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How do network meta-analyses address intransitivity when assessing certainty of evidence: a systematic survey

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ABSTRACT

Objectives To describe how systematic reviews with network meta-analyses (NMAs) that used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) NMA approach addressed intransitivity when assessing certainty of evidence.

Design Systematic survey.

Data sources Medline, Embase and Cochrane Database of Systematic Reviews from September 2014 to October 2022.

Eligibility criteria Systematic reviews of randomised controlled trials with aggregate data NMAs that used the GRADE NMA approach for assessing certainty of evidence.

Data extraction and synthesis We documented how reviewers described methods for addressing intransitivity when assessing certainty of evidence, how often they rated down for intransitivity and their explanations for rating down.

Results Of the 268 eligible systematic reviews, 44.8% (120/268) mentioned intransitivity when describing methods for assessing the certainty of evidence. Of these, 28.3% (34/120) considered effect modifiers and from this subset, 67.6% (23/34) specified the effect modifiers; however, no systematic review noted how they chose the effect modifiers. 15.0% (18/120) mentioned looking for differences between the direct comparisons that inform the indirect estimate. No review specified a threshold for difference in effect modifiers between the direct comparisons that would lead to rating down for intransitivity. Reviewers noted rating down indirect evidence for intransitivity in 33.1% of systematic reviews, and noted intransitivity for network estimates in 23.0% of reviews. Authors provided an explanation for rating down for intransitivity in 59.6% (31/52) of the cases in which they rated down. Of the 31 in which they provided an explanation, 74.2% (23/31) noted they detected differences in effect modifiers and 67.7% (21/31) specified in what effect modifiers they detected differences.

Conclusions A third of systematic reviews with NMAs using the GRADE approach rated down for intransitivity. Limitations in reporting of methods to address intransitivity proved considerable. Whether the problem is that reviewers neglected to address rating down for transitivity at all, or whether they did consider but not report, is not clear. At minimum systematic reviews with NMAs need to improve their reporting practices regarding intransitivity; it may well be that they need to improve their practice in transitivity assessment. How to best address intransitivity may remain unclear for many reviewers thus additional GRADE guidance providing practical instructions for addressing intransitivity may be desirable.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ We conducted a comprehensive systematic search of systematic reviews and network meta-analyses (NMAs) that used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) NMAs approach.

⇒ We conducted a detailed accounting of how the systematic reviews addressed intransitivity as one domain in the GRADE NMA approach, including description of methods for addressing intransitivity, and frequency and explanation for rating down for intransitivity.

⇒ Although all the included systematic reviews meet our criteria to be identified as using the GRADE NMA approach, we cannot rule out the possibility that some actually used the Confidence in Network Meta-Analysis (CINeMA)—another approach for assessing certainty of evidence from NMAs.

INTRODUCTION

Network meta-analysis (NMA), an analytic approach used to evaluate the comparative effects of multiple alternative interventions by combining both direct and indirect evidence, has gained considerable popularity.[1–3]

Using direct comparisons of intervention A versus C and B versus C as an example, NMAs can inform the relative effect of intervention A versus B through indirect comparisons via the common comparator C. One core assumption underlying the indirect comparison is transitivity: that is, effect modifiers between the direct comparisons A versus C and B versus C are similar enough to justify pooling.[1 4]

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group has developed an approach for assessing the certainty of evidence from NMAs which involves first rating the direct and indirect evidence separately.[5 6] Intransitivity represents one of the reasons for rating down the certainty of indirect evidence, and thus, when combined with the direct evidence, may influence the certainty of the network estimate. The GRADE NMA approach suggests that if effect modifiers differ in important ways across the direct comparisons that contribute to a specified indirect estimate (such as trials of A vs C and of B vs C that form the indirect comparison of A vs B), the likelihood of intransitivity may be high and therefore one should consider rating down the certainty of evidence from the indirect estimate.[5 6]

Although this conceptual basis of considering intransitivity as one reason for rating down the certainty of indirect evidence in the GRADE NMA approach is clear,[7 8] the practical application of this domain can be challenging. The challenges include how to identify important effect modifiers, how to compare effect modifiers between direct comparisons that form the basis for indirect comparison with different levels of effect modifiers, and deciding on a threshold for considering that these effect modifiers are different enough to warrant rating down for intransitivity. This remains relatively underdeveloped in terms of guidance from the GRADE working group.

To understand how NMA authors are addressing intransitivity (whether they addressed intransitivity and considered effect modifiers as suggested by the GRADE NMA approach, and how they solved problems in practical applications of the intransitivity domain), we conducted a systematic survey of systematic reviews (SRs) with NMAs in which authors used the GRADE NMA approach for assessing certainty of evidence. We determined how often authors rated down for intransitivity and how they described this assessment in the methods and results of their SRs.

METHODS

Eligibility criteria

We included SRs of randomised controlled trials in which authors conducted aggregate data NMAs and used the GRADE NMA approach for assessing the certainty of evidence.[5 6] To be identified as using the GRADE NMA approach, SRs must have met at least one of the following criteria:

1. cited at least one of the GRADE NMA approach general guidance papers[5 6] when describing their assessment of certainty of evidence in the Methods section of the article;
2. reported that they used the GRADE approach, and had at least one sentence describing an assessment of certainty of evidence for indirect or network estimates consistent with the GRADE NMA approach;
3. reported explicitly that they used the GRADE NMA approach or the GRADE approach for NMA, and absence of evidence suggesting they actually used the Confidence in Network Meta-Analysis (CINeMA) approach,[9 10] an alternative method for assessing the certainty of evidence from NMA.

We did not apply any restrictions on the topic of SRs. We excluded SRs not published in English and conference abstracts.

Search strategy and study selection

We searched Medline, Embase and the Cochrane Database of Systematic Reviews, from September 2014 to October 2022 (given the first GRADE NMA guidance article was published in September 2014) using a search strategy developed in collaboration with an experienced research librarian (online supplemental appendix 1). Pairs of reviewers screened, independently and in duplicate, titles and abstracts followed by full texts. Reviewers resolved conflicts by discussion or by consultation with a third reviewer.

Data extraction

Pairs of reviewers independently extracted the following information from each included SR, including appendices. They resolved discrepancies by discussion or by involving a third reviewer.

Methods describing the assessment of intransitivity

1. Whether authors mentioned the word intransitivity or not when describing methods for assessing the certainty of evidence from NMAs.
2. For SRs that mentioned intransitivity, whether or not authors noted the following as methods for addressing intransitivity (from the least to the most detailed description):
   - Consideration of effect modifiers (ie, mention of the words ‘effect modifiers’ or ‘effect modification’, or specification of effect modifiers).
     - Specification of what factors they considered as effect modifiers.
       - Methods for identifying effect modifiers.
3. For SRs that mentioned intransitivity, how authors expressed their evaluation of intransitivity (following are possible expressions):
   - Looking for differences between the direct comparisons that inform the specific indirect estimate (the optimal description).
   - Looking for differences across comparisons (inaccurate description).
   - Looking for differences between trials (inaccurate description).
   - Only mention of the word ‘differences’ without any other details (insufficient description).
   - No mention.
4. For SRs that mentioned intransitivity, considered effect modifiers, and mentioned looking for differences: whether authors reported the degree of difference in

effect modifiers between the direct comparisons that would lead them to rate down for intransitivity (ie, the threshold).

Frequency for rating down for intransitivity for indirect estimates

1. Whether authors presented certainty of evidence and reasons for rating down indirect estimates.
2. For SRs that presented certainty of evidence and reasons for rating down, whether authors rated down the certainty of any indirect estimate due to intransitivity.
3. For SRs that rated down for intransitivity, the total number of indirect estimates, and the number of indirect estimates rated down for intransitivity.
4. For comparisons in which authors rated down the indirect estimates for intransitivity, whether the decision regarding rating down for intransitivity affected the final certainty rating of indirect estimates. This is relevant because rating down for intransitivity will not always result in rating down the certainty of the indirect estimate (ie, if the certainty of the indirect evidence was very low before addressing intransitivity, the judgement of intransitivity will not impact the final rating of certainty of evidence).

Influence of rating down for intransitivity on network estimates certainty ratings

1. Whether authors presented certainty and reasons for rating down network estimates.
2. For SRs that presented certainty of evidence and reasons, whether authors noted intransitivity for any network estimate (ie, authors rated down the certainty of any indirect estimate due to intransitivity and the indirect estimate dominates the network estimate).

Explanations for rating down for intransitivity

For SRs that rated down the certainty of any indirect estimate for intransitivity:

1. Whether authors provided an explanation for rating down, in addition to mentioning 'serious' or 'very serious' intransitivity.
2. Whether authors noted each of the following as explanation for rating down:
   - They detected differences in effect modifiers.
     - Specified in what effect modifiers they detected differences.
       - How they chose the effect modifiers.
3. Whether authors specified they detected differences between the direct comparisons that inform the indirect estimate.

Rating down for indirectness

1. For SRs that did not rate down for intransitivity, whether they rated down the certainty of all indirect estimates due to indirectness.
2. For SRs that did not rate down for intransitivity, whether they rated down the certainty of indirect estimates due to indirectness for all comparisons that did not have direct evidence.

Data synthesis and analysis

We calculated the proportion of SRs in which authors rated down for intransitivity for any indirect and network estimate (ie, number of SRs that rated down for intransitivity/number of SRs that presented certainty of evidence and reasons).

For SRs rating down for intransitivity for indirect estimates, we calculated the proportion of indirect estimates authors rated down for intransitivity (ie, number of indirect estimates that rated down for intransitivity/total number of indirect estimates), and present the median and IQR across SRs.

For SRs rating down for intransitivity for indirect estimates, we calculated the proportion of indirect estimates for which rating down for intransitivity affected the final certainty of indirect estimates (ie, number of indirect estimates for which rating down for intransitivity affected the final certainty/number of indirect estimates that rated down for intransitivity), and present the median and IQR across SRs.

We conducted simple logistic regression analyses to explore, at the SR level, whether the outcome rating down for intransitivity (rating down at least one comparison vs not rating down any comparison) was related to the methods that authors described for addressing intransitivity. We separately considered whether there was: mention of intransitivity at least once in the manuscript vs no mention at all, consideration of effect modifiers (ie, mention of the words 'effect modifiers' or 'effect modification' or specification of effect modifiers, vs no such mention), specification of what factors the authors considered as effect modifiers versus no such specification, specification of looking for differences between the direct comparisons that inform the indirect estimate versus no mention of looking for such differences. Our hypothesis was that one reason that some SRs did not rate down for intransitivity might be that authors did not check intransitivity sufficiently (rather than they checked and concluded problematic transitivity was absent). We performed regression analyses using Stata V.15.1.

To explore the relationship between publication year and rating down for intransitivity, we compared the publication years between the SRs that rated down for intransitivity for at least one comparison and the SRs that did not rate down for intransitivity for any comparison.

Patient and public involvement

This survey did not involve patient or public in the design, or conduct, or reporting, or dissemination plans.

RESULTS

Search results

The search identified 3430 records, from which we screened 2077 titles and abstracts and 995 full texts. We included 268 SRs that used the GRADE NMA approach for assessing the certainty of evidence from NMAs

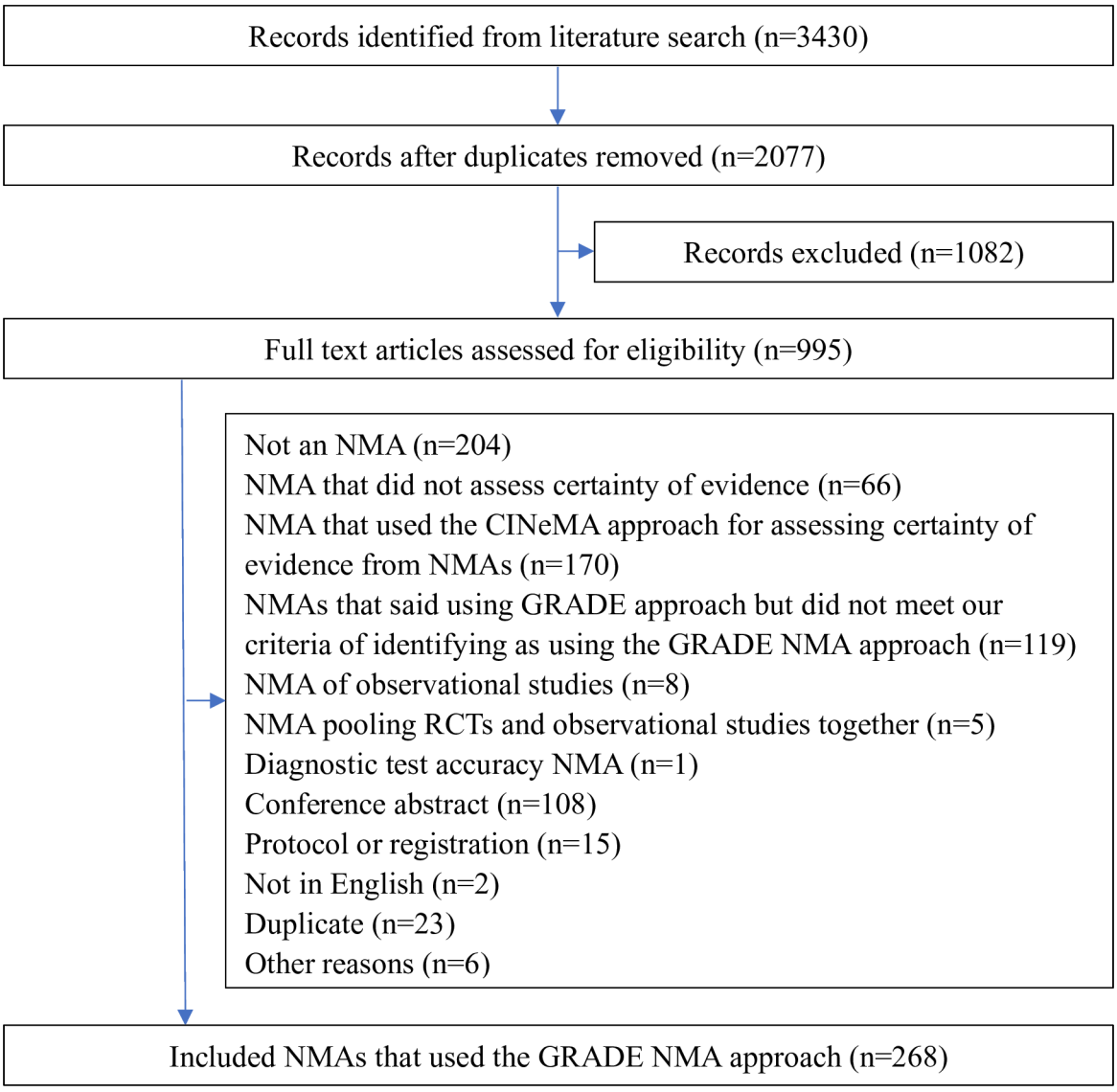

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of studies included in this systematic survey. NMA, network meta-analyses; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; RCTs, randomised controlled trials.

(figure 1). Online supplemental appendix 2 contains a list of included SRs and a list of excluded studies.

Methods for addressing intransitivity when assessing the certainty of evidence from NMAs

Of the eligible SRs, 44.8% (120/268) mentioned intransitivity when describing methods for assessing the certainty of evidence, among which 43.3% (52/120) provided no description at all about the methods for addressing intransitivity (table 1).

Among the 120 that mentioned intransitivity, 28.3% (34/120)[11–43] noted that they considered effect modification as the relevant issue when addressing intransitivity. Of these 34, 67.6% (23/34)[11–13 15 17 19–21 23–29 32 34–37 39 40 44] further specified which factors they considered as effect modifiers, none of which specified how they identified effect modifiers. The number of effect modifiers listed ranged from 1 to 9 (median 3). Effect modifiers included population characteristics (eg, age), disease status (eg, disease severity), intervention characteristics (eg, dosage), outcome characteristics (eg, follow-up time of outcome measurement), cointerventions, trial characteristics (eg, year of publication) and trial methodology (eg, risk of bias) (online supplemental appendix 3).

Of the 120 SRs that mentioned intransitivity, 15.0% (18/120)[14–17 21 30–32 37 45–51] explicitly said they looked for differences between the direct comparisons that inform the indirect estimate, of which 2[15 17] specified doing this in the comparisons forming a first order loop. Although about a third of SRs mentioned looking for differences, their description was insufficient or inaccurate: 8.3% (10/120) mentioned looking for differences across comparisons, 23.3% (28/120) mentioned looking for differences between trials, and 2.5% (3/120) only mentioned the word differences without any other details.

Table 1 Summary of how systematic reviews described methods for addressing intransitivity

Mention of intransitivity when describing methods for assessing the certainty of evidence from NMAs	**44.8% (120/268)**
Described methods for addressing intransitivity	
Yes	56.7% (68/120)
No	43.3% (52/120)
Information about effect modifiers	
Consideration of effect modifiers	28.3% (34/120)
Specification of effect modifiers	67.6% (23/34)
Methods for identifying effect modifiers	0% (0/23)
No consideration	71.7% (86/120)
Methods for comparing differences	
Looking for differences between the direct comparisons that inform the indirect estimate	15.0% (18/120)
Looking for differences across comparisons	8.3% (10/120)
Looking for differences between trials	23.3% (28/120)
Only mention of the word 'differences' without any other details	2.5% (3/120)
No mention	50.8% (61/120)
Mention of how much difference in effect modifiers between the direct comparisons would lead to rate down for intransitivity	
Ye	0% (0/120)
No	100% (120/120)

Table 2 Frequency of rating down for intransitivity

Indirect estimates (total number of systematic reviews presented certainty of indirect estimates and reasons for rating down=118)	
Systematic reviews rating down for intransitivity for any indirect estimate	33.1% (39/118)
Proportion of indirect estimates that rated down for intransitivity among all indirect estimates within one systematic review	Median 32.9% (IQR 21.5%–89.7%)
Proportion of indirect estimates for which rating down for intransitivity affected the ultimate certainty of indirect estimates	Median 100% (IQR 45.5%–100%)
Network estimates (total number of systematic reviews presented certainty of network estimates and reasons for rating down=196)	
Systematic reviews rating down for intransitivity for any network estimate	23.0% (45/196)

No SR explicitly reported how much difference in effect modifiers between the direct comparisons would warrant rating down for intransitivity (ie, the threshold). Two SRs[13 19] included tables that presented mean, median or mode of effect modifiers for each head-to-head comparison; however, it is unclear how these were calculated and how authors used them to inform rating down for intransitivity. Five SRs,[15 26 34 40 44] to inform whether to rate down for intransitivity, explored the impact of effect modifiers on effect estimates by conducting network meta-regression analyses. Two SRs explored the impact of effect modifiers by conducting sensitivity analysis.[52 53] Two SRs[54 55] addressed intransitivity by assessing whether all the direct comparisons contributing to the indirect estimate were consistent with the PICO (Population, Intervention, Comparator, and Outcome) question.

Frequency and reasons for rating down for intransitivity

One hundred and eighteen SRs presented assessments of certainty of indirect estimates and reasons for rating down, of which 33.1% (39/118) rated down the certainty of indirect estimates due to intransitivity (table 2). One hundred and ninety-six SRs presented certainty of network estimates and reasons for rating down, of which 23.0% (45/196) noted intransitivity for network estimates (ie, authors rated down the certainty of indirect estimates due to intransitivity and the indirect estimates dominate the network estimates). In total, 52 SRs rated down indirect estimates for intransitivity (including the 39 SRs noted rating down indirect estimates for intransitivity, and 13 SRs that did not noted rating down for intransitivity for indirect estimates but noted for network estimates).

For the 39 SRs that rated down the certainty of indirect estimates due to intransitivity, the proportion of indirect estimates that rated down for intransitivity among all indirect estimates within one SR varies with median proportion of 32.9% (IQR 21.5%–89.7%).

Among the 39 SRs rating down indirect estimates due to intransitivity, 15.4% (6/39)[14 19 20 56–59] rated down the certainty of all indirect estimates due to intransitivity while 7.7% (3/39)[22 60 61] rated down the certainty of indirect estimates due to intransitivity for all comparisons that did not have direct evidence.

Although they did not rate down for intransitivity, 10 SRs[44 58 62–69] rated down the certainty of indirect estimates due to indirectness, of which 4[58 66 67 69] rated down the certainty of all indirect estimates due to indirectness and other 6[44 62–65 68] rated down the certainty of indirect estimates due to indirectness for all comparisons that did not have direct evidence.

Explanations for rating down for intransitivity

Among the 52 SRs that rated down an indirect estimate due to intransitivity, 59.6% (31/52)[14 17–20 28 32 34 35 37 50 57–59 70–85] provided an explanation (table 3, online supplemental appendix 4).

Among the 31 SRs providing an explanation for rating down due to intransitivity, 74.2% (23/31)[14 17–20 28 32 34 35 37 50 57–59 70 71 76–82] noted they detected differences in effect modifiers; of which 23 SRs, 91.3% (21/23)[17 19 20 28 32 34 35 37 50 57–59 70 71 76–82] specified further

Table 3 Explanation for rating down for intransitivity

Provided explanation for rating down for intransitivity	59.6% (31/52)
Information about effect modifiers	
Detected differences in effect modifiers	74.2% (23/31)
Specified in what effect modifiers they detected differences	91.3% (21/23)
Methods for identifying effect modifiers	14.3% (3/21)
Detected differences between the direct comparisons that inform the indirect estimate	19.4% (6/31)

in what effect modifiers they detected differences. Three SRs[11 76 80] mentioned how they chose the effect modifiers: 2[11 80] were based on prior SR results and 1[76] was based on prior knowledge (Appendix 4).

19.4% (6/31) of the SRs[17 18 32 57 71 76] reported that they detected differences between the direct comparisons that informed the specific indirect estimate.

Ten SRs[56 59 61 77–79 82 83 85 86] considered indirectness and intransitivity as one domain or mentioned indirectness when they reported explanations for rating down for intransitivity.

Relationship between rating down for intransitivity and the methods they described for addressing intransitivity

Regression analyses suggested that mention of intransitivity, consideration of effect modifiers, specification of effect modifiers and mention of looking for differences between the direct comparisons that inform the indirect estimate in the Methods section, are associated with rating down for intransitivity (table 4).

Relationship between rating down for intransitivity and the publication year

From 2015 to 2018, the proportion of SRs that rated down for intransitivity for at least one comparison increased from 20.0% to 30.0%. After 2018, the proportion decreased (online supplemental appendix 5).

Table 4 Relationship between rating down for intransitivity and the methods they described for addressing intransitivity

Mention of intransitivity	OR 2.50, 95% CI 1.33 to 4.69
Consideration of effect modifiers	OR 3.71, 95% CI 1.72 to 7.99
Specification of effect modifiers	OR 5.13, 95% CI 2.08 to 12.63
Mention of looking for differences between the direct comparisons that inform the indirect estimate	OR 3.28, 95% CI 1.18 to 9.08

DISCUSSION

Over half of the SRs using the GRADE NMA approach failed to mention intransitivity when describing their use of the GRADE methodology. Of those that did mention intransitivity when introducing methods for assessing certainty of evidence, only approximately half described their methods for addressing intransitivity. Approximately one-third of the SRs rated down the certainty of indirect estimates for intransitivity; however, only a half of them provided an explanation for rating down.

Methodologists generally agree that judgement regarding intransitivity depends on inferences regarding effect modification.[5 8] About one-third of the SRs that mentioned of intransitivity noted consideration of effect modifiers when describing methods for addressing intransitivity. For the SRs that rated down the certainty of evidence for intransitivity, most noted they detected differences in effect modifiers and specified what effect modifiers they detected differences in as explanation for rating down.

However, authors seldom reported how they identified the effect modifiers. Two studies[11 80] cited prior SRs as their rationale for choosing the effect modifiers. Indeed, identification of effect modifiers should involve not only searching for evidence of effect modification, but also assessing the credibility of effect modification.[87]

To judge whether to rate down for intransitivity, one needs to judge if the effect modifiers differ in important ways between the direct comparisons that contribute to the indirect estimate.[8] Our results showed that only a small proportion of the SRs clearly specified that they looked for or detected differences between the direct comparisons that inform the indirect estimate.

Inaccurate descriptions included looking for differences across comparisons or between trials. For instance, in one NMA, there may be important differences between the direct comparisons of A versus C and B versus C, but no important differences between the direct comparisons of A versus C and D versus C. Thus, judging intransitivity for assessing certainty of evidence should be comparison specific.

How to compare effect modifiers between the direct comparisons that form the basis for indirect comparison with different levels of effect modifiers presents challenges in practice. Two studies[13 19] included tables that presented mean, median or mode of effect modifiers for each direct comparison, which may imply that they considered trials comparing the same interventions as a whole when comparing the distribution of effect modifiers. Other SRs did not make this point clear.

Judgements regarding whether to rate down for intransitivity is a threshold issue, which involves both how much credibility of effect modification would lead to consider the effect modifiers when judging intransitivity, and how much difference in effect modifiers between the direct comparisons would lead to rate down for intransitivity. No study clearly specified or addressed either of these issues.

Among the SRs rating down for intransitivity, proportions of indirect comparisons that rated down for intransitivity differ across studies. Notably, six studies[14 19 20 56–59] rated down the certainty of all indirect estimates due to intransitivity, and three[22 60 61] rated down the certainty of indirect estimates due to intransitivity for all comparisons that did not have direct evidence. These studies take the extreme position that there is always residual effect modification.

Some SRs confused intransitivity with indirectness. Two SRs[54 55] addressed intransitivity by assessing whether all the direct comparisons contributing to the indirect estimate were directly consistent with the PICO question, which is indirectness[88] rather than intransitivity in the GRADE system. Ten SRs[56 59 61 77–79 82 83 85 86] regarded indirectness and intransitivity as one domain or mentioned indirectness when they reported explanation for rating down for intransitivity. Although the first version of the GRADE NMA guidance[6] stated indirectness refers to two concepts: (1) differences between the question of interest and the body of evidence used to inform the question and (2) intransitivity; the latest GRADE NMA guidance[5] had specified the word indirectness refers only to the first concept and endorsed intransitivity as a separate issue. This inconsistency in GRADE guidance could contribute to confusion on the part of NMA authors.

Although this survey focused only on SRs using the GRADE NMA approach, CINeMA provides another approach for assessing certainty of evidence from NMAs.[9] These two approaches address intransitivity differently. The CINeMA approach addresses intransitivity in the indirectness domain.[9] However, in the GRADE NMA approach, intransitivity represents a separate domain.[5 6] This might explain why some SRs using the GRADE NMA approach confused intransitivity with indirectness.

Another domain in the GRADE NMA approach that is easily confused with intransitivity is incoherence, which addresses the inconsistency between the direct and indirect estimates.[5 89]

Regression analyses suggested that the SRs reporting methods for addressing intransitivity are associated with higher rate of rating down for intransitivity. This suggests that the reason why some SRs did not rate down for intransitivity might not be that they checked and failed to find intransitivity, but rather that the authors did not check for intransitivity at all.

This is the first systematic survey investigating how the SRs that used the GRADE NMA approach for assessing certainty of evidence from NMAs described methods for addressing intransitivity, frequency of rating down for intransitivity, explanation for rating down and whether rating down for intransitivity had an important influence on ultimate certainty. Strengths of this survey include comprehensive search, transparent eligibility criteria and thorough extraction of information regarding intransitivity. We identified existing reporting problem about intransitivity, providing areas in which reviewers can improve their reporting practices. In addition, we identified the practical problems of addressing intransitivity that reviewers face—these are the issues that the GRADE working group needs to address.

This systematic survey has limitations. Some SRs did not clearly present reasons for rating down the certainty of indirect estimates, so we cannot identify whether they have rated down for intransitivity. In accordance with the GRADE NMA approach, consideration of imprecision is unnecessary when assessing the direct and indirect estimates to inform the assessment of network estimates[5]; thus, some SRs did not assess imprecision for indirect estimates—we cannot determine whether their rating down for intransitivity affected the ultimate certainty of these indirect estimates. Although all the included SRs meet our criteria to be identified as using the GRADE NMA approach, because authors were sometimes unclear regarding the difference between the GRADE NMA approach and the CINeMA approach—especially for those SRs that considered intransitivity and indirectness together—we cannot rule out the possibility that some actually used the CINeMA approach. Because this is a methodological study (systematic survey) and does not meet the eligibility criteria for publication in PROSPERO,[90] we did not register a protocol. We did, however, work with a protocol that we refined as we became familiar with the eligible studies. Another limitation is we did not document number of outcomes and indirect estimates for each included SR.

In conclusion, this systematic survey showed that the majority of NMAs using the GRADE approach did not mention intransitivity as an issue in rating the certainty of indirect evidence and those that did had major limitations in reporting their methods for addressing intransitivity. Even for SRs rating down for intransitivity, reporting of the explanation for rating down proved to be often limited. Reasons why these reporting problems exist might be explained by conducting a qualitative study including interviews with authors of NMAs. However, the reporting problems may reflect failure to appropriately address transitivity or simply a reporting issue. If the problem is failure to address transitivity, additional GRADE guidance on how to address intransitivity practically may be desirable.

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extraction. YW analysed the data. YW, RBP and GG draft the manuscript. RX, TP, GEB, LH, MMB, YG, MW, DG, RAS, YF and BR reviewed, revised and approved this manuscript. YW is responsible for the overall content as guarantor.

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