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ORIGINAL ARTICLE

Improvement needed in the network geometry and inconsistency of Cochrane network meta-analyses: a cross-sectional survey

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Abstract

Objectives: The aim of the study was to investigate the general characteristics and methodological and reporting quality of network meta-analyses (NMAs) published in the Cochrane library.

Study Design and Setting: We conducted a comprehensive search of the Cochrane library in April 2018 and included 42 NMAs. We used the Assessing the Methodological Quality of Systematic Reviews (AMSTAR) 2 to assess methodological quality and Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)-NMA for reporting quality. Stratified analysis and correlation analysis were conducted to explore the factors that might affect the quality.

Results: A total of 42 NMAs investigated 29 topics. The compliance of PRISMA-NMA was moderate. Only 26.2% NMAs described the geometry of network, 64.3% presented the network plot, and 33.3% fully assessed the inconsistency. The overall methodological quality was low. Only 11.9% NMAs explained the selection of study designs, and 40.5% investigated the publication bias. The compliance of PRISMA-NMA was higher with the increase of the AMSTAR 2 compliance rates (Spearman's $\rho = 0.630$, $P = 0.000$). NMAs with statistical or epidemiological authors often better reported the titles ($P = 0.032$). Compared with nonfunding NMAs, nonindustry funding NMAs often better reported data collection process ($P = 0.028$), planned methods of analysis ($P = 0.034$), and synthesis of results ($P = 0.028$).

Conclusion: The quality still needs to be further improved, especially referring to the assessment of publication bias, the geometry of network, and assessment and exploration of inconsistency.

Keywords: Network meta-analyses; AMSTAR 2; PRISMA-NMA; Quality; Cochrane library; Meta-epidemiology

1. Introduction

Systematic reviews and meta-analyses are fundamental tools for generating reliable medical information for clinicians, decision-makers, and patients [1,2]. When comparing two interventions, a pairwise meta-analysis of the results obtained from the head-to-head trials can be performed [3–5]. However, this approach becomes problematic when there are no head-to-head trials comparing the two interventions or when more than two interventions need to be compared with each other simultaneously [6]. Network meta-analyses (NMAs; also called multiple or mixed treatment comparison [MTC] meta-analyses) permit the evaluation of the comparative effectiveness of multiple interventions [7–9]. Compared with pairwise meta-analyses, NMAs allow for visualization of a larger amount

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What is new?

Key findings

- Most NMAs failed to handle the multigroup trials, assess the similarity, describe the geometry of the network, and explore the inconsistency.

What this adds to what was known?

- This study aimed to investigate the general characteristics and assess the methodological and reporting quality of NMAs only published in the Cochrane library and compared the methodological and reporting quality of NMAs published in the Cochrane library and NMAs in the other fields.

What is the implication and what should change now?

- Considering the practicality and influence of network meta-analysis, the methodological quality, and reporting quality of NMA should be improved. Relevant authors of NMA should be further trained, and journal reviewers should pay more attention to the identified deficiencies in methodological and reporting quality of published NMAs.

of evidence, estimation of the relative effectiveness among all interventions, rank order of the interventions, borrow strength from indirect evidence to enhance certainty about all treatment comparisons, and allow for estimation of comparative effects that have not been investigated head to head in randomized clinical trials [10–12].

Over the past few years, NMAs have been increasingly used to compare healthcare interventions [13–16]. Although NMA approaches appear attractive, the application of their results requires understanding the quality of the evidence [17–20]. Empirical studies showed that the knowledge synthesis methods and analytical process for NMAs were poorly reported, but it is gratifying that this situation has improved in recent years [21,22]. However, 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 [21]. These methodological flaws in conducting NMAs could cause biased conclusions [23,24]. Previous studies found that Assessing the Methodological Quality of Systematic Reviews (AMSTAR) is a reliable methodological quality assessment tool with good agreement, construct validity, and feasibility [25–27]. The Preferred Reporting Items for Systematic Reviews and Meta-analyses extension statement (PRISMA-NMA) [1] was developed on the basis of PRISMA to assess the reporting quality of NMAs. It highlights information related to key considerations in the practice of NMAs [1].

Recently, some articles have evaluated the methodological and reporting quality of NMAs with AMSTAR and PRISMA checklists [14–16,28,29]. They all showed that the reporting rate of some important information in the NMAs was still very low, and the methodological quality and reporting quality needed to be improved. However, there was a lack of empirical evidence to evaluate the reporting quality using the PRISMA-NMA. According to our knowledge, there were no previous studies that evaluate the quality of all NMAs published in the Cochrane library using the AMSTAR 2 and PRISMA-NMA checklists.

The primary objective of this study was to investigate the general characteristics, methodological quality, and reporting quality of NMAs published in the Cochrane library. The secondary objective was to examine whether certain characteristics (e.g., statistical or epidemiological author and funding source) were associated with methodological and reporting quality. The third objective was to compare the differences between NMAs in the field of cancer [29] (Cancer NMAs), drug interventions [30] (Drug interventions NMAs), and NMAs published in the Cochrane Library (Cochrane NMAs).

2. Methods

2.1. Study collection

The Cochrane library was searched on April 3, 2018, to identify NMAs. The search terms included NMA, mixed treatment comparison meta-analysis, mixed treatment meta-analyses, multiple treatment meta-analysis, indirect comparison, and indirect treatment. Full details of the literature search strategy were shown in Appendix 1. There was no restriction on publication year. Both the NMAs of randomized controlled trials and NMAs with observational studies were included. We would only include the latest version whenever the NMAs have been updated. We excluded diagnostic meta-analyses, protocols, and methodological articles.

2.2. Study selection

Initially searched records were imported into EndNote X7 (Thomson Reuters Corporation, Stanford, USA) literature management software. Two reviewers (Y.G. and X.M.) independently selected studies by reviewing the titles and abstracts to identify possibly relevant studies. Any potential studies would be downloaded the full text, and the same reviewers further assessed the eligibility of each record according to the eligibility criteria. Conflicts were resolved by consulting a third reviewer (J.T.).

2.3. Data extraction and management

A draft data extraction sheet was developed using Microsoft Excel 2013 (Microsoft Corp, Redmond, WA,

USA; www.microsoft.com). Reviewers involved in data extraction piloted the form on a random sample of five included NMAs to ensure the agreement among the interpretation of data items. The form was revised when considered necessary. Then, one reviewer (Y.G., X.M., X.S., or M.L.) extracted data from the included NMAs, and a second reviewer (X.S., M.L., or J.T.) checked the extracted data. We resolved discordant evaluations by discussion. Data of interest included first author, year of publication, country of authors, whether statistician/epidemiologist/methodologist (based on the author's current academic position) was involved, funding source (industry, government, unfunded, or not reported), number of authors, number and design of included trials, sample size of included trials, categories of disease, software used for NMA, whether Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool was used, and number of interventions included in the whole network.

We identified the funding source of each NMA and planned to conduct a stratified analysis between industry funding, government funding, and no funding. Because all the included studies were not funded by the industry, we only performed a subgroup analysis between nonindustry funding and no funding. We also categorized involved authors with or without statistician, epidemiologist, or methodologist and identified NMAs using a Bayesian framework or Frequentist framework.

2.4. Reporting of literature search

We extracted the following information on literature search methods: number of databases searched (Chinese, English, or both), name of databases searched, whether the search formula was provided, whether the previous systematic reviews/meta-analyses were searched, name and number of other sources searched (e.g., reference lists checking, clinical trial registration platform, and conference abstracts or Websites).

2.5. Quality assessment

We assessed the methodological quality of included NMAs using the AMSTAR 2 tool, which could be used to assess systematic reviews based on randomized and/or nonrandomized studies [31]. The AMSTAR 2 contains 16 items, among which seven are critical domains. The overall confidence of the quality of the review was classified as high, moderate, low, and critically low. We responded to each item with "Yes" (item/question fully addressed), "No" (item/question not addressed), or "Partial Yes" (item/question not fully addressed). A score of 1 was attributed for each response of "Yes," 0.5 for "Partial Yes," and "0" for "No" [29].

The reporting quality of included NMAs was assessed according to the PRISMA-NMA, which is a checklist with 32 items. To indicate the degree of compliance, each checklist item was assigned one of the following four responses: "Yes" for total compliance; "Partial" for partial compliance; "No" for noncompliance; and "Cannot answer" for limited information. The total score of reporting quality was obtained by summing "1" point for each "Yes," "0.5" for each "Partial," and "0" point for any other responses ("No" and "Cannot answer") [29,32].

2.6. Data analysis

We extracted the information of authors and countries and further produced a co-occurrence matrix by BICOMBS-2 (China Medical University, China) software. NetDraw of UCINET 6.0 (Analytic Technologies Co., KY) was used to draw the social network diagram of authors. Median and range were used for calculating continuous data, and frequency and percentage were used for summarizing categorical data. For individual items of the AMSTAR 2 and PRISMA extension statement, we summarized the frequency of "Yes" response for all included systematic reviews. We performed chi-squared test and calculated odds ratio (OR) with 95% confidence intervals (95% CIs) and P value to compare the compliance of each item between NMAs with statistician or epidemiologist and without statistician or epidemiologist, between nonindustry funding and nonfunding, and between Bayesian and Frequentist. Analyses were conducted by using STATA (12.0; Stata Corporation, College Station, Texas, USA), and P values below 5% were considered statistically significant.

The complete compliance rate of the methodological quality was calculated with the number of acquired "Yes" of AMSTAR 2 and AMSTAR 2 maximum items for each NMA. The complete compliance rate of reporting quality was calculated with the number of acquired "Yes" and PRISMA-NMA maximum items. The normality of the variables was evaluated using the Shapiro–Wilk test and re-evaluated by the Q-Q normal map, which indicated that all variables were non-normally distributed. Therefore, we conducted nonparametric correlations with the Spearman test to explore the relationship of the AMSTAR 2 and PRISMA-NMA with the publication year, number of authors, and the number of included studies using the complete compliance rate. The correlation analyses were conducted in IBM SPSS Statistics v. 24.0 (IBM Corp., Armonk, NY, USA), and the statistical level of significance was set at $P < 0.05$.

3. Results

3.1. Search results

The search of the Cochrane library retrieved 994 records. According to the selection criteria, 919 studies were excluded after screening titles and abstracts. Further reading remaining 75 articles in full text, we excluded 33

articles, including 24 traditional pairwise meta-analyses, four diagnostic meta-analyses, and five articles did not conduct the meta-analysis. Finally, we included 42 NMAs, and the flow diagram of identification, screening, eligibility, and included process was shown in Fig. 1. The full list of included NMAs can be found in Appendix 2.

3.2. Characteristics of included NMAs

The first Cochrane NMA was published in 2004. The majority of NMAs were published between 2014 and 2017 (73.8%; Fig. 2). Forty-two NMAs covered 29 topics and mainly focused on rheumatoid arthritis (six NMAs) and liver transplantation/resection (three NMAs; Fig. 3).

Twenty-four countries involved in the production of Cochrane NMAs, 41 NMAs were from developed countries, and one was completed by developing countries. Among them, the United Kingdom participated in the publication of 24 NMAs, the United States and Canada participated in the publication of 13 NMAs, Australia participated in the publication of eight studies, and the rest of the countries published less than five studies (Fig. 4).

The mean number of authors was 6.1, and 17 NMAs involved statistical or epidemiologic authors. The main authors formed a close-knit social network centered on Pereira SP from the United Kingdom and Suarez-Almazor ME from the United States, which means they had the most collaborations with other coauthors. Authors around the network, although sparsely connected, have established cooperative relationships with the authors of the center (Fig. 5).

The median number of interventions included per NMA was 7 (range: 3–21), the median number of samples included in each NMA was 7,293 (range: 177–101,804). Six NMAs used the combination of RevMan (Cochrane Collaboration, Oxford, UK), Stata, and WinBUGS (MRC Biostatistics Unit, Cambridge University, UK) for data analysis, six used the combination of RevMan and WinBUGS, five used the combination of RevMan and Stata,

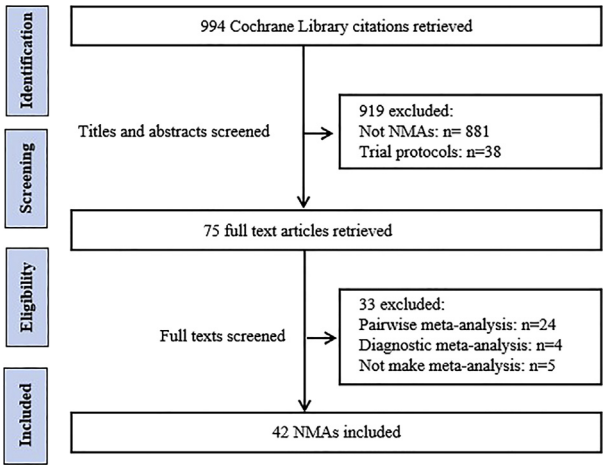

Fig. 1. The flow diagram of identification, screening, eligibility, and included process.

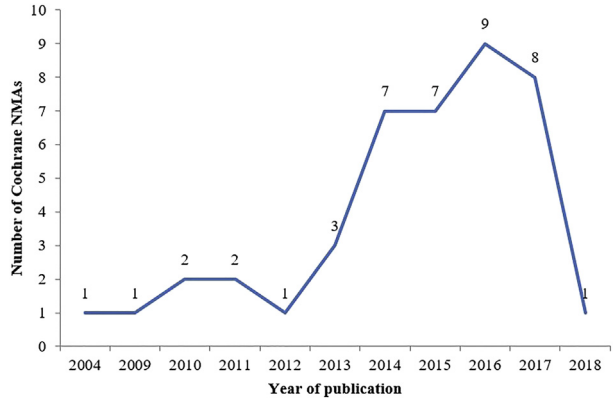

Fig. 2. Published years of the included NMAs. NMA, network meta-analyses.

and four used RevMan or Stata (Fig. 6). The Frequentist NMAs were more often use Stata, and Bayesian NMAs were more often use WinBUGS. Of the 42 NMAs, 30 were funded, and 20 were sponsored by the National Institute for Health Research of the United Kingdom, 12 were not funded. Thirty-four NMAs reported the use of GRADE, five NMAs considered two downgrade factors, three NMAs considered three downgrade factors, 12 NMAs considered four downgrade factors, and 14 NMAs considered five downgrade factors. The main characteristics of the included NMAs were shown in Table 1.

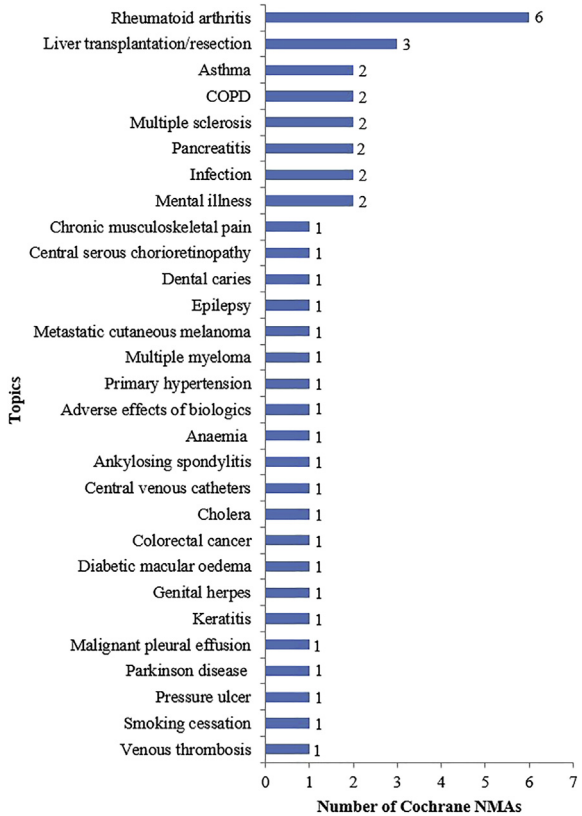

Fig. 3. Research topics of included NMAs. NMA, network meta-analyses.

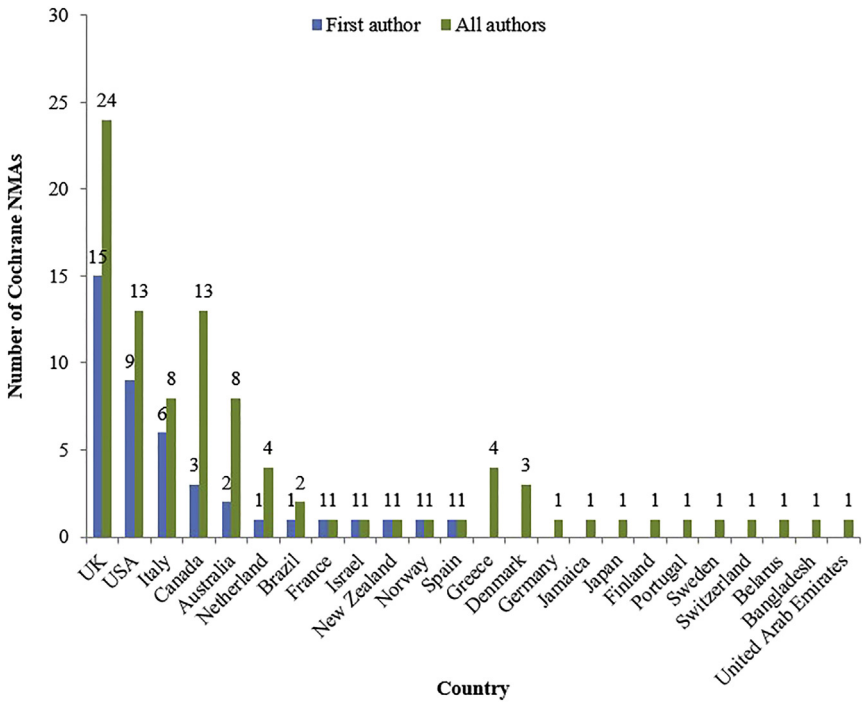

Fig. 4. Countries of the first author and all authors of included NMAs. NMA, network meta-analyses.

3.3. Reporting of literature search

As shown in Table 2, all NMAs reported the searched databases and retrieved English databases, but only one study retrieved Chinese databases. Sixteen NMAs searched three to four English databases, 15 NMAs searched five to six English databases. Forty-one studies reported search strategies, PubMed/MEDLINE was the single database with the most retrieval times, 34 NMAs retrieved EMBASE, 31 NMAs retrieved Cochrane Central Register of

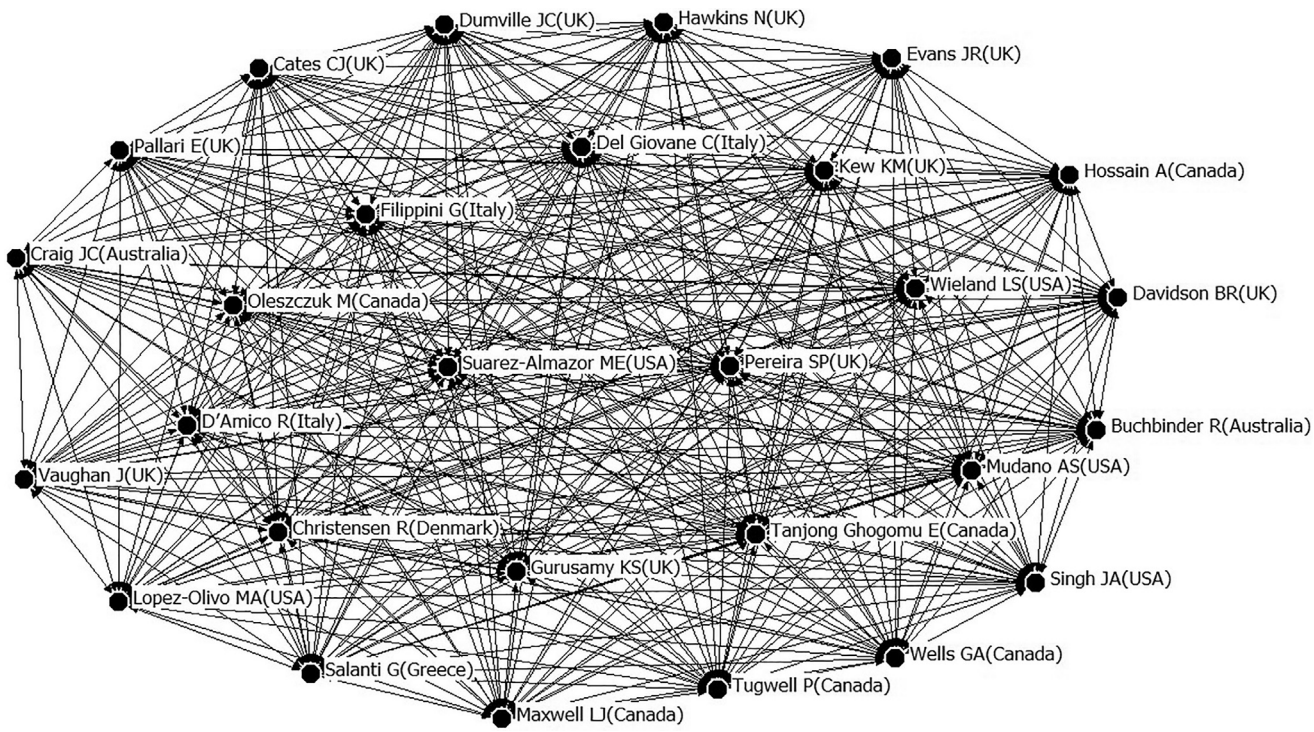

Fig. 5. Social network diagram of main authors of included NMAs. NMA, network meta-analyses.

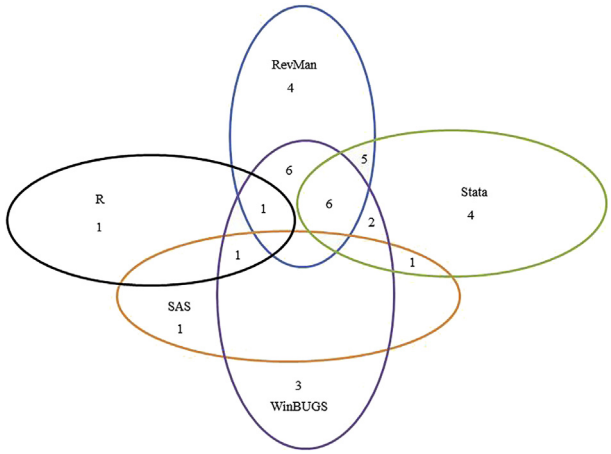

Fig. 6. Software used in included NMAs. NMA, network meta-analyses.

Controlled Trials (CENTRAL), 11 NMAs searched for WHO International Clinical Trials Registry and ClinicalTrials.gov separately, and the remaining databases were searched less than 10 times.

3.4. Results of methodological quality

Only three (7.1%) NMAs were of high quality, 11 (26.2%) were of moderate quality, 11 (26.2%) were of low quality, and 17 (40.5%) were of critical low quality (Appendix Table 1). The compliance rates of seven items were higher than 90.0%, they were "research questions and inclusion criteria for the review included the components of PICO," "used a comprehensive literature search strategy," "performed study selection in duplicate," "performed data extraction in duplicate," "described the included studies in adequate detail," "used a satisfactory technique for assessing the risk of bias in individual

Table 1. Characteristics of the included NMAs

Category	Characteristic	Frequency	Proportion (95% CI)
Number of authors	Mean (SD)	6.1 (3.0)	
Country of first author	Developed country	41	97.6 (87.4, 99.9)
	Developing country	1	2.4 (0.1, 12.6)
Statistician or epidemiologist	Yes	17	40.5 (25.6, 56.7)
Number of included studies	Median (range)	34 (4–206)	
Interventions	Median (range)	7 (3–21)	
Sample size	Median (range)	7,293 (177–101,804)	
Type of included study	RCT	37	88.1 (74.4, 96.0)
	Systematic review	3	7.1 (1.5, 19.5)
	RCT + CCT + OLE	1	2.4 (0.1, 12.6)
	RCT + observational study	1	2.4 (0.1, 12.6)
Funding sources	Industry	0	—
	Nonindustry	30	71.4 (55.4, 84.3)
	NIHR	20	66.7 (47.2, 82.7)
	AHRQ CERTs	2	6.7 (0.8, 22.1)
	NIAMS	2	6.7 (0.8, 22.1)
	NIA	2	6.7 (0.8, 22.1)
	NCI	2	6.7 (0.8, 22.1)
	Others	8	26.7 (12.3, 45.9)
	Nonfunding	12	28.6 (15.7, 44.6)
Was the GRADE used?	Yes	34	81.0 (65.9, 91.4)
GRADE used (n = 34)			
Classification of GRADE	4	34	100.0 (89.7, 100.0)
Number of downgrade factors	2	5	14.7 (5.0, 31.1)
	3	3	8.8 (1.9, 23.7)
	4	12	35.3 (19.7, 53.5)
	5	14	41.2 (24.6, 59.3)

Abbreviations: AHRQ CERTs, agency for health quality and research center for education and research on therapeutics, USA; CI, confidence interval; CCT, case–control trial; GRADE, grading of recommendations assessment, development and evaluation; NIA, national institute of aging, USA; NCI, national cancer institute, USA; NIAMS, national institute of arthritis, musculoskeletal and skin diseases, USA; NIHR, national institute for health research, UK; OLE, open-label extension studies; RCT, randomized controlled trial.

Table 2. Reporting information of literature search

Category	Characteristic	Frequency	Proportion (95% CI)
Reported database searched	Yes	42	100.0 (91.6, 100.0)
Language of database searched	English	41	97.6 (87.4, 99.9)
	English + Chinese	1	2.4 (0.1, 12.6)
Number of Chinese databases searched	0	41	97.6 (87.4, 99.9)
	2	1	2.4 (0.1, 12.6)
Number of English databases searched	1–2	4	9.50 (2.7, 22.6)
	3–4	16	38.1 (23.6, 54.4)
	5–6	15	35.7 (21.6, 52.2)
	7–12	7	16.7 (7.0, 31.4)
Reported search strategy	Yes	41	97.6 (87.4, 99.9)
Name of database	EMBASE	34	81.0 (65.9, 91.4)
	PubMed/MEDLINE	36	85.7 (71.5, 94.6)
	CENTRAL	31	73.8 (58.0, 86.1)
	ICTRP	11	26.2 (13.9, 42.0)
	ClinicalTrials.gov	11	26.2 (13.9, 42.0)
	CINAHL	7	16.7 (7.0, 31.4)
	LILACS	6	14.3 (5.4, 28.5)
	CDSR	6	14.3 (5.4, 28.5)
	Science Citation Index Expanded	5	11.9 (4.0, 25.6)
	metaRegister of Controlled Trials	4	9.5 (2.7, 22.6)

Abbreviations: CI, confidence interval; CDSR, cochrane database of systematic review; CENTRAL, cochrane central register of controlled trials; CINAHL, cumulative index to nursing and allied health literature; ICTRP, WHO international clinical trials registry platform; LILACS, latin American and caribbean health science information database.

studies," and "used appropriate methods for statistical combination of results." However, 88.1% of the included NMAs did not explain their selection of the study designs for inclusion in the review, and 59.5% of the NMAs did not carry out an adequate investigation of publication bias and discuss its likely impact on the results of the review. Some NMAs had not clarified the role of funders in research and the distribution of work between authors (Appendix Table 2). NMAs involving statistical or epidemiologic authors had higher compliance rates on items 5, 6, 9, 10, 13, 14, and 15 than those without statistical or epidemiologic authors, but there were no statistically significant differences between them. We observed the significant differences between nonindustry funding NMAs and nonfunding NMAs related to the "reported the sources of funding for the studies included in the review" (OR = 4.50, 95% CI: 1.01–20.11, P = 0.049). No significant difference was found between Bayesian NMAs and Frequentist NMAs (Appendix Table 2).

3.5. Results of reporting quality

The compliance rates of 16 items were >80.0%; among them, the compliance rates of items 2, 5, 6, 9, 13, 19, 22, and 24 were 100.0%. However, only 11.9% NMAs completely reported objectives in the Introduction section, and half of the studies could not be judged from the title as an NMA. Most NMAs did not clarify methods for assessing inconsistency and solutions to inconsistency in NMA, and some NMAs did not present the network plot (Appendix Table 3; Appendix Table 4). Compared with NMAs with statistical or epidemiologic authors, those without statistical or epidemiologic authors had lower compliance in reporting of titles (OR = 4.27, 95% CI: 1.13–16.05, P = 0.032). The compliance rates of items "data collection process" (OR = 6.43, 95% CI: 1.23–33.65, P = 0.028), "planned methods of analysis" (OR = 5.00, 95% CI: 1.13–22.05, P = 0.034), and "synthesis of results" (OR = 6.43, 95% CI: 1.23–33.65, P = 0.028) in the nonindustry funding NMAs were significantly higher than that of nonfunding NMAs. Bayesian NMAs often better reported the title, and the rest of the 31 items had no significant differences between Bayesian NMAs and Frequentist NMAs (Appendix Table 4).

3.6. Results of correlation analyses

The AMSTAR 2 and PRISMA-NMA complete compliance rates in recently published NMAs were slightly higher than previously published NMAs (Appendix Fig. 1). Weak but positive correlations were found for the AMSTAR 2 complete compliance rates (Spearman's ρ = 0.320, P = 0.002), PRISMA-NMA complete compliance rates (Spearman's ρ = 0.402, P = 0.008), and the publication year (Appendix Fig. 2, Appendix Fig. 3). There were no correlations between the AMSTAR 2 complete compliance rates

(Spearman's $\rho = -0.234$, $P = 0.136$), PRISMA-NMA complete compliance rates (Spearman's $\rho = -0.085$, $P = 0.593$), and the number of authors (Appendix Fig. 4, Appendix Fig. 5). Appendix Fig. 6 showed that there was no correlation between the AMSTAR 2 complete compliance rates and the number of included studies (Spearman's $\rho = 0.130$, $P = 0.412$). Appendix Fig. 7 presented a slight positive association between the PRISMA-NMA complete compliance rates and the number of included studies (Spearman's $\rho = 0.390$, $P = 0.011$). The analysis between the PRISMA-NMA complete compliance rates and the AMSTAR 2 complete compliance rates revealed a positive correlation (Spearman's $\rho = 0.630$, $P = 0.000$) as shown in Appendix Fig. 8.

3.7. Compared with other studies

3.7.1. Comparison of cancer NMAs and cochrane NMAs

About Cancer NMAs, 61 NMAs (59.8%) were conducted using a Bayesian framework (two reviews are Frequentist NMAs), and 43 reviews were Frequentist NMAs (two Frequentist NMAs use the Bayesian framework) [29]. As for Cochrane NMAs, 19 NMAs (59.8%) were conducted using a Bayesian framework (one review was Frequentist NMA), and 24 reviews were Frequentist NMAs (one Frequentist NMA use the Bayesian framework).

For NMAs using a Bayesian framework, more than 90.0% of studies did not report handling of multigroup trials, more than 85.0% of studies did not assess the similarity, and more than 84.0% of studies did not assess the publication bias. Compared with Cancer NMAs, Cochrane NMAs more often reported the model used, provided the model, reported the methods for assessing the model fit, assessed the heterogeneity in NMAs, assessed the inconsistency, and assessed the publication or reporting bias. Only 6.6% of Cancer NMAs used Tau^2 to assess heterogeneity in NMAs, but 42.1% of Cochrane NMAs used Tau^2 to assess heterogeneity. Cancer NMAs more often used the hypothesis test to assess inconsistency, whereas Cochrane NMAs more often used inconsistency/incoherence factors to assess inconsistency. Cochrane NMAs had a higher probability of performing subgroup or meta-regression analysis and using GRADE than Cancer NMAs. The details of the comparison of Cancer NMAs and Cochrane NMAs in Bayesian analysis were shown in Table 3.

For Frequentist NMAs, almost all NMAs conducted the traditional meta-analysis and reported summary measures, but more than 91.0% of NMAs did not report handling of multigroup trials, and more than 93.0% of NMAs did not assess the similarity. There were five items with statistically significant differences between Cancer NMAs and Cochrane NMAs. Eighty-five percent of Cochrane NMAs used random-effects or fixed- and random-effects model, no Cochrane NMAs used the Bucher model, but 82.1% of Cancer NMAs used the Bucher model. Cochrane NMAs had a higher probability of assessing the inconsistency, and more than 70.0% of Cochrane NMAs performed additional analyses, but the proportion of Cancer NMAs for additional analyses was less than 25.0%. The details of the comparison of Cancer NMAs and Cochrane NMAs in Frequentist analysis were presented in Table 4.

3.7.2. Comparison of drug intervention NMAs and cochrane NMAs

The study conducted by Tonin FS et al. [30] about the quality of NMAs of drug interventions showed that the compliance rates for items "scientific quality assessment and documentation," "scientific quality used in conclusions," and "assessment of publication bias" were less than 50.0%. Compared with Drug intervention NMAs, the Cochrane NMAs had the same low compliance rate for "assessment of publication bias" but had higher compliance rates for "scientific quality assessment and documentation" and "quality of science used in conclusions." Considering the reporting quality based on 32 PRISMA-NMA items, there were 20 items with statistically significant differences between Cochrane NMAs and Drug intervention NMAs. Cochrane NMAs had a higher compliance in reporting the structured summary (OR = 0.06, 95% CI: 0.00–0.91, $P = 0.043$), rationale (OR = 0.09, 95% CI: 0.01–0.69, $P = 0.020$), protocol and registration (OR = 0.00, 95% CI: 0.00–0.04, $P = 0.000$), search (OR = 0.06, 95% CI: 0.02–0.16, $P = 0.000$), geometry of the network (OR = 0.18, 95% CI: 0.08–0.40, $P = 0.000$), risk of bias across studies (OR = 0.11, 95% CI: 0.06–0.23, $P = 0.000$) in Methods section, additional analyses (OR = 0.32, 95% CI: 0.16–0.66, $P = 0.002$) in Methods section, summary of network geometry (OR = 0.27, 95% CI: 0.14–0.53, $P = 0.000$), risk of bias with studies (OR = 0.02, 95% CI: 0.00–0.29, $P = 0.005$), results of individual studies (OR = 0.42, 95% CI: 0.21–0.85, $P = 0.016$), exploration for inconsistency (OR = 0.39, 95% CI: 0.19–0.82, $P = 0.013$), risk of bias across studies (OR = 0.00, 95% CI: 0.00–0.05, $P = 0.000$) in Results section, and additional analyses (OR = 0.46, 95% CI: 0.24–0.89, $P = 0.020$) in Results section. However, Drug intervention NMAs could better report the title (OR = 10.09, 95% CI: 5.11–19.95, $P = 0.000$), objectives (OR = 23.84, 95% CI: 9.15–62.10, $P = 0.000$), data items (OR = 14.80, 95% CI: 7.34–29.84, $P = 0.000$), planned methods of analysis (OR = 2.10, 95% CI: 1.01–4.37, $P = 0.048$), synthesis of results (OR = 3.07, 95% CI: 1.32–7.14, $P = 0.009$), limitations (OR = 4.82, 95% CI: 2.43–9.56, $P = 0.000$), and funding (OR = 4.80, 95% CI: 2.49–9.28, $P = 0.000$), The details of the comparison of Drug intervention NMAs and Cochrane NMAs in PRISMA-NMA items were presented in Table 5.

Table 3. Comparison of Cancer NMAs and Cochrane NMAs in Bayesian analysis, *n*/*N* (%)

Items	Cancer NMAs ($n = 61$)	Cochrane NMAs ($n = 19$)	OR (95% CI)	*P* value
Was the traditional meta-analysis conducted? (Yes)	42/61 (68.9)	15/19 (79.0)	0.59 (0.17,2.01)	0.399
Were summary measures reported? (Yes)	57/61 (93.4)	19/19 (100.0)	0.33 (0.02, 6.36)	0.461
Planned methods of analysis				
What was the model used?				
Fixed effects	7/46 (15.2)	1/19 (5.3)	3.23 (0.37, 28.25)	0.289
Random effects	11/46 (23.9)	7/19 (36.8)	0.54 (0.17, 1.71)	0.293
Fixed and random effects	18/46 (39.1)	9/19 (47.4)	0.71 (0.34, 2.10)	0.541
Other models	10/46 (21.7)	2/19 (10.5)	2.36 (0.47, 11.98)	0.300
Not reported	15/61 (24.6)	0/19 (0)	13.00 (0.74, 228.22)	0.001
How to present the model code?				
Supplement	5/21 (23.8)	1/15 (6.7)	4.38 (0.45, 42.08)	0.201
Reference	16/21 (76.2)	14/15 (93.3)	0.23 (0.02, 2.20)	0.201
Not provided	40/61 (65.6)	4/19 (21.1)	7.14 (2.10, 24.26)	0.002
How to assess the model fit?				
Residual deviance	2/24 (8.3)	0/14 (0)	3.22 (0.14, 72.05)	0.460
Deviance information criterion	15/24 (62.5)	10/14 (71.4)	0.67 (0.16, 2.77)	0.577
Residual deviance + deviance information criterion	7/24 (29.2)	4/14 (28.6)	1.03 (0.24, 4.41)	0.969
Not reported	37/61 (60.7)	5/19 (26.3)	4.32 (1.38, 13.54)	0.012
Was handling of multigroup trials reported? (Yes)	5/61 (8.2)	0/19 (0)	3.80 (0.20, 71.85)	0.374
Were the prior distributions reported?				
Noninformative prior	18/31 (58.1)	7/13 (53.9)	1.19 (0.32, 4.37)	0.797
Informative prior	3/31 (9.7)	4/13 (30.8)	0.24 (0.05, 1.29)	0.096
Vague prior	10/31 (32.3)	8/13 (61.5)	0.30 (0.08, 1.15)	0.078
Not specified	30/61 (49.2)	6/19 (31.6)	2.10 (0.71, 6.24)	0.183
Sensitivity analysis based on priors	4/61 (6.6)	0/19 (0)	3.05 (0.16, 59.29)	0.461
Was the convergence assessed?				
Not reported	37/61 (60.7)	12/19 (63.2)	0.90 (0.31, 2.61)	0.053
Gelman Rubin statistic	21/24 (87.5)	7/7 (100.0)	0.41 (0.02, 8.89)	0.570
Visual plot inspection	13/24 (54.2)	3/7 (42.9)	1.58 (0.29, 8.61)	0.600
Observation of chain mix	2/24 (8.3)	0/7 (0)	1.67 (0.07, 38.77)	0.750
Was the heterogeneity in NMA assessed?				
Precision (Tau^2)	4/61 (6.6)	8/19 (42.1)	0.10 (0.02, 0.38)	0.001
Not reported	57/61 (93.4)	11/19 (57.9)	10.36 (2.65, 40.49)	0.001
Was the similarity in NMA assessed?				
Not reported	53/61 (86.9)	17/19 (89.5)	0.78 (0.15, 4.03)	0.776
Comparing patients' or trials' characteristics	5/8 (62.5)	2/2 (100.0)	0.31 (0.01, 8.68)	0.494
Investigating potential effect modifying covariates	3/8 (37.5)	0/2 (0)	3.18 (0.12, 87.92)	0.494
Was the publication or reporting bias assessed?				
Comparison-adjusted funnel plot	1/61 (1.6)	3/19 (15.8)	0.09 (0.01, 0.91)	0.042
Not reported	60/61 (98.4)	16/19 (84.2)	11.25 (1.10, 115.56)	0.042
Additional analyses				
Was a sensitivity analysis performed? (Yes)	24/61 (39.3)	12/19 (63.2)	0.38 (0.13, 1.10)	0.074
Was subgroup analysis or meta-regression performed? (Yes)	12/61 (19.7)	17/19 (89.5)	0.03 (0.01, 0.14)	0.000
Was the GRADE used? (Yes)	3/61 (4.9)	15/19 (79.0)	0.01 (0.00, 0.07)	0.000

Abbreviations: CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; NMA, network meta-analysis; OR, odds ratio.

Table 4. Comparison of Cancer NMAs and Cochrane NMAs in Frequentist analysis, *n*/*N* (%)

Items	Cancer NMAs (n = 43)	Cochrane NMAs (n = 24)	OR (95% CI)	*P* value
Was traditional meta-analysis conducted? (Yes)	42/43 (97.7)	22/24 (91.7)	3.82 (0.33, 44.48)	0.285
Were summary measures reported? (Yes)	41/43 (97.6)	24/24 (100.0)	0.34 (0.02, 7.35)	0.491
Planned methods of analysis in adjusted indirect comparisons				
What was the method used?				
Bucher	23/28 (82.1)	0/20 (0)	175.18 (9.12, 3,363.90)	0.001
Fixed effects	1/28 (3.6)	3/20 (15.0)	0.21 (0.02, 2.19)	0.192
Random effects	2/28 (7.2)	9/20 (45.0)	0.09 (0.02, 0.51)	0.006
Fixed and random effects	1/28 (3.6)	8/20 (40.0)	0.06 (0.01, 0.50)	0.010
Other methods	1/28 (3.6)	0/20 (0)	2.24 (0.09, 57.75)	0.628
Not reported	15/43 (34.9)	4/24 (16.7)	2.68 (0.77, 9.29)	0.120
Was the method presented or source cited?				
Manuscript	5/23 (21.7)	0/8 (0)	5.05 (0.25, 102.21)	0.291
Reference	18/23 (78.3)	8/8 (100.0)	0.20 (0.01, 4.00)	0.291
Not provided	20/43 (46.5)	16/24 (66.7)	0.43 (0.15, 1.23)	0.116
Was handling of multigroup trials reported? (Yes)	2/43 (4.7)	2/24 (8.3)	0.54 (0.07, 4.07)	0.547
Was the similarity assessed?	3/43 (7.0)	1/24 (4.2)	1.73 (0.17, 17.56)	0.645
Additional analyses				
Was a sensitivity analysis performed?	5/43 (11.6)	17/24 (70.8)	0.05 (0.02, 0.20)	0.000
Was subgroup analysis or meta-regression performed?	9/43 (20.9)	22/24 (91.7)	0.02 (0.00, 0.12)	0.000

Abbreviations: CI, confidence interval; NMA, network meta-analysis.

4. Discussion

4.1. Summary of main results of cochrane NMAs

Forty-two NMAs investigated 29 research topics, and rheumatoid arthritis was the most common. In recent years, the number of NMAs published in the Cochrane library has gradually increased. In addition, 97.6% of NMAs were completed by developed countries, 81.0% of the studies were completed by three to eight authors, and the main authors involved in the studies formed a collaborative network centered on Pereira SP from the United Kindom and Suarez-Almazor ME from the United States. The downgrade factors of GRADE mainly depended on five domains: risk of bias, inconsistency, imprecision, indirectness, and publication bias. The overall quality of evidence could be assessed as high, moderate, low, or very low [20,33,34]. All of the included NMAs, which reported GRADE divided the quality of evidence into four levels. However, most studies did not fully consider all five downgrade factors. Therefore, the standardization of using GRADE needs to be further improved.

The validity of the results of a systematic review is highly dependent on the results of the underlying data, and therefore a series of unbiased and complete related studies need to be identified as much as possible [35]. NMAs aimed to rank the benefits (or harms) of interventions, based on all available randomized controlled trials (RCTs). Thus, the identification of all relevant data is critical [29,36]. Fortunately, 97.6% of the NMAs reported search strategies, 90.5% of the NMAs retrieved more than two databases. PubMed/MEDLINE was the most frequently searched database and often combined with EMBASE and CENTRAL. But a study suggested that CENTRAL may be the best single source of controlled trials and should be the first source searched by those carrying out systematic reviews of healthcare intentions [37]. All studies retrieved English databases, but only one study retrieved the Chinese database [38]. Restricting searches may lead to important biases in the retrieved trials, as some studies were not published in English and therefore cannot be identified [35]. The Cochrane Collaboration suggested searching regional databases when relevant, citing Chinese biomedical database as an example of a Chinese database [34,39]. Thus, further studies should search for databases in different languages as much as possible to avoid language bias.

For methodological quality, 66.7% NMAs were rated as low or critical low quality, although the compliance rates of seven items were greater than 90.0%. Most NMAs did not explain the reason for the selection of study designs of the included studies, and some NMAs did not provide a satisfactory explanation for the heterogeneity observed in the results. About 60.0% of NMAs did not carry out an

Table 5. Comparison of Cochrane NMAs and Drug intervention NMAs in PRISMA-NMA items, *n*/*N* (%)

Items		Drug intervention NMAs ($n = 477$)	Cochrane NMAs ($n = 42$)	OR (95% CI)	*P*-value
Title	1. Title	434 (91.0)	21 (50.0)	10.09 (5.11, 19.95)	0.000
Abstract	2. Structured summary	394 (82.6)	42 (100.0)	0.06 (0.00, 0.91)	0.043
Introduction	3. Rationale	379 (79.5)	41 (97.6)	0.09 (0.01, 0.69)	0.020
	4. Objectives	364 (76.3)	5 (11.9)	23.84 (9.15, 62.10)	0.000
Methods	5. Protocol and registration	85 (17.8)	42 (100.0)	0.00 (0.00, 0.04)	0.000
	6. Eligibility criteria	422 (88.5)	42 (100.0)	0.09 (0.01, 1.48)	0.091
	7. Information sources	449 (94.1)	40 (95.2)	0.80 (0.18, 3.49)	0.768
	8. Search	164 (34.4)	38 (90.5)	0.06 (0.02, 0.16)	0.000
	9. Study selection	433 (90.8)	42 (100.0)	0.12 (0.01, 1.89)	0.130
	10. Data collection process	432 (90.6)	34 (81.0)	2.26 (0.99, 5.18)	0.054
	11. Data items	444 (93.1)	20 (47.6)	14.80 (7.34, 29.84)	0.000
	S1. Geometry of the network	29 (6.1)	11 (26.2)	0.18 (0.08, 0.40)	0.000
	12. Risk of bias in individual studies	316 (66.3)	24 (57.1)	1.47 (0.78, 2.79)	0.236
	13. Summary measures	446 (93.5)	42 (100.0)	0.17 (0.01, 2.77)	0.212
	14. Planned methods of analysis	408 (85.5)	31 (73.8)	2.10 (1.01, 4.37)	0.048
	S2. Assessment of inconsistency	156 (32.7)	14 (33.3)	0.97 (0.50, 1.90)	0.934
	15. Risk of bias across studies	116 (24.3)	31 (73.8)	0.11 (0.06, 0.23)	0.000
	16. Additional analyses	227 (47.6)	31 (73.8)	0.32 (0.16, 0.66)	0.002
Results	17. Study selection	440 (92.2)	41 (97.6)	0.29 (0.04, 2.17)	0.228
	S3. Presentation of network structure	231 (48.4)	27 (64.3)	0.52 (0.27, 1.01)	0.052
	S4. Summary of network geometry	157 (32.9)	27 (64.3)	0.27 (0.14, 0.53)	0.000
	18. Study characteristics	452 (94.8)	39 (92.9)	1.39 (0.40, 4.81)	0.603
	19. Risk of bias with studies	286 (60.0)	42 (100.0)	0.02 (0.00, 0.29)	0.005
	20. Results of individual studies	258 (54.1)	31 (73.8)	0.42 (0.21, 0.85)	0.016
	21. Synthesis of results	443 (92.9)	34 (81.0)	3.07 (1.32, 7.14)	0.009
	S5. Exploration for inconsistency	58 (12.2)	11 (26.2)	0.39 (0.19, 0.82)	0.013
	22. Risk of bias across studies	99 (20.8)	42 (100.0)	0.00 (0.00, 0.05)	0.000
	23. Additional analyses	216 (45.3)	27 (64.3)	0.46 (0.24,0.89)	0.020
Discussion	24. Summary of evidence	465 (97.5)	42 (100.0)	0.44 (0.03,7.53)	0.570
	25. Limitations	423 (88.7)	26 (61.9)	4.82 (2.43, 9.56)	0.000
	26. Conclusions	456 (95.6)	41 (97.6)	0.53 (0.07, 4.04)	0.540
Funding	27. Funding	407 (85.3)	23 (54.8)	4.80 (2.49,9.28)	0.000

Abbreviations: CI, confidence interval; NMA, network meta-analysis.

adequate investigation of publication bias and discuss its likely impact on the results. Although, there was a weak positive correlation between AMSTAR 2 complete compliance rates and the publication year, which suggests that the methodological quality of NMAs is improving. Even there were no significant differences between NMAs with statistical or epidemiologic authors and NMAs without statistical or epidemiologic authors, further improvement is also required. For example, 59.5% of the studies did not assess the likelihood of publication bias. The present study found that nonindustry funding NMAs had better methodological quality in terms of reporting the sources of funding for the studies included in the review. For methodological quality based on the AMSTAR 2 checklist, there was no statistical difference between Bayesian NMAs and Frequentist NMAs.

For reporting quality, eight items in the PRISMA-NMA were fully reported. However, only five NMAs completely reported objectives in the Introduction section, and because we considered study design as an important factor, most studies only reported participants, interventions, comparisons, and outcomes. More than 70.0% of NMAs did not report the geometry of the network. But an important element in understanding a network meta-analysis is the network geometry, knowing precisely the shape of the network is a preliminary step for researchers and readers to assess the available evidence base [10,12,40]. Authors of network meta-analyses should clearly describe methods

used to explore the geometry of the treatment network under study and potential biases related to it [1]. The evaluation of evidence inconsistency is an important aspect in network meta-analyses [41]. The NMAs should describe the statistical methods used to evaluate the agreement of direct and indirect evidence and results from investigations of inconsistency [1]. However, most of the included NMAs did not explore inconsistency both in the Methods and Results sections. The positive correlation was found between the PRISMA-NMA complete compliance rates and the publication year, which means that the reporting quality of NMAs published in the Cochrane library has gradually improved in recent years. The PRISMA-NMA complete compliance rates were positively correlated with the AMSTAR 2 complete compliance rates, indicating that NMAs with higher methodological quality generally have higher reporting quality. NMAs with statistical or epidemiologic authors had higher compliance in reporting of titles. Compared with nonfunding NMAs, nonindustry funding NMAs had relatively better reporting quality in reporting the data collection process, planned methods of analysis, and synthesis of results. Frequentist NMAs had lower compliance in reporting the titles.

4.2. Compared with other studies

For methodological quality, Cochrane NMAs were superior to Cancer NMAs and Drug intervention NMAs, especially in the aspects of considering the status of publication, assessing and documenting the scientific quality, and formulating conclusions appropriately. However, clarifying the method of assessing publication bias, appropriately combining the findings of studies, and clearly stating conflicts of interest were common aspects of NMA needs to be improved in different fields. As far as we know, all Cochrane NMAs have been registered, but most of the Cancer NMAs and Drug intervention NMAs did not report protocol details and registration. For reporting quality, the compliance rates of Cochrane NMAs were also better than Cancer NMAs and Drug intervention NMAs. However, there were also many common defects in these NMAs, such as ‘‘handle the multigroup trials,’’ ‘‘assess the similarity,’’ ‘‘described and presented the geometry of the network,’’ and ‘‘explore the inconsistency.’’ To our knowledge, two meta-epidemiologic studies published in 2017 evaluated the characteristics of NMAs from different perspectives [21,22]. These two studies are based on the same 456 NMAs published between 1999 and 2015. The study of Petropoulou M et al. mainly focused on statistical methodology and presentation of results. Zarin W et al.’s study mainly related to knowledge synthesis methods, analytical process, and methodological quality of NMAs (Appendix 5). These two empirical studies indicated that only 56.0% NMAs explored heterogeneity, 53.0% NMAs assessed inconsistency, and only 36.0% NMAs assessed publication bias [21,22]. But in our study, only about 45.0% NMAs provided a satisfactory explanation for heterogeneity, 33.0% NMAs assessed inconsistency, and 41.0% NMAs carried out an adequate investigation of publication bias. The compliance rates of these items were lower than that in previous studies. Differences in the sources and published years of the included studies may lead to this difference. Furthermore, we evaluated these characteristics through the AMSTAR 2 and PRISMA-NMA tools and set very strict standards, which may reduce the complete compliance rates of the items. However, both previous studies and our study have shown that less than 60.0% of NMAs perform these analyses. These are the key factors in implementing NMA. Further studies should pay more attention to these aspects and make improvements to improve the quality of NMA. Another important finding of our research is that only about 26.0% of NMAs reported the geometry of the network, and 64.0% presented the network structure, which also requires more attention from scholars.

4.3. Strengths and limitations

This study aimed to investigate the general characteristics and assess the methodological quality using AMSTAR 2 and reporting quality using PRISMA-NMA of NMAs only published in the Cochrane library. In addition to conducting stratified analysis to explore factors that may affect methodological and reporting quality, we also conducted correlation analysis. Furthermore, we compared the methodological and reporting quality of NMAs published in the Cochrane library and NMAs in the field of cancer and drug interventions. There are also several limitations to our study. First, we only retrieved a database of the Cochrane library and did not include NMAs published in other databases. But we want to explore the general characteristics, methodological quality, and reporting quality of NMAs published in the Cochrane library. The data of other NMAs will not affect our results. However, further studies are still required to explore the quality of NMAs published in other databases or in other fields. Second, the number of NMAs included was small, but we included all the NMAs published in the Cochrane library, which is sufficient to reflect the characteristics of NMAs in the current Cochrane library. In addition, we only included NMAs published in English, but it did not affect the number of studies we included.

5. Conclusions

The overall quality of NMAs published in the Cochrane library has improved over time. But the methodological and reporting quality still need to be further improved, especially referring to the assessment of the likelihood of publication bias, the geometry of the network, presentation of network structure, and assessment and exploration of inconsistency. Identified deficiencies in methodological and reporting quality should be given more attention in the future work.

CRediT authorship contribution statement

Ya Gao: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Visualization, Writing - original draft, Writing - review & editing. **Long Ge:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Visualization, Writing - review & editing. **Xueni Ma:** Data curation, Investigation, Resources, Visualization. **Xiping Shen:** Formal analysis, Methodology, Resources, Software, Validation. **Meng Liu:** Investigation, Resources, Validation, Visualization. **Jinhui Tian:** Conceptualization, Formal analysis, Methodology, Project administration, Resources, Software, Supervision, Validation, Writing - original draft, Writing - review & editing.

Supplementary data

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