

Confidence in Network Meta-analysis: Concept and Methodology

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Introduction

Methodology

Rating of confidence

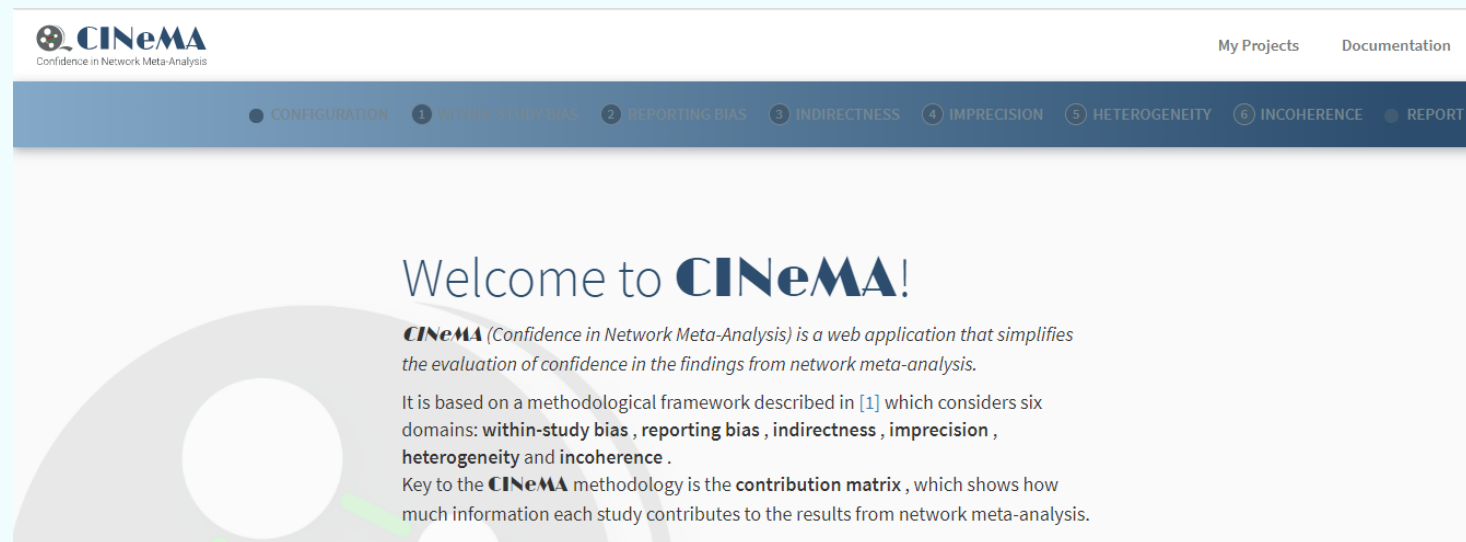
Introduction

Background

- **Network meta-analysis combines evidence from direct and indirect comparisons, to provide useful information for decision making in healthcare.**
 - **Establishing confidence in the Network meta-analysis (NMA) is important to enhance the credibility of the final results.**
- **Confidence In Network Meta-Analysis (CINeMA) is a framework designed to assess network meta-analysis results to establish confidence.**
 - **It assesses the process of conducting the systematic review to statistical analysis and results, using specific domains.**

Framework

- CINeMA framework can be applied to a NMA dataset through the free web application [<https://cinema.ispm.unibe.ch/>] (CINeMA, 2017)]



Source: CINeMA Confidence In Network Meta-Analysis <https://cinema.ispm.unibe.ch/>

Domains

The confidence of results of the NMA is assessed using six main domains.

1. Within-study bias

2. Reporting bias

3. Indirectness

4. Imprecision

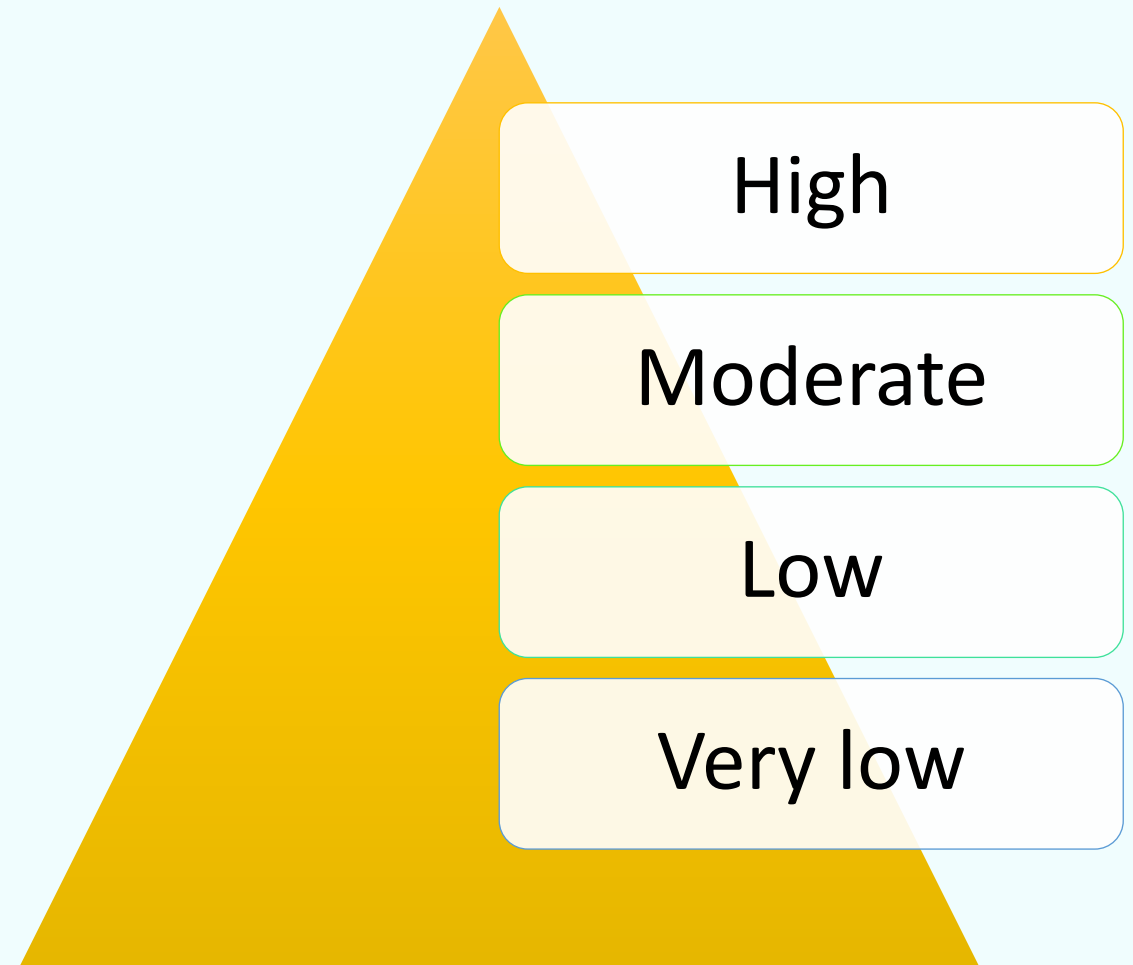
5. Heterogeneity

6. Incoherence

Each comparison of interest is rated by assigning judgements for the domains ('no concern', 'some concerns', 'major concerns').

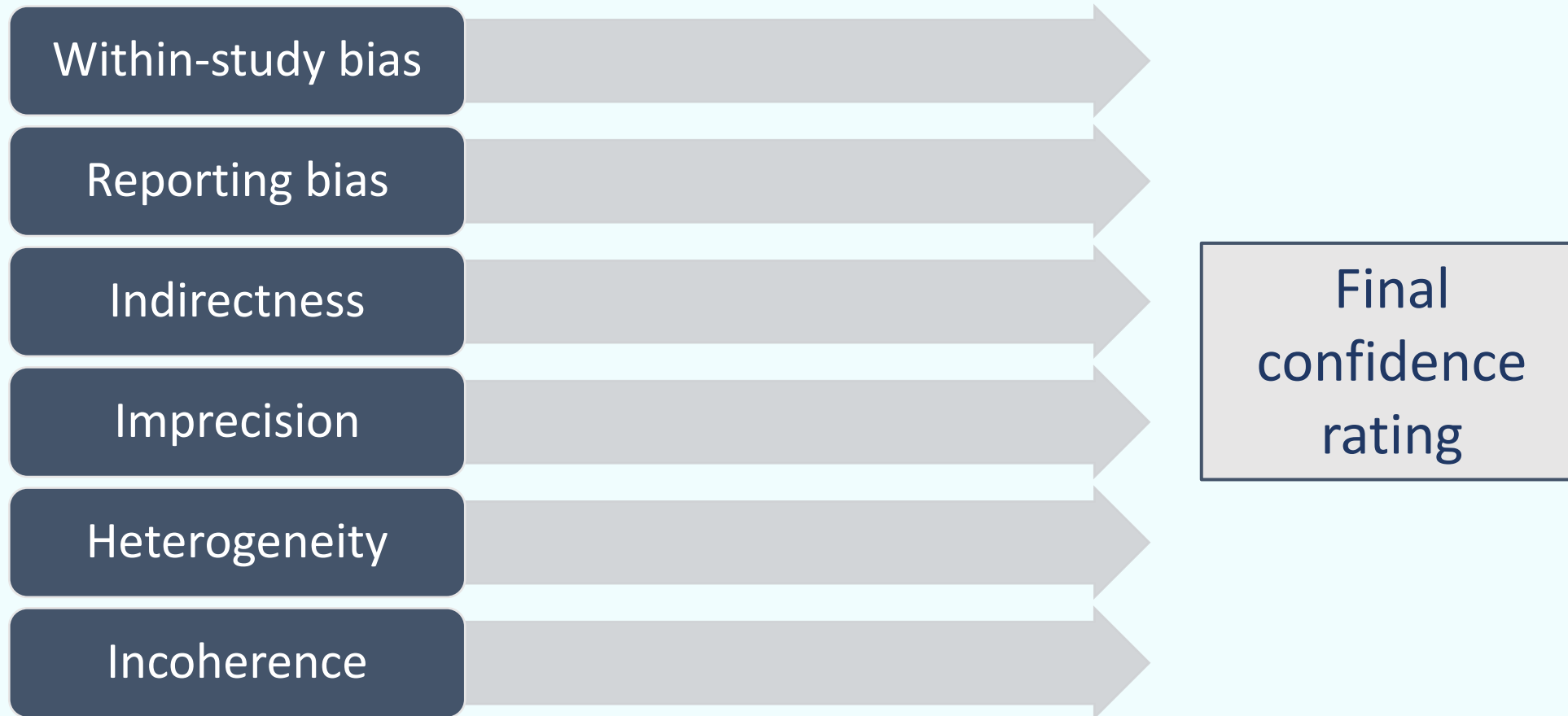
Levels of confidence

The final rating of confidence will be determined based on the judgments of each domain.



Methodology

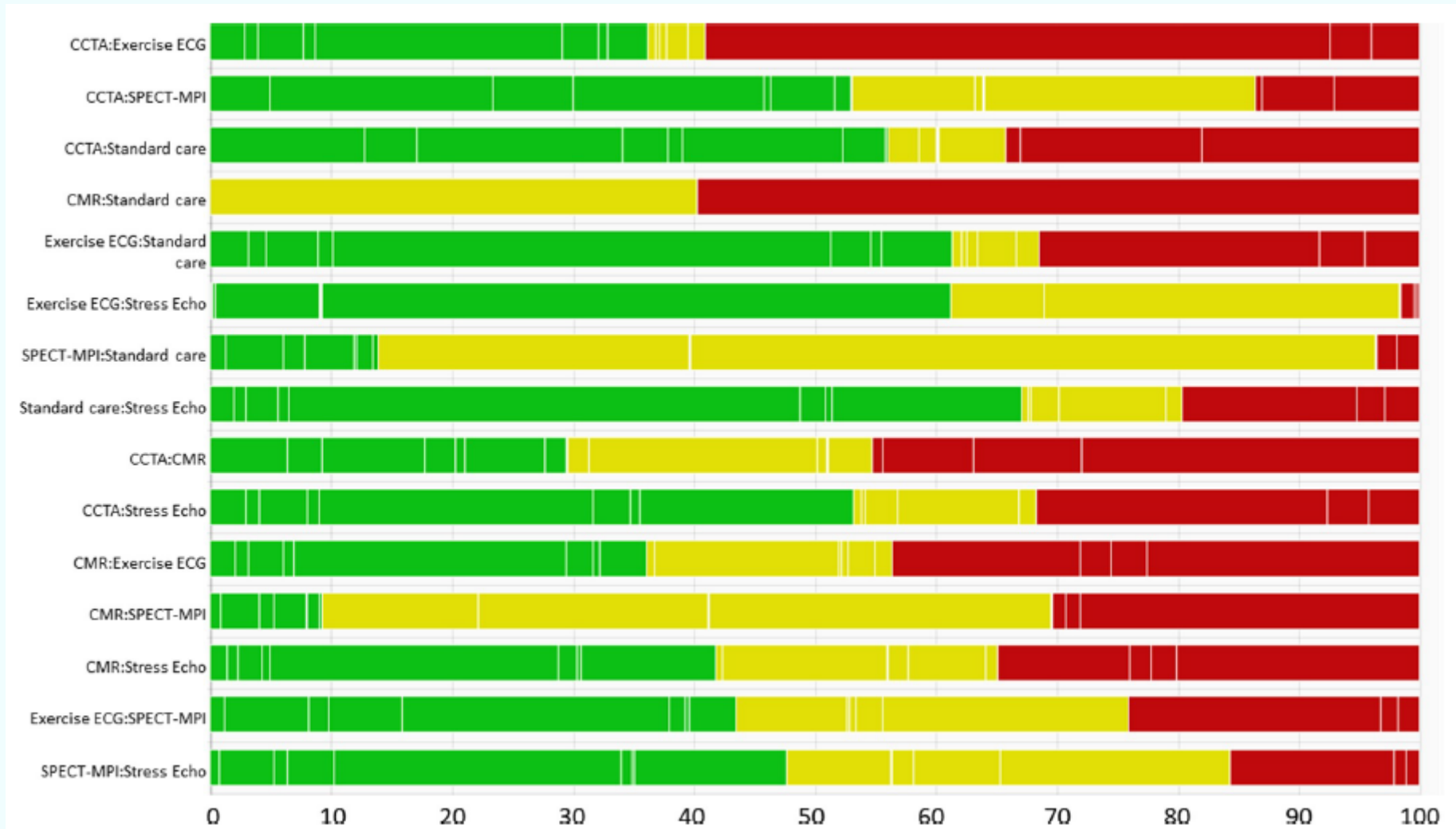
Domains



Within-study bias

- Within-study bias is based on the risk of bias assessment for each study.
- It evaluates the risk of bias of studies which provide both direct and indirect evidence for the treatment comparison of interest.
- In the first step, each study is ranked by the Risk of bias (RoB) assessment as **‘low’**, **‘moderate’**, **‘high’** risk.
- CINeMA evaluates the within-study bias using the ranks of each study and percentage of contribution of each study for the estimate from the NMA.

Within-study bias



Source: Nikolakopoulou A, et al. CINeMA: An approach for assessing confidence in the results of a network meta-analysis PLOS Medicine 2020 17 1-19

Within-study bias

The judgement of within-study bias included for the treatment comparison can be determined as,

- “majority RoB”- most prevalent bias level or
- “average RoB”- average bias of the included studies or
- “highest RoB”- maximum bias level,

for each comparison

Indirectness

- Indirectness assess relevance of the included studies to the research question and transitivity in the network meta-analysis.
- **Accordingly, each study can be categorized as ‘low’, ‘moderate’, or ‘high’ indirectness.**
- The level of judgement for each treatment comparison will be calculated similar to within-study bias, combining the study level judgement with percentage contribution from the respective studies.
- The levels of judgement can be selected based on the
 - “Majority Indirectness”, “Average Indirectness”, “Highest Indirectness”, chosen according to interest.

Reporting bias

- Reporting bias domain assess the effect of publication bias, time-lag bias and reporting bias.
- **The level of reporting bias can be ranked as “suspected” or “undetected”.**
- The characteristics of the published studies, their protocols and unpublished/ grey literature for each treatment comparison of interest, needs to be evaluated.
- Evaluation by comparison adjusted funnel plots, sensitivity analyses, and regression analyses can also assist the determination of the presence of reporting bias for each treatment comparisons.

Reporting bias

- The level of bias should be based on characteristics of studies and can be set according to assessment.

Suspected

- Failure to include unpublished data and data from grey literature.
- Meta-analysis is based on a small number of positive early findings.
- Treatment comparison is studied exclusively or primarily in industry-funded trials.

Undetected

- Data from unpublished studies have been identified. Their findings agree with those of published studies.
- Protocols or clinical trial registries do not indicate important discrepancies with published reports.
- Examination of patterns of results between small and large studies , using comparison-adjusted, regression or selection models do not indicate a difference of results in small studies.

Range of clinical equivalence

The assessment of the 3 domains of imprecision, heterogeneity, and incoherence will be based on the range of equivalence.

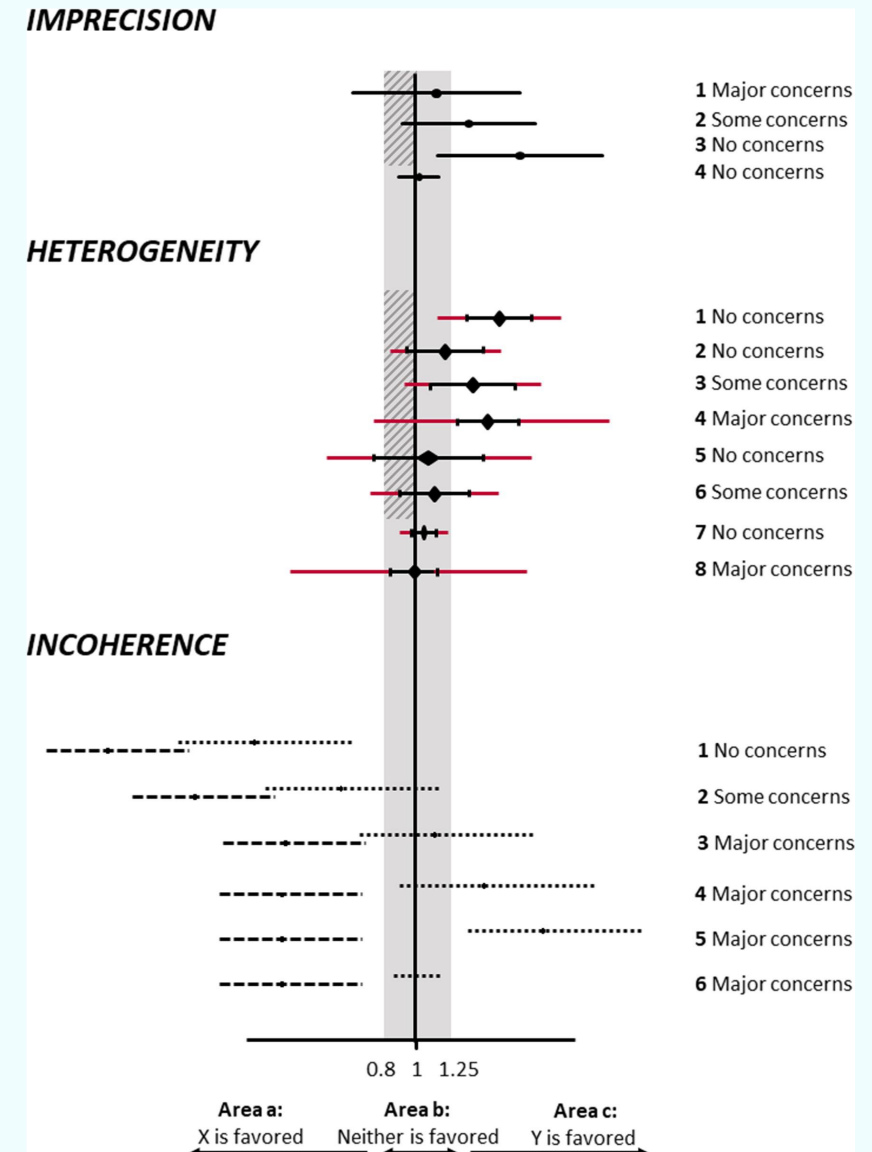
It corresponds to clinically unimportant differences of effect between interventions.

The range will be defined based on the relative treatment effect between interventions.

Range of clinical equivalence

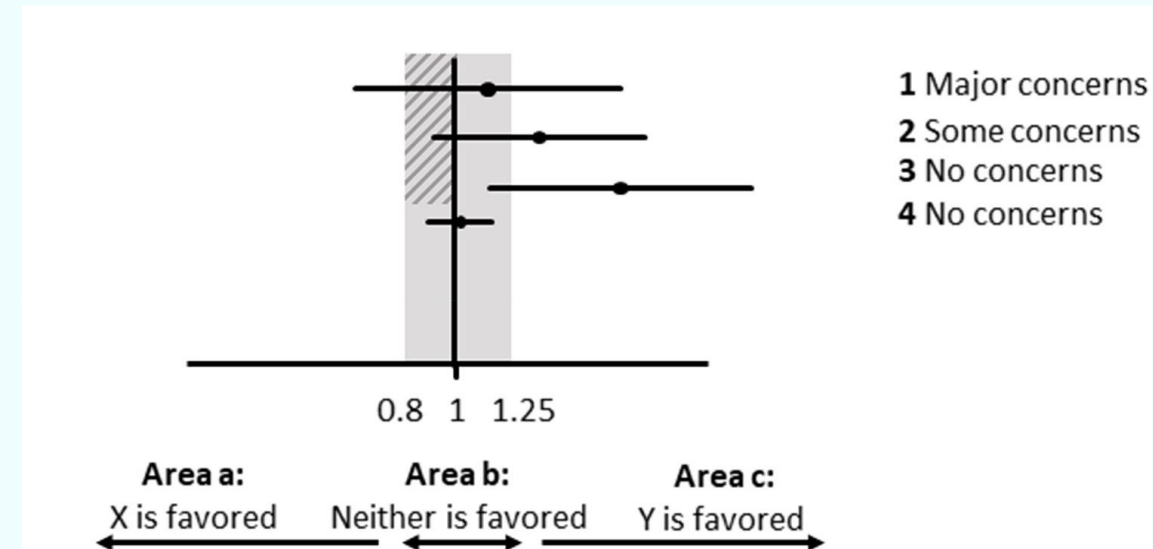
In CINeMA, the range will be symmetrical, and the values are set as determined by the user.

E.g., clinically important effect size set: Odds ratio less than 0.80 and more than 1.25 (= 1/0.8), range of equivalence (0.8-1.25).



Imprecision

- Imprecision is evaluated based on the relative treatment effect and the range of equivalence, to identify if a beneficial effect is shown.
- The 95% confidence interval (95% CI) of effect is compared with the range of equivalence and the intervention comparison is ranked as having,
 - “No concerns”
 - “Some concerns” or
 - “Major concerns”

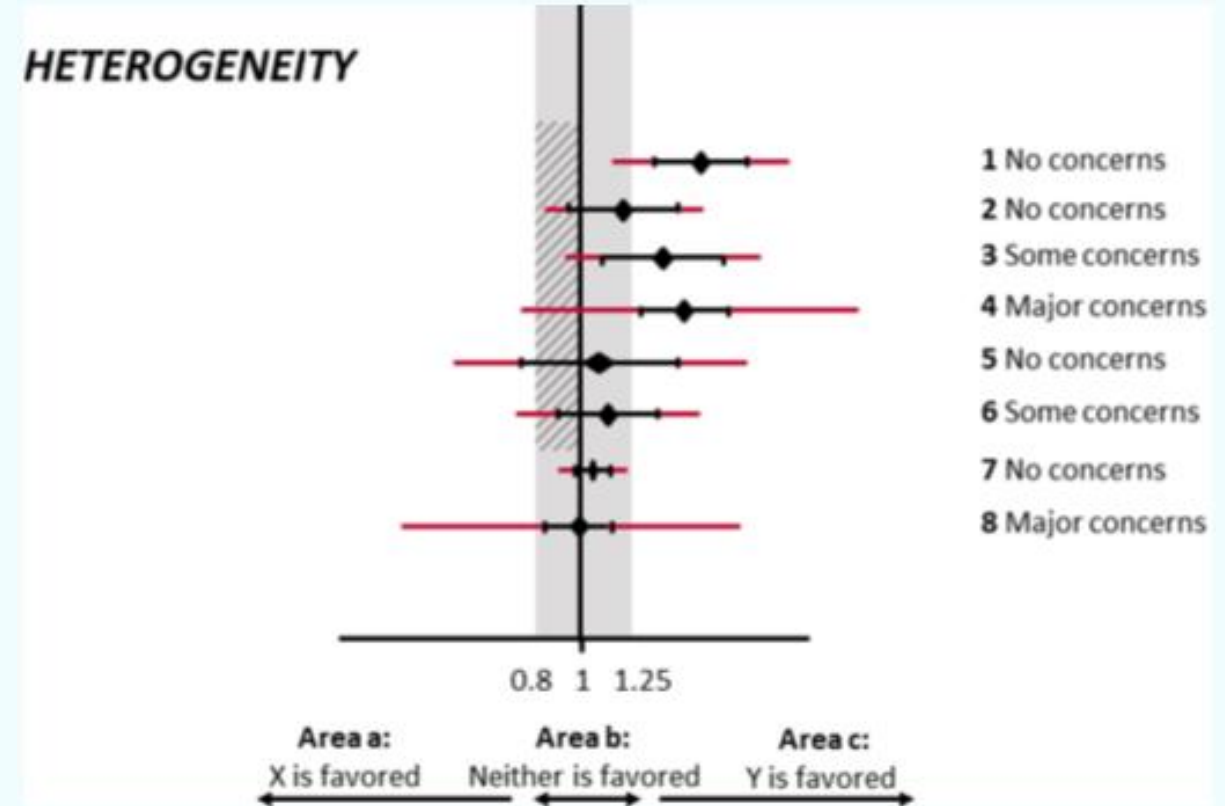


Source: Nikolakopoulou A, et al. CINeMA: An approach for assessing confidence in the results of a network meta-analysis PLOS Medicine 2020 17 1-19

Heterogeneity

- Heterogeneity is assessed by comparing the confidence intervals and prediction intervals of the treatment effect with the range of equivalence.
- The range of equivalence / clinically important size of effect will be same as specified earlier.
- The judgement of heterogeneity will be based on if the confidence intervals and prediction intervals lead to the same or different conclusion.

- “No concerns”
- “Some concerns”
- “Major concerns”



Black lines show confidence intervals(CI), and red lines prediction intervals(PrI).

Source: Nikolakopoulou A, et al. CINeMA: An approach for assessing confidence in the results of a network meta-analysis PLOS Medicine 2020 17 1-19

Incoherence

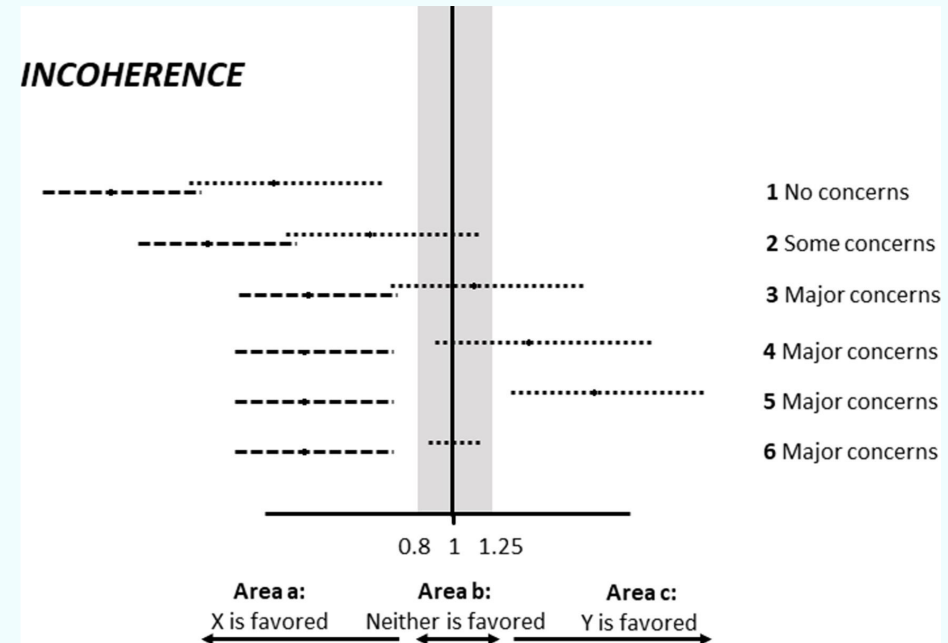
- Incoherence/ inconsistency occurs with the variation of direct and indirect evidence.
- In CINeMA, incoherence is assessed by both global approach and local approach (node splitting / SIDE method).
- The test of design-by-treatment model for global approach, and inconsistency factor of each comparison for local approach is used for the assessment.
- **Incoherence is further evaluated with visual inspection of the 95% CI of direct and indirect effect and the range of equivalence.**

Incoherence

- All comparisons with $p > 0.10$ value from SIDE is determined “No concerns”.
- For effect estimates with both direct and indirect evidence and with a $p < 0.10$ from SIDE, position of the 95% CI of direct effect and indirect effect relative to the range of equivalence determines incoherence as

“No concerns”, “Some concerns” or

“Major concerns”



Dashed lines- direct effects; dotted lines- indirect effects

Source: Nikolakopoulou A, et al. CINeMA: An approach for assessing confidence in the results of a network meta-analysis PLOS Medicine 2020 17 1-19

Incoherence

- If there is only direct or only indirect evidence, the p-value of the global design-by-treatment will be considered for incoherence.
 - “major concerns” if $p < 0.05$,
 - “some concerns” if p between 0.05 - 0.10, and
 - “no concerns” if $p > 0.10$.
 - “major concerns” if the design-by-treatment interaction test statistic cannot be computed due to the absence of closed loops.

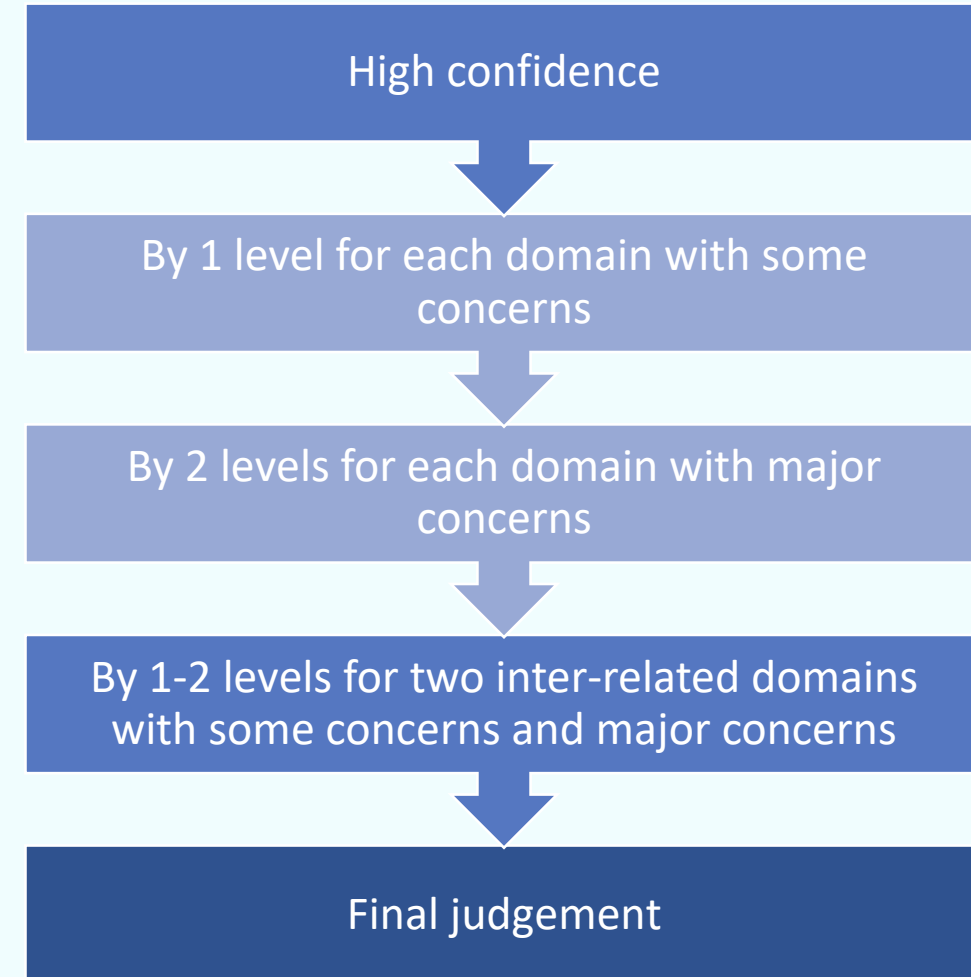
Global test based on a random-effects design-by-treatment interaction model
 χ^2 statistic: 3.137 (2 degrees of freedom), P value: 0.208

Comparison	A:D
Evidence: direct	
Direct risk ratio:	0.912(0.547,1.521)
Inconsistency measures: Not applicable	
Incoherence judgment	No concerns ▼

Rating of confidence

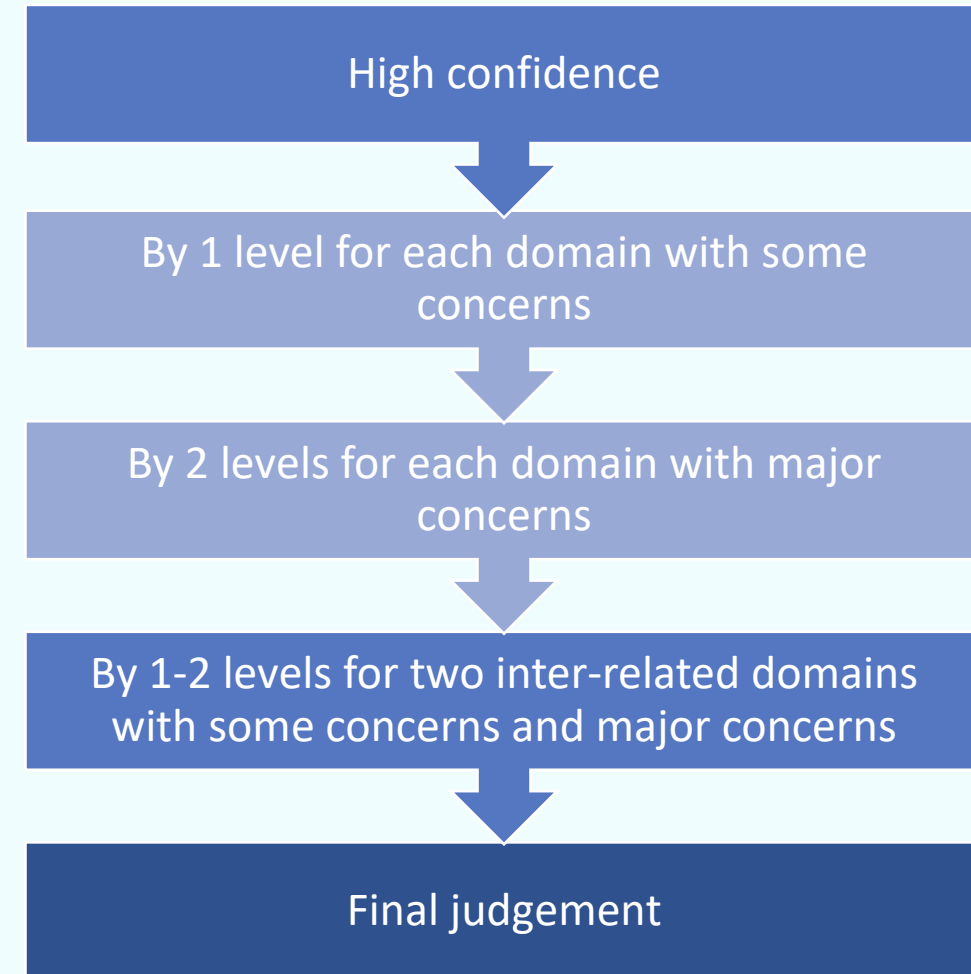
Judgement for level of confidence by 6 domains

- The final judgement for each comparison of the NMA is summarized by 4 levels of confidence,
 - **High**
 - **Moderate**
 - **Low**
 - **Very low.**
- The final judgement for each comparison can be rated down starting from high confidence to lower levels by dropping the level of confidence for domains rated some concerns, major concerns.



Judgements for level of confidence by 6 domains

- Due to the inter relations of certain domains with each other (i.e., indirectness with incoherence; heterogeneity with imprecision, incoherence), the level can be reduced considering all judgements of inter-related domains.



Final rating of confidence

Comparison	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating	Reason(s) for downgrading
A vs B	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	-
A vs C	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	"Imprecision"
B vs C	No concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Moderate	"Heterogeneity"

A final level of confidence for each comparison of the network can be determined using this method.

The framework helps to establish the confidence of the evidence from NMAs in a simplified process.

Reference

- Nikolakopoulou A, Higgins JPT, Papakonstantinou T, Chaimani A, Del Giovane C, Egger M & Salanti G. CINeMA: An approach for assessing confidence in the results of a network meta-analysis PLOS Medicine 2020 17(4): e1003082. [https:// doi.org/10.1371/journal.pmed.1003082](https://doi.org/10.1371/journal.pmed.1003082)
- Papakonstantinou T, Nikolakopoulou A, Higgins JPT, Egger M & Salanti G. CINeMA: Software for semiautomated assessment of the confidence in the results of network meta-analysis Campbell Systematic Reviews 2020 16 e1080. <https://doi.org/10.1002/cl2.1080>
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Thank you