The principles of indirect and mixed treatment comparisons

Kelly Fleetwood

Quantics Consulting

www.quantics.co.uk

Outline

QUANTICS

- Introduction to indirect and mixed treatment comparisons
- Assumptions of indirect and mixed treatment comparisons
- Methods

Introduction

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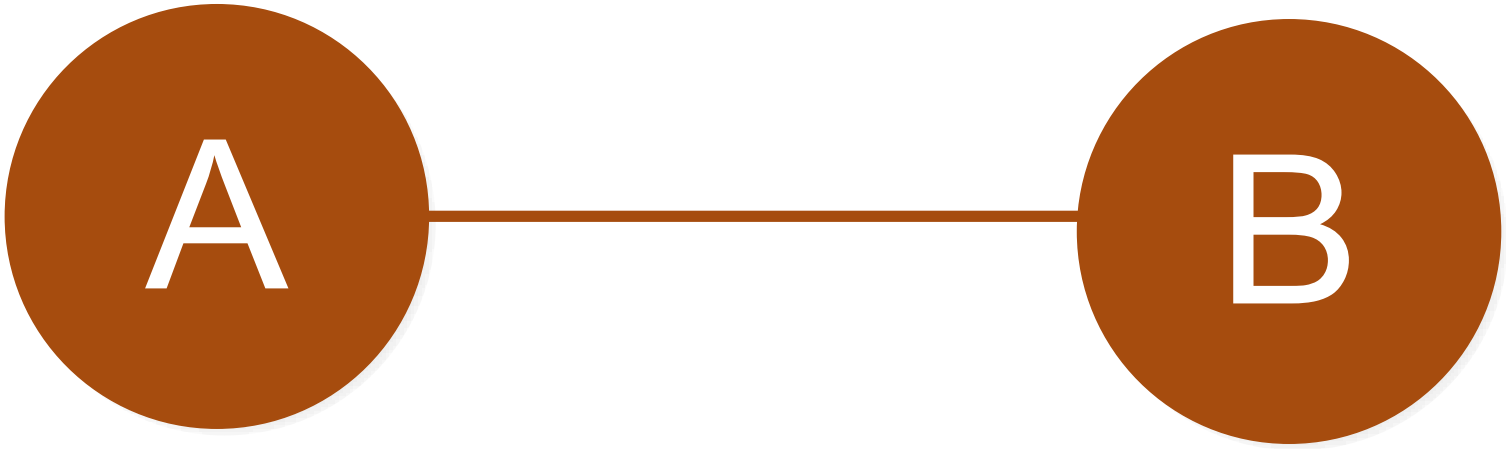

- Standard pairwise meta-analysis
- Based on direct randomised evidence

Introduction

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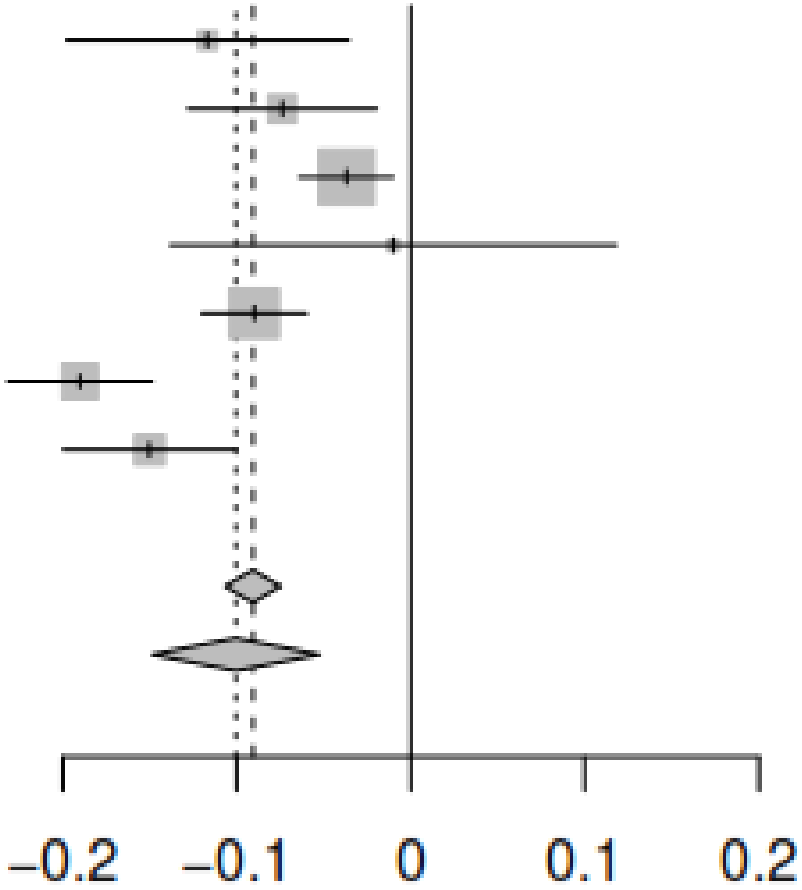

Fixed effect model
Random effects model
Heterogeneity: I–squared=86.6%

Introduction

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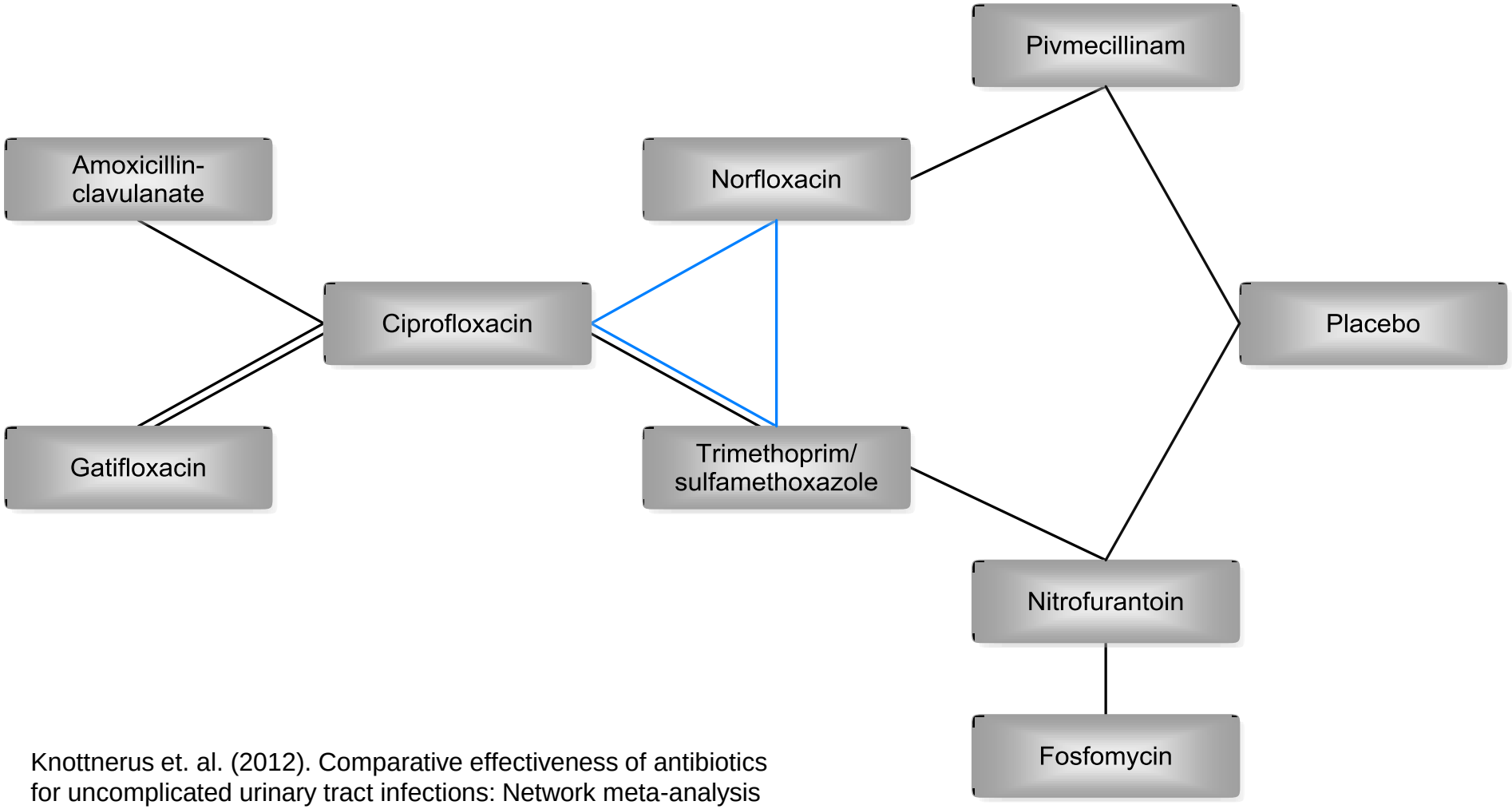

Knottnerus et. al. (2012). Comparative effectiveness of antibiotics for uncomplicated urinary tract infections: Network meta-analysis of randomized trials. Family Practice. Published online. DOI: 10.1093/fampra/cms029

Introduction

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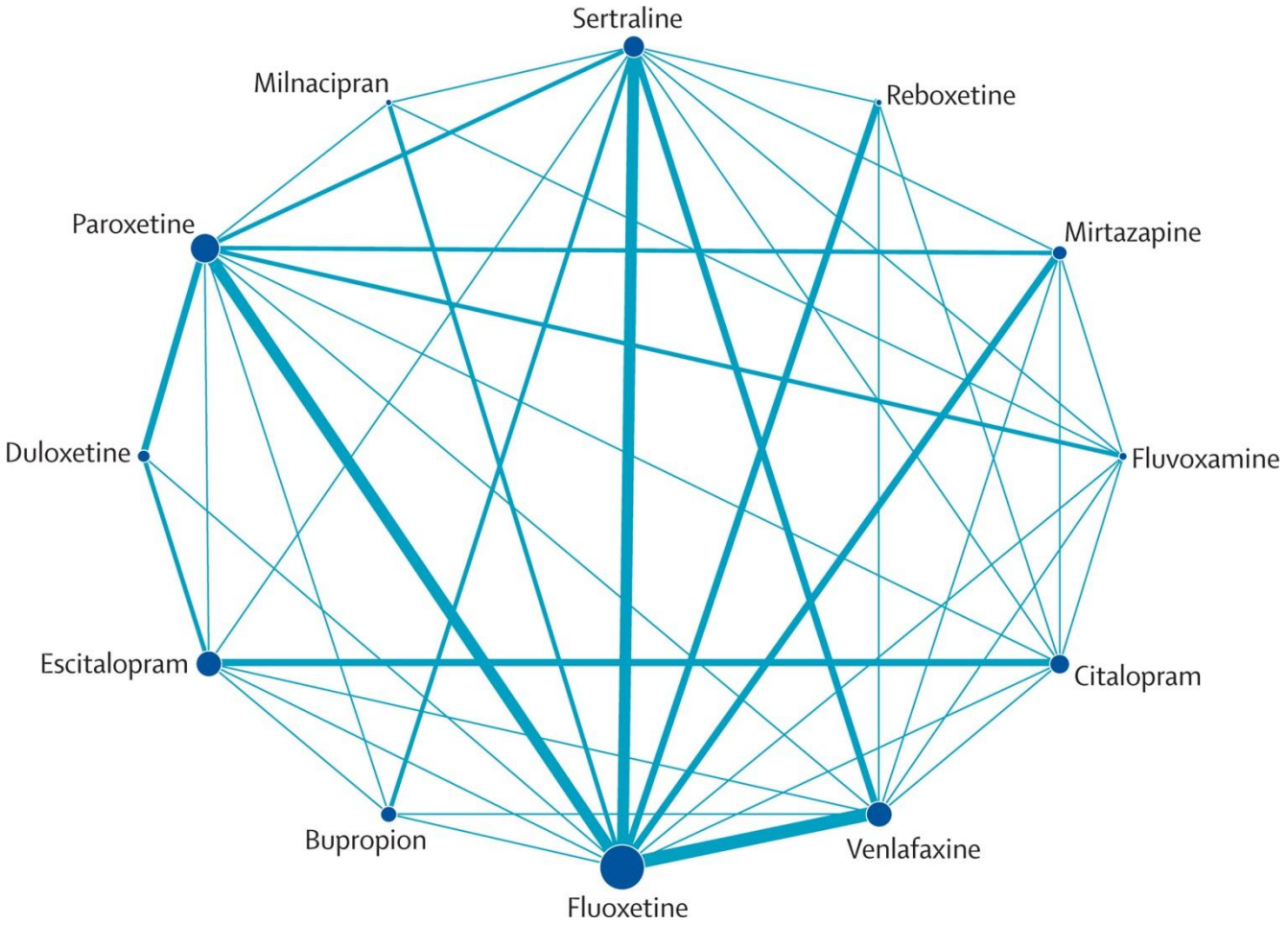


Cipriani et. al. (2009). Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. The Lancet. 373 (9665). pp 746 - 758

Introduction

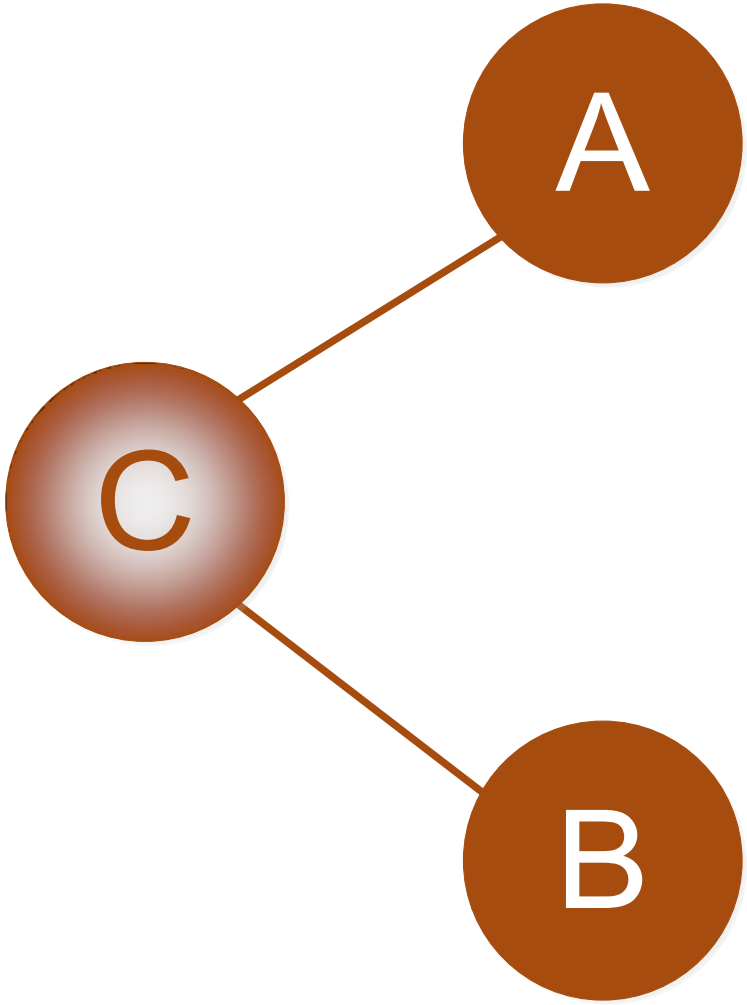
QUANTICS

1. No direct evidence
2. Insufficient direct evidence
3. More than two treatments

Introduction

QUANTICS

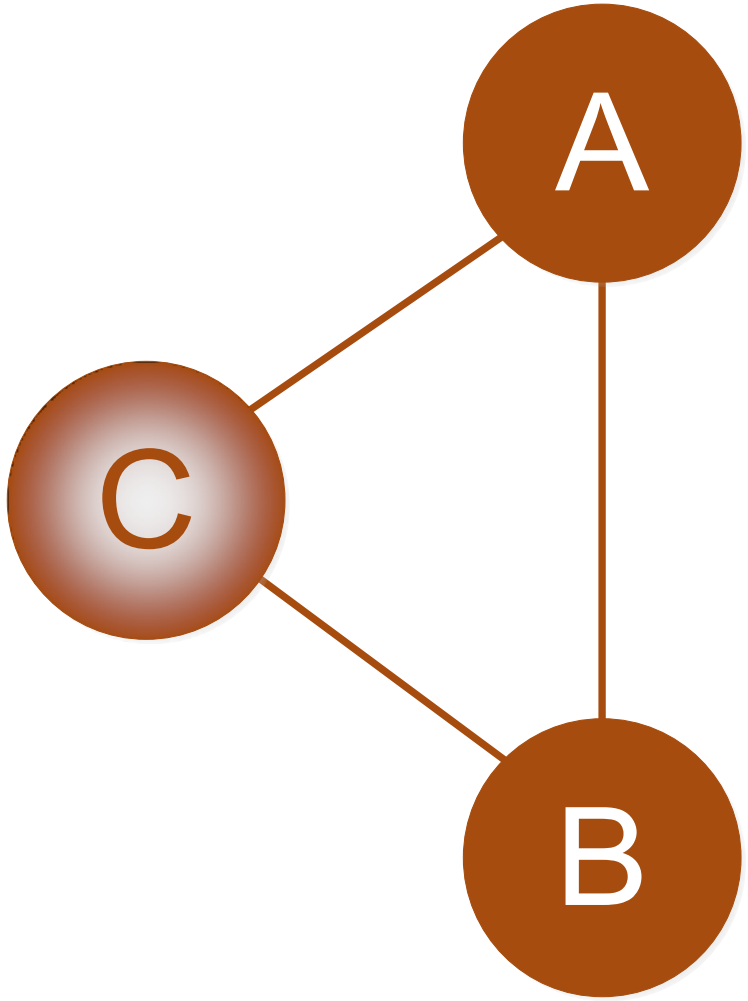
- No direct evidence available



Introduction

QUANTICS

- Insufficient direct evidence



Introduction

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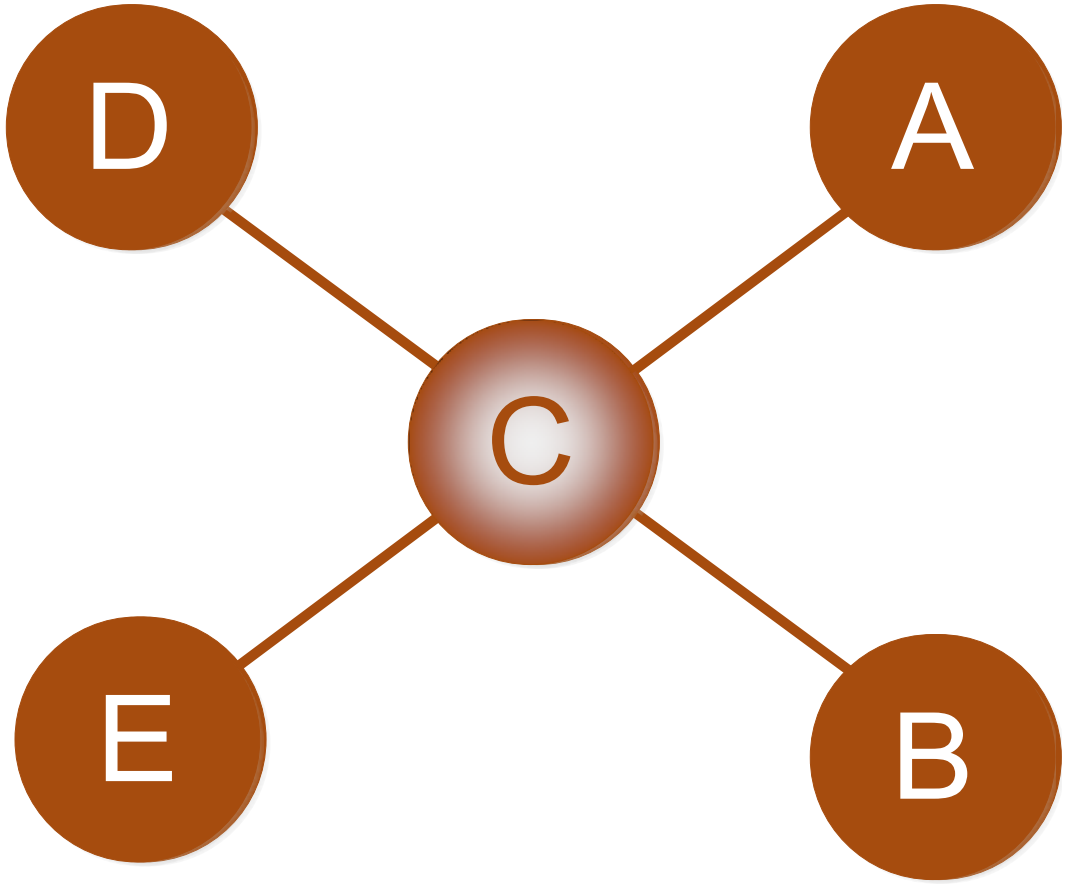
- More than two treatments



Introduction

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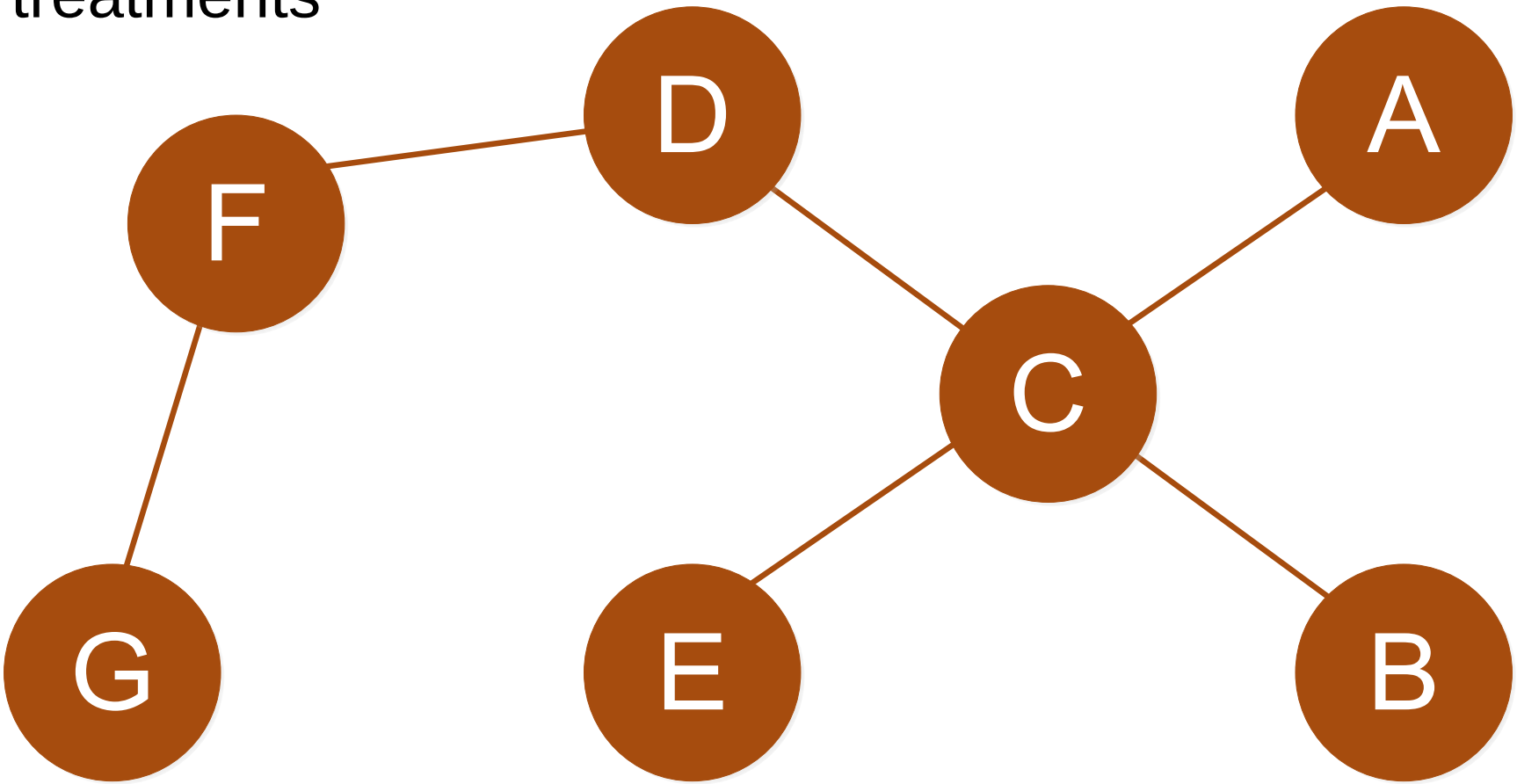
- More than two treatments



Terminology

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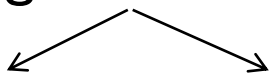
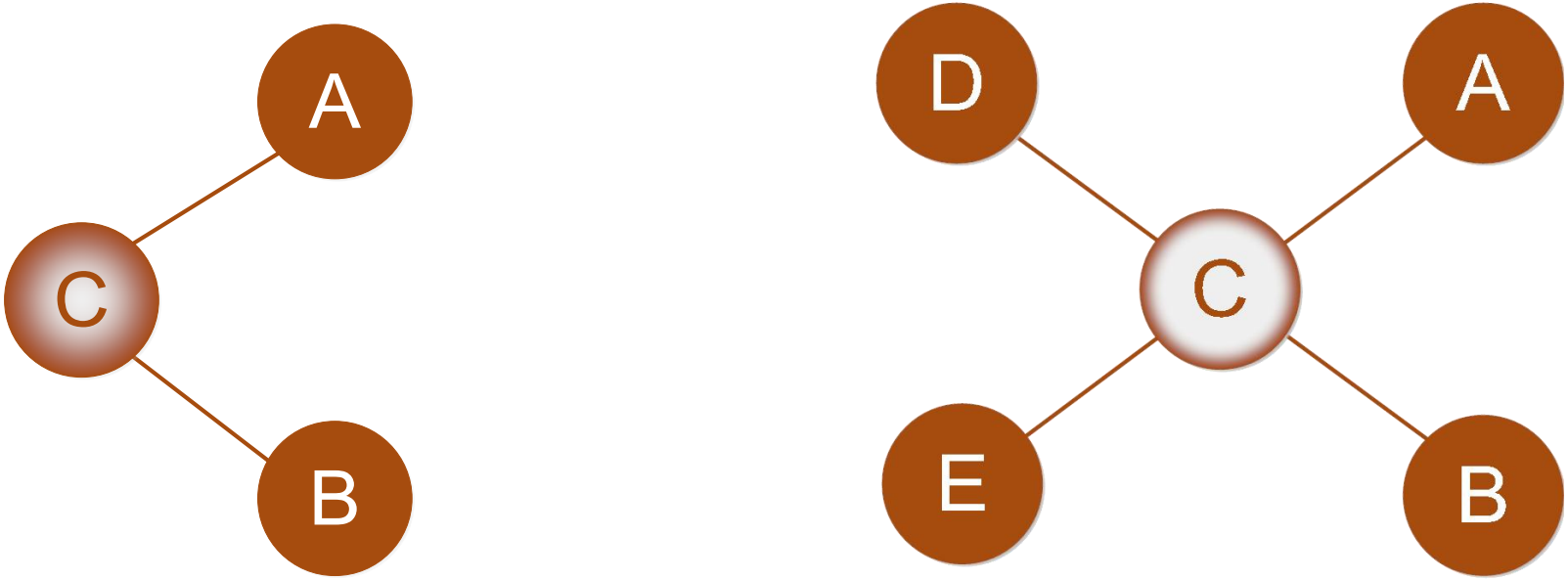
	2 treatments	More than 2 treatments
Review	• Systematic review	• Systematic review • Comparative effectiveness review • Comparing multiple interventions review
Analysis	• Meta-analysis • Pairwise meta-analysis • Conventional meta-analysis (CMA)	• Network meta-analysis (NMA) • Multiple treatments meta-analysis  ITC MTC

Indirect treatment comparison (ITC)



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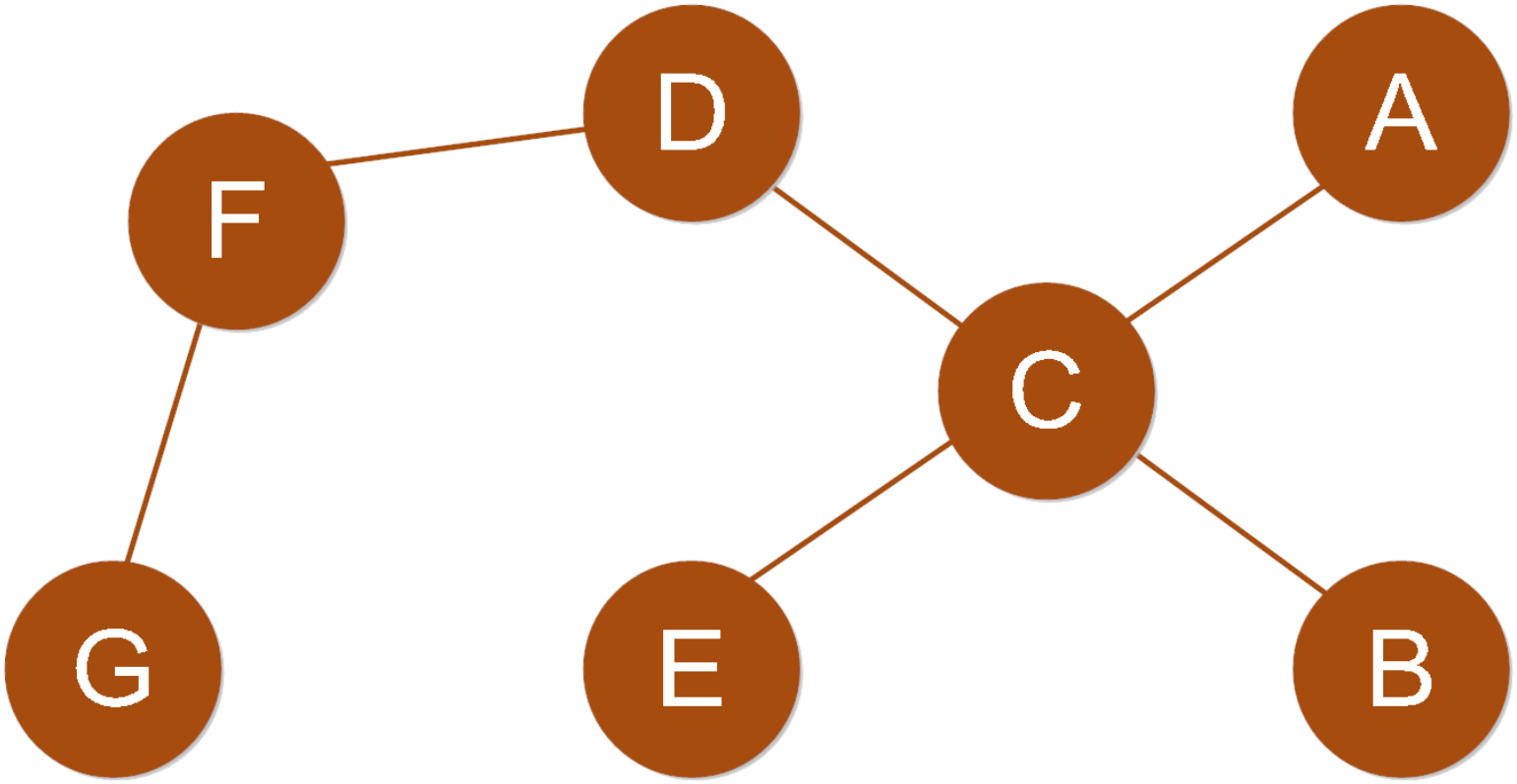

Mixed treatment comparison (MTC)

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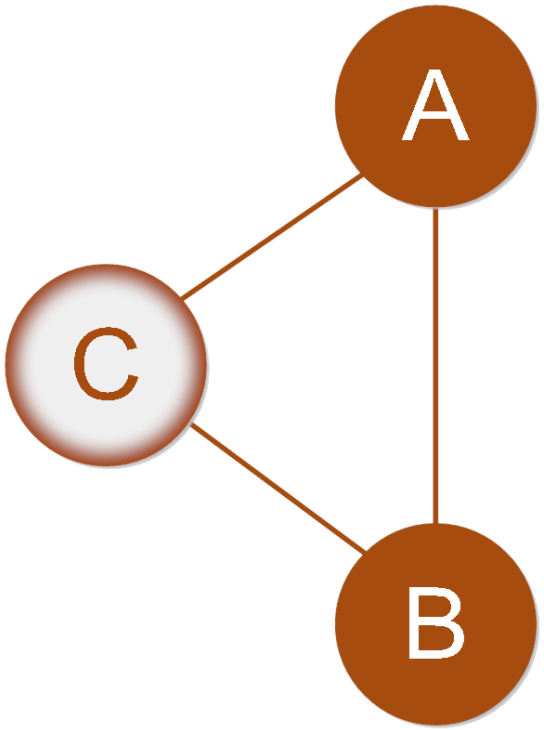
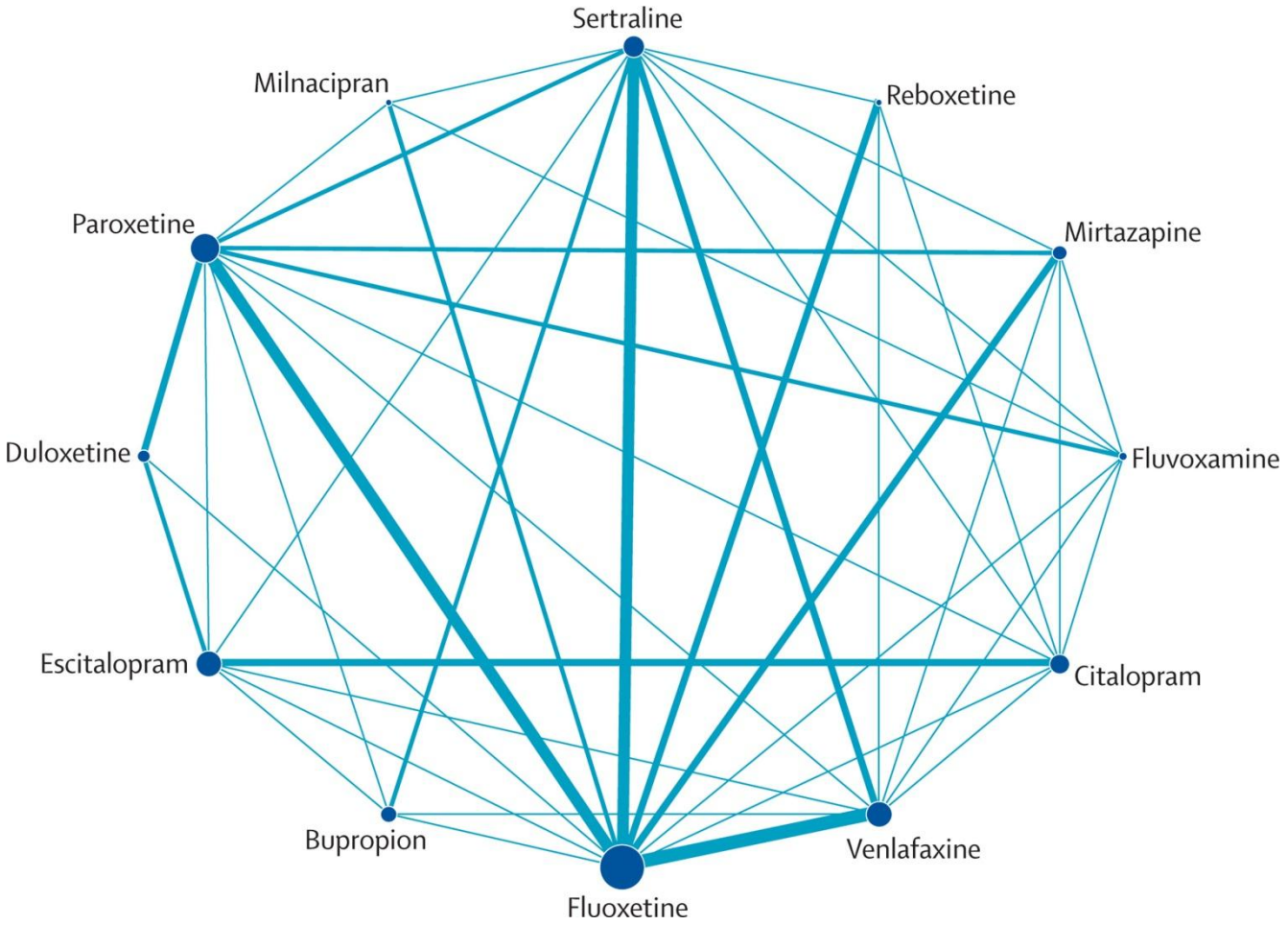


Mixed treatment comparison (MTC)



Cipriani et. al. (2009). Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. The Lancet. 373 (9665). pp 746 - 758

History

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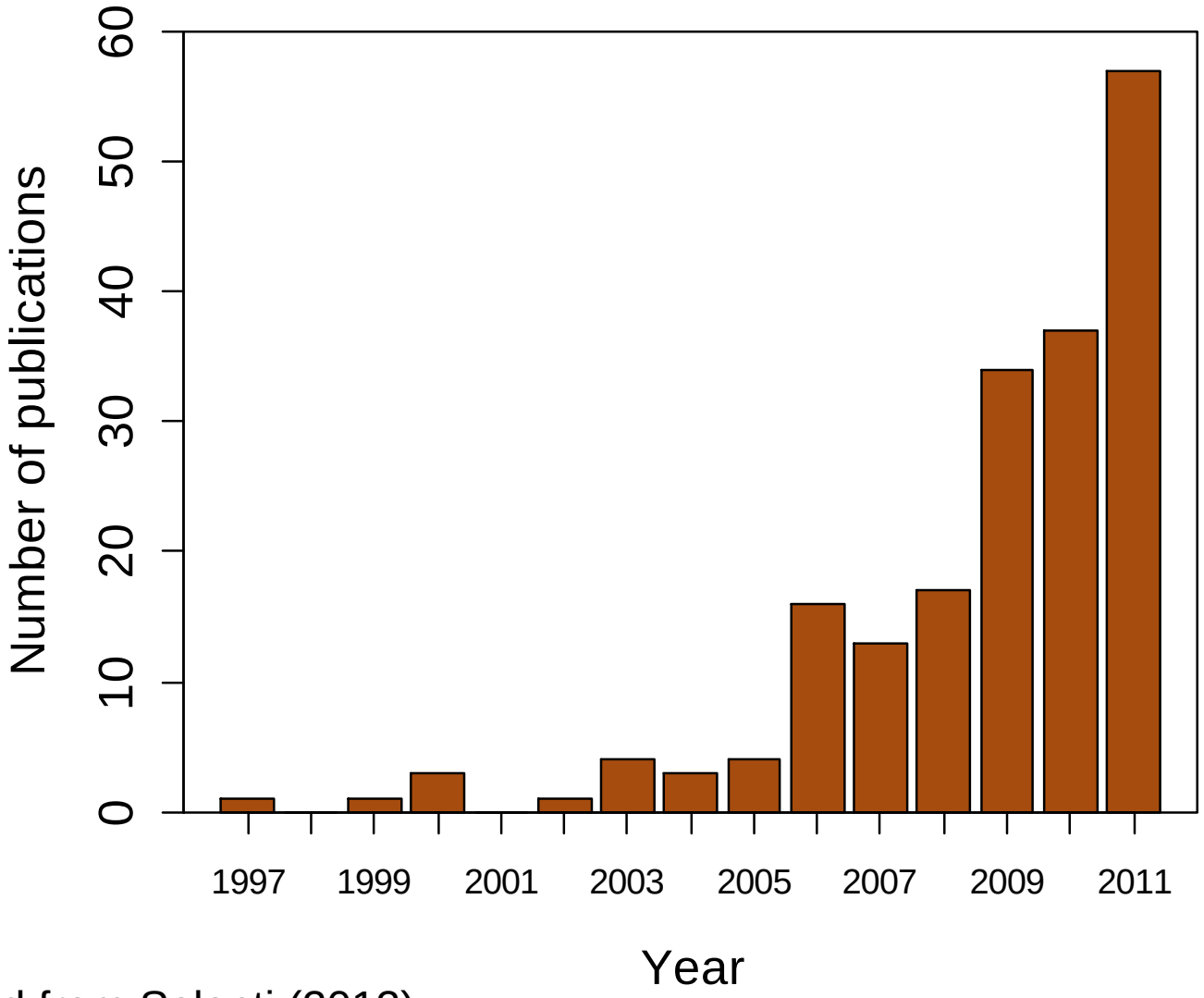

Adapted from Salanti (2012)

Opinions

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- ". . . to ignore indirect evidence either makes the unwarranted claim that it is irrelevant, or breaks the established precept of systematic review that synthesis should embrace all available evidence" - Lu & Ades, 2004

- "next generation evidence synthesis toolkit" – Salanti, 2012

Acceptance

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- NICE
- Canadian Agency for Drugs and Technologies in Health
- Pharmaceutical Benefits Advisory Committee (Australia)

NICE

QUANTICS

- Guide to the methods of technology appraisal (2008) (section 5.3.13 – 5.3.22)
- Preference for ‘head to head’ evidence
- No ‘head to head’ evidence
  - » ITC
- ‘Head to head’ evidence
  - » MTC (if it will add information)

Assumptions

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- All pairwise meta-analysis assumptions
  - All relevant studies are included
    - Adequate search strategy
    - Publication bias
  - Individual studies are not biased

Assumptions

QUANTICS

- All pairwise meta-analysis assumptions
  - Studies are homogeneous in terms of patient characteristic and study design
  - Need to consider effect modifiers – any aspect of patient characteristics or study design that may influence the relative treatment effect
  - Effect modifiers are absent or accounted for in the analysis (e.g. sub-group analysis, meta-regression)

Assumptions

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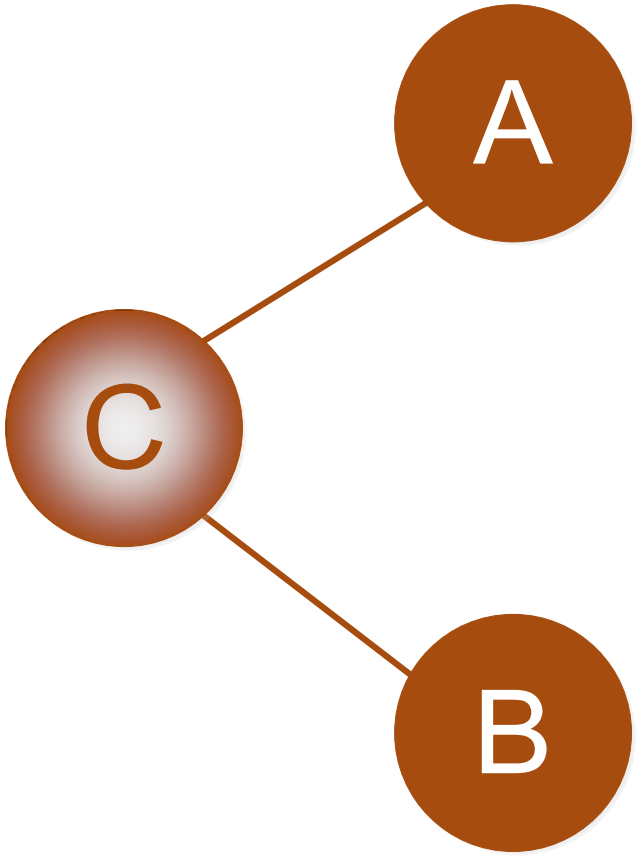
- Similarity (also called transitivity)
- Consistency

Similarity (transitivity)

QUANTICS

- Applies to ITCs and MTCs
- Indirect effects can be estimated from direct effects



Consistency

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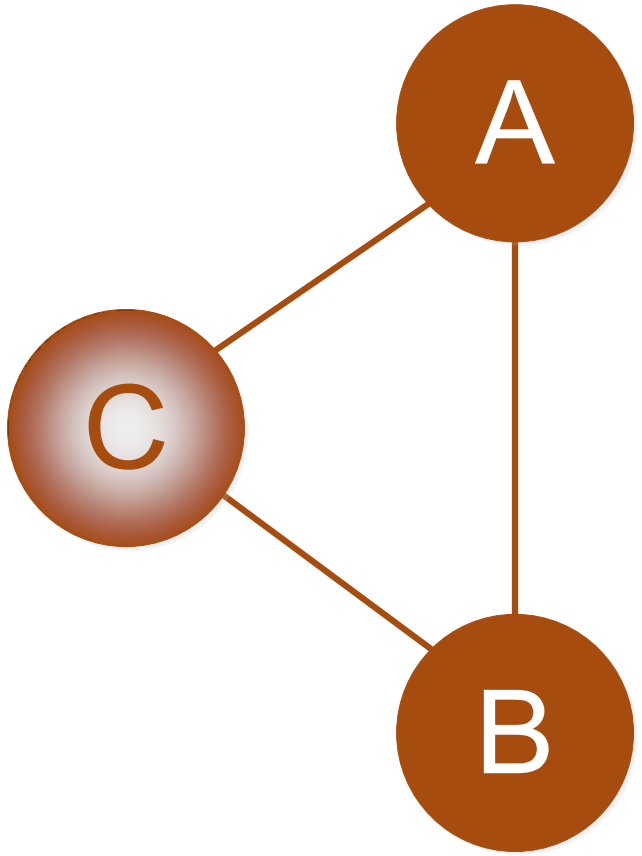
- Applies to MTCs only
- Direct and indirect evidence agree
- Compare direct and indirect evidence to evaluate



Consistency

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- Comparison of direct and indirect estimates (Song, 2003)
- Based on 44 comparisons of different interventions from 28 systematic reviews

Consistency

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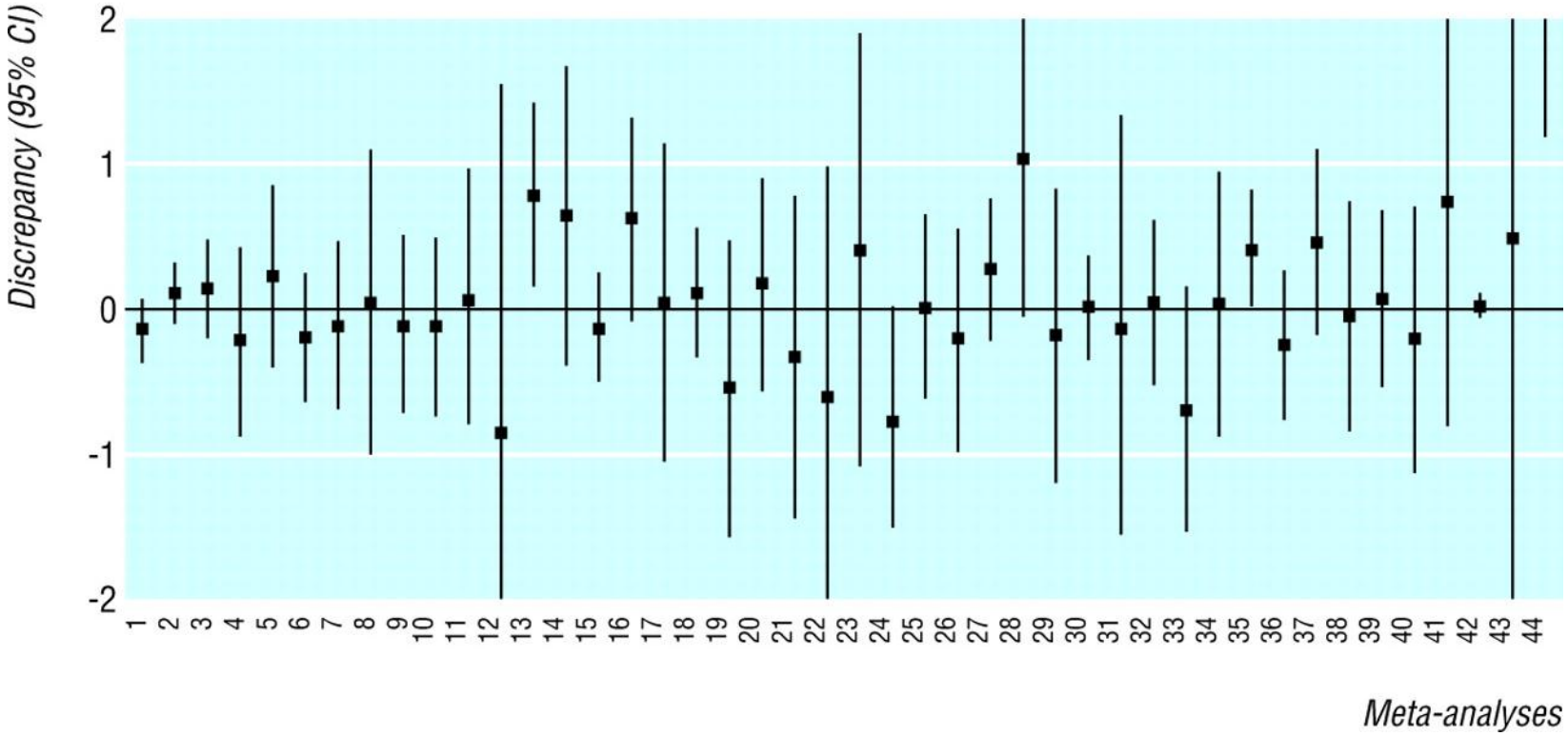
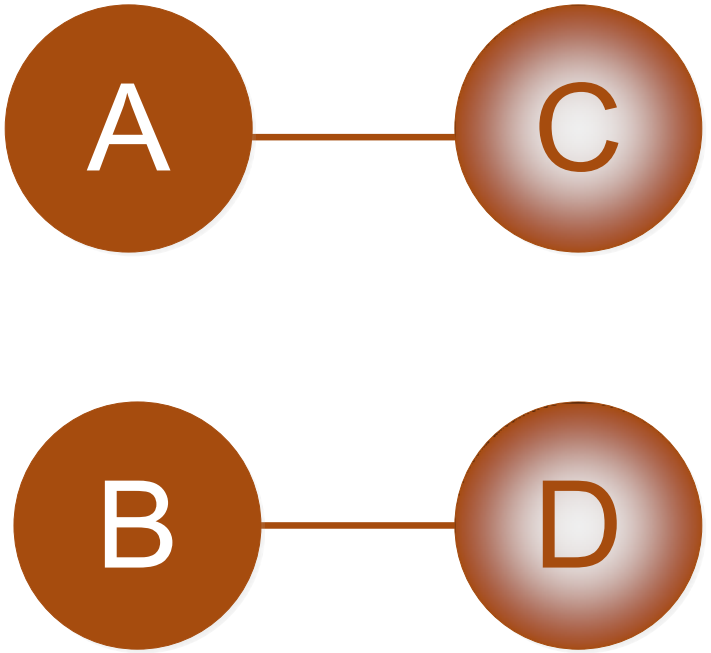


From: Song (2003)

Methods

Naïve indirect comparison

- Compare absolute effects from individual trial arms
- Benefits of randomisation lost
- **NEVER RECOMMENDED**

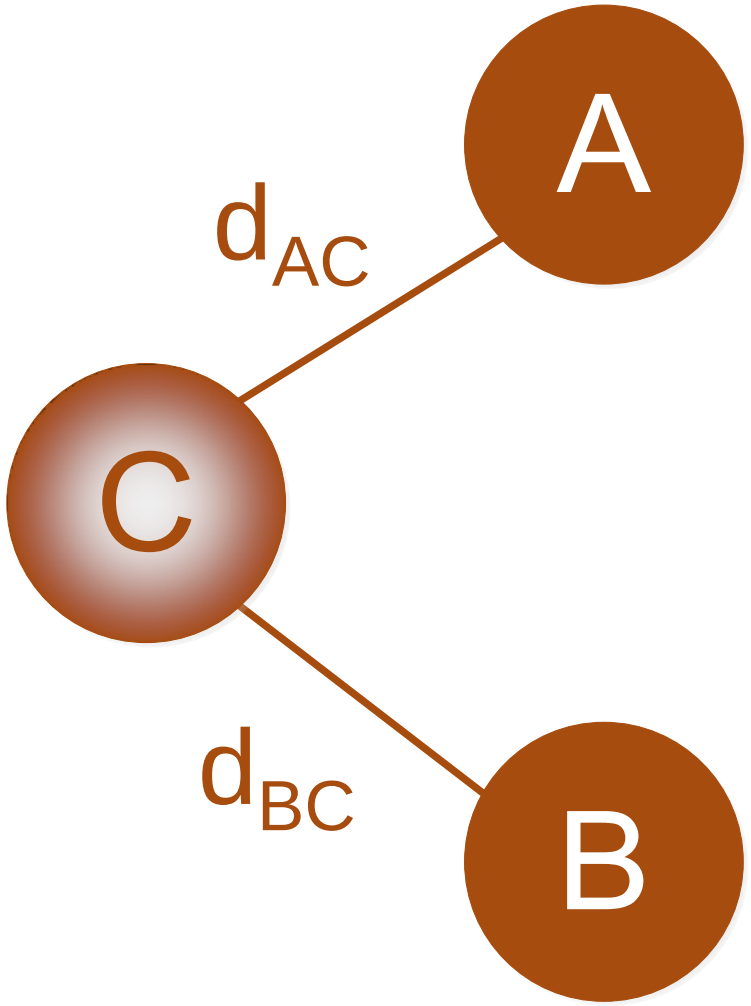


Methods

Stepwise approach

1. Direct evidence
   - pairwise meta-analysis techniques

- d_{AC}
  - Estimate of treatment effect: A – C
  - Could be log odds ratio, log hazards ratio, difference in mean response, …



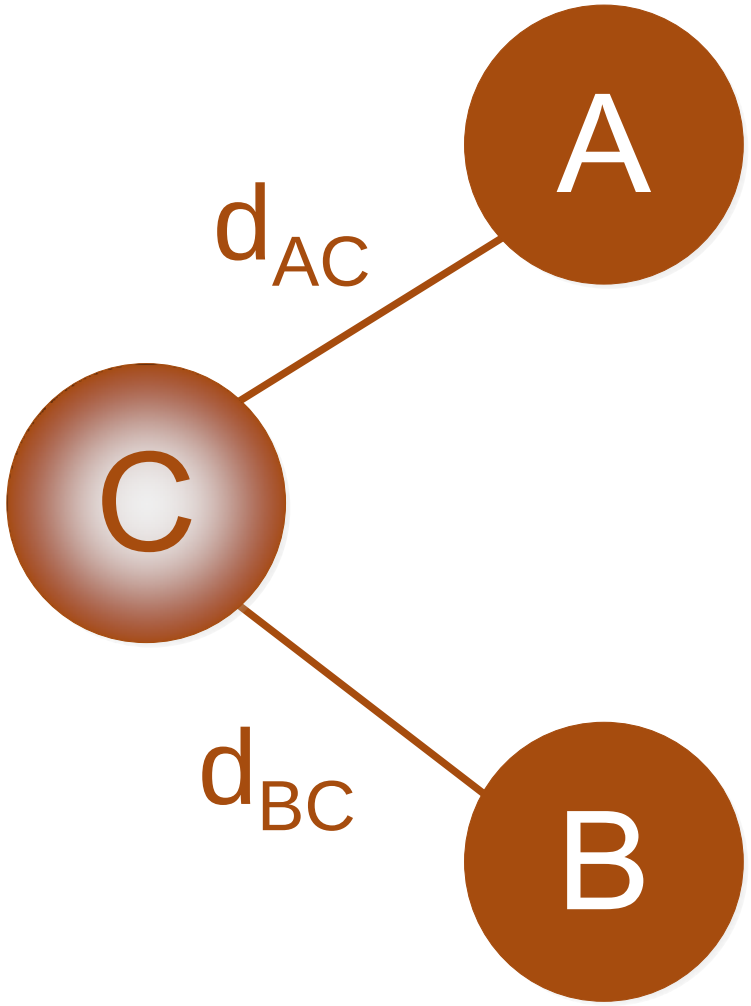
Methods

Stepwise approach

1. Direct evidence
   - pairwise meta-analysis techniques

2. No direct evidence
   - adjusted indirect treatment comparison (Bucher, 1997)

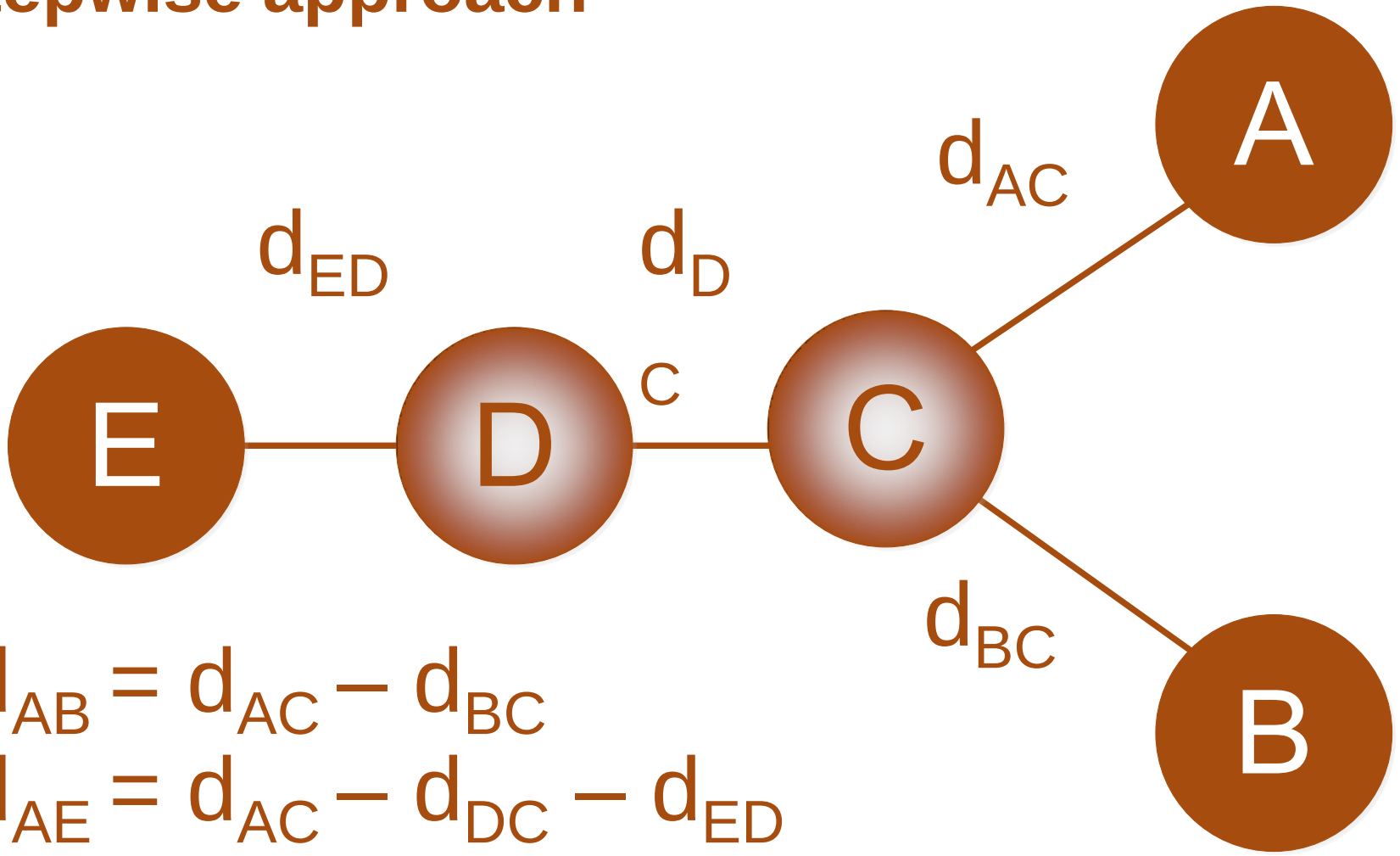
$$d_{AB} = d_{AC} - d_{BC}$$



Methods

QUANTICS

Stepwise approach



$$d_{AB} = d_{AC} - d_{BC}$$
$$d_{AE} = d_{AC} - d_{DC} - d_{ED}$$

Methods

QUANTICS

Stepwise approach

- Tedious for large networks
- Not suitable for MTC

Methods

QUANTICS

Statistical modelling approaches

- Complex ITCs and MTCs
- Bayesian hierarchical approach most common
  - Developed by Lu & Ades (2004)
  - ✓ ITCs and MTCs of any size
  - ✓ Can rank each treatment (as well as estimate relative treatment effects)
  - ✘ More difficult to implement

Methods

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Statistical modelling approaches

- Fixed effect models or random effects models
- Fixed effect models

  Key assumption: the true relative treatment effect is the same for each study
- Random effects models

  Key assumption: the true relative treatment effect are exchangeable (they are not exactly the same but follow a distribution)

A very brief introduction to Bayesian statistics

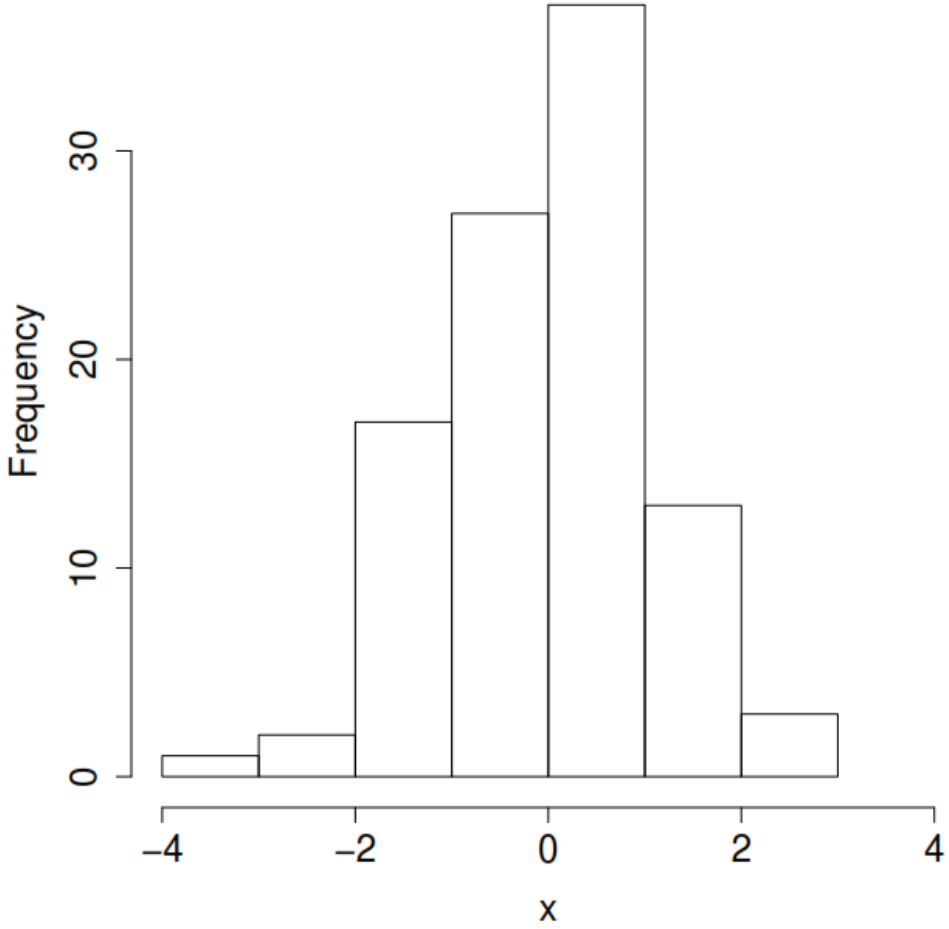
QUANTICS

- Most statistical inference in health is based on Frequentist approaches:
  - P-values, confidence intervals, …
- Bayesian statistics is a different approach to statistical interference
  - It combines data with prior information

A very brief introduction to Bayesian statistics

QUANTICS

In Frequentist statistics inferences about a parameter (e.g. the mean) are based only on the data.

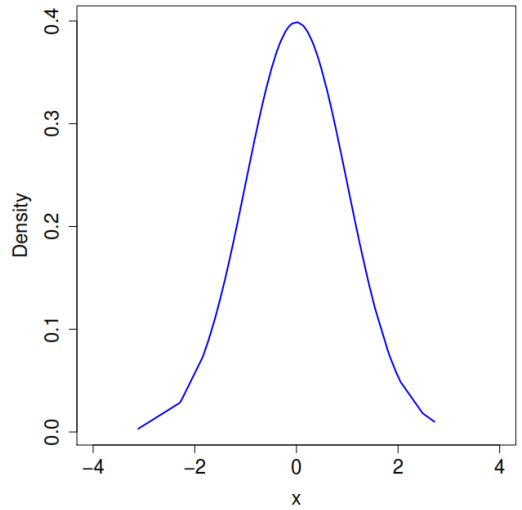


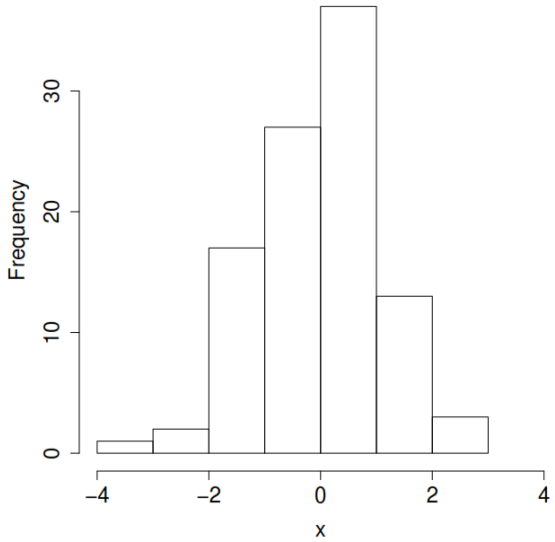
Mean (x) = 0

A very brief introduction to Bayesian statistics

QUANTICS

In Bayesian statistics inferences about a parameter (e.g. the mean) are based on a prior distribution of the parameter and the data.





Mean (x) = 0

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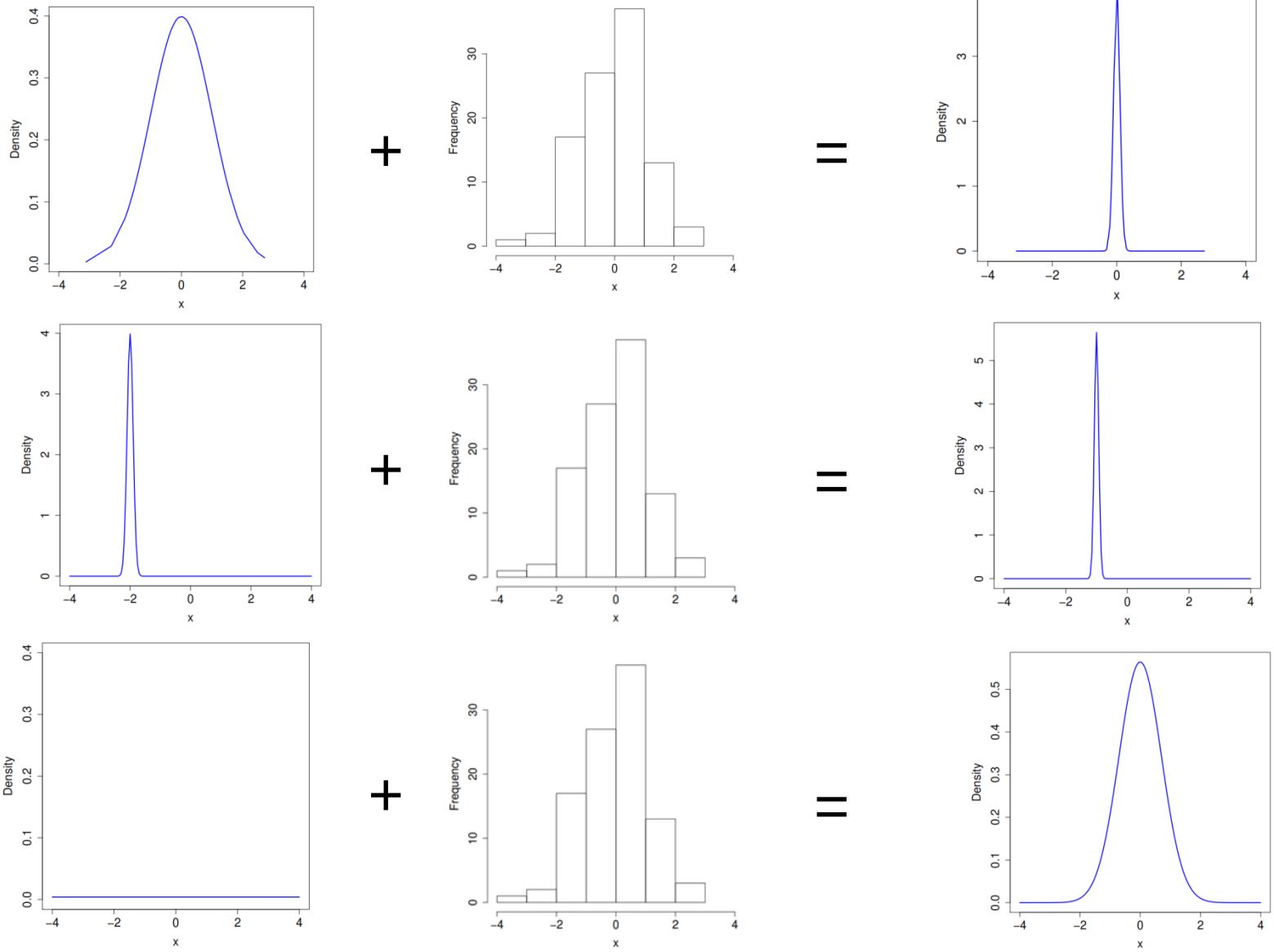


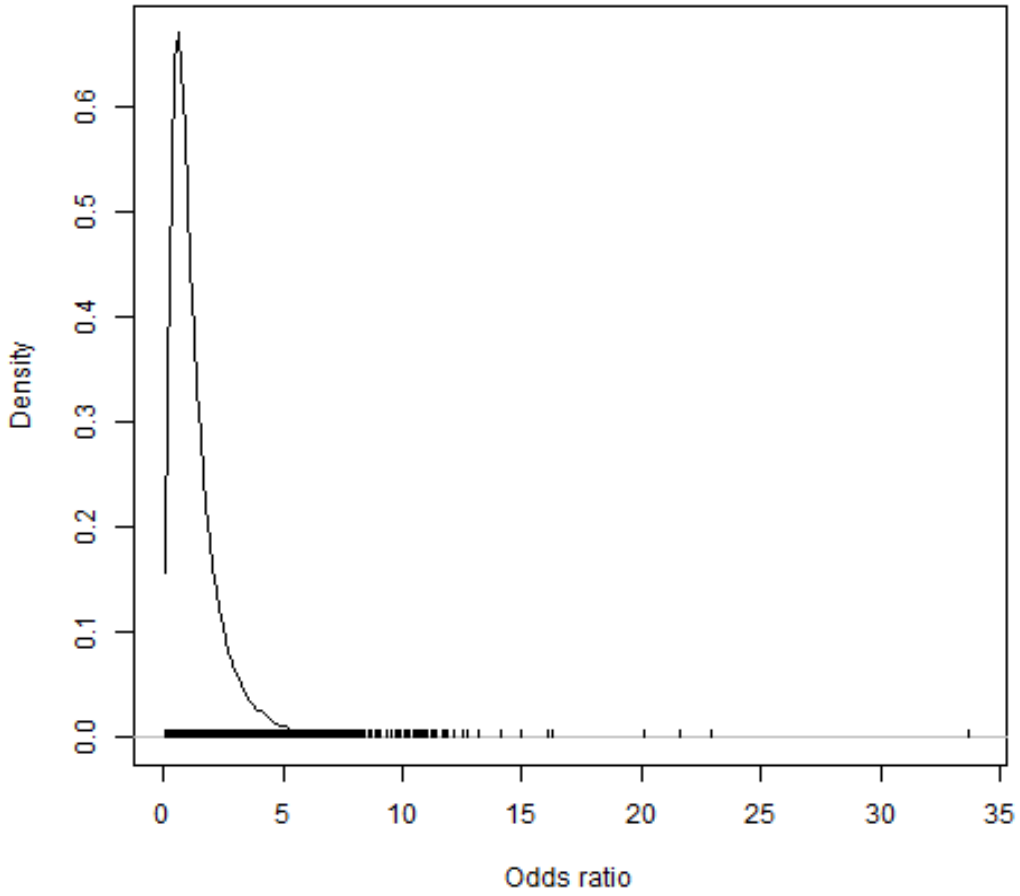
A very brief introduction to Bayesian statistics

QUANTICS

- Bayesian models can be harder to solve than Frequentist models
- Need to use simulation to get results (usually)
  - Markov Chain Monte Carlo (MCMC) methods
  - e.g. WinBUGS
- The simulation takes the prior distribution of the parameter (e.g. OR) and the data and produces the posterior distribution of the parameter

A very brief introduction to Bayesian statistics

QUANTICS



A very brief introduction to Bayesian statistics

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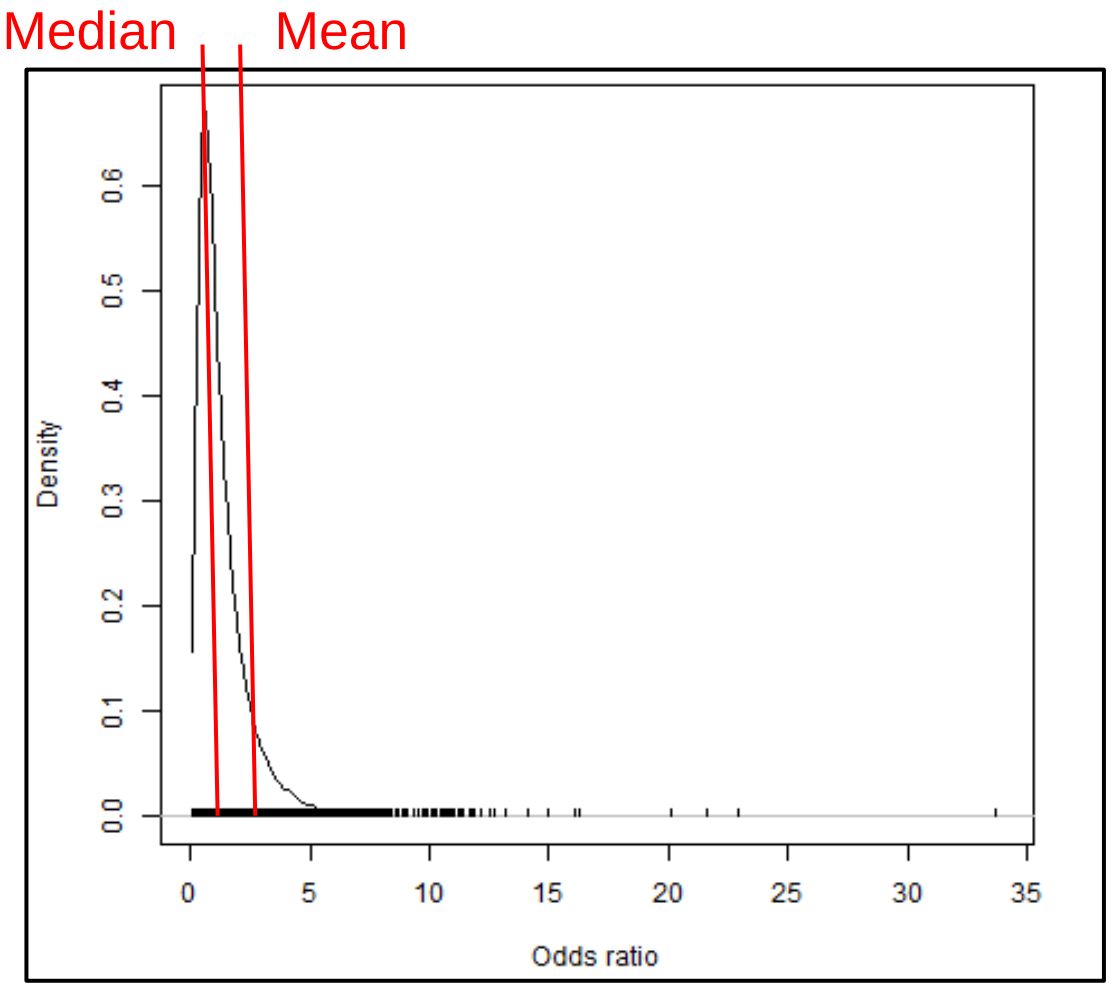

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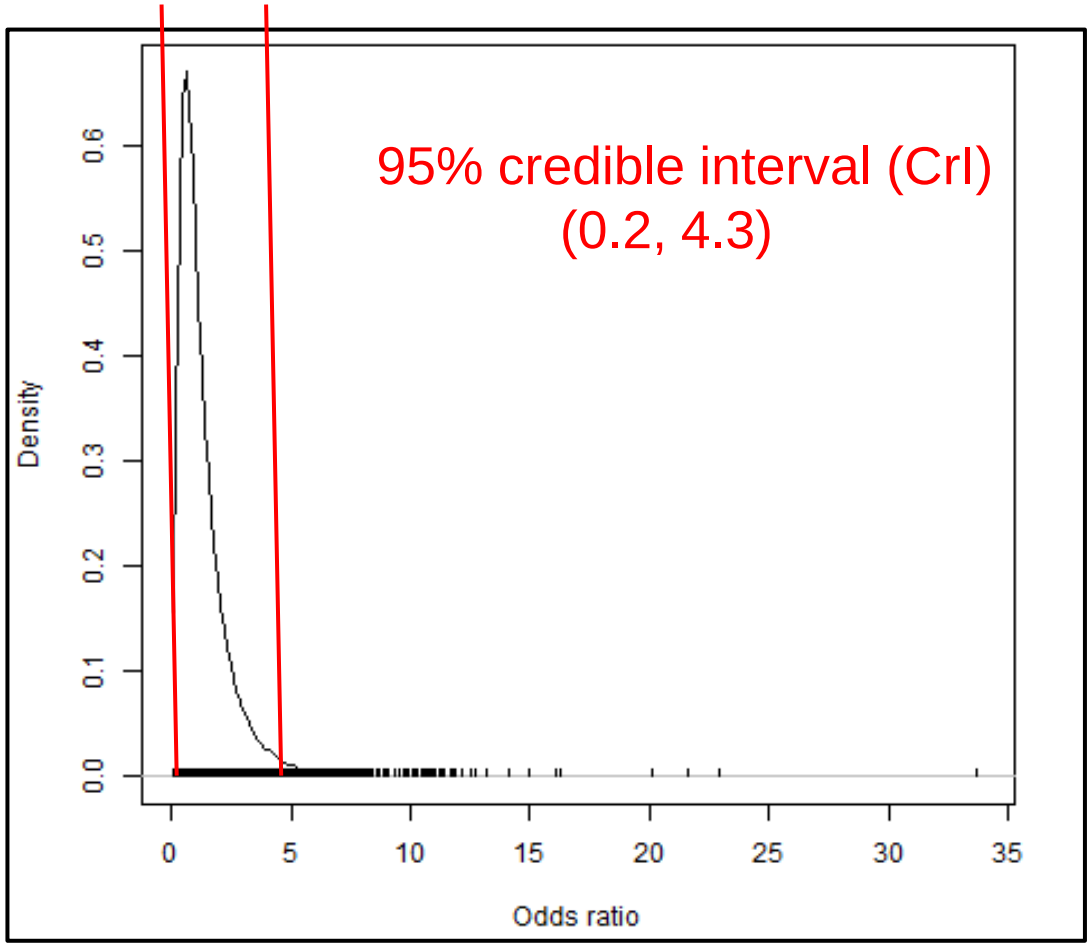

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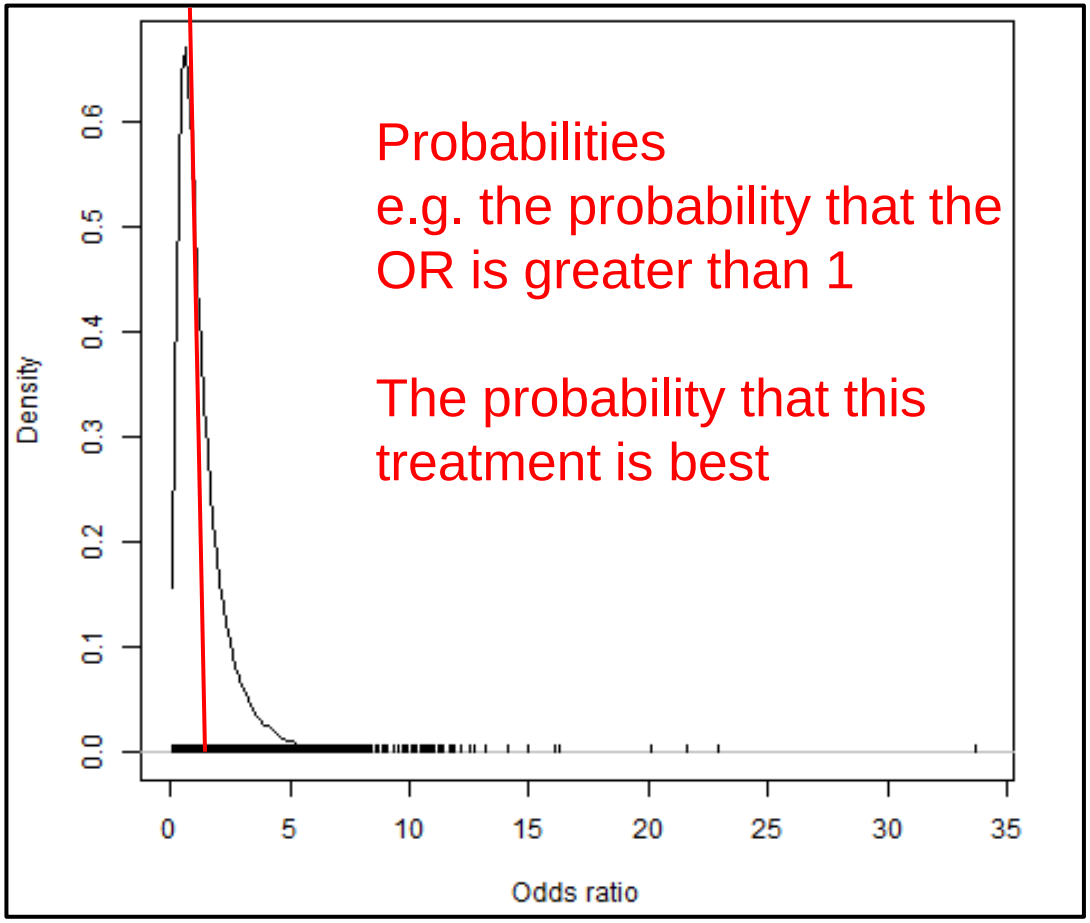

A very brief introduction to Bayesian statistics

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Advantages

- Can incorporate prior information if available
- Can rank treatments

Disadvantages

- Need simulation methods for complex models

A very brief introduction to Bayesian statistics

QUANTICS

Summary

- The choice of prior distribution for the parameter is critical
  - ITCs and MTCs usually use vague priors
- Requires simulation
  - Need to check the simulation has converged
- Produces credible intervals (rather than confidence intervals)

Summary

QUANTICS

- Indirect and mixed treatment comparisons can be applied when
  - there is no direct evidence
  - Insufficient direct evidence
  - More than two treatments
- Same assumptions as pairwise meta-analysis
  + similarity and consistency
- Bayesian methods are often applied to ITCs and MTCs

References

- Salanti, G. 2012. 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. Published online. DOI: 10.1002/jrsm.1037
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- Bucher et. al. 1997. The results of direct and indirect comparisons in meta-analysis of randomized controlled trials. Journal of Clinical Epidemiology. 50 (6). pp. 683-691.
- Lu, G. and Ades, A.E. 2004. Combination of direct and indirect evidence in mixed treatment comparisons. Statistics in Medicine. 23 (20). pp. 3104-3124.