Network meta-analysis

The next frontier for data

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Disclaimer

- This talk will be largely about concepts rather than statistics

Session objectives

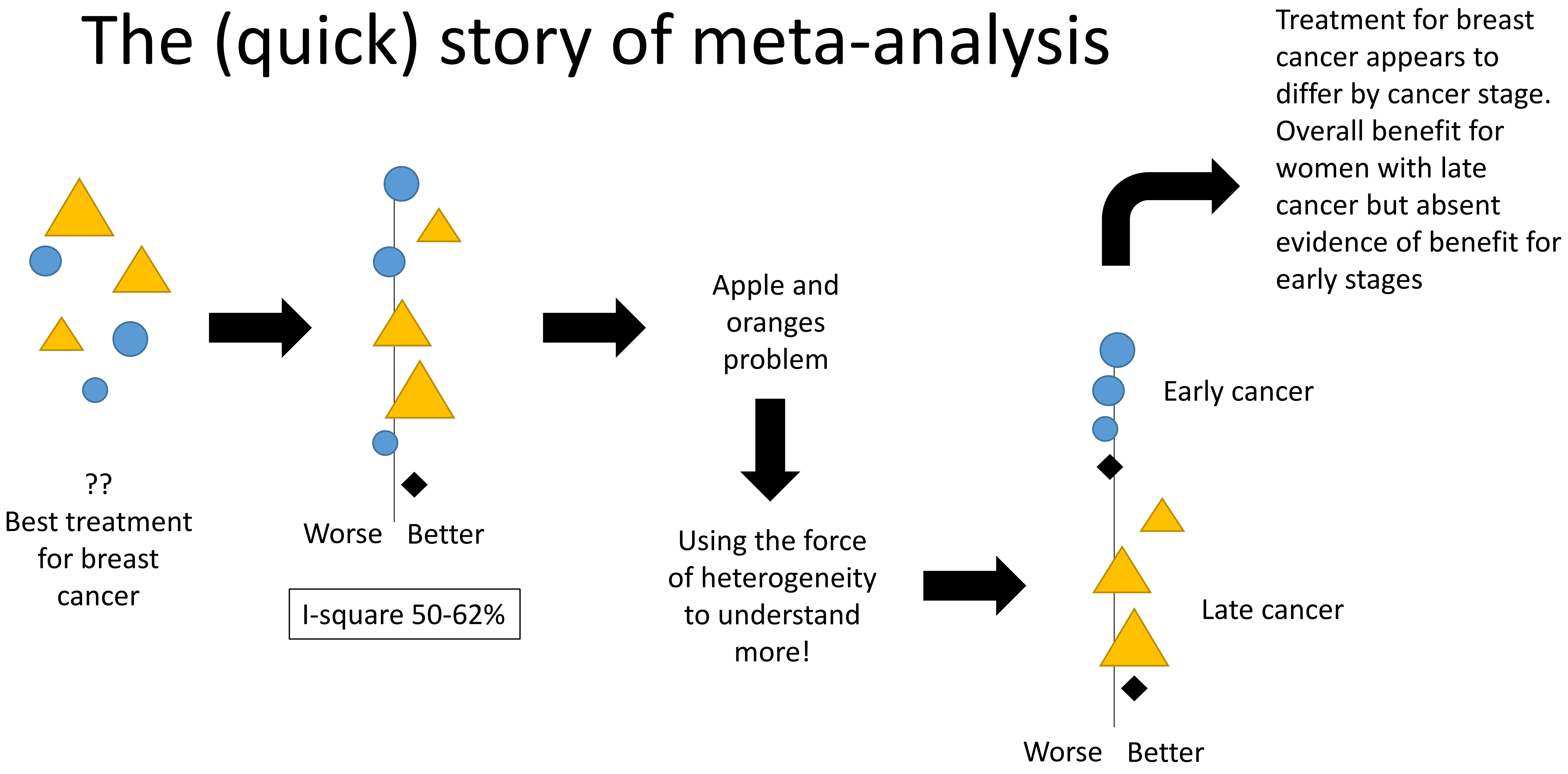
- By the end of this session, I hope you will have an understanding of
  - The role of network meta-analysis in the evaluation of data
  - The key principles of the statistical methods involved
  - The key problems that can distort network meta-analyses
  - Enthusiasm for how network meta-analysis might be applicable to your field!!

Two big problems with modern medicine

- Contradictory studies on almost every topic

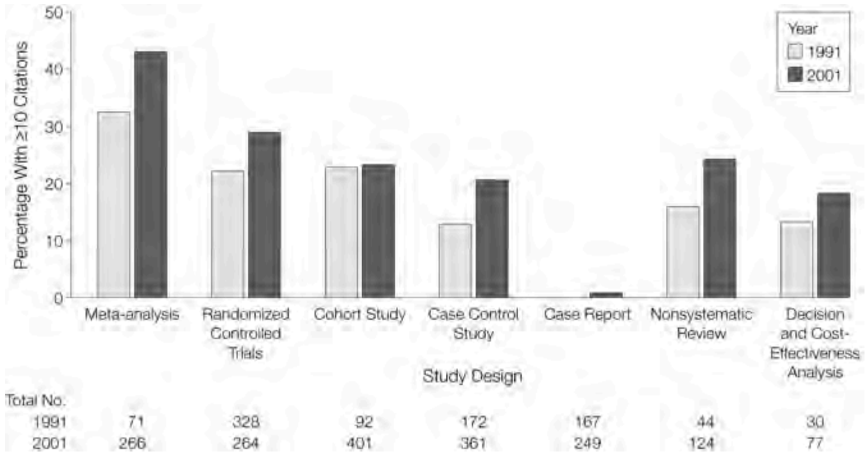
- Bewildering flood of new data

The (quick) story of meta-analysis



Huge advantages of meta-analysis

- Understand how different treatments work in different settings
- Find when treatments are harmful
- Compost huge volumes of data into something useable
- Understand the quality of the evidence
- Policy-making bodies love them
- <u>Highly cited and influential</u>



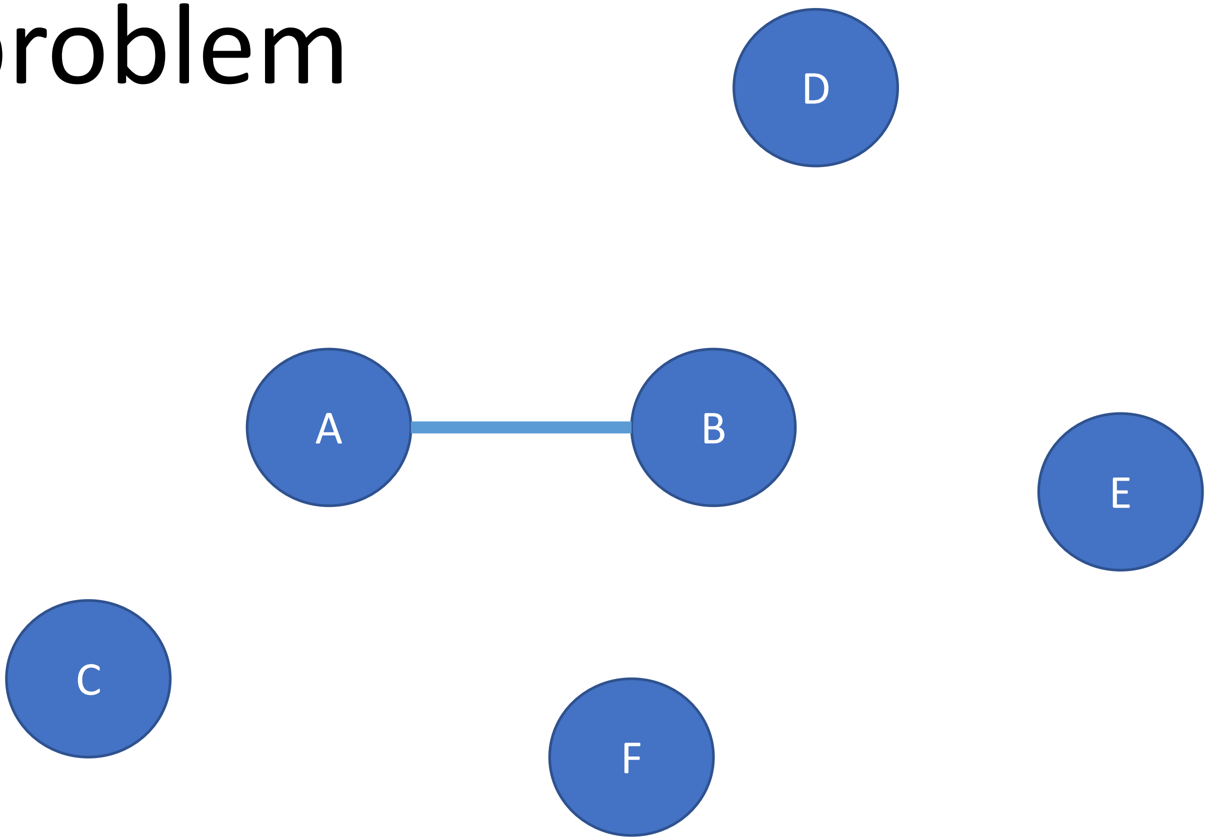
JAMA Ioannidis 2006

(Old) New problem

Traditional meta-analysis

Is treatment A better than treatment B?

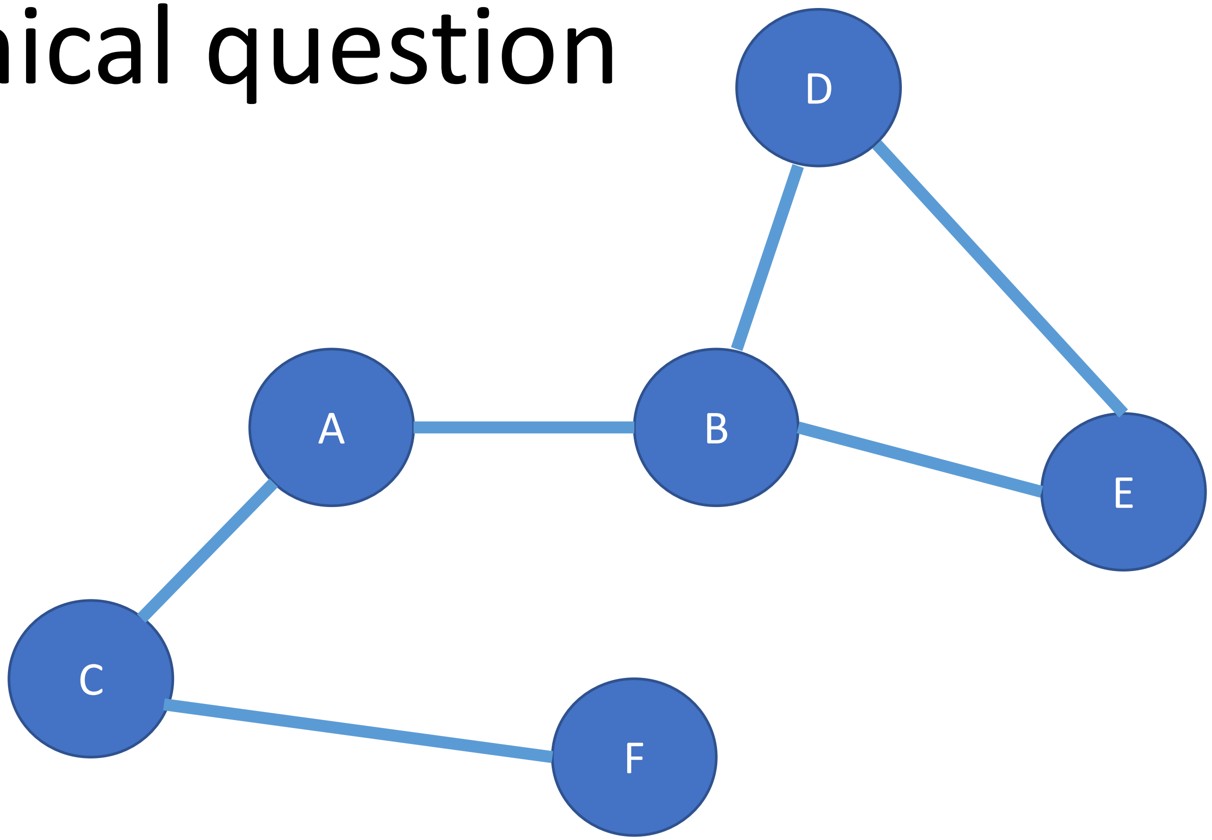
(Old) New problem



Traditional meta-analysis

Is treatment A better than treatment B?

The real clinical question



Which of the six available treatments is the most effective and safest?
Is treatment B better than treatment F?

Results: Twenty-six clinical trials conducted in primary care, secondary care and other settings met the inclusion criteria. On measures of wax clearance: <u>Cerumol, sodium bicarbonate, olive oil and water are all more effective than no treatment; triethanolamine polypeptide (TP) is better than olive oil; wet irrigation is better than dry irrigation; sodium bicarbonate drops followed by irrigation by nurse is more effective than sodium bicarbonate drops followed by self-irrigation; softening with TP and self-irrigation is more effective than self-irrigation only; and endoscopic de-waxing is better than microscopic dewaxing.</u>

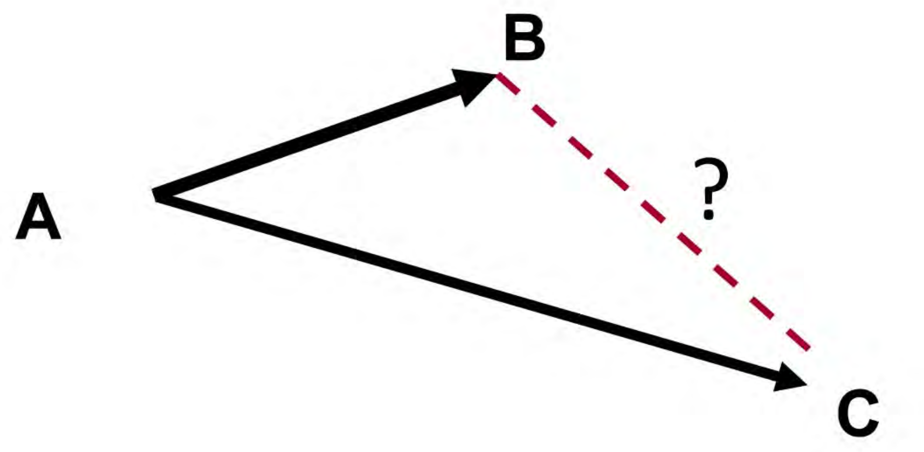
Networks: using indirect comparisons

- If we know how much taller building B is to A and how much taller is C to A, we know how much taller is B compared to C

- For any pair B and C, typical difference of C over B = difference of C over A minus difference of B over A

Indirect comparison

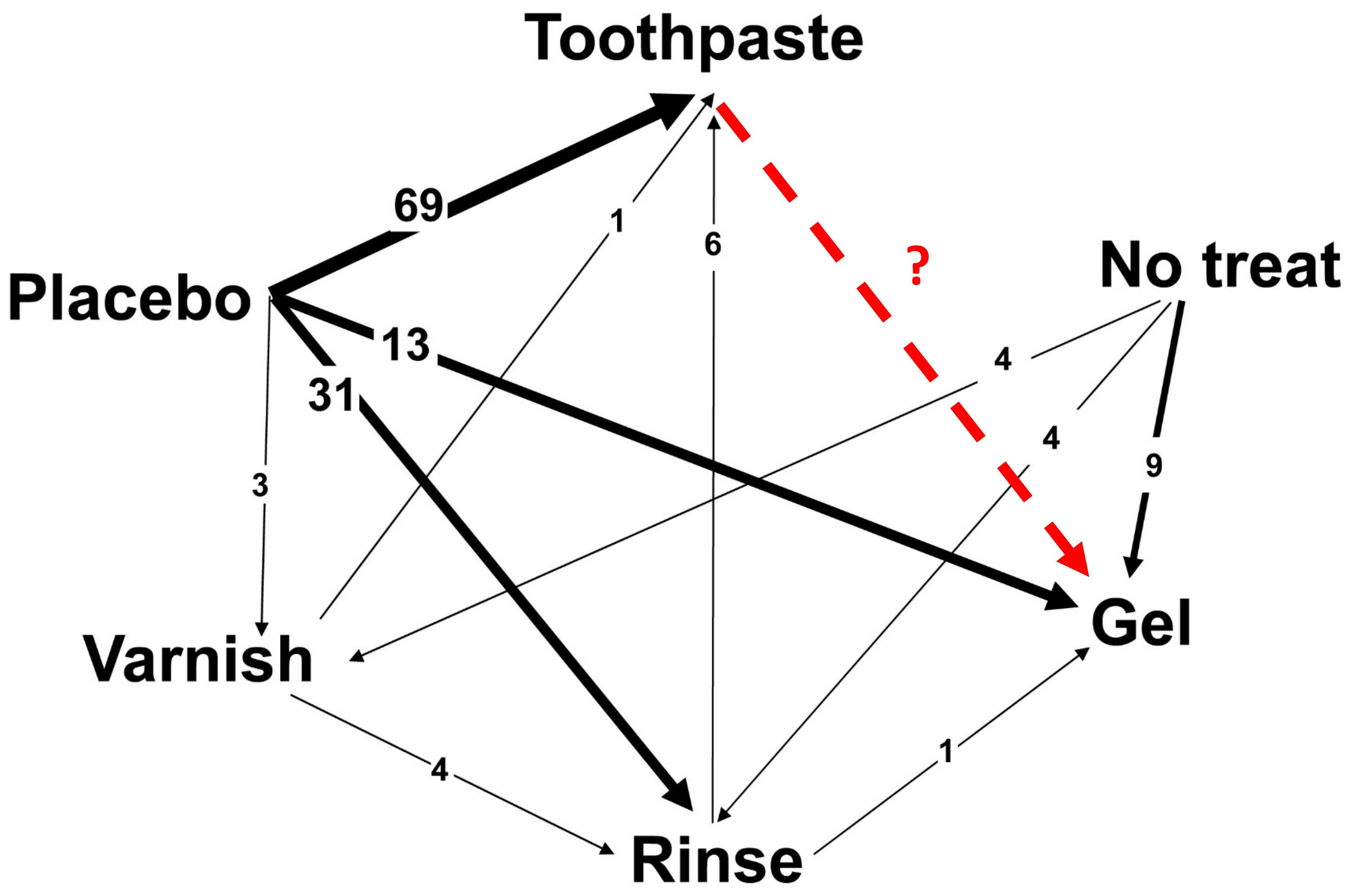
- We can obtain an indirect estimate of treatment effect for B vs C from trials comparing A v B and A v C



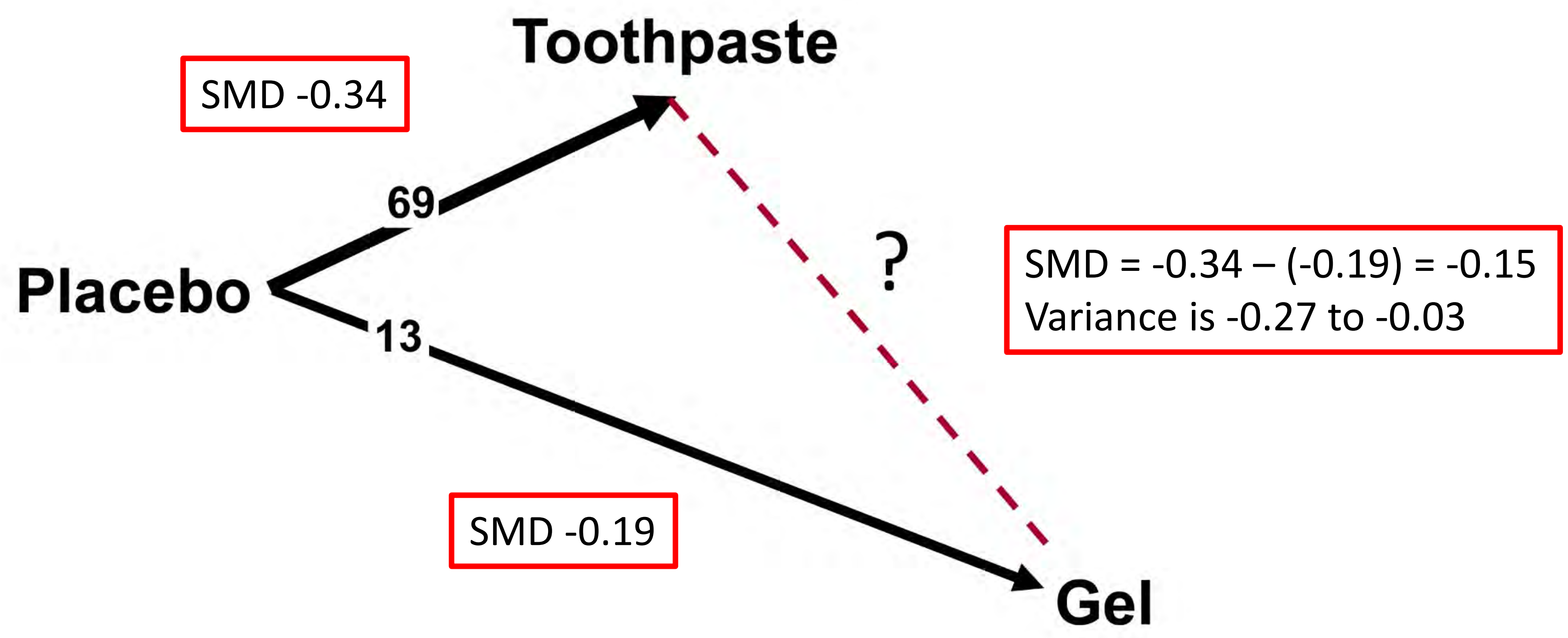
Treatment effect BC = Treatment effect AC – Treatment effect AB

Variance BC = variance AC + variance AB

Example: Toothpaste versus gel

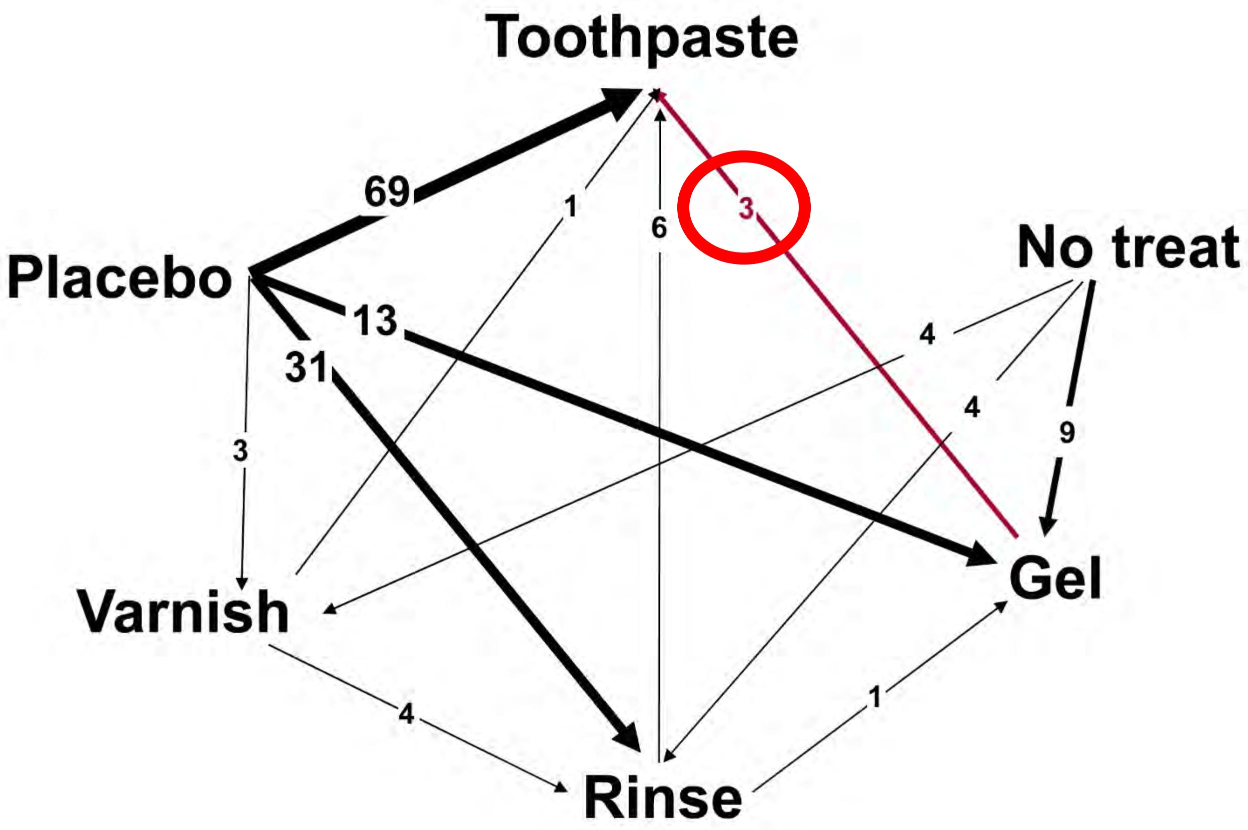


Example: Toothpaste versus gel

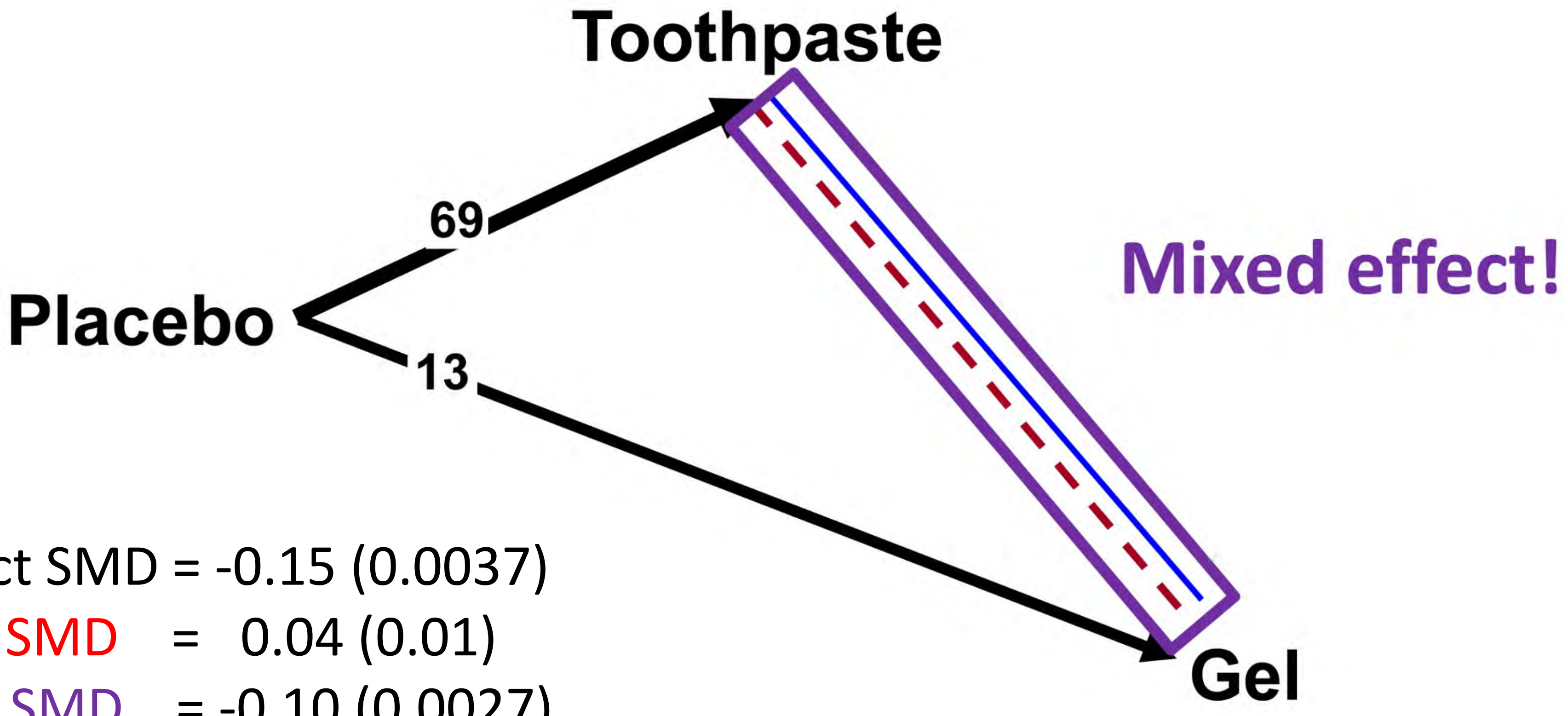


Even when there are no studies – we can estimate that toothpaste is better than gel

Using direct and indirect effects

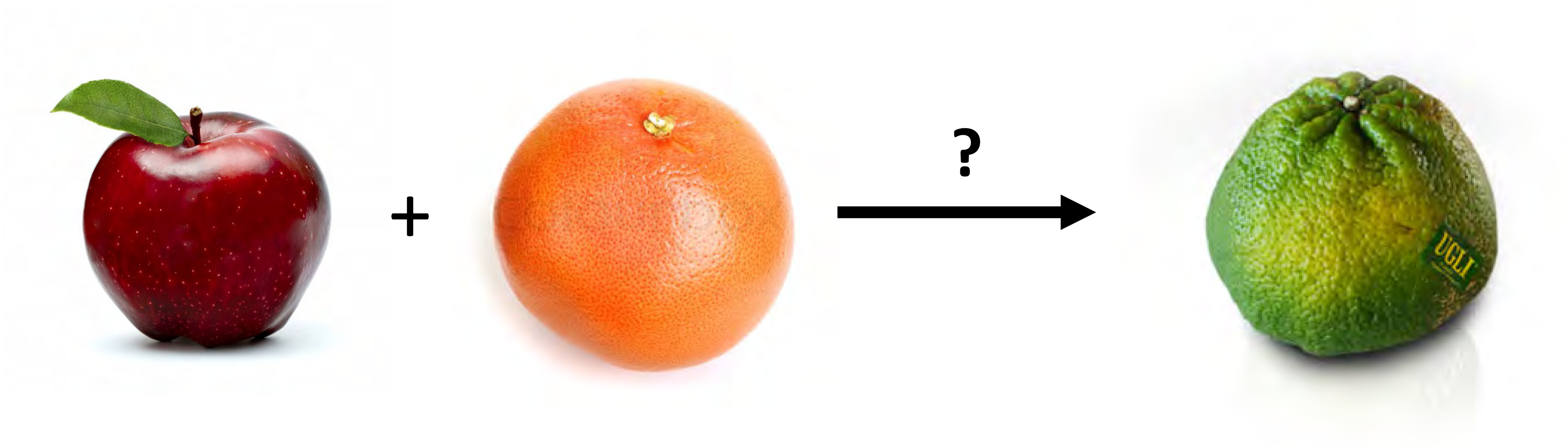


Mixed effects: more precise?



Indirect SMD = -0.15 (0.0037)
Direct SMD = 0.04 (0.01)
Mixed SMD = -0.10 (0.0027)

Problem of combining information



Criticism of indirect comparisons

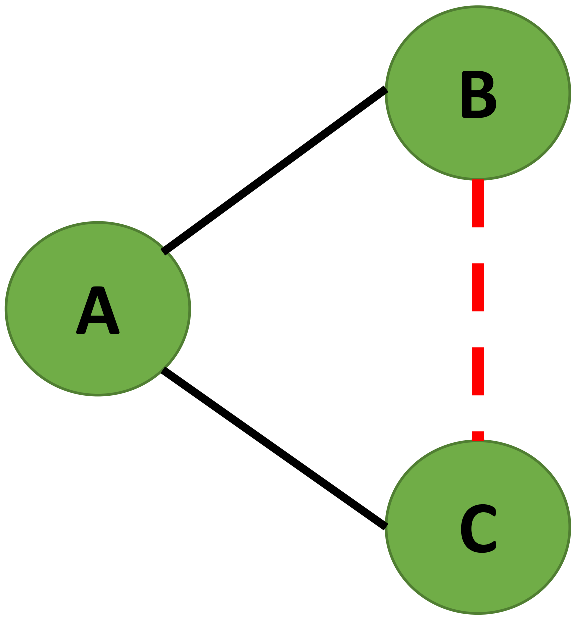
- Indirect comparison respects randomization but it is not randomized evidence
- Indirect and mixed effects (toothpaste versus gel) can answer policy questions taking a broad approach (e.g., which is the safest of all treatments)

- BUT

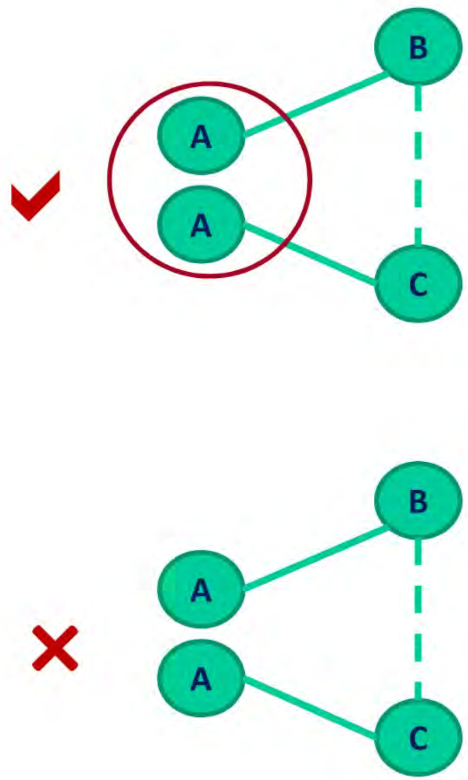
- They use non-randomized evidence and extra considerations are needed

Is network meta-analysis valid?

- That one can learn about B versus C via A
- (That one can learn about toothpaste versus gel via placebo)



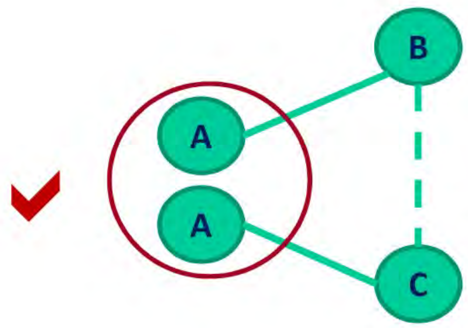
Is the common treatment similar?



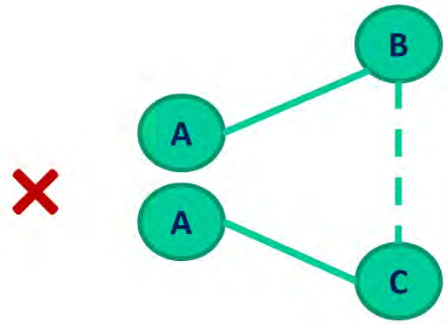
Treatment A is similar when it appears in AB and AC trials

Plausible when A is placebo given in different forms
(e.g. injection versus pill)?

Is the common treatment similar?

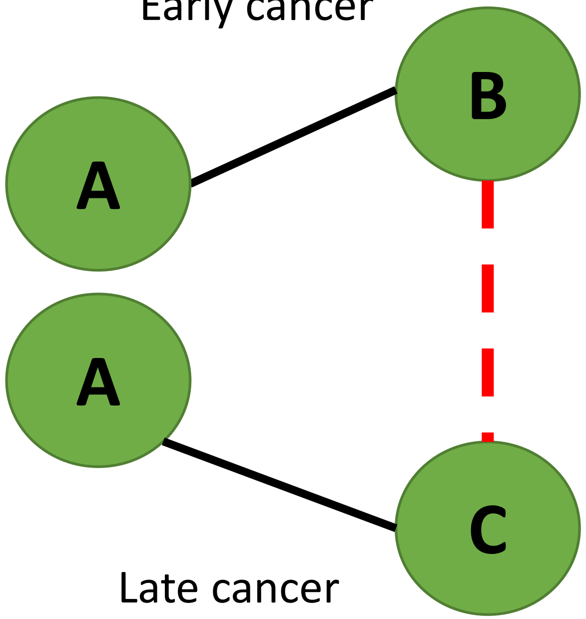


For example, placebo rinse and placebo toothpaste might not be comparable as the mechanical action of brushing might have a different effect on caries



Issue must be addressed when building the network (at the start of the project)

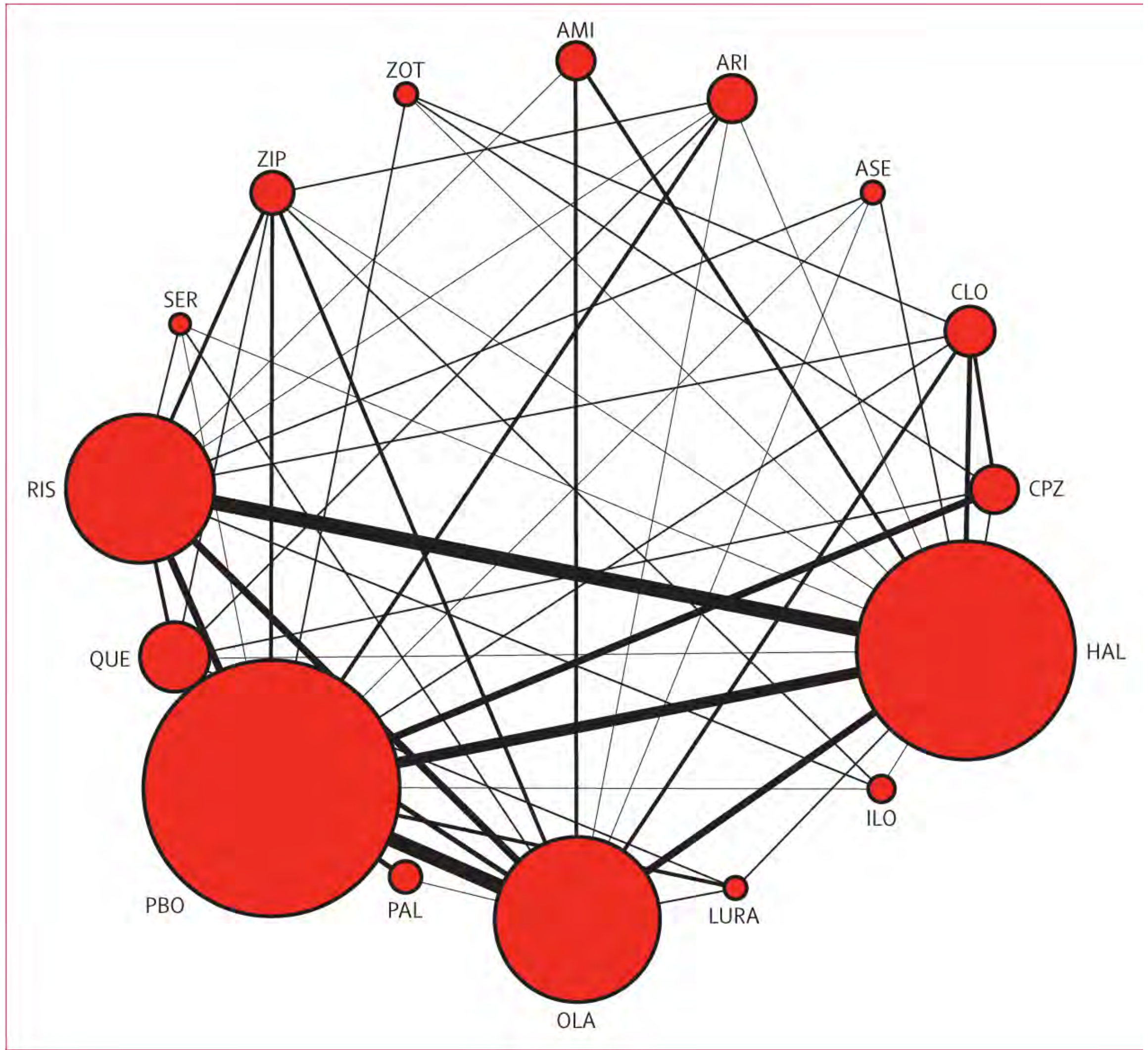
Are the populations in the network similar?



Just like in conventional meta-analysis, there are ways to explore and understand heterogeneity and inconsistency

Practical examples of the cool things you can do with networks

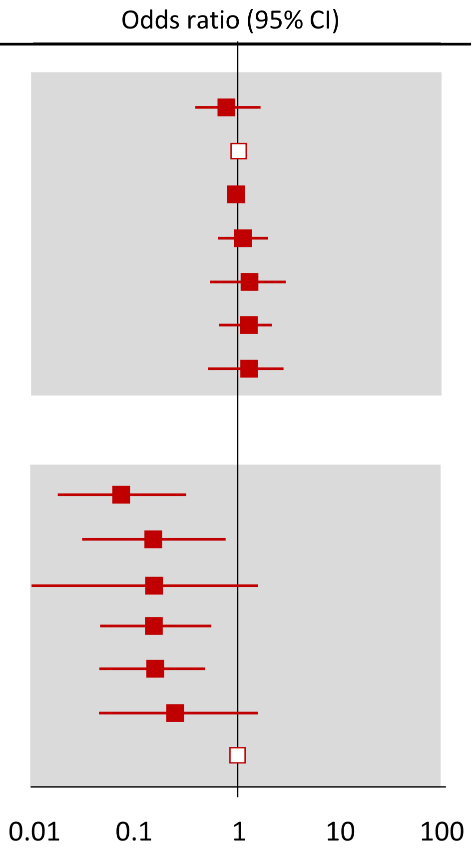
1. Show the geometry of the evidence (antipsychotics in schizophrenia)



Leucht Lancet 2013

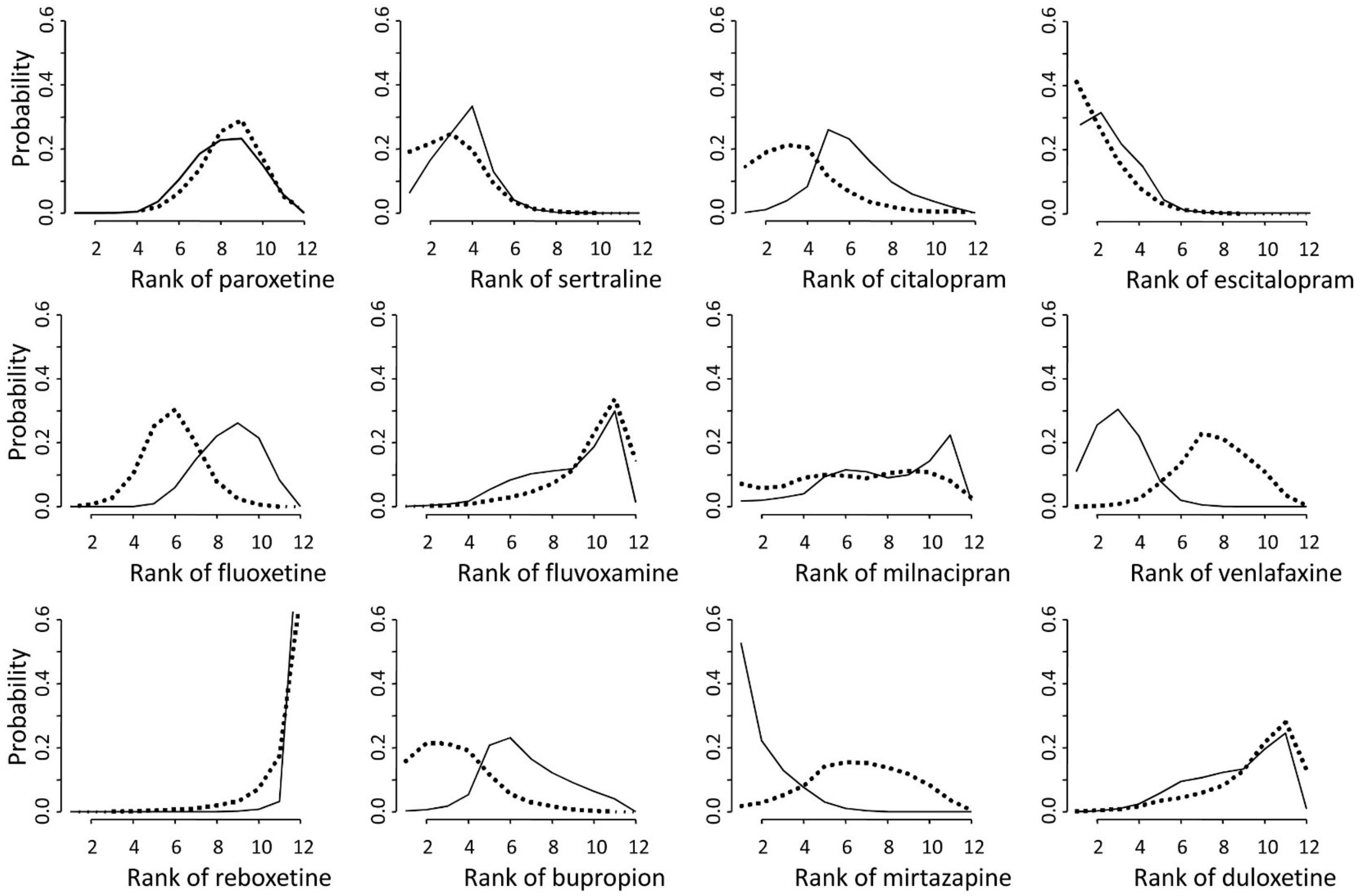
2. Show effects of drugs in which there are no trials

	Odds ratio (95% CI)
All-cause mortality	
Epoetin beta	0.82 (0.45-1.48)
Placebo	Reference
Darbepoetin alfa	1.06 (0.91-1.24)
Methoxy-polyethylene glycol epoetin beta	1.16 (0.74-1.82)
No treatment	1.22 (0.56-2.63)
Epoetin alfa	1.25 (0.71-2.21)
Biosimilar ESA	1.31 (0.65-2.62)
Transfusion	
Epoetin beta	0.09 (0.02-0.38)
Methoxy polyethylene glycol-epoetin beta	0.15 (0.03-0.70)
No treatment	0.15 (0.01-1.73)
Darbepoetin alfa	0.17 (0.05-0.57)
Epoetin alfa	0.18 (0.05-0.59)
Biosimilar ESA	0.27 (0.05-1.47)
Placebo	Reference



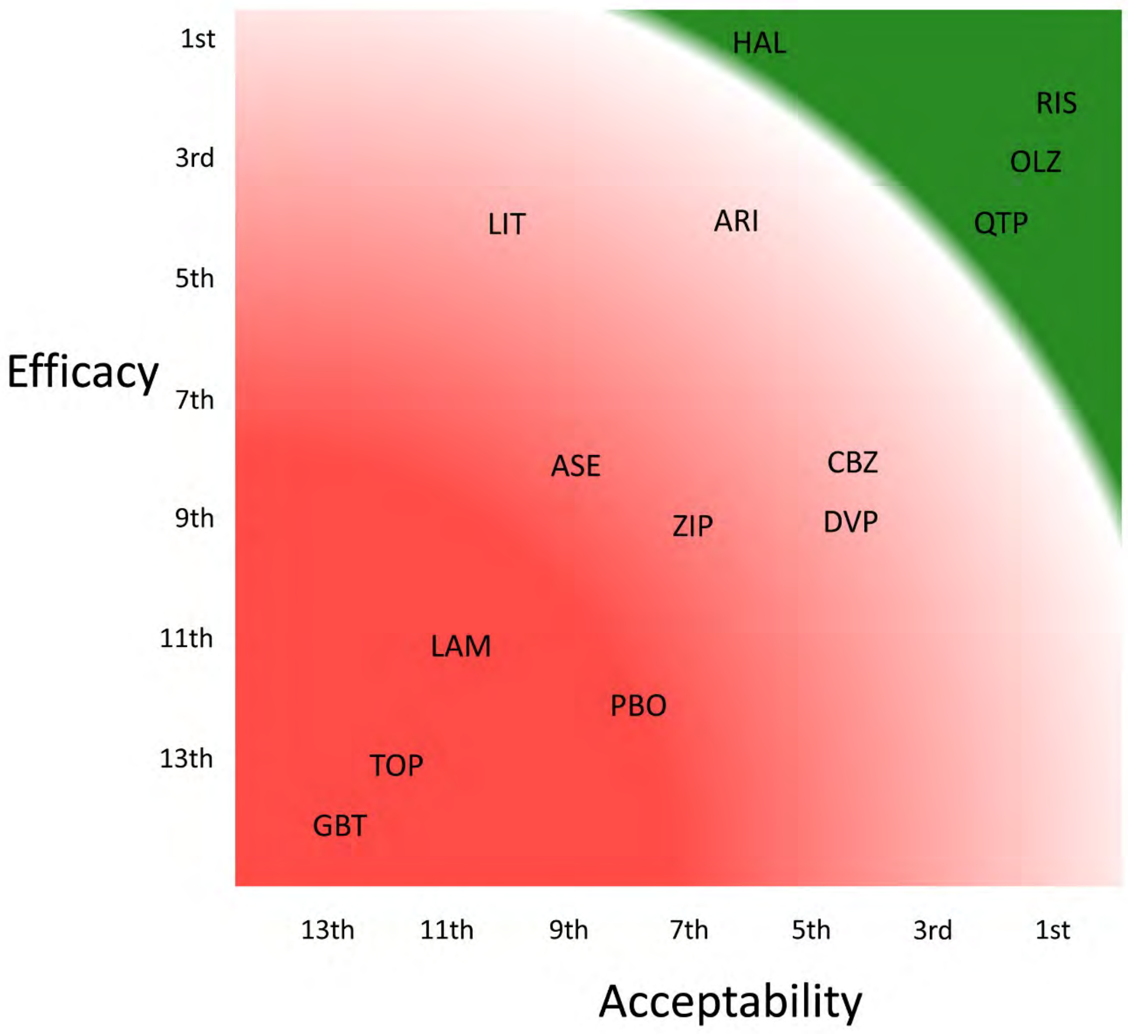
Palmer in press 2014

3. Rank treatments in order of best to worst (which antidepressant would you not want!)



Ranking for efficacy (solid line) and acceptability (dotted line). Ranking: probability to be the best treatment, to be the second best, the third best and so on, among the 12 comparisons).

4. Display in single graphic entire relative evidence for a condition or drug



Cipriani Lancet 2011

Excellent resource for “how to do: in STATA”

OPEN ACCESS Freely available online

PLOS | ONE

Graphical Tools for Network Meta-Analysis in STATA

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Abstract

Network meta-analysis synthesizes direct and indirect evidence in a network of trials that compare multiple interventions and has the potential to rank the competing treatments according to the studied outcome. Despite its usefulness network meta-analysis is often criticized for its complexity and for being accessible only to researchers with strong statistical and computational skills. The evaluation of the underlying model assumptions, the statistical technicalities and presentation of the results in a concise and understandable way are all challenging aspects in the network meta-analysis methodology. In this paper we aim to make the methodology accessible to non-statisticians by presenting and explaining a series of graphical tools via worked examples. To this end, we provide a set of STATA routines that can be easily employed to present the evidence base, evaluate the assumptions, fit the network meta-analysis model and interpret its results.

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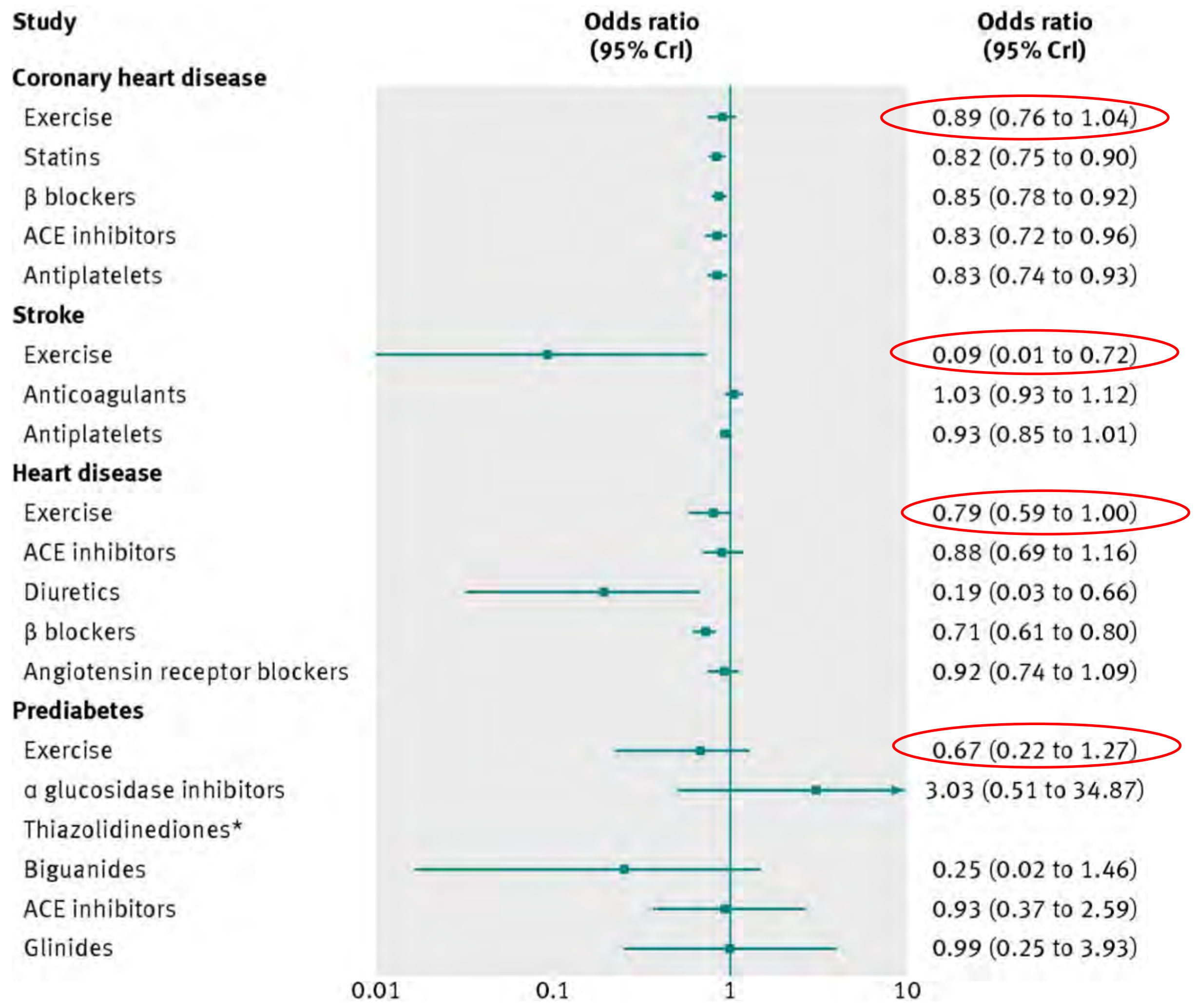
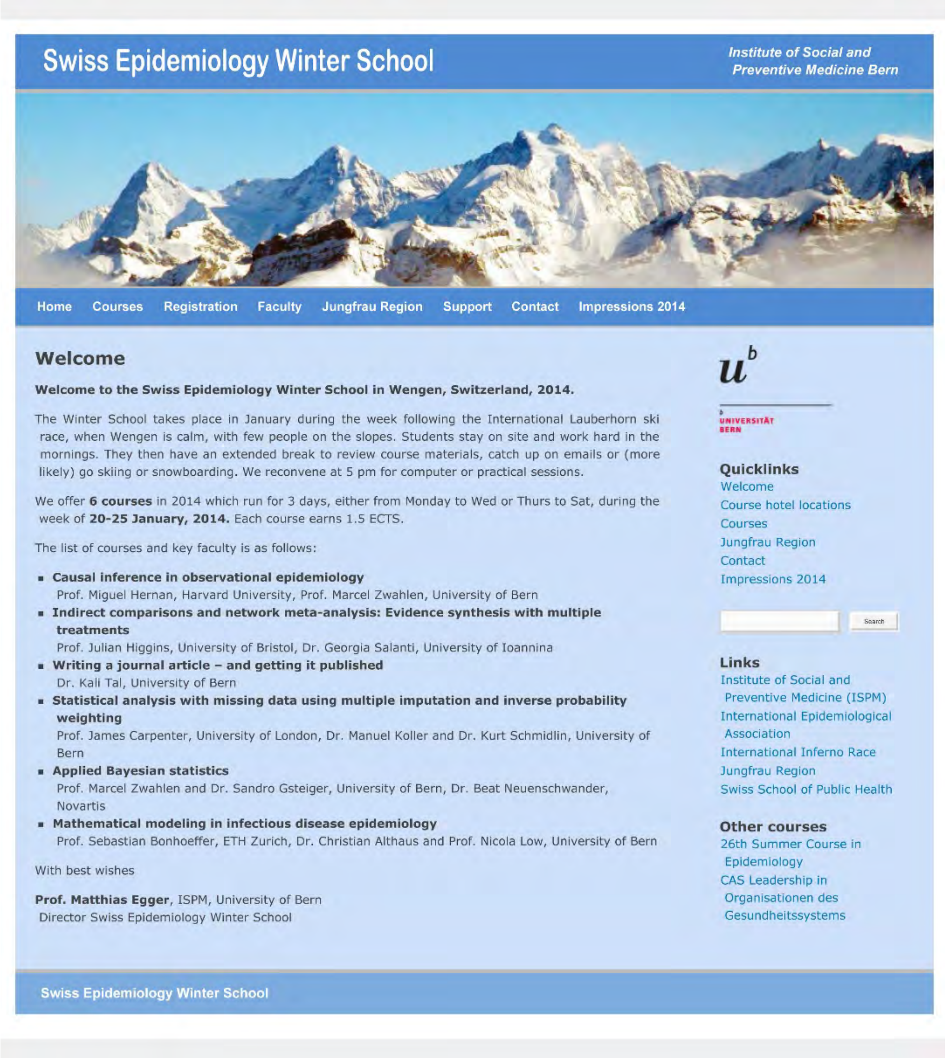
Exercise versus drugs in absence of trials (or why you should exercise more!)

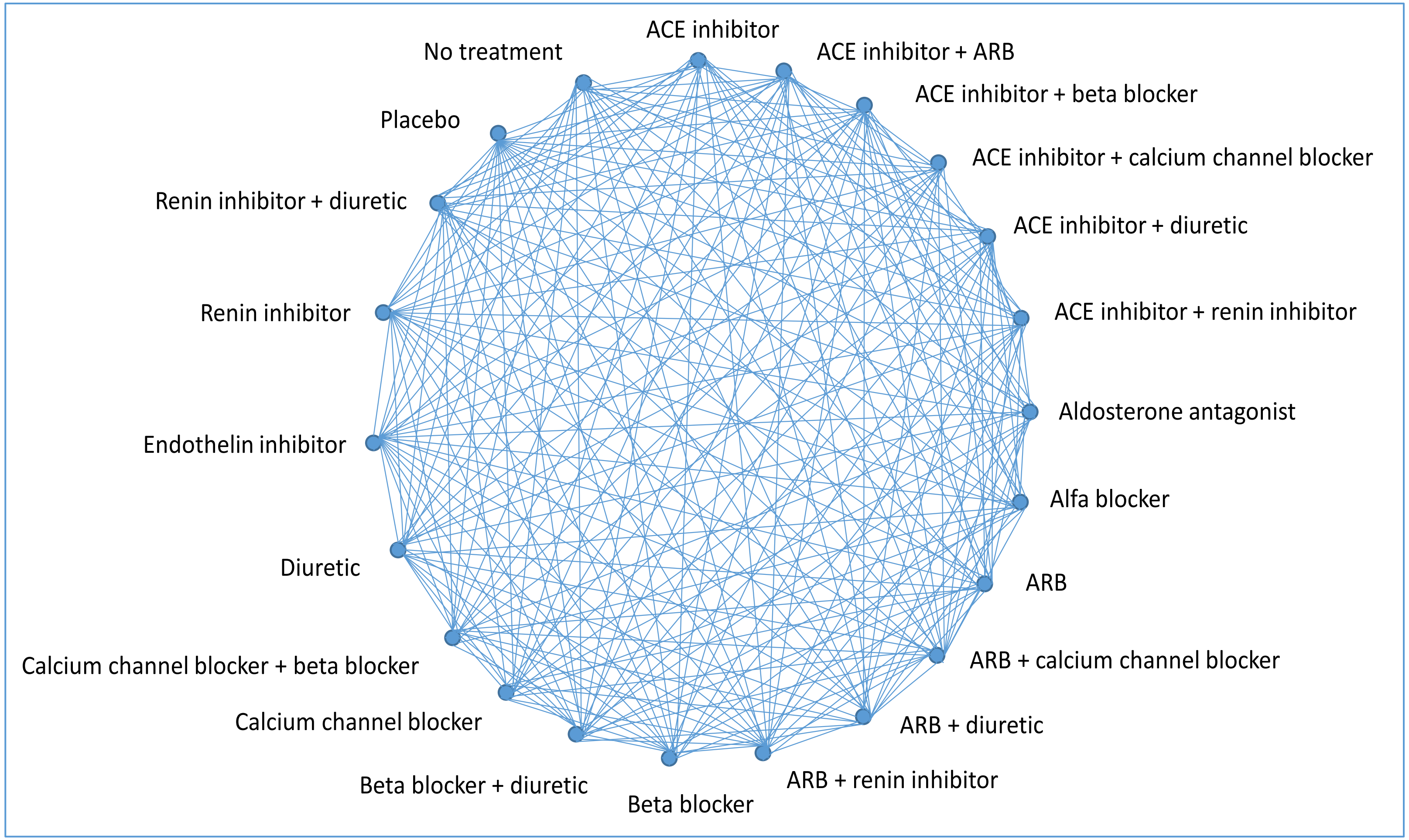


Naci BMJ 2014

An amazing practical way to learn network meta-analysis http://www.epi-winterschool.org/



Questions?



Network diagram for my next network meta-analysis