Introduction to Bayesian Network Meta-Analysis

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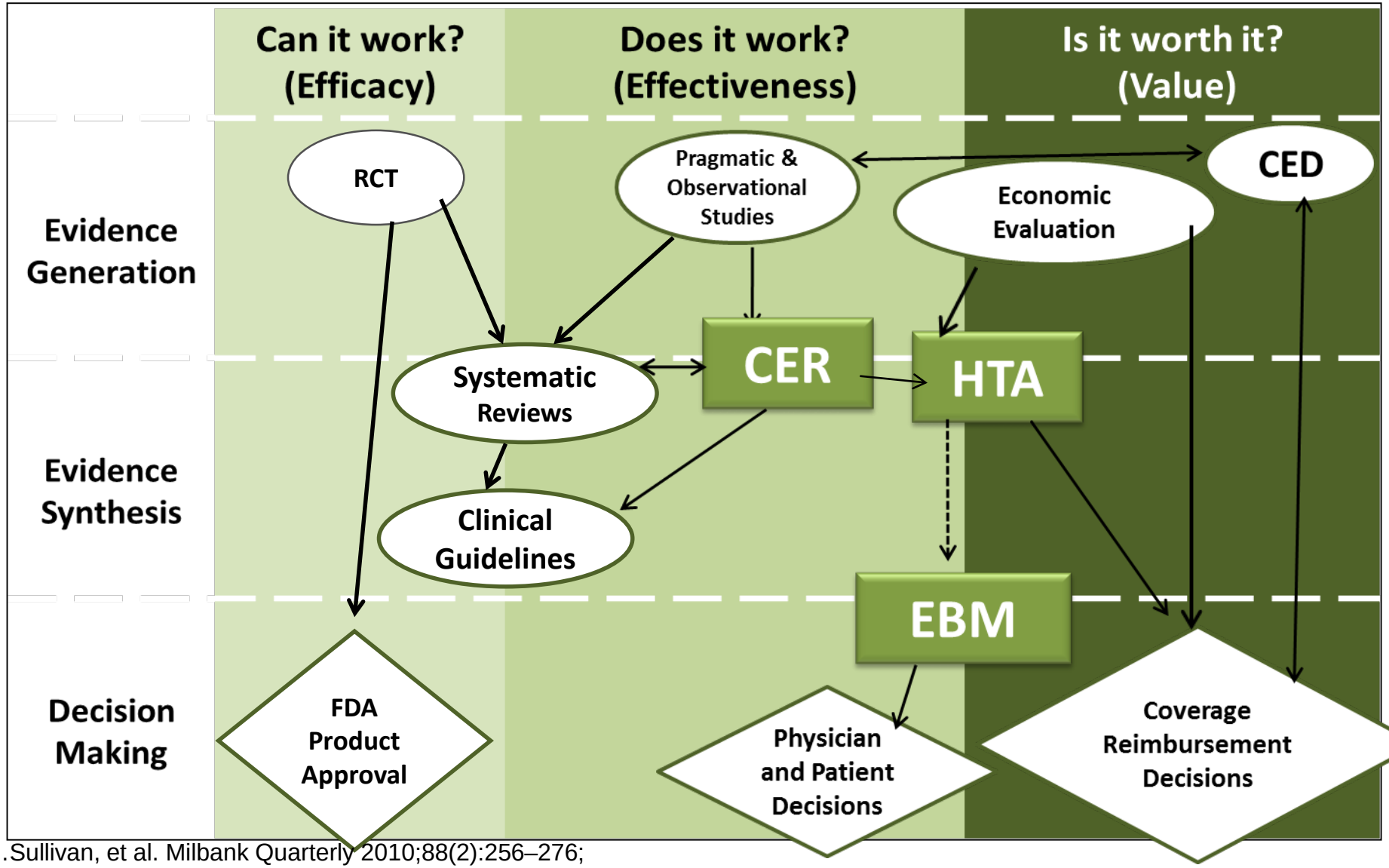
Outline

> **Part 1: Overview of Network Meta-Analysis (NMA)**
  - Context for Evidence Synthesis
  - From meta-analysis (MA) to NMA
  - Fundamentals of NMA

> **Part 2: Case Study**
  - Microvascular Benefits of New Anti-Diabetic Agents
    > NMA of Renal Outcomes

Evidence Synthesis in Comparative effectiveness research (CER); Health technology assessment (HTA)

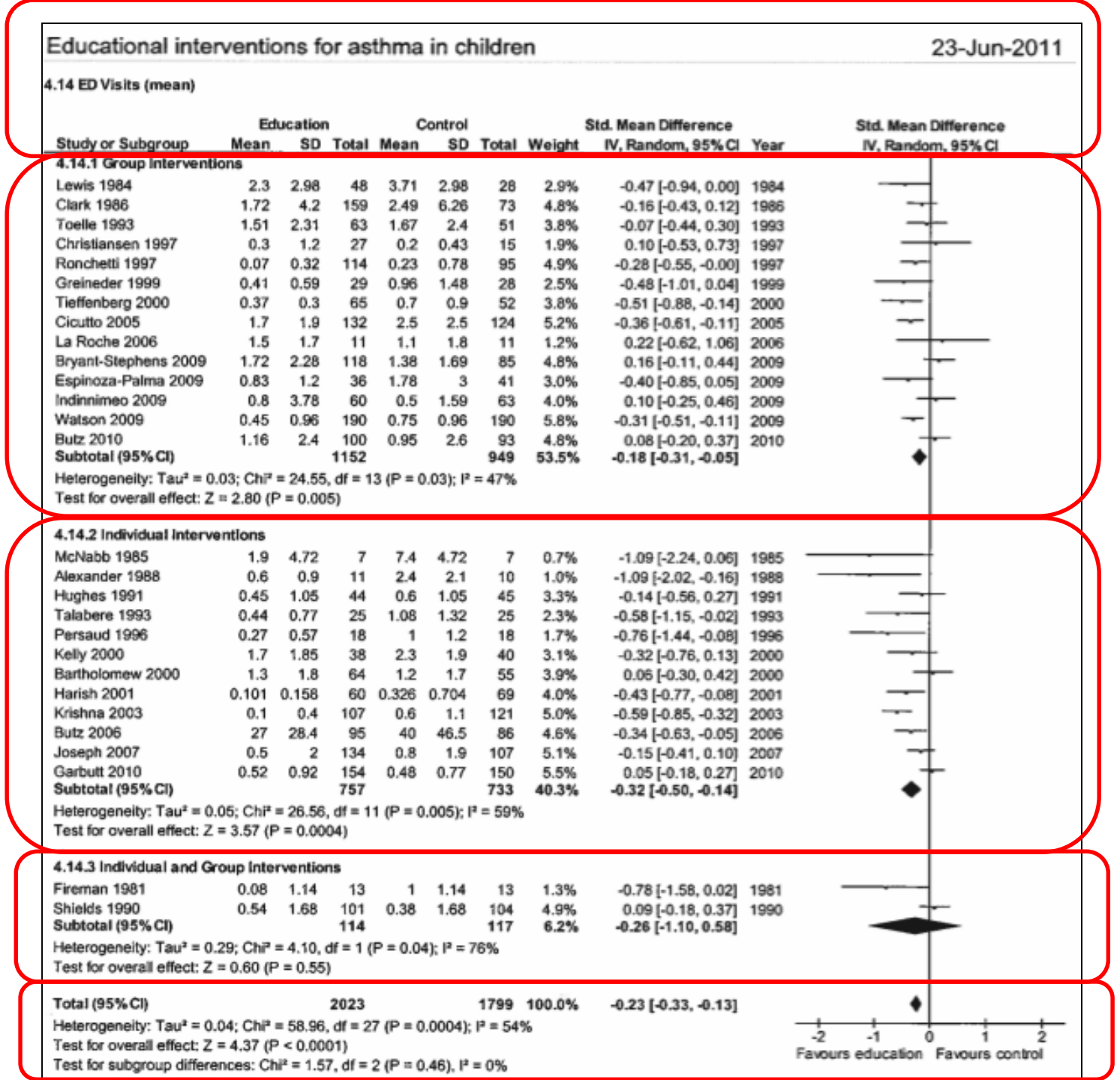


Adapted from Luce…Sullivan, et al. Milbank Quarterly 2010;88(2):256–276;
CED: coverage with evidence development; EBM = evidence-based medicine; RCT = randomized controlled trial

From Meta-Analysis to NMA

- Recall….
- Meta-analyses are useful for informing evidence-based decision-making
  - Quantitatively (statistically) pooling results
  - *Comparable* studies of the same intervention to the same comparator
  - Obtain overall estimate of effect
    - usually OR, RR, HR, or Standardized Mean Difference (SMD)
  - Each study weighted according to size and uncertainty (weighted mean)
  - Fixed effects and random effects models are used

Traditional Meta-analysis



Agapova, Devine, Nguyen, Wolf, Inoue
J. Comp. Eff. Res. 2014;3(4), 345–357

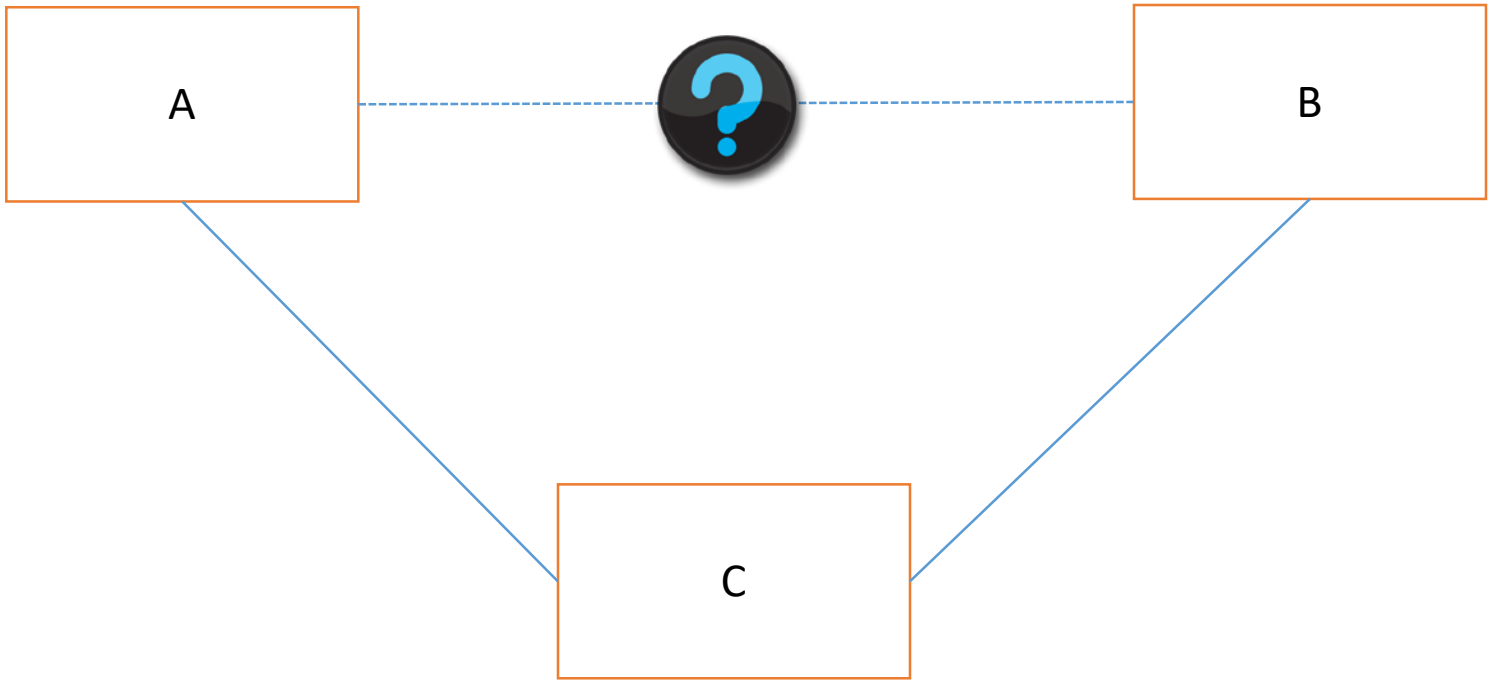
Introduction to Network MA Methods (1)

- But now…
- Network of studies involves > 2 drugs
  - Drug A to C ($study_{AC}$)
  - Drug B to C ($study_{BC}$)

- We wish to know how Drug A compared to Drug B – can make an indirect comparison

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

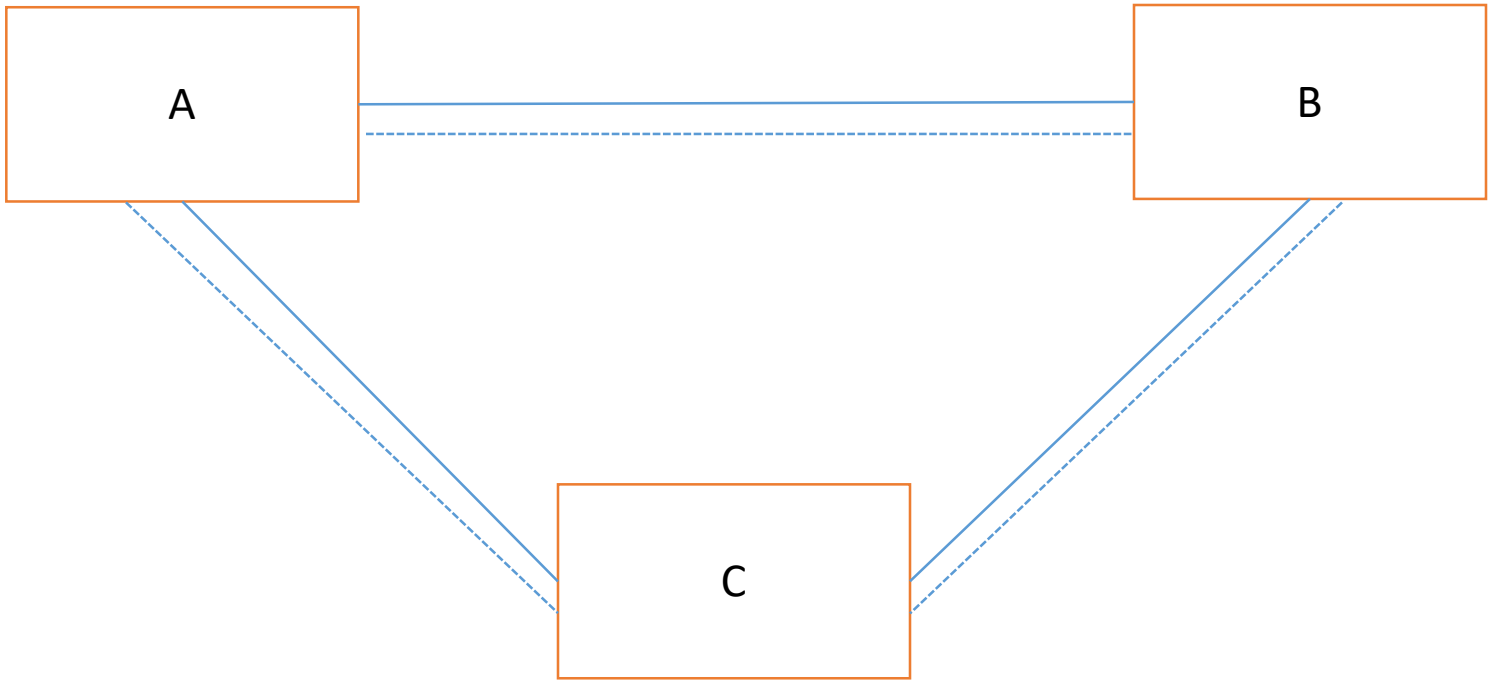
Introduction to Network MA Methods (2)



“Indirect Treatment Comparison (ITC)”

Statistical comparison of two or more agents that have not been directly compared to each other, but that have one comparator in common, thus creating a network

Introduction to Network MA Methods (3)

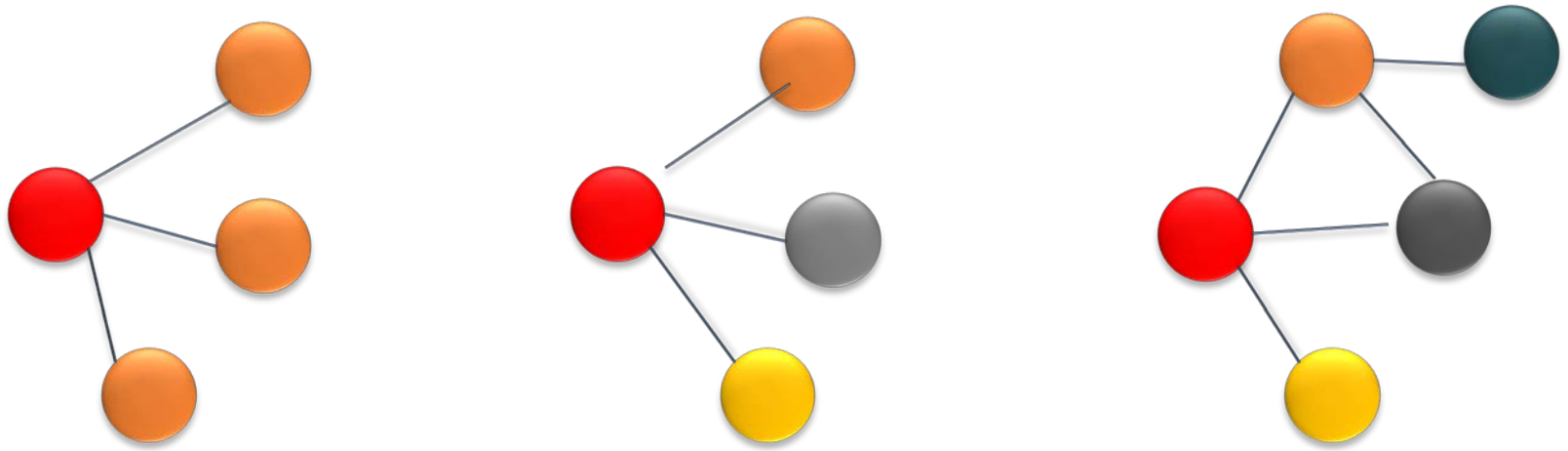


“Mixed treatment comparison (MTC)”

Extension of ITC where both direct and indirect evidence is included

Introduction to Network MA Methods (4)

	Network Meta-Analysis	
Meta-analysis	**Indirect Treatment Comparison**	**Mixed Treatment Comparison**
Quantitatively combined results of ***comparable*** studies of the ***same agent*** to obtain overall estimate of effect.	Statistical comparison of two or more agents that have ***not been directly compared to each other***, but that have ***one comparator in common***, thus creating a network	Extension of ITC where ***both direct and indirect*** evidence is included



Jansen. Value in Health 2008;11(5):956-64; 21:2313-24; Lu & Ades. Stat Med 2004;23:3105-24; Sutton & Ades. Pharmacoeconomics 2008;26(9);753-67

First, must conduct all systematic review steps

- Establish **PICOTS** criteria
  - Population, Interventions, Comparator(s), Outcomes, Timing (timing of literature search, duration of treatment, duration of follow-up), Setting/Study design
- Conduct search using multiple databases
- Dual review & reconciliation of titles, abstracts, full-text of included studies
- Conduct quality assessment on each included study using a risk of bias tool (dual review again)
- Extract data into evidence tables
- Address heterogeneity in protocol/analysis – pool at all? Subgroups? Meta-regression?

Fundamentals of NMA (1) – Preserve randomization

- Validity of evidence synthesis relies on methods that appreciate within trial randomization
- If within trial randomization not preserved then NMA has a fatal flaw
- A limitation inherent in the method is risk of bias due to lack of randomization across trials

Jansen. Value in Health 2008;11(5):956-64; 21:2313-24; Jansen, et al. Value in Health 2014;17:157-173

Fundamentals of NMA (2) - Heterogeneity

- Also recall…
  - in meta-analysis, heterogeneity of included studies must be taken into account
  - if assumption not met…….then conduct systematic review
- Similarity
  - qualitative assessment
  - compare studies on PICOTS criteria & study design
    - “P” = demographic and clinical characteristics
- Heterogeneity
  - quantitative assessment
  - percent of variation across studies due to heterogeneity, rather than chance
  - evaluate with I^2 statistic
  - primary goal of meta-analysis is to explore heterogeneity, rather than to calculate one effect

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Jansen. Value in Health 2008;11(5):956-64; 21:2313-24; Jansen, et al. Value in Health 2014;17:157-173

Fundamentals of NMA (3) – Two additional assumptions

> Transitivity
  - Validity of logical inference; potential modifiers of treatment effect similarly distributed across trials
  - If A=B, and B=C, then A=C
  - Qualitative assessment

> Consistency
  - If direct and indirect evidence, then quantitatively check consistency
  - If inconsistency…..then non-transitivity
  - Quantitative (statistical) measure of transitivity
  - If inconsistent, include a “Design by Treatment” interaction term in meta-regression model

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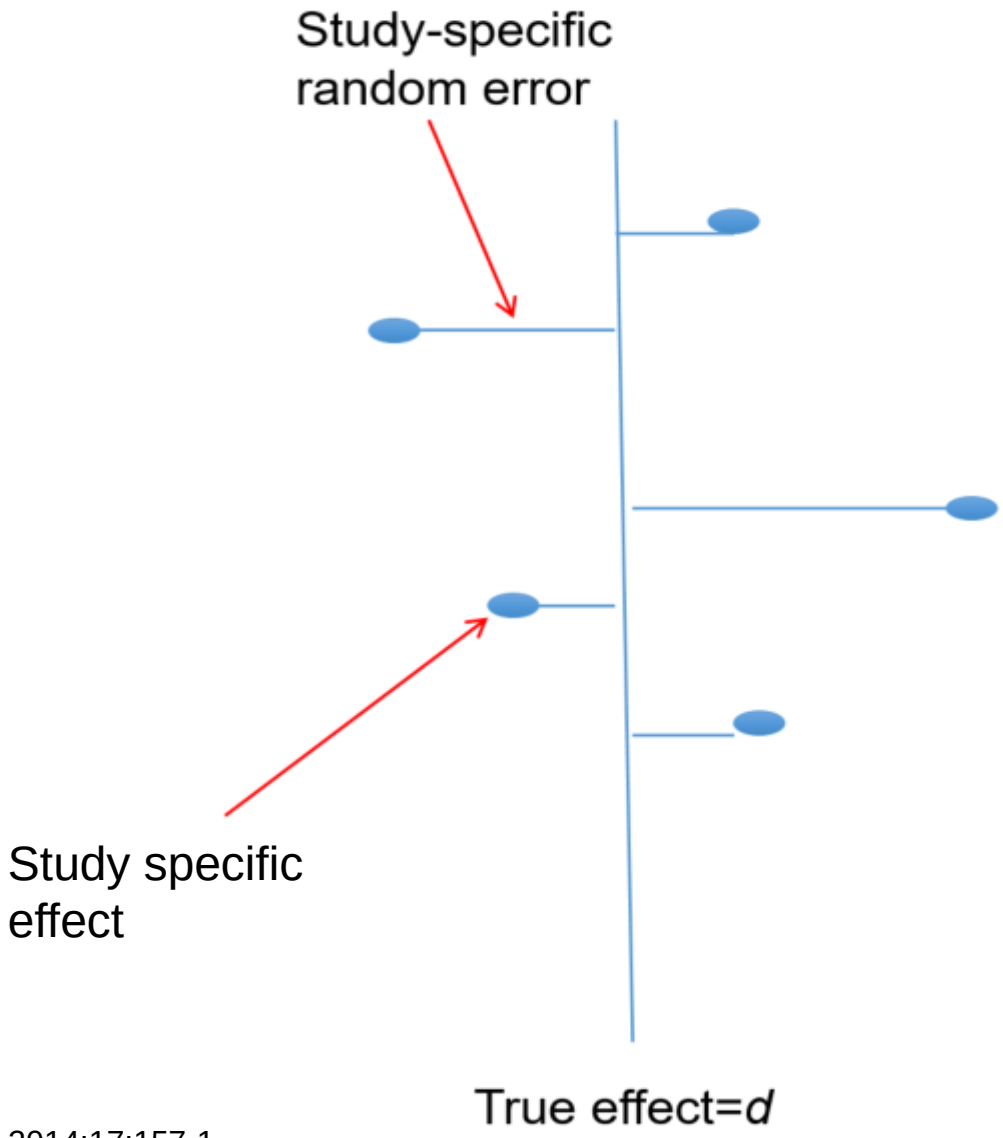
Jansen. Value in Health 2008;11(5):956-64; 21:2313-24; Jansen, et al. Value in Health 2014;17:157-173;
Neupane. NMA using R: Review of currently available automated packages. PLoS One. 2014;9(12):e115065

Fundamentals of NMA (4): Fixed Effects (FE) Model

- No heterogeneity
- We estimate the common true effect



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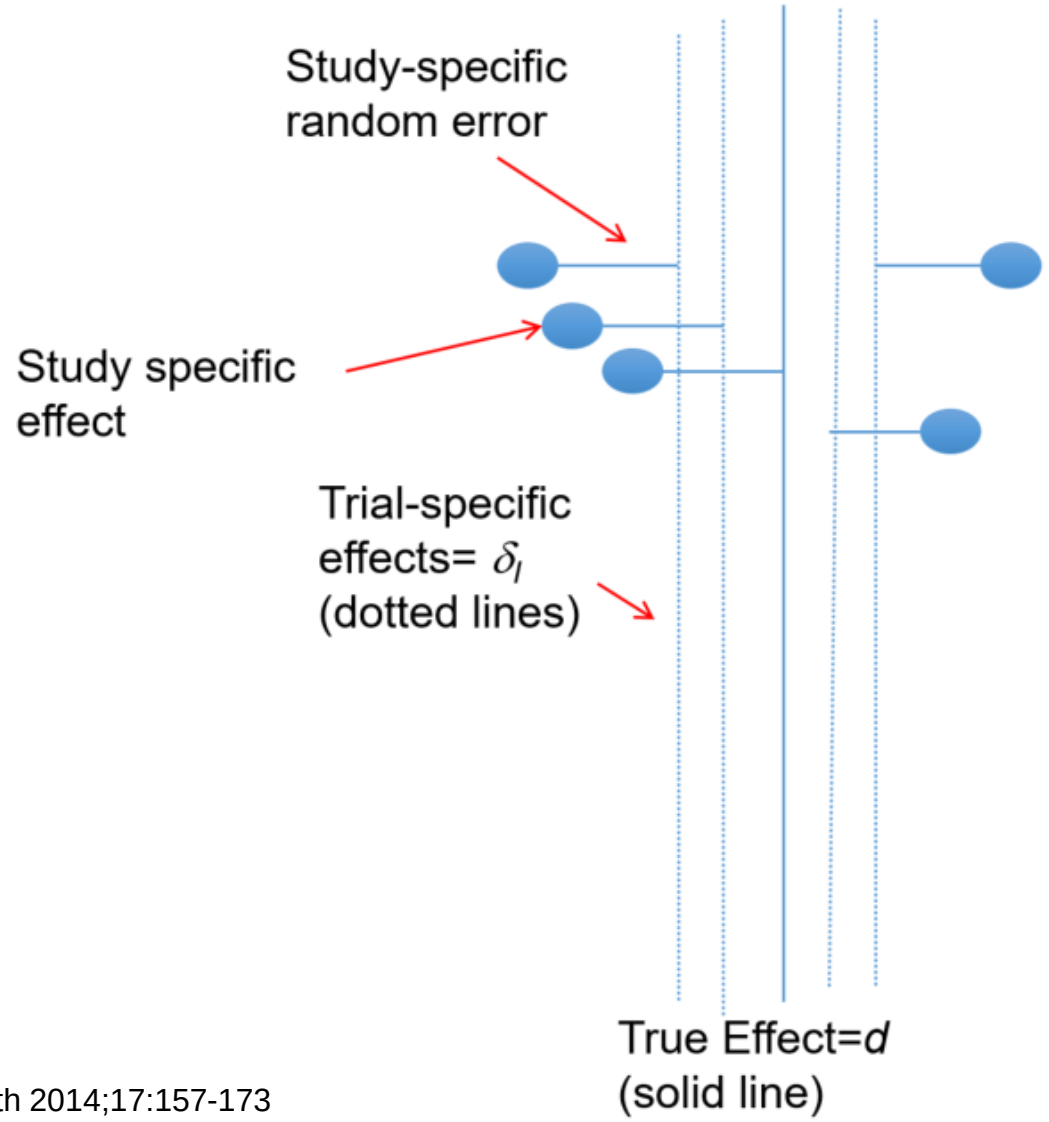
Fundamentals of NMA (5): Random Effects (RE) Model

- Across studies
- τ^2 = variability btwn studies
- RE model does not 'fix' heterogeneity;
- it simply acknowledges it



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Bayesian Framework for Analysis

- Start with what you know (prior information)
- Combine with what you observe (likelihood function)
- This gives you what you know after observing the data (posterior information)

likelihood **prior**

$$\Pr(B|A) = \frac{\Pr(A|B) \times \Pr(B)}{\Pr(A)}$$

posterior **scaling term**

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O'Hagan & Luce. A Primer on Bayesian Statistics. Center for Bayesian Statistics in Health Economics. MEDTAP International, 2003

Example of Bayes' Theorem

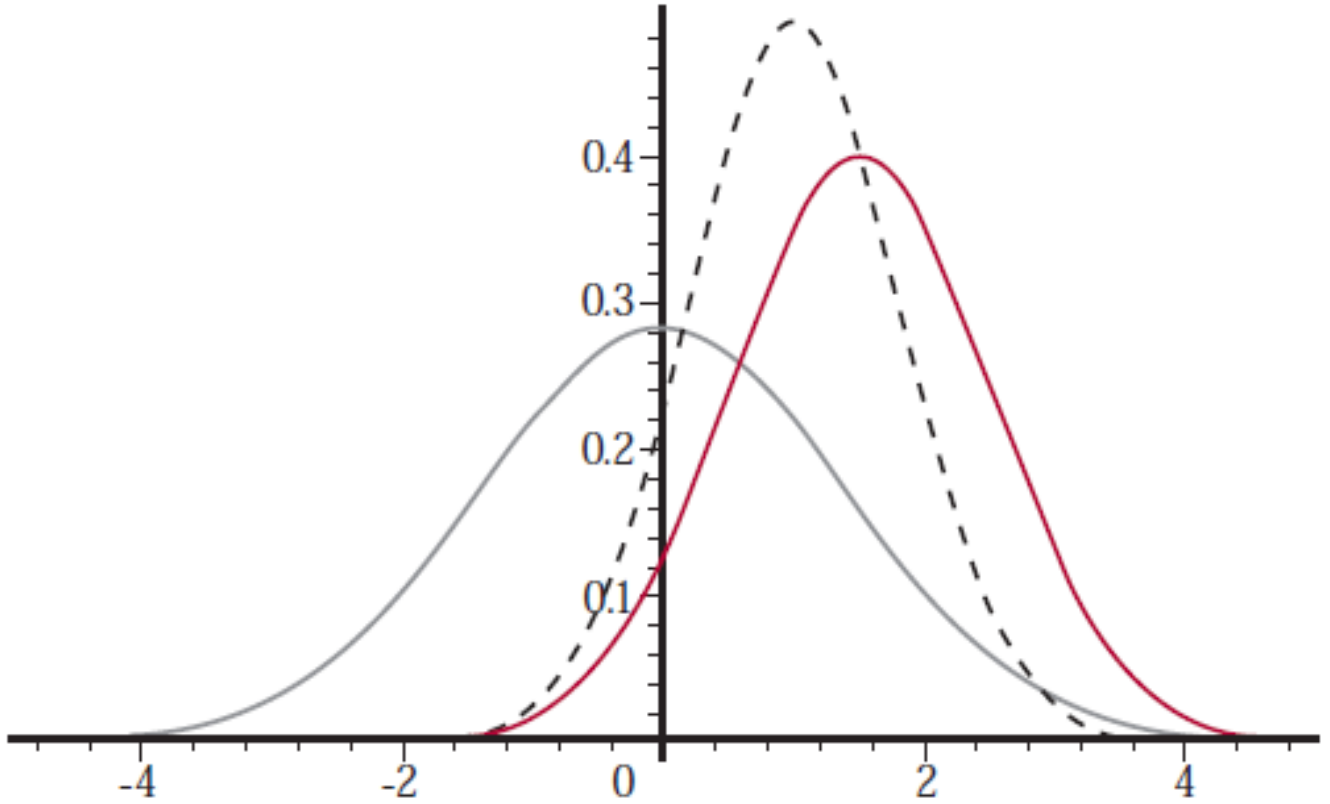

Figure 1. The prior distribution (grey) and information from the new data (red) are synthesized to produce the posterior distribution (black dotted).

O'Hagan & Luce. A Primer on Bayesian Statistics. Center for Bayesian Statistics in Health Economics. MEDTAP International, 2003

Bayesian Computational Methods (1) – Monte Carlo Simulation

- Estimates random sequence of chains, where
  - next chain relies only on its immediate predecessor - *Markov chain*
- Markov chain Monte Carlo simulation (MCMC)
  - set up a Markov chain whose distribution is the posterior distribution
- Chain must run to convergence before estimating posterior probabilities – *burn ins*
- A special type of algorithm - cycles through each model parameter one at a time is called *Gibbs sampling*
- JAGS ® = Just Another Gibbs Sampler

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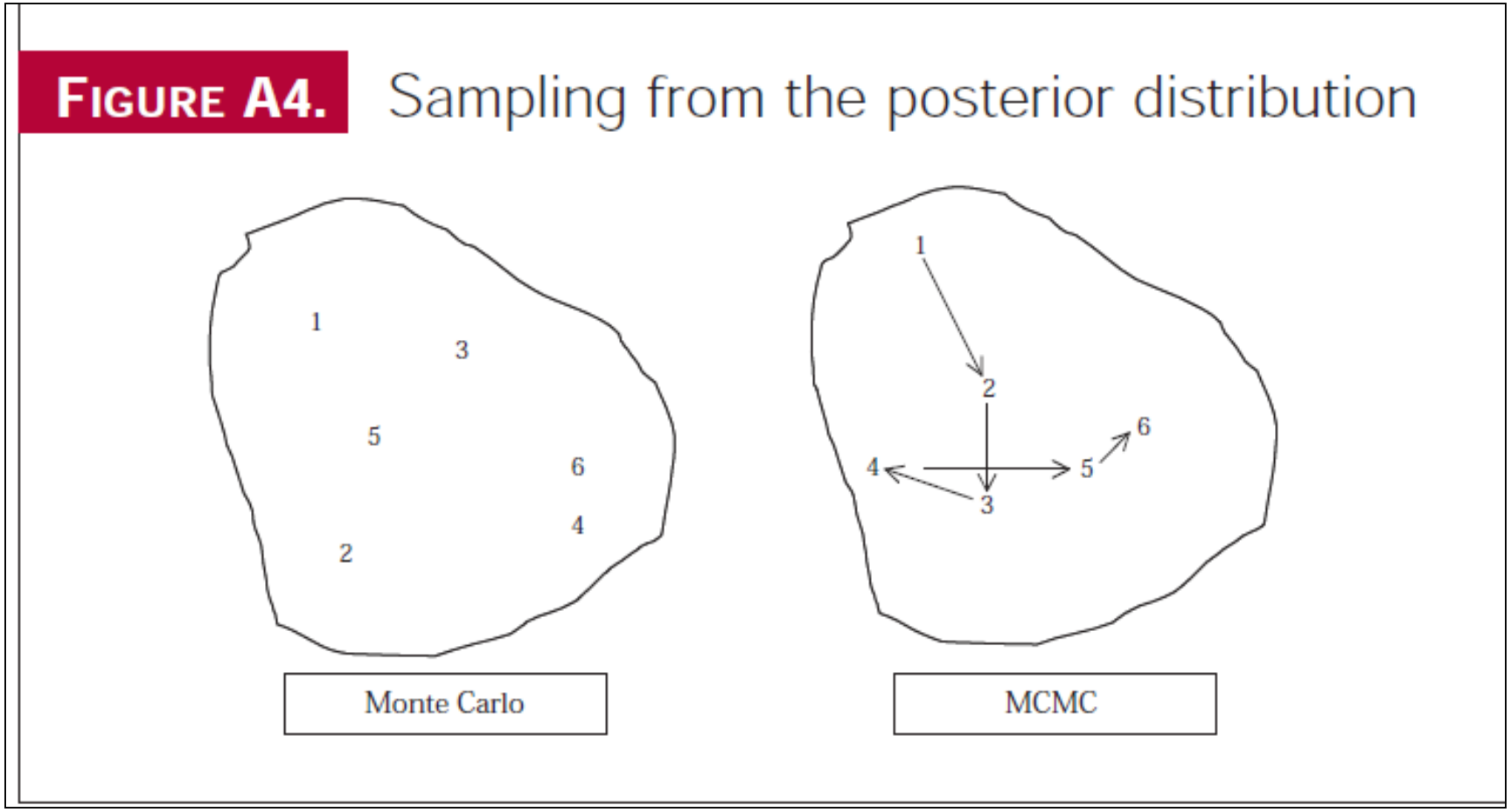
Bayesian Computational Methods (2)– Monte Carlo Simulation



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Frequentist *vs.* Bayesian Results of NMA

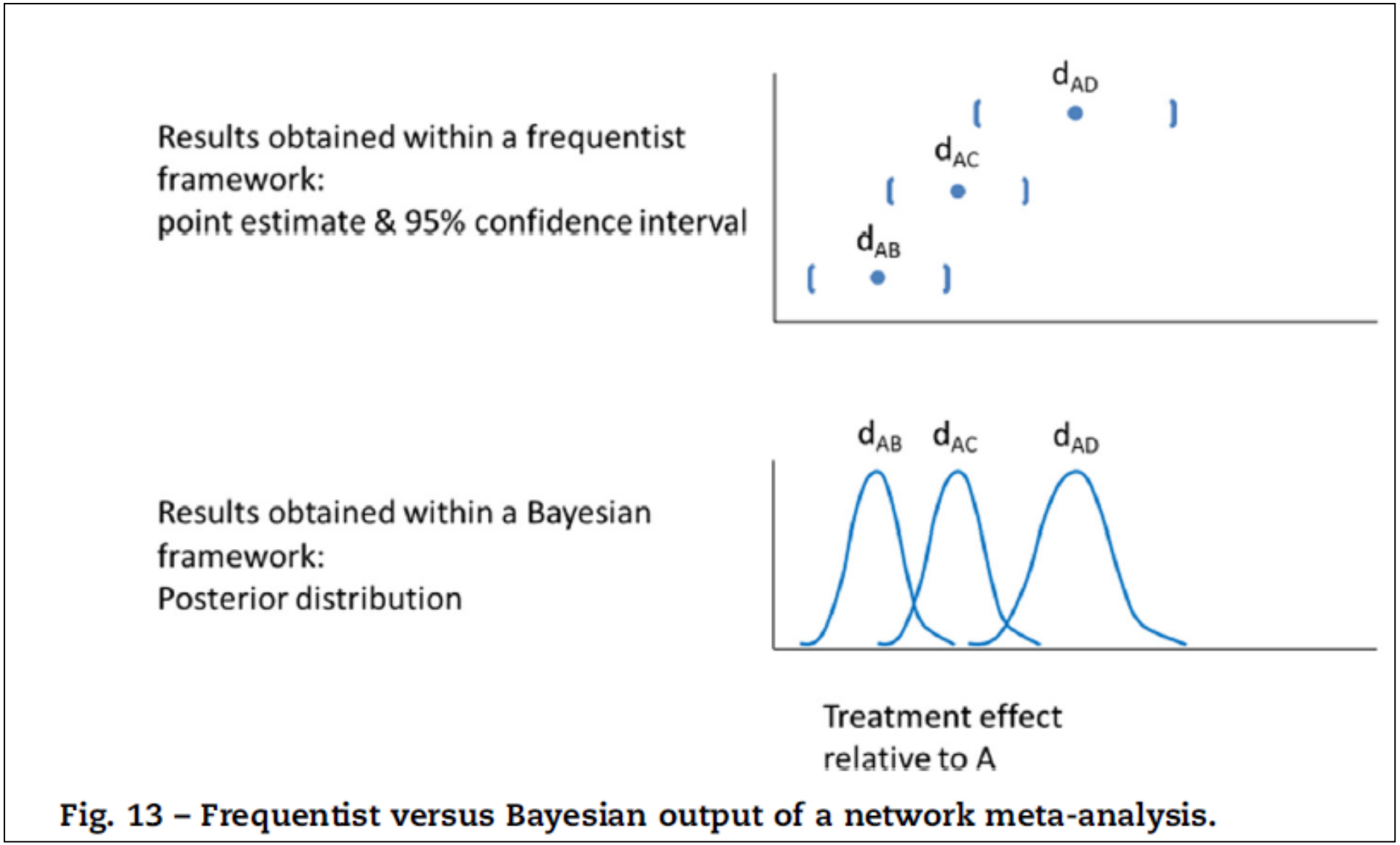

Fig. 13 – Frequentist versus Bayesian output of a network meta-analysis.

Jansen, et al. Value in Health 2014;17:157-173

Criticisms of Bayesian Approach (of NMA)

- Priors are subjective (differ between persons)
- Priors difficult to specify
  - An area of active research
- No single measure of “statistical significance “
  - No p-value
- Computationally more challenging
  - Computers have largely solved the problem
- Programming more challenging
  - New packages emerging

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Advantages of Bayesian Approach (of NMA)

- Inferences mean what you thought frequentist inferences meant!
- Exact sample size results (no asymptotics)
- Can incorporate prior knowledge
- More natural in context of decision-making
  - Can calculate probability of effect of each technology
  - Can rank order technologies

Jansen. Value in Health 2008;11(5):956-64; 21:2313-24; Jansen, et al. Value in Health 2014;17:157-173

Evolving Methods

- Use of individual patient data (IPD)
- Use of partial IPD and partial aggregate data
  - Matching adjusted indirect treatment comparisons
    - Signorovitch, et al. Comparative effectiveness without head-to-head trials. Pharmacoeconomics 2010;28:935-945
    - Signorovitch, et al. Matching-adjusted indirect comparisons: a new tool for timely CER. Value Health 2012;15:940-947
  - Simulated treatment comparisons
    - Caro & Ishak. No head-to-head trial? Simulate the missing arms. Pharmacoeconomics 2010;28:957-967
    - Ishak, et al. Simulation and matching-based approaches for indirect comparison of treatments. Pharmacoeconomics 2015;33:537-549

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Thank you!

Questions?

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