Assumptions of NMA

Georgia Salanti

CMIMG meeting – Stream 2

Bristol, 16-17 July 2013

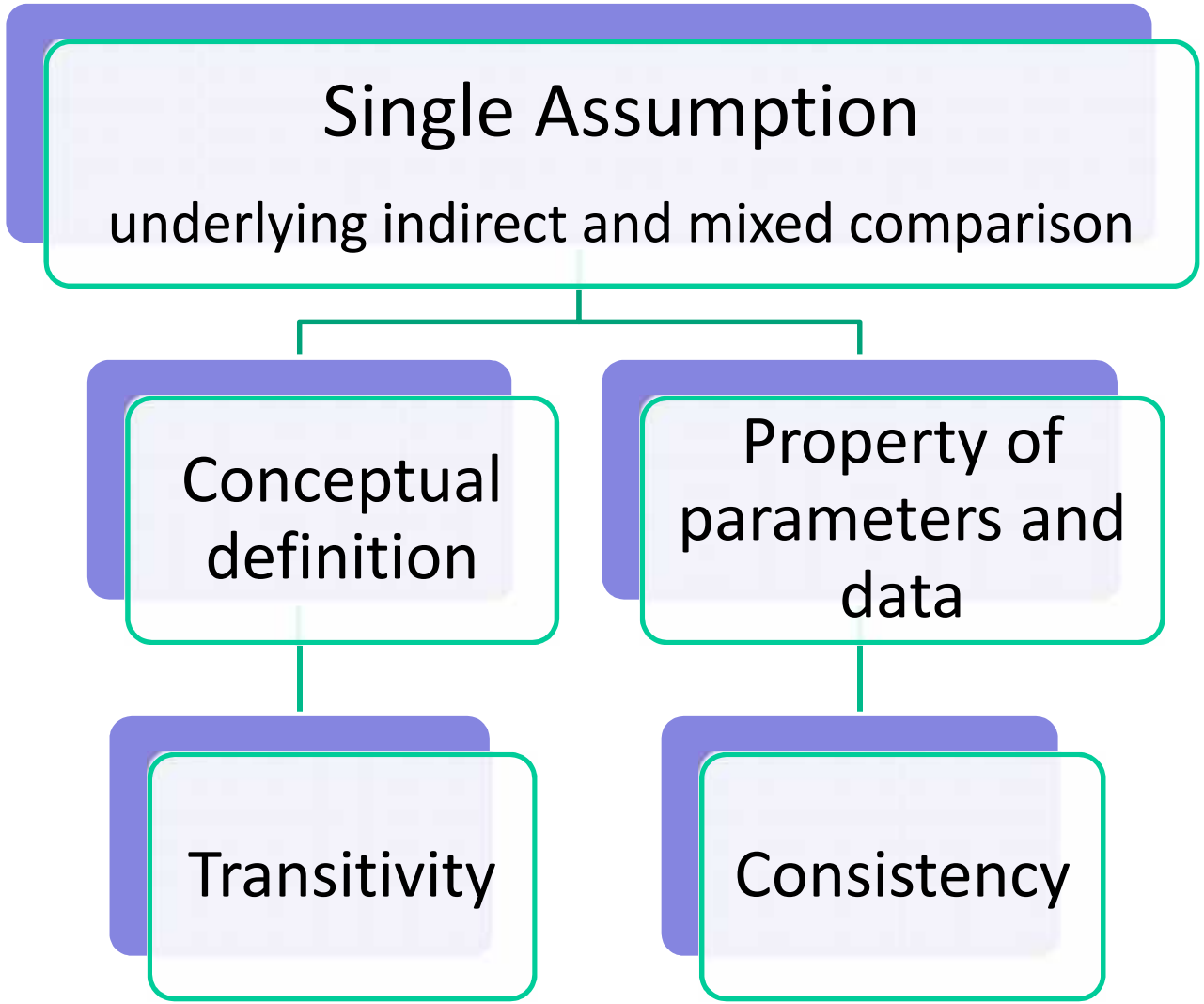
Criticism of indirect comparison

- 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 paiwise 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

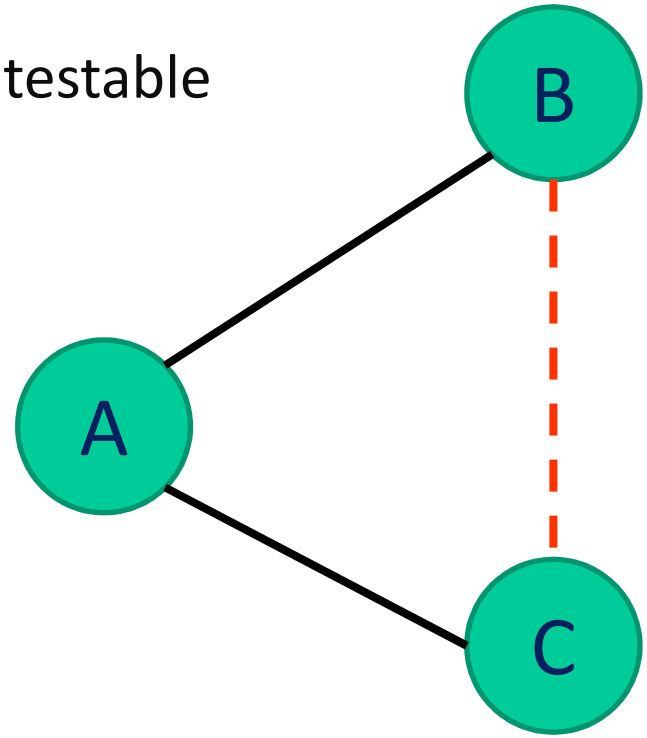
Assumption underlying indirect/mixed comparison (on the top of homogeneity)



Transitivity

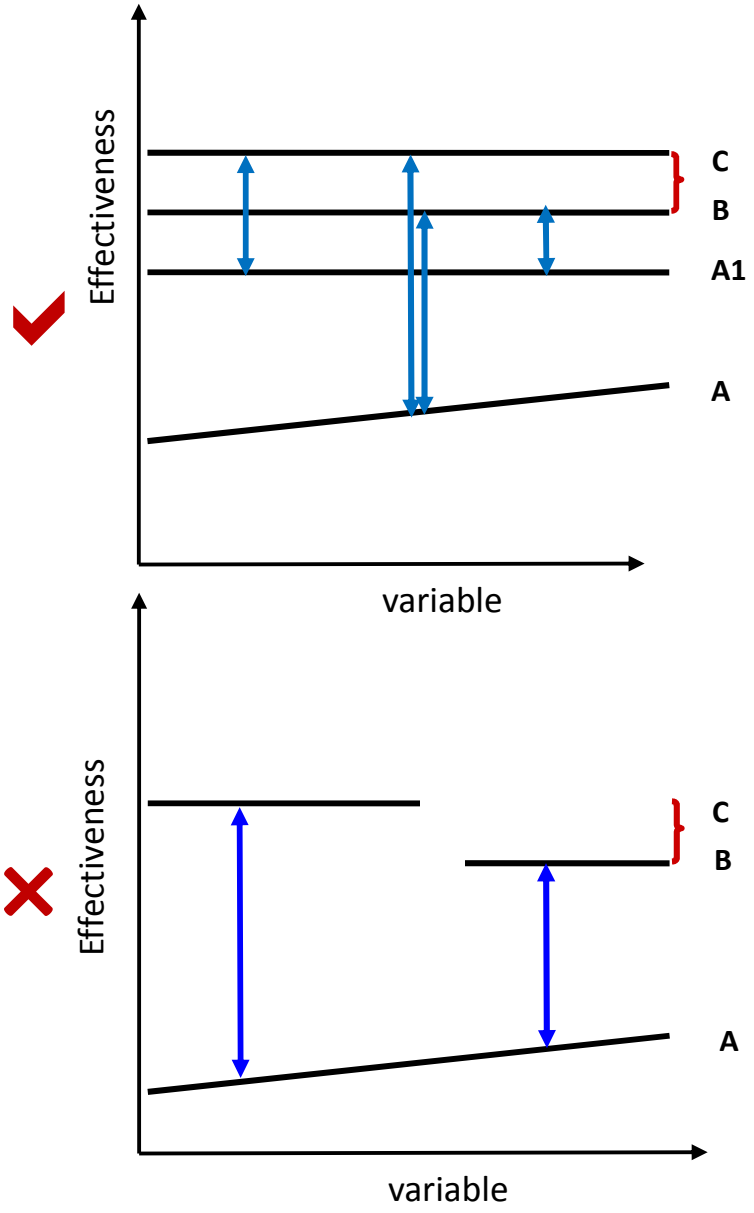
An underlying assumption when μ^{I}_{BC} is calculated is that one can learn about B versus C via A.

Sometime it is an untestable assumption



….but you can evaluate clinically and epidemiologically its plausibility

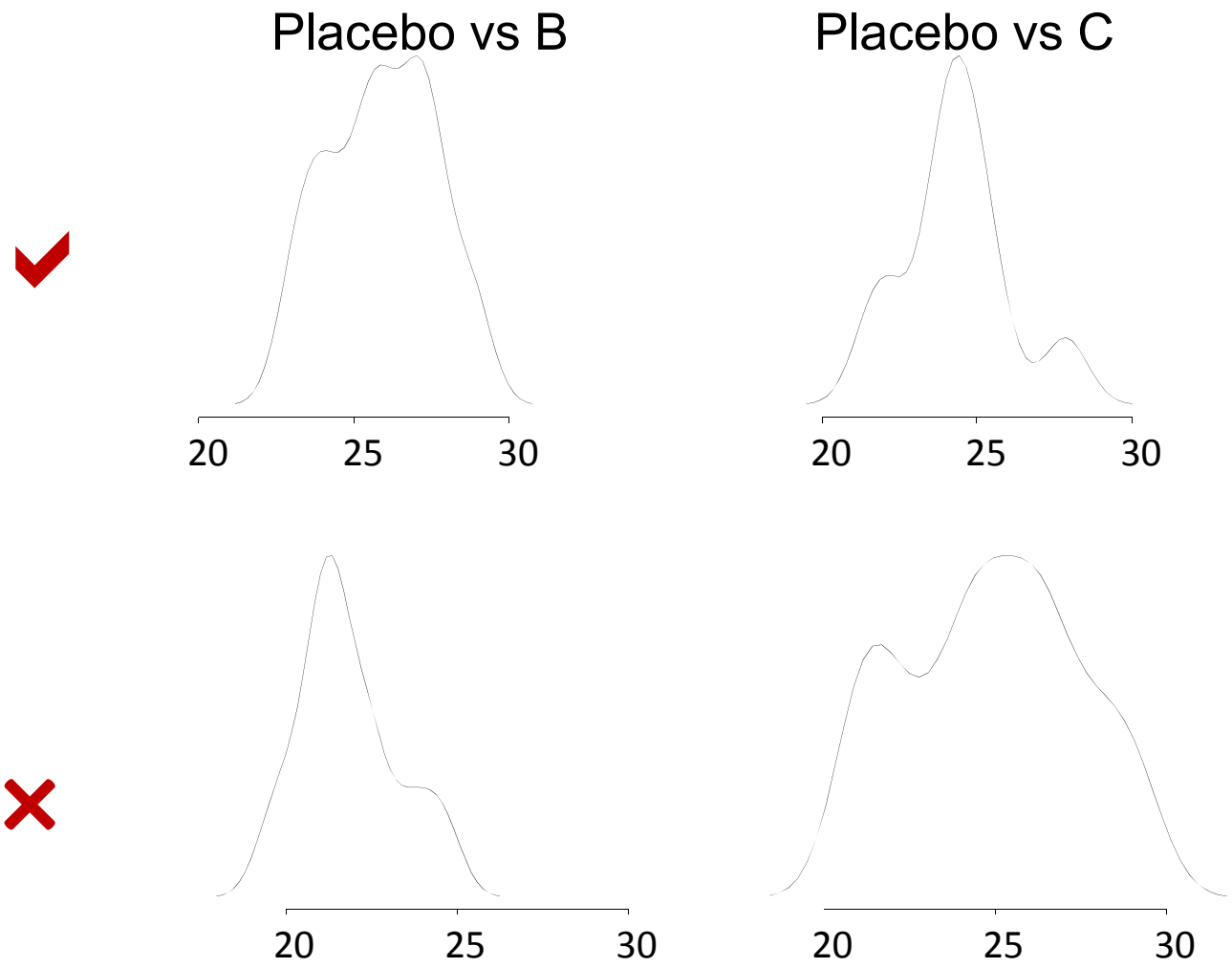
Transitivity means... (1)



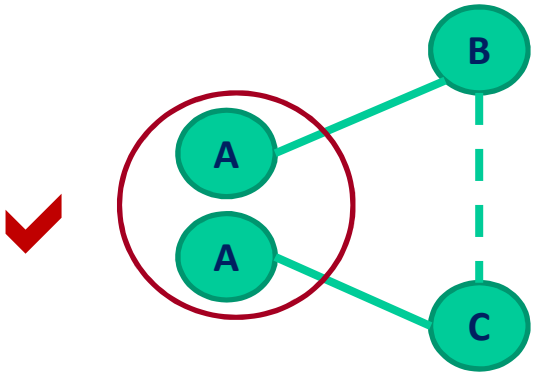
...that AC and AB trials do not differ with respect to the distribution of effect modifiers [not prognostic factors!]

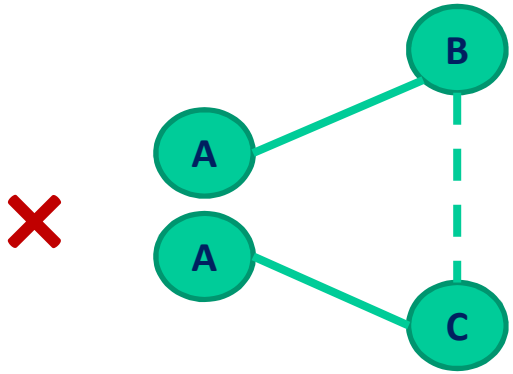
- Difficult to defend when you have older and newer treatments
- Variables are often unobserved

Transitivity means... (1)



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)

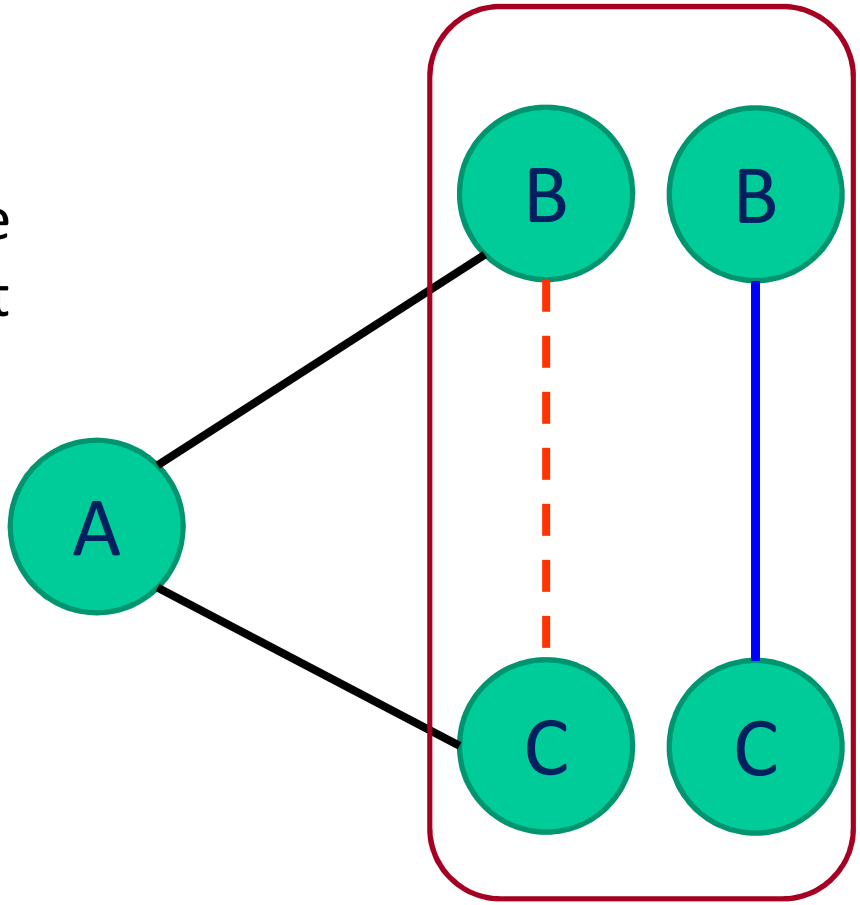
- The ‘missing’ arm is missing at random
- The AB studies do not have a ‘C’ arm and the AC studies do not have a ‘C’ arm.
  - This ‘form’ of transitivity is implicit when Ian suggests imputing the ‘missing reference treatment’ when fitting NMA via mvmeta

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

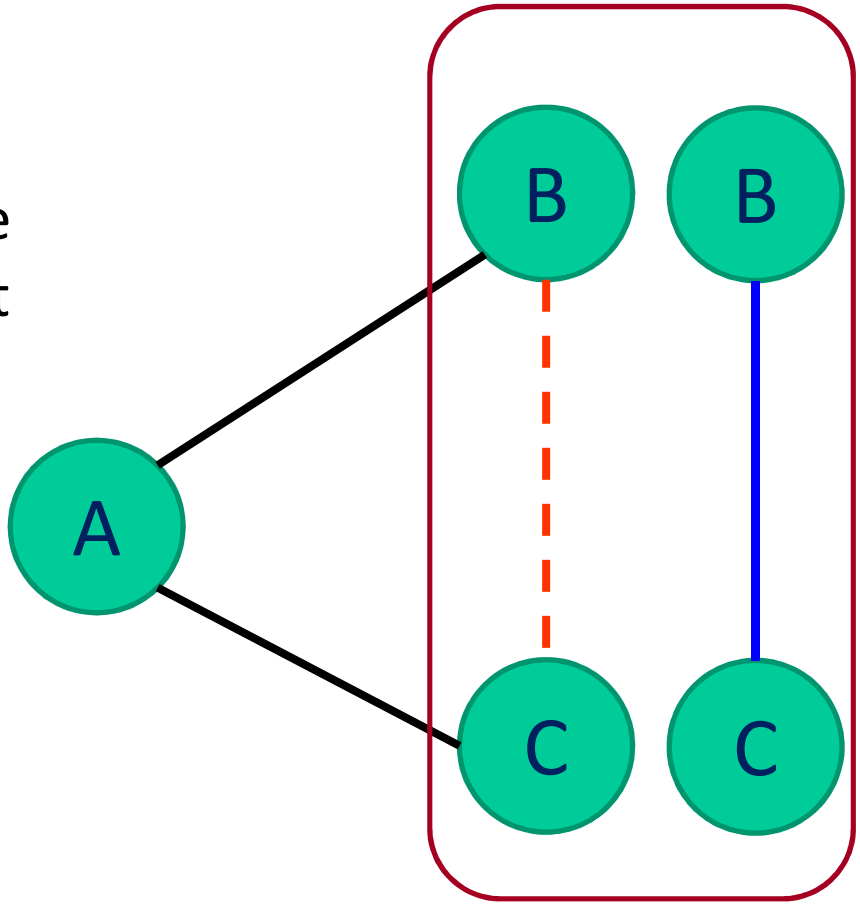
Direct and indirect evidence are in agreement



μ^{I}_{BC} μ^{D}_{BC} → μ^{M}_{BC}

Consistency

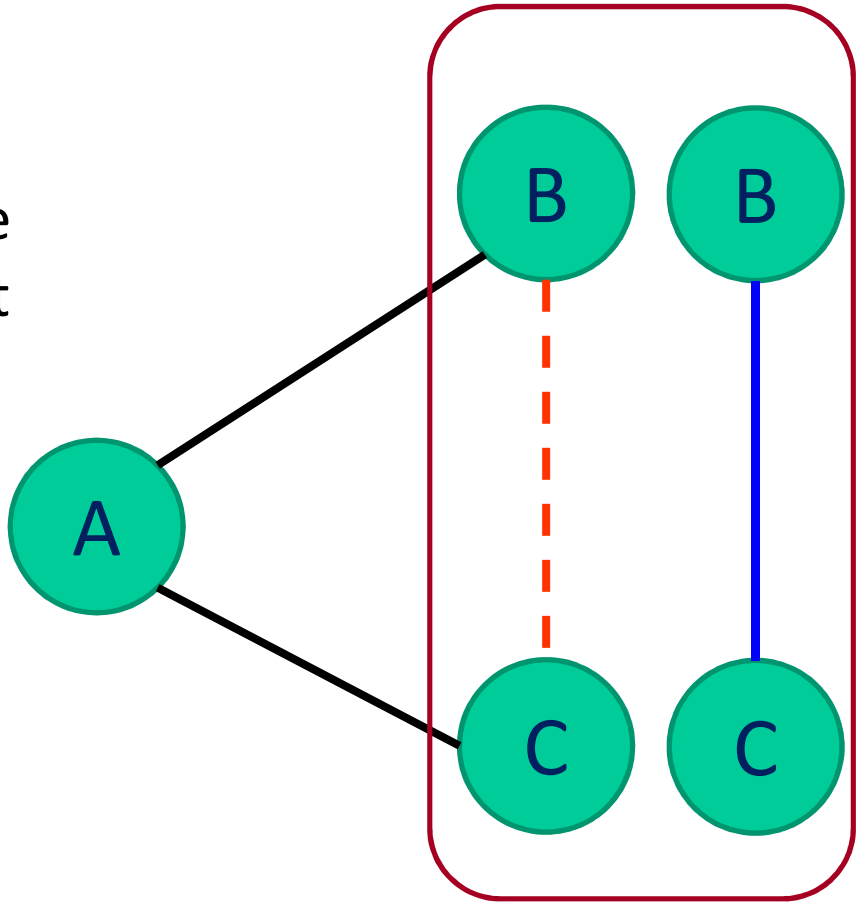
Direct and indirect evidence are in agreement



$\mu^{I}_{BC} = \mu^{D}_{BC}$

Consistency

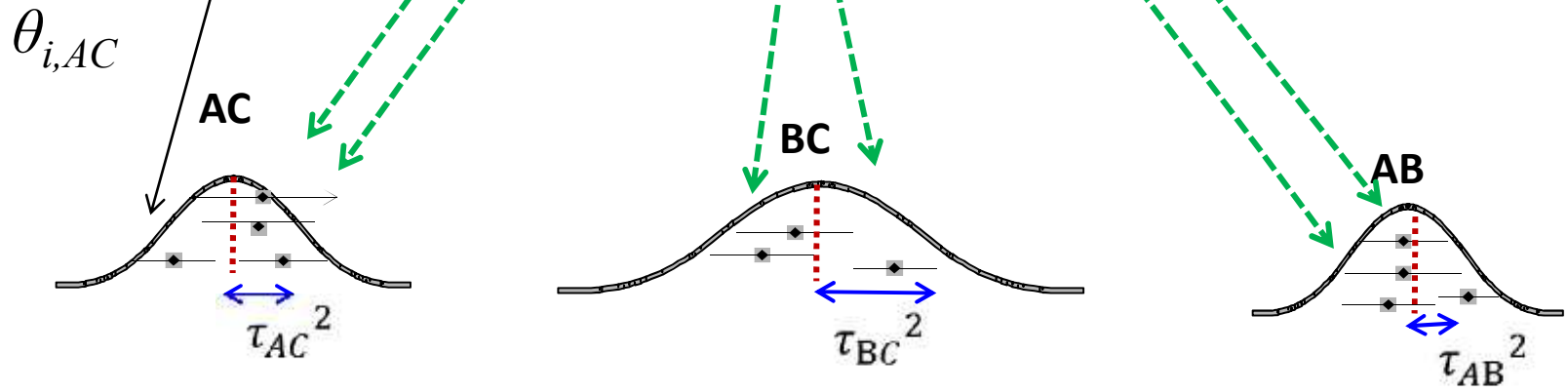
Direct and indirect evidence are in agreement



$$\mu^{D}_{AC} - \mu^{D}_{AB} = \mu^{I}_{BC} = \mu^{D}_{BC}$$

Study	Observed		
AC	$y_{i,AC}$		
BC		$y_{i,BC}$	
AB			$y_{i,AB}$

Study	If arm were included..	Observed and unobserved		
AC	B	$y_{i,AC}$	$y_{i,BC}$	$y_{i,AB}$
BC	A	$y_{i,AC}$	$y_{i,BC}$	$y_{i,AB}$
AB	C	$y_{i,AC}$	$y_{i,BC}$	$y_{i,AB}$



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