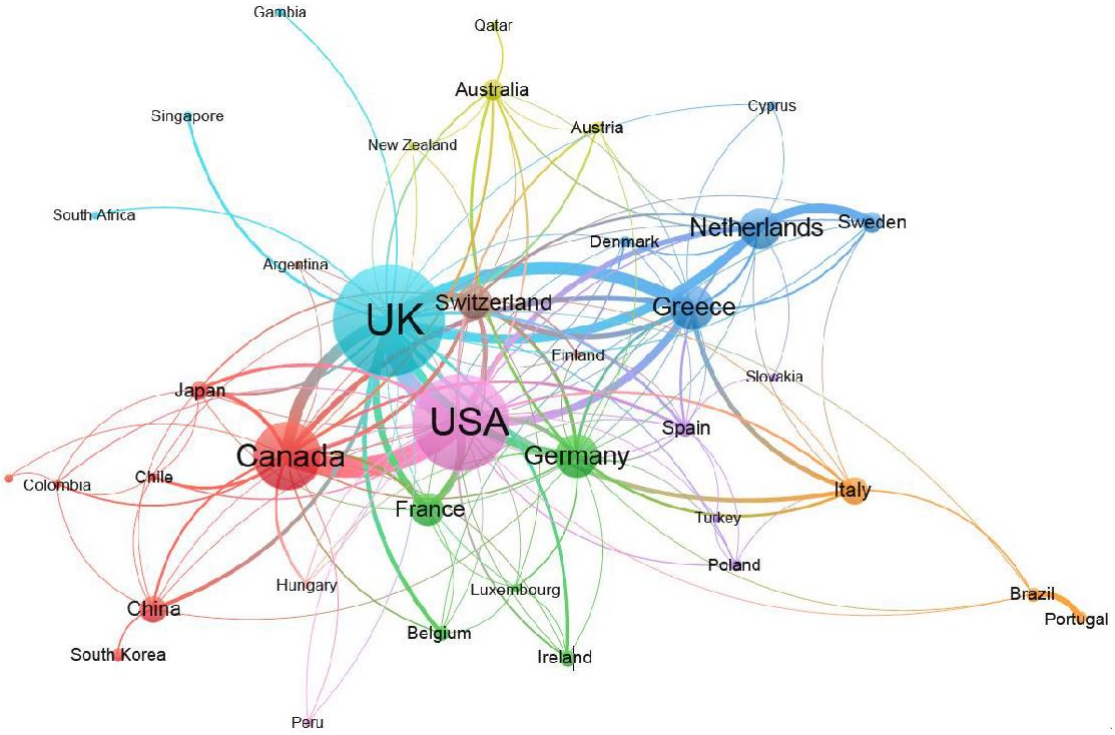
We extracted all countries participated in the studies. A total of 40 countries were involved in the publication of NMA methodological research. Table 1 shows the top

20 countries. The UK was the most productive country with 183 (40.31%) publications. The USA ranked second with 146 (32.16%) publications, followed by Canada (85, 18.72%), Greece (44, 9.69%), Germany (43, 9.47%), Netherlands (38, 8.37%), Switzerland (31, 6.83%), France (28, 6.17%), Italy (21, 4.63%), and China (20, 4.41%). These figures revealed that the developed countries had an absolute leading position in the NMA methodology as only China was a developing one of the top 10 productive countries. Therefore, how to promote the application of these new methods in developing countries may be a problem that needs to be solved.

Figure 3 shows the collaborative network map of the 40 countries. Of these, 38 countries have formed cooperative relationships with other countries, with Canada, UK, USA, Greece, and Germany having more collaborations and, locating in the center of the network. This suggested the development of NMA methodology was built on close cooperation between different countries.

Table 1. The top 20 countries contributing to NMA methodological studies[N(%)]

Rank	Country	N(%)	Rank	Country	N(%)
1	UK	183(40.31%)	11	Australia	13(2.86%)
2	USA	146(32.16%)	12	Sweden	13(2.86%)
3	Canada	85(18.72%)	13	Japan	11(2.42%)
4	Greece	44(9.69%)	14	Spain	10(2.20%)
5	Germany	43(9.47%)	15	Ireland	9(1.98%)
6	Netherlands	38(8.37%)	16	Belgium	8(1.76%)
7	Switzerland	31(6.83%)	17	Brazil	7(1.54%)
8	France	28(6.17%)	18	Poland	6(1.32%)
9	Italy	21(4.63%)	19	Portugal	6(1.32%)
10	China	20(4.41%)	20	South Korea	6(1.32%)


Gambia
Qatar
Australia
Singapore
Cyprus
Austria
New Zealand
South Africa
Netherlands
Sweden
Denmark
Argentina
UK
Switzerland
Greece
Finland
Slovakia
Japan
USA
Spain
Canada
Germany
Colombia
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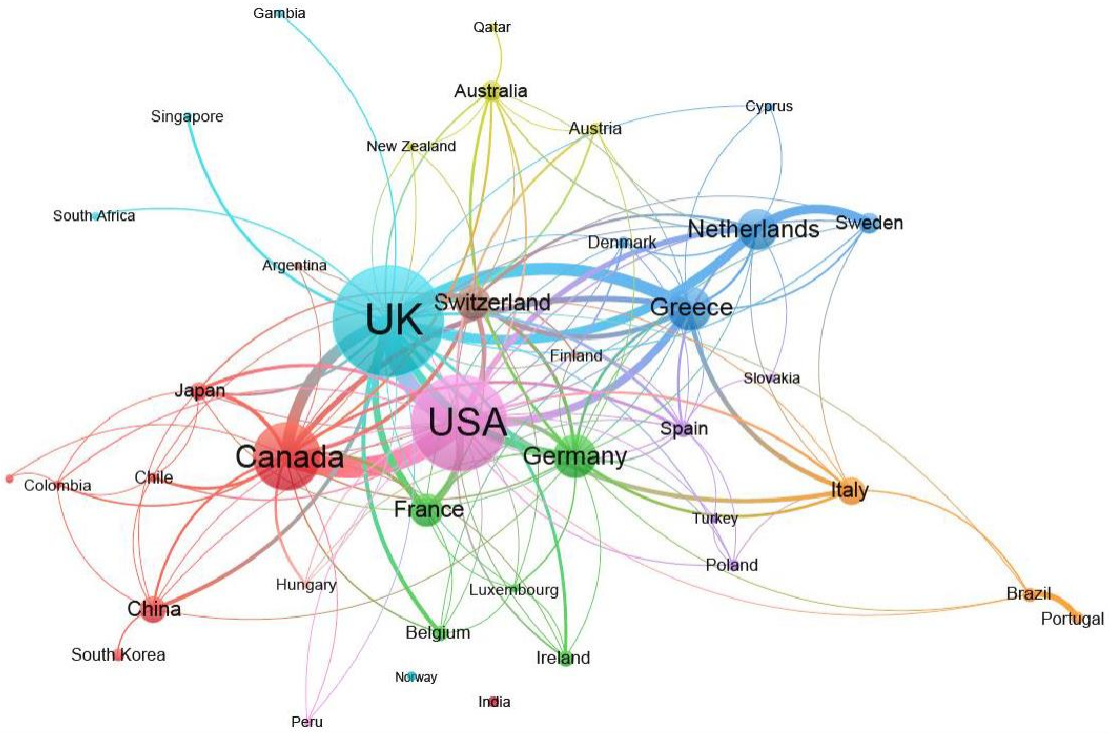

Figure 3. The network map of countries for NMA methodological studies

2.4 Distribution of institutions

Table 2 lists the top 18 institutions contributing to the NMA methodology. The University of Bristol ranked first in productivity with a total of 58 (12.78%) publications, followed by the University of Ioannina (44, 9.69%), University of Leicester (33, 7.27%), McMaster University (30, 6.61%), University of York (23, 5.07%), and University of Toronto (22, 4.85%). A total of 510 institutions contributed to the publication of NMA methodological research, but only 9.25% of the institutions published more than five studies, with 76.65% of institutions involved in only one publication. This means NMA methodology, although widely investigated, is not the main research area in most of these institutions.

The network map of institution collaboration which created a minimum of five publications is shown in Figure 4. Of 41 institutions which established close cooperative relationships, most were from developed countries.

Table 2. The top 18 institutions contributed to NMA methodological studies[N(%)]

Rank	Institute	N(%)	Rank	Institute	N(%)
1	University of Bristol (UK)	58(12.78%)	10	Stanford University (USA)	15(3.30%)
2	University of Ioannina (Greece)	44(9.69%)	11	University of Ottawa (Canada)	15(3.30%)
3	University of Leicester (UK)	33(7.27%)	12	St. Michael Hospital (Canada)	14(3.08%)
4	McMaster University (Canada)	30(6.61%)	13	University of London (UK)	13(2.86%)
5	University of York (UK)	23(5.07%)	14	University of Groningen (Netherlands)	12(2.64%)
6	University of Toronto (Canada)	22(4.85%)	15	University of Oxford (UK)	12(2.64%)
7	University of Bern (Switzerland)	18(3.96%)	16	AstraZeneca (UK)	11(2.42%)
8	University of Minnesota (USA)	17(3.74%)	17	Medical Research Council (UK)	11(2.42%)
9	Tufts University (USA)	16(3.52%)	18	Johns Hopkins Bloomberg School of Public Health (USA)	10(2.20%)

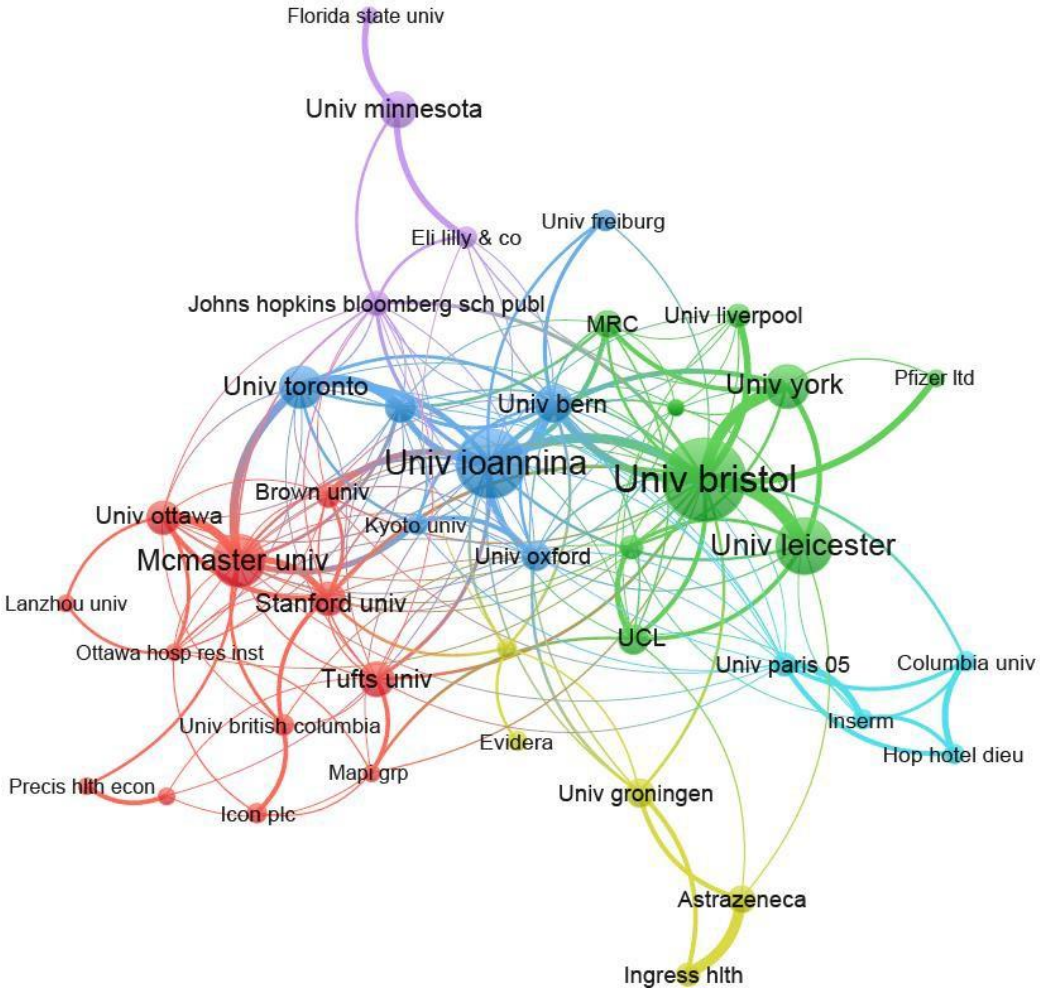

Figure 4. The network map of institutions for NMA methodological studies

2.5 Distribution of keywords

We identified 1387 keywords from the 454 studies, but 1047 keywords appeared only one time. The top 10 high-frequency keywords (Figure 5) were network meta-analysis (177, 38.99%), mixed treatment comparison (115, 25.33%), inconsistency (96, 21.15%), meta-analysis (90, 19.82%), trial (75, 16.52%), systematic review (58, 12.78%), consistency (56, 12.33%), indirect comparison (42, 9.25%), efficacy (41, 9.03%), and ISPOR task-force (41, 9.03%). These indicated one of the main focuses of NMA methodological research may lie on the inconsistency or consistency between indirect evidence and direct evidence or

between different indirect evidence. Other commonly used keywords included meta-regression, heterogeneity, models, individual participant data (IPD), and aggregate data (AD), corresponding to these frequently investigated areas.

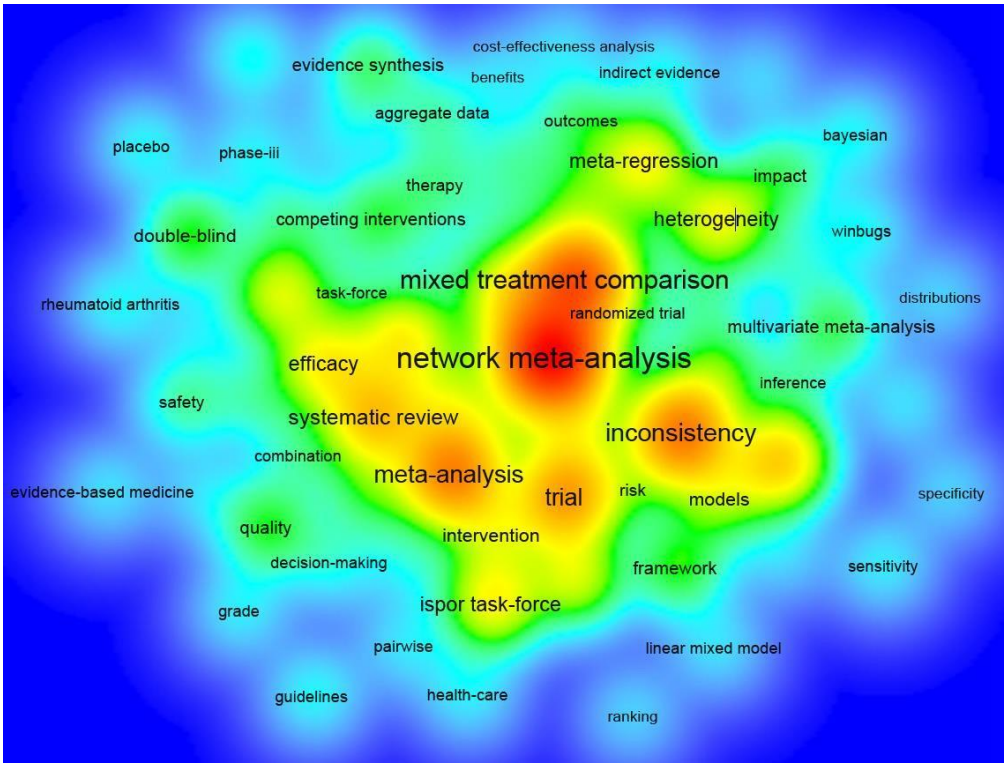

Figure 5. The density map of high-frequency keywords for NMA methodological studies

2.6 Top 20 cited papers

We extracted the number of citations of included studies from the Web of Science database. The top 20 cited studies are shown in Table 3. Of the 20 most cited studies, 50% were published between 2012 and 2013. One study focused on reporting standards, 16 focused on statistical analysis methods, 1 related to how results are presented, and 2 focused on evidence quality assessment. More than 1000 citations

were gained by three studies[30-32], 600 to 800 by four studies [16,33-35], and 200 to 500 by the remaining thirteen studies[5,36-47]. The top cited study was published by Hutton et al [30] in 2015. This study introduced the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) extension statement for reporting of systematic reviews incorporating network meta-analyses (PRISMA-NMA), which has now been widely used as a reporting standard for NMA results. The second most cited study was conducted by Lu et al[31] in 2004, in which the authors proposed a hierarchical Bayesian model using the Markov chain Monte Carlo (MCMC) software WinBUGS for combining direct and indirect evidence in mixed treatment comparisons. Among the top 20 cited NMA methodological studies, the earliest one was published in 1997 by Bucher et al [32]. This study presented an indirect comparison method that can estimate the differences between treatment and placebo in two sets of clinical trials while preserving the randomization of the originally assigned patient groups. The most recent study was published in 2015 by Rucker et al [47]. Theauthors proposed a ranking method in the frequentist framework, called P-scores, an analogue to the surface under the cumulative ranking curve (SUCRA) in Bayesian NMA methodology. This study also revealed that simply ranking treatments based on SUCRA or P-scores hads no major advantage compared to ranking treatments by their credible or confidence intervals.

Table 3. The top 20 cited NMA methodological studies

Rank	Publication	Citation
1	Hutton B, et al [30]. The PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses of Health Care Interventions: Checklist and Explanations. ANNALS OF INTERNAL MEDICINE. 2015; 162 (11): 777-784.	1367
2	Lu G, et al [31]. Combination of direct and indirect evidence in mixed treatment comparisons. STATISTICS IN MEDICINE. 2004; 23 (20): 3105-3124.	1189
3	Bucher HC, et al [32]. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. JOURNAL OF CLINICAL EPIDEMIOLOGY. 1997; 50 (6): 683-691.	1102
4	Dias S, et al [16]. Checking consistency in mixed treatment comparison meta-analysis. STATISTICS IN MEDICINE. 2010; 29 (7-8): 932-944.	770
5	Chaimani A, et al [33]. Graphical Tools for Network Meta-Analysis in STATA. PLOS ONE. 2013; 8 (10): Art. No. e76654	738
6	Dias S, et al [34]. Evidence Synthesis for Decision Making 2: A Generalized Linear Modeling Framework for Pairwise and Network Meta-analysis of Randomized Controlled Trials. MEDICAL DECISION MAKING. 2013; 33 (5): 607-617.	652
7	Lumley T [35]. Network meta-analysis for indirect treatment comparisons. STATISTICS IN MEDICINE. 2002; 21 (16): 2313-2324.	648
8	Salanti G [36]. Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence synthesis tool. RESEARCH SYNTHESIS METHODS. 2012; 3 (2): 80-97.	498
9	Higgins JPT, et al [37]. Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. RESEARCH SYNTHESIS METHODS. 2012; 3 (2): 98-110.	492
10	Glenny AM, et al [38]. Indirect comparisons of competing interventions. HEALTH TECHNOLOGY ASSESSMENT. 2005; 9 (26): 1-134, iii-iv.	404
11	Puhan MA, et al [39]. A GRADE Working Group approach for rating the quality of treatment effect estimates from network meta-analysis. BMJ. 2014; 349: Art. No. g5630.	401
12	White IR, et al [40]. Consistency and inconsistency in network meta-analysis: model estimation using multivariate meta-regression. RESEARCH SYNTHESIS METHODS. 2012; 3 (2): 111-125.	397
13	Cipriani A, et al [41]. Conceptual and Technical Challenges in Network Meta-analysis. ANNALS OF INTERNAL MEDICINE. 2013; 159 (2): 130-W54.	366
14	Mills EJ, et al [5]. Demystifying trial networks and network meta-analysis. BMJ. 2013; 346: Art. No. f2914.	337
15	Salanti G, et al [42]. Evaluating the Quality of Evidence from a Network Meta-Analysis. PLOS ONE. 2014; 9 (7): Art. No. e99682.	311
16	Song FJ, et al [43]. Methodological problems in the use of indirect comparisons for evaluating healthcare interventions: survey of published systematic reviews. BMJ. 2009; 338: Art. No. b1147.	248
17	Jansen JP, et al [44]. Is network meta-analysis as valid as standard pairwise meta-analysis? It all depends on the distribution of effect modifiers. BMC MEDICINE. 2013; 11: Art. No. 159.	227
18	van Valkenhoef G, et al [45]. Automating network meta-analysis. RESEARCH SYNTHESIS METHODS. 2012; 3 (4): 285-299.	225
19	Mills EJ, et al [46]. How to Use an Article Reporting a Multiple Treatment Comparison Meta-analysis. JAMA. 2012; 308 (12): 1246-1253.	216
20	Rucker G, et al [47]. Ranking treatments in frequentist network meta-analysis works without resampling methods. BMC MEDICAL RESEARCH METHODOLOGY. 2015; 15: 58.	211

3. Methodological Progress of Different Types of Network Meta-Analyses

In our bibliometric analysis, we also identified the development of NMA methodology was reflected in seven types of NMA. We provided an overview of the methodological progress for each type of NMA.

3.1 Network meta-analyses of diagnostic test accuracy

Network meta-analysis of diagnostic test accuracy is the combination of meta-analysis of diagnostic test accuracy and NMA, which allows simultaneous comparison of the diagnostic values of multiple tests [48-50]. Trikalinos et al [51] published an article in 2014, specifying the models for the joint meta-analysis of studies comparing multiple diagnostic tests on the same participants in paired designs. These models preserve the grouping of data by studies, account for the within-study correlation between the tests' true-positive rates (TPRs, also known as sensitivity) and between their false-positive rates (FPRs, equivalent to 1-specificity), and allow for between-study correlations between TPRs and FPRs (such as those induced by threshold effects) [51]. The models are mainly applicable when the tests are conducted in the same patients with the cross-classification results from several tests provided in a large number of studies. However, this method is not suitable for combined diagnostic tests or excessive number of diagnostic tests. In 2015, Menten et al[52], inspired by mixed-treatment comparison meta-analyses of randomized controlled trials, proposed a model using Bayesian methods that allows for the comparison of the accuracy of two diagnostic tests using direct (head-to-head) comparisons as well as indirect comparisons through a third test. In addition, the model allows correction of imperfect reference tests and can

incorporate prior knowledge about the diagnostic accuracy of reference tests used. However, this method requires sufficient information of the reference tests used described in the primary studies. Otherwise, this method may not be applicable. In 2016, Dimou et al[53] presented an extension method of the classic bivariate random-effects meta-analysis[54,55] for the log-transformed sensitivity and specificity for two or more diagnostic tests. This method allows for the direct calculation of sensitivity and specificity, diagnostic odds ratio, the area under curve, and the parameters of the summary receiver operating characteristic curve, along with the means for formal comparison of these quantities for different tests. Inaddition, there is no need for individual patient data or the simultaneous evaluation of both diagnostic tests in all studies. Nyaga et al[56] developed an arm-based hierarchical model (ANOVA model) to perform Bayesian NMA of diagnostic test accuracy. This model expresses the logit-transformed sensitivity and specificity as the sum of fixed effects for the test and correlated study effects to model the inherentcorrelation between sensitivity and specificity. The authors compared the results with those from a contrast-based model (expresses the linear predictor as a contrast to a comparator test) and found that the arm-based model, with the use of all available data, yielded narrower credible intervals and permitted more straightforward

interpretation of the parameters [56]. Cheng[57] extended the HSROC model and decompose the study-level positivity and accuracy parameters into test-specific effects representing overall mean positivity and accuracy parameters for each test across study-types. Hoyer et al[58] proposed a four-variable (sensitivity and specificity of diagnostic test 1, sensitivity and specificity of diagnostic test 2) linear mixed model to compare the values of two diagnostic tests with a common gold standard. In 2018, Owen et al[59] proposed a bivariate NMA model using MCMC methods to incorporate multiple tests and multiple explicit thresholds of the same test. This model also accounts for the correlations between multiple test accuracy measures from the same study. However, when information on the thresholds used is not available, this model is unable to estimate the performance of a test under a threshold or estimate the full summary receiver operating characteristic (SROC) plots across different thresholds. Ma et al[60] developed a missing data framework and a Bayesian hierarchical model for NMA of diagnostic tests. Regardless of whether a gold standard is available, this model can combines studies with different sets of candidate tests and takes into account heterogeneity across studies and complex correlation structure among multiple tests. Lian et al[61], in 2019, extendedthe Bayesian hierarchical summary receiver operating characteristic (HSROC) model[62]to a NMA of diagnostic tests to simultaneously compare multiple tests within a missing

data framework. This method allows different studies to include different subsets of diagnostic tests, provides flexibility in the choice of summary statistics, and accounts for correlations between multiple tests and heterogeneity between studies. Built on the consistency assumption, however, this model is not suitable where inconsistency exists between direct evidence and indirect evidence, which was often observed in diagnostic accuracy studies[63].

3.2 Network meta-analyses of individual participant data

Network meta-analyses of individual participant data (IPD-NMA) is a combination and extension of individual participant data meta-analysis and NMA, which the original data of each participant are required [64,65]. IPD- NMAs can better explore the heterogeneity and inconsistency and, identify interactions of patient-level effect modifiers through more flexible subgroup analysis and modelling, thereby increasing the applicability of research results, and improving the credibility of the results [66-70]. In 2012, Saramago et al[71] developed a series of novel Bayesian statistical mixed treatment comparisons(MTC) models for the simultaneous synthesis of IPD and AD, taking into account the study and individual-level covariates and covariate effects based on between-study and within-study variability. Jansen[72] proposed non-linear NMA models for combining IPD and AD to reduce bias and uncertainty of direct and indirect treatment effects in the presence of heterogeneity. In 2013, Donegan et al[67] introduced random-effects MTC models to combine IPD and AD for a dichotomous outcome. In 2014, Saramago et al[73] presented a novel NMA modeling method that allows the synthesis of IPD on time to event (with censoring) and AD on event count (for a given follow-up time) by assuming an underlying distribution of time to healing. In 2015, Hong et al proposed[74] a Bayesian IPD NMA modeling framework

for multiple continuous outcomes under both contrast-based and arm-based parameterizations. Thom et al[75] proposed a covariate-adjusted random-effects Bayesian NMA model that can include single-arm, before-and-after, observational studies to complete disconnected networks. In 2016, Saramago et al[76] described an IPD-NMA model for continuous outcomes using the analysis of covariance framework. In 2017, Freeman et al[77] provided a computationally practical and flexible IPD Bayesian NMA model for time-to-event data. In 2018, Freeman et al[78] proposed a practical framework to conduct one-stage IPD-NMA with treatment-covariate interactions. In 2020, Gao et al[79] investigated statistical methods and assessed the reporting and methodological quality of published IPD-NMAs, which indicated the reporting of statistical methods and compliance rates of methodological and reporting of IPD-NMAs were suboptimal. Therefore, researchers should continue to focus on IPD-NMA methodology to improve the quality of IPD-NMA to provide the best evidence for clinical practice.

3.3 Network meta-analyses of survival data

In 2010, Ouwens et al[80] proposed a method for NMA of time-to-event data with

treatment effects based on the shape and scale parameters of parametric survival curves, which allows for a better fit to the data and the expected survival of competing interventions for cost-effectiveness analysis[81]. In 2016, Vickers[82] compared two methods of NMA on survival outcomes (including overall survival and progression-free survival) based on aggregated hazard ratios or reconstructed patient-level data (using fractional polynomials), respectively. The study showed the later method using reconstructed patient-level data had some clear advantages over the former method. However, the hazard ratio method may still be the preferred method where only Kaplan-Meier charts were reported in the primary studies. In 2019, Petit et al[83] evaluated whether IPD-NMAs using restricted mean survival time difference differed from those using hazard ratios through a case study on locoregionally advanced nasopharyngeal carcinomas. This study indicated the use of either hazard ratios or restricted mean survival time difference affected the results of primary outcomes although the results for secondary outcomes were overall in agreement.

3.4 Component network meta-analysis

In 2009, Welton et al[84] developed a new NMA method, component network meta-analysis (CNMA), as an extension of standard NMA that can be used to disentangle and compare the treatment effects of different components included in

composite interventions while taking advantage of the whole network of randomized evidence [85]. In 2019, Rücker et al[86] introduced a frequentist analysis approach to CNMA, which can be implemented using the open-source R package netmeta. In 2020, Rücker et al[87] used CNMA models to bridge the gap between two disconnected networks of treatments for multiple myeloma and compared the results to those obtained using the matching method through single-arm observational studies. The CNMA model is suitable for a disconnected network with common components shared in different subsets of the network. Currently, CNMA is mainly used to evaluate the effects of psychological interventions.In the future, this method may play an important role in systematic reviews of complex interventions involving multiple components.

3.5 Dose-response network meta-analyses

In 2013, Giovane et al[88] proposed a series of NMA models on dose-effects accounting for the variability of treatment definitions. In 2015, Owen et al[89] developed a three-level hierarchical NMA model that incorporates dose-related constraints using Bayesian MCMC methods. In 2016, Mawdsley et al[90] proposed a model-based framework network meta-analysis (MBNMA), which not only respects randomization, but also allows estimation and prediction for multiple agents and a range of doses. In 2017, the study conducted by Normand et al[91] explored the relationship between duration of exposure and outcomes by IPD-NMA suggesting combining treatment-exposure curves could help in the assessment of evidence compatibility from direct and indirect comparisons. In 2021, Hamza et al[92] proposed a Bayesian hierarchical dose-response model with normal or binomial likelihood and the cluster-specific dose–response model. Pedder et al[93] proposed a dose-response

model-based NMA method that suits disconnected networks through a dose-response relationship when evidence on multiple doses is available.

3.6 Prediction model network meta-analyses

Predictive models, which can estimate a person's risk of developing a disease or other outcome, have gained increasing use to support decision-making in public health and clinical practice [94,95]. Several prediction model meta-analysis methods have been proposed to assess individual risks of adverse outcomes or to aidin risk-based decision making [96-98]. However, there are many models but lack of comparative research on the accuracy of prediction between different models, resulting in poor application of existing models. The prediction model NMA proposed by Haile et al[99] in 2017, permits concurrent external validation and comparisons of prognostic scores using IPD arising from a large-scale international collaboration.

3.7 Living network meta-analyses

In 2014, Elliott et al[100] proposed a method called "living systematic reviews". This type of systematic review is continually updated when new evidence becomes available. In 2017, the *Journal of Clinical Epidemiology* published a series of studies[101-104] on the methodology of the living systematic reviews. Topics covered in these studies included the key issues in these reviews (including searching, updating scenarios, production processes, peer review and publication;–), novel methods (such as text mining, machine learning, and crowd sourcing),; statistical issues associated with repeated meta-analysis,; and the opportunities to link these reviews with living guidelines. Despite many challenges in statistical methods, production processes, peer review, and publications [100,103], asevidence updates

accelerate, living systematic reviews may play a more important role[105].

Nikolakopoulou et al's study[106] in 2018 revealed that it would be earlier for a living NMA to provide strong evidence against the null hypothesis than the corresponding updated pairwise meta-analysis. In 2019, the study by Crequit et al[107] on the feasibility of living NMA indicated the analysis of the pace of evidence generation could help in determining the optimal update frequency. Lerner et al[108] developed an algorithm for automatically screening citations for updating NMAs of randomized controlled trials. In 2020, the first Cochrane living NMA[109] was published, which compared the efficacy and safety ofconventional systemic agents, small molecules, and biologics for people with moderate-to-severe psoriasis. The current COVID-19 pandemic, witnessed the use of living NMAs to timely produce high-quality evidence considering the prevention and treatment of COVID-19 to support guideline developments and clinical practice[110,111]. Over this period, living NMA attracted more attention as a crucial approach to summarize available evidence to respond to the challenges in the pandemic.

4. Challenges of Network Meta-Analyses

4.1 Data retrieval

NMAs usually include a wide range of interventions for a specific condition, which requires obtaining all available evidence for a comprehensive review. Insufficient searches may fail to identify all existing evidence, resulting in biased results [112]. Therefore, a comprehensive literature search is essential. For living NMAs, routine update of the evidence is necessary to obtain new evidence in time and reflect dynamic evidence. To meet the challenges in updating

systematic reviews due to increasing number of publications, it is urgent to develop a convenient automatic screening tool with high sensitivity and specificity to support NMA updates. For IPD-NMAs, reviewers need to request IPD from the authors of the original studies or collect through data- sharing platforms[113-115]. However, IPD retrieval was generally disappointing, with only 25% to 59.8% of IPD meta-analyses able to obtainIPD from all included studies [113,115-117]. Therefore, more efforts are still required to improve IPD data sharing.

4.2 Ranking competing treatments

One of the advantages of NMA is that it allows for the ranking of competing treatments. Several methods available for the ranking. Within a Bayesian framework, researchers can report the distribution of ranking probabilities (that is, the probability of being at each possible rank, from best to worst), the mean rank or the surface under the cumulative ranking curve (SUCRA) [118]. For the frequentist framework, authors can use the P-score [119]. However, treatment ranking has gained much criticism over the last years [120]. The main criticisms include: (1) ranking of treatments most often is not interpreted due to the limitations of the evidence base (such as risk of bias) [121]; (2) rankings may give the false sense that some interventions are superior to others when the relative effects are in fact not different from the null beyond chance [14,122]; (3) the widely used ranking methods focuses on the best probability of each treatment without considering the whole ranking distribution and produces misleading results [121,123]. The previous study also has revealed simply ranking treatments based on SUCRA or P-scores has no major advantage compared to ranking treatments by their point estimates [119]. Therefore, further studies are needed to address these issues.

4.3 Inconsistency assessment

An important aspect of a network meta-analysis is to assess the consistency of different sources of evidence. Several methods have been developed to evaluate the inconsistency in intervention NMAs, such as 'design-by-treatment' model method[124], node splitting method[125]. However, methods available for assessing inconsistency in NMAs of diagnostic test accuracy are very limited, which deserves more attention.

4.4 Certainty of evidence

The application of NMA results requires an understanding of the quality of the evidence. In 2014, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group presented a four-step approach to rate the certainty of the evidence from NMA[126]. Salanti et al[127] proposed another NMA evidence rating approach (Confidence in Network Meta-Analysis, CINeMA) in 2014, Nikolakopoulou et al[128] improved this method by introducing the methodological framework and application in details. In 2019, the GRADE working group presented the guidelines for addressing incoherence and avoiding spurious judgments of imprecision in sparse networks when assessing the certainty in the evidence from NMA[129,130]. In 2020, the GRADE working group proposed two frameworks, minimally contextualized framework and partially contextualized framework, to draw conclusions from an NMA based on the GRADE approach[131,132]. Currently, the GRADE approach has been widely used to assess the quality of evidence from aggregated NMAs. However, a previous study showed that only 9.5% of the 21 included IPD-NMAs used GRADE to assess the quality of evidence[79]. Therefore, it is necessary to develop more specific methods for assessing the quality of evidence to adapt to different types of NMA.

5. Conclusion

In the past few years, the NMA methods have been rapidly developed, and different types of NMA have been proposed. Increased use of these methods would facilitate evidence-based clinical decision- making and guideline development.

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Competing interests

The authors declare that they have no competing interests.

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