# Validity of indirect comparisons

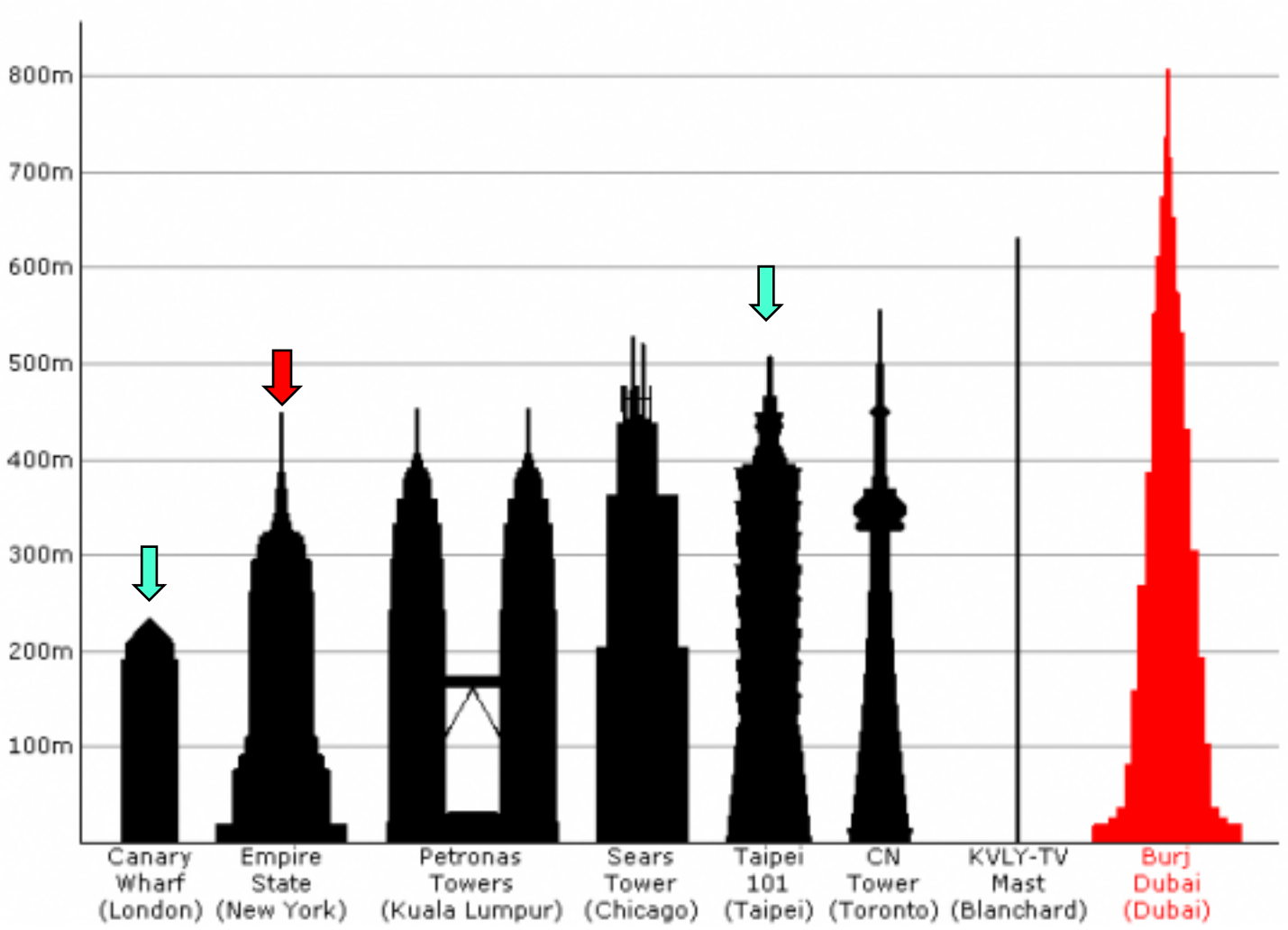
Georgia Salanti

Institute of Social and Preventive Medicine

University of Bern

Acknowledgments for sharing a couple of slides: Julian Higgins

# Indirect comparison via *Empire State*



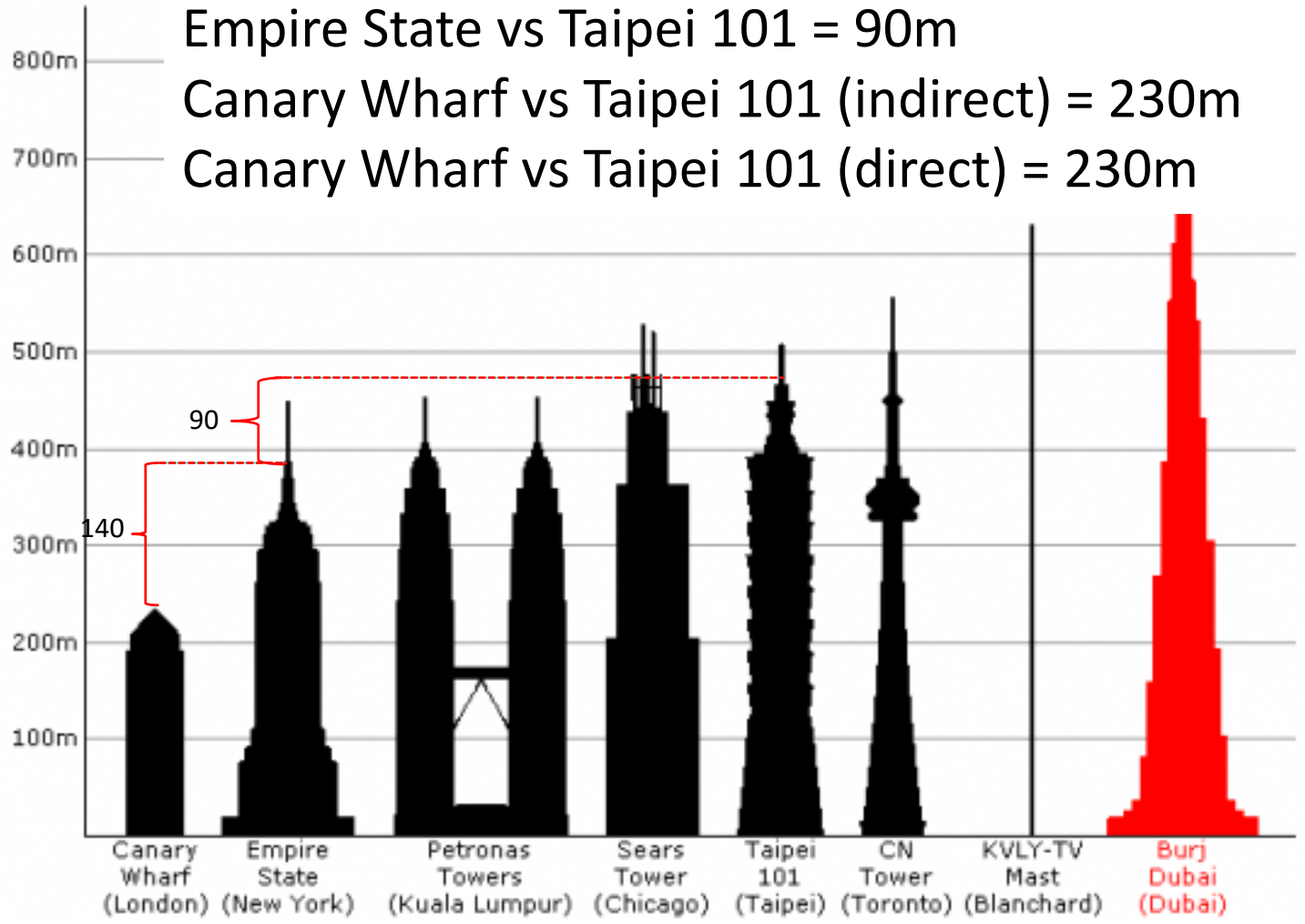
# Indirect comparison via *Empire State*

Canary Wharf vs Empire State = 140m

Empire State vs Taipei 101 = 90m

Canary Wharf vs Taipei 101 (indirect) = 230m

Canary Wharf vs Taipei 101 (direct) = 230m



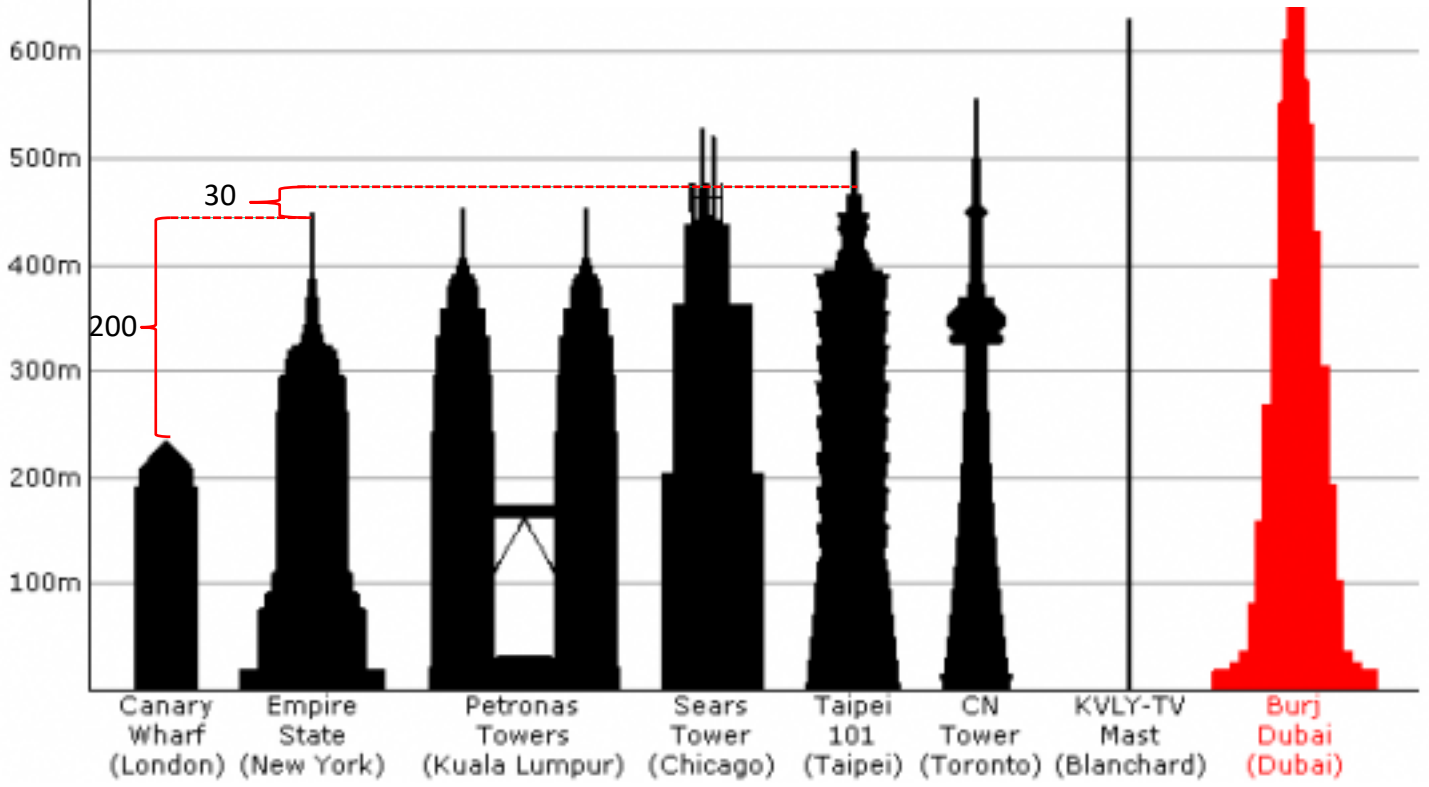
# Indirect comparison via *Empire State plus mast*

Canary Wharf vs Empire State+mast = 200m

Empire State+mast vs Taipei 101 = 30m

Canary Wharf vs Taipei 101 (indirect) = 230m

Canary Wharf vs Taipei 101 (direct) = 230m



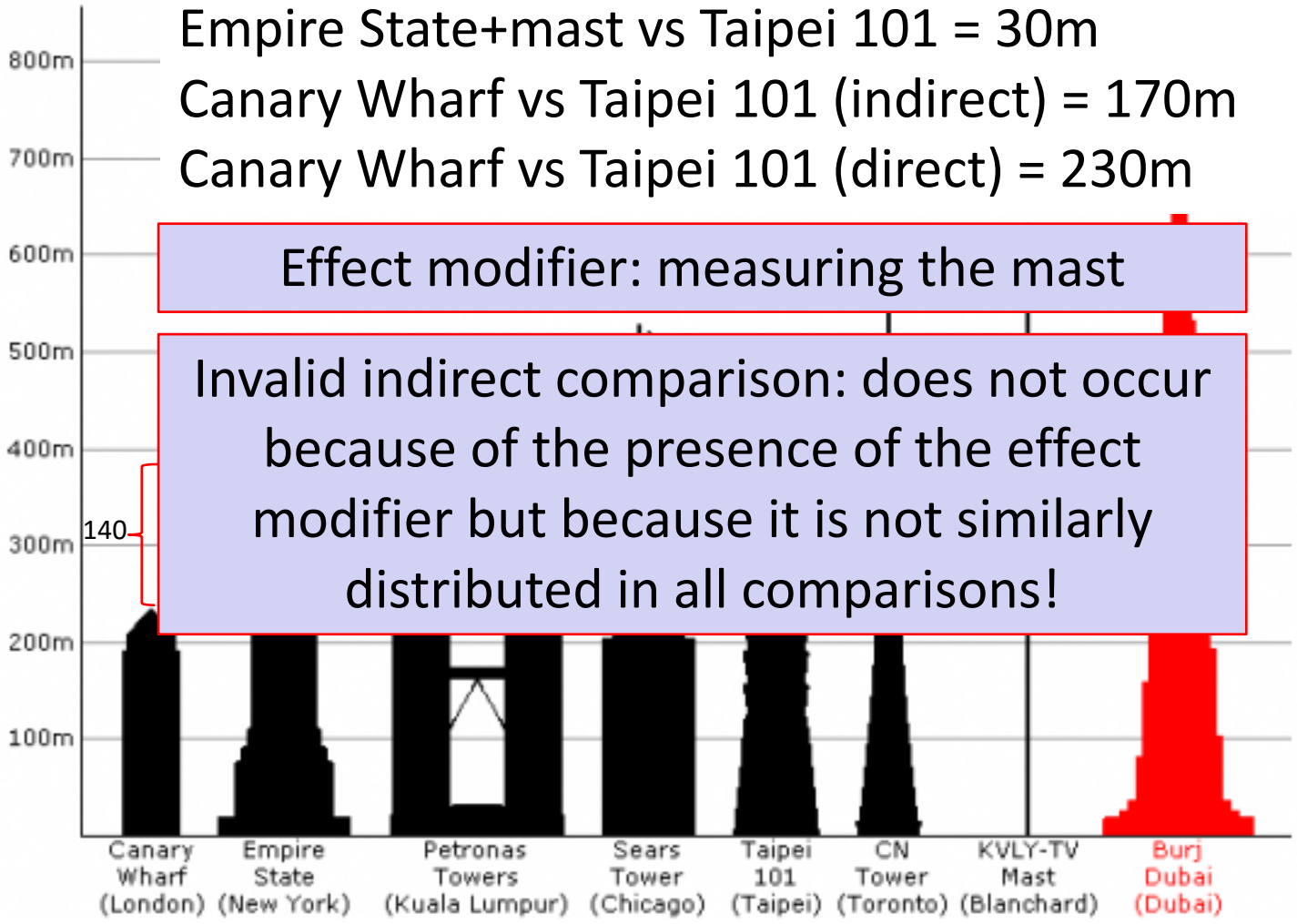
# Inconsistent indirect comparison

Canary Wharf vs Empire State = 140m

Empire State+mast vs Taipei 101 = 30m

Canary Wharf vs Taipei 101 (indirect) = 170m

Canary Wharf vs Taipei 101 (direct) = 230m

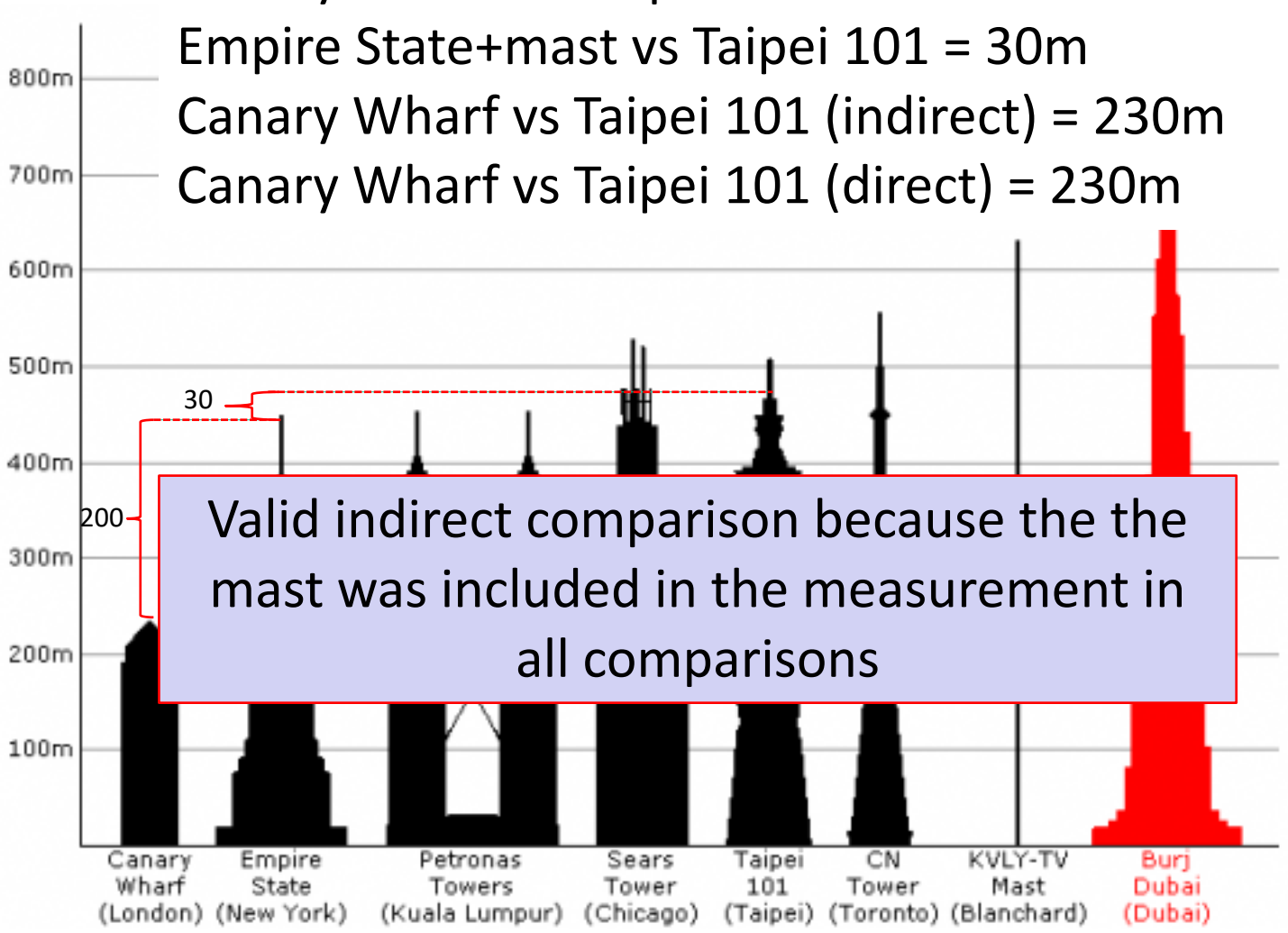



Effect modifier: measuring the mast

Invalid indirect comparison: does not occur because of the presence of the effect modifier but because it is not similarly distributed in all comparisons!

# Indirect comparison via *Empire State plus mast*

Canary Wharf vs Empire State+mast = 200m
Empire State+mast vs Taipei 101 = 30m
Canary Wharf vs Taipei 101 (indirect) = 230m
Canary Wharf vs Taipei 101 (direct) = 230m




Valid indirect comparison because the the mast was included in the measurement in all comparisons

# Inconsistent indirect comparison

Canary Wharf vs Empire State = 140m

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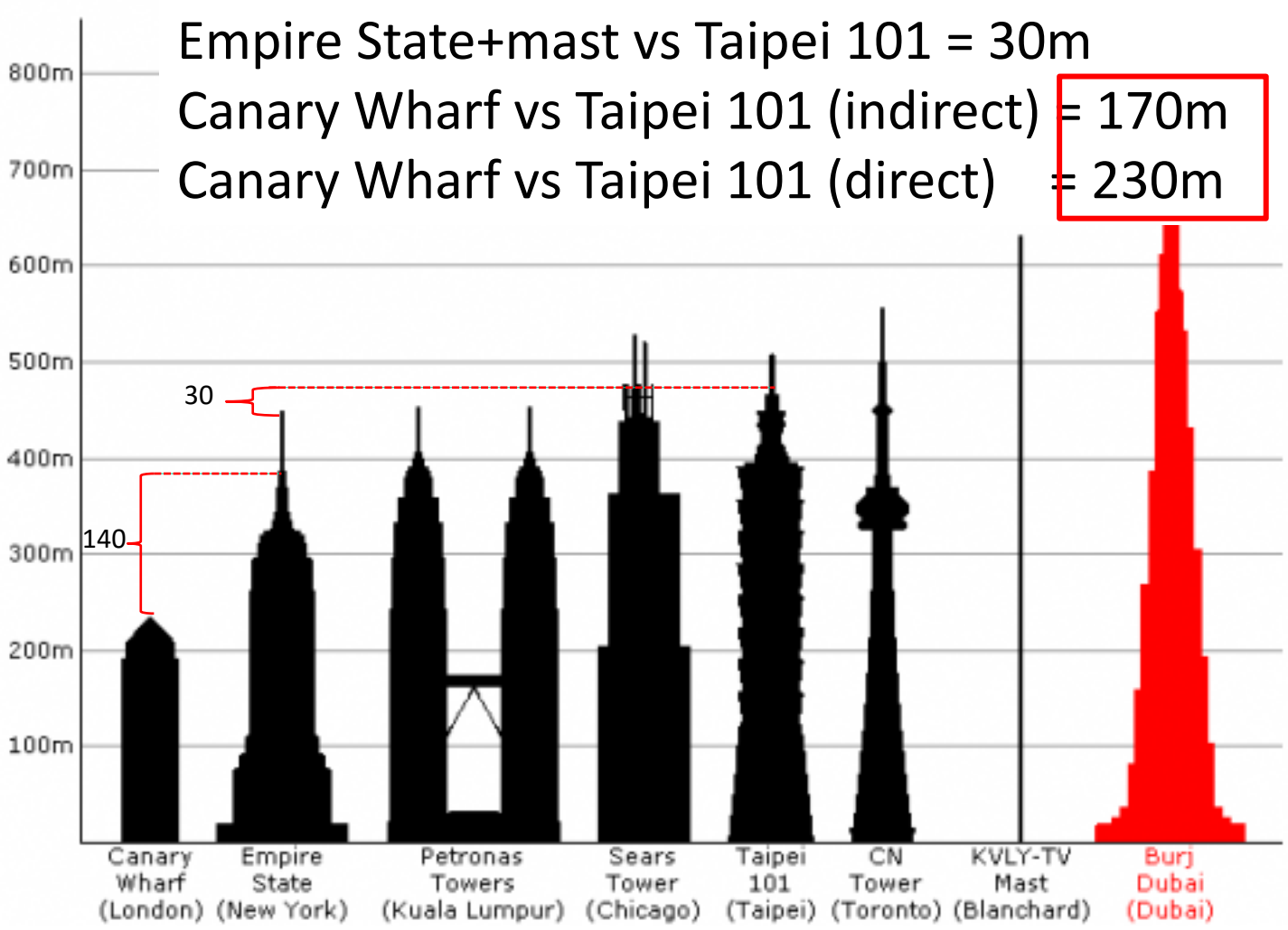



Inconsistency

# Network meta-analysis is great*

*it can become a dangerous weapon if undertaken carelessly!

# Criticism of indirect comparison

- Indirect comparison respects randomization but **it is not randomized evidence**
  - The treatment comparisons have not been randomized across studies
  - Meta-regression and subgroup analysis provide **observational evidence** as the covariate hasn't been randomized across studies
  - Indirect comparison is a special type of regression (using the comparison as explanatory variable)

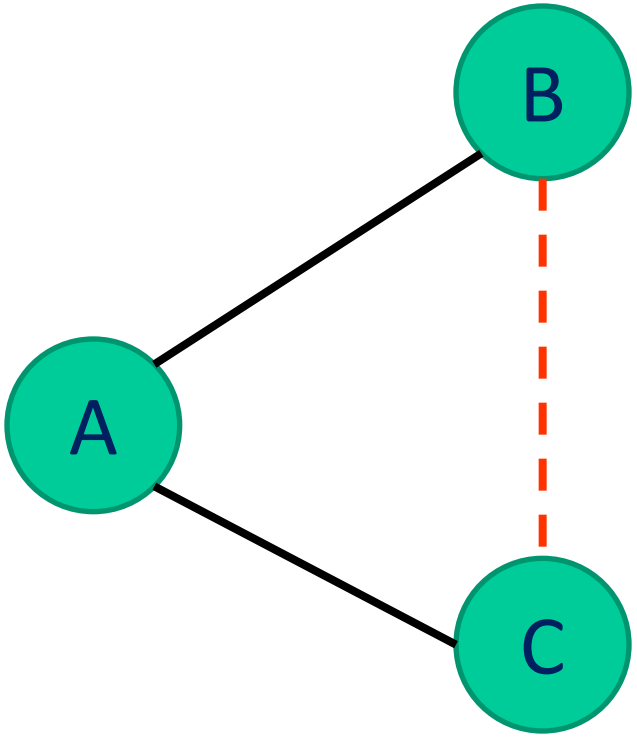
# Transitivity

The underlying assumption when $\mu^{I}_{BC}$ is calculated is that

**we can learn about B versus C via A.**

# Transitivity

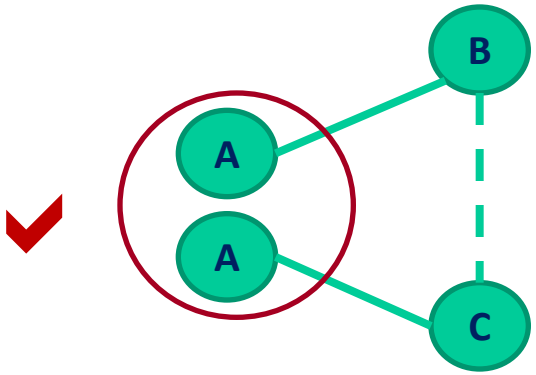
advantage of B over C =
advantage of B over A + advantage of A over C

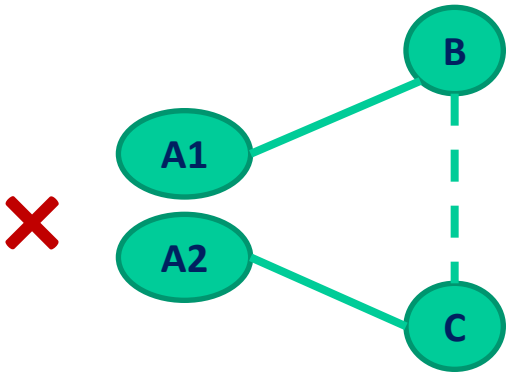



Often it is an untestable assumption

….but we can evaluate clinically and epidemiologically its plausibility

# Ways of looking at transitivity... (1)



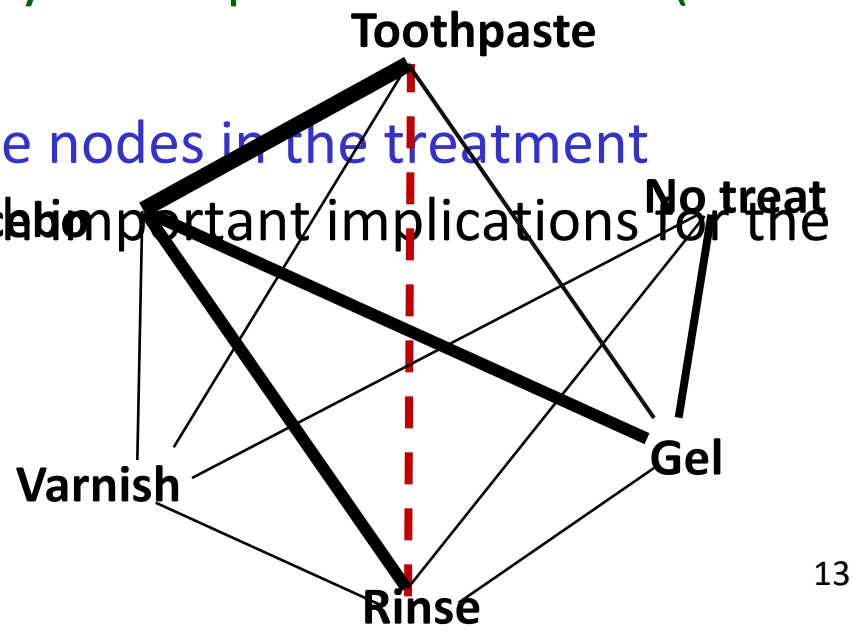




Treatment A must be similar when it appears in AB and AC trials

Plausible when A can be given in different forms?
(e.g. Compare paikillers and the same drug can be given as an injection or as a pill)?
Placebo or legacy treatments are often problematic

# Ways of looking at transitivity... (1)

- **Example:** When comparing different fluoride treatments, comparison between fluoride toothpaste and fluoride rinse can be made via placebo
  - However, placebo toothpaste and placebo rinse might not be comparable as the mechanical function of brushing might have a different effect on the prevention of caries
  - If this is the case, the transitivity assumption is doubtful (Salanti et al. JCE 2009)
- Consequently, the definition of the nodes in the treatment network is a **challenging issue** with important implications for the joint analysis

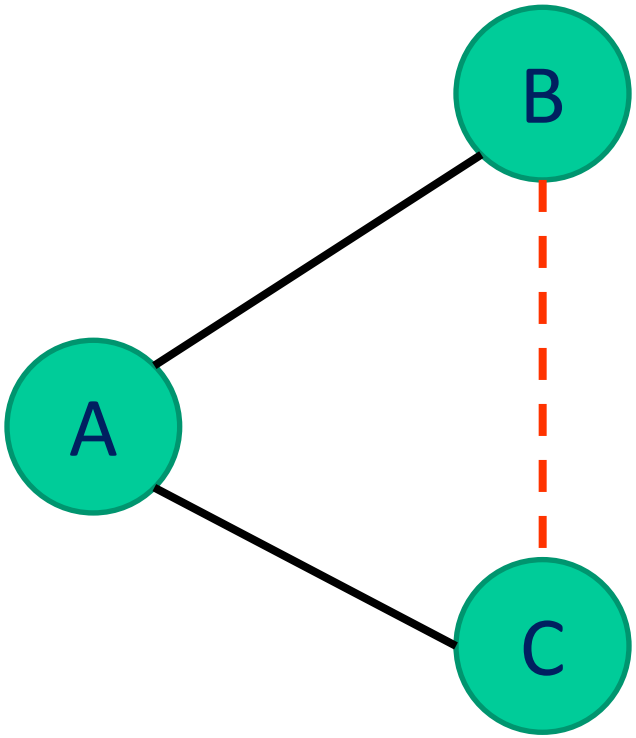


# Ways of looking at transitivity... (2)

- AC trials do not have B arms and AB trials do not have treatment C
- Another way to think about the transitivity assumption is to consider these 'missing' arms are missing at random (Lu and Ades 2006)
- If the choice of the comparison is associated, directly or indirectly, with the relative effectiveness of the interventions then the assumption of transitivity is violated

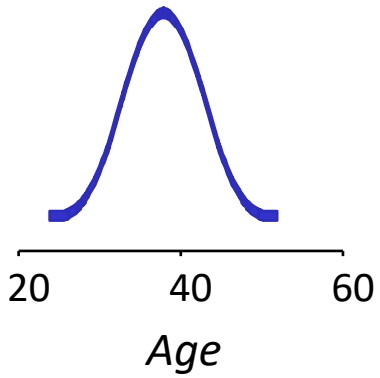
# Ways of looking at transitivity... (3)

... AC and AB trials do not differ with respect to the distribution of effect modifiers

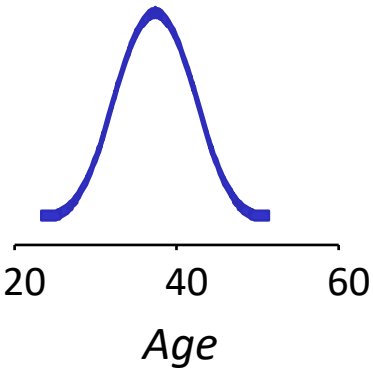


# Ways of looking at transitivity... (3)

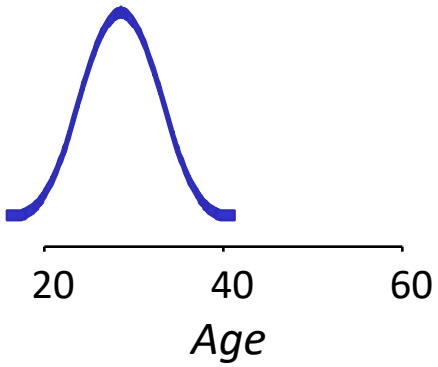
Placebo vs B

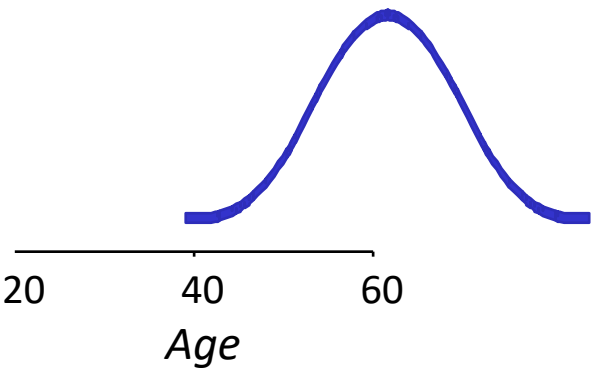



Placebo vs C

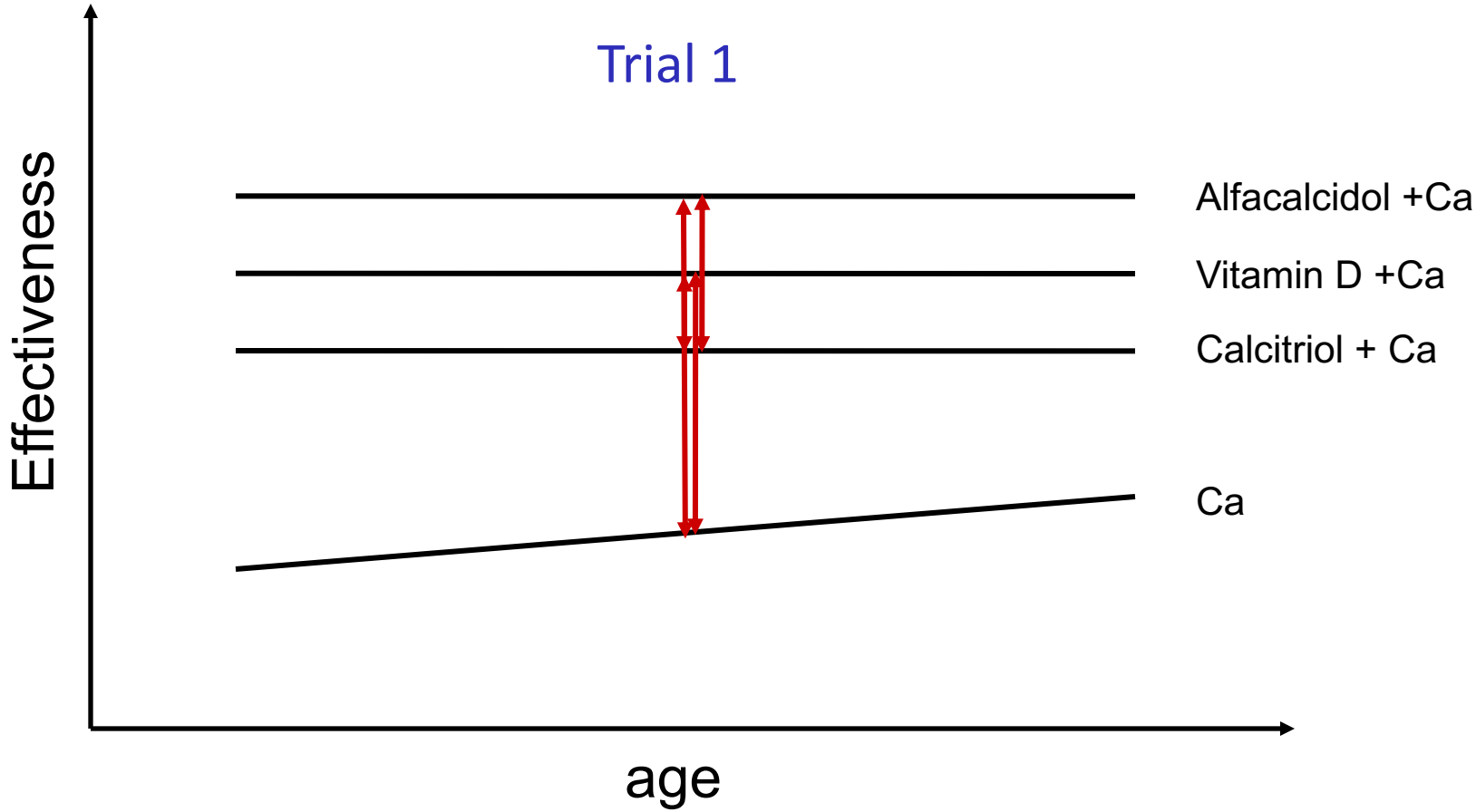



Distribution of an effect modifier across studies



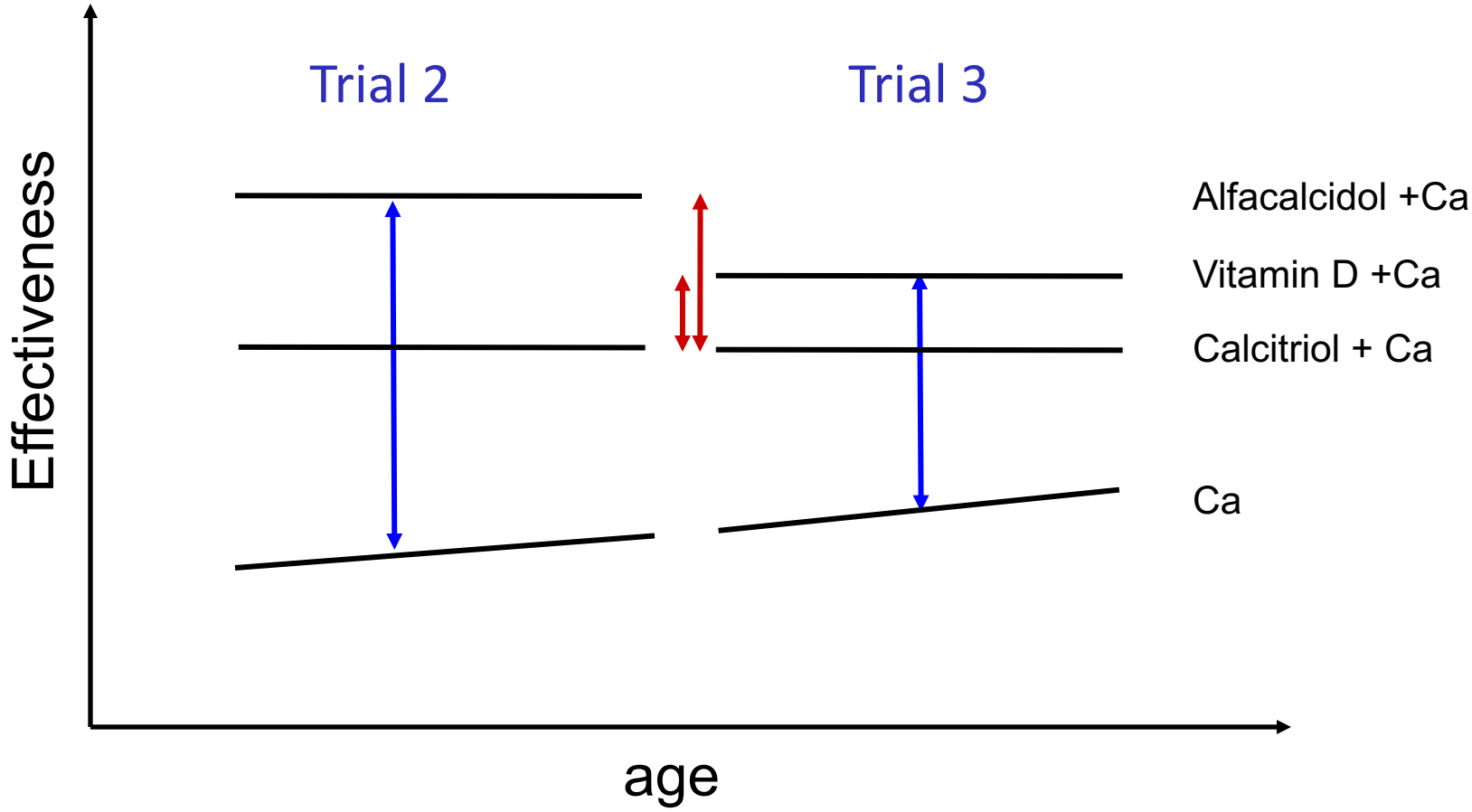



# Ways of looking at transitivity... (3)




**Calcif Tissue 2005** Richy et al

# Ways of looking at transitivity... (3)




**Calcif Tissue 2005** Richy et al

# Ways of looking at transitivity... (3)

- This formulation facilitates evaluation of the transitivity assumption.
  - Distribution of effect modifiers of the relative treatment effects for similarity in AC and AB trials
- Clinicians and methodologists that aim to synthesize evidence from many comparisons should identify a priori possible effect modifiers and compare their distributions across comparisons.

# Ways of looking at transitivity... (3)

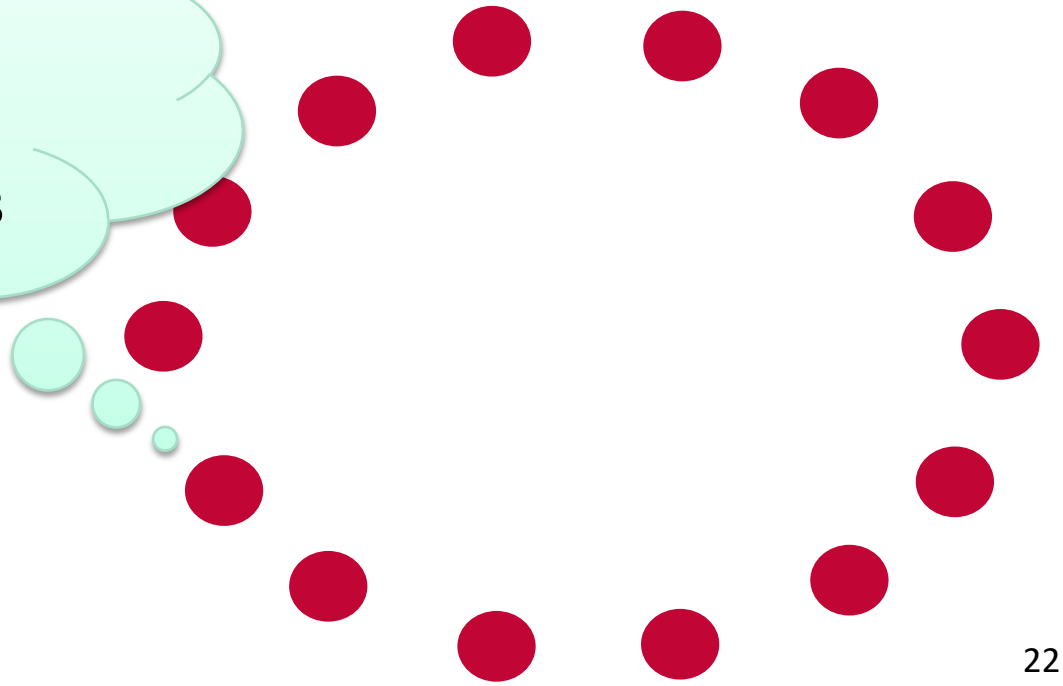
- It is important to note however that the transitivity assumption holds for the mean effect sizes
  - that is, between the mean summary effects for AC and AB
- Consequently, an effect modifier that differs across studies that belong to the same comparison but has a similar distribution across comparisons will not necessarily violate the transitivity assumption.
  - For example, if age is an effect modifier and AB trials differ in terms of mean age of participants (which will be presented as heterogeneity in AB studies) but the same variability is observed in the set of AC trials then transitivity may hold even if age is an effect modifier.

# Ways of looking at transitivity... (4)

… that all treatments are "**jointly randomizable**"

***for the patients and study settings you consider***

**think of a multi-arm trial including all competing treatments**



# Ways of looking at transitivity... (4)

- All treatments are "**jointly randomizable**"
- **This consideration is a fundamental one** and should be addressed when building the evidence network
- The assumption of transitivity could be violated if interventions have different indications.
  - E.g. treatment A is a chemotherapy regimen administered as a second line treatment, whereas treatments B and C can be either first or second line
  - we cannot assume that participants in a BC trial could have been randomized in an AC trial
- Treatments can be comparable in theory but not in practice
  - E.g. interferon and natalizumab are used for relapsing-remitting MS patients mitoxantrone for patients with a progressive disease.
  - However, evidence to support this clinical 'tradition' is not solid and it would be appealing to compare the three treatments.

# Transitivity assumption - terminology

- In the literature this assumption has been often referred to as the similarity assumption (e.g. Donegan et al. PloS 2010)
  - The term 'transitivity' describes better the aim of the assumption (to compare two treatments via a third one).
  - 'similarity' may wrongly suggest that similarity is required for all characteristics of trials and patients across the evidence base
    - when in reality valid indirect comparison can be obtained even when studies are dissimilar in characteristics that are not effect modifiers
- The violation of the assumption is often referred to in statistical models as 'treatment-by-trial' interaction.

# Implications for practice

When writting the protocol of a review you need to define

- **Types of interventions**
- Outcomes
- Health condition
- Type of population/settings

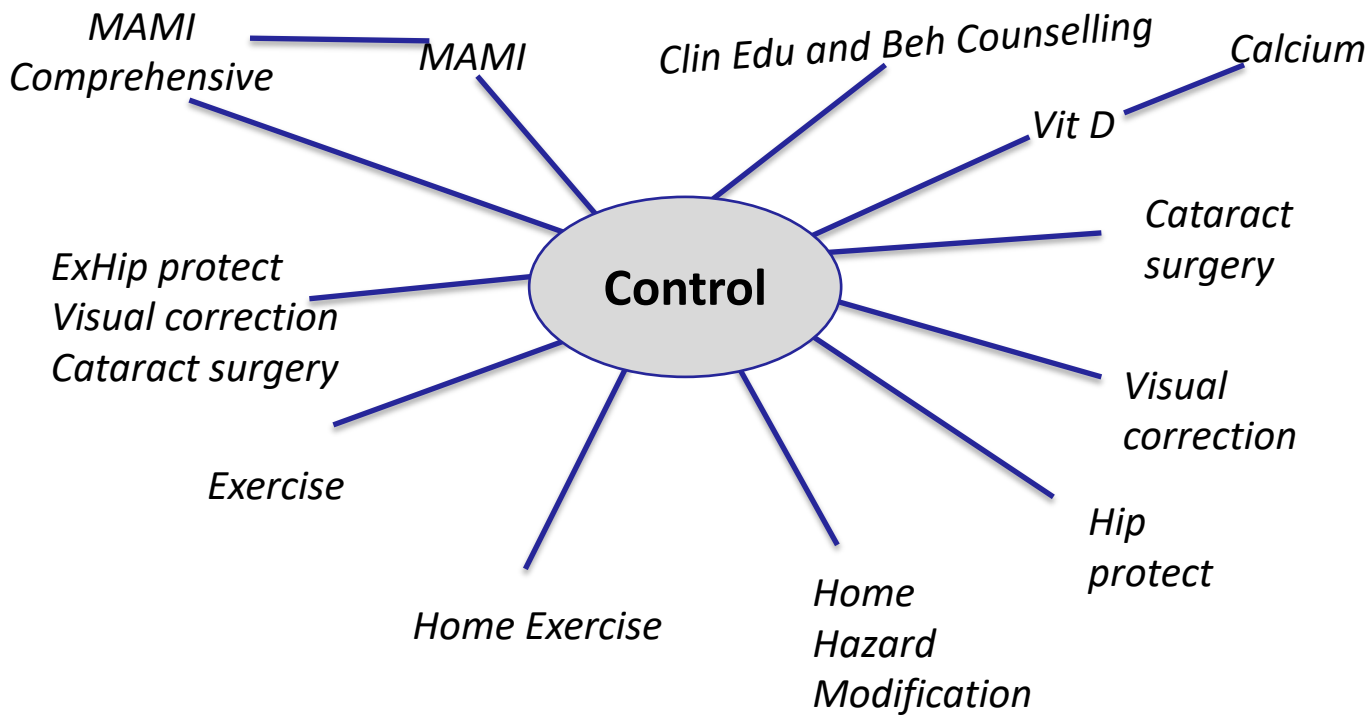
*This needs to consider issues of transitivity*

You have to make a statement that you assume the treatments to be jointly randomizable.

# What to keep in mind when deciding which interventions to include

- Restricting your review to compare few interventions
  - limits its usefulness and applicability
  - you must justify your choice
  - risk to have unconnected networks
  - few data, low power (depends on the setting)
- Expanding the database too much to include many treatments
  - Jeopardizes the transitivity assumptions (or at least makes its defense challenging)
  - Renders review process long and data management difficult
- **Watch out for:** old and new treatments, ad-on treatments, intransitive legacy treatments

# Intervention to reduce falls in elderly




What do you think about the transitivity assumption?

# Assumption in NMA

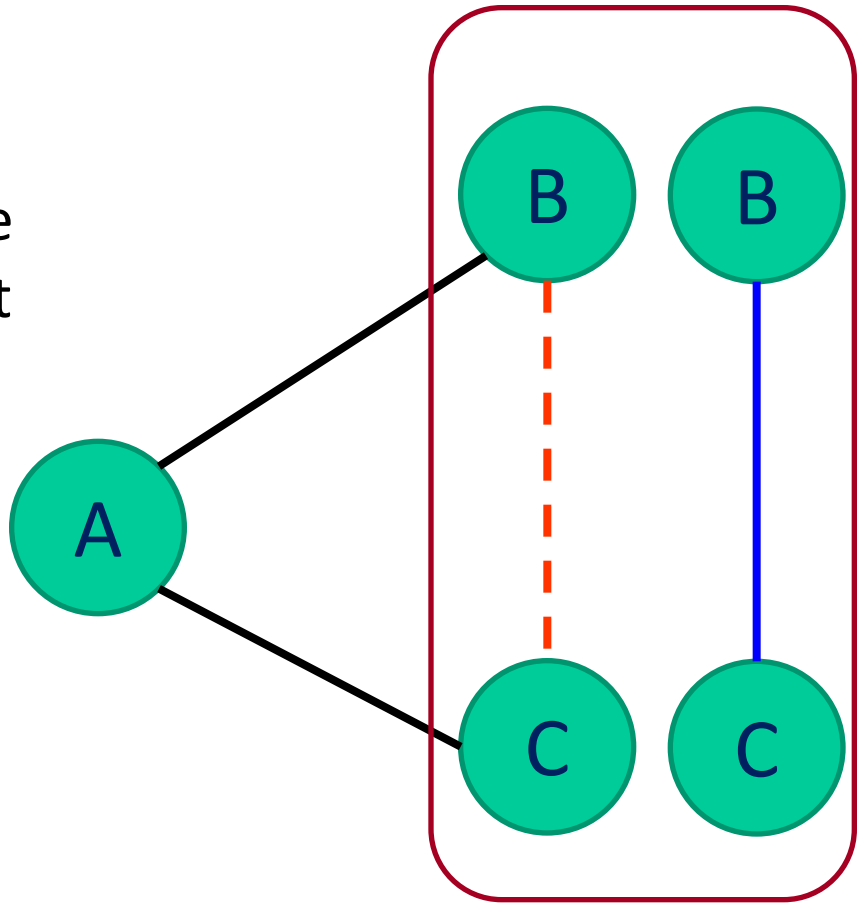
## *Transitivity, congruence, consistency….*

| In the outset | When you find the studies | When you extract the outcomes |
|---|---|---|
| The treatments we compare are *in principle* jointly randomizable | The groups of studies that compare them do not differ with respect to the distribution of effect modifiers | Direct and indirect treatment effects are in statistical agreement |
| They have the same indication, I can imagine a mega-trial with all treatments being compared etc | You can test this assumption if you have enough studies per comparison | Various statistical tests |

Cipriani A et al. *Conceptual and Technical Challenges in Network Meta-analysis* **Annals of Internal Medicine** 2013

# Consistency

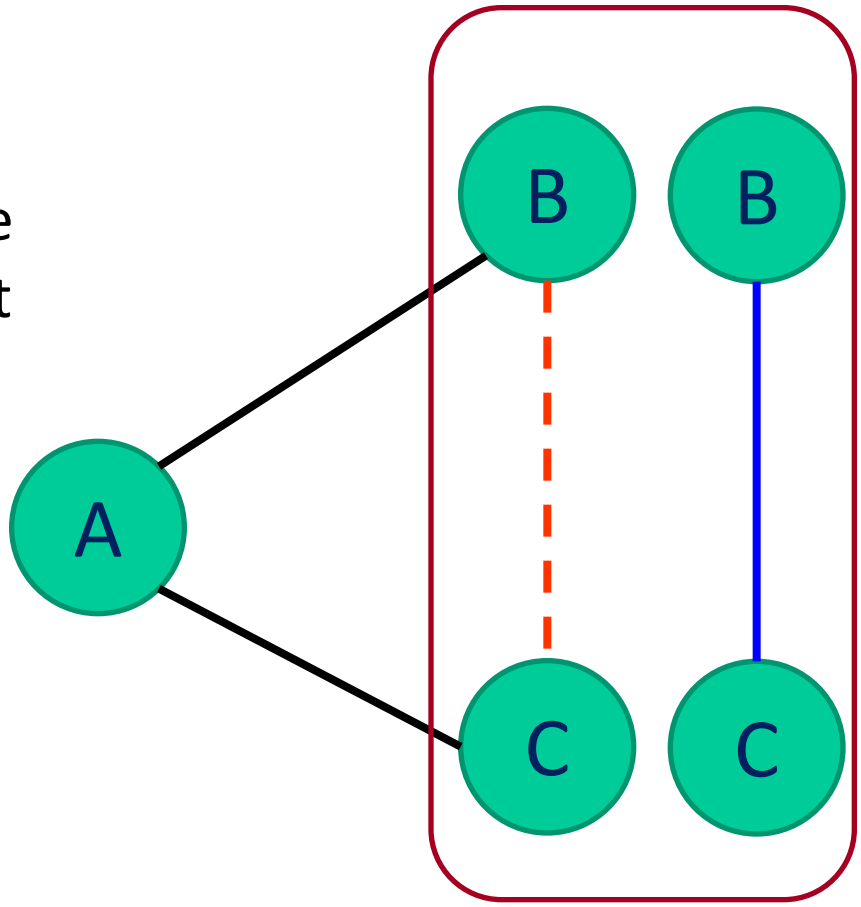
Direct and indirect evidence are in agreement




$\mu^{I}_{BC}$ $\mu^{D}_{BC}$ → $\mu^{M}_{BC}$

# Consistency

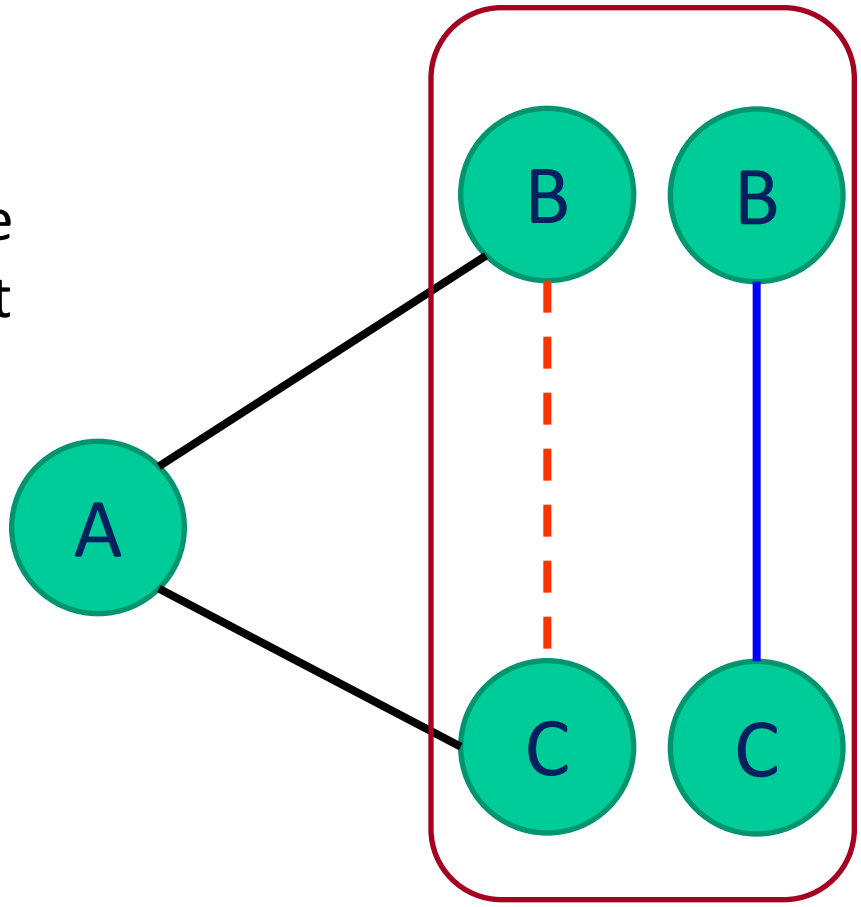
Direct and indirect evidence are in agreement




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

# Consistency

Direct and indirect evidence are in agreement




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

# Consistency equation

$$\mu_{BC} = \mu_{AC} - \mu_{AB}$$

# References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