

Identifying Effective Components of Complex Interventions: Component Network Meta-Analysis (II)

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Overview

- Component Network Meta-Analysis Models
 - Common effect (“lumped” MA)
 - Additive component effects
 - Two-way interaction models
 - Full interaction models (“split” NMA)
- Illustrative examples
 - Psychological interventions for CHD
 - Electronic interventions for smoking cessation
 - CBT for depression
 - Combination therapies for COPD



Psychological Interventions for CHD

Welton *et al*, *AJE* 2009: 169: 1158-1165

- Updated Cochrane review (Rees *et al*. Cochrane 2004)
 - 51 studies identified
- **Binary outcomes**
 - Total mortality, cardiac mortality, non-fatal MI
 - Binomial likelihood and model on the log-odds ratio $\delta_{i,k}$ in study i arm k , relative to arm 1
- **Continuous outcomes**
 - Total cholesterol, systolic BP, diastolic BP, **Depression**, anxiety
 - Normal likelihood and model mean difference in $\delta_{i,k}$
 - ... or standardised mean difference

🌟 Network Meta-Analysis Model

- Relative effect in study i arm k relative to arm 1

- Fixed Effect Model:

Log-odds ratio or
mean difference
or SMD

$$\delta_{i,k} = d_{Int_{i,k}} - d_{Int_{i,1}}$$

Intervention on
arm k of study i

Intervention on
arm 1 of study i

- Random Effects Model:

$$\delta_{i,k} \sim N\left(d_{Int_{i,k}} - d_{Int_{i,1}}, \tau^2\right)$$

- d_{Int} is the effect of intervention Int relative to reference intervention
- **Component models given to d_{Int}**

Between study
variance

Interventions

- Interventions were classified as combinations of the following characteristics:
 - Usual care (USUAL)
 - Education (EDU)
 - Behavioural (BEH)
 - Cognitive (COG)
 - Relaxation (RELAX)
 - Support (SUPP)
- For example
 - EDU + COG + RELAX; EDU + BEH; etc.
- 32 possible combinations
 - 19/32 with evidence (all outcomes); 10/32 (depression)



Overview of Component NMA Models

Model M1: Single effect: interventions are “lumped” together as a single comparator

Model M2: Additive main effects: separate effect for each component within an intervention

Model M3: Two way interactions: interaction between components (synergistic / antagonistic effects)

Model M4: Full interaction: each combination of components has a different effect (i.e. “split” NMA)



🌿 Model M1: Single effect

- All psychological interventions have the same effect compared with usual care:

$$d_{Int} = \begin{cases} 0 & Int = USUAL \\ \beta_{PSYCH} & Int \neq USUAL \end{cases}$$

- Same as standard pairwise meta-analysis
- Can answer the question:
 - “Are psychological interventions, in general, effective compared with usual care?”

🌟 Model M2: Additive main effects

- The effect of each intervention is the sum of the effects of the component parts

$$d_{Int} = \beta_{EDU} I_{Int \supset EDU} + \beta_{BEH} I_{Int \supset BEH} + \beta_{COG} I_{Int \supset COG} \\ + \beta_{RELAX} I_{Int \supset RELAX} + \beta_{SUPP} I_{Int \supset SUPP}$$

$I_{Int \supset EDU}$ is 1 if there is an *EDU* component in *Int* and 0 otherwise, etc.

- E.g. if $Int = BEH + COG$, then $d_{Int} = \beta_{BEH} + \beta_{COG}$
- Can answer the question:
 - “Are psychological intervention containing a specific component effective compared with interventions without that component (all other things being equal)?”
- Can predict effect for combinations not included in RCTs

🌟 Model M3: Two-Way Interaction Model

- Allows pairs of components to have a bigger (synergistic) or smaller (antagonistic) effect than the sum of the 2 component main effects

$$\begin{aligned}d_{Int} = & \beta_{EDU} I_{Int \supset EDU} + \beta_{BEH} I_{Int \supset BEH} + \beta_{COG} I_{Int \supset COG} \\ & + \beta_{RELAX} I_{Int \supset RELAX} + \beta_{SUPP} I_{Int \supset SUPP} \\ & + \beta_{EDU, BEH} I_{Int \supset EDU} I_{Int \supset BEH} + \beta_{EDU, COG} I_{Int \supset EDU} I_{Int \supset COG} + \dots\end{aligned}$$

- E.g. if $Int = BEH + COG$, then

$$d_{Int} = \beta_{BEH} + \beta_{COG} + \beta_{BEH, COG}$$

Interaction term

- Can answer the question:
 - “Are psychological intervention containing specific pairs of components effective (all other things being equal)?”

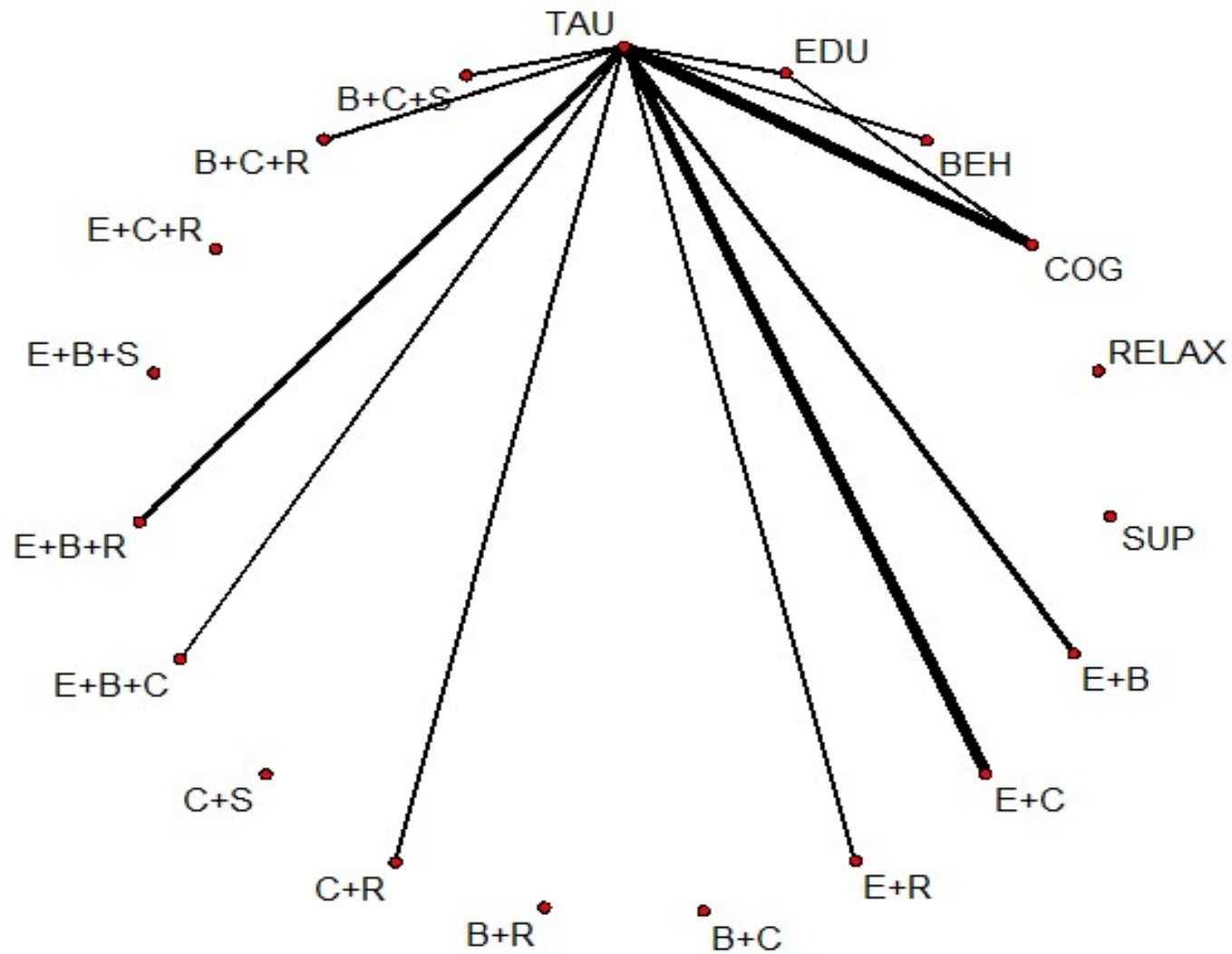
🌟 Model M4: Full Interaction Model

- Each possible combination of components has a distinct effect

$$d_{Int} = \beta_{Int}$$

- Same as standard network meta-analysis where each combination of components is a separate “treatment”
- Can answer the question:
 - “Are psychological intervention with a particular combination of components effective compared with usual care?”
 - ... but only for the combinations that are included in the RCTs

🔥 Network plot: full interaction model



🌿 Model Selection

Model M1: **Single effect**

Model M2: **Additive main effects**

Model M3: **Two way interactions**

Model M4: **Full interaction**



Increased complexity

Reduced Assumptions

Less Generalisable

Less Precise Estimates

- We prefer simpler models
- Compare measures of model fit (deviance, DIC)
- Compare heterogeneity estimates
- Inspect the credible intervals around the regression parameters, β

🌟 Results: Depression

M1: Single Effect
(DIC=121.9, $\sigma=.19$)

Any Psychological
Intervention vs Usual Care

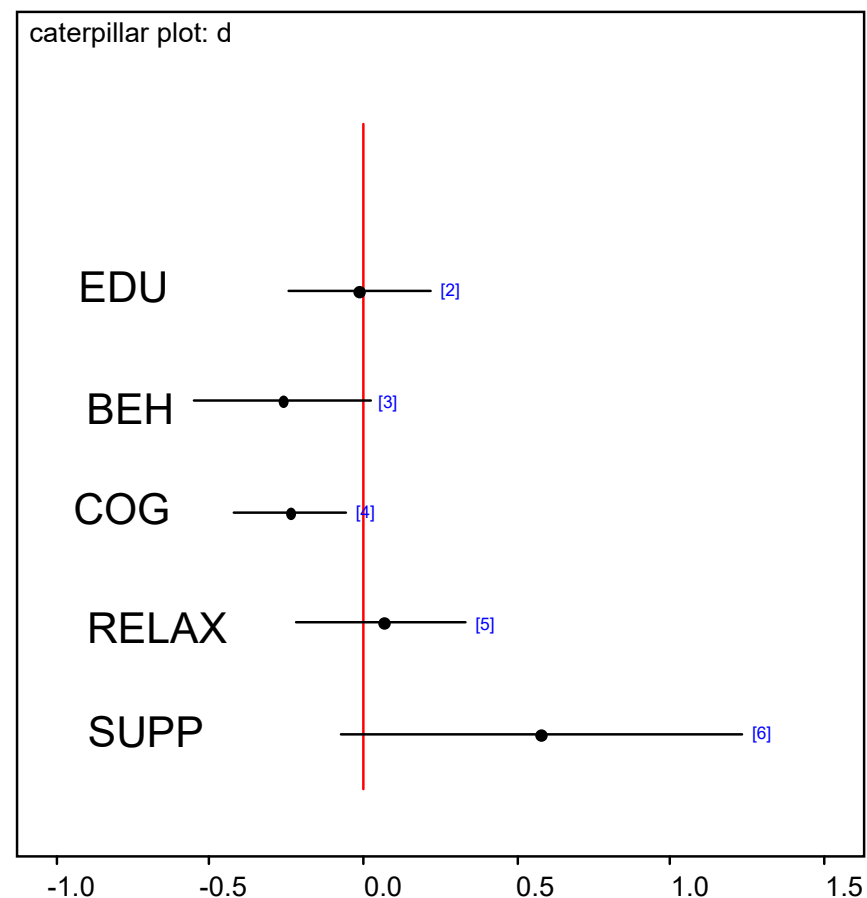
Standardised Mean Diff:

-0.23 (-0.36, -0.11)

M3: 2-way Interaction
(DIC=121.6, $\sigma=.11$)

M4: Full Interaction
(DIC=123.2, $\sigma=.11$)

M2: Main Effects (DIC=123.5, $\sigma=.19$)



Electronic Aids for Smoking Cessation

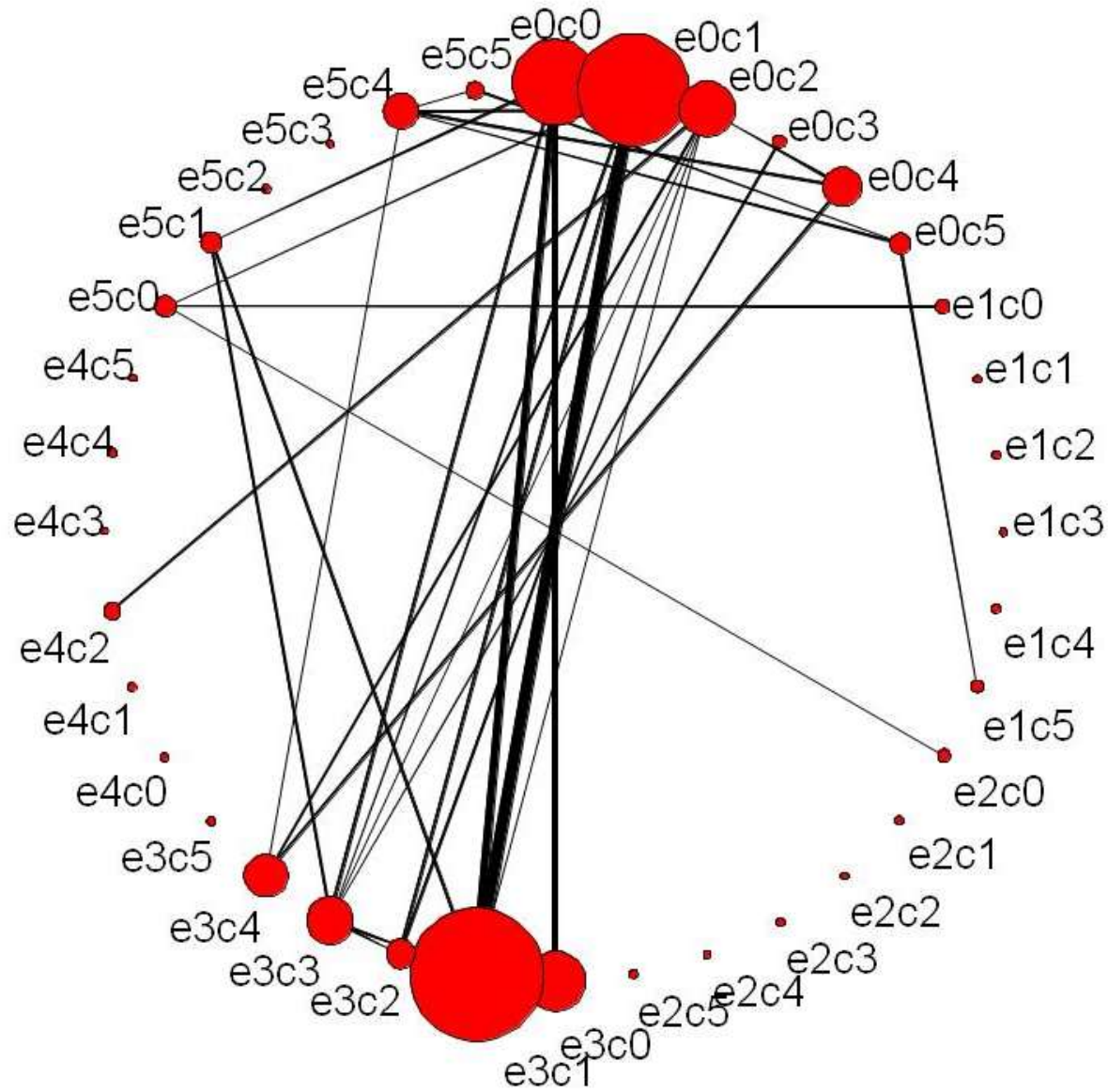
Chen et al HTA 2012 16:38, Madan (2014)

- What is the effectiveness of internet, PC and other electronic aids to help people stop smoking?
- Interventions defined as a combination of an electronic component and a non-electronic (control) component



Electronic interventions/components		Non-Electronic interventions/components	
Code	Definition	Code	Definition
e0	Nothing (no electronic component)	c0	Nothing (no non-electronic component)
e1	Single generic component	c1	Generic self-help material
e2	Multiple generic components	c2	Brief advice
e3	Single tailored component	c3	Telephone or face to face counselling
e4	Single tailored component (+ generic component(s))	c4	Pharmacotherapy
e5	Multiple tailored components (\pm generic component(s))	c5	Counselling + pharmacotherapy





- 19 of the 35 possible combinations are included in the network

Intervention	Additive Model (M2)	Single Effect (M1)
Non-Electronic interventions:		
c1 (self-help)	1.04 (0.94-1.14)	
c2 (brief advice)	0.99 (0.84-1.17)	
c3 (counselling)	0.95 (0.79-1.12)	
c4 (pharmacotherapy)	1.00 (0.75-1.30)	
c5 (counselling+pharmacotherapy)	0.85 (0.59-1.17)	
Electronic interventions:		0.87 (0.83-0.92)
e1 (single generic)	0.89 (0.66-1.16)	
e2 (multiple generic)	0.98 (0.78-1.21)	
e3 (single tailored)	0.88 (0.83-0.93)	
e4 (single tailored+generic)	1.02 (0.78-1.32)	
e5 (multiple tailored)	0.85 (0.75-0.96)	

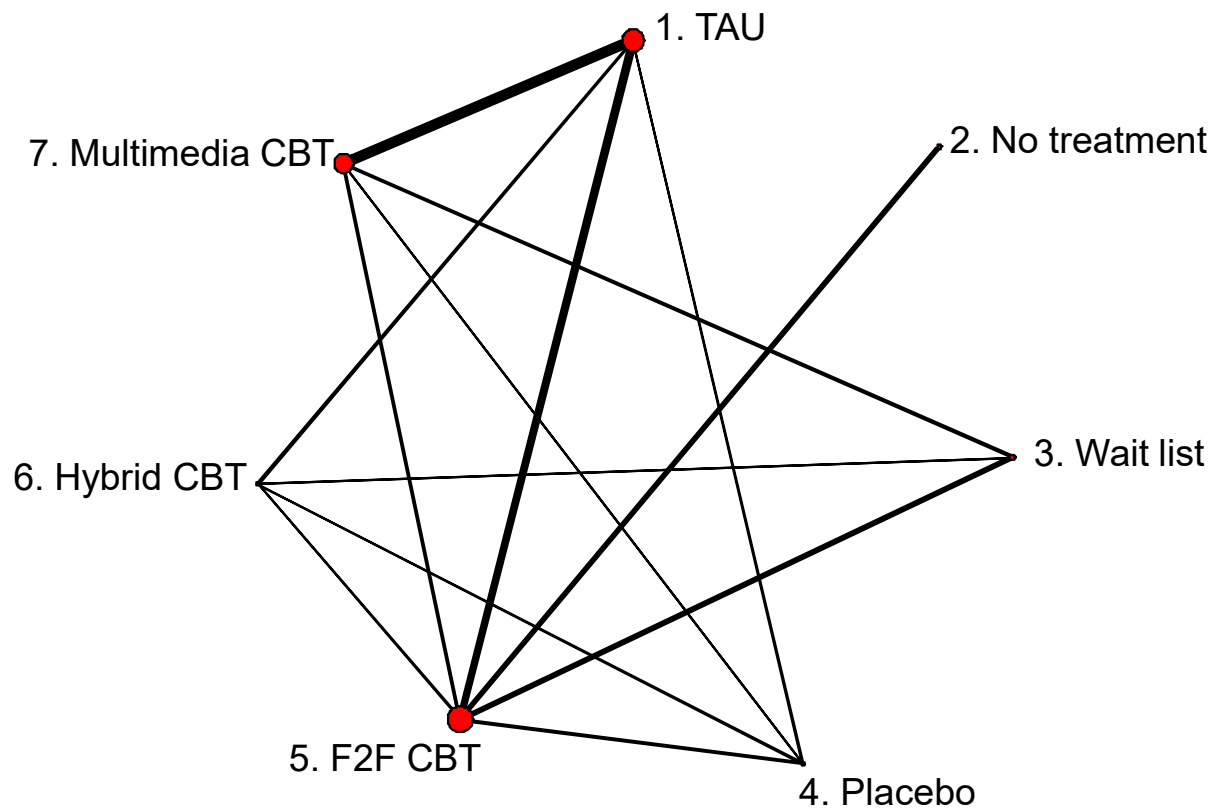
Results Summary

- Overall there is evidence that electronic interventions are effective
- Single tailored and multiple tailored electronic interventions were effective
 - Majority of evidence was on these formats

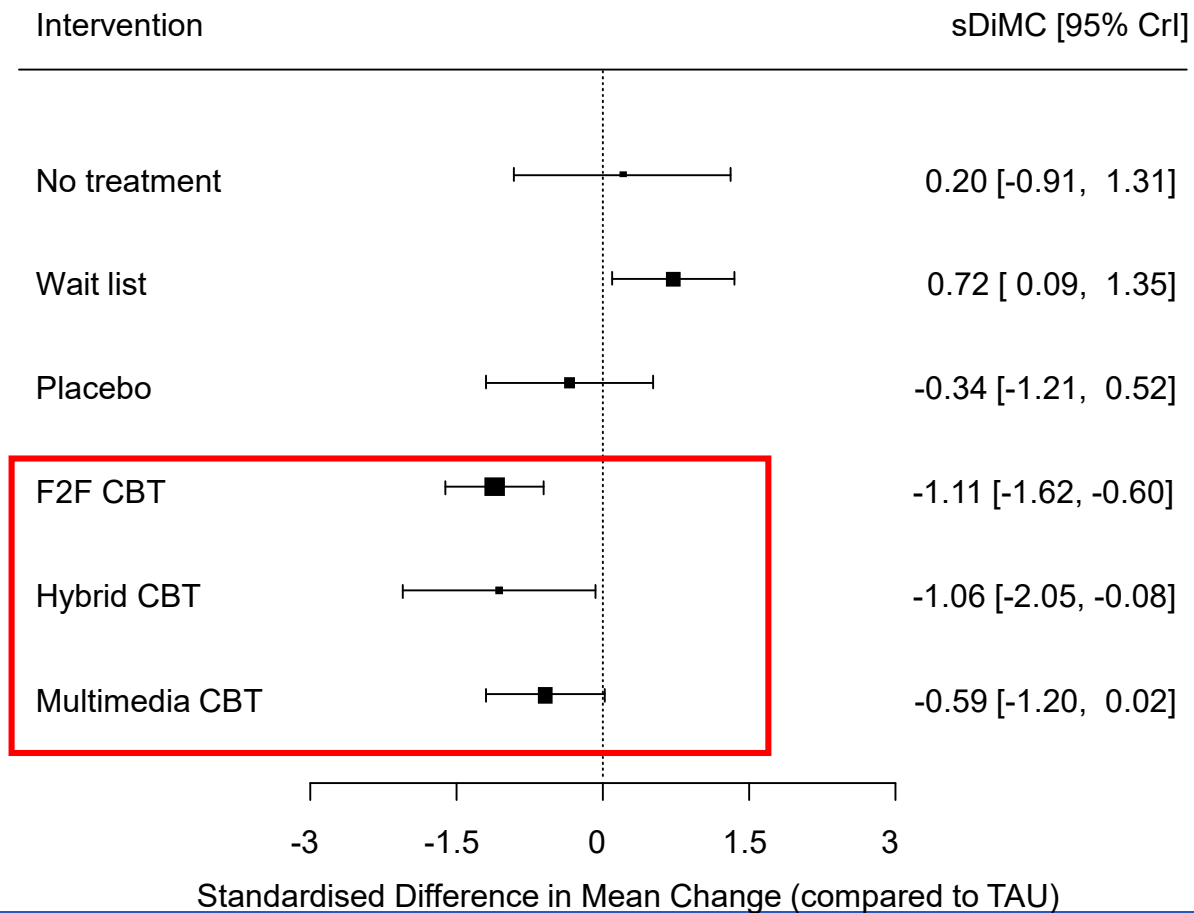


🔥 CBT Interventions for Depression in Adults (INTERACT) Lopez-Lopez (2019)

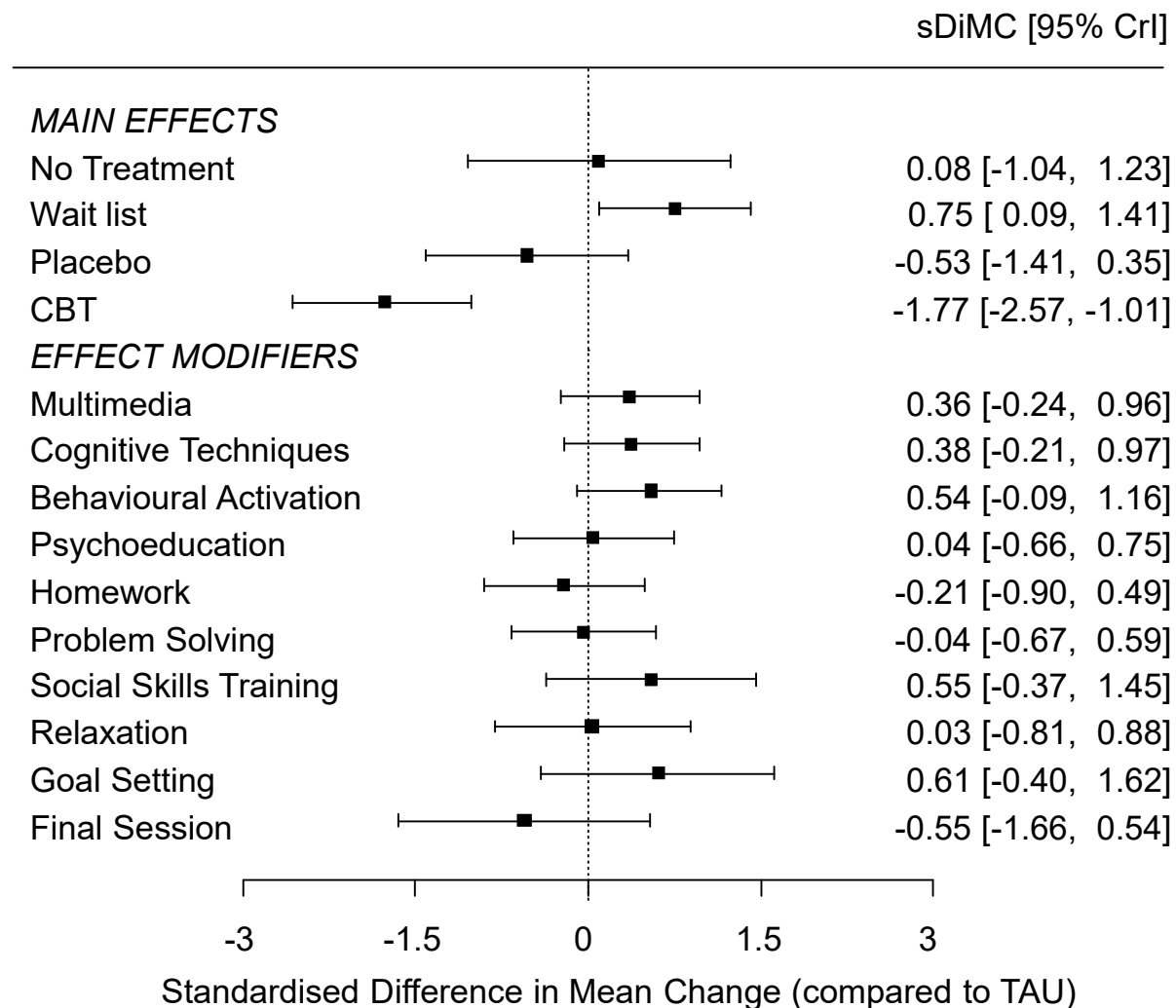
- 76 studies, 6973 patients



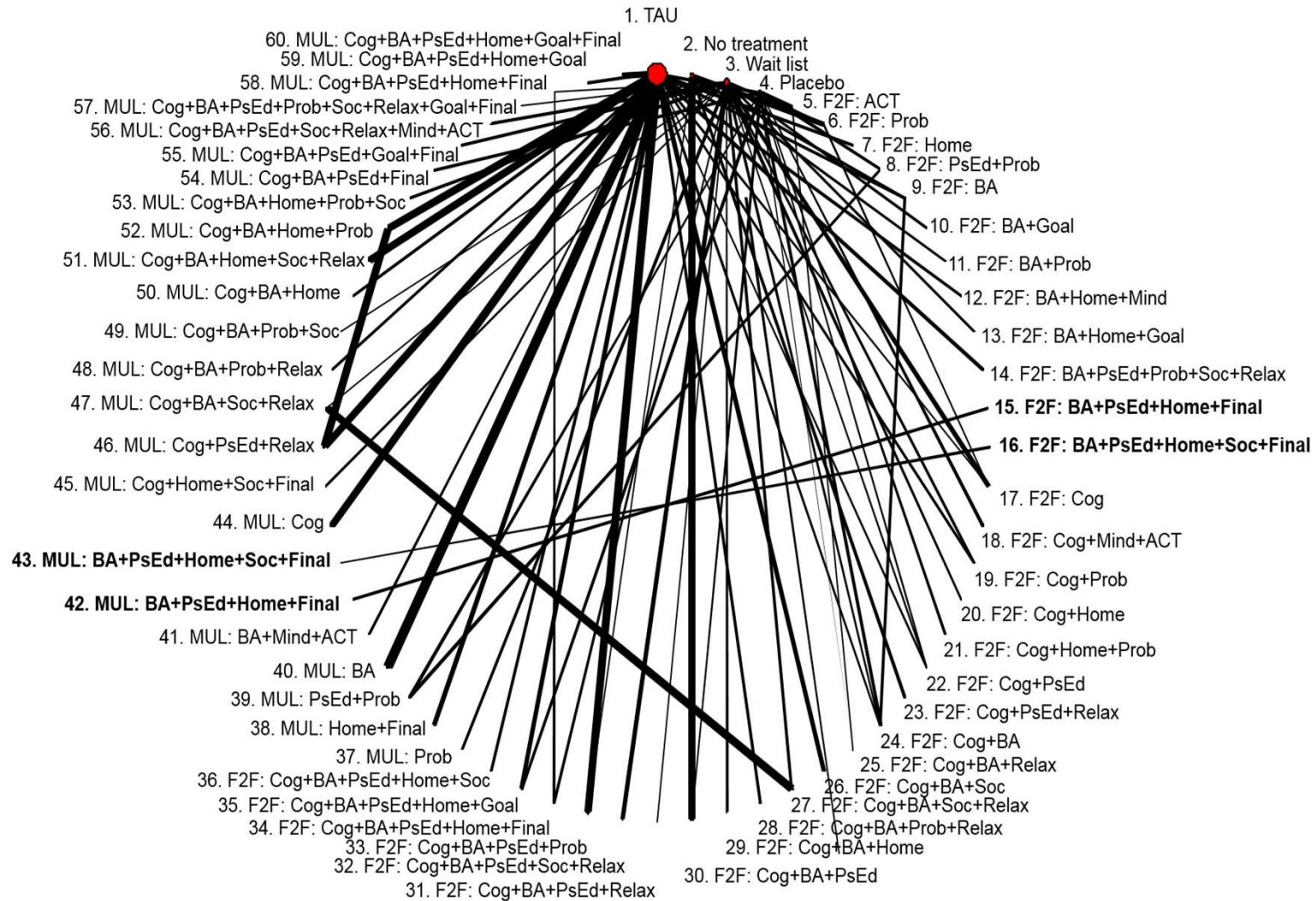
Results: Change in depression scores



🔥 Main Effects + Additive Components



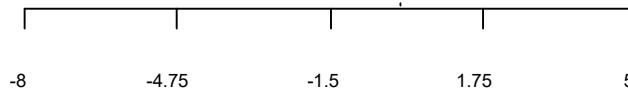
Full interaction model



Intervention

sDiMC [95% CrI]

2. No treatment	-0.57	[-2.14, 1.01]
3. Wait list	0.93	[-0.29, 2.13]
4. Placebo	-0.32	[-1.64, 1.01]
5. F2F: ACT	-1.71	[-4.39, 1.01]
6. F2F: Prob	-2.02	[-3.46, -0.58]
7. F2F: Home	-6.92	[-9.29, -4.58]
8. F2F: PsEd+Prob	-1.75	[-4.45, 0.94]
9. F2F: BA	-1.57	[-2.65, -0.50]
10. F2F: BA+Goal	-0.35	[-3.01, 2.30]
11. F2F: BA+Prob	-2.29	[-5.13, 0.53]
12. F2F: BA+Home+Mind	0.88	[-1.47, 3.23]
13. F2F: BA+Home+Goal	0.55	[-1.74, 2.84]
14. F2F: BA+PsEd+Prob+Soc+Relax	-0.62	[-2.97, 1.72]
17. F2F: Cog	-1.42	[-2.83, -0.01]
18. F2F: Cog+Mind+ACT	-0.75	[-3.46, 1.95]
19. F2F: Cog+Prob	-1.79	[-3.38, -0.22]
20. F2F: Cog+Home	-2.29	[-4.25, -0.36]
21. F2F: Cog+Home+Prob	1.10	[-1.88, 4.14]
22. F2F: Cog+PsEd	-0.52	[-2.07, 1.02]
23. F2F: Cog+PsEd+Relax	-2.68	[-5.50, 0.16]
24. F2F: Cog+BA	-0.70	[-1.87, 0.46]
25. F2F: Cog+BA+Relax	-1.48	[-4.19, 1.24]
26. F2F: Cog+BA+Soc	0.08	[-2.26, 2.42]
27. F2F: Cog+BA+Soc+Relax	-0.66	[-2.93, 1.64]
28. F2F: Cog+BA+Prob+Relax	-0.50	[-2.84, 1.85]
29. F2F: Cog+BA+Home	-0.27	[-2.62, 2.12]
30. F2F: Cog+BA+PsEd	-1.34	[-3.39, 0.71]
31. F2F: Cog+BA+PsEd+Relax	0.55	[-2.09, 3.19]
32. F2F: Cog+BA+PsEd+Soc+Relax	0.50	[-1.42, 2.40]
33. F2F: Cog+BA+PsEd+Prob	-1.37	[-3.23, 0.48]
34. F2F: Cog+BA+PsEd+Home+Final	-1.64	[-4.32, 0.99]
35. F2F: Cog+BA+PsEd+Home+Goal	-0.41	[-1.99, 1.18]
36. F2F: Cog+BA+PsEd+Home+Soc	-0.47	[-2.83, 1.87]
37. MUL: Prob	0.13	[-2.52, 2.81]
38. MUL: Home+Final	-0.82	[-3.17, 1.55]
39. MUL: PsEd+Prob	-1.08	[-3.78, 1.63]
40. MUL: BA	-0.80	[-3.14, 1.56]
41. MUL: BA+Mind+ACT	0.05	[-2.29, 2.42]
44. MUL: Cog	-0.41	[-1.94, 1.13]
45. MUL: Cog+Home+Soc+Final	-0.12	[-2.79, 2.54]
46. MUL: Cog+PsEd+Relax	0.00	[-2.33, 2.38]
47. MUL: Cog+BA+Soc+Relax	-0.85	[-3.36, 1.67]
48. MUL: Cog+BA+Prob+Relax	-0.58	[-2.92, 1.78]
49. MUL: Cog+BA+Prob+Soc	-0.87	[-3.53, 1.78]
50. MUL: Cog+BA+Home	-2.08	[-4.47, 0.34]
51. MUL: Cog+BA+Home+Soc+Relax	-0.19	[-2.22, 1.82]
52. MUL: Cog+BA+Home+Prob	0.15	[-2.18, 2.49]
53. MUL: Cog+BA+Home+Prob+Soc	0.14	[-2.50, 2.79]
54. MUL: Cog+BA+PsEd+Final	-1.67	[-4.38, 1.04]
55. MUL: Cog+BA+PsEd+Goal+Final	-0.52	[-2.91, 1.86]
56. MUL: Cog+BA+PsEd+Soc+Relax+Mind+ACT	-0.10	[-2.49, 2.28]
57. MUL: Cog+BA+PsEd+Prob+Soc+Relax+Goal+Final	0.02	[-2.64, 2.71]
58. MUL: Cog+BA+PsEd+Home+Final	-1.44	[-4.09, 1.22]
59. MUL: Cog+BA+PsEd+Home+Goal	-0.81	[-3.13, 1.55]
60. MUL: Cog+BA+PsEd+Home+Goal+Final	-1.08	[-3.43, 1.26]



Standardised Difference in Mean Change (compared to TAU)

Summary of findings

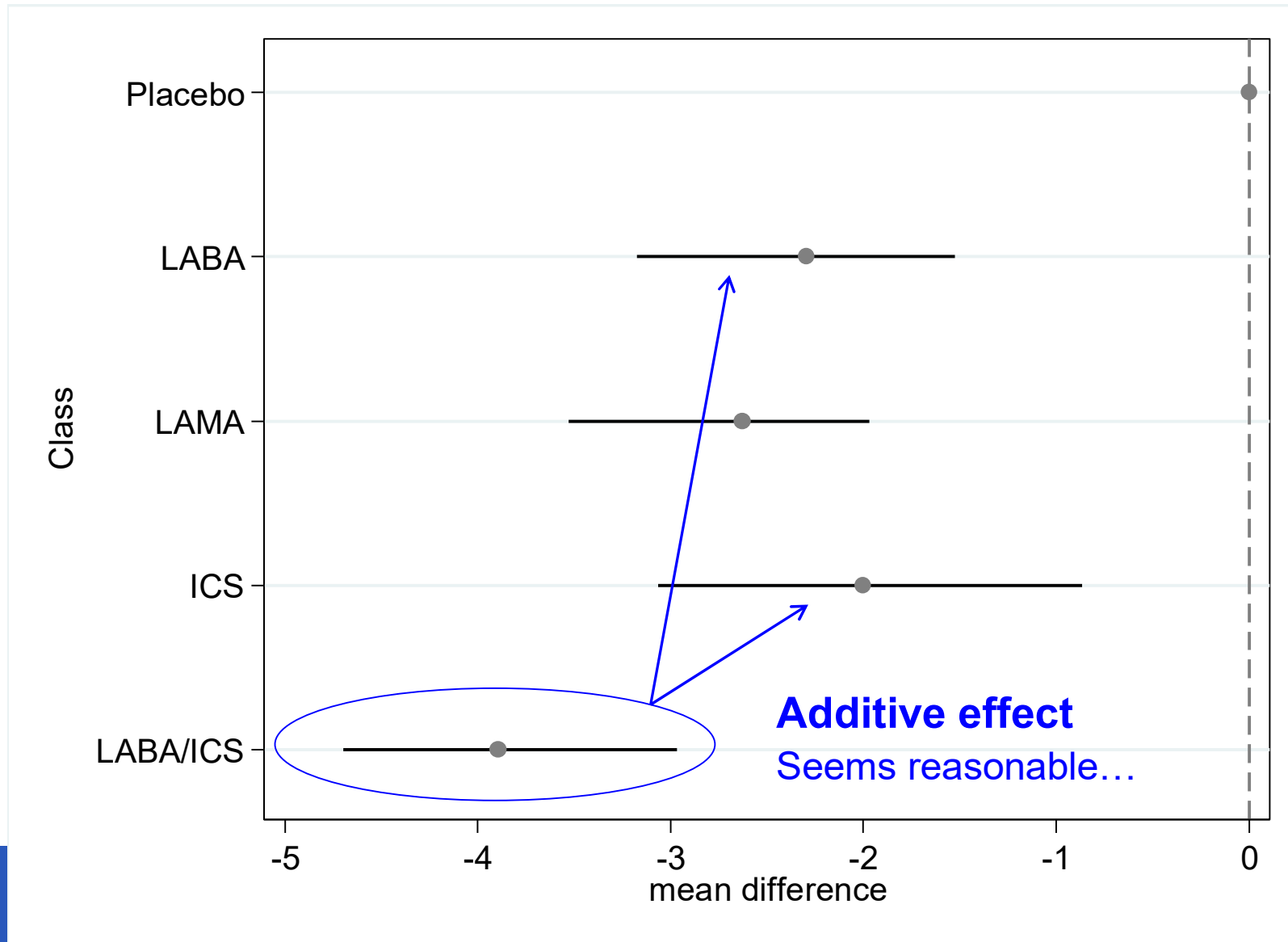
- CBT interventions are effective in the reduction of depressive symptoms
- Results do not suggest a substantial difference between multimedia, hybrid, and face-to-face CBT
- No evidence that any content component increases treatment effectiveness

Combination Therapies

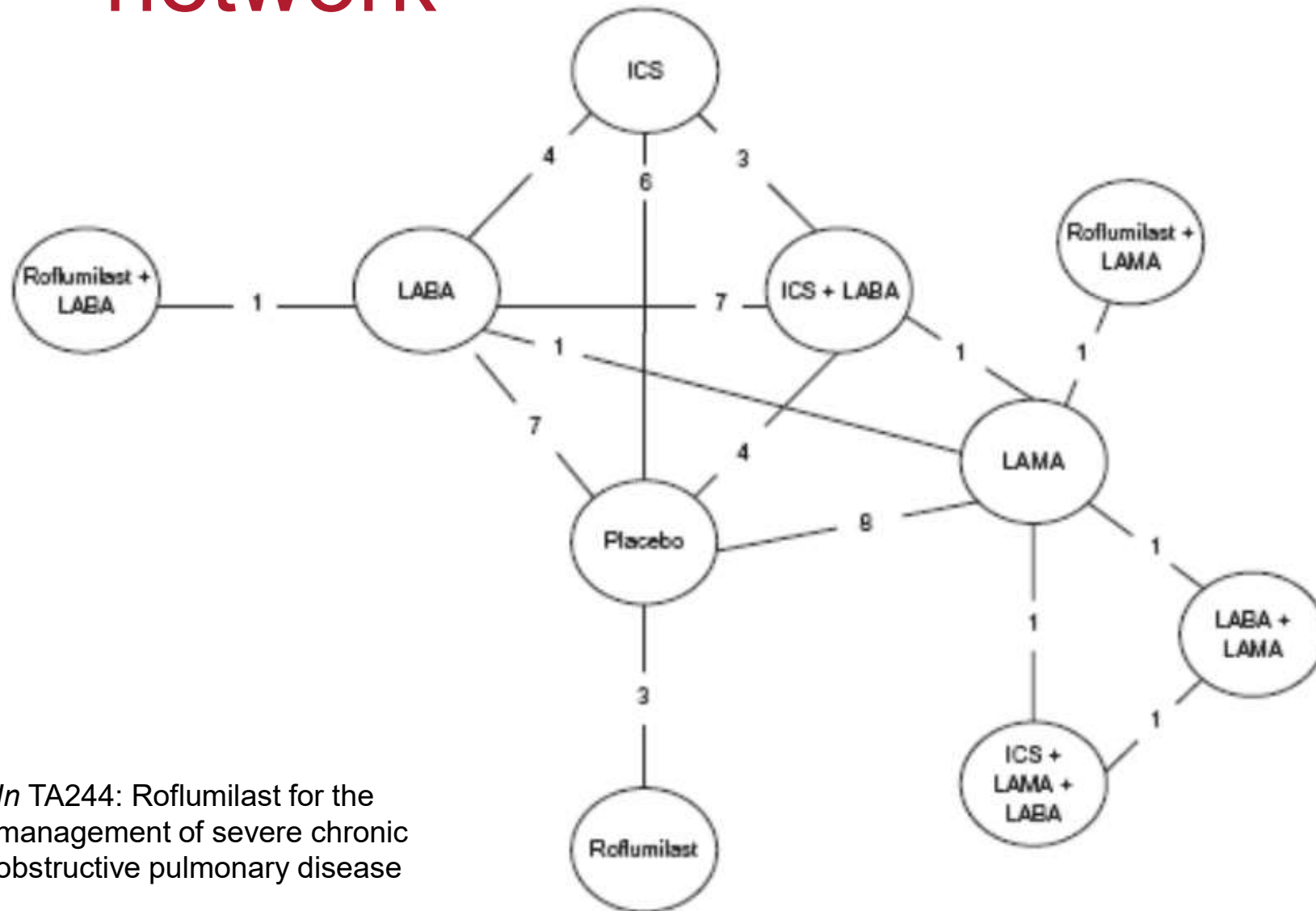
- Additive effect models can also be used for combination therapies and add-on treatments
 - Assuming no interactions
- E.g. in COPD (Kew et al 2014)
 - Long-acting beta-agonists (LABA)
 - Long-acting muscarinic antagonists (LAMA)
 - Inhaled corticosteroids (ICS)
 - Combined LABA+ICS



COPD: SGRQ 6 months: Additive effects?



🌿 Roflumilast: Treatment network



In TA244: Roflumilast for the management of severe chronic obstructive pulmonary disease



Summary

- Component NMA models have the potential to identify active ingredients of complex interventions
- Additive models
 - allow more precise estimates than standard NMA
 - estimates for combinations not included in RCTs can be obtained
 - ... but assume no interactions, which is difficult to verify in practise due to insufficient evidence
- Limited power to estimate additive effects (let alone interaction effects)
 - Need very rich evidence sources eg dismantling studies



References

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