Network Meta-Analysis: A Short Introduction

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March 17th, 2025
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Agenda

- Introduction to Network Meta-Analysis (20-25 min)
- First hands-on coding portion (30 min)
- Further details on Network Meta-Analysis (15-20 min)
- Second hands-on coding portion (20 min)

Motivation for combining evidence

- Strengthens results
- Quantifies bias, heterogeneity, etc.
- Allows for inclusion of only high-quality studies

Note that in this workshop we will only be dealing with aggregated data (usually from publically-available published study data), not patient-level data.

How can we combine evidence?

Methods to synthesize evidence from multiple sources [2]:

- Traditional/Narrative Reviews
  - Common into the 1980s
  - No rules on included studies, how to make conclusions
- Systematic Literature Reviews
  - Clear and transparent rules for study selection
  - Synthesize outcomes in a systematic way
- Meta-analyses
  - Usually in combination with a systematic review
  - Combines results **quantitatively**

See the Cochrane Handbook for Systematic Reviews of Interventions (`https://training.cochrane.org/handbook`), as well as the Cochrane RoB Tool (`https://methods.cochrane.org/bias/resources/rob-2-revised-cochrane-risk-bias-tool-randomized-trials`).

What is a Meta-Analysis?

What is a meta-analysis?

- *"An analysis of analyses" - Gene Glass*

What is the goal of a meta-analysis?

- "to combine, summarize and interpret all available evidence pertaining to a clearly defined research field or research question" [3].

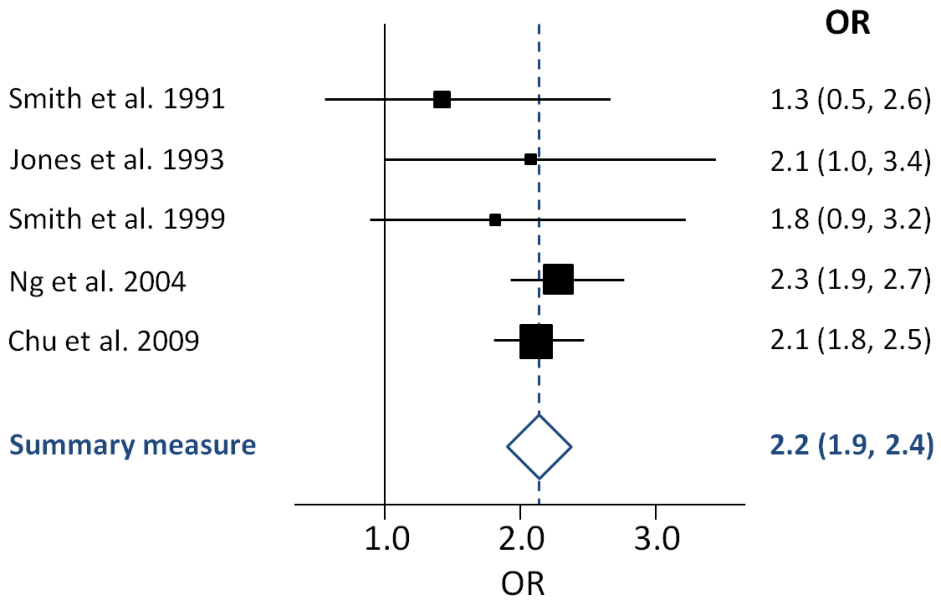


Figure: Example forest plot from `https://en.wikipedia.org/wiki/Forest_plot`

Pairwise Meta-Analysis pools effect sizes

- A standard, pairwise meta-analysis pools quantitative estimates from different studies
- Usually one of the two below types:
  - Fixed effect model: assumes true effect sizes are fixed; effect sizes vary between studies only due to sampling error.
  - Random effect model: assumes that there is not only one true effect size but a distribution of true effect sizes; effect sizes vary due to sampling error AND between-study heterogeneity.
- Typically consists of a weighted average of k study estimates, e.g.

$$\hat{\theta}_{pooled} = \frac{\sum_{i=1}^{k} w_i \hat{\theta}_i}{\sum_{i=1}^{k} w_i},$$

  where $\hat{\theta}_i$ is the estimate of quantity θ from study i, and w_i is the weight assigned to the i^{th} study
- Typically $w_i = 1/V(\hat{\theta}_i)$, with modification by $\hat{\tau}^2$ for RE

Network Meta-Analysis allows all treatment comparisons to be estimated

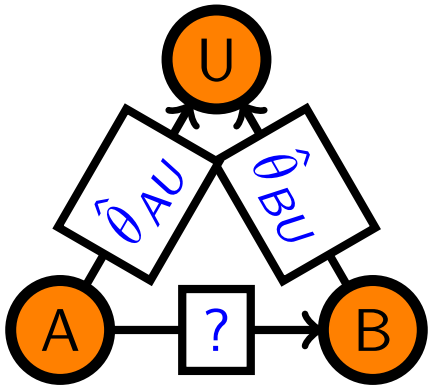
Drawbacks of standard pairwise MA:

- Pairwise MA does not allow for inclusion of *indirect evidence* (conclusions inferred from data but not directly measured)
- Additionally, treatments cannot be ranked when there are more than two as only binary comparisons can be made

Network Meta-Analysis allows us to use indirect evidence to estimate treatment/intervention comparisons not available (or as available) in the data, while allowing a ranking of multiple treatments/interventions.

Calculate Indirect Effects from Direct Evidence

A **network meta-analysis** utilizes a graphical network structure to combine direct and indirect evidence for effect estimates:



Suppose we are comparing two treatments A and B, but only have estimates for how they each compare to unvaccinated patients. We can compute the **indirect estimate** $\hat{\theta}^{ind}_{AB}$ by:

$$\hat{\theta}^{ind}_{AB} = \hat{\theta}^{dir}_{AU} - \hat{\theta}^{dir}_{BU},$$

with variance $V(\hat{\theta}^{ind}_{AB}) = V(\hat{\theta}^{dir}_{AU}) + V(\hat{\theta}^{dir}_{BU})$ (since AU and BU estimates are from different studies and must be **independent**).

Combine Direct and Indirect Effects to get Network Meta-Analytic Estimate

Suppose we have a direct and indirect estimate for each treatment comparison. We can combine them as follows:

$$\hat{\theta}_{AB}^{Pooled} = \frac{w_{AB}^{ind}\hat{\theta}_{AB}^{ind} + w_{AB}^{dir}\hat{\theta}_{AB}^{dir}}{w_{AB}^{ind} + w_{AB}^{dir}},$$

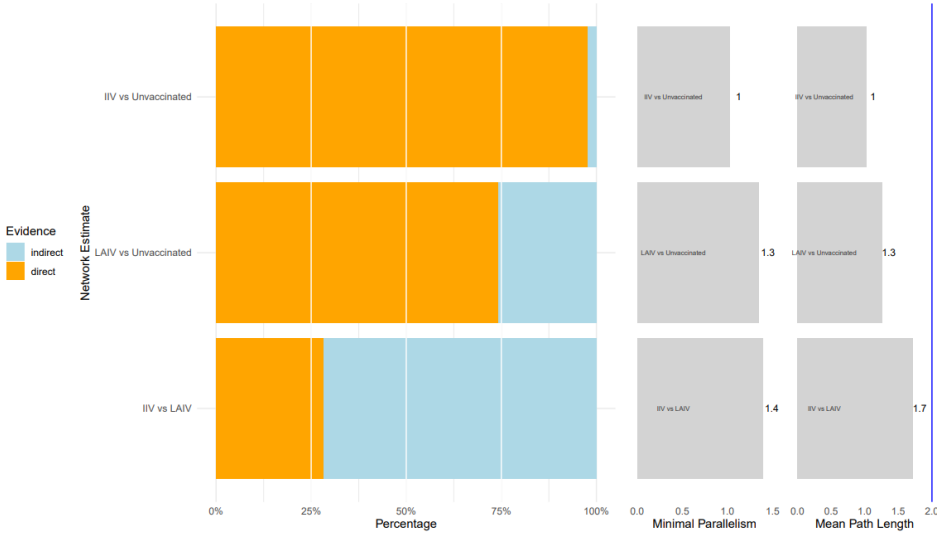
where $w_{AB}^{dir} = 1/V(\hat{\theta}_{AB}^{dir})$ and $w_{AB}^{ind} = 1/V(\hat{\theta}_{AB}^{ind}) = 1/(V(\hat{\theta}_{AU}^{dir}) + V(\hat{\theta}_{BU}^{dir}))$.

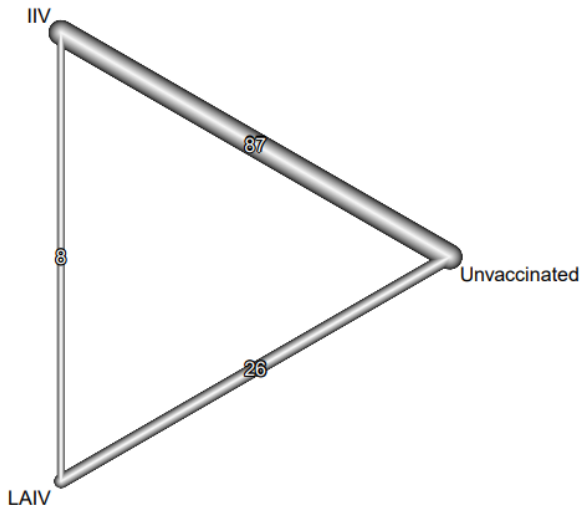
- Repeat process for other comparisons to get coherent estimates
- With many estimates, need to solve a rank-deficient matrix equation (where the graph-theoretic part comes in, see [4], [1] for details)
- **Important to check consistency of direct and indirect estimates before accepting the combined estimate!**

Implementing NMA with the *netmeta* package in R

Some functions in (or using output from) package *netmeta* (see [2] for a complete hands-on guide):

- *netmeta*(): main function, takes as input **pairwise treatment comparisons** and their SEs
- *netgraph*() (see below right), *direct.evidence.plot*() (this is in package *dmetar*, see below left), many other functions





Main difficulty in using the package is making sure data is formatted correctly (functions included to create contrasts).

Implementing NMA with the *netmeta* package in R (cont.)

Packages needed to be installed:

- *dmetar* (dependency for *netmeta*)
- *netmeta* (package used for NMA)
- *dplyr* (package used to more easily manipulate R dataframes)

Important considerations:

- For each study in data, if n treatments/interventions are present, $\frac{n(n-1)}{2}$ treatment comparisons must be provided
- The ranking algorithm implemented in *netmeta* is a frequentist analog to (Bayesian) SUCRA (see [5] for a similarity analysis of the two methods)

References

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

[2] 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.

[3] Mark Lipsey and David Wilson. *Practical Meta-Analysis*. 1st. Thousand Oaks, CA: SAGE, 2000. ISBN: 9780761921677.

[4] Rucker and Schwarzer. "Reduce dimension or reduce weights? Comparing two approaches to multi-arm studies in network meta-analysis". In: *Statistics in Medicine* 33.25 (2014), pp. 4353–69. DOI: 10.1002/sim.6236.

[5] Schwarzer G. Rücker G. "Ranking treatments in frequentist network meta-analysis works without resampling methods.". In: *BMC Med Res Methodol* (July 2015). DOI: 10.1186/s12874-015-0060-8.