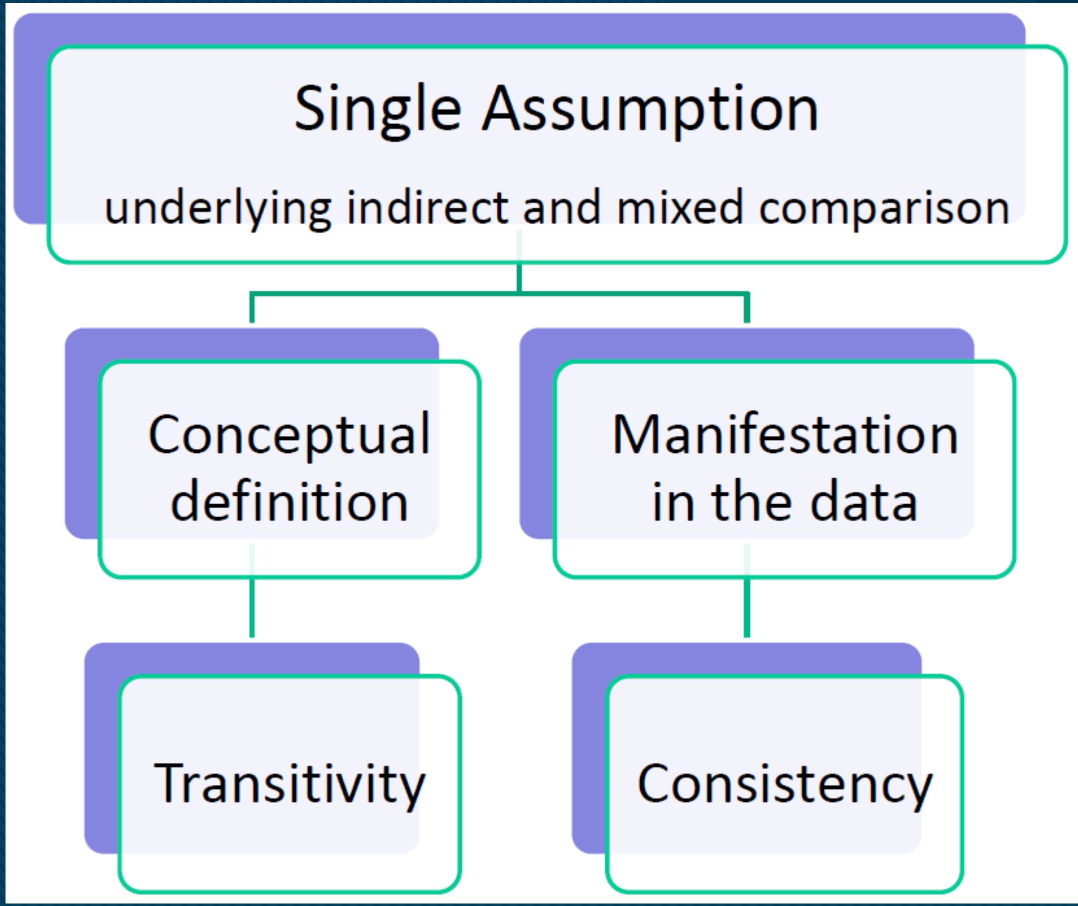
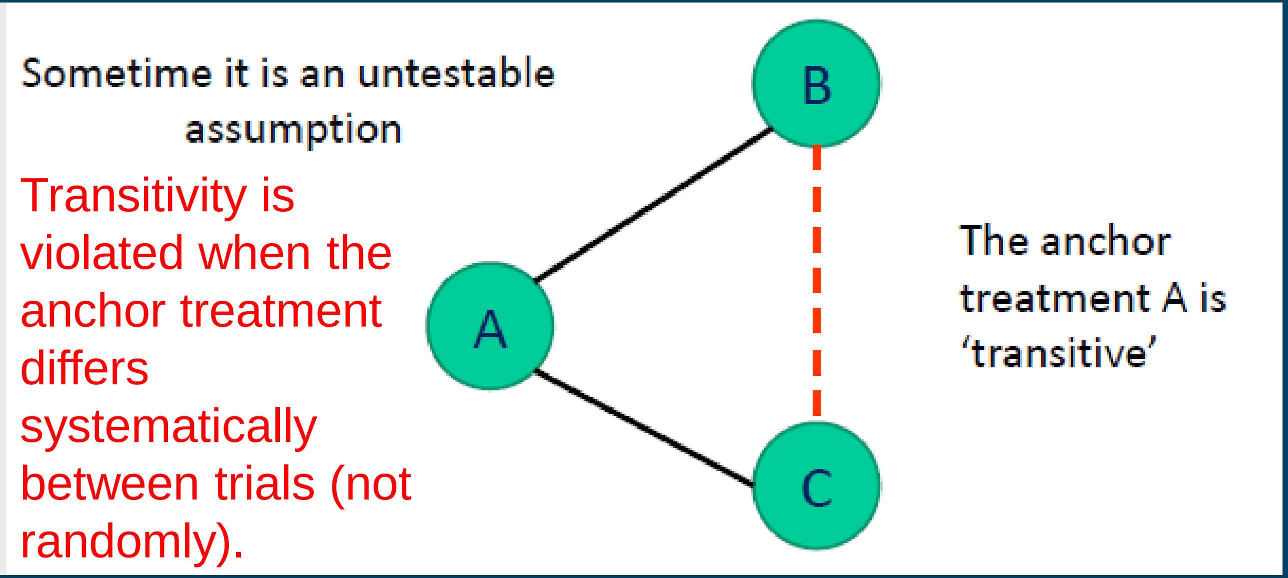
Assumption in Network Meta-analysis

Assumption Underlying Indirect/Mixed Comparison

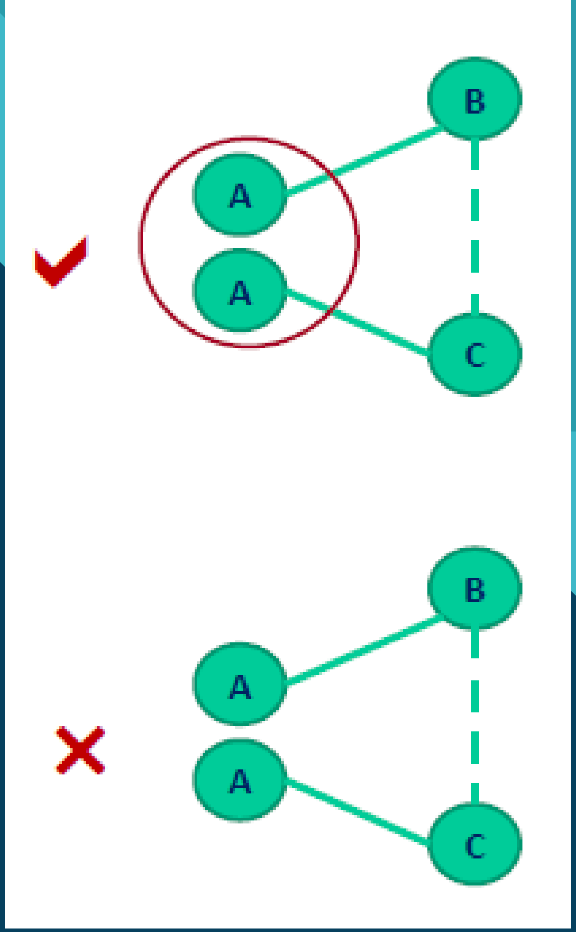


Transitivity

- Underlying assumption when μ_{BC} is calculated is that one can learn about B versus C via A.
- Treatment A is similar when it appears in AB and AC trials



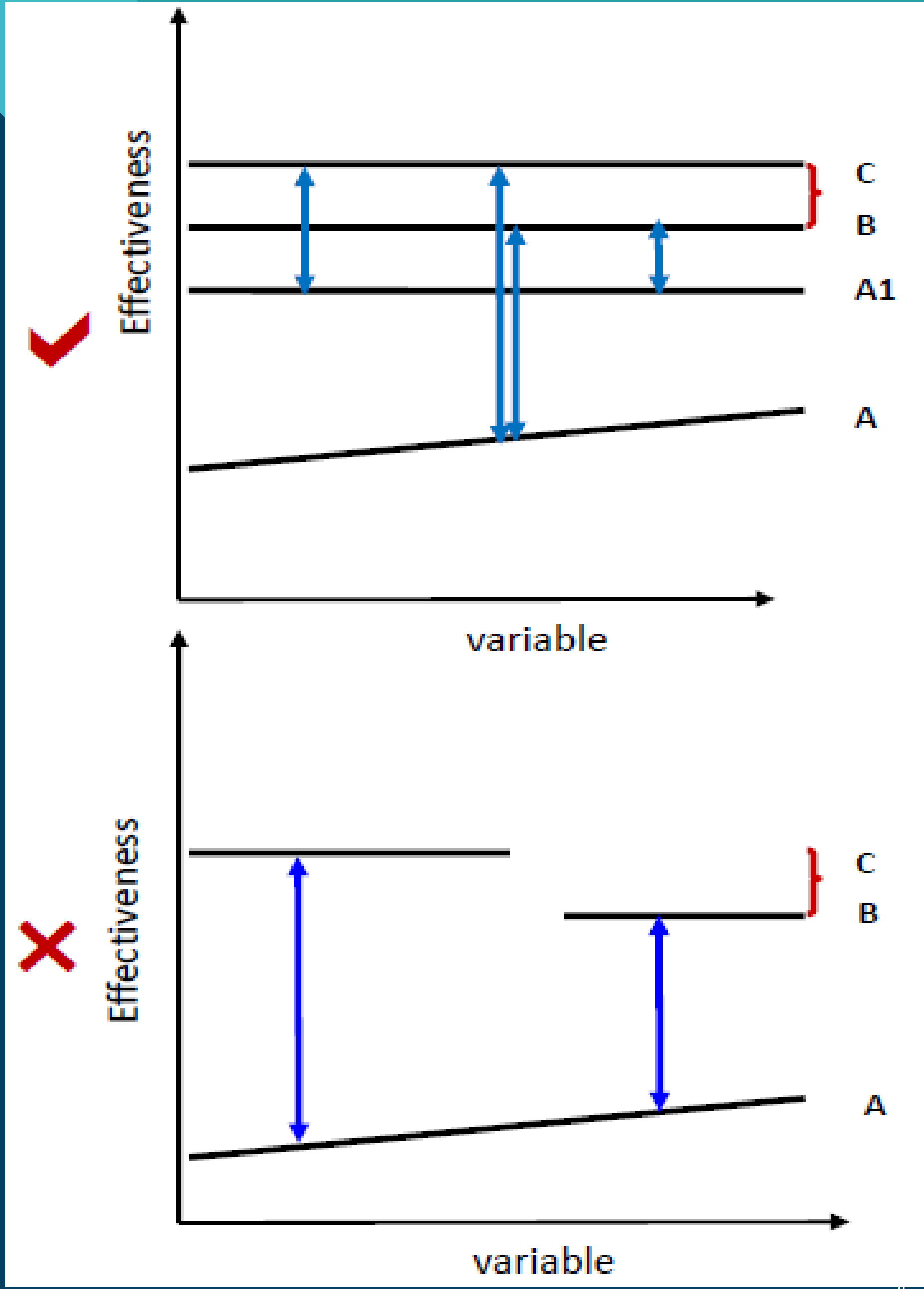
When comparing different fluoride treatments, comparison between fluoride toothpaste and fluoride rinse can be made via placebo.



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. The transitivity assumption is doubtful (Salanti et al. JCE 2009).

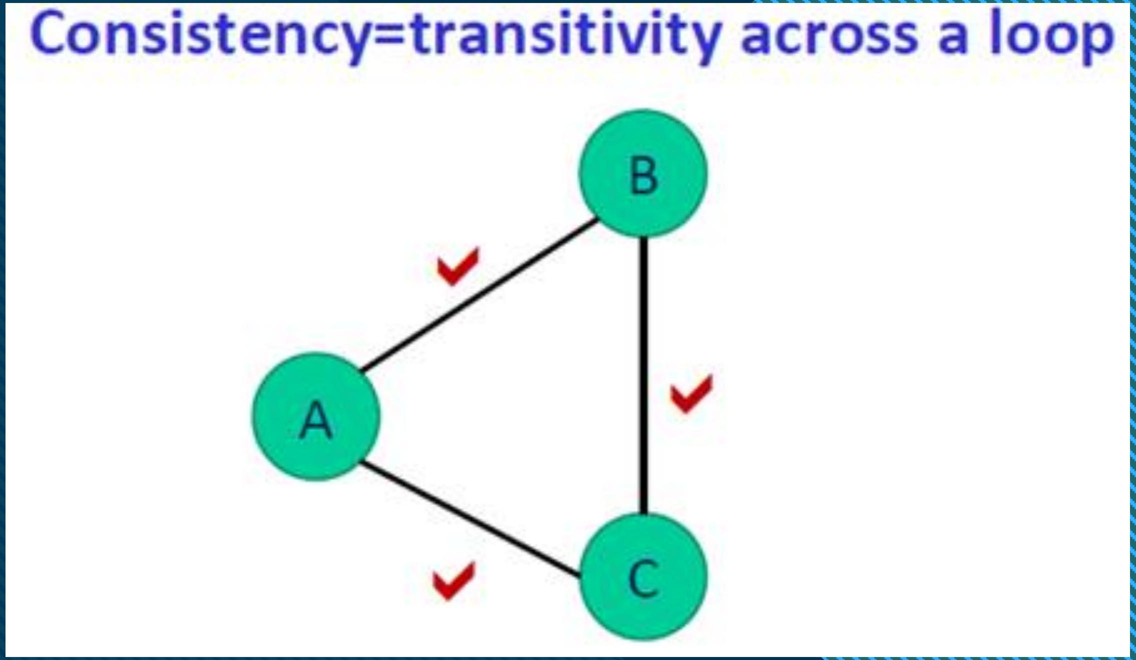
Transitivity

- Distribution of effect modifiers of the relative treatment effects for similarity in AC and AB trials
- Should identify a priori possible effect modifiers and compare their distributions across comparisons.
- An effect modifier that differs across studies that belong to the same comparison but has a similar distribution across comparisons will not violate the transitivity assumption.



Consistency

- A property of a ‘closed loop’ or ‘cycle’
- In a simple triangular loop consistency holds when transitivity can be assumed for at least 2 out of the 3 nodes A, B and C (as if A and B are transitive then C is transitive as well).
- All sets of trials grouped by comparison are similar with respect to the distribution of effect modifiers
- The ‘missing’ treatments in each trial in the loop are missing at random

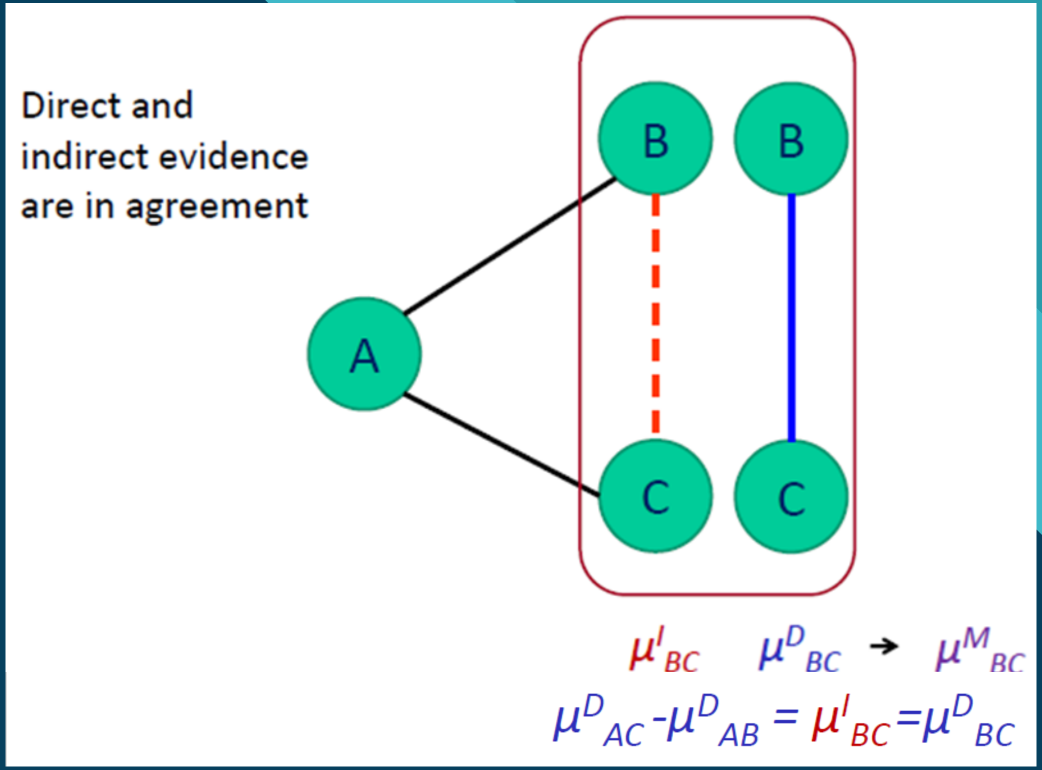


Statistical consistency

- Consistency can be evaluated statistically by comparing $\mu^D BC$ and $\mu^I BC$ in a simple z-test or estimate the inconsistency as 'inconsistency factors'

  IF= $|\mu^D BC - \mu^I BC|$ and confidence interval

- •If consistency holds, it may be reasonable to pool $\mu^D BC$ and $\mu^I BC$
- A statistically significant difference between $\mu^D BC$ and $\mu^I BC$ typically defines statistical inconsistency.



Inconsistency/Heterogeneity

- 2 components
- Within-design heterogeneity = true effect size differences between studies which included exactly the same conditions
- Between-design inconsistency = variation between designs
- If both the within-design heterogeneity and between-design inconsistency are highly significant, random-effects model may be indicated by calculating the total inconsistency based on the full design-by-treatment interaction random-effects model (J. Higgins et al. 2012).

Estimating Inconsistency

In a ABC loop of evidence:

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

$$var(IF) = var(\mu^{I}_{BC}) + var(\mu^{D}_{BC})$$

$$95\%CI : IF \pm 1.96\sqrt{var(IF)}$$

If the 95% CI excludes zero, then there is statistically significant inconsistency

A test for H_0: IF=0

$$z = \frac{IF}{\sqrt{var(IF)}} \sim N(0,1)$$

Estimating inconsistency

Local approach

- Loop specific method (ifplot command)
  - By estimate inconsistency factor (IF) of a specific loop
- Node splitting (network sidesplit command)
  - Relative treatment effects are estimated from direct and indirect NM, and then compared using Z test for IF as above.
  - A drawback is it is not properly handle with multi-treatment comparisons.

Estimating inconsistency

Global approach

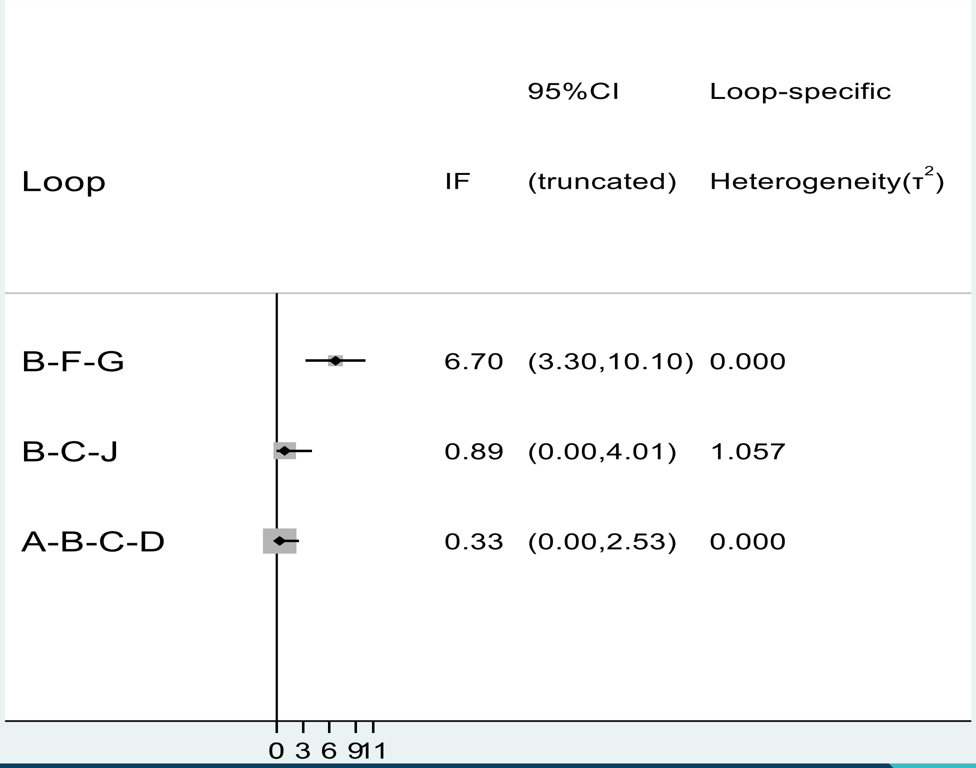
- Lu and Ades model
  - Consider IF in inconsistency model for each specific loop as

$$\mu_{BC} = \mu_{AC} - \mu_{AB} + IF_{ABC}$$

  - Different loops with different reference/comparator may yield different estimated relative treatment effect.
- Design-by-treatment interaction model
  - Considers both loop and design: treatment effect of A vs C from AC design may be different from ACD multi-arm design
  - This model can handle both conditions.

In STATA

- Pair format (local tests)
  - ifplot _y _stderr _t1 _t2 ID
  - network sidesplit all
- Augmented format (global tests)
  - network meta i, lua
  - network meta i/*design-by-treatment' interaction model is default*/




```
. network sidesplit all
```

Side	Direct Coef.	Std. Err.	Indirect Coef.	Std. Err.	Difference Coef.	Std. Err.	P>|z|
B C	.5261749	.9731115	-1.081962	2.954844	1.608137	3.113146	0.605
B D	-.6361977	1.920482	-.7411348	3.241475	.1049372	3.767164	0.978
B F *	1.831116	1.095774	6.079558	6.410378	-4.248441	6.556043	0.517
B G	7.925215	1.676028	-1.099425	1.491215	9.02464	2.112182	0.000
B H	.	.	.	.	.	.	.
B I	.	.	.	.	.	.	.
B J *	1.130948	1.375049	.7616223	3.719363	.3693255	3.90885	0.925
A C	1.5	2.270059	1.394554	3.006085	.1054464	3.766924	0.978
A D	.3999965	2.107886	.50599	3.124073	-.1059935	3.76869	0.978
A E *	3.2	2.073276	2.172537	132.9064	1.027463	132.9229	0.994
C J	1.16604	1.765574	-.0066397	2.235459	1.17268	2.802514	0.676
C L *	-.112168	1.54683	-1.041193	62.16512	.9290249	62.18507	0.988
F G *	-.485948	.9876255	14.62237	2.312362	-15.10832	2.444857	0.000
K L *	-1.58	2.039045	.5256149	154.7203	-2.105615	154.7341	0.989

```
Testing for inconsistency:
 ( 1)  [_y_D]groupA = 0
 ( 2)  [_y_G]groupF = 0

          chi2(  2) =    0.36
        Prob > chi2 =    0.8354
```

```
Testing for inconsistency:
 ( 1)  [_y_C]des_BCJ = 0
 ( 2)  [_y_D]des_BD = 0
 ( 3)  [_y_F]des_BFG = 0
 ( 4)  [_y_J]des_BJ = 0
 ( 5)  [_y_G]des_FG = 0

          chi2(  5) =   57.01
        Prob > chi2 =    0.0000
```

Statistical inconsistency

- Evaluation of the consistency assumption should include

– Checking for effect modifiers that differ across comparisons: patients characteristics, interventions, outcomes, study design, methodological characteristics, etc

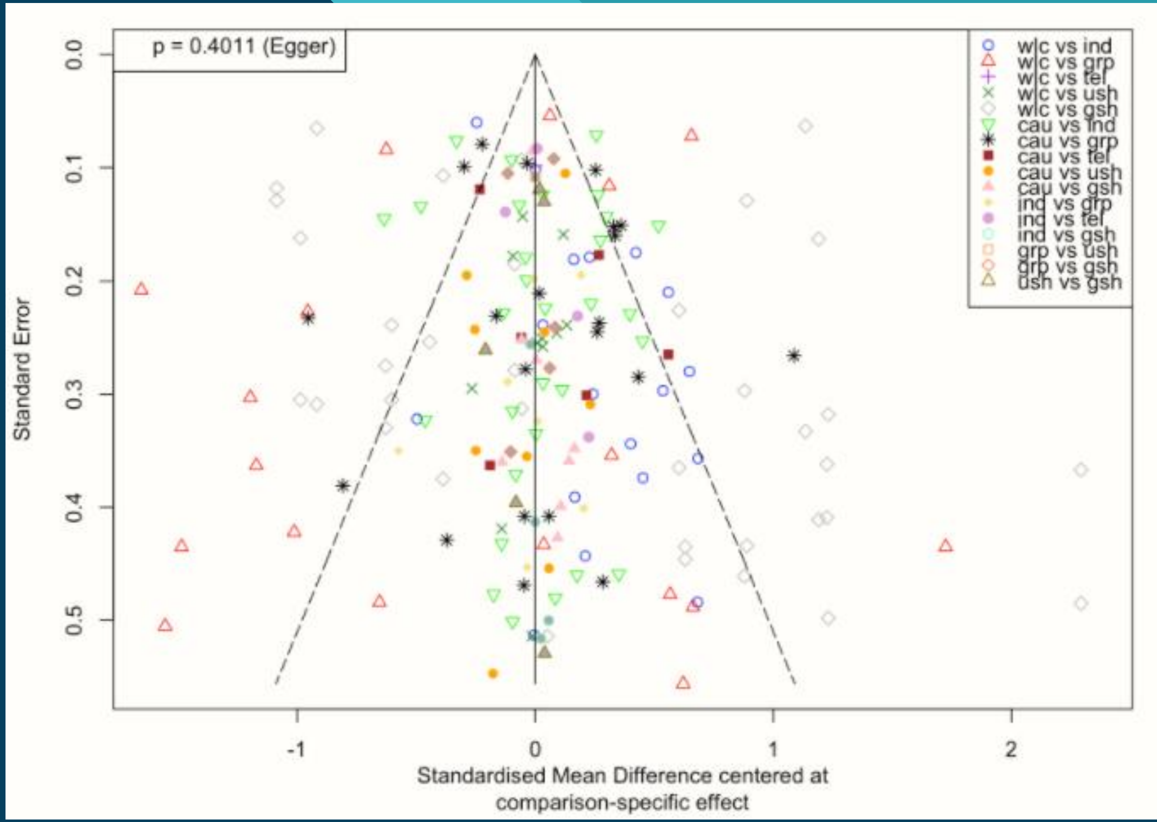
– Checking the definition of each node/treatment

Publication bias

- May be created by studies with “novel” findings are more likely to get published – even if they have a small sample size.
- With decreasing sample size, the benefit of the new treatment must be increasingly large to become significant, and thus merit publication & create the characteristic asymmetrical funnel plot (similar to standard meta-analyses).
- “Small-study effects” is a generic term for the phenomenon that smaller studies sometimes show different, often larger, treatment effects than large ones.
- All studies do not have common reference line or symmetry.
- Need to apply comparison-adjusted funnel plot.

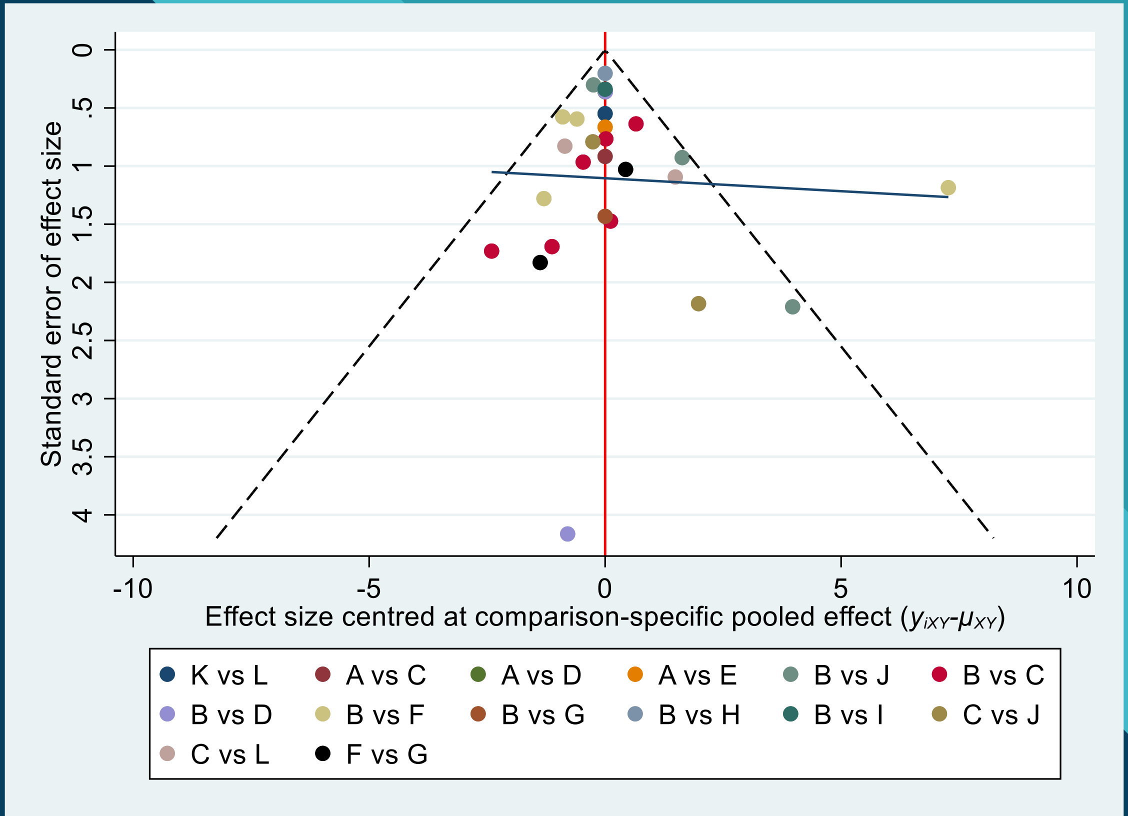
Comparison-Adjusted Funnel Plots

- X-axis is Yixy
- Y-axis is variance/precision of Yixy
- All studies are expected to line around 0
- Need to order treatments in a meaningful way and makes the assumption how small studies differ from large ones.
- The plot looks quite symmetrical corroborated by Egger’s test (p = 0.401).
- Not indicate small-study effects in the network



In STATA

- network convert pair
- netfunnel _y _stderr _t1 _t2, random bycom addplot(lfit _stderr _ES_CEN)
- Apply Egger's test for consistency model using centralized point estimates.
- metabias _ES_CEN _stderr, egger



15 comparisons

Egger's test for small-study effects:
Regress standard normal deviate of intervention
effect estimate against its standard error

Number of studies = 28 Root MSE = 1.461

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	-.2005697	.2646705	-0.76	0.455	-.7446076	.3434682
bias	.4386811	.4666847	0.94	0.356	-.5206029	1.397965

Test of H0: no small-study effects P = 0.356

References

- https://methods.cochrane.org/sites/methods.cochrane.org.cmi/files/public/uploads/E4L%20Key%20assumptions%20in%20indirect%20comparisons%20and%20network%20metaanalyses.pdf
- https://www.rama.mahidol.ac.th/ceb/sites/default/files/public/pdf/ACADEMIC/2019/RACE618/Network%20Meta-analysis.pdf

Thank You