Assumptions of NMA

Georgia Salanti
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Criticism of indirect comparison

• Indirect comparison respects randomisation but it is not randomized evidence
  – The treatment comparisons have not been randomized across studies
  – Indirect comparison is a special type of regression (using the comparison as explanatory variable)
  – Meta-regression and subgroup analysis provide observational evidence as the characteristic they regress on hasn’t been randomized across studies

• Some would argue that pairwise meta-analysis is observational evidence
Assumption in NMA

- Assumption 1: Homogeneity (as in pairwise meta-analysis)
- Assumption 2: Consistency-transitivity-congruence-coherence
- Consistency is a form of homogeneity
  - But we will reserve the term for a pairwise comparison
- More assumptions (such as normality in the RE, correct model, known variances etc)
- We will focus on Assumption 2
Assumption underlying indirect/mixed comparison (on the top of homogeneity)

Single Assumption
underlying indirect and mixed comparison

Conceptual definition

Transitivity

Clinical/method homogeneity

Property of parameters and data

Consistency

Statistical homogeneity
Transitivity

An underlying assumption when $\mu'_{BC}$ is calculated is that one can learn about B versus C via A.

Sometime it is an untestable assumption

....but you can evaluate clinically and epidemiologically its plausibility
Transitivity means... (1)

...that AC and AB trials do not differ with respect to the distribution of effect modifiers [not prognostic factors!]

- Difficult to defend when you have older and newer treatments
- Variables are often unobserved
Transitivity means... (1)

Placebo vs B

Placebo vs C

✓

✗
Transitivity means... (2)

Treatment A is similar when it appears in AB and AC trials

Plausible when A is placebo given in different forms (e.g. injection versus pill)?
Transitivity (3)

• The ‘missing’ arm is missing at random
• The AB studies do not have a ‘C’ arm and the AC studies do not have a ‘C’ arm.
  – This ‘form’ of transitivity is implicit when Ian suggests imputing the ‘missing reference treatment’ when fitting NMA via mvmeta
Transitivity means... (4)

• ... that all treatments are “jointly randomizable”
• This consideration is a fundamental one and should be addressed when building the evidence network
Consistency

Direct and indirect evidence are in agreement

\[ \mu^I_{BC} \quad \mu^D_{BC} \quad \mu^M_{BC} \]
Consistency

Direct and indirect evidence are in agreement

\[ \mu^I_{BC} = \mu^D_{BC} \]
Consistency

Direct and indirect evidence are in agreement

\[ \mu^D_{AC} - \mu^D_{AB} = \mu^I_{BC} = \mu^D_{BC} \]
### Study

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<thead>
<tr>
<th>Study</th>
<th>Observed</th>
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<tbody>
<tr>
<td>AC</td>
<td>$\gamma_{i,AC}$</td>
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<tr>
<td>BC</td>
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<tr>
<td>AB</td>
<td>$\gamma_{i,AB}$</td>
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<table>
<thead>
<tr>
<th>Study</th>
<th>If arm were included..</th>
<th>Observed and unobserved</th>
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<tbody>
<tr>
<td>AC</td>
<td>B</td>
<td>$\gamma_{i,AC}$</td>
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<td>AB</td>
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$\theta_{i,AC}$

$\tau_{AC}^2$

$\tau_{BC}^2$

$\tau_{AB}^2$

**Consistency:** Observed and unobserved estimates do not differ beyond what can be explained by heterogeneity.
Assumptions and NMA

• They need to be considered when building the network of evidence
  – Possibly there is a trade-off between large networks and the plausibility of the assumption