Interactive workshop: How to elaborate high quality research work

Principles of Network Meta-Analysis

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Learning objectives

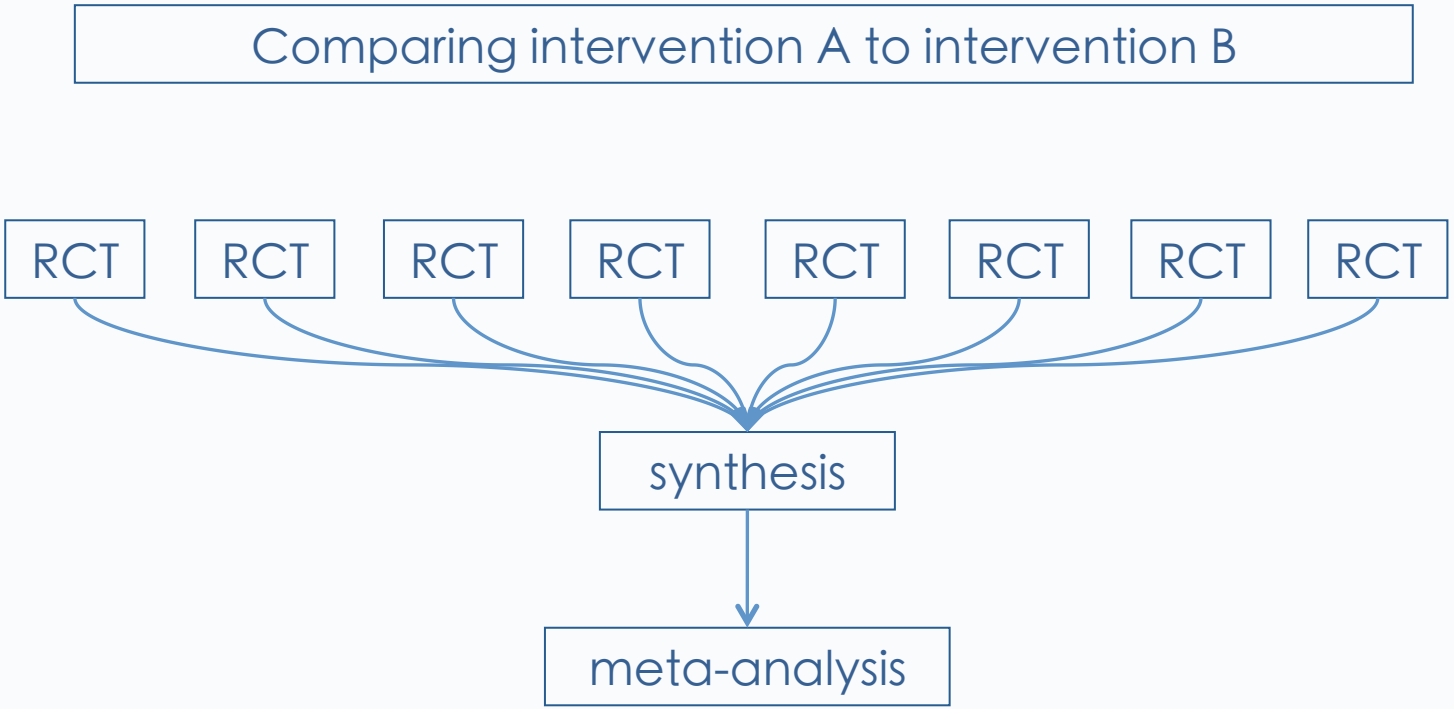
By the end of this lecture you will be able to:

- Understand in depth the concept of network meta-analysis (NMA)
- Evaluate its assumptions
- Present its main findings
- Interpret its basic results

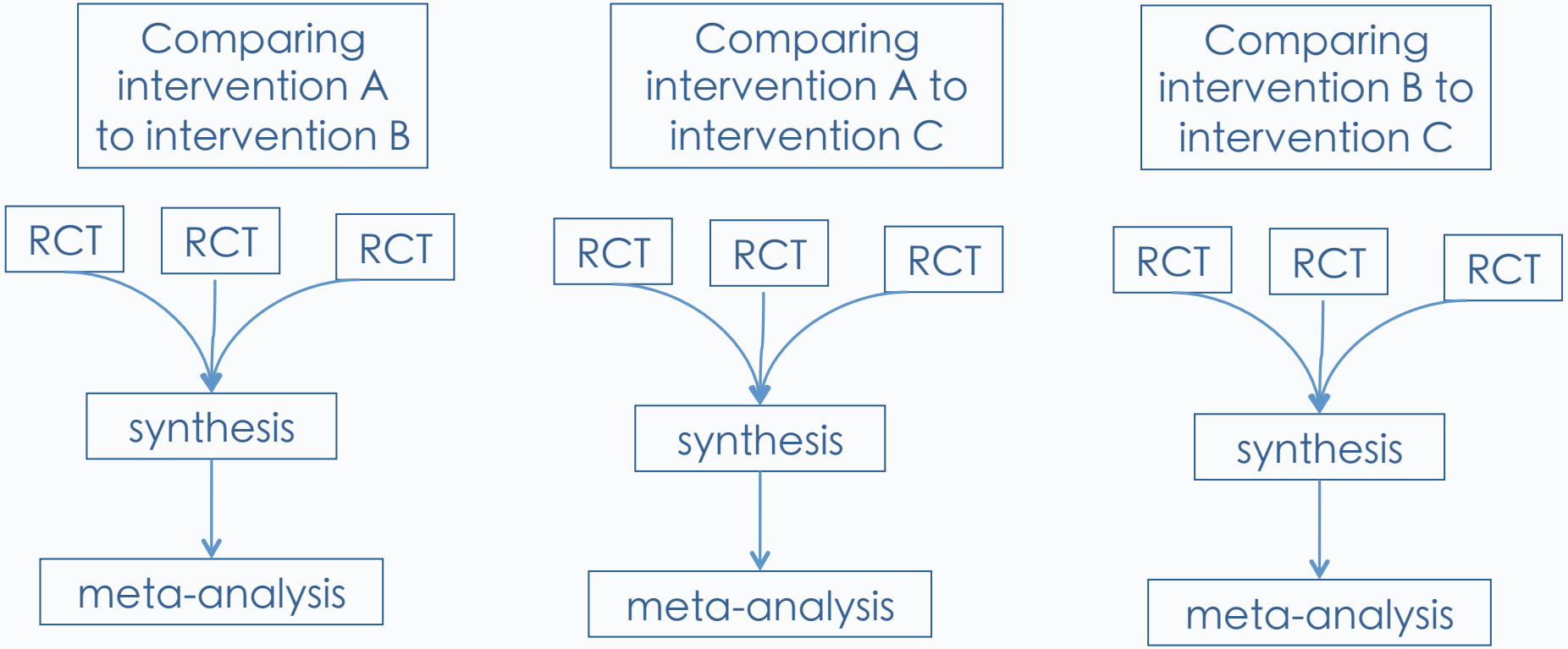
Lecture outline

- Definition of network meta-analysis
- Network geometry
- Transitivity
- Consistency
- Contribution plot
- Estimating the model
- Ranking interventions

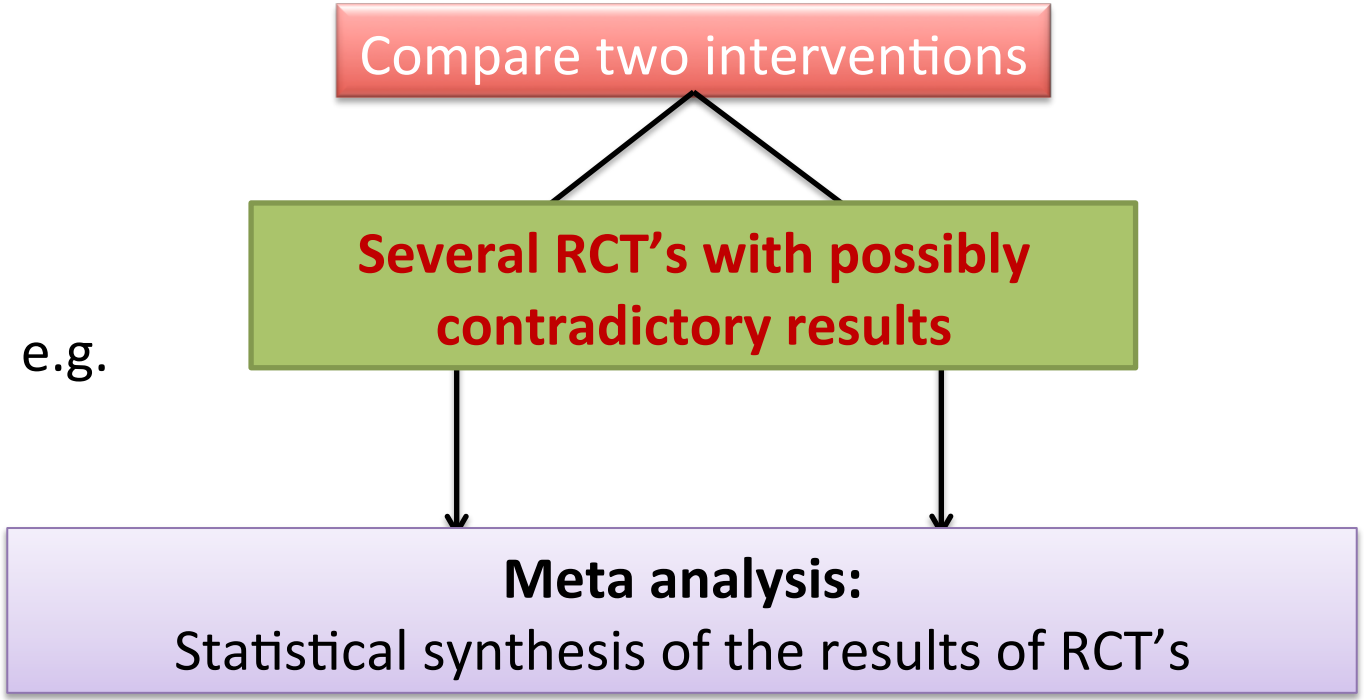
The concept


Comparing intervention A to intervention B
RCT
RCT
RCT
RCT
RCT
RCT
RCT
RCT
synthesis
meta-analysis

The concept


Comparing intervention A to intervention B
RCT
RCT
RCT
synthesis
meta-analysis
Comparing intervention A to intervention C
RCT
RCT
RCT
synthesis
meta-analysis
Comparing intervention B to intervention C
RCT
RCT
RCT
synthesis
meta-analysis

The concept

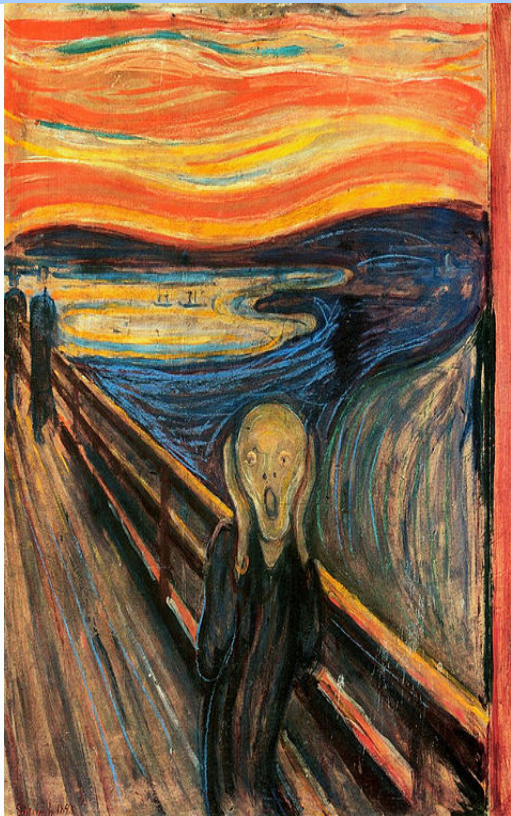

Compare two interventions
Several RCT's with possibly contradictory results
e.g.
Meta analysis:
Statistical synthesis of the results of RCT's

Anxiety Disorder

Ipser JC, SteinDJ,Hawkridge S,Hoppe L. **Pharmacotherapy** for anxiety disorders in children and adolescents. Cochrane Database of Systematic Reviews 2009, Issue 3. [DOI:10.1002/14651858.CD005170.pub2]

James AC, James G, Cowdrey FA, Soler A, Choke A. **Cognitive behavioural therapy** for anxiety disorders in children and adolescents. Cochrane Database of Systematic Reviews 2013, Issue 6. Art. No.: CD004690. DOI: 10.1002/14651858.CD004690.pub3.

Larun L, Nordheim LV, Ekeland E, Hagen KB, Heian F. **Exercise** in prevention and treatment of anxiety and depression among children and young people. Cochrane Database of Systematic Reviews 2006, Issue 3. Art. No.: CD004691. DOI: 10.1002/14651858.CD004691.pub2.



12 new generation antidepressants

sertraline

milnacipran

reboxetine

paroxetine

mirtazapine

?

duloxetine

fluvoxamine

escitalopram

citalopram

bupropion

venlafaxine

fluoxetine

Several meta-analyses have been conducted

"Although Mirtazapine is likely to have a faster onset of action than Sertraline and Paroxetine no significant differences were observed..."

"...meta-analysis highlighted a trend in favour of Sertraline over other Fluoxetine"

"...statistically significant differences in terms of efficacy .... between Fluoxetine and Venlafaxine, but the clinical meaning of these differences is uncertain..."

"Venlafaxine tends to have a favorable trend in response rates compared with duloxetine"

12 new generation antidepressants

paroxetine —— reboxetine

duloxetine —— mirtazapine

escitalopram —— fluvoxamine

milnacipran —— citalopram

sertraline —— venlafaxine

bupropion —— fluoxetine

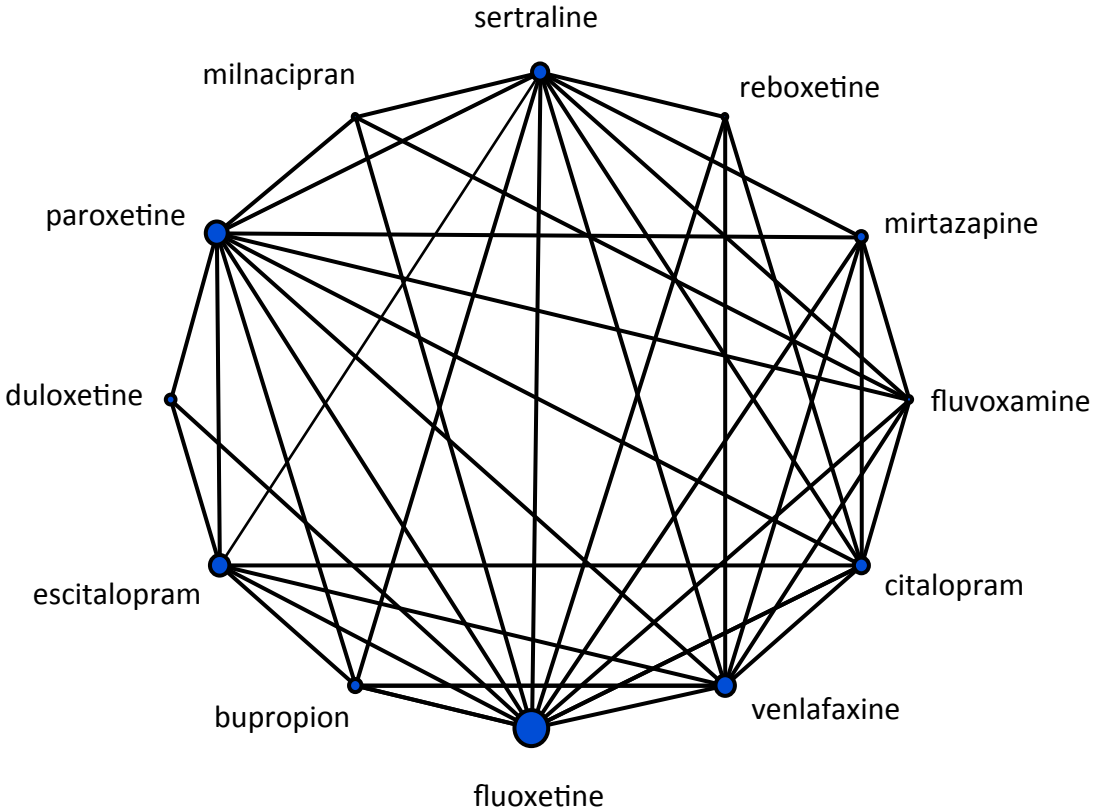
milnacipran —— paroxetine

sertraline ? duloxetine

bupropion —— escitalopram

fluvoxamine —— milnacipran

12 new generation antidepressants

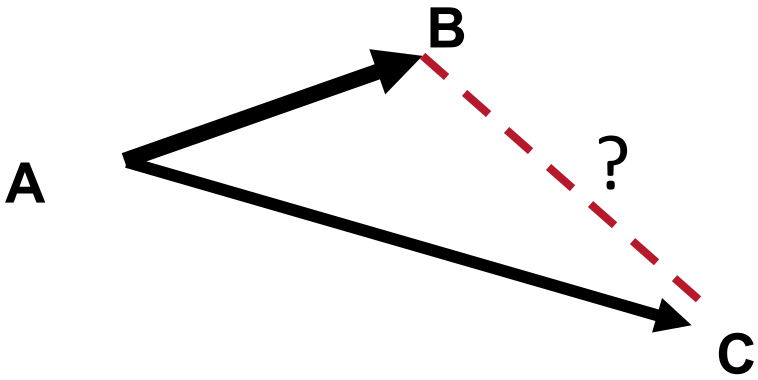


Indirect comparison

- **If we know how much taller is Averail to Joe and how much taller is Jack to Joe, we know how much taller is Averail to William**

Indirect comparison

- We can obtain an indirect estimate for B vs C from RCTs comparing A vs C and A vs B:



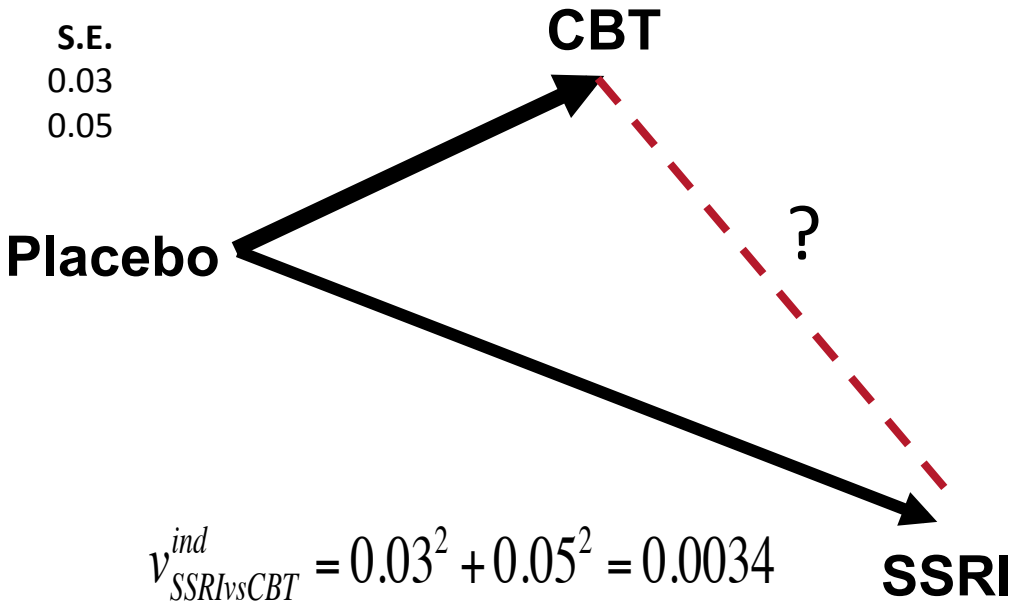
$$\mu_{BC}^{ind} = \mu_{AC}^{dir} - \mu_{AB}^{dir}$$

$$\mathrm{var}\left(\mu_{BC}^{ind}\right) = \mathrm{var}\left(\mu_{AC}^{dir}\right) + \mathrm{var}\left(\mu_{AB}^{dir}\right)$$

95% CI $\quad \mu_{BC}^{ind} \pm 1.96\sqrt{\mathrm{var}\left(\mu_{BC}^{ind}\right)}$

Indirect comparison

Comparison	SMD	CIs	S.E.
Placebo vs CBT	-0.34	(-0.41, -0.28)	0.03
Placebo vs SSRI	-0.19	(-0.30, -0.10)	0.05



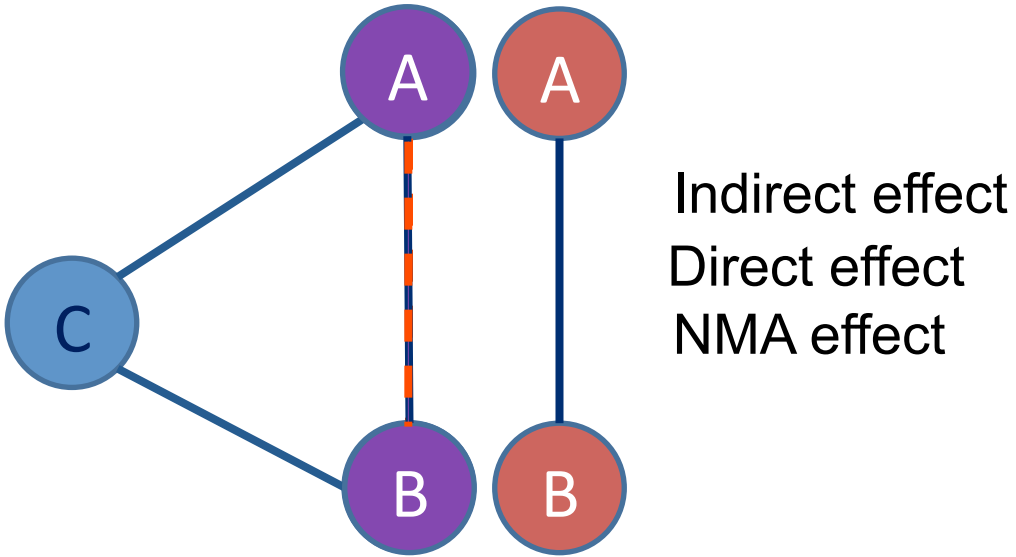
How to compare SSRI to CBT ?
Estimate indirect SMD and a 95% CI

$$\mu^{ind}_{SSRIvsCBT} = -0.34 - (-0.19) = -0.15$$

$$v^{ind}_{SSRIvsCBT} = 0.03^2 + 0.05^2 = 0.0034$$

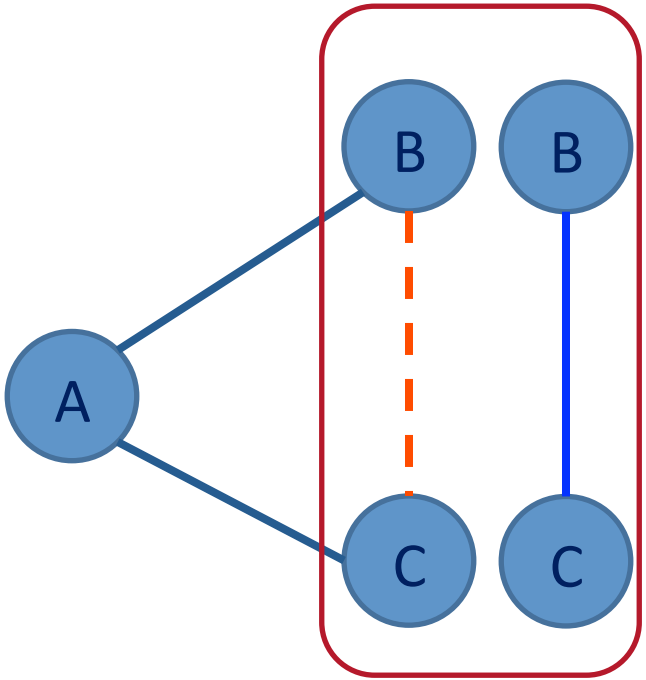
$$\mu^{ind}_{SSRIvsCBT} \pm 1.96\sqrt{v^{ind}_{SSRIvsCBT}} = -0.15 \pm 1.96\sqrt{0.0034} = (-0.26, -0.04)$$

Indirect comparison

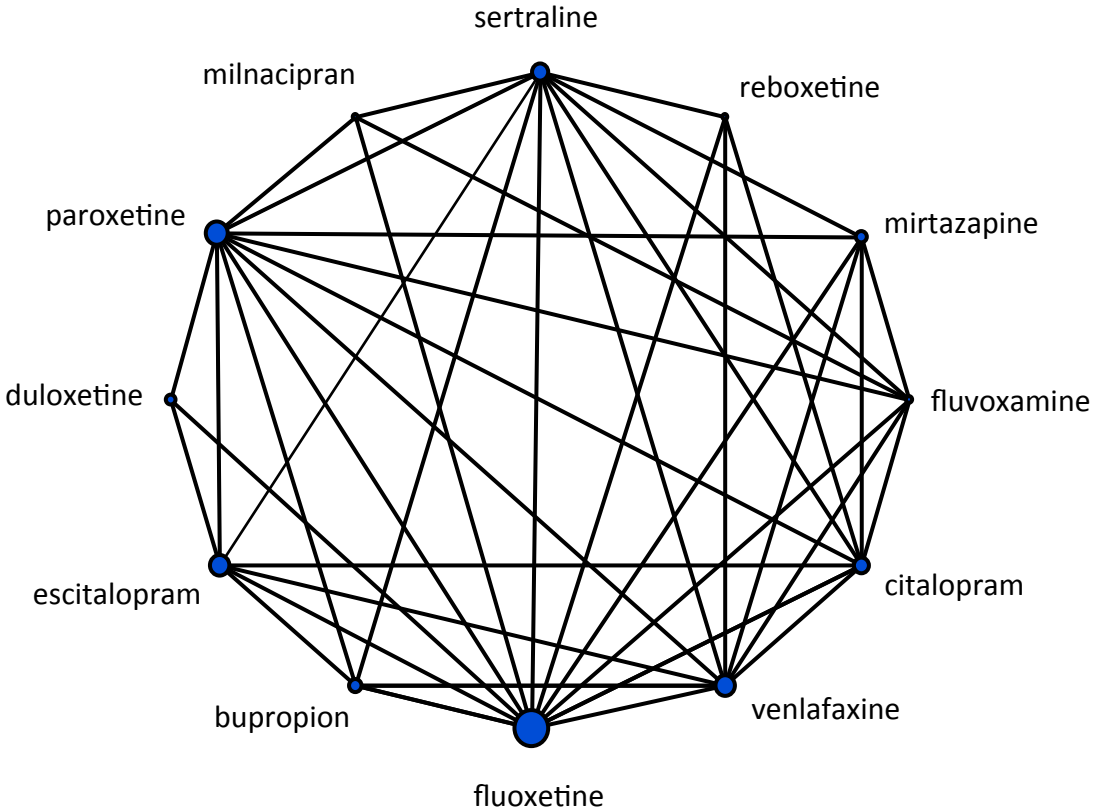


Indirect comparison

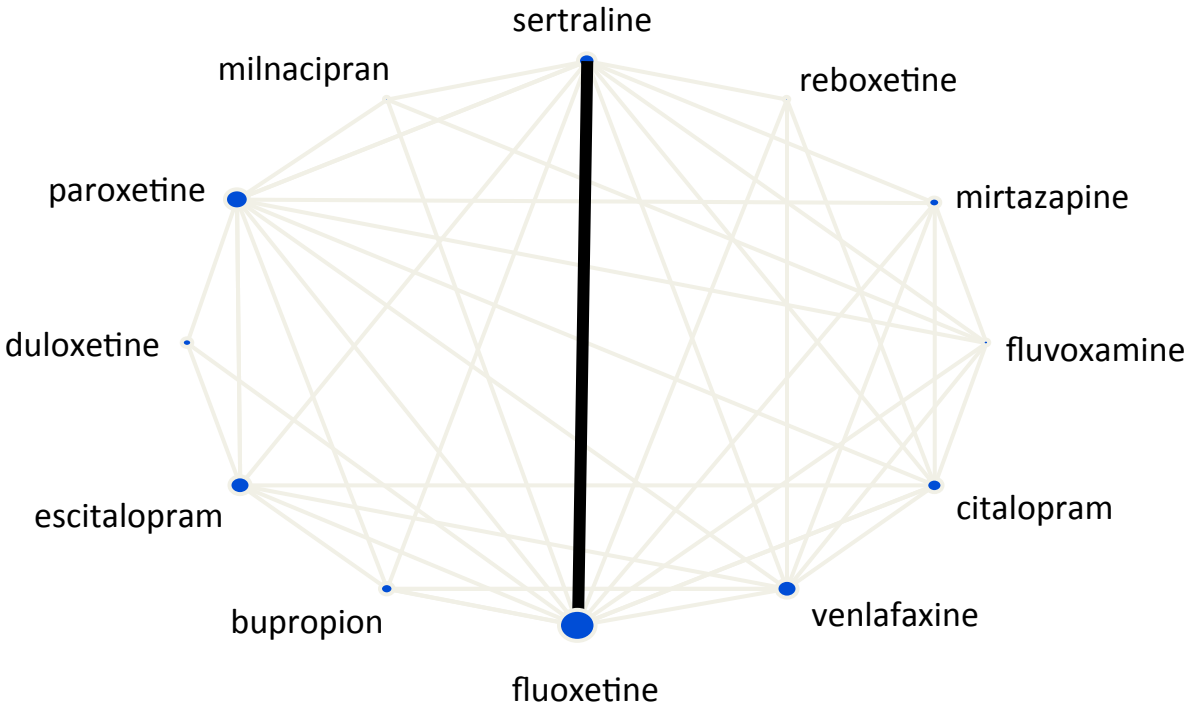
Direct and indirect evidence are in agreement



12 new generation antidepressants



12 new generation antidepressants



Lancet 2009 *Cipriani, Fukurawa, Salanti et al*

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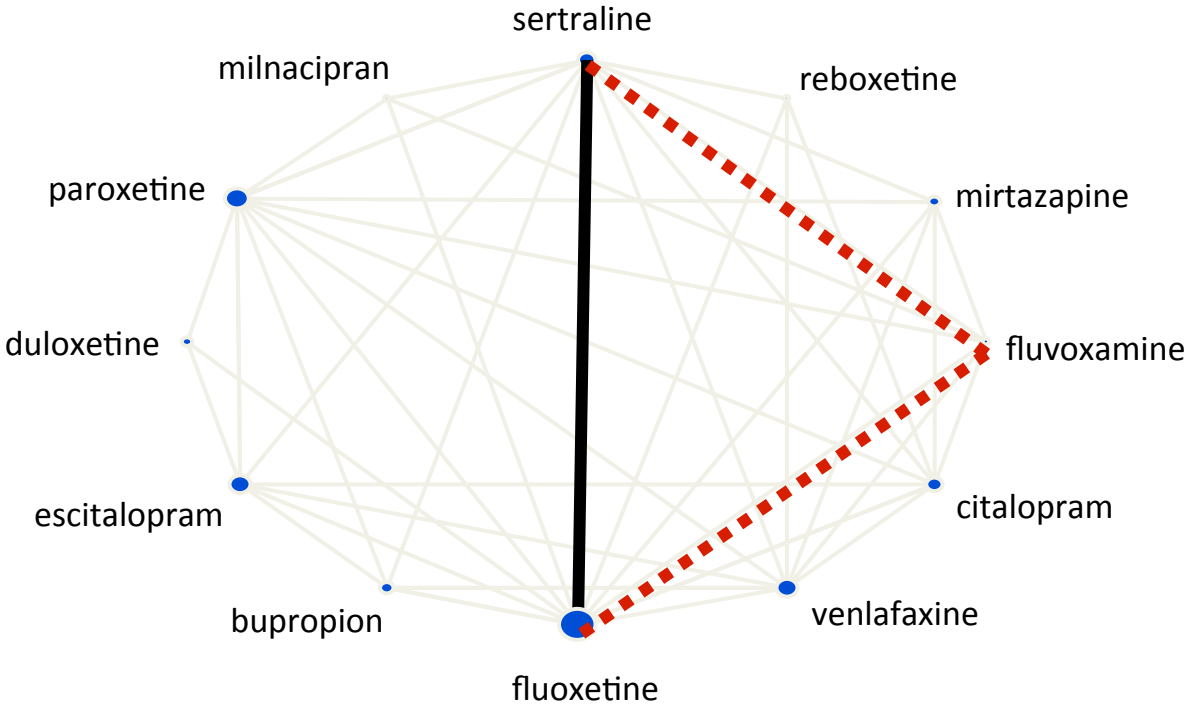

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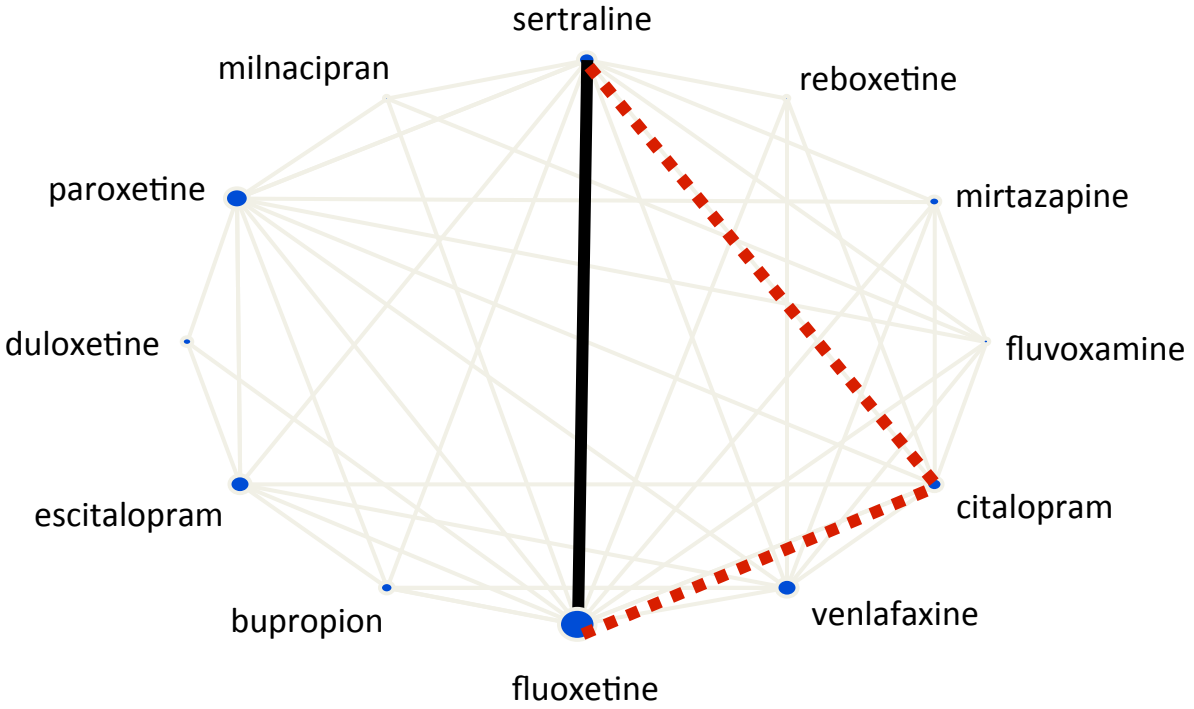

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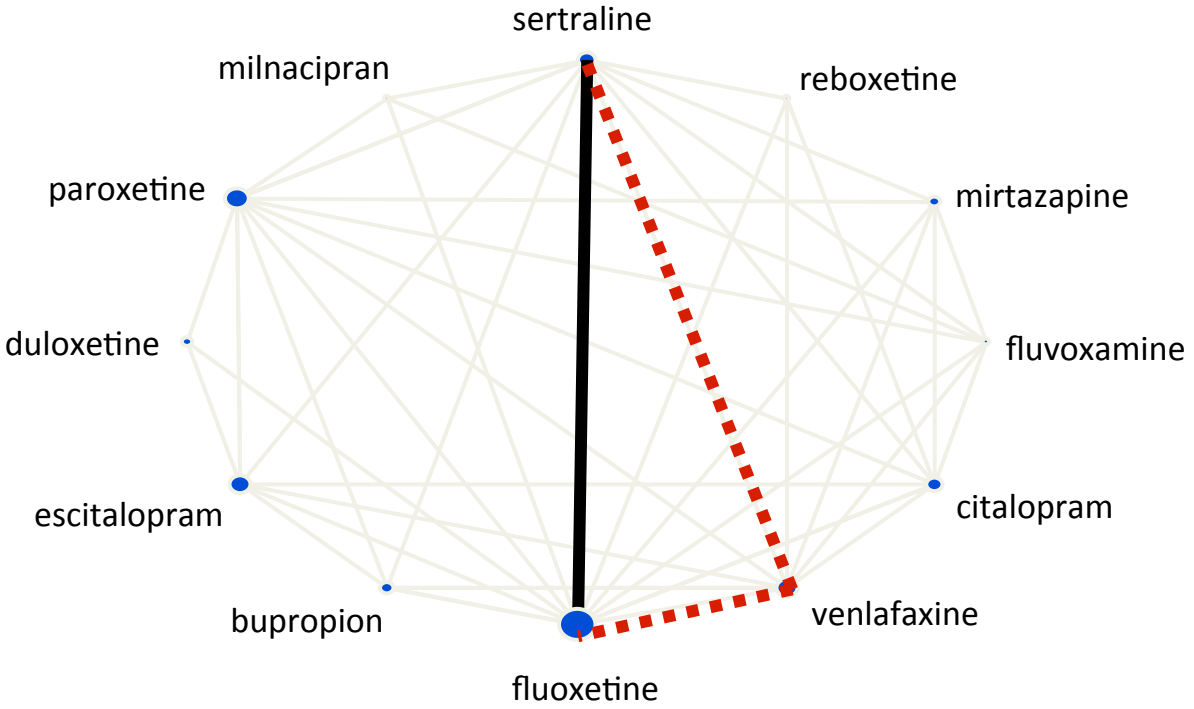

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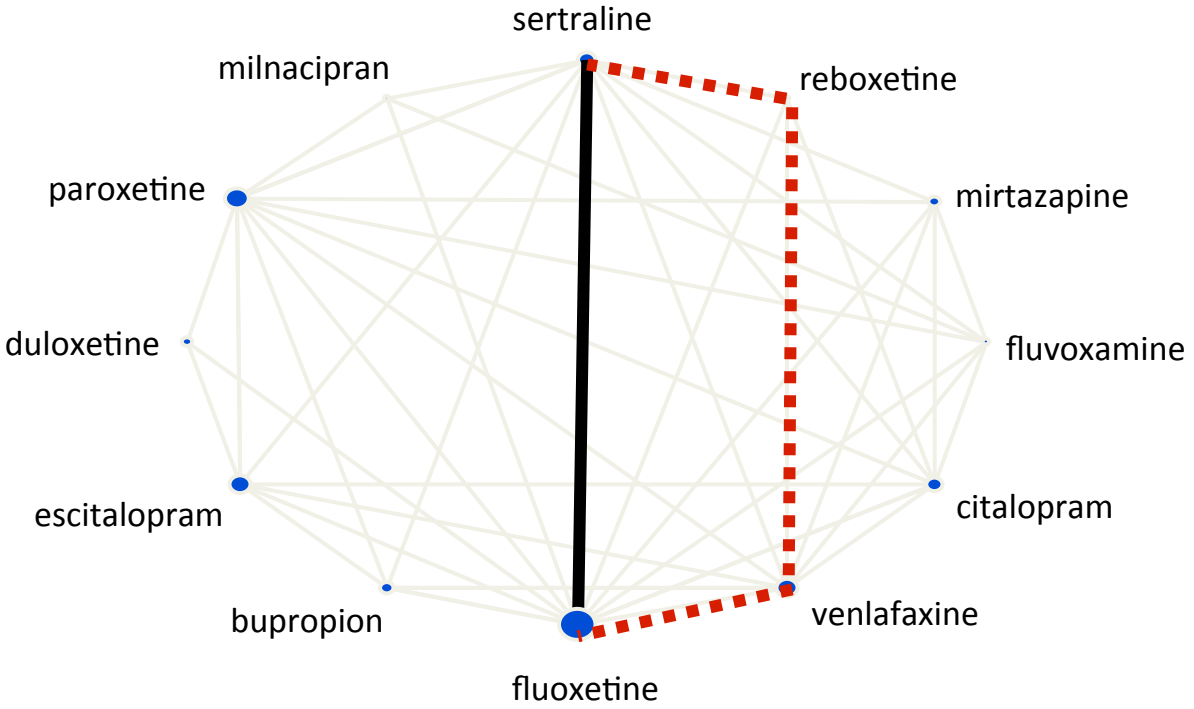

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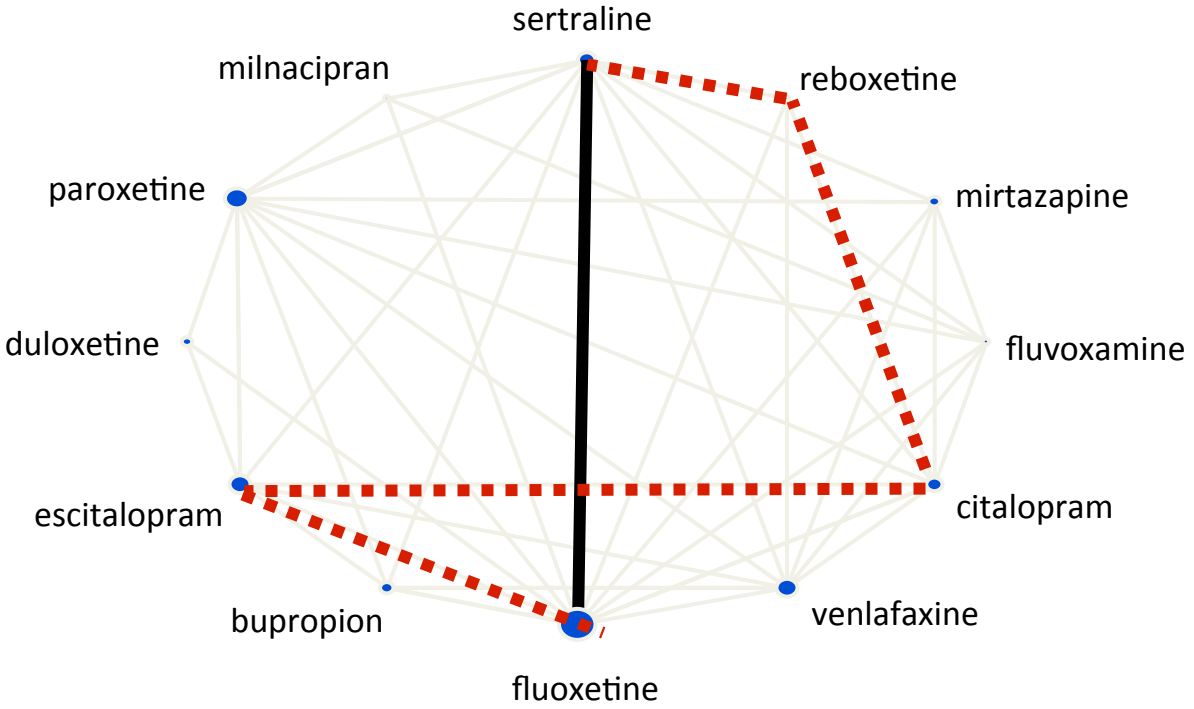

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Benefits of NMA

Network meta-analysis (NMA)

- synthesizes direct and indirect evidence in a network of trials that compare multiple interventions

Advantages

- enables drawing inference for treatment comparisons never appeared in individual studies
- usually gives estimates with increased precision compared to pairwise meta-analysis
- provides an estimate of the treatment relative ranking according to the studied outcome

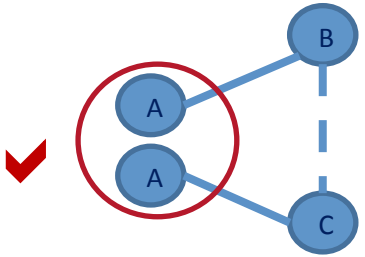
Limitations of NMA

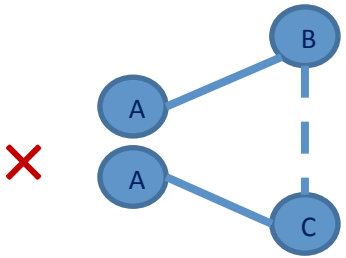
- Indirect comparisons provide observational results because the treatments being compared have not been randomized across trials
- Differences in patient characteristics at baseline or in effect modifiers across treatment comparisons
- Indirect comparisons are valid if the distribution of effect modifiers does not differ across trials (the intervention effects are transitive)

THE TRANSITIVITY ASSUMPTION

- Transitivity refers to the genuine ability to learn about a pairwise comparison via an intermediate treatment via an indirect root
- It requires the intermediate treatment to be equivalent when compared against each of the treatments of interest
- It requires that studies contributing to the indirect comparison do not differ in important ways

Transitivity requires

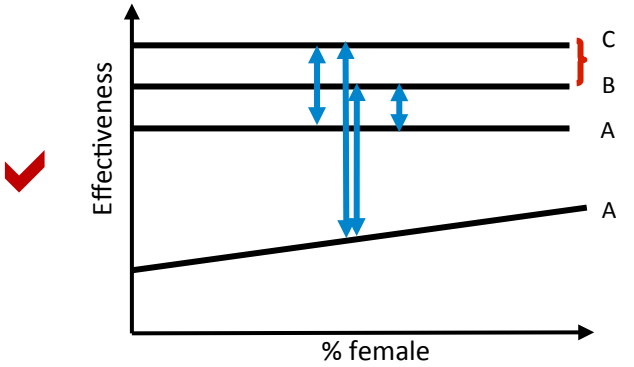




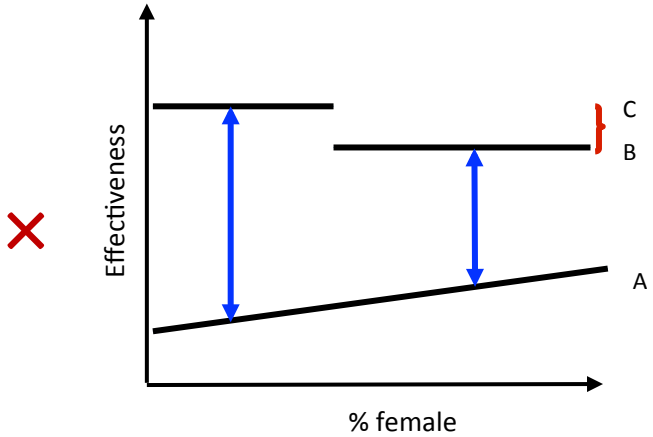
- the ‘anchor’ treatment A to be similarly defined when it appears in AB and AC trials. e.g. a treatment given at different doses but no systematic difference in the *average* dose of A across AB and AC comparison

- the ‘anchor’ treatment A may be different in AB and AC studies e.g. a pharmacological placebo may not be identical in terms of effectiveness to a non-pharmacological placebo

Transitivity means

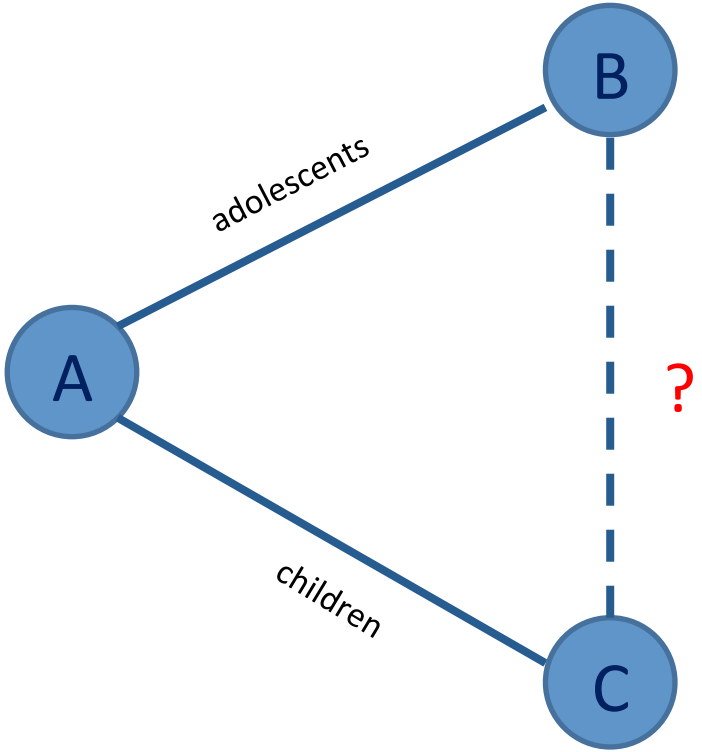


...that AC and AB trials do not differ with respect to the distribution of effect modifiers



Difficult to defend when you have older and newer treatments

Is indirect evidence valid?



Is age an effect modifier?

Is indirect evidence valid?

In an ABC network you may have invalid indirect comparisons if AB studies and AC studies differ considerably

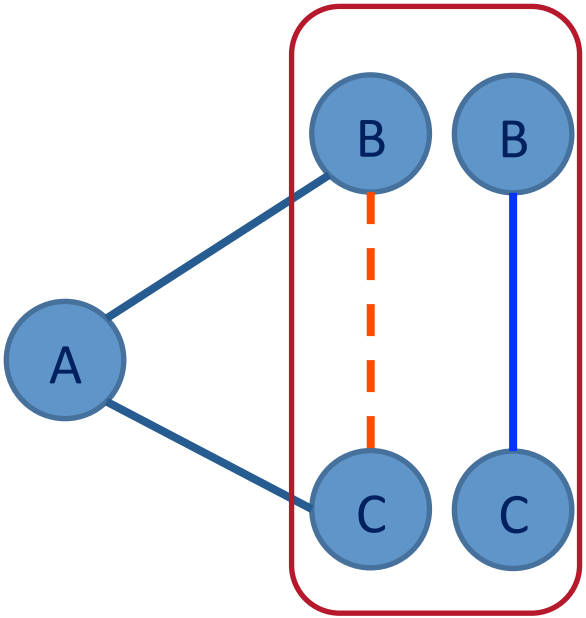
AB comparisons	AC comparisons
before 1990	after 1990
A is implemented in a conventional way	A is implemented in a non-conventional way
developed countries	developing countries
children	adolescents
low baseline risk	high baseline risk
short period of time	long period of time

Consistency

- Statistical manifestation of transitivity
- The consistency assumption states that direct and indirect evidence should be in agreement.
- Check the consistency assumption
  - Estimate the disagreement between direct and indirect evidence

Consistency

Direct and indirect evidence are in agreement

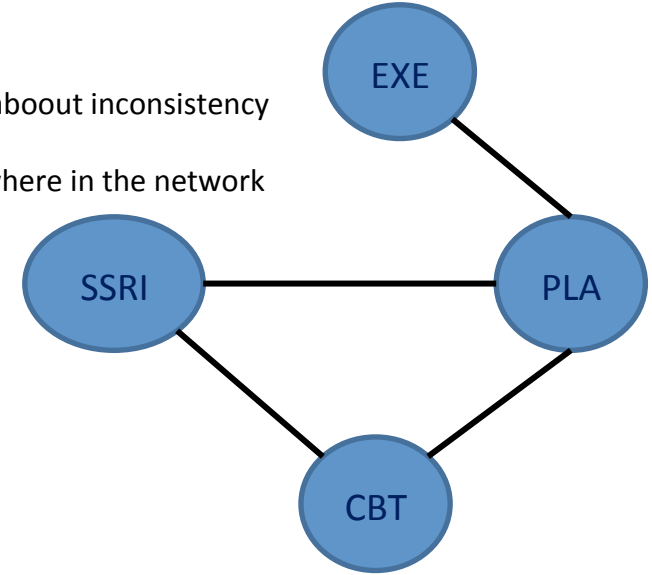


$$\mu^{ind} = \mu^{dir}$$

Network plot

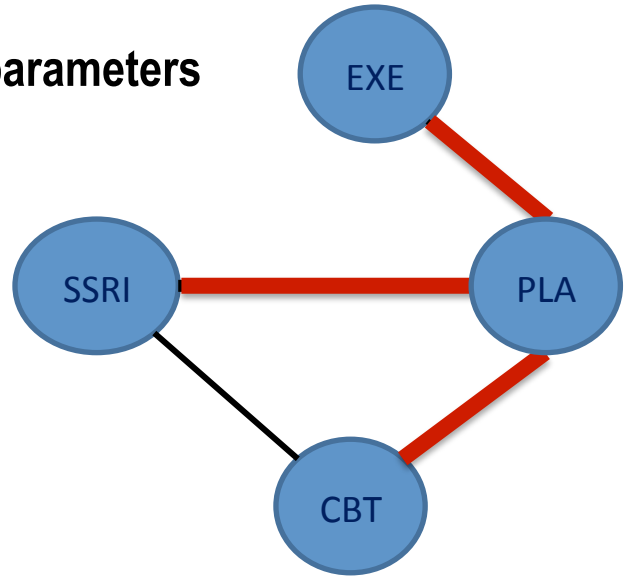
only closed loops can tell us aboout inconsistency

can assess transitivity everywhere in the network

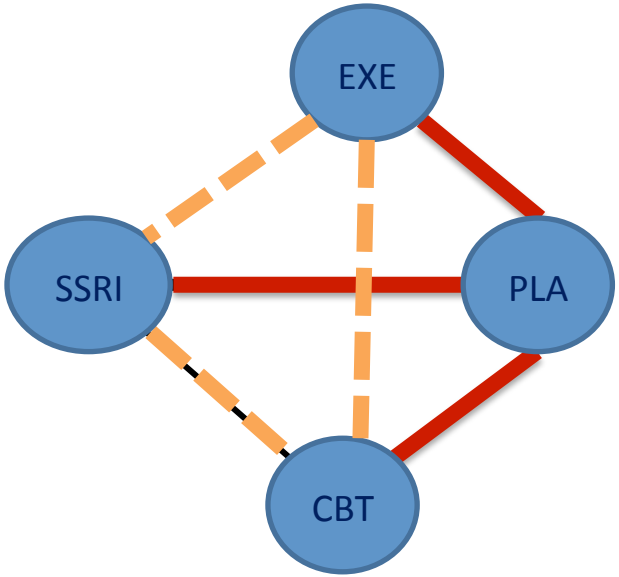


Estimating the model

- **choose a reference treatment**
- **choose basic parameters**



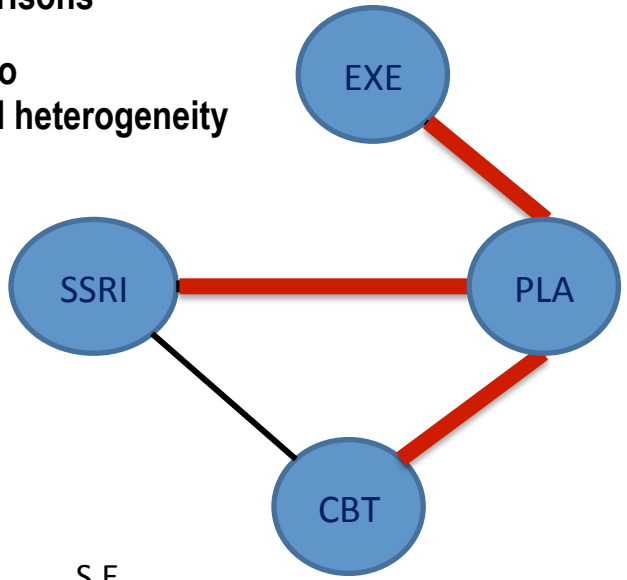
Estimating the model – functional parameters



Estimating the model – basic parameters

There are four direct comparisons

With T treatments we need to estimate T-1 parameters and heterogeneity



Comparison	SMD	CIs	S.E.
Placebo vs CBT	-0.34	(-0.41, -0.28)	0.03
Placebo vs SSRI	-0.19	(-0.30, -0.10)	0.05
Placebo vs exercise	-0.23	(-0.31, -0.15)	0.04

Inconsistency Factor

$$\left.\begin{array}{l} SMD^{ind}_{SSRIvsCBT} = -0.15 \\ SMD^{dir}_{SSRIvsCBT} = 0.04 \end{array}\right\} \quad IF = \left|SMD^{dir}_{SSRIvsCBT} - SMD^{ind}_{SSRIvsCBT}\right| = \left|0.04 - (-0.15)\right| = 0.19$$

$$\mathrm{var}\left(IF\right) = \mathrm{var}\left(SMD^{dir}_{SSRIvsCBT}\right) + \mathrm{var}\left(SMD^{ind}_{SSRIvsCBT}\right) = 0.004 + 0.011 = 0.015$$

You can do this with any measure... lnOR, lnRR, RD, mean difference, HR e.t.c

Inconsistency Factor

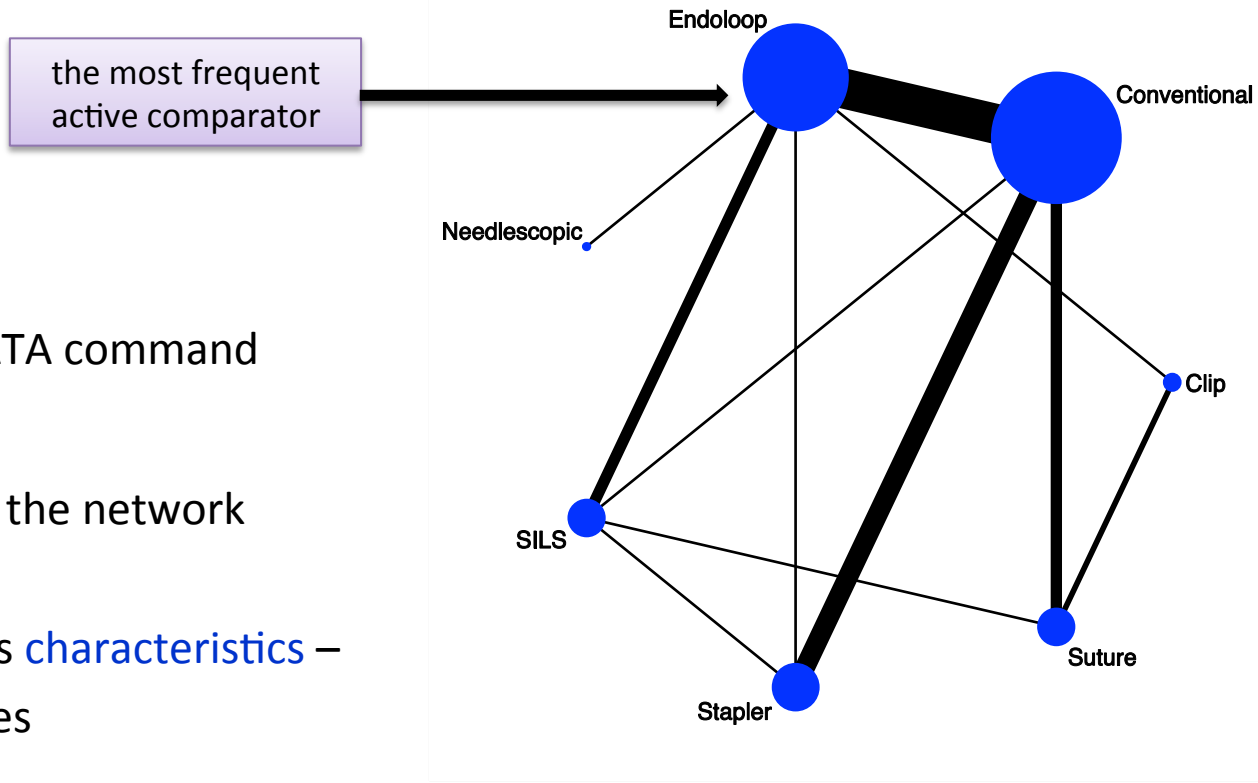
$$Z = \frac{IF}{\sqrt{\mathrm{var}(IF)}}$$

$$IF \pm 1.96\sqrt{\mathrm{var}(IF)}$$

$$0.19 \pm 1.96\sqrt{0.015}$$

$$(-0.05, 0.43)$$

Optimal stump management for laparoscopic appendectomy



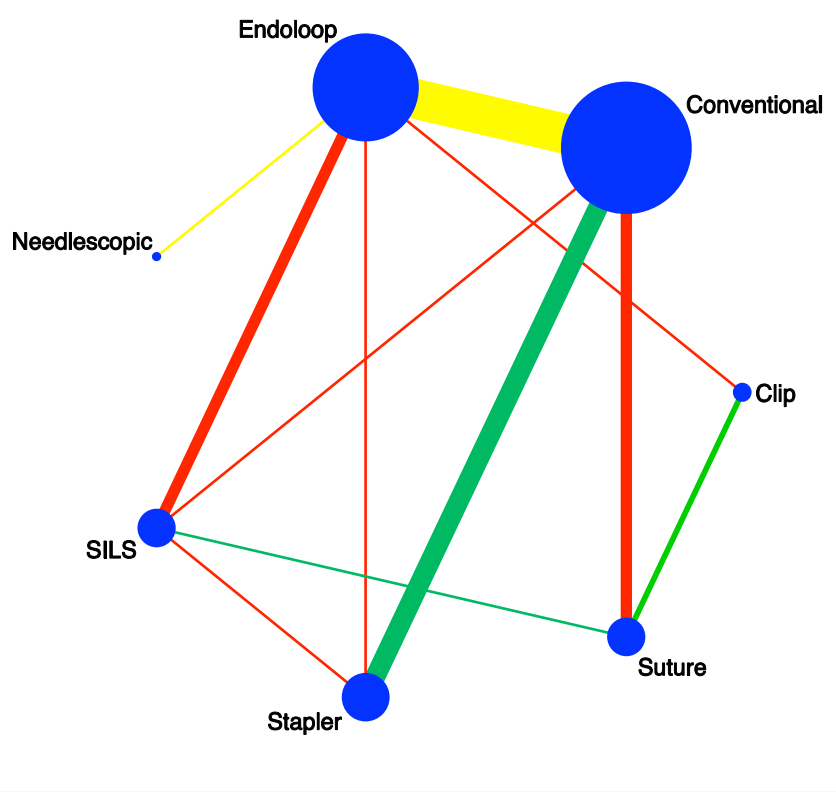
Network plot/diagram (STATA command `networkplot`)

- visual representation of the network structure
- concise description of its characteristics – use of weighting schemes

Optimal stump management for laparoscopic appendectomy

Network plot/diagram (STATA command `networkplot`)

- risk of bias → important study-level characteristic
- some comparisons may include trials with design limitations – use of coloring schemes



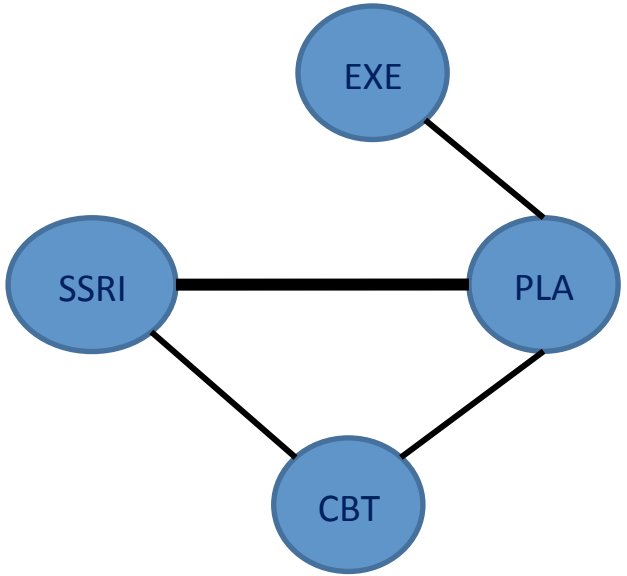
Blinding

Study-specific bias level=low(green),unclear(yellow),high(red)

Comparison-specific bias level=inverse variance weighted average

Contributions from and to comparisons

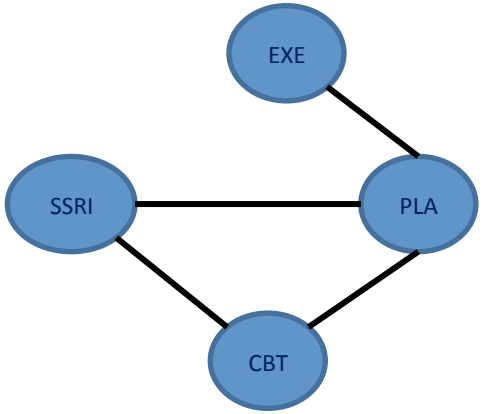
- How much each direct comparison contributes to the entire network
- How much each direct comparison contributes to each network summary estimate
- How much is the contribution of indirect evidence



Contributions from and to comparisons

Contribution plot/diagram (STATA command `netweight`)

- Identify the most influential comparisons in the network

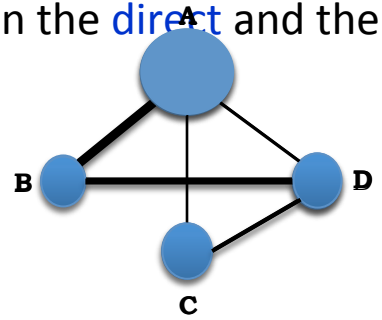


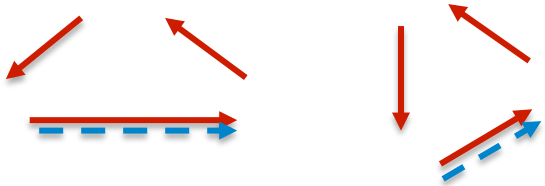
		Direct comparisons in the network			
		PLA vsEXE	PLA vsCBT	PLA vsSSRI	CBTvsSSRI
Network meta-analysis estimates	Mixed estimates				
	PLA vs EXE	100.0			
	PLA vs CBT		68.0	16.0	16.0
	PLA vsSSRI		29.5	41.0	29.5
	CBTvsSSRI		28.1	28.1	43.7
	Indirect estimates				
	EXE vs CBT	45.7	37.0	8.7	8.7
	EXE vsPTCA	41.4	17.3	24.1	17.3
Entire network		31.2	29.6	20.2	19.0
Included studies		30	33	23	14

Measuring inconsistency

Inconsistency plot (STATA command `ifplot`)

- loop-specific approach → look at each closed loop in the network separately
- estimate the absolute difference between the direct and the indirect estimate for one comparison

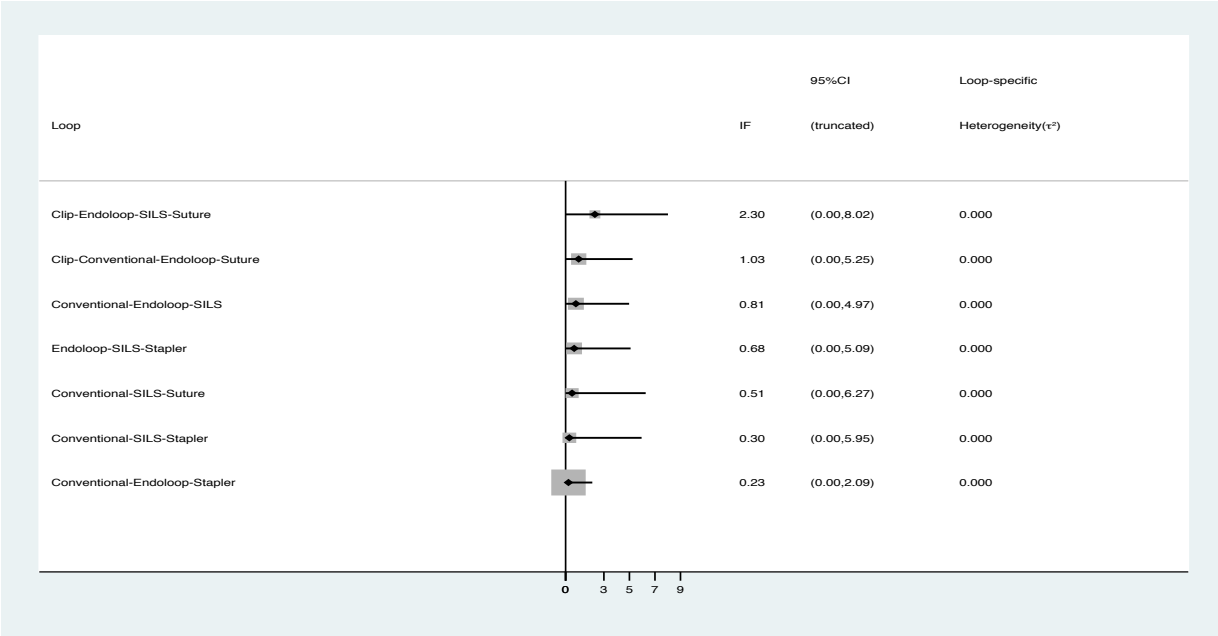




Inconsistency plot

Inconsistency plot (STATA command `ifplot`)

- loop-specific approach → look at each closed loop in the network separately



Ranking interventions

Ranking probabilities (STATA command sucra)

- ranking probability→ the probability for a treatment of being at a particular rank

$$p\downarrow rt = \#\ simulations\ (t{=}r)/total\ \#\ simulations$$

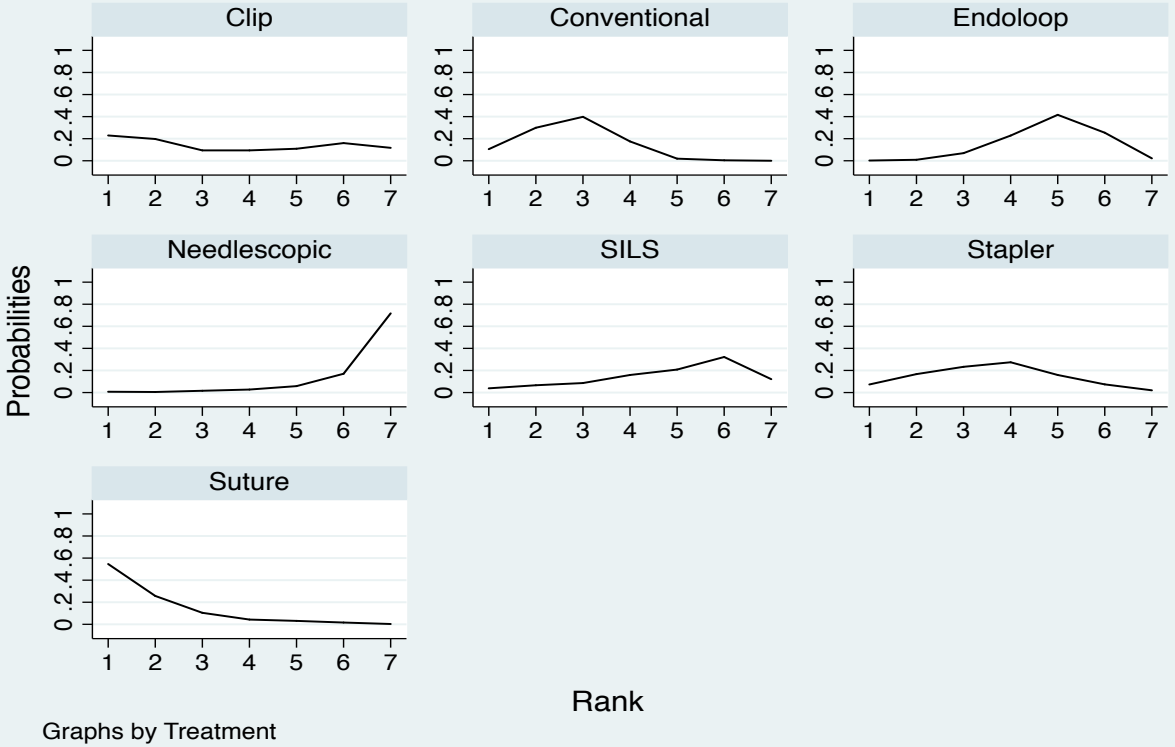
conclusions based on the probability of being best often are misleading

- inference on relative ranking should account for the uncertainty in ranking
- show the entire distribution of the ranking probabilities

Ranking interventions

Ranking probabilities (STATA command `sucra`)

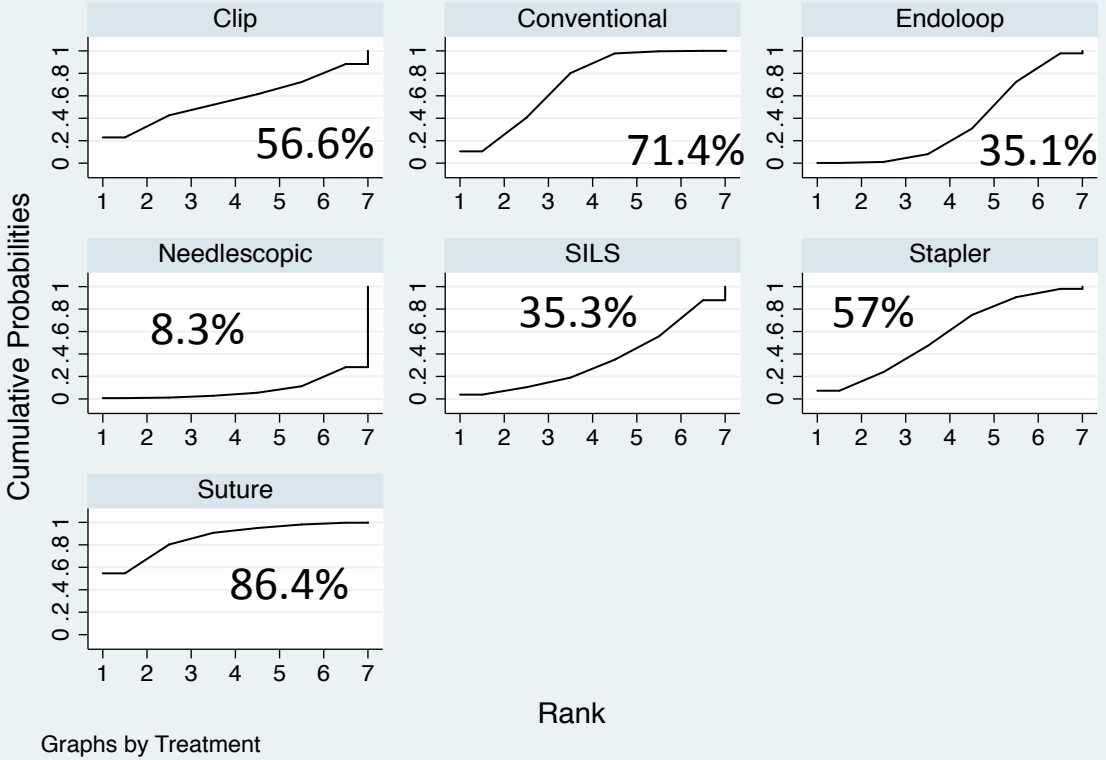
- draw the rankograms for all competing treatments in the network



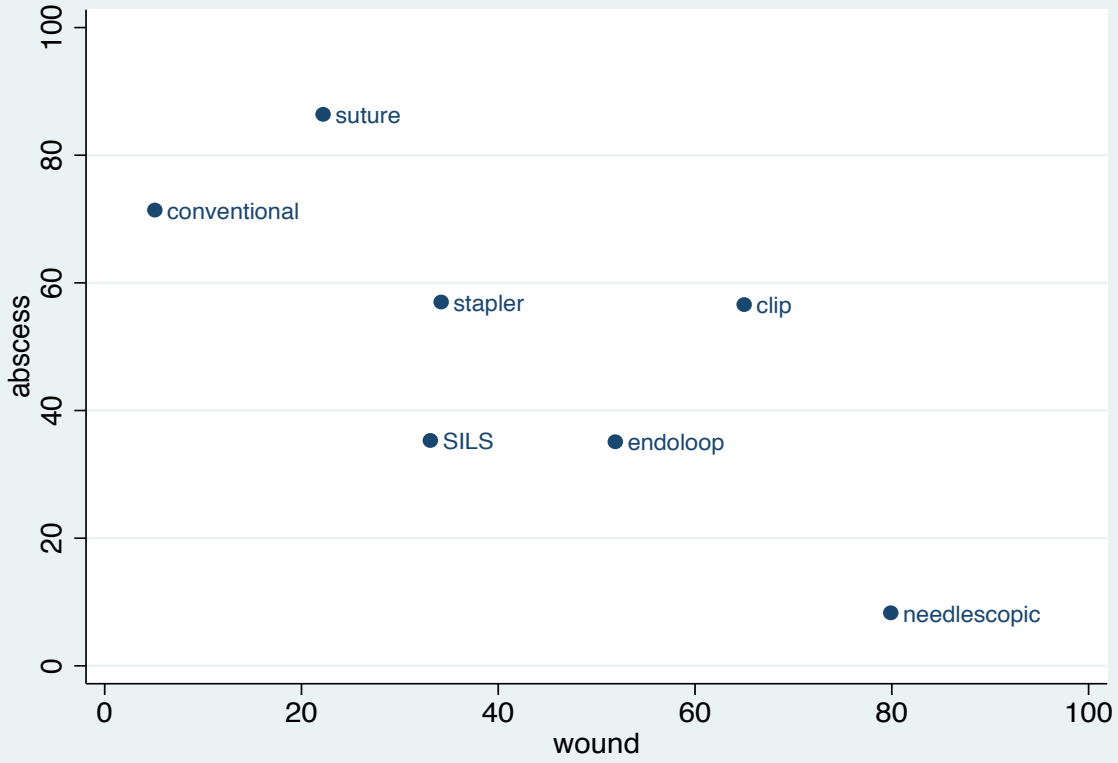
Ranking interventions

Ranking probabilities (STATA command `sucra`)

- cumulative ranking probability → the probability for a treatment of being within the first r places
- Sucra values represent the percentage an intervention achieves with reference to an imaginary interventions which is always the best without uncertainty



Ranking interventions



League Table abscess

- Odds ratio and 95% CI for the relative effects of all pairs of interventions

Suture	1.65 (0.48,5.64)	2.06 (0.49,8.59)	1.94 (0.28,13.36)	3.15 (0.61,16.10)	2.97 (0.80,11.08)	7.73 (1.13,52.96)
0.61 (0.18,2.08)	Conventional	1.25 (0.59,2.63)	1.18 (0.15,9.28)	1.91 (0.59,6.17)	1.80 (1.04,3.14)	4.69 (1.03,21.25)
0.49 (0.12,2.03)	0.80 (0.38,1.69)	Stapler	0.95 (0.11,8.35)	1.53 (0.41,5.70)	1.45 (0.62,3.39)	3.76 (0.73,19.44)
0.51 (0.07,3.53)	0.85 (0.11,6.67)	1.06 (0.12,9.35)	Clip	1.62 (0.16,16.20)	1.53 (0.19,12.16)	3.97 (0.32,48.64)
0.32 (0.06,1.63)	0.52 (0.16,1.70)	0.65 (0.18,2.44)	0.62 (0.06,6.19)	SILS	0.95 (0.32,2.78)	2.46 (0.42,14.44)
0.34 (0.09,1.25)	0.55 (0.32,0.97)	0.69 (0.29,1.62)	0.65 (0.08,5.20)	1.06 (0.36,3.11)	Endoloop	2.60 (0.64,10.59)
0.13 (0.02,0.89)	0.21 (0.05,0.97)	0.27 (0.05,1.38)	0.25 (0.02,3.08)	0.41 (0.07,2.39)	0.38 (0.09,1.57)	Needlescopic

League Table wound

Suture	4.90 (1.81,13.23)	2.96 (0.94,9.37)	1.35 (0.26,7.15)	2.97 (0.82,10.73)	2.22 (0.79,6.24)	0.48 (0.02,11.85)
0.20 (0.08,0.55)	Conventional	0.60 (0.34,1.09)	0.28 (0.05,1.53)	0.61 (0.25,1.45)	0.45 (0.32,0.64)	0.10 (0.00,2.08)
0.34 (0.11,1.07)	1.65 (0.92,2.97)	Stapler	0.46 (0.07,2.79)	1.00 (0.36,2.82)	0.75 (0.38,1.46)	0.16 (0.01,3.63)
0.74 (0.14,3.91)	3.62 (0.65,20.08)	2.19 (0.36,13.36)	Clip	2.19 (0.33,14.47)	1.64 (0.30,9.08)	0.35 (0.01,11.57)
0.34 (0.09,1.22)	1.65 (0.69,3.95)	1.00 (0.36,2.81)	0.46 (0.07,3.01)	SILS	0.75 (0.33,1.71)	0.16 (0.01,3.76)
0.45 (0.16,1.27)	2.21 (1.57,3.11)	1.34 (0.68,2.62)	0.61 (0.11,3.38)	1.34 (0.58,3.06)	Endoloop	0.21 (0.01,4.51)
2.10 (0.08,52.27)	10.29 (0.48,219.91)	6.22 (0.28,140.36)	2.84 (0.09,93.32)	6.23 (0.27,145.97)	4.65 (0.22,97.61)	Needlescopic

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Thank you