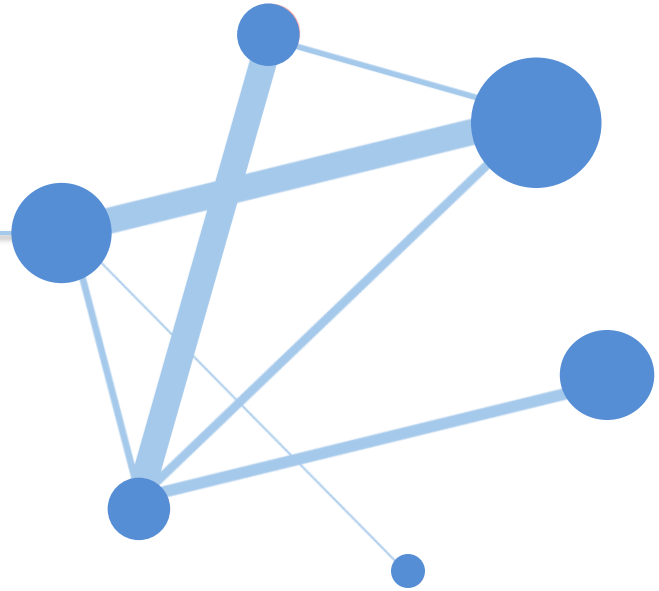
A gentle introduction to network meta-analysis. Current state and future challenges



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Some basics about this presentation

- We are interested in research questions of the type

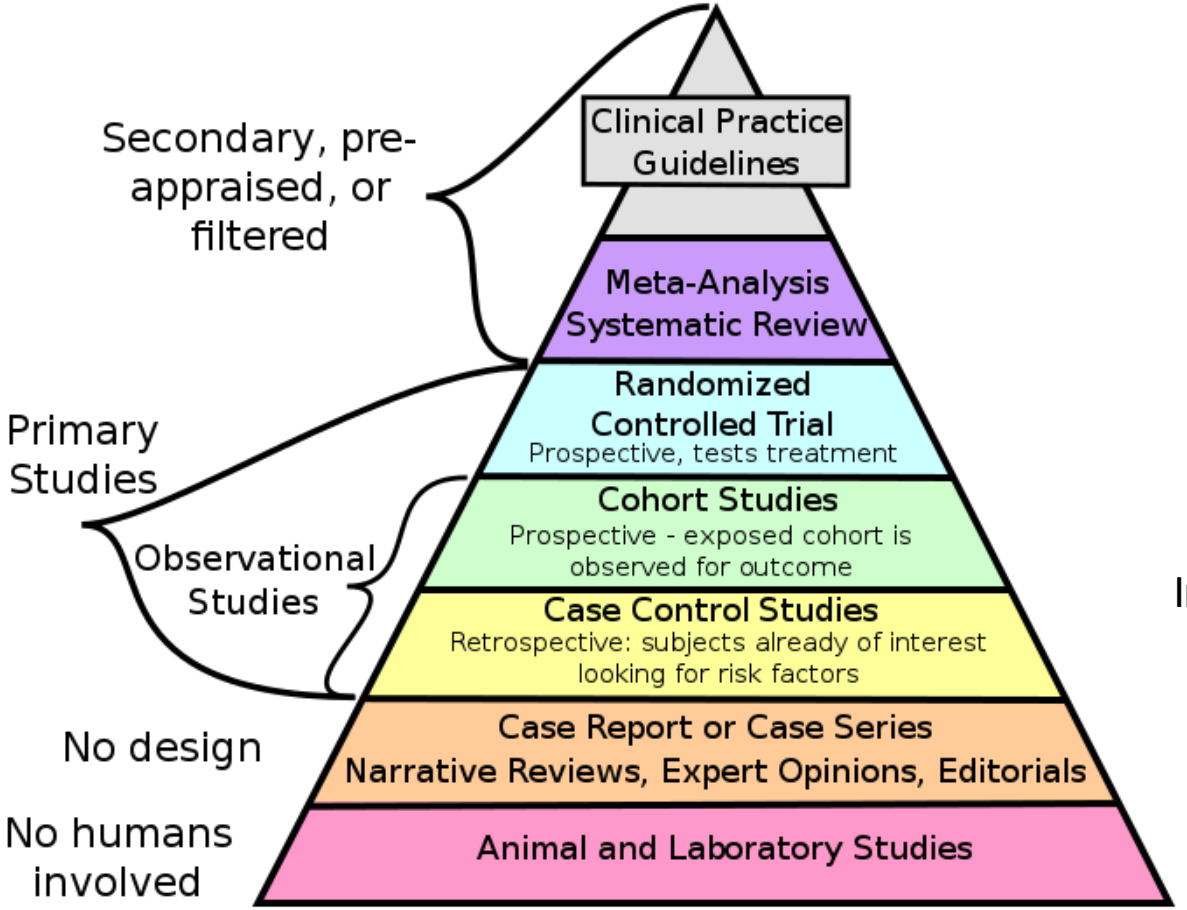
Does this intervention work for improving this outcome in this population (intervention studies)

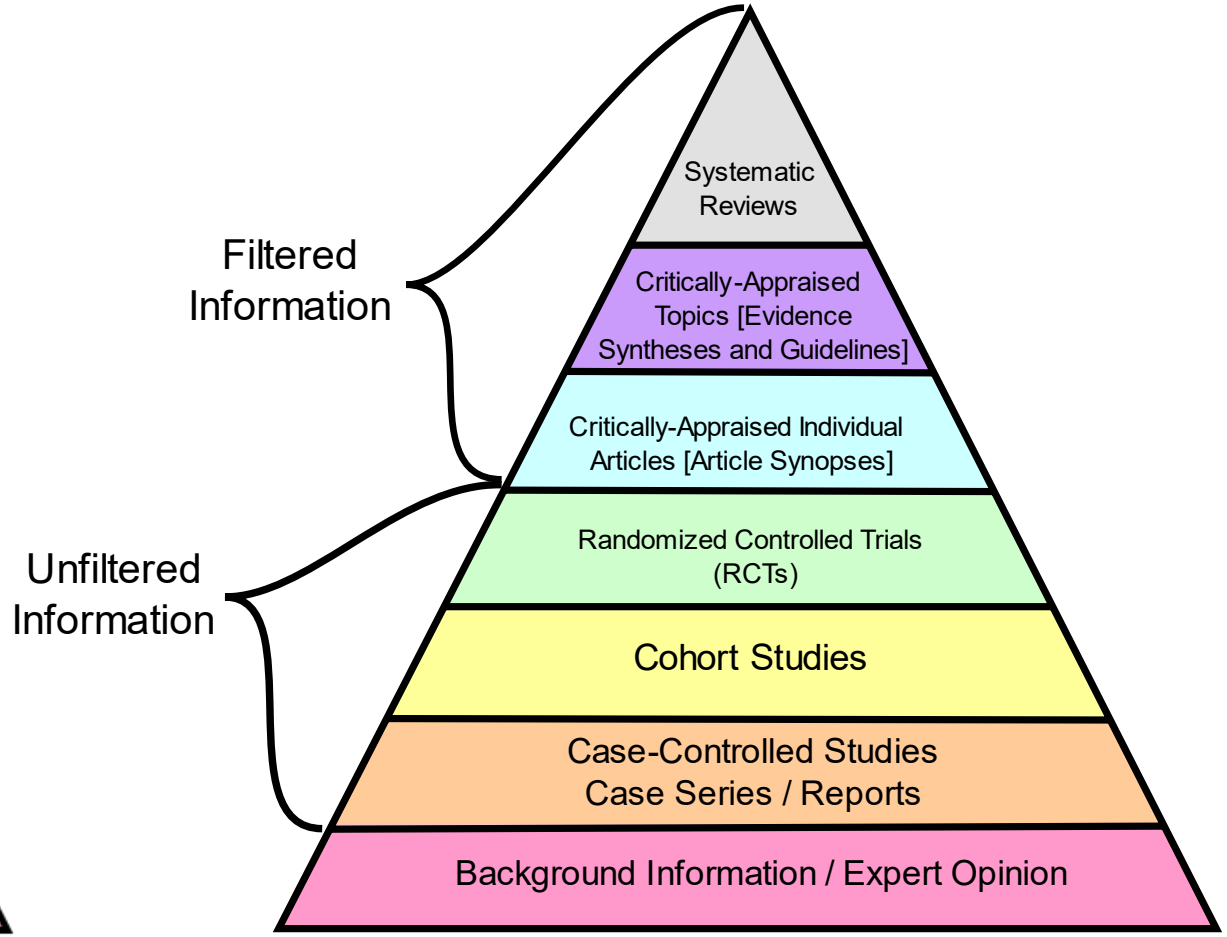
- We have an intervention arm/group and a control arm/group (could have more).
- We have several studies addressing this research question and we want to synthesize quantitatively their findings
- Typically, studies give aggregate data (means, standard deviations, number of events, sample sizes per arm)
- Or could give an effect size and its standard error.
- We may have access to Individual Participant Data (IPD), that is the actual outcome and covariate values for each individual in each study. This is not very common.

PICO criteria

P = POPULATION
I = INTERVENTION
C = COMPARISON
O = OUTCOME

Hierarchy of Evidence





https://en.wikipedia.org/wiki/Hierarchy_of_evidence

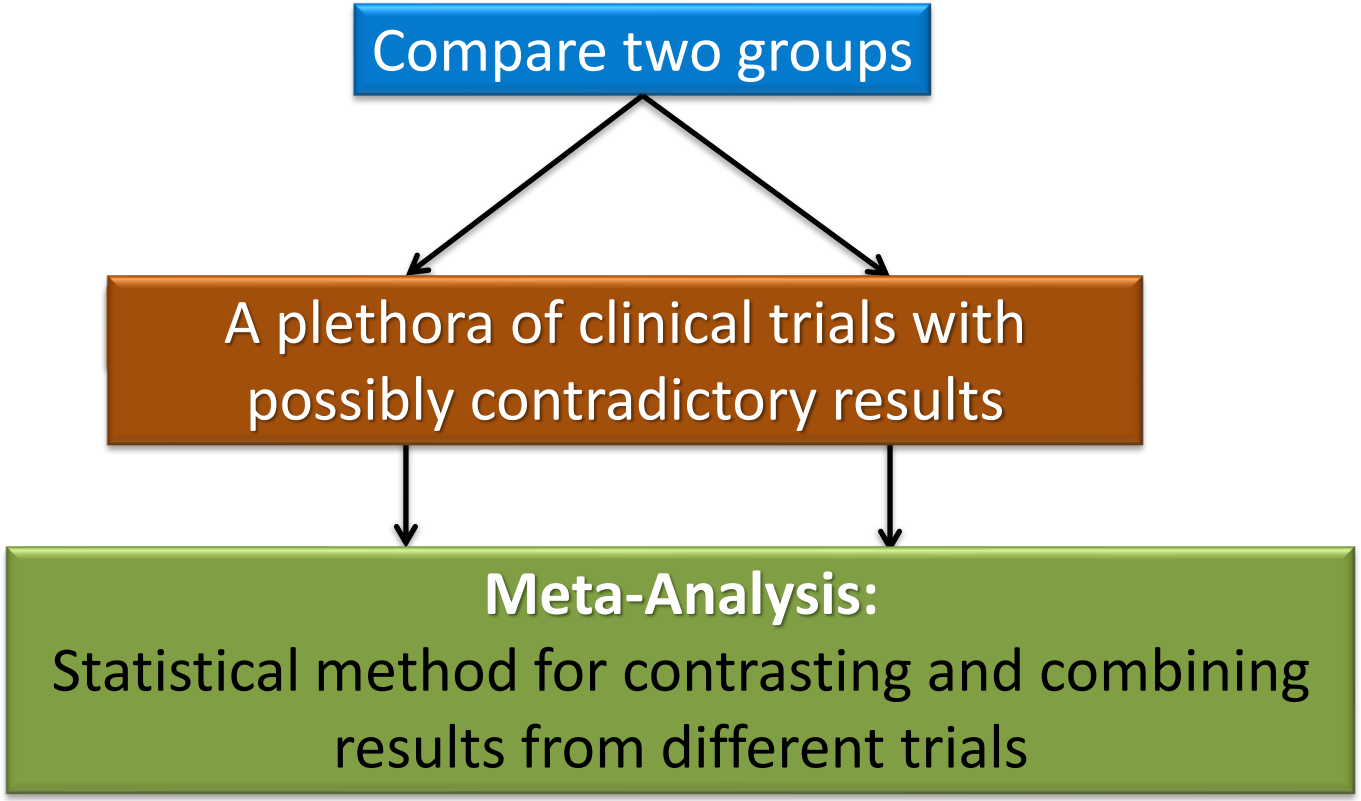
Cochrane Handbook for Systematic Review of Interventions

1. Forming the research question, inclusion and exclusion criteria (part 2, chapters 1,2,3)
2. Search and selection of relevant studies part 2, chapter 4)
3. Data collection (part 2,chapter 5)
4. Risk of Bias assessment (part 2, chapters 7,8,13)
5. Synthesis of results (part 2, chapters 6,9,10 possibly 11,12)
6. Interpretation (part 2, chapters 14, 15)

Available here: https://training.cochrane.org/handbook/current

Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.5 (updated August 2024). Cochrane, 2024. Available from www.training.cochrane.org/handbook.

Intravenous administration of streptokinase for patients with myocardial infarction (outcome:mortality)



A well-known example

- Since 1970 there were multiple RCTs (5000 in total), whose synthesis would have clearly shown the beneficial effect of streptokinase
- We had to wait for an extra decade and randomize an extra 30K patients before adopting administration of streptokinase in practice.

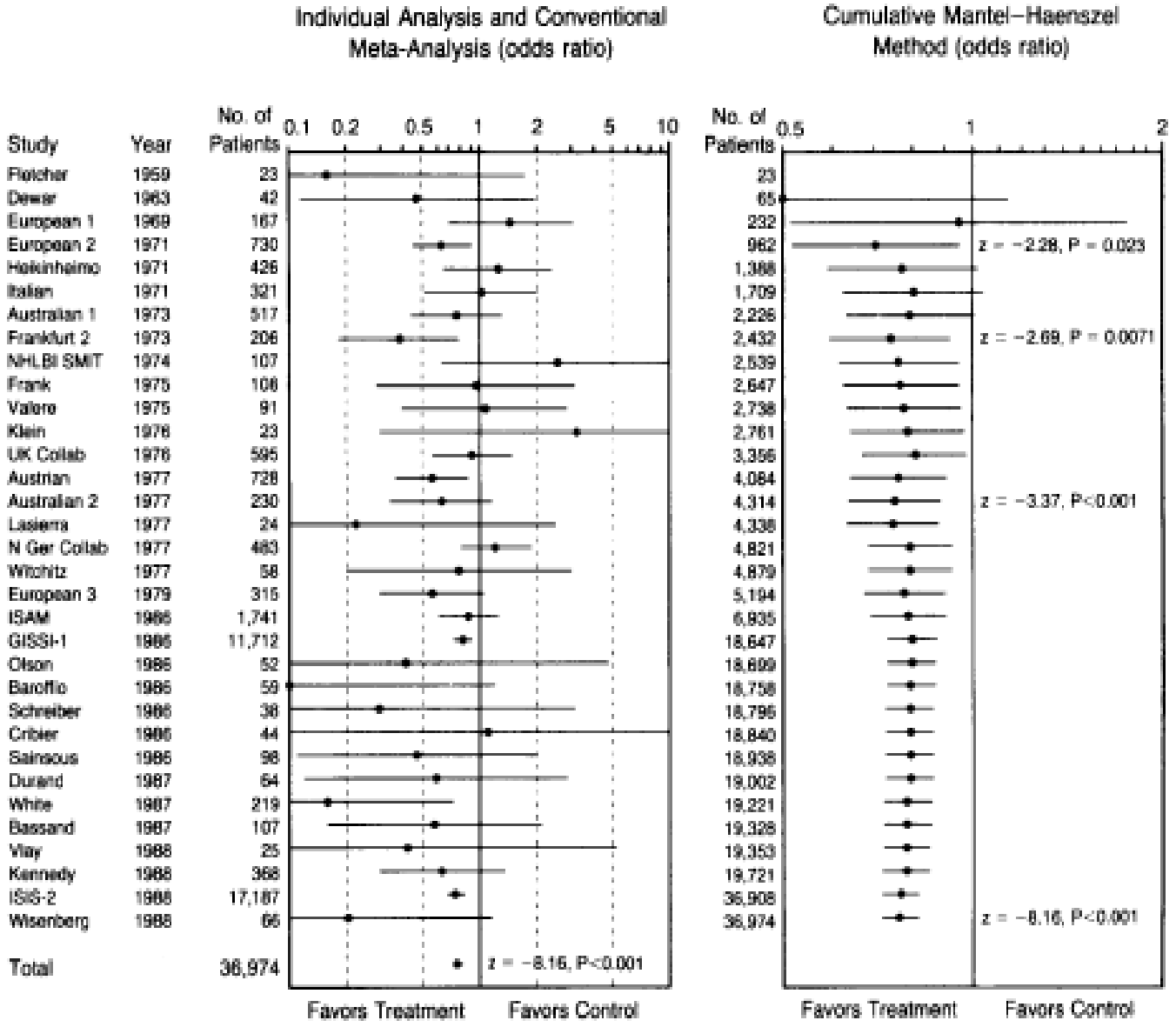


Figure 1. Conventional and Cumulative Meta-Analyses of 33 Trials of Intravenous Streptokinase for Acute Myocardial Infarction. The odds ratios and 95 percent confidence intervals for an effect of treatment on mortality are shown on a logarithmic scale. A bibliography of the published trial reports is available from the authors.

Lau J et al. 1992. Cumulative meta-analysis of therapeutic trials for myocardial infarction. New England Journal of Medicine 327(4): 248-254

Anxiety disorder in children and adolescents

- 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.

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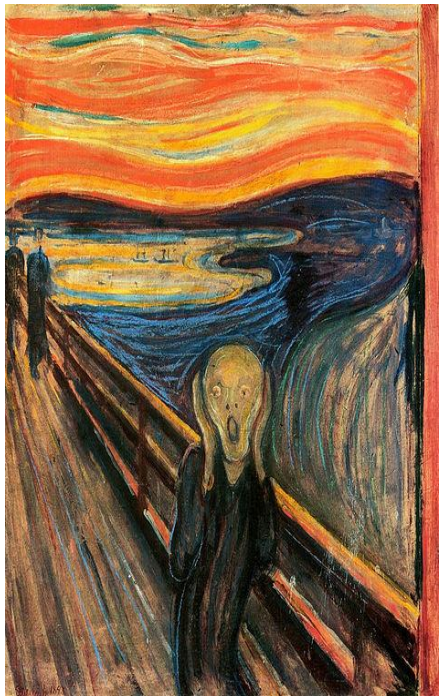
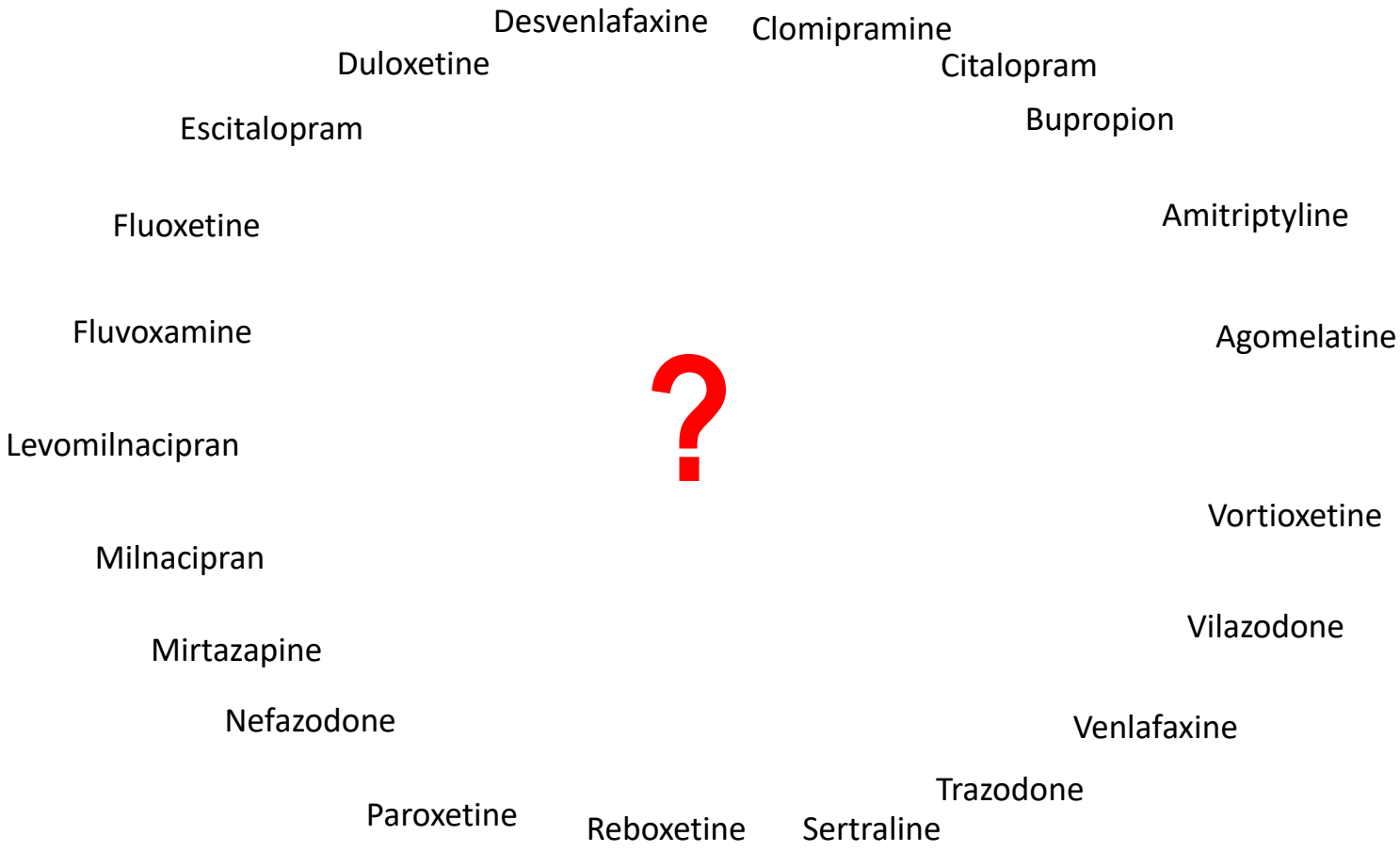


21 new generation antidepressants



Cipriani, Andrea et al. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis The Lancet, Volume 391, Issue 10128, 1357 - 1366

21 new generation antidepressants

Hundreds of meta-analyses have been published

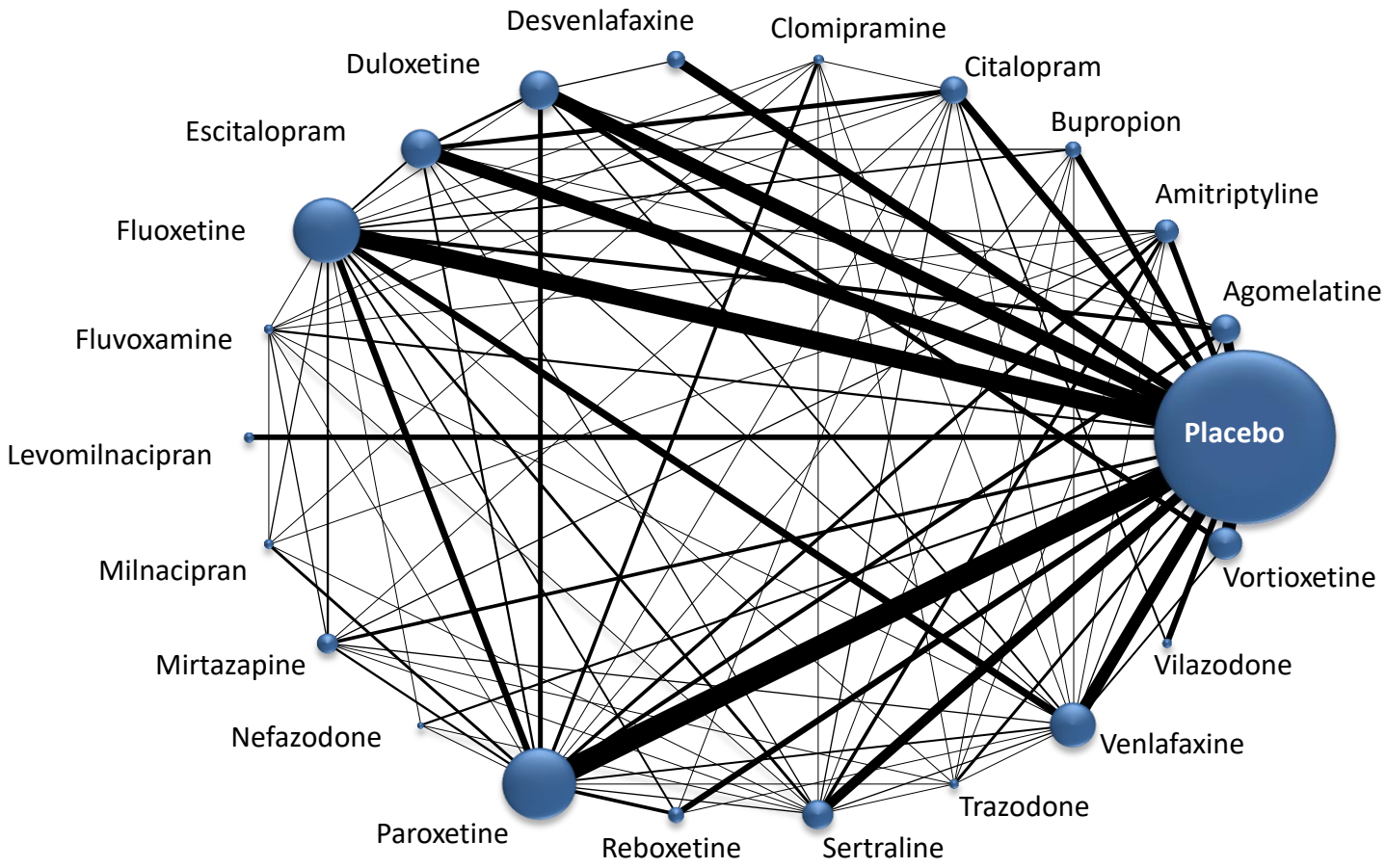
"Although Mirtazapine is likely to have a faster onset of action than Sertraline and Paroxetine no significant differences were observed..."

"...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"

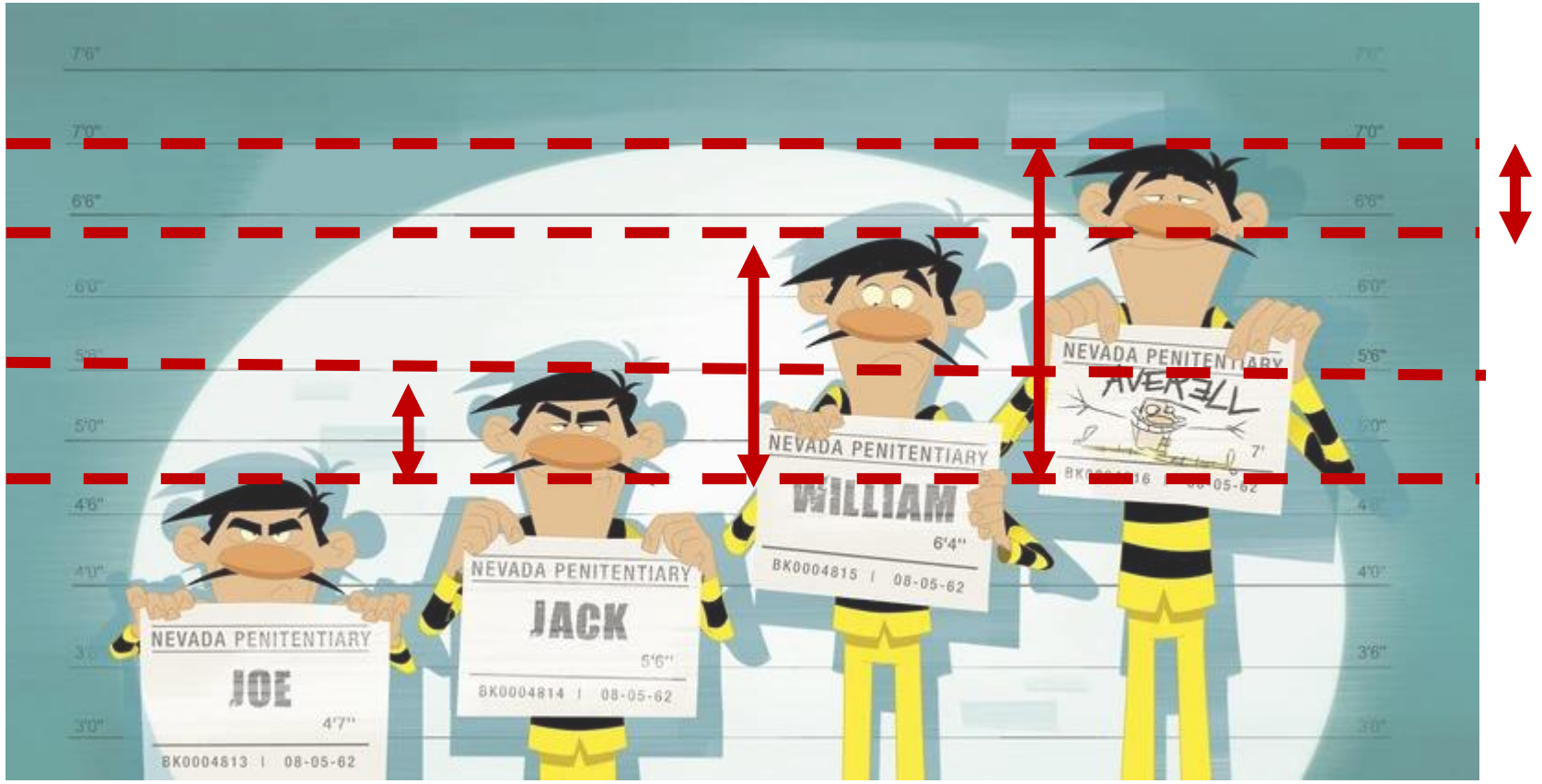
Network plot



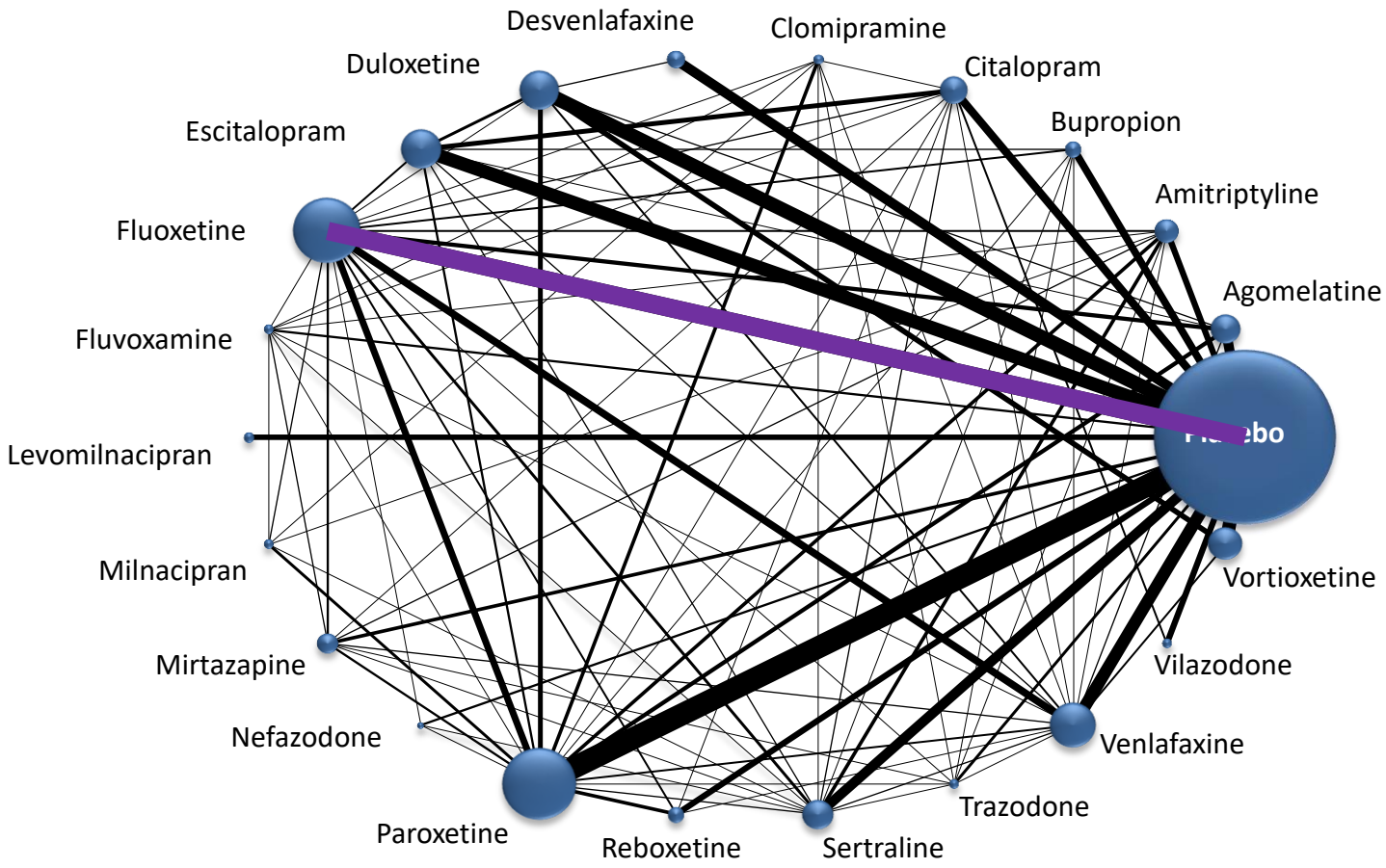
Cipriani, Andrea et al. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis The Lancet, Volume 391, Issue 10128, 1357 - 1366

Indirect comparisons

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

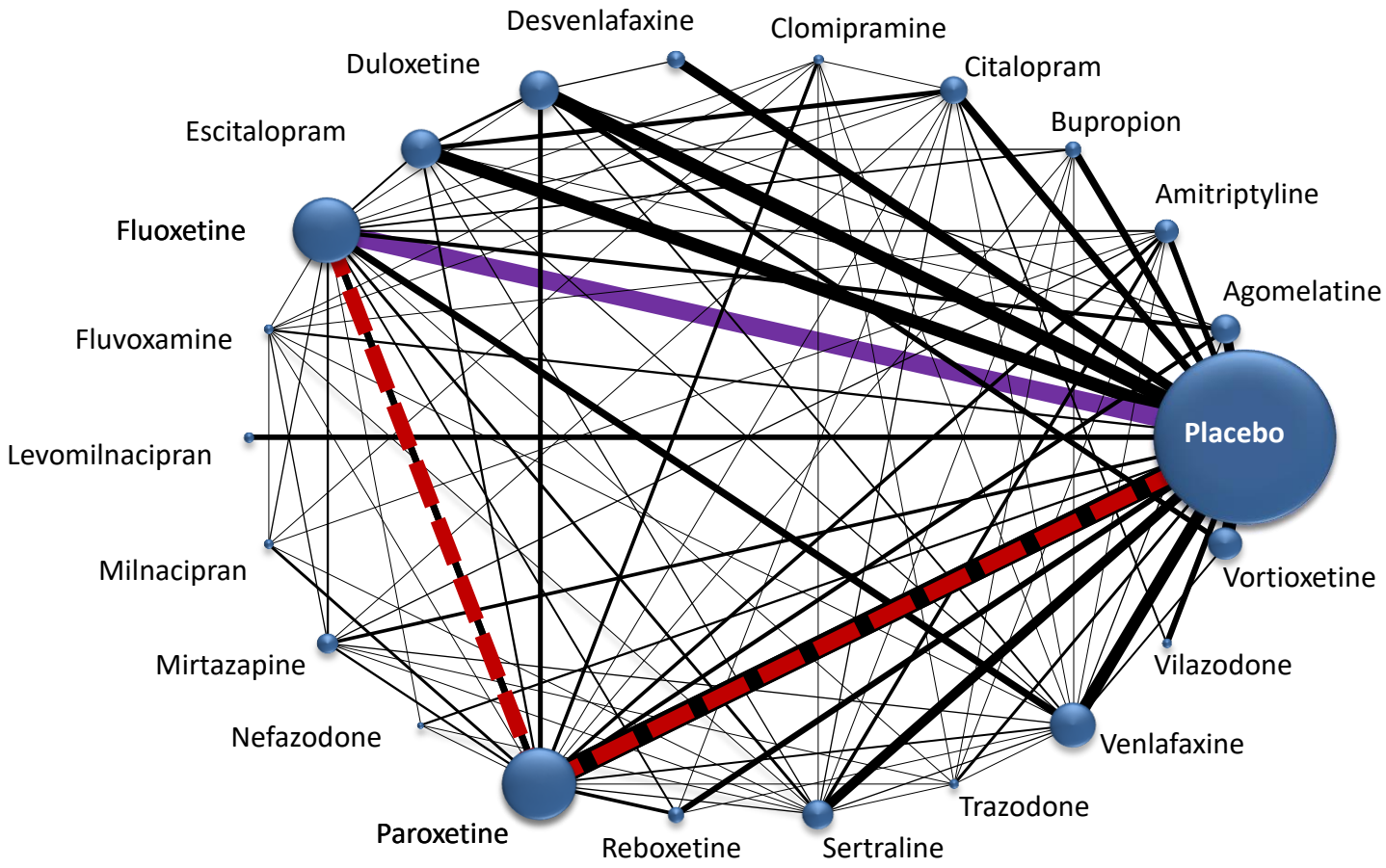


Network plot



Cipriani, Andrea et al. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis The Lancet, Volume 391, Issue 10128, 1357 - 1366

Indirect routes in the network



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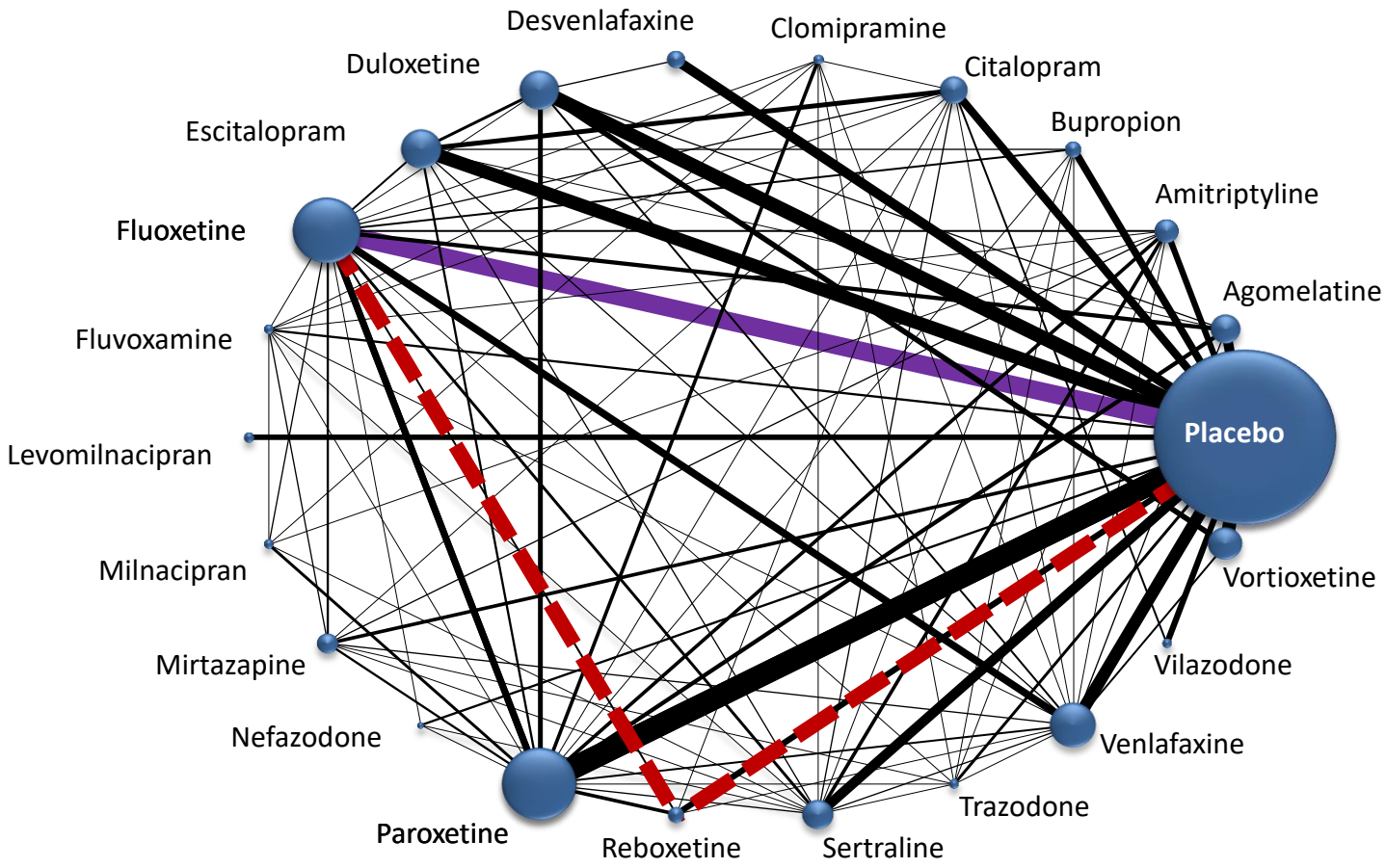

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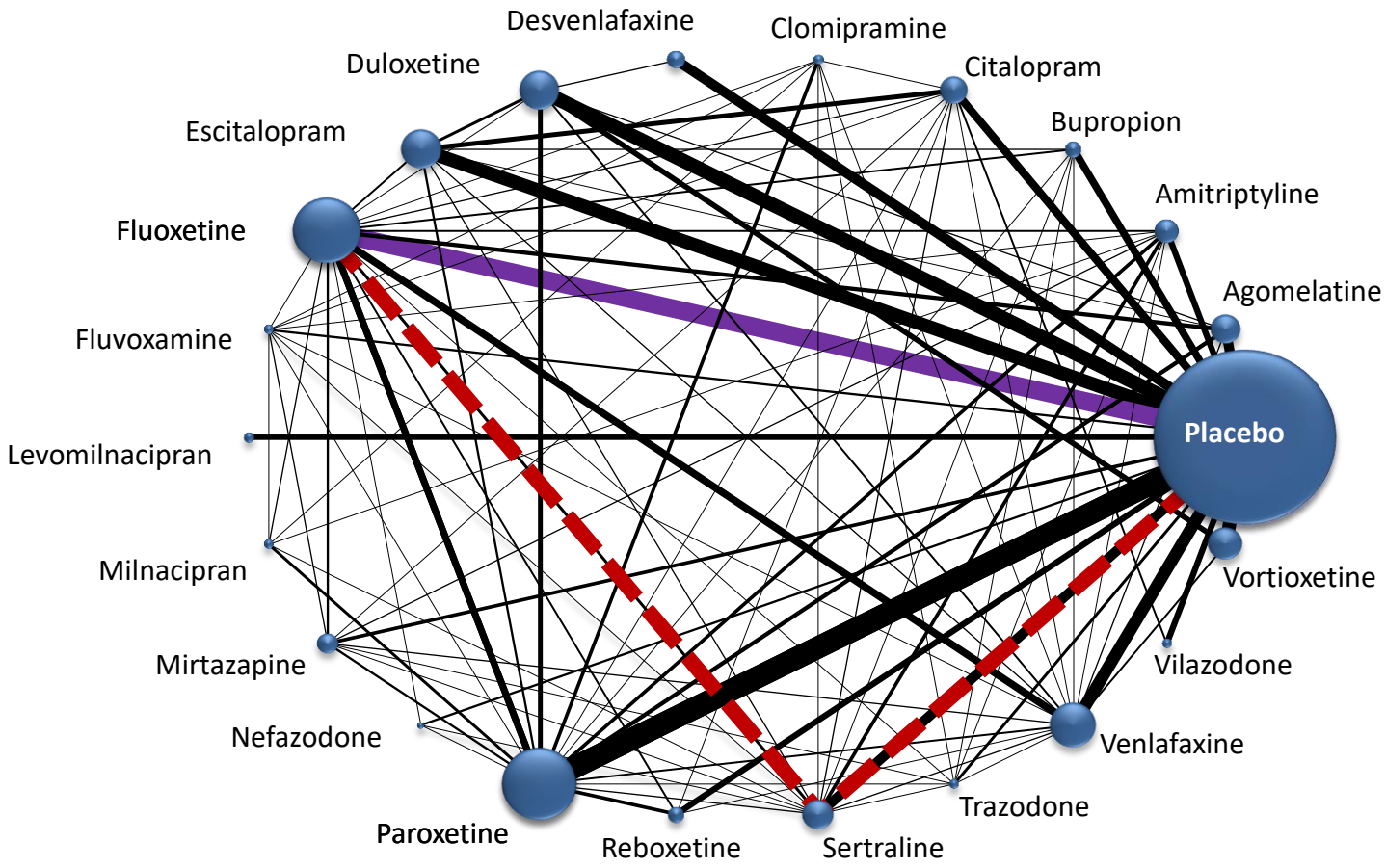
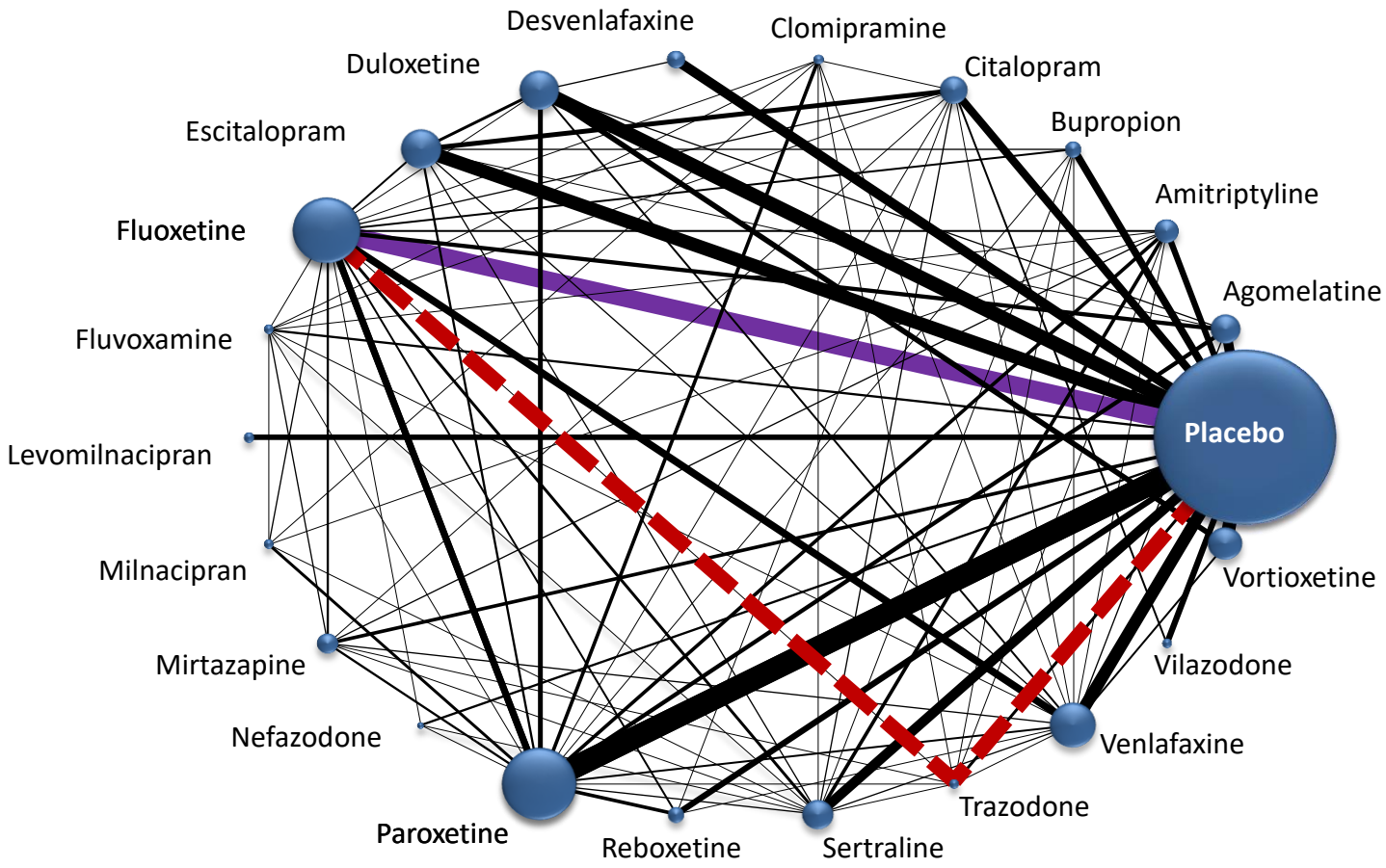


Indirect routes in the network



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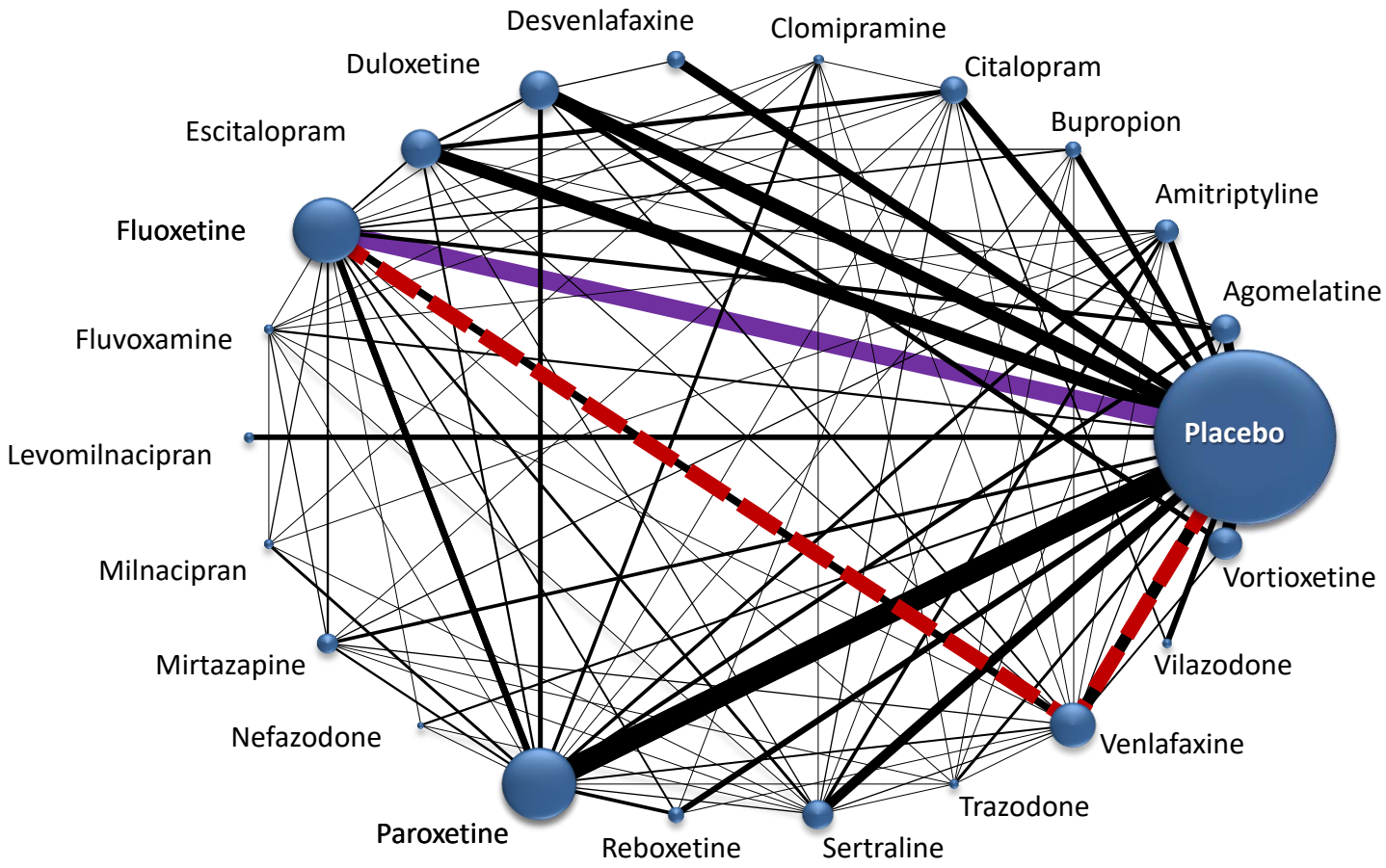
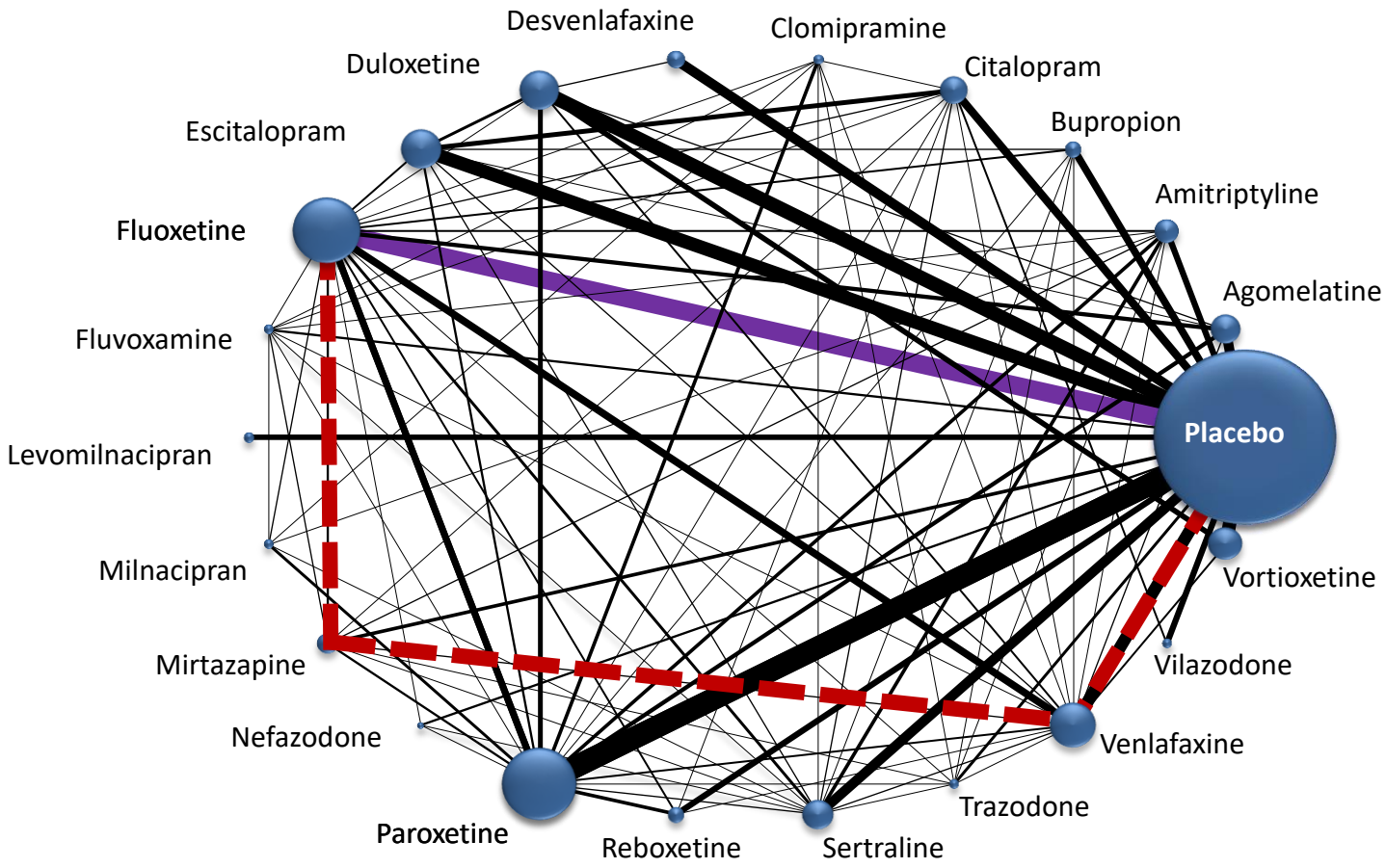


Indirect routes in the network



Network meta-analysis (NMA)

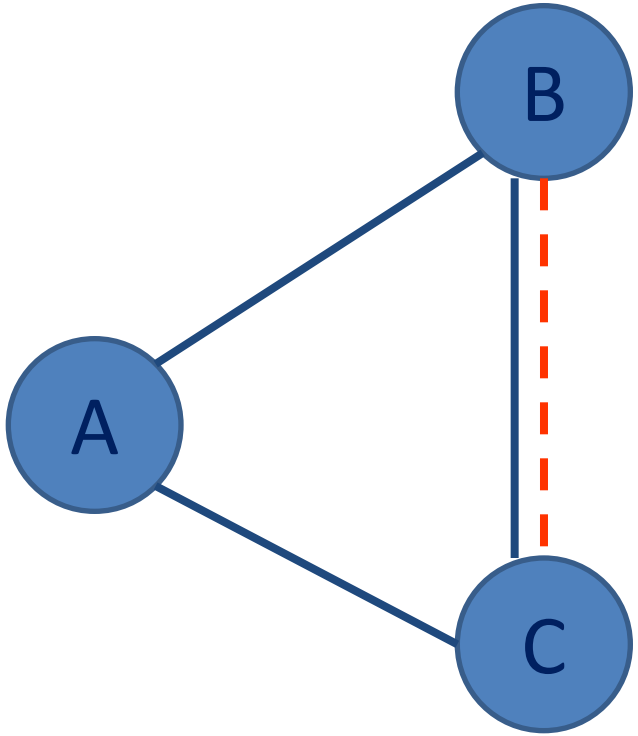
- Synthesizes both direct and indirect evidence
- Allows estimating the relative effectiveness between interventions that have never been compared to each other
- Provides a ranking of competing interventions
- NMA, like any statistical model, requires some background assumptions
- Incorrect assumptions can generate inaccurate conclusions

NMA assumption
Transitivity/Similarity/Exchangeability

It requires that distribution of effect modifiers is similar across treatment comparisons (Salanti 2012)

Most often it is an untestable assumption…because there are few studies per comparison

…but you can evaluate clinically and epidemiologically its plausibility.



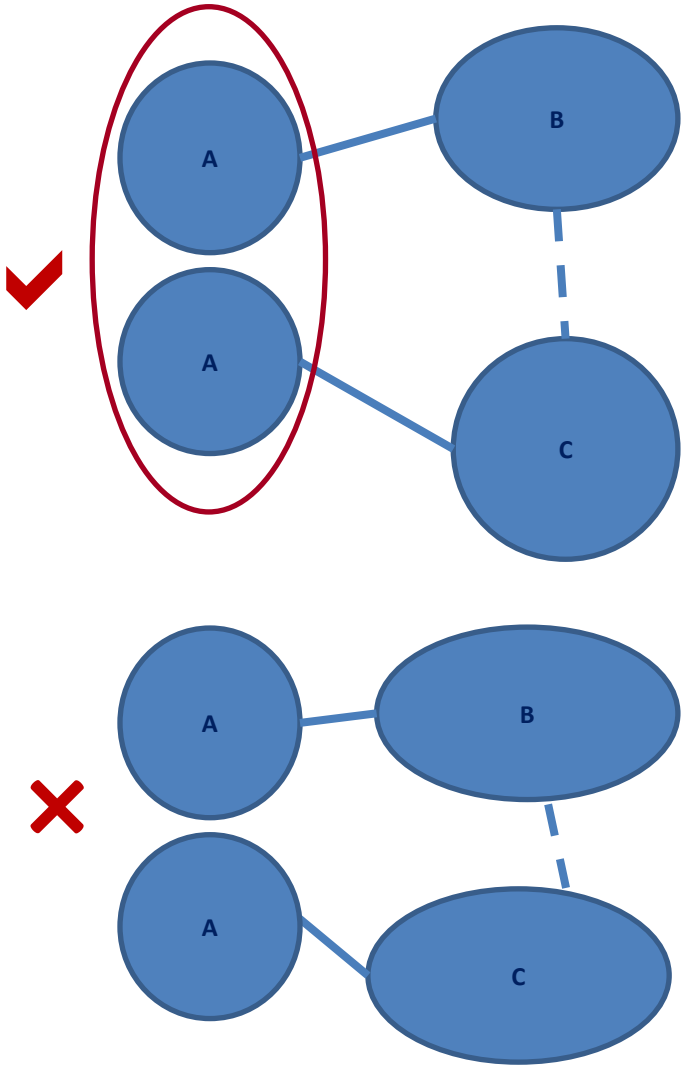
Consistency equation

$$\mu_{BC}^{DIR} = \mu_{BC}^{IND}$$

$$\mu_{BC}^{DIR} = \mu_{AC}^{DIR} - \mu_{AB}^{DIR}$$

- *Ades AE, Welton NJ, Dias S, Phillippo DM, Caldwell DM. Twenty years of network meta-analysis: Continuing controversies and recent developments. Res Synth Methods. 2024 Jan 18. doi: 10.1002/jrsm.1700.*
- *Salanti G. Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence synthesis tool. Research Synthesis Methods. 2012 3 (2): 80.*

Definition of treatments



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

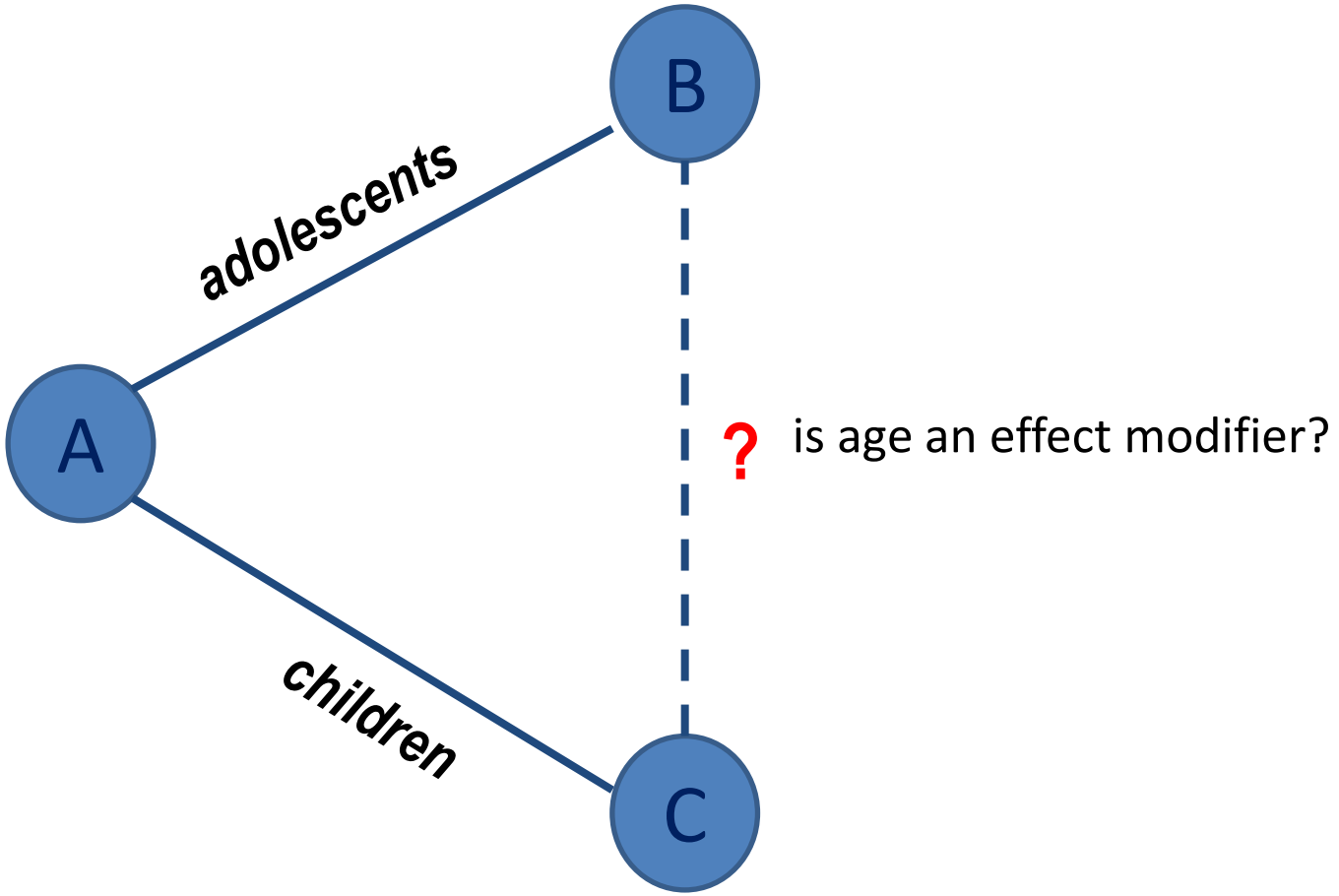
What if A is given in different forms/ mechanism?

e.*g. injection vs. pill*

placebo pill vs. placebo psychotherapy/exercise

Treatments should be **similarly defined** across different treatment comparisons

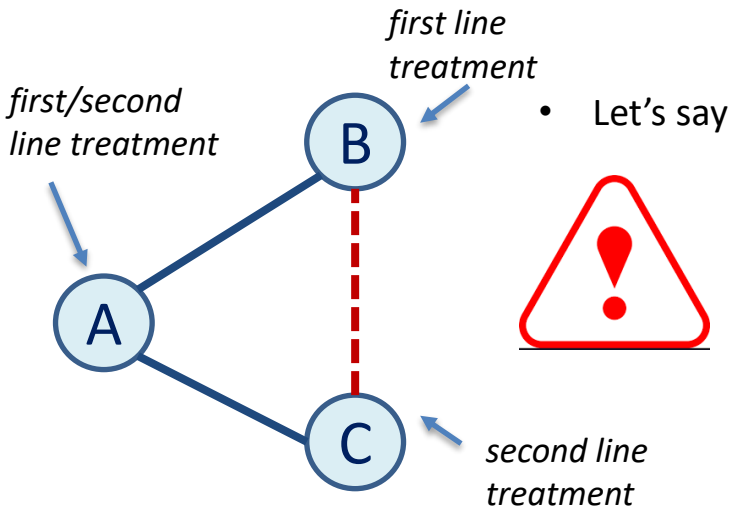
Validity of indirect comparisons



- Specify a-priori a few effect modifiers
- Transitivity requires that the distributions of effect modifiers is similar across treatment comparisons

Transitivity

- Transitivity assumes that all interventions are "jointly randomizable".
  In principle, all participants could have been randomized to any of the available interventions
- This consideration is a fundamental one and should be addressed when building the evidence network
- The assumption of transitivity could be violated if interventions have different indications.

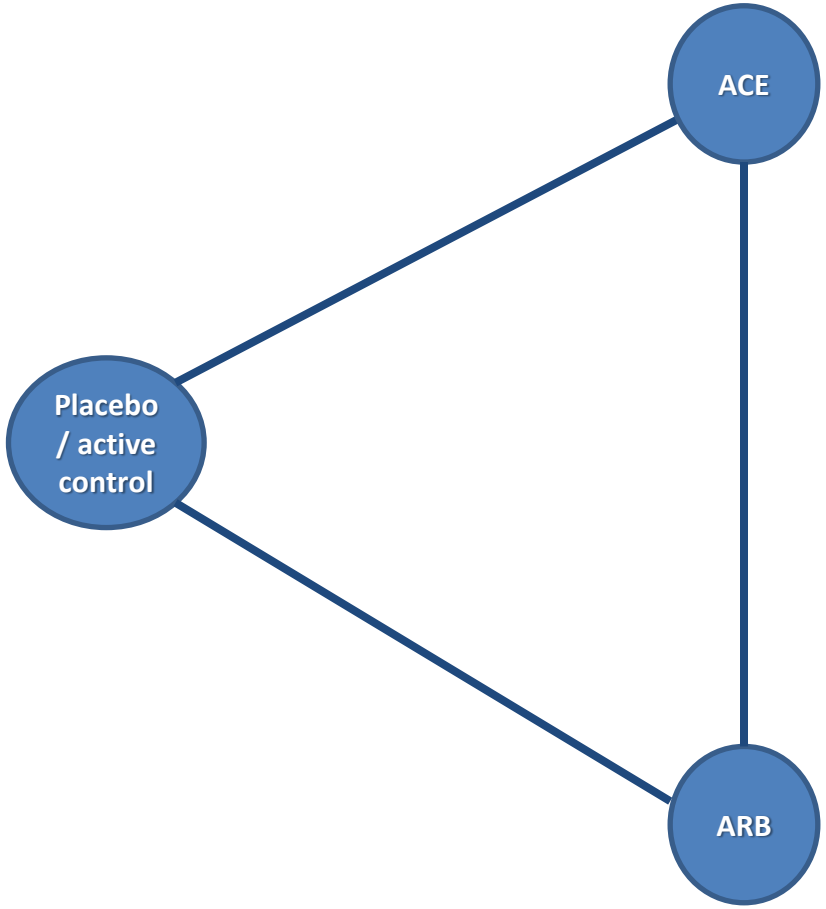


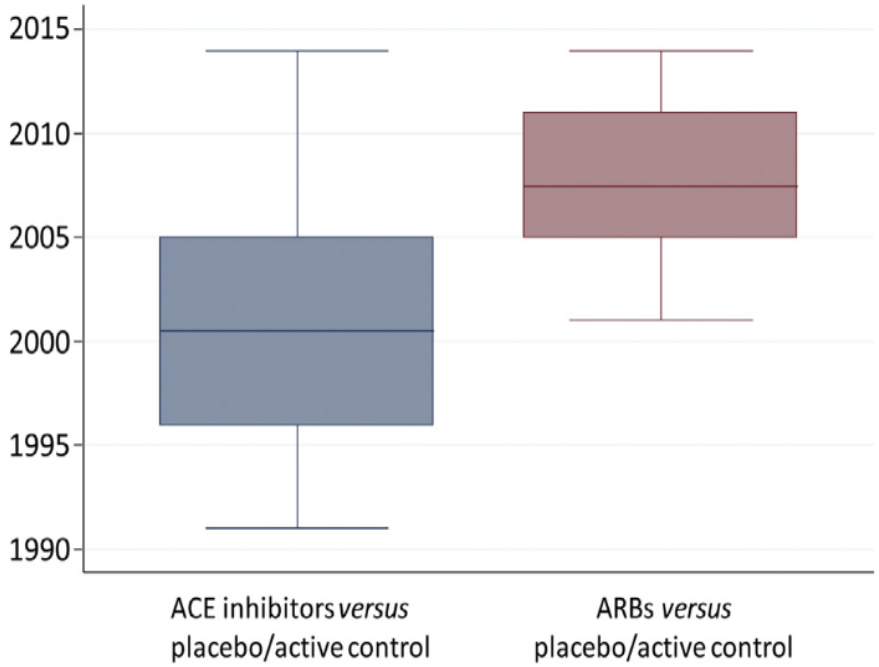
- Let's say A, B, C are chemotherapy regimens

We cannot assume that participants in an AB trial could have been randomized in an AC trial!

All participants in the network are eligible for all interventions –
assigning an intervention does not depend on participants' characteristics

Poor overlap in time





Mavridis D, Palmer SC, Strippoli GF. Comparative Superiority of ACE Inhibitors Over Angiotensin Receptor Blockers for People With CKD: Does It Matter? Am J Kidney Dis. 2016 May;67(5):713-5. doi: 10.1053/j.ajkd.2016.02.031.

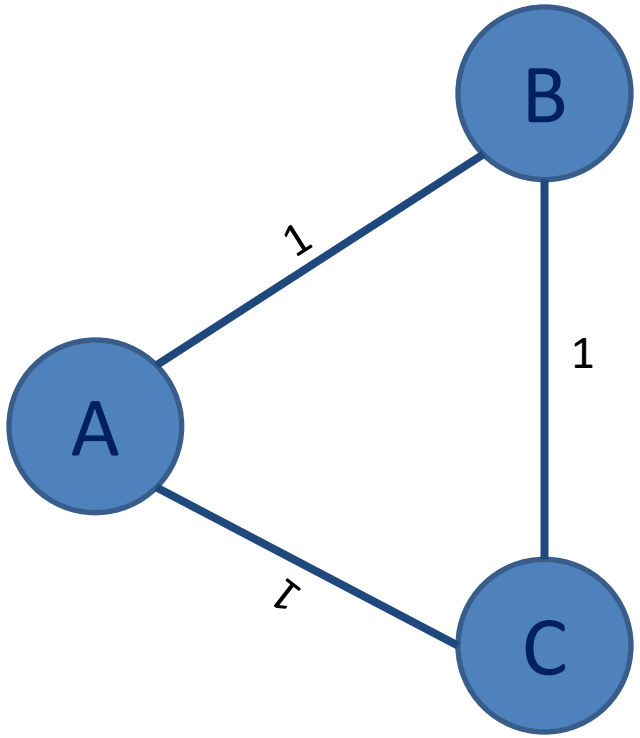
In a nutshell, transitivity requires

- Similar distribution of effect modifiers across treatment comparisons
- Similar definition of nodes across treatment comparisons
- Interventions are missing for reasons that are not related to their efficacy (missing completely at random)
- Difficult to defend when interventions do not overlap chronologically
- All participants could have been randomized to any of the available treatments

NMA model – a weighted regression model

Consistency equation

$$\mu_{BC} = \mu_{AC} - \mu_{AB}$$



Each study gives an effect size y and its standard error s

$$\begin{pmatrix} y_{1,AB} \\ y_{2,AC} \\ y_{3,BC} \end{pmatrix} = \begin{pmatrix} 1 & 0 \\ 0 & 1 \\ -1 & 1 \end{pmatrix} \times \begin{pmatrix} \mu_{AB} \\ \mu_{AC} \end{pmatrix} + \begin{pmatrix} \delta_1 \\ \delta_2 \\ \delta_3 \end{pmatrix} + \begin{pmatrix} \varepsilon_1 \\ \varepsilon_2 \\ \varepsilon_3 \end{pmatrix}$$

$$\boldsymbol{y} = \mathbf{X}\boldsymbol{\mu} + \boldsymbol{\delta} + \boldsymbol{\epsilon}$$

$$\boldsymbol{\epsilon} \sim N\left(\mathbf{0}, \boldsymbol{\Sigma} = diag(\boldsymbol{s^2})\right)$$

$$\boldsymbol{s^2} = \left(s^2_{1,AB}, s^2_{2,AC}, s^2_{3,BC}\right)'$$

$$\boldsymbol{\delta} \sim N(\mathbf{0}, \boldsymbol{\Delta} = diag(\tau^2))$$

- We assume a common τ^2 across treatment comparisons
- With T interventions, there are $\binom{T}{2} = \frac{T \times (T-1)}{2}$ effect estimates , we estimate $T - 1$ effect sizes and the between-study (heterogeneity) variance τ^2

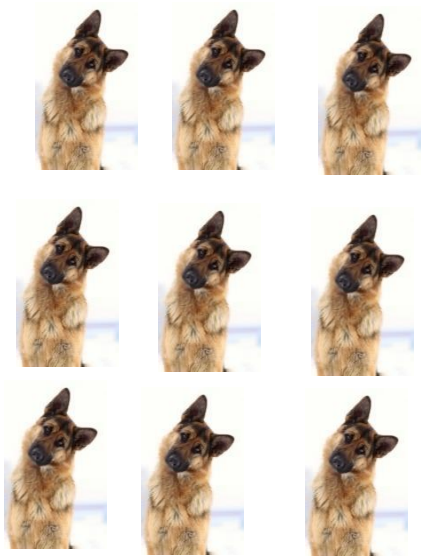
Randomized (RCTs) and non-randomized evidence (NRE)

Randomized clinical trials (RCTs) are considered the gold standard

Efficacy refers to how well an intervention performs under ideal conditions

Effectiveness refers to how well an intervention performs in everyday life

RCTs

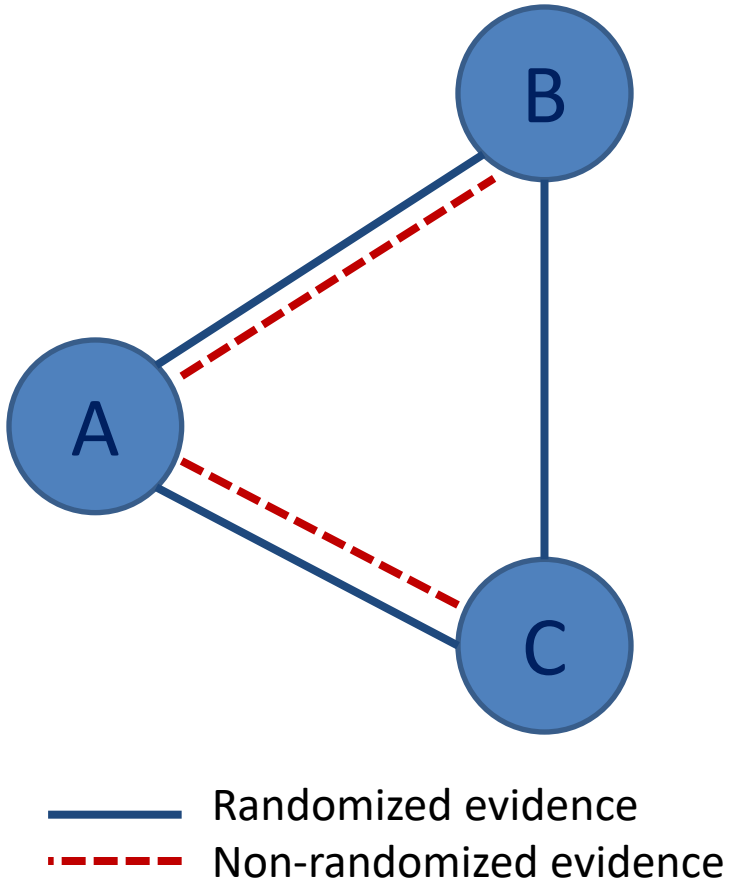


Real world

RCTs: minimize bias due to confounding but
-aim at efficacy, not effectiveness
-large internal but low external validity
- more homogeneous participants (e.g., multimorbid patients, children, pregants, elderly, immigrants are excluded)
- small follow-up period, not helpful for long-term and rare outcomes
-not all interventions can be randomized
- costly
- few trials, small sample sizes and number of events, very imprecise effects.

Three broad categories of statistical models
1) Design-adjusted analysis (estimates from NRE are adjusted for bias and overprecision)
2) Using informative priors (NRE is used to inform results from RCTs)
3) Three-level hierarchical models (NRE and RCTs are analyzed separately and then pooled together)

Using non-randomized evidence as prior information



- Common approaches include adding a bias term and downweighing to increase uncertainty

$$\mu_{XY} \sim N\left(\mu_{XY}^{NRE} + \zeta, \frac{var(\mu_{XY}^{NRE})^2 + \tau^2}{a}\right)$$

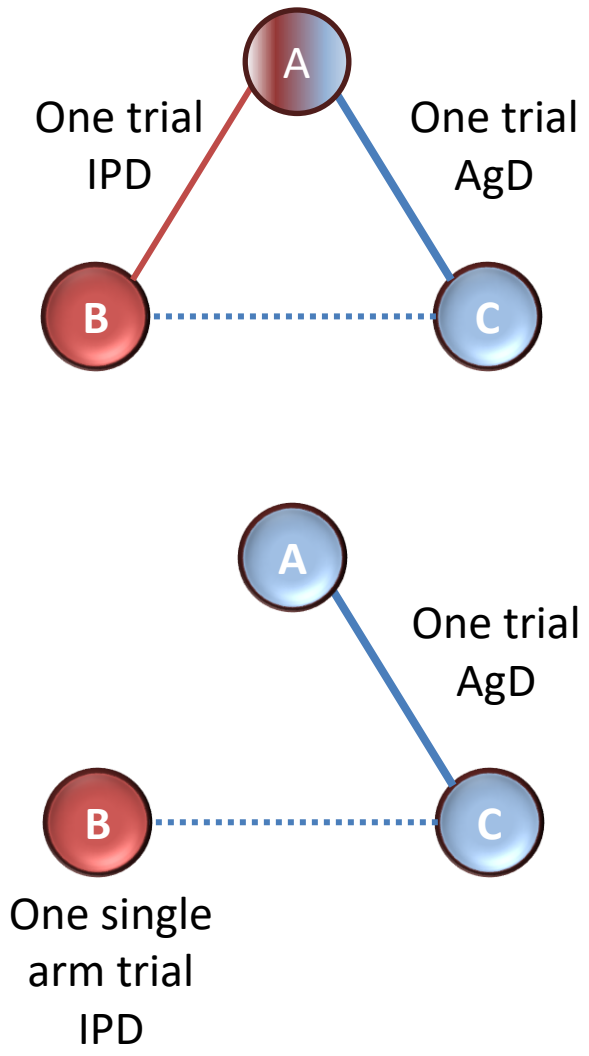
$$\alpha \in [0,1]$$

- Power prior approach

$$f(\mu|\mathrm{RCT}, \mathrm{NRE}) \propto L(\mu|RCT) \times L(\mu|NRE)^{\alpha} \times f(\mu)$$

- Very helpful when we have studies with rare events
- Inform parameters using expert opinion, external data or conduct sensitivity analysis

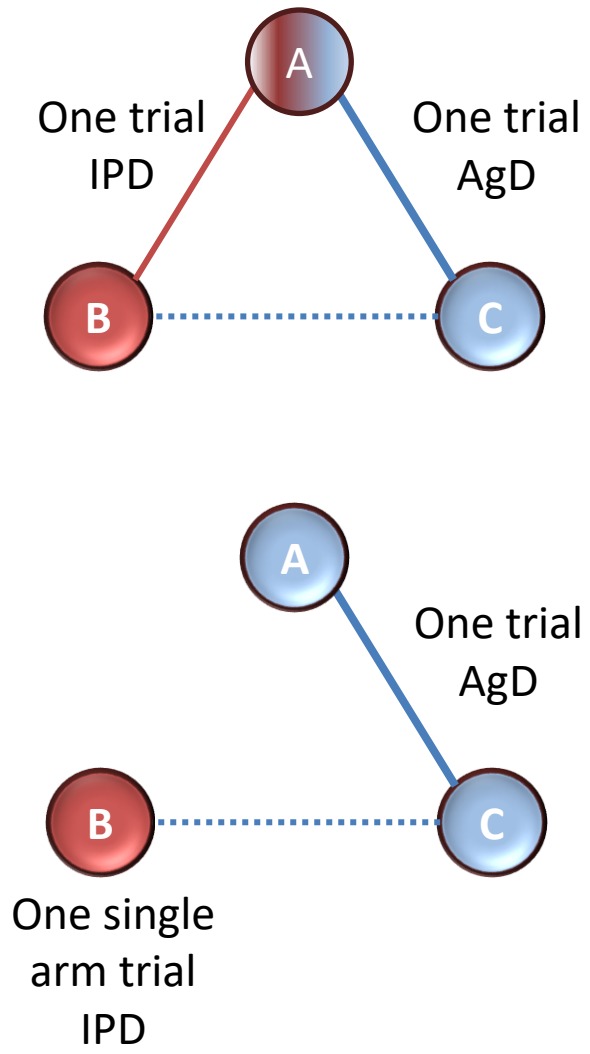
Population adjustment methods and single-arm trials



$$\mu_{BC} = \mu_{AC} - \mu_{AB}$$

- Suppose that transitivity is violated
- Population adjustment methods (Matching Adjusted Indirect Comparison - MAIC, Simulated Treatment Comparison - STC, MultiLevel Network Meta Regression - ML-NMR) are used when there are concerns about the similarity/transitivity assumption
- It is very common to have IPD in some trials and aggregate data (AgD) in others.
- A company has IPD for its own trial (AB trial or just B trial).
- Available aggregate data from the competitor's trial (AC trial).
- 44% of recent EMA oncology approvals are based on evidecne from single-arm trials.
- We adjust the imbalance to get an unbiased relative treatment effect estimate for B vs C.

Matching Adjusted Indirect Comparison (MAIC)



- Identify patient baseline characteristics (effect modifiers or both effect modifiers and prognostic factors)
- Match the two trials according to averages of the baseline characteristics.
- This is achieved by re-weighting individual patients from the AB trial to match the mean baseline characteristics reported in the trial with aggregate data.

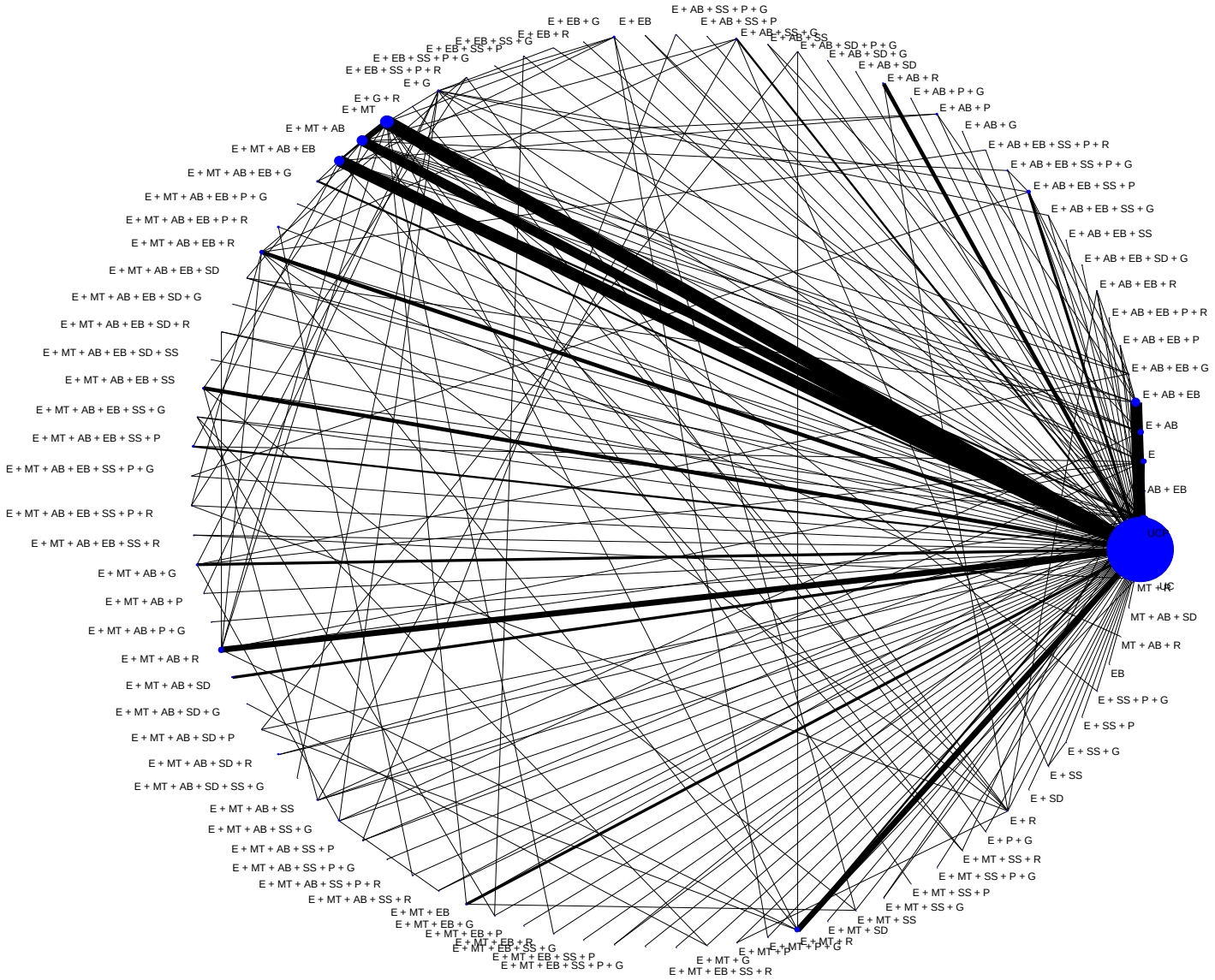
$$\mu_{BC} = \mu_{AC} - \mu^*_{AB}$$

μ^*_{AB} is the relative efficacy for B vs A after re-weighting

The μ_{BC} estimate refers to the AC population

Signorovitch JE, Wu EQ, Yu AP, et al. 2010. Comparative effectiveness without head-to-head trials a method for matching-adjusted indirect comparisons applied to psoriasis treatment with adalimumab or etanercept. Pharmacoeconomics. 2010;28:935–45

Multicomponent interventions



Abrev.	Component
AB	Action- based behavioural change techniques
E	Education
EB	Emotional- based behavioural change techniques
F	Face to Face
G	Group
I	Individual
M	Multidisciplinary
MT	Monitoring techniques
P	Peers and lay persons
R	Remote
SD	Shared decision making
SS	Social support
U	Use of external resources
UC	Usual Care
UCP	Usual Care Plus

Interest lies in estimating the components' effects

HISTORICAL REVIEW | Open Access

Twenty years of network meta-analysis: Continuing controversies and recent developments

This article relates to:

A. E. Ades, Nicky J. Welton, Sofia Dias, David M. Phillippo, Deborah M. Caldwell

First published: 18 January 2024 | https://doi.org/10.1002/jrsm.1700 | Citations: 16

Two decades of network meta-analysis: Roadmap to their applications and challenges

Areti Angeliki Veroniki, Ivan Florez, Brian Hutton, Sharon E. Straus, Andrea C. Tricco

Volume 15, Issue 5, Research Synthesis Methods | pages: 741-746 | First Published online: July 31, 2024

Network meta-analysis: Looping back

Thomas Lumley

Volume 15, Issue 5, Research Synthesis Methods | pages: 728-730 | First Published online: July 25, 2024

The use of fixed study main effects in arm-based network meta-analysis

Hans-Peter Piepho, Laurence V. Madden, Emlyn R. Williams

Volume 15, Issue 5, Research Synthesis Methods | pages: 747-750 | First Published online: May 9, 2024

Response to discussant comments on "NMA, the first 20 years"

A. E. Ades, Nicky J. Welton, Sofia Dias, Deborah M. Caldwell, David M. Phillippo

Volume 15, Issue 5, Research Synthesis Methods | pages: 751-757 | First Published online: July 26, 2024

'Twenty years of network meta-analysis: Continuing controversies and recent developments': A health technology assessment perspective

Dan Jackson, Landan Zhang, Robert Hettle, Miranda Cooper

Volume 15, Issue 5, Research Synthesis Methods | pages: 731-734 | First Published online: July 30, 2024

Broad versus narrow research questions in evidence synthesis: A parallel to (and plea for) estimands

Antonio Remiro-Azócar, Anders Gorst-Rasmussen

Volume 15, Issue 5, Research Synthesis Methods | pages: 735-740 | First Published online: August 9, 2024

Current practice that will intensify problems that will probably bother us in the future

- Artificial Technology advancements are revolutionalising evidence synthesis (e.g., searching for trials, data extraction, assessing risk of bias).
- Living evidence synthesis may be the norm.
- Clinical guidelines and market authorization massively depends on evidence synthesis.
- Much controversy around population adjustment methods is anticipated.
- Rare events/diseases
- All the progress we have made in these last 20-30 years in evidence synthesis would be redundant if trialists were willling to share the IPD of the studies.

References

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