Network Meta-Analysis: Some Subtleties and Extra Details

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General NMA Validity[1]

- Exchangeability
  - **Definition**: The assumption that the included studies are sufficiently similar in terms of population, intervention, outcome, and methodology, such that their results can be meaningfully combined without introducing systematic bias. It is measured statistically by consistency.
  - This is a key assumption in NMA that gives some people pause when interpreting results, however this is already an assumption in pairwise MA.
- Reliability of indirect evidence compared with direct evidence
  - Under many circumstances, meta-analytic estimates based on direct and indirect evidence are equally prone to error
  - Under some circumstances, indirect evidence may be more biased and direct virtually unbiased. [2]

Consistency [1]

Definition: *Consistency* is the statistical measure of transitivity/exchangeablity. A model is said to be *consistent* when, for conditions A and B and for true effect size θ, the relative effect of the comparison between A and B based on direct evidence does not differ from the relative effect of the same comparison based on indirect evidence.

Expressed symbolically:

$$\theta_{A,B}^{\text{indirect}} = \theta_{A,B}^{\text{direct}}$$

- A model is said to be *inconsistent* if it is not consistent.
- **Net-splitting** (or node-splitting) measures pairwise inconsistency between all comparisons.

CINeMA Paradigm [4]

The Confidence in Network Meta-Analysis (CINeMA) approach is a method for determining the validity of conclusions drawn from NMAs based on six domains:

- within-study bias
- reporting bias
- indirectness
- imprecision
- heterogeneity
- incoherence (inconsistency)

The specifics of the paradigm are beyond the scope of this presentation, however awareness of the criticisms of NMAs is vital to the development of the topic.

Checking consistency in *netmeta*

netheat():

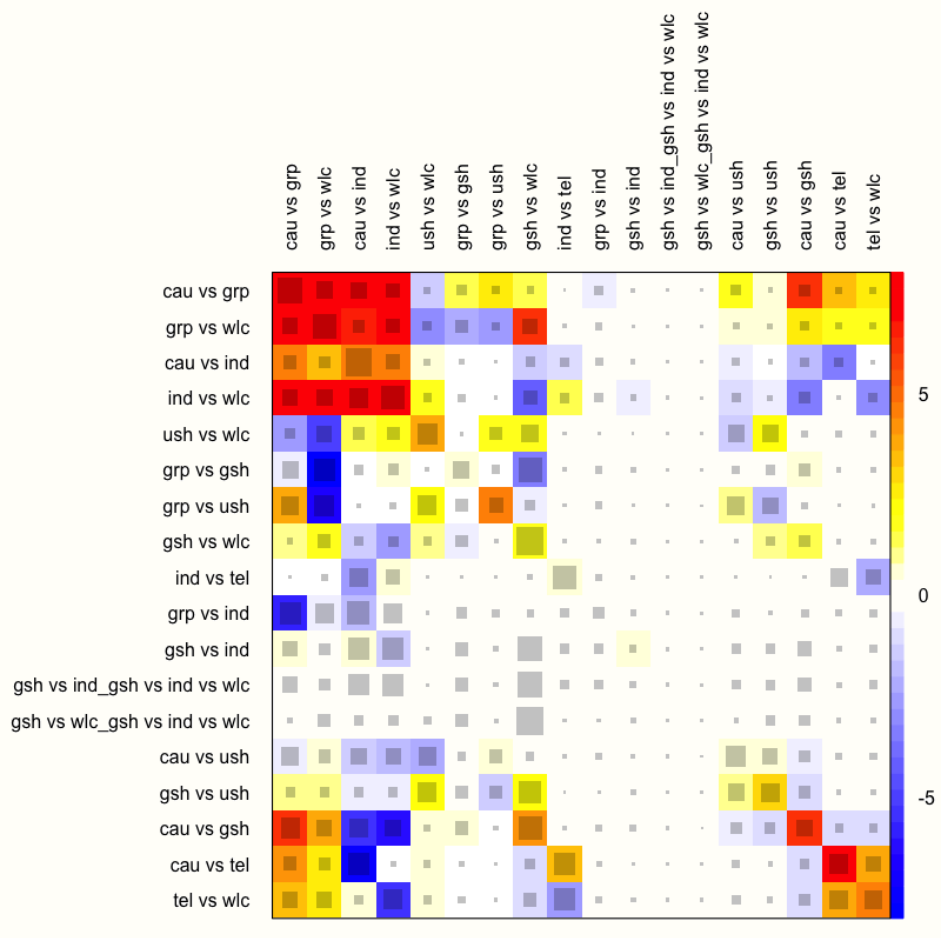

Figure: Example netheat plot from [3]. Size of gray box is importance of comparison, background color is level of inconsistency.

Checking consistency in *netmeta* (cont.)

netsplit():

```
## Separate indirect from direct evidence using back-calculation method
##
## Fixed effects model:
##
##  comparison  k prop     nma  direct  indir.    Diff     z  p-value
##  grp vs cau 21 0.58 -0.5767 -0.3727 -0.8628  0.4901  8.72 < 0.0001
##  gsh vs cau  8 0.22 -0.3940 -0.5684 -0.3442 -0.2243 -2.82   0.0048
##  ind vs cau 30 0.71 -0.6403 -0.7037 -0.4863 -0.2174 -3.97 < 0.0001
##  tel vs cau  6 0.35 -0.5134 -0.7471 -0.3867 -0.3604 -3.57   0.0004
##  ush vs cau  9 0.35 -0.1294 -0.1919 -0.0953 -0.0966 -1.06   0.2903
##  [...]
##
## Legend:
##  [...]
##  Diff       - Difference between direct and indirect estimates
##  z          - z-value of test for disagreement (direct vs. indirect)
##  p-value    - p-value of test for disagreement (direct vs. indirect)
```

Figure: Example netsplit table from [3]

Checking consistency in *netmeta* (cont.)

netsplit() %>% forest():

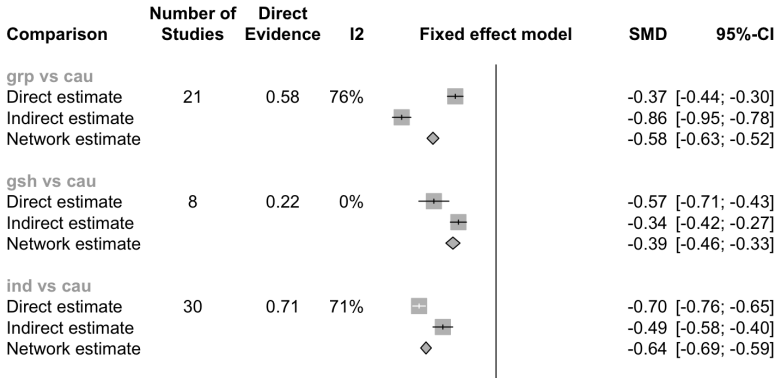

Figure: Example netsplit forest plot from [3]

Example of technique to estimate effects

When using R package *netmeta* $\frac{n(n-1)}{2}$ treatment comparisons must be provided for a study that has n treatments/interventions present. How do we deal with a situation when this is not possible?

- E.g. suppose I am comparing treatments A, B, and C in a NMA. Study 2 reports two odds ratios, $\theta_{A,B}$ and $\theta_{A,C}$
- Study 2 has $n = 3$, as all treatments appear in the reported odds ratios, so $\frac{3(3-1)}{2} = 3$, so we are missing an estimate, $\theta_{B,C}/\theta_{C,B}$
- 3rd treatment comparison would need to be consistent with the other two comparisons, so natural to calculate as if it were indirect evidence
- Variance estimate more complicated, can add/subtract the variance estimates and modify by the estimated covariance
  - One way to estimate covariance is multiplying the correlation between estimates by the produce of their standard deviations
  - Here we still need an estimate for correlation, and 0.5 is a good default, as if sample sizes are equal in each arm this will lead to exact covariance

References

[1] Ades et al. *Network Meta-Analysis for Decision Making*. Wiley Press, 2018. ISBN: 9781118951651.

[2] SJ Edwards et al. "Indirect comparisons of treatments based on systematic reviews of randomised controlled trials". In: *IJCP* (May 2009). DOI: 10.1111/j.1742-1241.2009.02072.x.

[3] Mathias Harrer et al. *Doing Meta-Analysis With R: A Hands-On Guide*. 1st. Boca Raton, FL and London: Chapman & Hall/CRC Press, 2021. ISBN: 9780367610074.

[4] Adriani Nikolakopoulou et al. "CINeMA: An approach for assessing confidence in the results of a network meta-analysis". In: *PLOS Medicine* 17.4 (Apr. 2020), pp. 1–19. DOI: 10.1371/journal.pmed.1003082.