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Quantifying and presenting overall evidence in network meta-analysis

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Summary

Network meta-analysis (NMA) has become an increasingly-used tool to compare multiple treatments simultaneously by synthesizing direct and indirect evidence in clinical research. However, many existing studies did not properly report the evidence of treatment comparisons and show the comparison structure to audience. Also, nearly all treatment networks presented only direct evidence, not overall evidence that can reflect the benefit of performing NMAs. This article classifies treatment networks into three types under different assumptions; they include networks with each treatment comparison's edge width proportional to the corresponding number of studies, sample size, and precision. Also, three new measures (i.e., the effective number of studies, the effective sample size, and the effective precision) are proposed to preliminarily quantify overall evidence gained in NMAs. They permit audience to intuitively evaluate the benefit of performing NMAs, compared with pairwise meta-analyses based on only direct evidence. We use four case studies, including one illustrative example, to demonstrate their derivations and interpretations. Treatment networks may look fairly differently when different measures are used to present the evidence. The proposed measures provide clear information about overall evidence of all treatment comparisons, and they also imply the additional number of studies, sample size, and precision obtained from indirect evidence. Some comparisons may benefit little from NMAs. Researchers are encouraged to present overall evidence of all treatment comparisons, so that audience can preliminarily evaluate the quality of NMAs.

Keywords

direct and indirect evidence; effective number of studies; effective sample size; effective precision; network meta-analysis

1 | INTRODUCTION

Systematic reviews and meta-analyses have become commonly-used statistical tools in the recent decades for synthesizing evidence of comparisons between treatments in clinical research and many other scientific areas.¹ As new treatments are being continuously

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Conflict of interest

The author declares no potential conflict of interests.

developed for various diseases, network meta-analysis (NMA), also known as mixed-treatment comparison or multiple-treatment meta-analysis, is increasingly popular in this era of data sharing.² As an extension of traditional pairwise meta-analyses, an NMA compares multiple treatments at one time and synthesizes both direct and indirect evidence for the comparisons. Due to its appealing features, researchers can obtain more precise treatment effect estimates, compare treatments that lack direct evidence, and rank all available treatments for better decision making.^{3,4,5,6}

So far, much attention has been given to modeling NMAs. Various methods have been proposed for NMAs from different statistical perspectives, such as Bayesian hierarchical models,^{4,5,7} frequentist methods,^{8,9} graph theory,¹⁰ etc. Extensive research has also focused on checking critical assumptions (e.g., transitivity, consistency, and heterogeneity) and conducting diagnostics in NMAs.^{11,12,13,14,15,16} However, less attention was paid to reporting NMAs, and the results were usually reported fairly differently.¹⁷

We may distinguish the reporting of an NMA into two classes. One is the pre-analysis reporting before applying rigorous statistical models to perform the NMA. This includes presenting characteristics of the collected studies and treatments and showing the structure of treatment comparisons. Such pre-analysis evidence allows audience to preliminarily evaluate the NMA's quality. Currently, comparisons are usually presented using a treatment network, also known as an evidence network, in which each node represents a treatment and each edge shows a comparison between the corresponding treatments.^{6,18} For example, if all treatments are compared with only a common comparator, they form a star-shaped network, which may not be connected well and contain few sources of evidence. If all treatments are mutually compared, their network is often referred to as a fully-connected network, which contains many sources of direct and indirect evidence for treatment comparisons. Reporting the network is simple, straightforward, and intuitive. However, according to the survey by Bafeta et al.,¹⁷ among 121 NMAs, 83% did not report treatment networks. Another class is the post-analysis reporting, which presents the results derived from direct evidence, indirect evidence, and the synthesis by an NMA and provides information about treatment ranking.^{9,19,20,21,22} In the same survey by Bafeta et al.,¹⁷ however, many NMAs still did not report these post-analysis results that were important for decision making. Recently, the PRISMA-NMA statement²³ appeared in the literature; hopefully it will provide a better guideline for properly conducting and reporting future NMAs.

This article focuses on the pre-analysis reporting of NMAs. Although treatment networks seem simple, they are usually reported inconsistently. For example, in the PRISMA-NMA statement²³, the width of a network edge was proportional to the number of studies that directly compared the corresponding treatments. However, in an NMA of non-acute coronary artery disease,²⁴ the edge width was proportional to the cumulative number of patients for each comparison. Both types of networks have certain advantages and flexibility. Since the number of studies for each comparison is always available in an NMA, we can present the former type of networks in all cases. Some papers may not report the total number of patients, so the latter network may be infeasible in this situation. Nevertheless, because in practice the collected studies differ in their sizes and thus contribute different strength of evidence, and the latter network provides more accurate evidence than the former

one. In fact, when we use the treatment network with each edge proportional to the number of studies, the presented evidence is based on the condition that each study contributes equal evidence. Using the network with each edge proportional to the cumulative number of patients, the evidence is based on the condition that each patient in all studies contributes equal evidence. Although both conditions may be unrealistic, these treatment networks are essential and critical for researchers preliminarily understanding the structures of treatment comparisons in NMAs.

Nearly all current treatment networks present direct evidence. However, preliminarily assessing overall evidence obtained in an NMA is equivalently important, because it gives us some insight about how much the NMA improves treatment effect estimates compared with the much simpler pairwise meta-analyses. Motivated by the foregoing networks of direct evidence, this article proposes the effective number of studies, the effective sample size, and the effective precision to quantify the overall evidence in NMAs at the pre-analysis stage.

2 | METHODS

2.1 | The effective number of studies: an example

Consider an NMA with N studies; each study compares a subset of K treatments. Let N_{hk} be the number of studies that directly compare treatment k vs. h for $1 \leq h < k \leq K$, so $N_{hk} = N_{kh}$ and $N = \sum_{h < k} N_{hk}$.

We take the NMA of non-acute coronary artery disease by Trikalinos et al.²⁴ as an illustrative example. It has a binary outcome (death) and compares $K = 4$ treatments: medical therapy, percutaneous transluminal balloon coronary angioplasty, bare-metal stents, and drug-eluting stents. Originally, 61 trials have been collected. Among them, one trial compares percutaneous trans-luminal balloon coronary angioplasty vs. medical therapy in stratified patients with single- and double-vessel coronary artery disease, and another trial compares slow- and moderate-release paclitaxel-eluting stents vs. bare-metal stents. Trikalinos et al.²⁴ treated each of these two trials as two data entries in the NMA, and this article follows their analysis. Therefore, the NMA effectively contains $N = 63$ unique studies; $N_{12} = 7$, $N_{13} = 4$, $N_{23} = 34$, and $N_{34} = 18$. Its treatment network is in Figure 1(a); the edge width is proportional to the corresponding N_{hk} . Treatments 1, 2, and 3 form an evidence cycle, but 4 vs. 3 is not in any cycle.

In this convenient example, each of the 63 studies compares two treatment arms. However, an NMA may contain a few multi-arm studies. To derive the effective number of studies, we treat the treatment comparisons in a multi-arm study as separate comparisons from different studies, so the effective number of studies may be overestimated (see more details in Section 4). For example, if a study compares treatments 1, 2, and 3, then it is decomposed as three studies of 2 vs. 1, 3 vs. 2, and 3 vs. 1. In addition, we tentatively assume that all studies contribute the same strength of evidence to the NMA and their estimated effect sizes (e.g., the log odds ratio for binary outcomes) share a common within-study variance σ^2 . This assumption was also used to derive the popular I^2 statistic for assessing between-study heterogeneity.²⁵

First, we focus on the overall evidence of 2 vs. 1. Let $y_{12,0}$ be the relative effect estimate using the direct evidence. Since N_{12} studies directly compare 2 vs. 1, the variance of $y_{12,0}$ is $v_{12,0} = \sigma^2 N_{12}^{-1}$ under the fixed-effects setting. The NMA incorporates the indirect evidence from comparisons 3 vs. 1 and 2 vs. 3 in the overall evidence of 2 vs. 1, and we denote the relative effect estimate using such indirect evidence as $y_{12,1} = y_{13,0} + y_{32,0}$. Here, $y_{13,0}$ and $y_{32,0}$ are the relative effect estimates using the direct evidence of 3 vs. 1 and 2 vs. 3, respectively, so the variance of $y_{12,1}$ is $v_{12,1} = \sigma^2 (N_{13}^{-1} + N_{23}^{-1})$. Using the traditional inverse-variance method, the overall relative effect of 2 vs. 1 is estimated as

$$y_{12} = (v_{12,0}^{-1} y_{12,0} + v_{12,1}^{-1} y_{12,1}) / (v_{12,0}^{-1} + v_{12,1}^{-1}),$$

and its variance is

$$v_{12} = (v_{12,0}^{-1} + v_{12,1}^{-1})^{-1} = \sigma^2 [N_{12} + (N_{13}^{-1} + N_{23}^{-1})^{-1}]^{-1}.$$

The effective number of studies for the overall evidence of 2 vs. 1, denoted as E_{12} , is defined as the quantity that satisfies $v_{12} = \sigma^2 E_{12}^{-1}$. Therefore,

$$E_{12} = N_{12} + (N_{13}^{-1} + N_{23}^{-1})^{-1} = 10.6; \quad (1)$$

that is, approximately 10.6 studies effectively contribute to the overall evidence of 2 vs. 1. Similarly, the effective numbers of studies for 3 vs. 1 and 3 vs. 2 are $E_{13} = 9.8$ and $E_{23} = 36.5$.

Equation (1) indicates that the indirect evidence effectively contributes additional $(N_{13}^{-1} + N_{23}^{-1})^{-1} = 3.6$ studies to the overall effect estimate for 2 vs. 1. The indirect evidence depends on each part (3 vs. 1 and 2 vs. 3) that consists of it. Because $(N_{13}^{-1} + N_{23}^{-1})^{-1}$ does not exceed the minimum of N_{13} and N_{23} , so any part with weak evidence will contaminate the whole indirect evidence. In an extreme case, if $N_{13} = 0$, then $(N_{13}^{-1} + N_{23}^{-1})^{-1} = 0$.

Second, consider the comparison 4 vs. 3. Because the overall relative effect y_{34} is informed only by the direct evidence $y_{34,0}$ with variance $\sigma^2 N_{34}^{-1}$, its effective number of studies is $E_{34} = N_{34} = 18$.

Finally, for the comparison of 4 vs. 1, its overall relative effect y_{14} is informed only by the indirect evidence, but such evidence has two sources: a) 4 vs. 3 plus 3 vs. 1; and b) 4 vs. 3 plus 3 vs. 2 plus 2 vs. 1. Equivalently, we may view the overall relative effect as a combination of the direct evidence of 4 vs. 3 and the overall evidence of 3 vs. 1; that is, $y_{14} = y_{13} + y_{34,0}$. Its variance is $v_{14} = \sigma^2 (E_{13}^{-1} + N_{34}^{-1})$, so the effective number of studies for 4 vs.

1 is $E_{14} = (E_{13}^{-1} + N_{34}^{-1})^{-1} = 6.3$. Similarly, the effective number of studies for 4 vs. 2 is $E_{24} = (E_{23}^{-1} + N_{34}^{-1})^{-1} = 12.1$. Figure 1(d) presents the network based on the E_{hk} 's.

2.2 | Generalizing the effective number of studies

The above calculation is simple and straightforward for networks with a few treatments and evidence cycles; however, it becomes much more complicated when more cycles appear. This section explores the general formula of the effective number of studies. Again, E_{hk} is the quantity that satisfies $v_{hk} = \sigma^2 E_{hk}^{-1}$, where v_{hk} is the variance of the overall relative effect estimate of k vs. h . Clearly, $E_{hk} = E_{kh}$. Let θ_{hk} be the true relative effect of k vs. h . If the two treatments are directly compared, let $y_{hk,0}$ be the relative effect estimate using the direct evidence, whose population mean is θ_{hk} . Also, suppose that there are M sources of the indirect evidence for k vs. h . In the illustrative example, $M=0$ for 4 vs. 3, $M=1$ for 2 vs. 1, 3 vs. 1, and 3 vs. 2, and $M=2$ for 4 vs. 1 and 4 vs. 2. If $M>0$, denote $y_{hk,m}$ as the relative effect estimate using the m th source ($0 < m \leq M$) of the indirect evidence. Each source is a combination of the direct evidence of certain different comparisons; that is, there is a path via treatment nodes $\ell_1, \ell_2, \dots, \ell_q$ that link treatments h and k in the network, so $y_{hk,m} = y_{h\ell_1,0} + y_{\ell_1\ell_2,0} + \dots + y_{\ell_{q-1}\ell_q,0} + y_{\ell_q k,0}$. Under the assumption of consistency between direct and indirect evidence, the relative effect estimate using each source of the indirect evidence has the same population mean θ_{hk} . Consequently, we consider a fixed-effect model:

$$\mathbf{y} = (y_{hk,0}, y_{hk,1}, \dots, y_{hk,M})^T \sim N(\theta_{hk} \mathbf{1}, \mathbf{V}_{hk}),$$

where $\mathbf{1}$ is an $(M+1)$ -dimensional vector with all elements being one, and $\mathbf{V}_{hk} = (v_{hk,rs})$ is the variance-covariance matrix of the relative effect estimates using different sources of evidence for k vs. h . The maximum likelihood method yields an overall relative effect estimate

$$\hat{\theta}_{hk} = (\mathbf{1}^T \mathbf{V}_{hk}^{-1} \mathbf{1})^{-1} (\mathbf{1}^T \mathbf{V}_{hk}^{-1} \mathbf{y})$$

with variance

$$v_{hk} = (\mathbf{1}^T \mathbf{V}_{hk}^{-1} \mathbf{1})^{-1}.$$

Under the tentative assumption that all studies have the equal variance σ^2 , the variance of the relative effect estimate using the direct evidence is $v_{hk,0} = \sigma^2 N_{hk}^{-1}$, and the variance of that using the m th source of the indirect evidence is

$$v_{hk,m} = \sigma^2 \left(N_{h\ell_1}^{-1} + N_{\ell_1\ell_2}^{-1} + \dots + N_{\ell_{q-1}\ell_q}^{-1} + N_{\ell_q k}^{-1} \right).$$

If both direct and indirect evidence is available, the correlation between their relative effect estimates is zero; that is, the first row

and column of $\mathbf{V}_{hk}$ are all zero except the first diagonal element $v_{hk,0}$. If the relative effect estimates $y_{hk,r}$ and $y_{hk,s}$ ($0 < r, s \leq M$) using different sources of the indirect evidence share some common treatment comparisons, say ℓ_j vs. ℓ_i , then their covariance is

$$v_{hk,rs} = \sigma^2 \sum_{(i,j)} N_{\ell_i \ell_j}^{-1}.$$

Consequently, the variance-covariance matrix can be written as $\mathbf{V}_{hk} = \sigma^2 \mathbf{S}_{hk}$, where the matrix $\mathbf{S}_{hk}$ depends only on the N_{hk} 's. Because the variance of the overall relative effect estimate is $v_{hk} = \sigma^2 E_{hk}^{-1} = \sigma^2 (\mathbf{1}^T \mathbf{S}_{hk}^{-1} \mathbf{1})^{-1}$, the effective number of studies for the overall evidence of k vs. h is calculated as

$$E_{hk} = \mathbf{1}^T \mathbf{S}_{hk}^{-1} \mathbf{1}.$$

When a comparison is informed by many sources of evidence, some sources may be linear combinations of others; therefore, the matrix $\mathbf{S}_{hk}$ may be positive semidefinite and thus $\mathbf{y}$ may follow a degenerate multivariate normal distribution.²⁶ Using eigen-decomposition of $\mathbf{S}_{hk}$, we can project $\mathbf{y}$ to a lower dimension that retains all evidence and calculate the effective number of studies as $E_{hk} = \mathbf{1}^T \mathbf{Q}_{hk}^+ (\mathbf{\Lambda}_{hk}^+)^{-1} (\mathbf{Q}_{hk}^+)^T \mathbf{1}$, where $\mathbf{\Lambda}_{hk}^+$ is the diagonal matrix of all positive eigenvalues of $\mathbf{S}_{hk}$ and their corresponding eigenvectors form the columns of $\mathbf{Q}_{hk}^+$.

We revisit the illustrative example to demonstrate the general formula of E_{hk} . Consider the comparison 2 vs. 1; it is informed by the direct evidence, providing the relative effect estimate $y_{12,0}$, and one source of the indirect evidence, providing the estimate $y_{12,1} = y_{13,0} + y_{32,0}$. Therefore, the matrix $\mathbf{S}_{12}$ is

$$\mathbf{S}_{12} = \begin{bmatrix} N_{12}^{-1} & 0 \\ 0 & N_{13}^{-1} + N_{23}^{-1} \end{bmatrix},$$

and the effective number of studies for 2 vs. 1 is $E_{12} = \mathbf{1}^T \mathbf{S}_{12}^{-1} \mathbf{1} = 10.6$. For 4 vs. 1, it is informed by no direct evidence but two sources of the indirect evidence, providing the relative effect estimates $y_{14,1} = y_{13,0} + y_{34,0}$ and $y_{14,2} = y_{12,0} + y_{23,0} + y_{34,0}$. Then, the matrix $\mathbf{S}_{14}$ is

$$\mathbf{S}_{14} = \begin{bmatrix} N_{12}^{-1} + N_{34}^{-1} & N_{34}^{-1} \\ N_{34}^{-1} & N_{12}^{-1} + N_{23}^{-1} + N_{34}^{-1} \end{bmatrix};$$

thus, $E_{14} = \mathbf{1}^T \mathbf{S}_{14}^{-1} \mathbf{1} = 6.3$.

2.3 The effective sample size

The assumption of equal variance in each study is unrealistic in practice. If the sample size of each study is available, then we may relax this assumption: the precision of the relative

effect estimate provided by each study is proportional to its sample size. Specifically, denote n_i as the total sample size in all treatment groups in study i ($i = 1, 2, \dots, N$). Suppose the variance of the relative effect estimate provided by study i is $v_i = cn_i^{-1}$, where c is a common constant across studies. For example, the constant c can reflect the variance of the samples' responses within each study when the effect size is the mean difference; it differs from the σ^2 in Section 2.1 which denotes the variance of study i 's summary result.

Let $\mathcal{A}_{hk}$ be the set of studies that directly compare treatments h and k . Using the inverse-variance method, the variance of the relative effect estimate using the direct evidence of k vs. h is $v_{hk,0} = \left(\sum_{i \in \mathcal{A}_{hk}} v_i^{-1} \right)^{-1} = c \left(\sum_{i \in \mathcal{A}_{hk}} n_i \right)^{-1}$. That is, for each treatment comparison, the sample size that effectively contributes to the direct evidence is the cumulative number of patients in the studies that directly give the comparison. Denote this cumulative sample size for the comparison k vs. h as $n_{hk} = \sum_{i \in \mathcal{A}_{hk}} n_i$. This was used in Trikalinos et al.²⁴ to present the network of the direct evidence; Figure 1(b) gives the network with edge width proportional to the n_{hk} 's.

To derive the sample size that effectively contributes to the overall evidence for each comparison, we follow the foregoing calculation of the effective number of studies. Now, the variance of the relative effect estimate using the direct evidence is $v_{hk,0} = cn_{hk}^{-1}$, instead of $\sigma^2 N_{hk}^{-1}$ as in Section 2.2. Denote the effective sample size for the overall evidence of k vs. h as ESS_{hk} ; similarly, it can be calculated as $ESS_{hk} = \mathbf{1}^T \mathbf{S}_{hk}^{-1} \mathbf{1}$. The matrix $\mathbf{S}_{hk}$ here is based on the cumulative number of patients n_{hk} , not the number of studies N_{hk} . In the illustrative example, 25,388 patients were included in the NMA, and the cumulative numbers of patients for the direct comparisons are $n_{12} = 1991$, $n_{13} = 4619$, $n_{23} = 11,020$, and $n_{34} = 7758$. Consequently, the effective sample size for the overall evidence of 2 vs. 1 is $ESS_{12} = n_{12} + (n_{13}^{-1} + n_{23}^{-1})^{-1} = 5246$; similarly, $ESS_{13} = 6305$ and $ESS_{23} = 12,411$. As 4 vs. 3 is informed only by direct evidence, $ESS_{34} = n_{34} = 7758$. For the comparison 4 vs. 1,

$$\mathbf{S}_{14} = \begin{bmatrix} n_{13}^{-1} + n_{34}^{-1} & n_{34}^{-1} \\ n_{34}^{-1} & n_{12}^{-1} + n_{23}^{-1} + n_{34}^{-1} \end{bmatrix},$$

so $ESS_{14} = \mathbf{1}^T \mathbf{S}_{14}^{-1} \mathbf{1} = 3478$. Similarly, $ESS_{24} = 4774$ for 4 vs. 2. Figure 1(e) presents the network with edge width proportional to the effective sample size.

2.4 | The effective precision

We can further refine the measure of the overall evidence in an NMA if more information is available for each study. For example, for binary outcomes, suppose that we know all four cells of the 2×2 table of each study, and denote them as n_{j00} , n_{j01} , n_{j10} , and n_{j11} for study i . Here, the first index of 0/1 in the subscript indicates treatment group (control/treatment) and the second one indicates outcome (no/yes). When the log odds ratio is used as the effect size,

the within-study variance is usually approximated as $v_i = n_{i00}^{-1} + n_{i01}^{-1} + n_{i10}^{-1} + n_{i11}^{-1}$; a correction of 0.5 can be added to each cell if any cell in the 2×2 table is zero.²⁷ Therefore, as in Section 2.3, the variance of the relative effect estimate using the direct evidence of k vs. h is $v_{hk,0} = \left(\sum_{i \in \mathcal{A}_{hk}} v_i^{-1} \right)^{-1}$, where $\mathcal{A}_{hk}$ contains the studies that directly compare treatments h and k . Thus, the precision of the direct evidence is $P_{hk} = v_{hk,0}^{-1}$, and Figure 1(c) shows the network with edge width proportional to this precision. Furthermore, we can use these variances/precisions to obtain the matrix $\mathbf{S}_{hk}$ as in the calculation of the effective number of studies, and the effective precision of the overall evidence is similarly defined as $EP_{hk} = \mathbf{1}^T \mathbf{S}_{hk}^{-1} \mathbf{1}$. Note that, to derive the effective precision, the variances $v_{hk,0}$ do not involve other parameters such as σ^2 and c in Sections 2.1–2.3, so the matrix $\mathbf{S}_{hk}$ equals to the variance-covariance matrix $\mathbf{V}_{hk}$. In the NMA by Trikalinos et al.,²⁴ which has a binary outcome (death), the effective precisions of the overall evidence are $EP_{12} = 67.4$, $EP_{13} = 102$, $EP_{23} = 65.2$, $EP_{34} = 25.3$, $EP_{14} = 20.3$, and $EP_{24} = 18.2$. Figure 1(f) shows the comparisons with edge width proportional to the effective precision.

When the outcome is continuous, suppose that we know the sample sizes in both treatment groups in each study, denoted as n_{i0} and n_{i1} in study i . Assuming that the treatment groups share a common population variance within each study, the mean difference and the standardized mean difference (including Cohen's d and Hedges' g) are widely used as the effect size.^{28,29} The mean difference's within-study variance is estimated as $v_i = (n_{i0}^{-1} + n_{i1}^{-1}) s_{ip}^2$, where s_{ip}^2 is the pooled sample variance in the two groups of study i . The standardized mean difference's within-study variance is often approximated as $v_i = n_{i0}^{-1} + n_{i1}^{-1} + \frac{y_i^2}{2(n_{i0} + n_{i1})}$, where y_i is the estimated standardized mean difference.²⁹ Based on these, the effective precision for continuous outcomes can be similarly calculated.

3 | MORE COMPLICATED EXAMPLES

We apply the proposed measures of overall evidence to three NMAs with more complicated structures; they all have binary outcomes. The first NMA was conducted by Welton et al.³⁰ to compare psychological interventions in coronary heart disease, and the outcome is total mortality. The second one was conducted by Elliott and Meyer³¹ to investigate the effect of antihypertensive drugs on incidence diabetes mellitus. The last one was collected by Picard and Tramèr³² to compare interventions to prevent pain on injection with propofol.

The treatment networks in the upper panels of Figures 2–4 show the direct evidence of all treatment comparisons in the three NMAs; those in the lower panels demonstrate the overall evidence using the proposed measures. The exact results of the effective number of studies, the effective sample size, and the effective precision are in the Supplementary Information.

The NMA by Welton et al.³⁰ contains 35 studies, including 4 three-arm studies. It compares a total of 16 treatments. The treatment names are shown in Figure 2's legend. Although its network seems large, most pairs of treatments are compared by no more than one study. The

large networks based on the direct evidence in Figures 2(a)–(c) might make audience believe that the NMA could greatly improve the effect estimate of each comparison. However, among all $16 \times 15/2 = 120$ possible pairs of treatments, only 8 (7%) pairs are effectively compared by at least three studies. The effective sample size and the effective precision also indicate that the overall evidence of most comparisons is limited. Figures 2(d)–(f) show that the edge of 4 vs. 1 is the thickest in the networks, so this comparison has the strongest overall evidence from the NMA. The edges of other comparisons are much thinner than 4 vs. 1. Also, using different measures of evidence, the networks look different. For example, the comparisons 6 vs. 1, 7 vs. 1, and 14 vs. 1 have noticeably thicker edges in Figure 2(d) compared with those in Figures 2(e) and 2(f), while the edge of 11 vs. 1 in Figure 2(e) is thicker compared with the other two networks.

Figure 3 presents the direct and overall evidence in the NMA by Elliott and Meyer,³¹ which contains 22 studies, comparing a total of six treatments. Among the 22 studies, 4 are three-armed. Figure 3's legend gives the treatment names. All treatments are directly compared except 5 vs. 3, so the network is well-connected and contains many cycles that can synthesize the direct and indirect evidence. The upper panel in Figure 3 shows that the comparison 6 vs. 4 has the strongest direct evidence; the edges of 2 vs. 1, 3 vs. 1, and 6 vs. 3 are also thicker than most other comparisons. Using the proposed measures of overall evidence, Figure 3's lower panel demonstrates that the edges of nearly all comparisons are noticeably thickened compared with the networks of the direct evidence. They indicate that much indirect evidence is gained from the NMA beyond the direct evidence.

For the NMA by Picard and Tramèr,³² 43 studies have been collected to compare eight treatments, which are detailed in Figure 4's legend. It contains 12 three-arm studies and 3 four-arm studies. Like the NMA by Elliott and Meyer,³¹ this NMA is also well-connected, and only five pairs of treatments among all $8 \times 7/2 = 28$ possible pairs are not directly compared. The networks in Figure 4's upper panel based on different measures indicate similar strength of the direct evidence. The comparison of 4 vs. 1 has the strongest direct evidence. The NMA greatly improves the evidence of all comparisons, because most edges in Figure 4's lower panel of the overall evidence are much thicker than those in the networks of the direct evidence. For example, although only two studies directly compare treatments 1 and 2, they are effectively compared by 14 studies after incorporating the indirect evidence. Also, for the same comparison, the sample size is increased from 133 to 907 and the precision is increased from 5.1 to 41.3 by performing the NMA.

4 | DISCUSSION

Because currently many NMAs did not properly report the structure of treatment comparisons and the existing methods present only direct evidence,¹⁷ this article focused on the strategy of presenting overall evidence in NMAs and proposed three new measures for this purpose. The case studies of four real NMAs showed that the new measures intuitively quantified the overall evidence, so that the potential benefit of performing NMAs could be easily evaluated at the preliminary stage. Some NMAs, such as the one by Welton et al.,³⁰ may not greatly outperform the traditional pairwise meta-analyses, primarily because their networks may contain few cycles and thus the synthesis of direct and indirect evidence is

limited. Prestigious journals tend to accept meta-analyses having many studies, because they may contain more evidence and produce more precise estimates than small meta-analyses. However, using the traditional concept of “the number of studies” to evaluate an NMA is a black box for journal editors and reviewers. The NMA may collect many studies, but most may focus on comparing a few frequently-investigated or well-established treatments. As NMAs claim to synthesize all available evidence, editors and reviewers may have little concerns about too few studies for certain comparisons. For example, despite that the NMA by Welton et al.³⁰ contains 35 studies, most of them compare three treatments with the control among the total of 16 treatments, and the effective numbers of studies for many comparisons are less than two. The NMA may provide little benefit for these comparisons, because meta-analysis is usually considered as a method to synthesize multiple (i.e., at least two) studies. The new measures of overall evidence may be good additions to reporting treatment networks for preliminarily evaluating NMAs.

The three new measures of overall evidence are based on different assumptions. The effective number of studies requires the strongest assumption that each study contributes equal evidence, and the effective sample size assumes that the precision of each study is proportional to its total sample size. The effective precision requires a weaker assumption by using estimated within-study variances, but its interpretation may not be as intuitive as the former two measures. Researchers may choose a proper measure based on how they want to interpret the evidence in an NMA.

The measures of overall evidence are designed to help researchers preliminarily understanding and evaluating NMAs; they are not intended to supersede formal statistical analyses. To be more rigorous, we may view the new measures as the upper bound of the number of studies, sample size, or precision that effectively informs overall evidence because of three reasons below. First, a fixed-effect model was used to derive the new measures, so the variance of the overall effect estimate of each treatment comparison may be underestimated if heterogeneity is not ignorable in an NMA.³³ Since the new measures of overall evidence are proportional to the inverse of the variance, they may be overestimated. Second, we also assumed consistency between direct and indirect evidence for all comparisons; nevertheless, a noticeable number of NMAs in the literature were found to suffer from evidence inconsistency.¹⁶ If the NMA model accounts for inconsistency, the overall evidence may be weakened because the variances of the overall effect estimates increase due to the additional uncertainties introduced by inconsistency. Third, some NMAs may contain several multi-arm studies, which compare more than two treatments. The derivations of the new measures simply treated them as separate two-arm studies, leading the proposed measures to be overestimated.

In summary, because the new measures may serve as upper bounds to quantify overall evidence, if they indicate that many treatment comparisons in an NMA have weak overall evidence (e.g., the effective number of studies is less than two), then researchers may gain little benefits from the NMA. Table 1 briefly summarizes the interpretations, assumptions, limitations, and advantages of the three proposed measures of overall evidence.

In the literature, the statistical methods for NMAs may be classified into two groups: the contrast-based methods that focus on estimating relative effects of treatment contrasts,⁴ and the arm-based methods that directly estimate absolute effects of treatment arms.^{5,34} The contrast-based methods are currently the most popular tools for NMAs, while the arm-based methods recently become increasingly acceptable.^{35,36} This article derived the measures of overall evidence from the contrast-based perspective. Similar measures of overall evidence for the arm-based NMAs may require different assumptions, and we leave these as future work.

In addition, the three proposed methods may be considered as absolute measures of overall evidence, and we can use them to further derive relative measures to assess the benefits of performing NMAs. For example, we may define the proportion of information provided by indirect evidence among overall evidence as $(1 - N_{hk}/E_{hk}) \times 100\%$, $(1 - n_{hk}/ESS_{hk}) \times 100\%$, or $(1 - P_{hk}/EP_{hk}) \times 100\%$. These proportions are in the range between 0% and 100%, and they also have attractive interpretations for assessing the indirect evidence at the pre-analysis stage. They are similar to the borrowing of strength (BoS) statistic proposed by Jackson et al.,³⁷ which is calculated as $BoS = (1 - E) \times 100\%$, where the efficiency E is the ratio of the variance of the effect estimate using the NMA to that using only the direct evidence. However, the BoS statistic uses the results from strict NMA models at the post-analysis stage, and it varies when using different statistical models. In future work, we will empirically investigate the magnitude of the relative measures based on published NMAs and provide a guideline to assess the quality of NMAs.

The R code to calculate the proposed measures of overall evidence is in the Supplementary Information. An important step in the calculation is to find all sources of indirect evidence for each treatment comparison. We used the R package “igraph” to realize this step.³⁸ When a network contains many treatments and evidence cycles, there may be exponentially many paths between two treatment nodes, leading to computational difficulties. Although the number of sources of indirect evidence may be huge, most of them can be expressed as combinations of certain sources in a small basis set. This is closely related to the concept of independent cycles for assessing inconsistency.¹¹ Future work also includes efficiently identifying the basis set of indirect evidence so that the new measures of overall evidence can be calculated much faster and easily applied in large networks.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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FIGURE 1.

Treatment networks of the NMA by Trikalinos et al.²⁴ Each network's edge width is proportional to the measure shown in the subfigure's title. The treatment IDs are: (1) medical therapy; (2) percutaneous transluminal balloon coronary angioplasty; (3) bare-metal stents; and (4) drug-eluting stents.

FIGURE 2.

Treatment networks of the NMA by Welton et al.³⁰ Each network's edge width is proportional to the measure shown in the subfigure's title. The treatment IDs are: (1) usual control; (2) educational; (3) behavioral; (4) cognitive; (5) support; (6) educational + behavioral; (7) educational + cognitive; (8) educational + relaxation; (9) behavioral + cognitive; (10) behavioral + relaxation; (11) cognitive + relaxation; (12) cognitive + support; (13) educational + behavioral + cognitive; (14) educational + behavioral + relaxation; (15) educational + cognitive + relaxation; and (16) behavioral + cognitive + support.

FIGURE 3.

Treatment networks of the NMA by Elliott and Meyer.³¹ Each network's edge width is proportional to the measure shown in the subfigure's title. The treatment IDs are: (1) placebo; (2) thiazide diuretic; (3) converting-enzyme inhibitor; (4) calcium-channel blocker; (5) angiotensin-receptor blocker; and (6) β blocker.

FIGURE 4.

Treatment networks of the NMA by Picard and Tramèr.³² Each network's edge width is proportional to the measure shown in the subfigure's title. The treatment IDs are: (1) placebo; (2) no treatment; (3) lidocaine before; (4) lidocaine mixed; (5) lidocaine + tourniquet; (6) opioids; (7) metoclopramide; and (8) temperature.

TABLE 1

The three proposed measures of overall evidence for NMAs.

Measure of Overall Evidence	Interpretation	Assumption	Limitation & Advantage
The effective number of studies	The maximum number of studies that effectively contribute to the overall evidence	All studies share a common within-study variance; that is, all studies contribute the same strength of evidence	Its assumption is unlikely true in practice, so it is a rough measure; however, it has an intuitive interpretation and provides importation information for meta-analysts
The effective sample size	The maximum number of samples that effectively contribute to the overall evidence	Each study's variance is proportional to the inverse of its sample size with a common proportion coefficient; that is, all samples contribute the same strength of evidence	Its assumption may be violated in some cases (e.g., when the studies have different treatment allocation ratios), while its interpretation is straightforward and informative
The effective precision	The best precision (the inverse of the variance) of the overall evidence	The within-study variance for each treatment comparison in each study is available	Some papers may not report all within-study variances that are required for calculating this measure, and its interpretation is less intuitive than the other two, while it is more accurate