

November 4, 2016

Quantifying indirect evidence in network meta-analysis

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Summary

Network meta-analysis enables comprehensive synthesis of evidence concerning multiple treatments and their simultaneous comparisons based on both direct and indirect evidence. A fundamental pre-requisite of network meta-analysis is the consistency of evidence that is obtained from different sources, particularly whether direct and indirect evidence are in accordance with each other or not, and how they may influence the overall estimates. We have developed an efficient method to quantify indirect evidence, as well as a testing procedure to evaluate their inconsistency using Lindsay's composite likelihood method. We also show that this estimator has complete information for the indirect evidence. Using this method, we can assess the degree of consistency between direct and indirect evidence and their contribution rates to the overall estimate. Sensitivity analyses can be also conducted with this method to assess the influences of potentially inconsistent treatment contrasts on the overall results. These methods can provide useful information for overall comparative results that might be biased from specific inconsistent treatment contrasts. We also provide some fundamental requirements for valid inference on these methods concerning consistency restrictions on multi-arm trials. In addition, the efficiency of the developed method is demonstrated based on simulation studies. Applications to a network meta-analysis of 12 new-generation antidepressants are presented.

Key words: network meta-analysis; indirect evidence; likelihood factorization; composite likelihood methods; inconsistency; sensitivity analysis.

1. Introduction

In evidence-based medicine, meta-analysis has been an essential methodology to assemble and summarize evidence from individual studies that is relevant to a specific research question. In evaluating the efficacy of a particular treatment of interest in comparison with a control treatment, one limitation of conventional meta-analysis is that its application is restricted to only studies with direct pairwise comparisons of these treatments [1]. To overcome this limitation, network meta-analysis has been proposed to allow for a comprehensive synthesis and simultaneous comparison of evidence from multiple treatments, even when head-to-head studies may be missing. The network meta-analysis can synthesize both direct and indirect evidence for the treatment comparison of interest, and provides more precise estimates of treatment efficacy or safety, borrowing strengths from the indirect evidence [2-6].

A fundamental problem in assuring the validity of a network meta-analysis is the *consistency* of evidence from different sources of evidence. A typical definition of *inconsistency* is the disagreement between direct and indirect evidence in the network. Since the problem of inconsistency can raise serious concerns about the validity and interpretation of the network meta-analysis, various statistical methods have been proposed to assess inconsistency [7]. In particular, many researchers are especially interested in the fundamental question of how much the indirect evidence contributes to the total estimates of treatment effects obtained from a network meta-analysis. Recently, Dias et al. [8] developed two methods to decompose direct and indirect estimates for a specific treatment contrast on the network, as well as formal testing procedures for assessing their inconsistency in the Bayesian framework. Although their methods enable quantitative interpretations of the

indirect evidence and are widely applied, they have potential biases and their efficiencies are not theoretically assured (as shown later). Also, researchers would be substantially interested in assessing these methods' influences on the overall results (e.g., due to potential biases) after identifying potentially inconsistent treatment contrasts.

To resolve these problems, we have developed an efficient inference method to quantify indirect evidence and evaluate inconsistency, as well as a sensitivity analysis method that assess the influences of potentially inconsistent treatment contrasts on the overall results. Also, we provide some fundamental requirements for valid inference on these methods concerning consistency restrictions on multi-arm trials that are required for the methods of Dias et al. [7]. The inference method is based on a complete factorization of the total likelihood obtained from the entire body of evidence in the network into separate component likelihoods pertaining to the direct and indirect treatment comparisons. The latter component likelihood, which can be interpreted as a composite likelihood [9, 10], has complete information for the indirect treatment comparison, and thus an efficient estimator based on the indirect comparison can be obtained. Based on this factorization of the total likelihood, the overall estimate can be decomposed as a weighted average of the two estimates representing the direct and indirect comparisons. The inconsistency between direct and indirect evidence can also be evaluated on the basis of this estimator, and a formal statistical test for detecting the inconsistency can be developed. In addition, after identifying potential inconsistency treatment contrasts, influences of these treatment contrasts on the overall estimates can be evaluated by the proposed framework. This framework can provide intuitive interpretations about influences of the inconsistency and enable the assessment of robustness of overall estimates and treatment rankings. Indeed, applications of our proposed method to

a network meta-analysis of 12 new-generation antidepressants in unipolar major depression [11] yielded insights concerning their comparative efficacy.

2. Quantifying the indirect evidence

2.1 Network meta-analysis: A frequentist formulation

Suppose a network meta-analysis using multivariate random-effects models [12-14]. Let Y_{ir} denote an estimator of treatment effect in contrast to a reference treatment (formally defined in this model) for the r th treatment in the i th trial ($i = 1, 2, \dots, N; r = 1, 2, \dots, p$) and the covariates x_{ir} (a $q_r \times 1$ vector; q_r is the number of covariates). Commonly used effect measures include mean difference, standardized mean difference, risk difference, risk ratio, odds ratio, and hazard ratio. Typically, in constructing Y_{ir} , the ratio measures are transformed into a logarithmic scale to use approximations based on normal distributions. We consider here the general multivariate random-effects model of White et al. [12] and White [13], i.e., the mean of Y_{ir} is assumed to be $\beta_r x_{ir}$, where β_r is a $1 \times q_r$ vector. After that, the marginal model is expressed as

$$Y_{ir} \sim N(\mu_{ir}, s_{ir}^2)$$

$$\mu_{ir} \sim N(\beta_r x_{ir}, \tau_r^2)$$

For standard meta-analysis, $x_{ir} = (1)$, a vector of ones. The discussion in this paper can be adapted to a general meta-regression framework as discussed in Section 3. For matrix notation, we define $Y_i = (Y_{i1}, Y_{i2}, \dots, Y_{ip})^T$. Also, its within-study variance-covariance matrix S_i (a $p \times p$ matrix) is assumed to be known and fixed to its valid estimate (e.g., using Trikalinos and Olkin [15]’s estimators for binary outcomes). We can then write the

joint model,

$$Y_i \sim N(\mu_i, S_i)$$

$$\mu_i \sim N(X_i \beta, \Sigma)$$

$$S_i = \begin{pmatrix} s_{i1}^2 & \rho_{i12} s_{i1} s_{i2} & \cdots & \rho_{i1p} s_{i1} s_{ip} \\ \rho_{i12} s_{i1} s_{i2} & s_{i2}^2 & \cdots & \rho_{i2p} s_{i2} s_{ip} \\ \vdots & \vdots & \ddots & \vdots \\ \rho_{i1p} s_{i1} s_{ip} & \rho_{i2p} s_{i2} s_{ip} & \cdots & s_{ip}^2 \end{pmatrix}$$

$$X_i = \begin{pmatrix} x_{i1} & 0 & \cdots & 0 \\ 0 & x_{i2} & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & x_{ip} \end{pmatrix}, \Sigma = \begin{pmatrix} \tau_1^2 & \kappa_{12} \tau_1 \tau_2 & \cdots & \kappa_{1p} \tau_1 \tau_p \\ \kappa_{12} \tau_1 \tau_2 & \tau_2^2 & \cdots & \kappa_{2p} \tau_2 \tau_p \\ \vdots & \vdots & \ddots & \vdots \\ \kappa_{1p} \tau_1 \tau_p & \kappa_{2p} \tau_2 \tau_p & \cdots & \tau_p^2 \end{pmatrix}$$

where $\mu_i = (\mu_{i1}, \mu_{i2}, \dots, \mu_{ip})^T$, $\beta = (\beta_1, \dots, \beta_p)^T$, and Σ is the between-studies variance-covariance matrix. We denote all the parameters in the model as $\theta = (\beta_1, \dots, \beta_p, \tau_1, \dots, \tau_p, \kappa_{12}, \dots, \kappa_{(p-1)p})^T$ and the inverse of the marginal variance-covariance matrix as $W_i = (\Sigma + S_i)^{-1}$. This network meta-analysis model is the “contrast-based” model in the sense of Salanti et al. [5].

For estimation of the unknown parameter θ , a standard and efficient approach is the maximum likelihood (ML) estimation [13, 14]. The log likelihood function can be written as

$$\begin{aligned} \ell(\theta) &= \sum_{i=1}^N \log p(y_{i1}, \dots, y_{ip} | \theta) \\ &= -\frac{1}{2} \sum_{i=1}^N \{ \log |\Sigma + S_i| + (y_i - X_i \beta)^T W_i (y_i - X_i \beta) + p_i \log 2\pi \} \end{aligned}$$

where p_i is the number of treatments compared to the reference in trial i . When the corresponding comparisons are not involved in the i th trial, the corresponding component is

shrunk to the sub-vector and sub-matrix associated with the involved treatments. Also, if the i th trial does not include the reference treatment, the standard data augmentation approach proposed by White et al. [12] can be adopted, in which case there is a quasi-small data in the reference arm, e.g., 0.001 events for 0.01 patients for binary outcomes. When the structured model is correctly specified, θ is consistently and efficiently estimated.

2.2 Likelihood factorization and quantifying indirect evidence

Suppose the decomposition of the direct and indirect comparison estimates for a specific pairwise comparison on the network. Figure 1 shows the concept of the decomposition, and we aim to validly assess the inconsistency of the direct and indirect evidence for a specific pairwise comparison. We refer to all of the information on the network that is not direct evidence as the indirect evidence. Without loss of generality, we regard the target pairwise comparison to be the first component of Y_i s (Y_{11}, \dots, Y_{N1}) in the network. Conveniently, here we write the comparison of the first two treatments as A vs. B. For synthesizing full information on the head-to-head comparisons of A vs. B, the conventional univariate meta-analysis model can be applied, which is based on the random-effects model, $Y_{i1} \sim N(\mu_{i1}, s_{i1}^2)$, $\mu_{i1} \sim N(\beta_1 x_{i1}, \tau_1^2)$. The log likelihood function of the direct comparison model [16, 17] is written as

$$\ell_{\text{dir}}(\theta) = \sum_{i=1}^{N_{\text{dir}}} \log p(y_{i1} | \beta_1, \tau_1^2) = -\frac{1}{2} \sum_{i=1}^{N_{\text{dir}}} \left\{ \log(\tau_1^2 + s_{i1}^2) + \frac{(y_{i1} - \beta_1 x_{i1})^2}{\tau_1^2 + s_{i1}^2} + \log 2\pi \right\}$$

where N_{dir} is the sum of numbers of direct comparisons. Intuitively, this log likelihood involves the full information on the direct comparison of A vs. B on the network. In addition,

we would expect the information on the indirect evidence to be summarized in the residual part of the total log likelihood $\ell(\theta)$, with the exception of $\ell_{\text{dir}}(\theta)$. As shown below, the total log likelihood can be exactly decomposed to an additive form of $\ell_{\text{dir}}(\theta)$ and the remaining part. Here, we denote the component of each trial in the log likelihood as $\ell_i(\theta) = \log p(y_{i1}, y_{i2}, \dots, y_{ip} | \theta)$.

All of the trials involved can then be classified into the following three categories based on whether they involve direct and/or indirect evidence. First, if the i th trial is a two-arm comparative study of treatments A and B, the log likelihood is written as $\ell_i(\theta) = \log p(y_{i1} | \beta_1, \tau_1^2)$, which involves only the direct comparison log likelihood. Second, if the i th trial is a multi-arm trial (more than two arms) involving both of the treatments A and B, the log likelihood is decomposed to $\ell_i(\theta) = \log p(y_{i1} | \beta_1, \tau_1^2) + \log p(y_{i2}, \dots, y_{ip} | y_{i1}, \theta)$ where the first term corresponds to the direct comparison log likelihood, and thus the second term is the residual conditional log likelihood on y_{i1} that would involve the information on the non-direct evidence (i.e., indirect evidence) for A vs. B. Lastly, if the i th trial does not involve both treatments A and B, the log likelihood does not contain the direct comparison component. Then, denoting the index sets of the three categories as Ξ_I, Ξ_{II} , and Ξ_{III} , the total log likelihood can be decomposed to

$$\begin{aligned} \ell(\theta) = & \sum_{i \in \Xi_I} \log p(y_{i1} | \beta_1, \tau_1^2) + \sum_{i \in \Xi_{II}} \log p(y_{i1} | \beta_1, \tau_1^2) + \sum_{i \in \Xi_{II}} \log p(y_{i2}, \dots, y_{ip} | y_{i1}, \theta) \\ & + \sum_{i \in \Xi_{III}} \log p(y_{i2}, \dots, y_{ip} | \theta) \end{aligned}$$

Note that the sum of the first two terms exactly accords to the direct comparison log likelihood. Therefore, we define the residual part of the log likelihood as

$$\ell_{\text{ind}}(\theta) = \sum_{i \in \Xi_{\text{II}}} \log p(y_{i2}, \dots, y_{ip} | y_{i1}, \theta) + \sum_{i \in \Xi_{\text{III}}} \log p(y_{i2}, \dots, y_{ip} | \theta)$$

Intuitively, it would be supposed that the log partial likelihood $\ell_{\text{ind}}(\theta)$ involves the full information on the indirect evidence except for the direct comparison evidence.

For synthesizing the indirect evidence with the exclusion of the direct comparison trials, we formally use the log partial likelihood as a log pseudo-likelihood function. Although the log partial likelihood $\ell_{\text{ind}}(\theta)$ is not an ordinary log likelihood, it is regarded as a log pseudo-likelihood composed by a combination of marginal or conditional likelihoods. Thus, the estimation procedure based on $\ell_{\text{ind}}(\theta)$ can be interpreted as the composite likelihood method [9, 10]. We denote the maximum composite likelihood estimator that is obtained through maximizing $\ell_{\text{ind}}(\theta)$ as $\hat{\theta}_{\text{ind}}$.

Remark A. The composite likelihood estimator $\hat{\theta}_{\text{ind}}$ is the consistent estimator of θ , and $\hat{\theta}_{\text{ind}}$ has an asymptotic distribution,

$$\hat{\theta}_{\text{ind}} \sim N(\theta, I_{\text{ind}}^{-1}(\theta)),$$

where $I_{\text{ind}}(\theta) = -E[\partial^2 \ell_{\text{ind}}(\theta) / \partial \theta \partial \theta^T]$.

An outline of proof is provided in Appendix A in the Supporting Information Materials. Following Remark A, through the estimation using the log partial likelihood $\ell_{\text{ind}}(\theta)$, the model parameter θ is validly estimable and has the corresponding information $I_{\text{ind}}(\theta)$. The ML estimator $\hat{\theta}$ obtained by maximizing the total log likelihood $\ell(\theta)$ has an information matrix $I(\theta) = -E[\partial^2 \ell(\theta) / \partial \theta \partial \theta^T]$, and the ML estimator $\hat{\theta}_{\text{dir}}$ obtained by maximizing the direct comparison log likelihood $\ell_{\text{dir}}(\theta)$ has an information matrix $I_{\text{dir}}(\theta) =$

$-E[\partial^2 \ell_{\text{dir}}(\theta)/\partial\theta\partial\theta^T]$. Since the total log likelihood can be decomposed to $\ell(\theta) = \ell_{\text{dir}}(\theta) + \ell_{\text{ind}}(\theta)$, the information matrix can also be decomposed to $I(\theta) = I_{\text{dir}}(\theta) + I_{\text{ind}}(\theta)$. Therefore, the total information for all the evidence of the network can be completely decomposed to $I_{\text{dir}}(\theta)$ and $I_{\text{ind}}(\theta)$, and it can be interpreted that $\hat{\theta}_{\text{ind}}$ has the full information of the residual network after excluding the contributions of the direct evidence. Thus, the composite likelihood estimator $\hat{\theta}_{\text{ind}}$ can be interpreted as a synthesized summary of the indirect evidence of the entire network.

Based on the factorization of the total likelihood, the total estimator $\hat{\theta}$ can also be decomposed into the two estimators representing the direct and indirect treatment comparisons. It is shown that the total estimator $\hat{\theta}$ can be explicitly decomposed to a weighted mean of the direct and indirect estimators as follows. For the notation of β , here we use $\beta_{\text{dir}} = (\beta_{1,\text{dir}}, \dots, \beta_{p,\text{dir}})^T$ for the direct comparison component and $\beta_{\text{ind}} = (\beta_{1,\text{ind}}, \dots, \beta_{p,\text{ind}})^T$ for the indirect comparison component, assuming possible inconsistencies between the two sources of evidence.

Remark B. Using the large sample approximation, the overall estimator $\hat{\beta}$ is decomposed to direct and indirect comparison estimators as

$$\hat{\beta}_1 = w_{\text{dir}}(\theta)\hat{\beta}_{1,\text{dir}} + w_{\text{ind}}(\theta)\hat{\beta}_{1,\text{ind}}$$

$$\hat{\beta}_j = \hat{\beta}_{j,\text{ind}}, (j = 2, \dots, p),$$

where the weights are given as $w_{\text{dir}}(\theta) = I_{11,\text{dir}}(\theta)/I_{11}(\theta)$ and $w_{\text{ind}}(\theta) = 1 - w_{\text{dir}}(\theta)$.

Also, the components of the weights are $I_{11,\text{dir}}(\theta) = -E[\partial^2 \ell_{\text{dir}}(\theta)/\partial\beta_1^2]$ and $I_{11}(\theta) = -E[\partial^2 \ell(\theta)/\partial\beta_1^2]$, which represent the information for the direct and total comparison

likelihoods, respectively, for β_1 .

The proof is provided in Appendix B in the Supporting Information Materials. Remark B explicitly indicates that the ML estimator $\hat{\beta}_1$ on the entire network can be decomposed to a weighted mean of $\hat{\beta}_{1,\text{dir}}$ and $\hat{\beta}_{1,\text{ind}}$, with weights of the fractions of information for direct and indirect evidence. In addition, the weights $w_{\text{dir}}(\theta)$ and $w_{\text{ind}}(\theta)$ are interpreted as the contribution rates of the direct and indirect evidence to the final estimate $\hat{\beta}_1$. These quantities can be used as measures of how direct and indirect evidence contributes to the final estimate. It should be noted that $\hat{\beta}_j = \hat{\beta}_{j,\text{ind}}$, ($j = 2, \dots, p$) means that the composite likelihood estimator based on the indirect comparison network involves all of the information for β_2, \dots, β_p for the whole network. A similar relationship holds for the estimator of the variance–covariance matrix Σ (see Appendix B in the Supporting Information Materials). Again, this result also shows that $\hat{\beta}_{\text{ind}}$ contains the full information of the residual network, with the exception of the direct comparison evidence.

Note that these results indicate that the back-calculation estimator of Dias et al. [8] is generally biased. Dias et al. [8] presumed that the overall estimator of β_1 is expressed as an inverse-variance-weighted average of the direct and indirect estimators as follows (equation (5) of their paper) and proposed back-calculating the indirect estimate; $V_{1,\text{ind}}^{-1} = V_1^{-1} - V_{1,\text{dir}}^{-1}$, $\hat{\beta}_{1,\text{ind}} = (\hat{\beta}_1/V_1 - \hat{\beta}_{1,\text{dir}}/V_{1,\text{dir}}) \times V_{1,\text{ind}}$, where $V_1, V_{1,\text{dir}}$, and $V_{1,\text{ind}}$ are marginal variances of total, direct, and indirect estimators of β_1 , respectively. However, because of the theoretical results discussed above, their presumptions were substantially incorrect, because of the factorization formula in Remark B and $V_{1,\text{ind}}^{-1} \neq V_1^{-1} - V_{1,\text{dir}}^{-1}$ generally. Thus, when

the non-diagonal components of the covariance matrix of β are non-zero, the back-calculation estimator of Dias et al. [8] has asymptotic bias.

2.3 Notes on consistency restriction for multi-arm trials

When the network does not include any multi-arm trials (more than two arms) involving both target treatments A and B, we can simply obtain valid estimators for $\beta_{1,\text{dir}}$ and $\beta_{1,\text{ind}}$ using the methods above. However, when the network involves multi-arm trials, there are several requirements for assuring the validity of inference. Note that the potential inconsistencies of $\beta_{1,\text{dir}}$ and $\beta_{1,\text{ind}}$ are assumed in the direct comparison of A vs. B, but we do not consider the other inconsistent components in the rest of the network in the above discussions. Then, the following problem may possibly occur:

Remark C. In multi-arm trials, consistency is restrictively fulfilled within a trial. Thus, when there are multi-arm trials that involve the target treatments A and B, if adequate inconsistency parameters for the remaining pairs are not addressed in the network meta-analysis models, the consistency assumption between direct and indirect comparisons of A vs. B is restrictively fulfilled in the model.

As a simple example, suppose there is a three-arm trial with A vs. B vs. C in the network of Figure 1, and the comparisons A vs. B, B vs. C, and A vs. C are restrictively consistent in this trial. For the evaluation of inconsistency between $\beta_{1,\text{dir}}$ and $\beta_{1,\text{ind}}$ in the network (possibly, under $\beta_{1,\text{dir}} \neq \beta_{1,\text{ind}}$), if the rest of the network besides A vs. B is assumed to be consistent, B vs. C and A vs. C in this trial and those in the rest of the network are consistent. Then,

within the three-arm trial, the differences in treatment effects of B vs. C and A vs. C can be expressed as $\beta_2 - \beta_{1,dir}$ and β_2 (β_2 is defined as the difference between A and C). Further, in the rest of the network, these can be expressed as $\beta_2 - \beta_{1,ind}$ and β_2 . Therefore, under these assumptions, $\beta_{1,dir} = \beta_{1,ind}$ is restrictively fulfilled by the model definition. So, if the consistency restriction within the multi-arm trials is not addressed, the resultant estimators are possibly biased by the model misspecification (although the model misspecification cannot occur if $\beta_{1,dir}$ and $\beta_{1,ind}$ are consistent).

To resolve this problem, the consistency restriction should be circumvented. The most straightforward approach is to relax the consistency assumption within multi-arm trials by using the meta-regressions in Section 2.1 to model inconsistency parameters for the remaining comparisons beside that of the target pair in these trials. This can be regarded as the design-by-treatment interaction of Higgins et al. [18]. For the above example, in the three-arm trial with A vs. B vs. C, a meta-regression model can be used such that the comparisons B vs. C and C vs. A are rendered possibly inconsistent with the rest of the network via involvement of a free parameter. Then, the restrictive consistency of $\beta_{1,dir} = \beta_{1,ind}$ can be circumvented in the model, and the indirect estimator $\hat{\beta}_{1,ind}$ obtained by the composite likelihood method is not biased. Note Dias et al. [8]’s two methods did not consider this problem, thus their estimators are possibly biased under certain conditions when $\beta_{1,dir} \neq \beta_{1,ind}$.

3. Tests for the inconsistency between direct and indirect evidence

Another relevant concern is the test for inconsistency between the direct and indirect evidence. In Figure 1, we now consider whether the underlying parameter β_1 for A vs. B between the direct and indirect components of the whole network are consistent or not. The testing problem is formulated by the test of the null hypothesis $H_0: \beta_{1,\text{dir}} = \beta_{1,\text{ind}}$. Therefore, using the ordinary direct comparison estimate $\hat{\beta}_{1,\text{dir}}$, and the indirect estimate $\hat{\beta}_{1,\text{ind}}$ obtained under the inconsistency assumption (if there are multi-arm trials that involve A and B, adequate models should be adopted as shown in Section 2.3), the pseudo-Wald test of $H_0: \beta_{1,\text{dir}} = \beta_{1,\text{ind}}$ is derived via the ordinary form of the test statistic,

$$Z_{\text{IC}} = (\hat{\beta}_{1,\text{dir}} - \hat{\beta}_{1,\text{ind}}) / \sqrt{\widehat{\text{Var}}(\hat{\beta}_{1,\text{dir}}) + \widehat{\text{Var}}(\hat{\beta}_{1,\text{ind}})},$$

which has an approximately standard normal distribution under the null hypothesis. The variance estimates are also obtained through the inference methods in Section 2. As other options, the pseudo likelihood ratio test and pseudo score test can also be constructed for the developed method.

4. Sensitivity analysis for assessing the influences of potentially inconsistent treatment contrasts

After the inconsistency tests are conducted, several significant inconsistent treatment contrasts are typically found on the whole network. Some of the significant results might be solely type-I errors because there are usually several dozen inconsistent tests. However, if these significant treatment contrasts are systematically inconsistent, they might impart serious biases to the overall results. One of the well-known relevant biases would be industry

sponsorship bias [19]. Therefore, the significant treatment contrasts are usually further investigated for possible causes of biases that might influence the overall results and conclusions. The method developed in Section 2 can be directly applied to sensitivity analyses that evaluate the influences of suspected inconsistent treatment contrasts.

For the composite likelihood method, we can obtain the corresponding estimate by maximizing the log partial likelihood $\ell_{\text{ind}}(\theta)$. As shown in Section 2, it provides an estimate of all comparisons on the network, β , which has sufficient information of the residual network. These sensitivity analyses methods can be straightforwardly implementable, and should also be useful for assessing influences of possibly inconsistent treatment contrasts by the well-known local inconsistency test of Bucher et al. [20].

5. Applications to a network meta-analysis of 12 antidepressants

To illustrate our method, we analyzed the dataset from a network meta-analysis by Cipriani et al. [11]. This is the first and one of the largest network meta-analyses published in the field of psychiatry. The authors reviewed 117 randomized controlled trials (25298 participants) from 1991 to 2007, which compared 12 antidepressants (bupropion, citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, milnacipran, mirtazapine, paroxetine, reboxetine, sertraline and venlafaxine) for the acute treatment of unipolar major depression. The efficacy outcome was the response to the allocated treatment, defined as a reduction of at least 50% from baseline to week 8 on the Hamilton Depression Rating Scale or the Montgomery-Åsberg Depression Rating Scale, or a rating of much improved or very much improved on the Clinical Global Impression scale. Cipriani et al. [11] assessed the comparative efficacy

using odds ratios (ORs) for the responses based on each treatment arm. We present a network plot for this network meta-analysis in Figure 2.

We analyzed the network meta-analysis data using the multivariate random-effects model (the reference treatment in the analysis model was set to fluoxetine). We also used our methods to evaluate the direct and indirect estimates and their inconsistencies. Results of all pairwise comparisons for the 12 antidepressants are presented in Appendix C in the Supporting Information Materials. For illustrative purposes, we present several selected results for specific pairwise comparisons that have the smallest P-values in the test of inconsistencies in Table 1. For the composite likelihood method, three of the 42 pairwise comparisons that involve at least one direct comparison were significant at 5% levels. As noted in Section 4, the sources of bias should be carefully investigated for possibly inconsistent treatment contrasts.

The most significant treatment contrast on the network was citalopram vs. escitalopram. The direct comparison estimate was 0.68 (95% CI: 0.54–0.85), indicating a significant difference, while the indirect comparison estimates were 1.05 (95% CI: 0.84–1.31), implying nearly equivalent efficacy between the two treatments. The P-values of the tests of inconsistency were 0.007 and 0.008. Although the overall estimate of this comparison was 0.84 (95% CI: 0.71–0.99), indicating that escitalopram was significantly more efficacious than citalopram, potential sources of inconsistency should be carefully evaluated (escitalopram is a derivative drug of citalopram, both of which were developed by the same company). In addition, the indirect evidence (excluding the direct comparisons) was mainly constructed by comparing escitalopram or citalopram vs. other drugs, comparisons that would not explicitly involve such biases. In Figure 3, we present a forest plot for the

individual direct comparisons of citalopram vs. escitalopram, as well as the summary estimate of the indirect evidence in the residual network. All four trials showed favorable results for escitalopram (two of them were significant). It is intuitive that although the estimated contribution rate of the direct evidence was relatively small (26.0%), the significant difference between the overall results was mostly due to this direct evidence. Similar trends could be found for mirtazapine vs. venlafaxine, citalopram vs. paroxetine, and several other pairs. However, note that these post hoc explanations have only limited value as pointed out by Dias et al. [8].

If the treatment contrast, citalopram vs. escitalopram, is inconsistent due to substantial biases, then to adequately interpret the overall evidence it would be important to consider how the overall estimate was influenced, which itself depends on the consistency assumption of the whole network. As discussed in Section 4, our method can be used to conduct sensitivity analyses that exclude the possibly inconsistent evidence in the network. Table 2 shows the results of sensitivity analyses based on the indirect network, excluding citalopram vs. escitalopram, using the proposed method, as well as the overall estimate based on the entire evidence (reference treatment: fluoxetine). In these sensitivity analyses, the efficacy estimates for all drugs but escitalopram and citalopram were mostly similar to the overall estimates. These results indicate that the validity of the corresponding components of the overall analyses are robust even if the direct comparison of citalopram vs. escitalopram was biased. Further, the efficacy estimates of escitalopram and citalopram changed. In these results, escitalopram was nearly equivalent in efficacy to citalopram, and both were significantly more efficacious than fluoxetine. Also, the efficacy estimates of escitalopram were now smaller. These results possibly suggest that the overall results based on the entire

evidence might underestimate the efficacy of citalopram. The overall treatment rankings might also be influenced, and these sensitivity analyses would provide relevant information for the overall conclusions.

In addition, we should note that the number of pairwise comparisons on this network was so large (in this case, 42 tests were conducted) that corresponding type-I errors possibly occurred due to multiplicity. In the original analysis of Cipriani et al. [11], a similar proportion of loop inconsistency tests was reported as significant (6/133). Thus, the frequencies of the significant results in both analyses were not obviously above that expected by chance alone (5%; note that we did not conduct multiplicity adjustments in these analyses). In addition, our sensitivity analyses were wholly post hoc, and it is still uncertain which results were true. However, we can add the caveat that these results may be underestimating the efficacy of citalopram, which may be as efficacious as escitalopram as suggested by these sensitivity analyses. Thus the statistical information based on our developed methods would be relevant for interpretations of entire network meta-analyses.

We also conducted simulation experiments to assess the efficiencies of the developed method. The designs and results of these studies are presented in Appendix D of the Supporting Information Materials.

6. Discussion

The methodological issue of inconsistency is one of the most important problems in assuring the validity of network meta-analyses. While most of the literature on network meta-analyses defines inconsistency as “the disagreement between direct and indirect evidence” [21], there have been only a few effective statistical methods for straightforwardly evaluating such

inconsistency. This study proposes efficient methods for quantifying the indirect evidence and assessing the inconsistency. These methods should be useful for scientific evaluation and interpretations of network meta-analyses.

In addition, the developed method for summarizing indirect evidence for the network should be an effective approach for explicitly interpreting the results of network meta-analyses. As far as we are aware, many publications on network meta-analyses have presented the overall and direct comparison estimates as reference information to aid in the rough assessment of inconsistency, but this statistical information is not intuitive. Through the explicit method developed in this study, the indirect evidence is explicitly summarized, and the overall estimate is interpreted as a synthesized estimate of the indirect evidence and the conventional direct comparison meta-analysis (as shown theoretically by Remark B). The method enable the intuitive and quantitative evaluation of the indirect evidence in the whole network, and the test of inconsistency should be an effective method for exploring sources of bias in practice. Furthermore, the indirect comparison estimates can also be used in sensitivity analyses, as illustrated in the example in Section 5, which would be useful for evaluating various biases (e.g., reporting, publication, and sponsorship biases) in practice. Similar investigations for assessing the influences of individual trials were previously conducted in [22-24], and our method provides additional relevant information for evaluating the validity of network meta-analysis. Comprehensive comparison of these approaches is outside the scope of this paper, but it is an important subject for future research. Also, it should be noted that there might be limitations to many of these methods, involving our developed method, because their validities are founded on large-sample theory.

In conclusion, this study proposes intuitive and effective methods for assessing the

inconsistency between direct and indirect evidence. These methods should provide useful information for the scientific evaluation and interpretation of network meta-analyses.

Acknowledgement

This study was supported by Grants-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan (Grant numbers: 26670314, 15K01351, 15K15954). Andrea Cipriani is supported by the NIHR Oxford Cognitive Health Clinical Research Facility.

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Table 1. Direct and indirect estimates between the pairwise comparisons of antidepressants (selected pairs with the smallest P-values for the inconsistency test).

	N_{dir}	Entire evidence [†]	$\hat{w}_{\text{dir}}^{\ddagger}$	Direct evidence	Indirect evidence	P-value [¶]
Citalopram vs. Escitalopram	4	0.84 (0.71, 0.99)	26.0%	0.68 (0.54, 0.85)	1.05 (0.84, 1.31)	0.007
Mirtazapine vs. Venlafaxine	2	1.07 (0.88, 1.29)	8.3%	1.53 (1.03, 2.27)	0.96 (0.77, 1.19)	0.042
Bupropion vs. Fluoxetine	3	1.06 (0.91, 1.25)	8.0%	0.82 (0.61, 1.11)	1.19 (0.98, 1.44)	0.042
Citalopram vs. Paroxetine	1	1.09 (0.92, 1.29)	6.3%	1.54 (1.03, 2.31)	1.02 (0.85, 1.23)	0.068
Bupropion vs. Sertraline	3	0.87 (0.73, 1.03)	16.3%	1.07 (0.79, 1.46)	0.78 (0.63, 0.97)	0.103
Fluoxetine vs. Sertraline	8	0.81 (0.71, 0.94)	29.3%	0.70 (0.56, 0.89)	0.88 (0.74, 1.06)	0.126
Fluvoxamine vs. Milnacipran	1	0.98 (0.71, 1.36)	11.4%	0.57 (0.26, 1.24)	1.10 (0.77, 1.58)	0.132
Fluvoxamine vs. Venlafaxine	1	0.77 (0.61, 0.98)	1.9%	0.42 (0.18, 0.97)	0.82 (0.64, 1.05)	0.137
Citalopram vs. Mirtazapine	1	0.81 (0.66, 1.01)	5.3%	1.32 (0.65, 2.68)	0.77 (0.62, 0.97)	0.153
Fluvoxamine vs. Sertraline	2	0.79 (0.62, 1.01)	4.2%	1.18 (0.65, 2.17)	0.74 (0.57, 0.96)	0.158
Fluoxetine vs. Venlafaxine	11	0.79 (0.70, 0.90)	39.1%	0.74 (0.61, 0.88)	0.85 (0.71, 1.02)	0.253
Fluvoxamine vs. Mirtazapine	1	0.73 (0.57, 0.92)	15.5%	0.88 (0.58, 1.32)	0.65 (0.48, 0.88)	0.259
Milnacipran vs. Sertraline	1	0.81 (0.6, 1.08)	0.5%	2.09 (0.35, 12.5)	0.79 (0.58, 1.06)	0.292

[†] The estimates of OR and 95% confidence intervals.

[‡] Contribution rate of the component of direct comparison trials estimated by the information fraction.

[¶] P-values of the tests of inconsistency between direct and indirect evidence.

Table 2. Results of sensitivity analyses that exclude direct evidence of citalopram vs. escitalopram (reference treatment: fluoxetine).

	Entire evidence		Indirect evidence [†]	
	OR (95% C.I.)	P-value	OR (95% C.I.)	P-value
Fluoxetine vs.				
Bupropion	0.94 (0.80, 1.11)	0.457	0.96 (0.82, 1.13)	0.617
Citalopram	0.92 (0.78, 1.07)	0.273	0.81 (0.68, 0.97)	0.021
Duloxetine	1.02 (0.83, 1.26)	0.866	1.07 (0.87, 1.32)	0.510
Escitalopram	0.77 (0.67, 0.89)	0.001	0.85 (0.72, 1.00)	0.045
Fluvoxamine	1.02 (0.82, 1.28)	0.834	1.01 (0.81, 1.26)	0.929
Milnacipran	1.01 (0.77, 1.31)	0.966	1.01 (0.78, 1.31)	0.950
Mirtazapine	0.74 (0.62, 0.89)	0.001	0.74 (0.62, 0.88)	0.001
Paroxetine	1.00 (0.89, 1.13)	0.955	1.02 (0.90, 1.14)	0.796
Reboxetine	1.48 (1.18, 1.86)	0.001	1.43 (1.14, 1.79)	0.002
Sertraline	0.81 (0.71, 0.94)	0.004	0.82 (0.71, 0.94)	0.005
Venlafaxine	0.79 (0.70, 0.90)	< 0.001	0.80 (0.71, 0.91)	0.001

[†] Estimates of comparative OR on the whole network that excludes direct evidence of citalopram vs. escitalopram.