

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

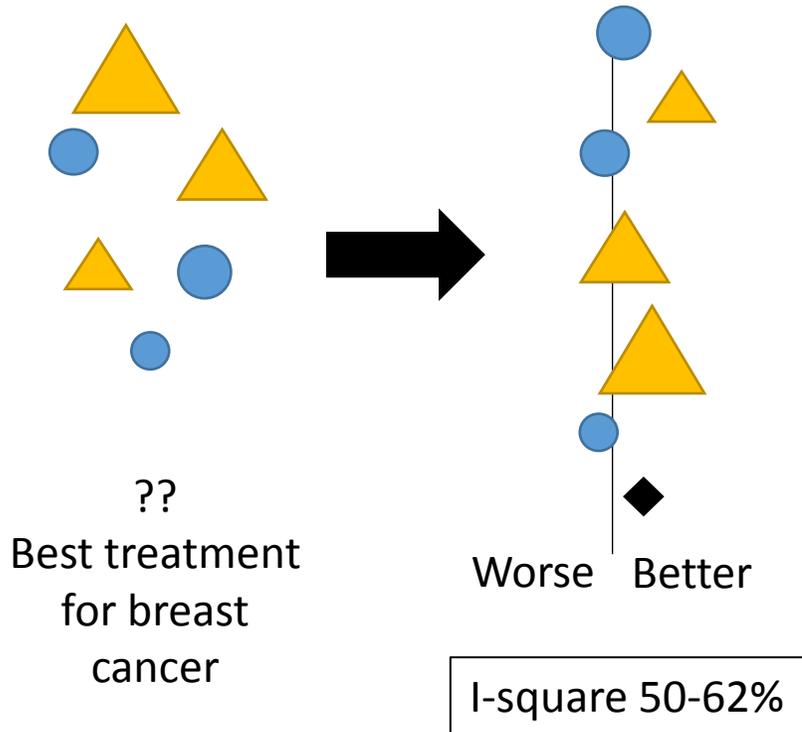
- By the end of this session, I hope you will have an understanding of
 - The role of network meta-analysis in the evaluation of data
 - The key principles of the statistical methods involved
 - The key problems that can distort network meta-analyses
 - Enthusiasm for how network meta-analysis might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

Two big problems with modern medicine

- Contradictory studies on almost every topic
- Bewildering flood of new data



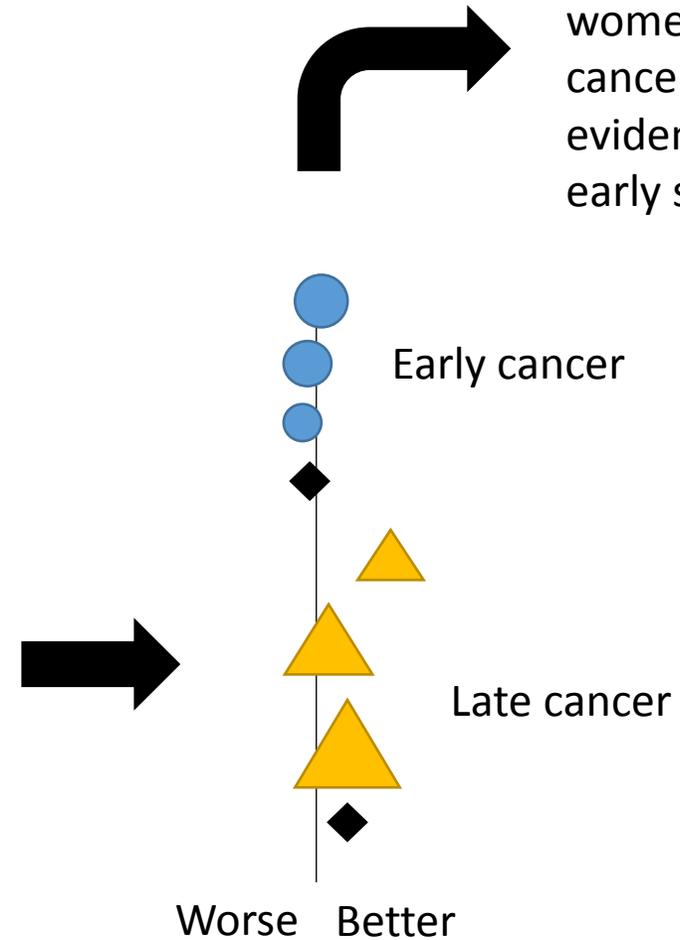
The (quick) story of meta-analysis



Apple and oranges problem

Using the force of heterogeneity to understand more!

The text 'Apple and oranges problem' is centered. A downward arrow points to the text 'Using the force of heterogeneity to understand more!'.

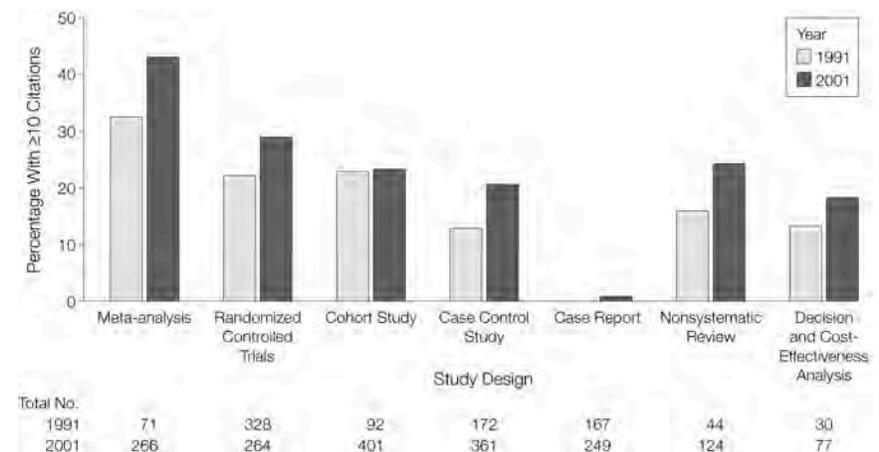


Treatment for breast cancer appears to differ by cancer stage. Overall benefit for women with late cancer but absent evidence of benefit for early stages

The text is positioned to the right of the stratified forest plot. A large, thick, curved arrow points from the forest plot towards this text.

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
- Highly cited and influential



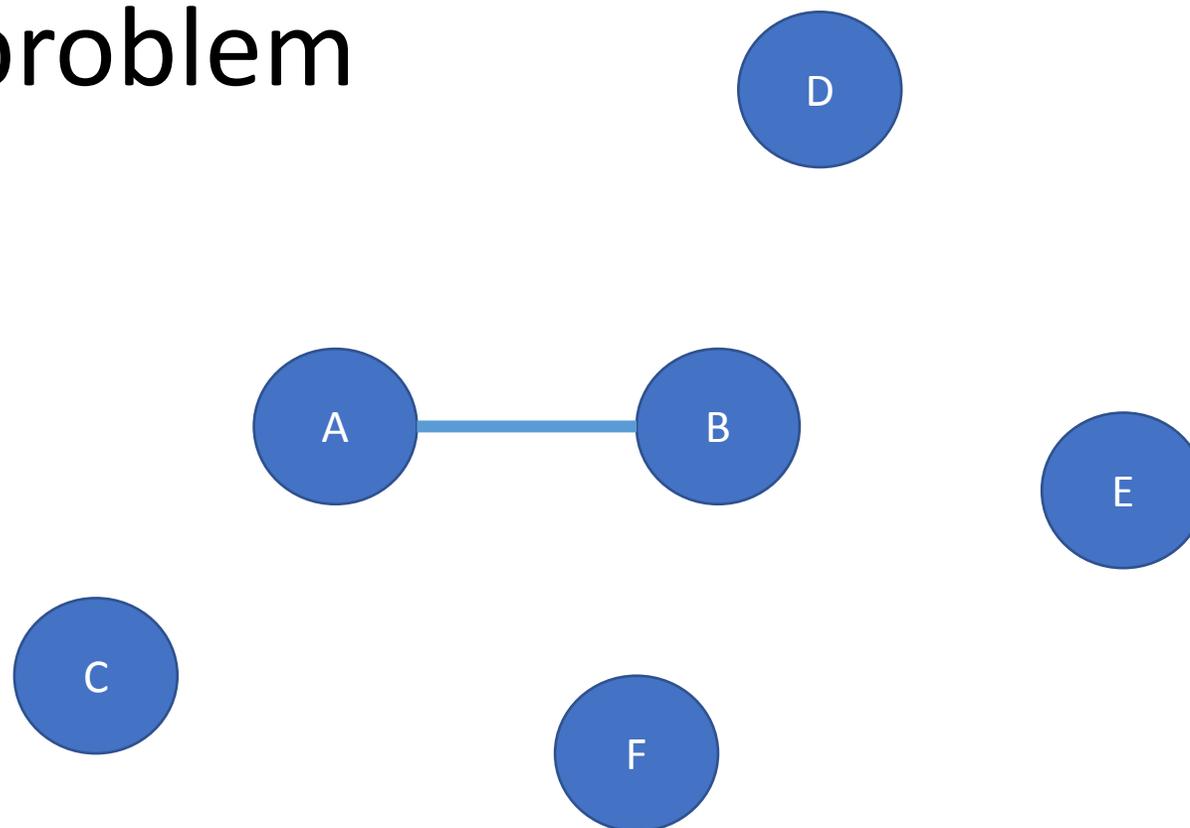
(Old) New problem



Traditional meta-analysis

Is treatment A better than treatment B?

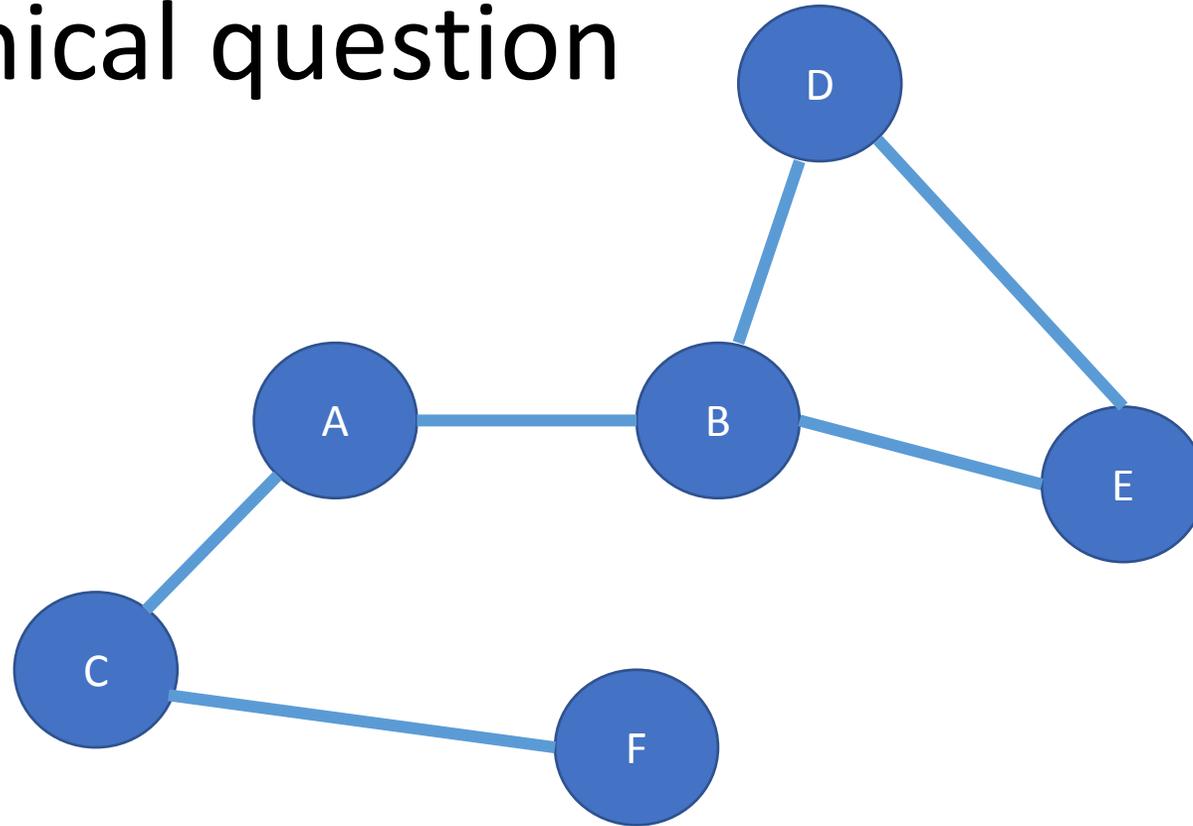
(Old) New problem



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: 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.



Networks: using indirect comparisons

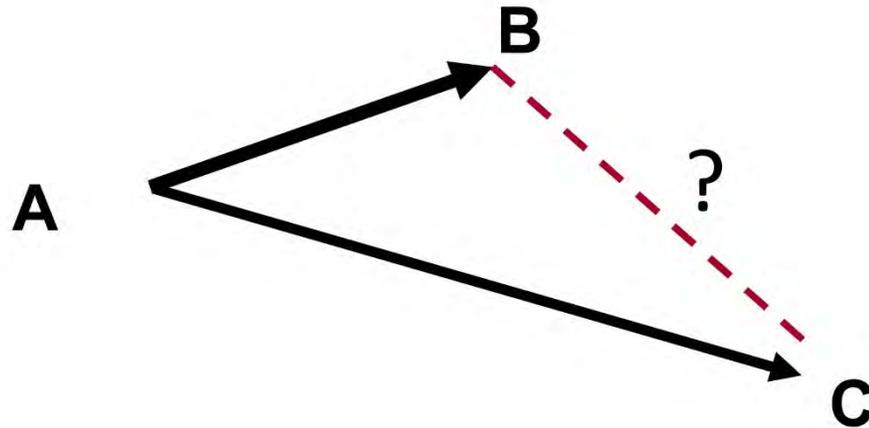
- If we know how much taller building B is to A and how much taller is C to A, we know how much taller is B compared to C



- 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

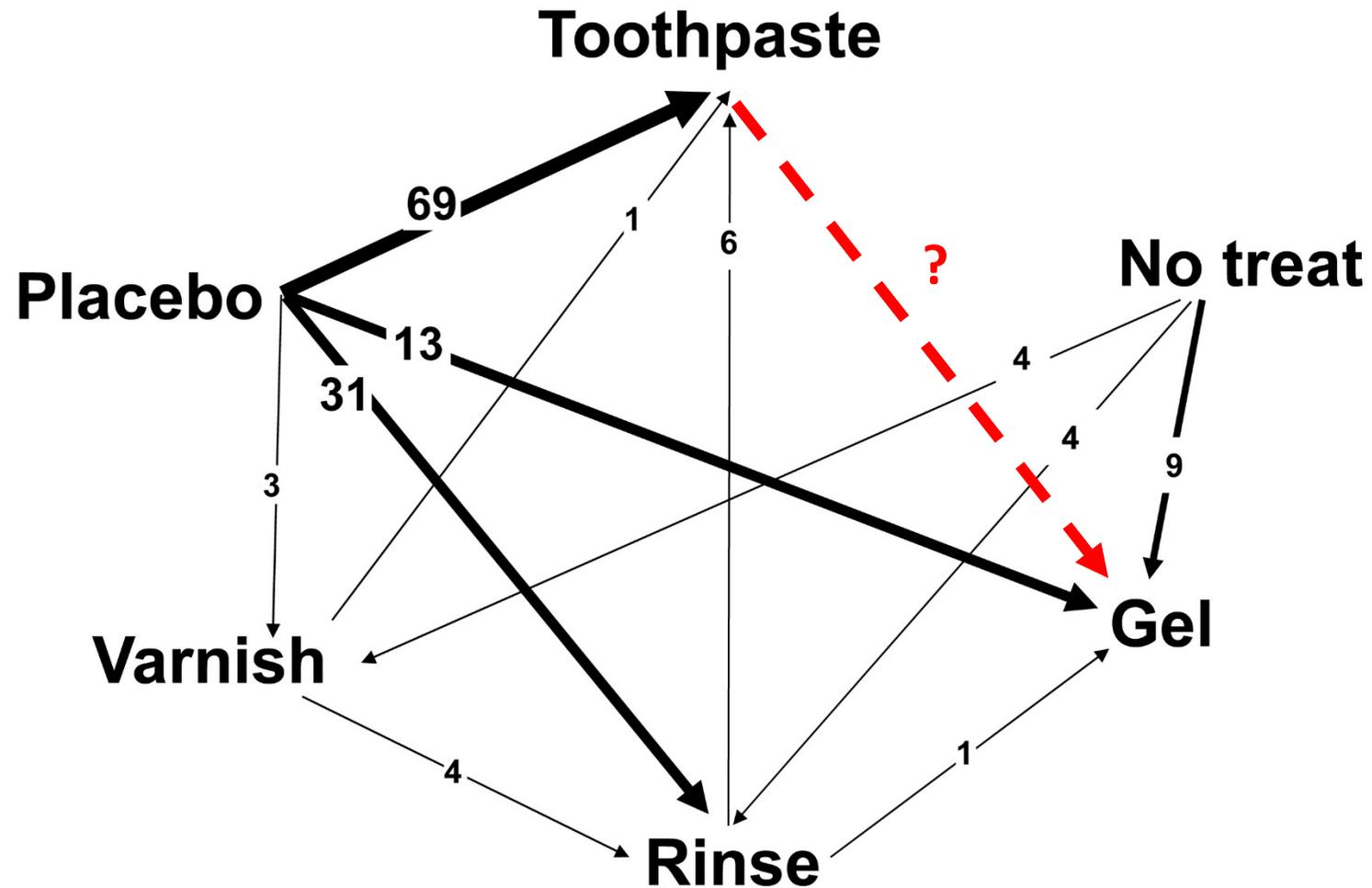
- We can obtain an **indirect estimate** of treatment effect for B vs C from trials comparing A v B and A v C



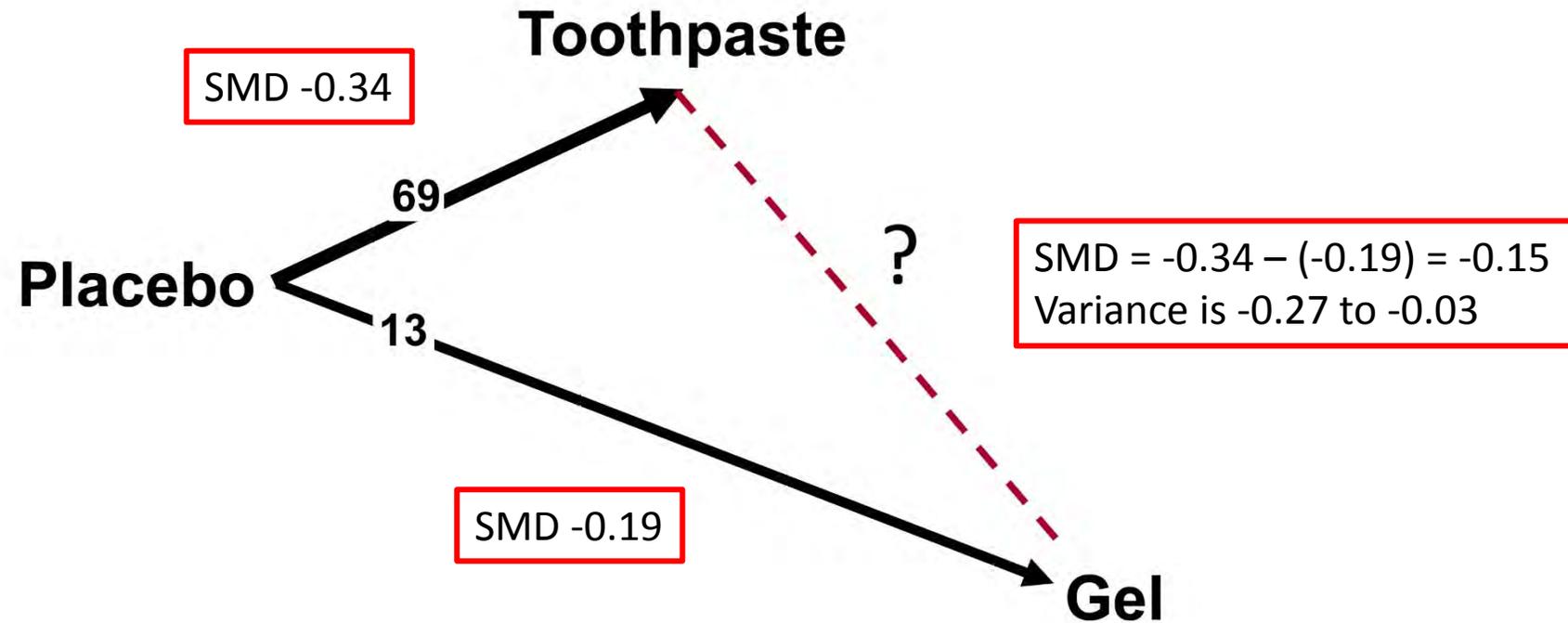
Treatment effect BC = Treatment effect AC – Treatment effect AB

Variance BC = variance AC + variance AB

Example: Toothpaste versus gel

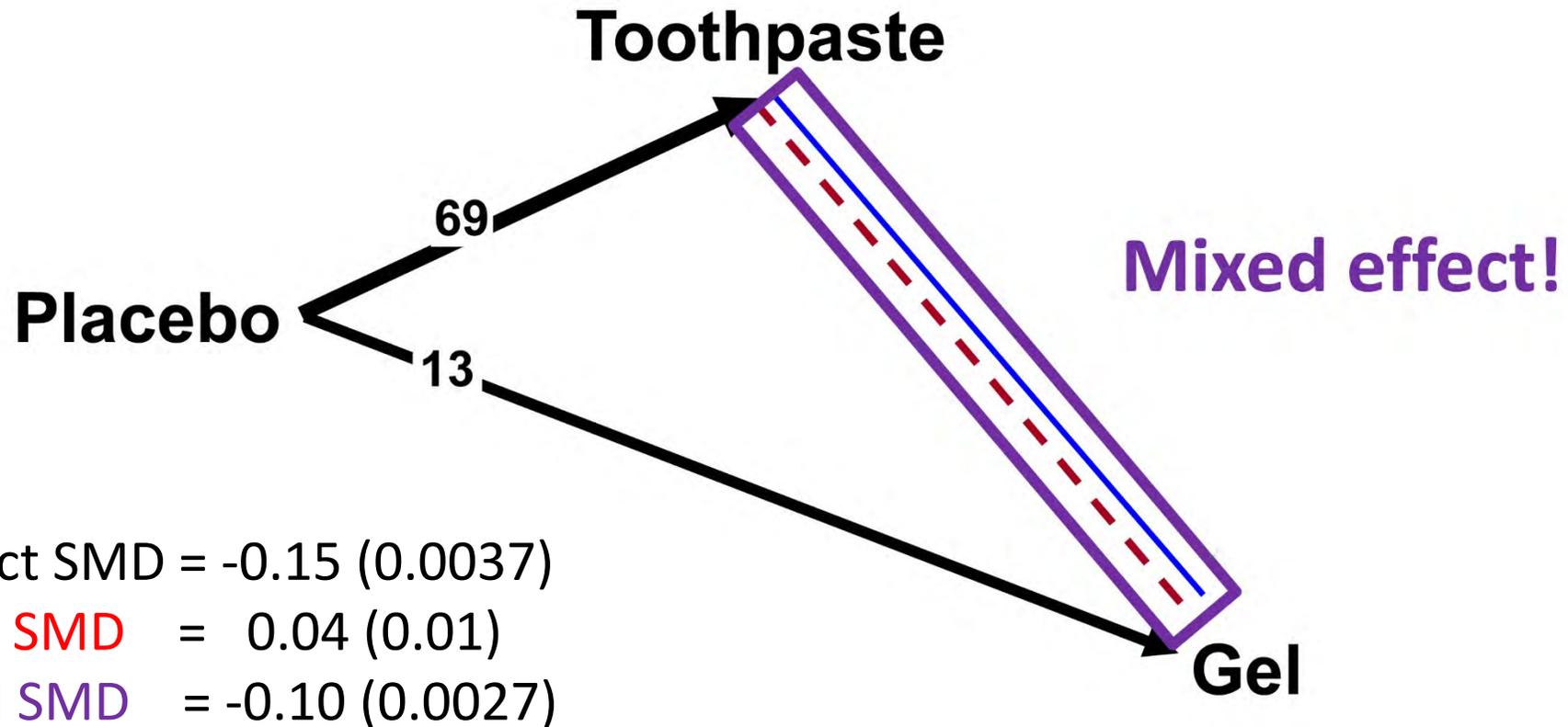


Example: Toothpaste versus gel



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

Mixed effects: more precise?



Problem of combining information



+



?

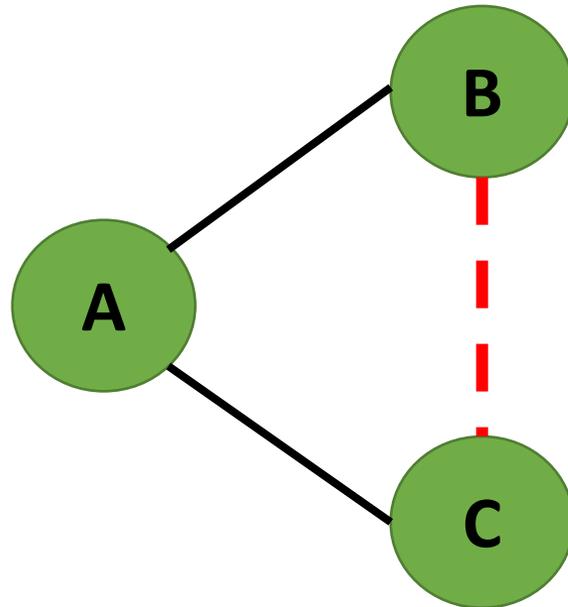


Criticism of indirect comparisons

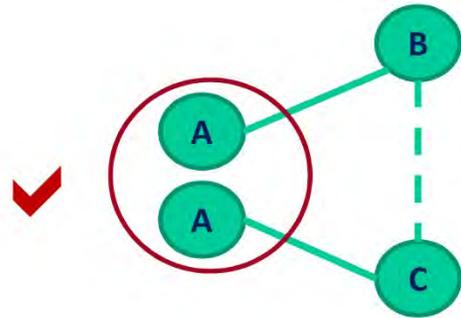
- Indirect comparison respects randomization but it is not randomized evidence
- Indirect and mixed effects (toothpaste versus gel) can answer policy questions taking a broad approach (e.g., which is the safest of all treatments)
- BUT
- They use non-randomized evidence and extra considerations are needed

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)

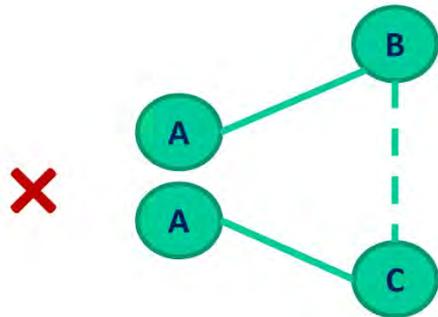


Is the common treatment similar?

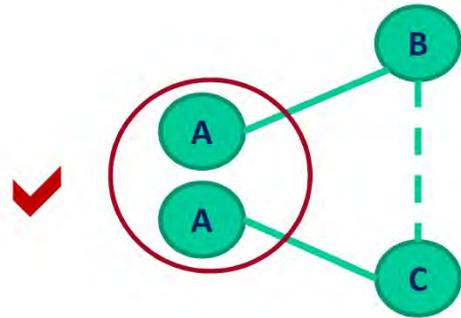


Treatment A is similar when it appears in AB and AC trials

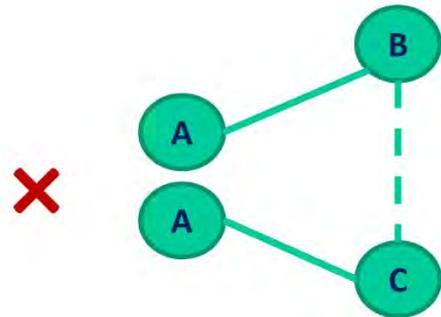
Plausible when A is placebo given in different forms (e.g. injection versus pill)?



Is the common treatment similar?

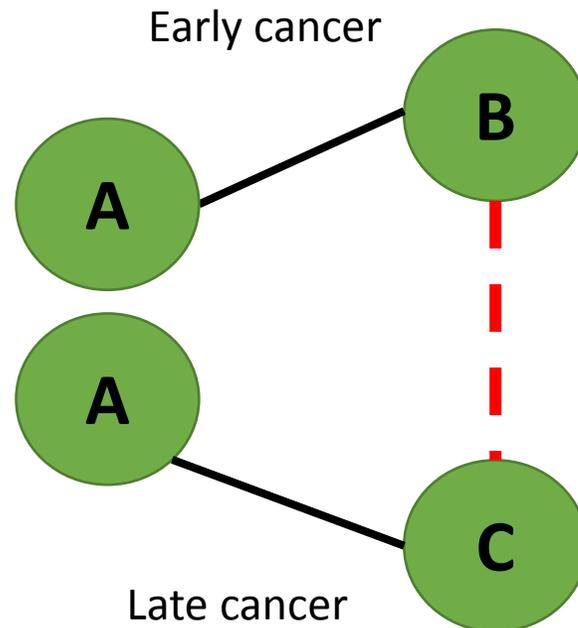


For example, placebo rinse and placebo toothpaste might not be comparable as the mechanical action of brushing might have a different effect on caries



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

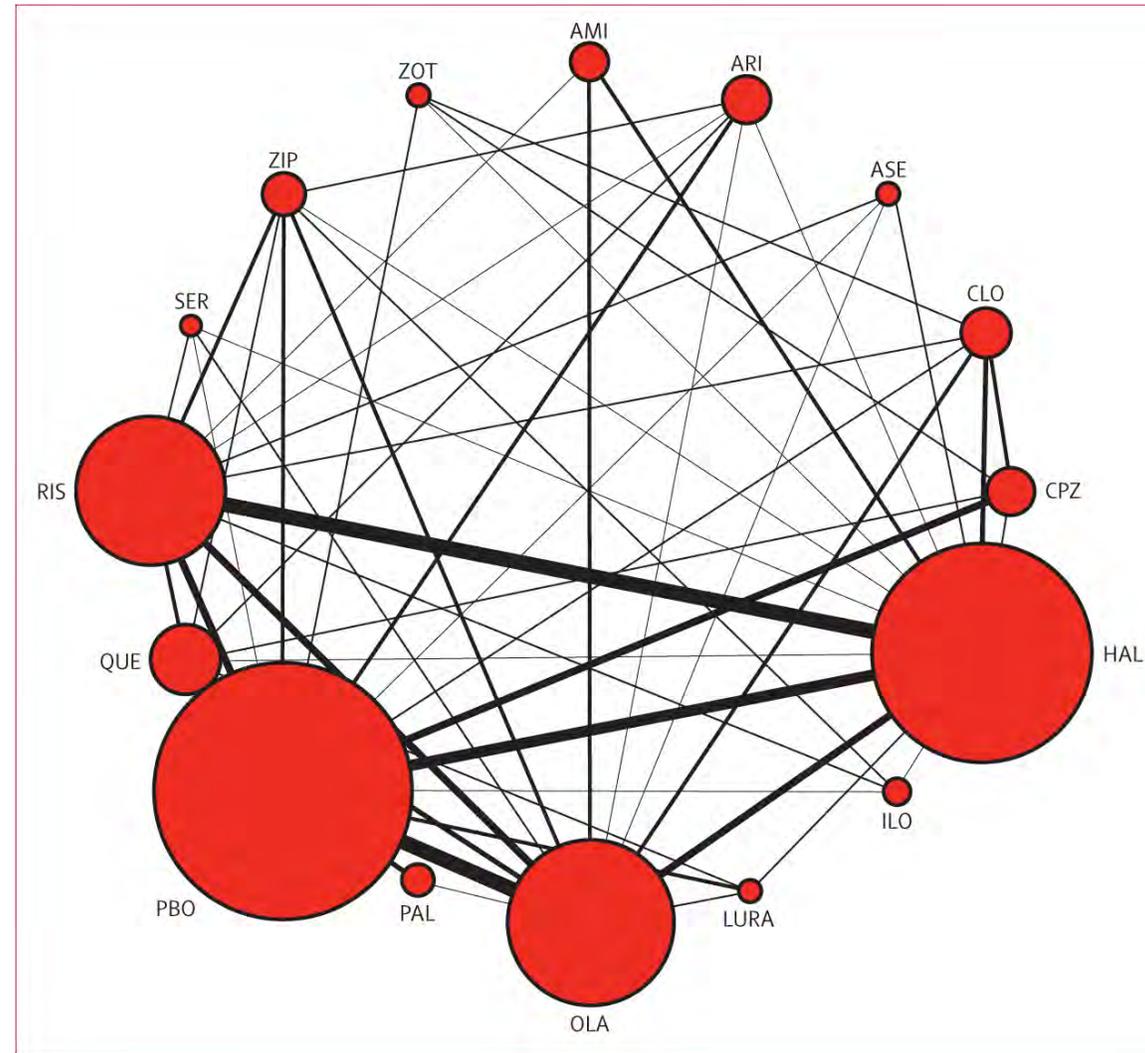
Are the populations in the network similar?



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)



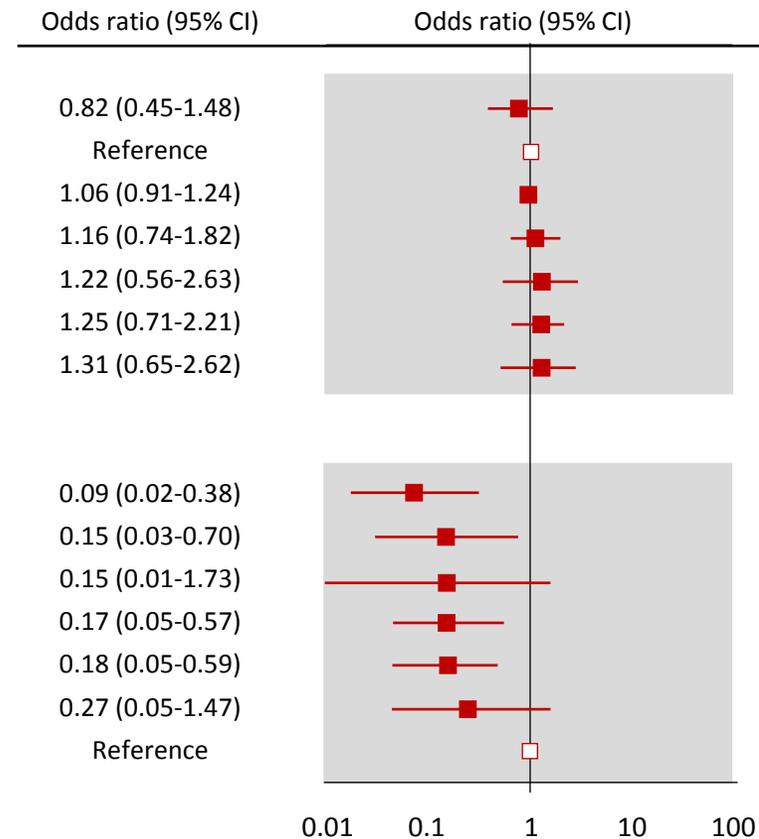
2. Show effects of drugs in which there are no trials

All-cause mortality

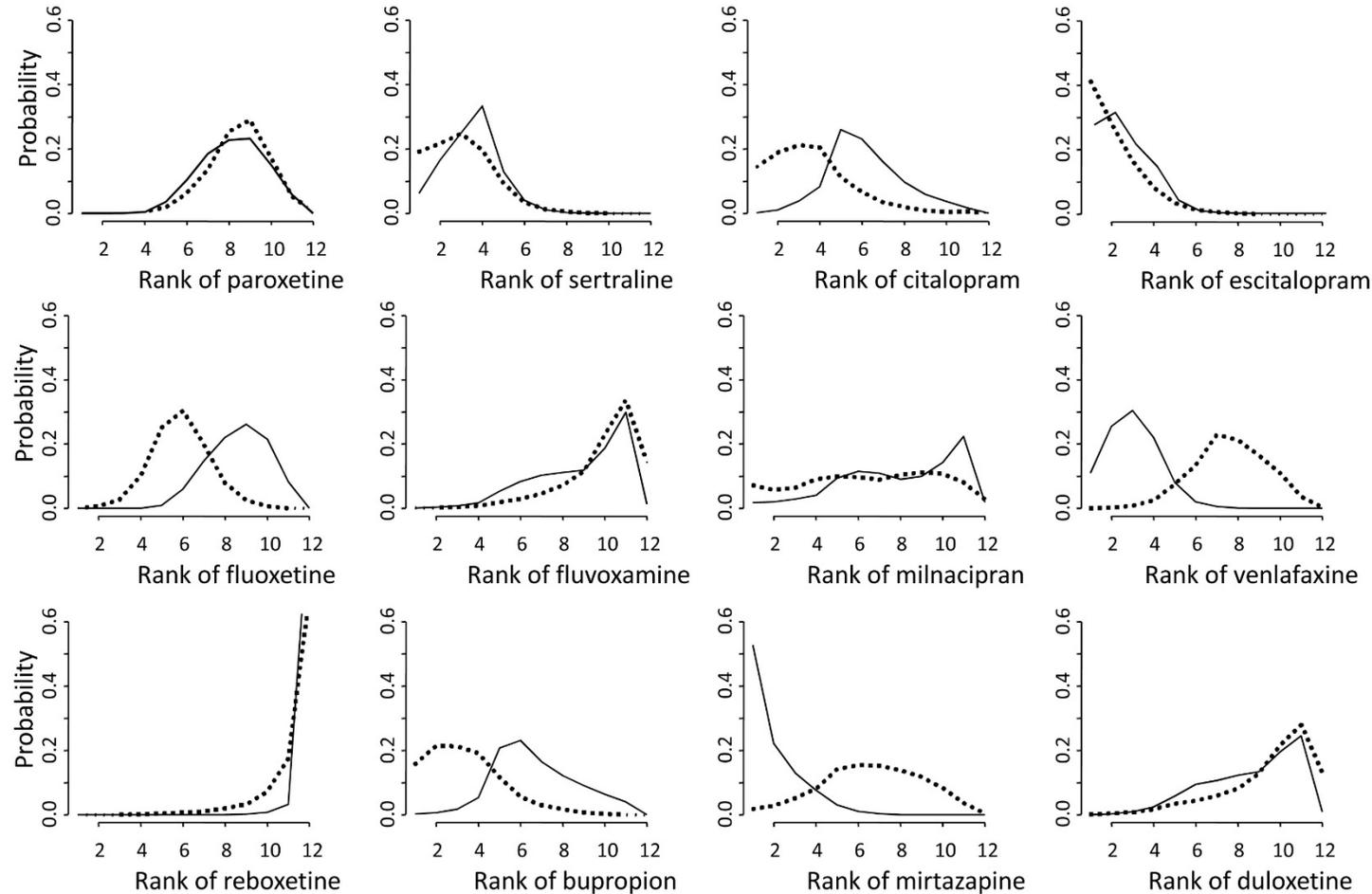
Treatment	Odds ratio (95% CI)
Epoetin beta	0.82 (0.45-1.48)
Placebo	Reference
Darbepoetin alfa	1.06 (0.91-1.24)
Methoxy-polyethylene glycol epoetin beta	1.16 (0.74-1.82)
No treatment	1.22 (0.56-2.63)
Epoetin alfa	1.25 (0.71-2.21)
Biosimilar ESA	1.31 (0.65-2.62)

Transfusion

Treatment	Odds ratio (95% CI)
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

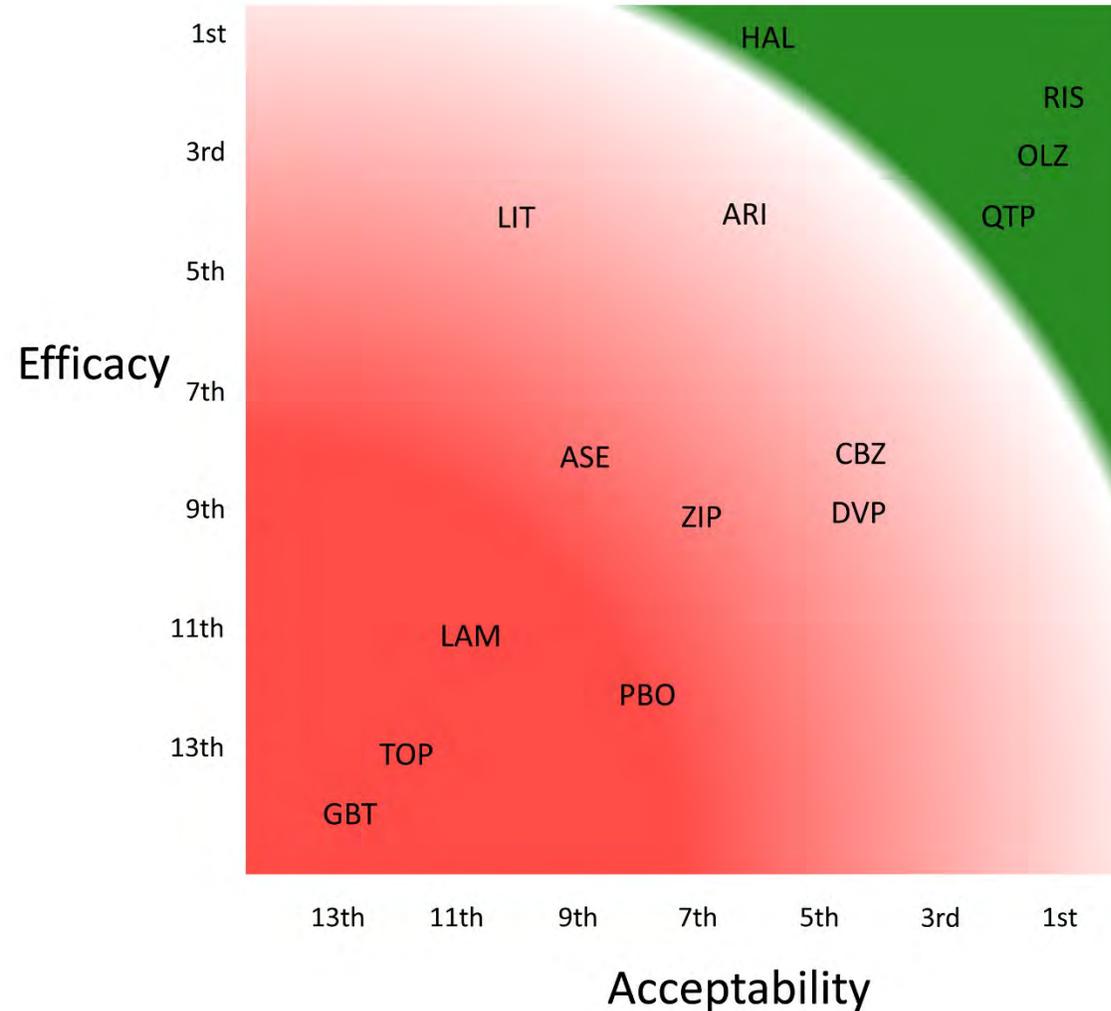


3. Rank treatments in order of best to worst (which antidepressant would you not want!)



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). 17

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



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.

Citation: Chaimani A, Higgins JPT, Mavridis D, Spyridonos P, Salanti G (2013) Graphical Tools for Network Meta-Analysis in STATA. PLoS ONE 8(10): e76654. doi:10.1371/journal.pone.0076654

Editor: Benjamin Haibe-Kains, Institut de recherches cliniques de Montréal (IRCM), Canada

Received: May 16, 2013; **Accepted:** August 27, 2013; **Published:** October 3, 2013

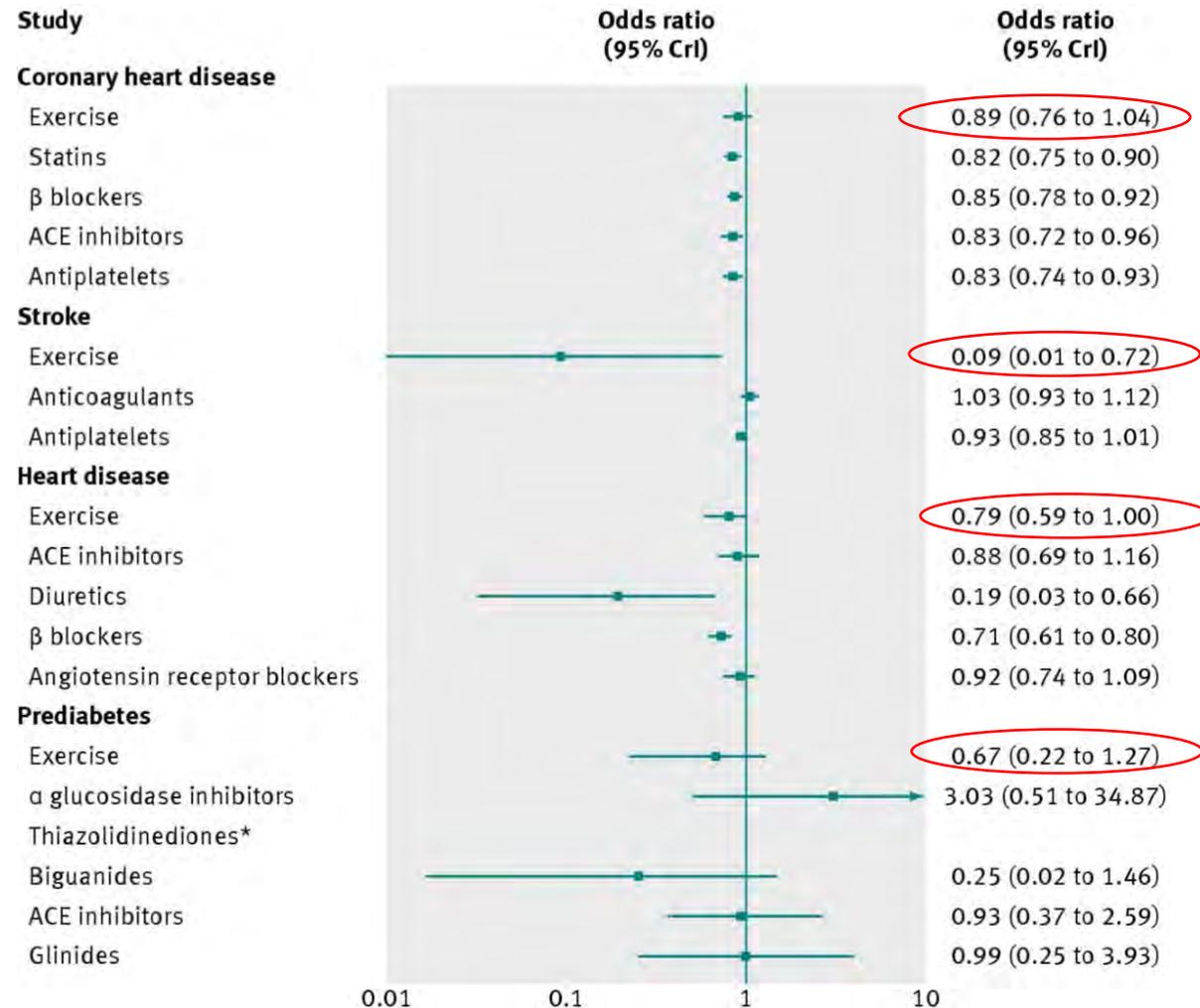
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Funding: AC, DM and GS received funding from the European Research Council (IMMA 260559 project). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

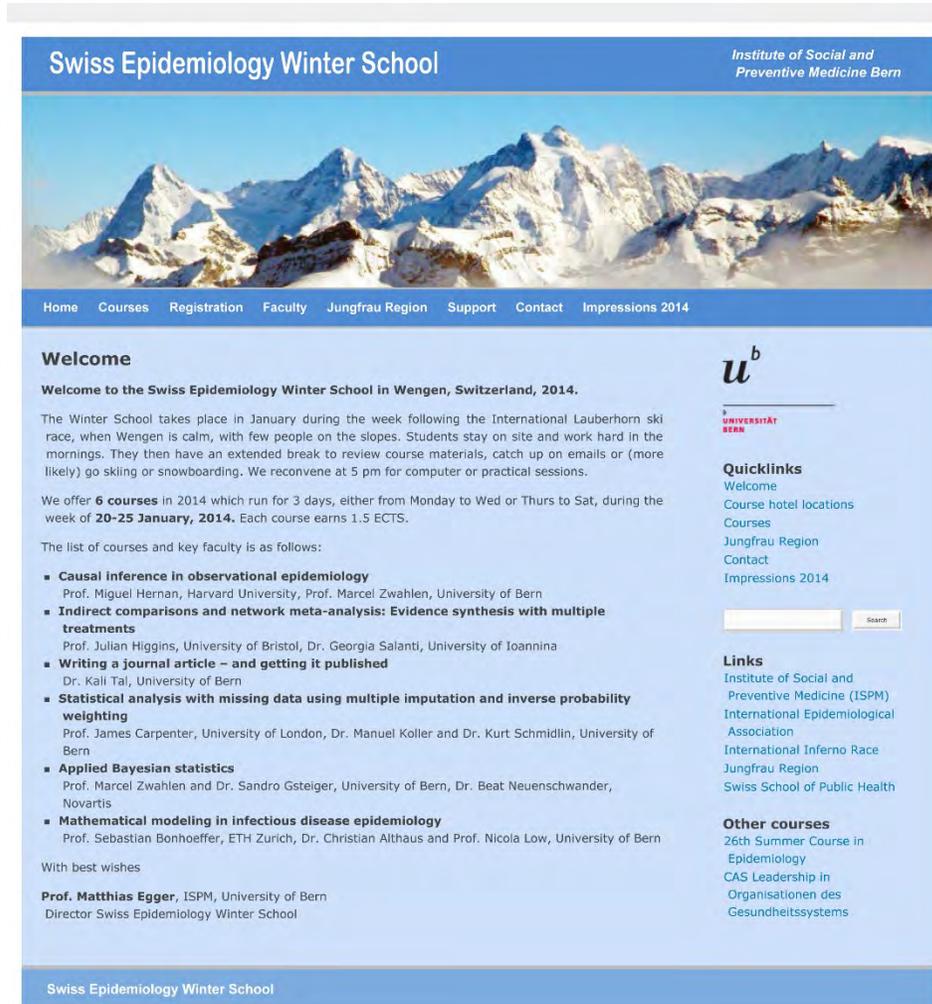
Competing Interests: The authors have declared that no competing interests exist.

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



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



Swiss Epidemiology Winter School Institute of Social and Preventive Medicine Bern

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Welcome

Welcome to the Swiss Epidemiology Winter School in Wengen, Switzerland, 2014.

The Winter School takes place in January during the week following the International Lauberhorn ski race, when Wengen is calm, with few people on the slopes. Students stay on site and work hard in the mornings. They then have an extended break to review course materials, catch up on emails or (more likely) go skiing or snowboarding. We reconvene at 5 pm for computer or practical sessions.

We offer **6 courses** in 2014 which run for 3 days, either from Monday to Wed or Thurs to Sat, during the week of **20-25 January, 2014**. Each course earns 1.5 ECTS.

The list of courses and key faculty is as follows:

- **Causal inference in observational epidemiology**
Prof. Miguel Hernan, Harvard University, Prof. Marcel Zwahlen, University of Bern
- **Indirect comparisons and network meta-analysis: Evidence synthesis with multiple treatments**
Prof. Julian Higgins, University of Bristol, Dr. Georgia Salanti, University of Ioannina
- **Writing a journal article – and getting it published**
Dr. Kali Tal, University of Bern
- **Statistical analysis with missing data using multiple imputation and inverse probability weighting**
Prof. James Carpenter, University of London, Dr. Manuel Koller and Dr. Kurt Schmidlin, University of Bern
- **Applied Bayesian statistics**
Prof. Marcel Zwahlen and Dr. Sandro Gsteiger, University of Bern, Dr. Beat Neuenschwander, Novartis
- **Mathematical modeling in infectious disease epidemiology**
Prof. Sebastian Bonhoeffer, ETH Zurich, Dr. Christian Althaus and Prof. Nicola Low, University of Bern

With best wishes

Prof. Matthias Egger, ISPM, University of Bern
Director Swiss Epidemiology Winter School

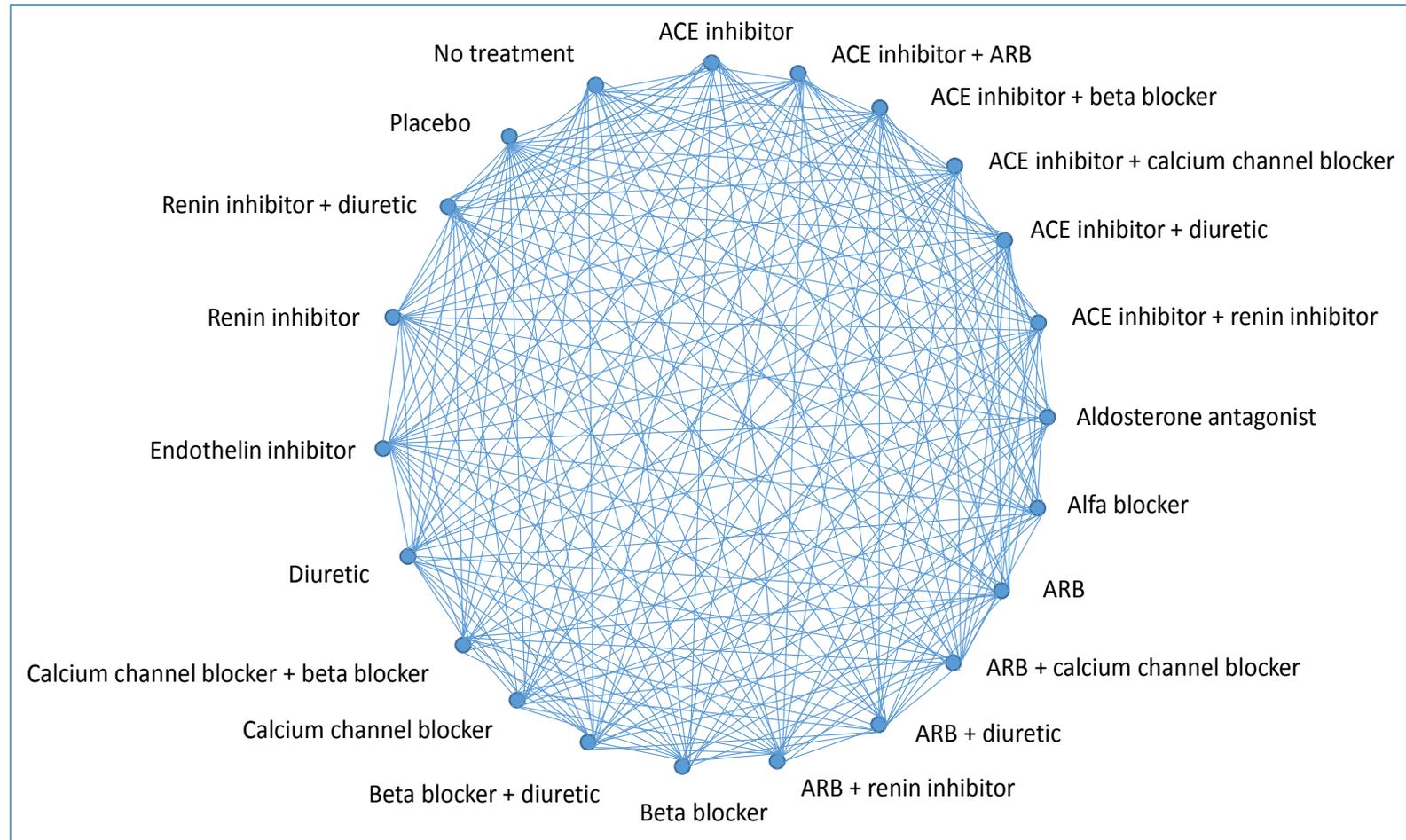
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Other courses
26th Summer Course in Epidemiology
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Questions?



Network diagram for my next network meta-analysis