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Bibliographic study showed improving statistical methodology of network meta-analyses published between 1999 and 2015

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Keywords: multiple interventions; meta-epidemiology; mixed-treatment comparisons; inconsistency; reporting
Abstract

**Objective:** To assess the characteristics and core statistical methodology specific to network meta-analyses (NMAs) in clinical research articles.

**Study Design and Setting:** We searched Medline, Embase and the Cochrane Database of Systematic Reviews from inception until April 14, 2015 for NMAs of randomized controlled trials (RCTs) including at least four different interventions. Two reviewers independently screened potential studies, while data abstraction was performed by a single reviewer and verified by a second.

**Results:** A total of 456 NMAs, which included a median (interquartile range) of 21 (13 to 40) studies and 7 (5 to 9) treatment nodes were assessed. A total of 125 NMAs (27%) were star networks; this proportion declined from 100% in 2005 to 19% in 2015 (p=0.01 by test of trend). An increasing number of NMAs discussed transitivity or inconsistency (0% in 2005, 86% in 2015, p<0.01) and 150 (45%) used appropriate methods to test for inconsistency (14% in 2006, 74% in 2015, p<0.01). Heterogeneity was explored in 256 NMAs (56%), with no change over time (p=0.10). All pairwise effects were reported in 234 NMAs (51%), with some increase over time (p=0.02). The hierarchy of treatments was presented in 195 NMAs (43%), the probability of being best was most commonly reported (137 NMAs, 70%) but use of SUCRA (surface under the cumulative ranking curves) increased steeply (0% in 2005, 33% in 2015, p<0.01).

**Conclusion:** Many NMAs published in the medical literature have significant limitations in both the conduct and reporting of the statistical analysis and numerical results. The situation has however improved in recent years, in particular with respect to the evaluation of the underlying assumptions, but considerable room for further improvements remains.

278 words
What is new?

Key findings
Although the amount of evidence (the number of treatments and studies) included in published NMAs remains stable, the undertaking and reporting of statistical methods have significantly improved over the years. The assumptions underlying NMA are increasingly discussed and evaluated using appropriate methods. Less than 10% of NMAs published in 2014 and 2015 failed to evaluate the assumptions of the joint synthesis.

What this adds to what is known
This meta-epidemiological study presents the largest collection of published NMAs over the past 16 years. It provides an overview of the structural characteristics and statistical methodology of 456 published networks of interventions. It shows that the statistical methods in NMA have considerably improved in all aspects and some, such as the use of appropriate methods to evaluate the plausibility of the assumptions, are now routinely performed. We conclude that the increasingly populous community of NMA methodologists is quickly advancing through the learning curve of statistical methods employed in NMA.

What is the implication, what should change now
The updated description of the structural characteristics of the published NMAs can be used to inform pragmatic simulations studies and the development of methods that are relevant to the type of networks typically found in the medical literature. Future tutorials and training should be focused on improving the methodology and reporting on items that, although they have improved, their prevalence remains low, such as the formal exploration of heterogeneity and inconsistency and the presentation of all pairwise treatment effects.
1 Introduction

Network meta-analysis (NMA) is becoming increasingly popular for evidence synthesis [1–4] with enthusiasts considering NMA as the ‘new norm’ for comparative effectiveness research [5]. However, empirical studies exploring the characteristics of published NMAs of interventions have raised the need for improving the quality of the application of NMA methods [1,2,6–9]. Concerns about inappropriate applications of NMA methods and inadequate and non-transparent reporting of methods and results have been identified as major issues [10–12]. For instance, Nikolakopoulou et al. found that 68% of the NMAs published by the end of 2012 used either inappropriate or unspecified methods to assess inconsistency, while Bafeta et al. concluded that reporting guidelines are necessary to reduce heterogeneity in presentation of NMA results [1,6].

The importance of empirical evidence in a novel, rapidly evolving methodological field is illustrated by the role such studies played in shaping the methodology for conventional pairwise meta-analysis. The assessment of risk of bias in the included studies [13–15], the magnitude and determinants of heterogeneity [16–18], the relative advantages of different methods to evaluate publication bias and small-study effects, [19–21] and the importance of a comprehensive search for relevant studies [22] are examples of meta-epidemiological studies that have guided the choice of optimal methods. We are aware of only three such meta-epidemiological studies in NMA: Song et al. evaluated the prevalence of inconsistency in networks with three treatments [23,24], Veroniki et al. studied the prevalence of inconsistency in complex NMAs that included at least four treatments using two alternative methods [25] while Chaimani et al. have provided empirical evidence about the impact of risk of bias and small study effects [26].

In recent years, the methodology of NMA has been further refined and many tutorials and guidance papers have been published [12,27–31]. Efthimiou et al., in a recent review of methodological articles published until March 2014, [32] found a steep increase after 2011 in the number of relevant publications. In 2012 and 2013, 83 methodological articles were published compared to 58 articles between 2005-2011. For example, until recently most networks were fitted within a Bayesian framework as hierarchical models [1], but new NMA methods include publications by White et al. suggesting NMAs can be viewed as a specific case of multivariate meta-regression, and by Higgins et al. presenting a new test for inconsistency [33,34]. Their work enables researchers to fit models using frequentist software. Stata routines were made available by White et al. and Chaimani et al. that simplified NMA implementation by non-statisticians [35–39].
In this paper, we aim to describe how methodologies specific to NMA and reporting quality of results has evolved over time, monitor the rate of adoption for the new methodological developments and provide an updated overview of the characteristics of published networks.

2 Methods

2.1 Inclusion criteria
Networks of randomized controlled trials (RCTs) were eligible if they included at least four different interventions (defined as different drugs or other medical treatments, or different schedules, doses or formulations of the same treatment) including placebo, no treatment, waiting list or other control interventions. We excluded networks that included observational or diagnostic test accuracy studies, NMAs in which the number of trials was smaller than the number of interventions and articles that performed naive indirect comparisons by pooling data across study arms.

2.2 Literature search
An expert librarian compiled the literature search, which was peer-reviewed by a second librarian using the Peer Review of Electronic Search Strategies (PRESS) checklist [40]. Subsequently, Medline, Embase and the Cochrane Database of Systematic Reviews were searched from inception until April 14, 2015. The full literature search strategy is provided in the Appendix. There were no language restrictions on our search.

2.3 Screening
After a pilot-test of the eligibility criteria, pairs of reviewers (MG, AC, MP, AAV, PR, AV, SS) independently screened the titles and abstracts from the literature search. Potentially relevant full-text papers were screened in the same manner. Conflicts were resolved by a third reviewer (AAV, AN, AC, GS, PR) to increase consistency.

2.4 Data extraction and data items
One reviewer (MP, AN, AC, AAV, MG, PR, AV, SS or WZ) abstracted data from the included studies and then data was checked by another reviewer. Data items included general publication characteristics: e.g., year of publication, country of corresponding author and journal of publication. We recorded whether the primary outcome measured efficacy or safety and classified outcomes as dichotomous, continuous, time-to-event or rate. For networks that indicated none or more than one outcome as primary, we used discussion to reach consensus for a final decision. We extracted the total number of compared interventions (termed nodes of the network henceforth), the reference intervention when reported (placebo, usual care, no
treatment, or active treatment). We categorized each network according to the type of treatment comparisons as pharmacological versus placebo, pharmacological versus pharmacological or non-pharmacological versus any treatment (for details see Turner et al. [41] and Nikolakopoulou et al. [1]). When the reference treatment was not explicitly defined, one of the following was selected as the reference treatment node: placebo, usual care, or no treatment. We also categorised the shape of network according to the presence or absence of at least one closed loop.

We only examined methodological characteristics that are specific to NMA methodology, with an emphasis on statistical analysis and reporting. We recorded whether and how the authors evaluated the plausibility of transitivity (the comparability of the distribution of effect modifiers across treatment comparisons) prior to the data synthesis [27]. For networks including at least one closed loop, we also recorded the use of any statistical method to evaluate consistency (e.g. statistical methods such as those described in Donegan et al. (2013)) [42]. We categorized the method used to derive indirect and/or network estimates (e.g. a Bayesian hierarchical model, a multivariate meta-analysis approach), effect measure employed to undertake the analysis (such as odds ratio or mean difference) and whether fixed-effects model, random-effects model or both computational models were used. We also assessed any secondary analyses such as subgroup, network meta-regression, or sensitivity analyses that the authors performed to investigate potential sources of heterogeneity or inconsistency. We examined whether authors assessed small-study effects, whether they considered the potential for publication bias and the methods they applied to evaluate their impact on the results. We recorded whether all possible relative effects were presented (in the main text or as supplementary material) or only a subset of them. We also examined whether the authors presented the estimated hierarchy of the included interventions and which measure was used for this purpose (such as probability of being the best or surface under the cumulative ranking (SUCRA) curve [11,43,44]).

2.5 Statistical analysis

We performed a descriptive analysis for all the characteristics we extracted from the eligible networks of interventions. For characteristics that have been previously identified as needing improvement [1,2,45] – such as the adoption of appropriate methods to evaluate consistency, the uptake of frequentist methods for NMA, and the transparency of reporting – we evaluated whether there was a change in frequency over time. We formally tested the trend using a $X^2$ test for trends in proportions for dichotomous characteristics and the Cox-Stuart test for trends in continuous characteristics [46]. We also investigated any associations between methods employed and the complexity of the evidence-base such as the number of nodes and the
presence of closed loops. All analyses were performed in R software [47] using the trend library [48].

3 Results
The search identified 3727 citations and after screening the titles and abstracts, 877 potentially relevant full text articles were reviewed. In total, 456 NMAs met all inclusion criteria. The full selection process for the included networks is presented in Figure 1.

Figure 1 Flow chart of the selection process for the included networks.

Table 1 presents a description of the sample. The median number of studies per network was 21 (interquartile range (IQR) 13 to 40) and the median number of treatments was 7 with an IQR of 5 to 9. The majority of NMAs included at least one closed loop (331, 73%) while nearly a quarter of the networks (125 NMAs, 27%) did not contain a closed loop of evidence (called star-shaped networks). The majority of the included NMAs had a beneficial primary outcome (260 NMAs, 57%) that was commonly measured using a dichotomous outcome (267 NMAs, 59%). The primary outcome was measured using continuous data in 135 NMAs (30%). Two-thirds of the networks compared pharmacological treatments and included placebo (299 NMAs, 66%) while one in five compared only pharmacological interventions (88 NMAs, 19%). A small number of networks had a mixture of pharmacological, non-pharmacological and control treatments (69 NMAs, 15%).

Table 1 Characteristics of 456 NMAs published until 2015. IQR: Interquartile range.

Most of the included articles were published in general medicine journals (183 NMAs, 40%), the most common was the British Medical Journal (28 NMAs, 6%) followed by Current Medical Research & Opinion (24 NMAs, 5%). Corresponding authors of 234 NMAs (51%) had an affiliation in a European country (92 NMAs, 20% for United Kingdom) and 140 NMAs (31%) had an affiliation in the United States.

3.1 Time trends in the characteristics of NMAs
Between 1999 and 2004 only 6 NMAs were published (1 in 1999, 2 in 2000, 1 in 2003 and 2 in 2004). The number of NMAs published per year after 2004 is presented in Table 2. It is evident that the number of published studies applying NMA methods to clinical research questions has been increasing significantly over the last two decades (p=0.04). Overall, the networks of published NMAs do not seem to include more studies (p=0.08, data not shown) or to compare more treatments in recent years (p=0.72, data not shown).
However, the proportion of star-shaped networks has decreased with time while the number of networks with at least one closed loop has increased (p=0.01, Table 2).

**Table 2 Networks published between 2005 and 2015 (until 15 April) and their characteristics.** The entries in the table show number of networks and respective percentages. P-values are from a trend test. *There are 6 networks published before 2005 and are included in the total NMA group. **In the test for trend for the total number of published NMAs we excluded the year 2015 as it is not complete. ***Here the denominator is the number of articles with at least one closed loop (number of NMAs published minus the star-shaped NMA).

### 3.1.1 Evaluation of clinical and statistical assumptions

In three quarters of the included articles (353 NMAs, 77%) we could not identify any statement suggesting that the transitivity (or similarity) assumption was considered or evaluated (Table 2). However, this has improved considerably over time, with 77% of the networks published in 2015 discussing transitivity (p<0.01). In five networks, the authors expressed concerns about the presence of potential non-transitivity and its impact on the results. Among the remaining 100 networks that did report how transitivity was evaluated, the majority compared the study characteristics (76 networks) (Appendix Table 1). One in five of the published networks (22%) reported that the transitivity assumption is likely to hold; the rate of articles reporting this information has increased over time (p<0.01).

Statistical evaluation of consistency was possible for 331 networks that included at least one closed loop. Almost one third of these NMAs (94 NMAs, 28%) did not report any method used for the statistical evaluation of consistency. Nearly half of the networks (150 NMAs, 45%) used appropriate statistical methods to evaluate consistency; their uptake has increased over time (p<0.01, Table 2).

The exact method used for assessing inconsistency in each network is detailed in Appendix Table 2. The loop-specific approach [49] was the most commonly employed method (59 NMAs, 18%), followed by the node-splitting approach [50] (39 NMAs, 12%). The design-by-treatment interaction model [34] that was introduced in 2012 was used in very few networks (5 NMAs, 2%). The proportion of NMAs that considered transitivity or consistency using any method increased significantly over time (p<0.01, Table 2); 86% of the articles published in 2015 reported mentioned at least one of the two terms.

Appendix Table 1 Reporting and evaluation of transitivity. Number of articles and percentages.

Appendix Table 2 Statistical methods used to evaluate the consistency assumption in 331 NMAs with at least one closed loop.
In total we found 76 networks that did not evaluate either transitivity or inconsistency (23% for the networks where assessment of both was possible); the percentage has dropped from 35% in 2010 to 19% in 2012 and to 8% in 2014/2015 (p<0.01).

### 3.1.2 Statistical synthesis of data

We found that the odds ratio (177 NMAs, 39%) and the mean difference (89 NMAs, 20%) were the most frequently used effect sizes for networks with dichotomous and continuous data respectively. It was not always clear whether the random or fixed effects model was used although reporting improved with time (p=0.01, Table 2). The majority of the included networks (230 NMAs, 50%) performed the analysis using a random-effects model. Of the 170 networks (37%) that used the fixed-effect model, the majority (141 NMAs, 83%) also applied the random-effects approach either as a sensitivity analysis or with the aim to choose between the two models.

The percentage of articles reporting the statistical method used to fit NMA has increased over time (p<0.01, Table 2) and only a small proportion of networks (24 NMAs, 5%) did not report the NMA method used. The Bayesian hierarchical model remains the most popular approach for NMA (302 NMAs, 64%). Only 80 (18%) networks which included at least one multi-arm study employed methods to derive the treatment effect that ignored correlations (e.g. adjusted indirect comparison meta-analysis or Bucher method). NMAs using multivariate meta-analysis or multivariate meta-regression was encountered in only 5 publications while the graph-theoretical method for NMA was employed in one network.

**Figure 2 Method used to synthesize the data in relation to the shape of the network. If a network applied more than one method, it is included in all relevant categories.**

Figure 2 illustrates that review authors tend to employ a Bayesian hierarchical approach and meta-regression more often in the presence of closed loops.

Approximately half of the networks (256 NMAs, 56%) investigated potential sources of heterogeneity or inconsistency via the use of subgroup, meta-regression or sensitivity analysis. This remained unchanged over time (p=0.10). Small-study effects and publication bias were assessed in 143 (31%) networks. Funnel plots (116 NMAs, 81%) and regression tests (82 NMAs, 57%) were the most prevalent methods for the assessment of publication bias and 7 NMAs (5%) applied trim and fill method (Appendix Table 3). These methods were primarily applied to the direct comparisons and only a handful of networks (6 NMAs, 4%) considered the extensions for the aforementioned approaches into the context of NMA, such as the comparison adjusted funnel plot and extended selection models [36,51–53].

**Appendix Table 3 Methods employed to assess small-study effects and/or publication bias in 143 NMAs.**
3.1.3 Presentation of results

The percentage of NMAs that report outcome data for the primary outcome decreased with time \((p=0.03)\). Half of the included reviews (234 NMAs, 51\%) presented all possible relative treatment effects; the other half present only a selective set of comparisons of interest. Newer articles tend to be more inclusive and present all pairwise effects \((p=0.02, \text{Table 2})\). One network \((0.2\%)\) did not report any relative treatment effect. The relative hierarchy of the treatments was presented in 43\% \((195 \text{ NMAs})\) of networks. Probability of being the best was the most popular ranking measure employed to derive a treatment hierarchy \((166 \text{ NMAs}, 85\%)\) followed by SUCRA \((39 \text{ NMAs}, 20\%)\) (Appendix Figure 1). While the frequency of exclusive use of the ‘probability of being the best’ has not changed significantly over time \((p=0.86, \text{Table 2})\), the use of SUCRAs has increased sharply \((p<0.01, \text{Table 2})\).

Appendix Figure 1 Ranking measures used in the included networks per year (1999-2015).

4 Discussion

We identified 456 NMAs that were published between 1999 and 2015 by searching three bibliographic databases and assessed the characteristics of their statistical analysis and reporting of results. We found that many NMAs published during this time period have significant methodological limitations, but that the application of some methodological elements improved in recent years. For example an increasing number of published NMAs addressed transitivity or inconsistency, by 2015 about three quarters of analyses used appropriate methods to test for inconsistency. The quality and transparency of reporting also increased: in recent years around 90\% of articles clearly reported whether a random-effects or fixed-effect model was used, and in 2015 all reports included a description of the statistical methods used. However, important deficiencies in the application of NMA methods remain: discussion of the transitivity assumption was rare and only about half of the articles reported the results of all pairwise comparisons with no increase in recent years. It should be noted that the Bayesian hierarchical model remained the most popular approach for NMA during the study period: only five articles reported the use of frequentist multivariate meta-analysis or meta-regression.

Our study has several strengths. Expert librarians conducted a comprehensive literature search in multiple bibliographic databases and our study team peer reviewed the literature search, screened articles in duplicate using standardized tools, and extracted and verified the relevant information using standardized forms. Calibration exercises among all reviewers preceded
each step of the review. We identified 456 NMAs, which were published over the past 17 years and although our search may have missed some articles, it is very likely that we identified a set of NMAs that accurately reflects current and past practice and methodological development. To the best of our knowledge, this is the largest and most up-to-date collection of published NMAs compiled to date. It includes nearly three times the data included in Bafeta et al. [2], more than twice the data included in Nikolakopoulou et al., [1] and about 40% more data compared to the collection recently published by Chambers et al. [54]. This is also the first study to formally investigate the changes in the methodology and reporting of NMAs over time.

Previous empirical studies have motivated various groups to develop recommendations to improve the practice and reporting of NMAs. For example, Hutton et al. developed an extension of the PRISMA statement (Preferred Reporting Items for Systematic reviews and Meta-analysis) for the reporting of systematic reviews that include NMAs of health care interventions [45]. The National institute of Clinical excellence (NICE) in the UK and the International Society For Pharmacoeconomics and Outcomes Research (ISPOR) have also developed relevant guidance [31,55].

We observed an important improvement in the statistical methodology and reporting of NMAs over time. The PRISMA statement was published only recently and we do not expect it to have had any major impact on the improvements in reporting observed in our study. The educational papers published several years ago [12,27,28,56,57] might, however, have had some impact. Alternatively, improvements in NMA methods might be due to statisticians and clinicians becoming more experienced with NMA techniques. This ‘learning curve’ could be accelerated by developments making methods more accessible and more widely available.

We found that features adding to the complexity of evidence structures, such as closed loops and large numbers of studies, were more common in NMAs performed within a Bayesian framework. The frequentist approaches to NMA that can cope with large and complex networks, such as the routine in Stata that fits the multivariate random-effects meta-analysis model [33,39], have not been applied widely but are expected to be increasingly used in the next years. Similarly, the design-by-treatment interaction model to test for inconsistency [34] that was introduced in 2012 was used in only few networks. This may be explained by the fact that the parameterization of this model is complex and until recently no dedicated software was available [39].

The transitivity assumption is imperative for a valid NMA and also needs to be met when informally comparing effects estimates from separate pairwise meta-analyses. In our large collection of networks, the vast majority of reports did not mention the transitivity assumption and only a handful of NMA reviews assessed it through the comparison of the distribution of
effect modifiers. Suggestions of accompanied detailed protocols on which authors should base their NMA reviews [12,27] have started to be applied. Among other merits, establishment of NMA protocol registration could substantially improve reporting and evaluation of transitivity through the a priori description of approaches that will be used to assess it.

Almost 10 years ago Sutton and Higgins stated that “time will tell whether this [NMA] is how efficacy of treatments will be routinely compared in the future” [58]. The substantial increase in published NMAs supports the notion that the rationale, importance, and methodology of comparing multiple treatments simultaneously has now become acknowledged among researchers, national and international health-care institutions [56]. It would be useful if the database used for this study was to be regularly updated to monitor developments in NMA publication and serve as a resource for further empirical research to better define the place of NMA in comparative effectiveness research. Several such projects are ongoing or planned: the quality of the systematic reviews providing data for each of the 456 networks is currently being evaluated, networks are currently being re-analysed to estimate the prevalence of statistical inconsistency, updating previous empirical research [25], and a subset of the included NMAs is being evaluated with respect to their conclusiveness using sequential methods. Additionally, the methodology to compare different doses of the same intervention within NMA is not well developed and an ongoing scoping review plans to describe the approaches currently available in the published literature. Finally, our database could inform simulation studies and scenarios evaluating the performance of various methodological approaches so that simulations reflect the most common encountered circumstances, as was previously done in Veroniki et al. [61].

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5 References


Table 1 Characteristics of 456 NMAs published until 2015. IQR: Interquartile range.

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<tr>
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<td>(51%)</td>
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<tr>
<td>Corresponding author with affiliation in USA</td>
<td>140</td>
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\(^1\) Includes the categories Medicine, General & Internal, Pharmacology & Pharmacy, Multidisciplinary Sciences, Medicine, Research & Experimental, Primary Health Care.

\(^2\) Includes the categories Health Care Sciences & Services, Health Policy & Services.
Table 2 Networks published between 2005 and 2015 (until 15 April) and their characteristics. The entries in the table show number of networks and respective percentages. P-values are from a trend test. *There are 6 networks published before 2005 and are included in the total NMA group. **In the test for trend for the total number of published NMA we excluded the year 2015 has it is not complete. ***Here the denominator is the number of articles with at least one closed loop (number of NMAs published minus the star-shaped NMAs).

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<td>19%</td>
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<td>17%</td>
</tr>
<tr>
<td>Evaluation of clinical and statistical assumptions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No information or discussion on transitivity</td>
<td>353</td>
<td>6</td>
<td>100%</td>
<td>12</td>
<td>100%</td>
<td>7</td>
<td>78%</td>
<td>11</td>
<td>92%</td>
<td>23</td>
<td>85%</td>
<td>26</td>
<td>87%</td>
</tr>
<tr>
<td>Reported that transitivity is likely to hold</td>
<td>98</td>
<td>0</td>
<td>0%</td>
<td>0</td>
<td>0%</td>
<td>1</td>
<td>11%</td>
<td>1</td>
<td>8%</td>
<td>4</td>
<td>15%</td>
<td>4</td>
<td>13%</td>
</tr>
<tr>
<td>Use appropriate methods to test for inconsistency***</td>
<td>150</td>
<td>NA</td>
<td>NA</td>
<td>1</td>
<td>14%</td>
<td>2</td>
<td>29%</td>
<td>2</td>
<td>33%</td>
<td>6</td>
<td>30%</td>
<td>4</td>
<td>17%</td>
</tr>
<tr>
<td>Discuss transitivity or inconsistency (at least one of the two)</td>
<td>285</td>
<td>0</td>
<td>0%</td>
<td>2</td>
<td>17%</td>
<td>3</td>
<td>33%</td>
<td>5</td>
<td>42%</td>
<td>12</td>
<td>44%</td>
<td>17</td>
<td>57%</td>
</tr>
<tr>
<td>Statistical synthesis of data</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clearly reported whether random or fixed effects are used</td>
<td>400</td>
<td>5</td>
<td>83%</td>
<td>10</td>
<td>83%</td>
<td>7</td>
<td>78%</td>
<td>10</td>
<td>83%</td>
<td>20</td>
<td>74%</td>
<td>25</td>
<td>83%</td>
</tr>
<tr>
<td>Method for NMA reported</td>
<td>432</td>
<td>4</td>
<td>67%</td>
<td>8</td>
<td>67%</td>
<td>9</td>
<td>100%</td>
<td>11</td>
<td>92%</td>
<td>23</td>
<td>85%</td>
<td>30</td>
<td>100%</td>
</tr>
<tr>
<td>Use Bayesian hierarchical model to fit NMA</td>
<td>302</td>
<td>1</td>
<td>17%</td>
<td>3</td>
<td>25%</td>
<td>3</td>
<td>33%</td>
<td>4</td>
<td>33%</td>
<td>13</td>
<td>48%</td>
<td>19</td>
<td>63%</td>
</tr>
<tr>
<td>Formal exploration of heterogeneity</td>
<td>256</td>
<td>2</td>
<td>33%</td>
<td>9</td>
<td>75%</td>
<td>5</td>
<td>56%</td>
<td>6</td>
<td>50%</td>
<td>16</td>
<td>59%</td>
<td>20</td>
<td>67%</td>
</tr>
<tr>
<td>Presentation of results</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All pairwise effects are presented</td>
<td>234</td>
<td>1</td>
<td>17%</td>
<td>3</td>
<td>25%</td>
<td>2</td>
<td>22%</td>
<td>4</td>
<td>33%</td>
<td>15</td>
<td>56%</td>
<td>17</td>
<td>57%</td>
</tr>
<tr>
<td>Available outcome data</td>
<td>308</td>
<td>4</td>
<td>67%</td>
<td>8</td>
<td>67%</td>
<td>8</td>
<td>89%</td>
<td>10</td>
<td>83%</td>
<td>23</td>
<td>85%</td>
<td>24</td>
<td>80%</td>
</tr>
<tr>
<td>Use Pbest as the only method of ranking</td>
<td>137</td>
<td>1</td>
<td>17%</td>
<td>2</td>
<td>17%</td>
<td>3</td>
<td>33%</td>
<td>1</td>
<td>8%</td>
<td>10</td>
<td>37%</td>
<td>13</td>
<td>43%</td>
</tr>
<tr>
<td>Use SUCRA to rank treatments</td>
<td>39</td>
<td>0</td>
<td>0%</td>
<td>0</td>
<td>0%</td>
<td>0</td>
<td>0%</td>
<td>0</td>
<td>0%</td>
<td>0</td>
<td>0%</td>
<td>1</td>
<td>2%</td>
</tr>
</tbody>
</table>

*There are 6 networks published before 2005 and are included in the total NMA group. **In the test for trend for the total number of published NMA we excluded the year 2015 has it is not complete. ***Here the denominator is the number of articles with at least one closed loop (number of NMAs published minus the star-shaped NMAs).
Two networks reported more than one approach to evaluate transitivity, the denominator is the total number of networks (456). Authors stated that they assume on the outset that the transitivity assumption is likely to hold without justifying this decision.

### Appendix Table 1. Reporting and evaluation of transitivity: number of articles and percentages.

| Reported concerns about potential intransitivity | 5 (1.1%) |
| Nothing relevant reported | 353 (77.4 %) |
| Transitivity established | 100* (21.9 %) |

<table>
<thead>
<tr>
<th>Method to evaluate transitivity among those claiming transitivity*</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Compare the distribution of the effect modifiers across studies grouped by comparison</td>
<td>11 (11%)</td>
</tr>
<tr>
<td>Compare the characteristics of the included trials</td>
<td>76 (76%)</td>
</tr>
<tr>
<td>Use of meta-regression</td>
<td>9 (9%)</td>
</tr>
<tr>
<td>Assumed on the outset**</td>
<td>4 (4%)</td>
</tr>
</tbody>
</table>
Appendix Table 2. Statistical methods used to evaluate the consistency assumption in 331 NMAs with at least one closed loop.

*13 networks used more than one method to evaluate consistency. Here the denominator is the number of networks with at least one closed loop (331).

<table>
<thead>
<tr>
<th>Inconsistency methods</th>
<th>Number of networks*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Appropriate methods</strong></td>
<td></td>
</tr>
<tr>
<td>Loop-specific [1]</td>
<td>59 (17.8 %)</td>
</tr>
<tr>
<td>Node-splitting [2]</td>
<td>39 (11.8 %)</td>
</tr>
<tr>
<td>Back-calculation [2]</td>
<td>8 (2.4 %)</td>
</tr>
<tr>
<td>Comparisons of model fit and parsimony (DIC) [3]</td>
<td>21 (6.3%)</td>
</tr>
<tr>
<td>Inconsistency models (Lumley model [4], Lu and Ades model [5], Design-by treatment model [6])</td>
<td>33 (10 %)</td>
</tr>
<tr>
<td>$I^2$ [7]</td>
<td>3 (0.9 %)</td>
</tr>
<tr>
<td>Generalized Cochran Q [8]</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td><strong>Inappropriate methods</strong></td>
<td></td>
</tr>
<tr>
<td>Comparison of NMA results with direct meta-analysis results</td>
<td>65 (19.6 %)</td>
</tr>
<tr>
<td>Comparison of the results with previously published results</td>
<td>23 (6.9 %)</td>
</tr>
<tr>
<td>No method reported</td>
<td>94 (28.3 %)</td>
</tr>
</tbody>
</table>
**Appendix Table 3** Methods employed to assess small-study effects and/or publication bias in 143 NMAs.

<table>
<thead>
<tr>
<th>Method</th>
<th>Number of networks*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Funnel plots (standard or contour-enhanced [9], [10])</td>
<td>116 (81.1 %)</td>
</tr>
<tr>
<td>Regression tests (Egger’s [9], Begg’s [11], Harbord’s [12], Peter’s [13])</td>
<td>82 (57.3 %)</td>
</tr>
<tr>
<td>Trim and Fill method [14]</td>
<td>7 (4.8 %)</td>
</tr>
<tr>
<td>Comparison-adjusted funnel plots [15]</td>
<td>5 (3.4 %)</td>
</tr>
<tr>
<td>Extended selection models in NMA [16]–[18]</td>
<td>1 (0.6 %)</td>
</tr>
<tr>
<td>L’ Abbe plot [19]</td>
<td>1 (0.6 %)</td>
</tr>
<tr>
<td>Fail-safe number (Nfs) (Number of studies with zero effect size that would be needed to increase the p-value for the meta-analysis to above 0.05 [20])</td>
<td>2 (1.3 %)</td>
</tr>
<tr>
<td>Tolerance level for future null results (Number of studies averaging null results that must be in the file drawers before the overall probability of a Type I error is brought to any desired level of significance [20])</td>
<td>1 (0.6 %)</td>
</tr>
<tr>
<td>Other (e.g. analyses the publication rates of the included studies; investigated from previous completed reviews; comparison the results with other study)</td>
<td>4 (2.7 %)</td>
</tr>
</tbody>
</table>

*55 networks applied more than one method. Here the denominator is the number of networks which assess small-study effects and/or publication bias (143).
References


Figure 1

Identified

Additional records identified through other sources (n = 252)

Citations identified through database (Cochrane Library, Embase, Medline, PubMed) searching (n = 3727)

Citations after duplicates removed (n = 3538)

Records excluded (n = 2913)
- Not an NMA (n=2601)
- NMA includes observational studies (n=61)
- Includes <4 treatments (n=216)
- Commentary/Protocol (n=35)

Screening

Citations screened (n = 3538)

Full-text articles assessed for eligibility (n = 877)

Full-text excluded (n = 421)
- Unable to locate (n = 3)
- Duplicate (n=16)
- Commentary/Protocol (n = 70)
- Invalid NMA (n = 99)
- NMA includes observational studies (n = 21)
- Includes <4 treatments (n = 70)
- No. of treatments > no. of studies (n = 76)
- Companion report (n = 29)
- Methodological articles (n=37)

Included

Studies included in qualitative synthesis (n= 456)
Figure 2

With closed loop(s)
Without closed loop(s)

Bayesian hierarchical model
Bucher method
Meta-regression
Not reported or unclear
Multivariate meta-analysis/meta-regression
Indirect synthesis method
NMA using graph theoretical methods

Number of networks

Network meta-analysis methods

302 NMAs
88 NMAs
44 NMAs
25 NMAs
5 NMAs
3 NMAs
1 NMAs

64.5%
18.8%
9.4%
5.4%
1.1%
0.6%
0.2%
Appendix Figure 1

This figure shows the number of networks over publication years, with different graphical elements representing various probabilities and ranks. The x-axis represents the publication years from 1999 to 2015, and the y-axis represents the number of networks.