



NETWORK META-ANALYSIS

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BROWN
School of Public Health

Outline

- Background
- Indirect Comparisons
- Networks
- Heterogeneity
- Exchangeability
- Consistency
- Models
- Ranking

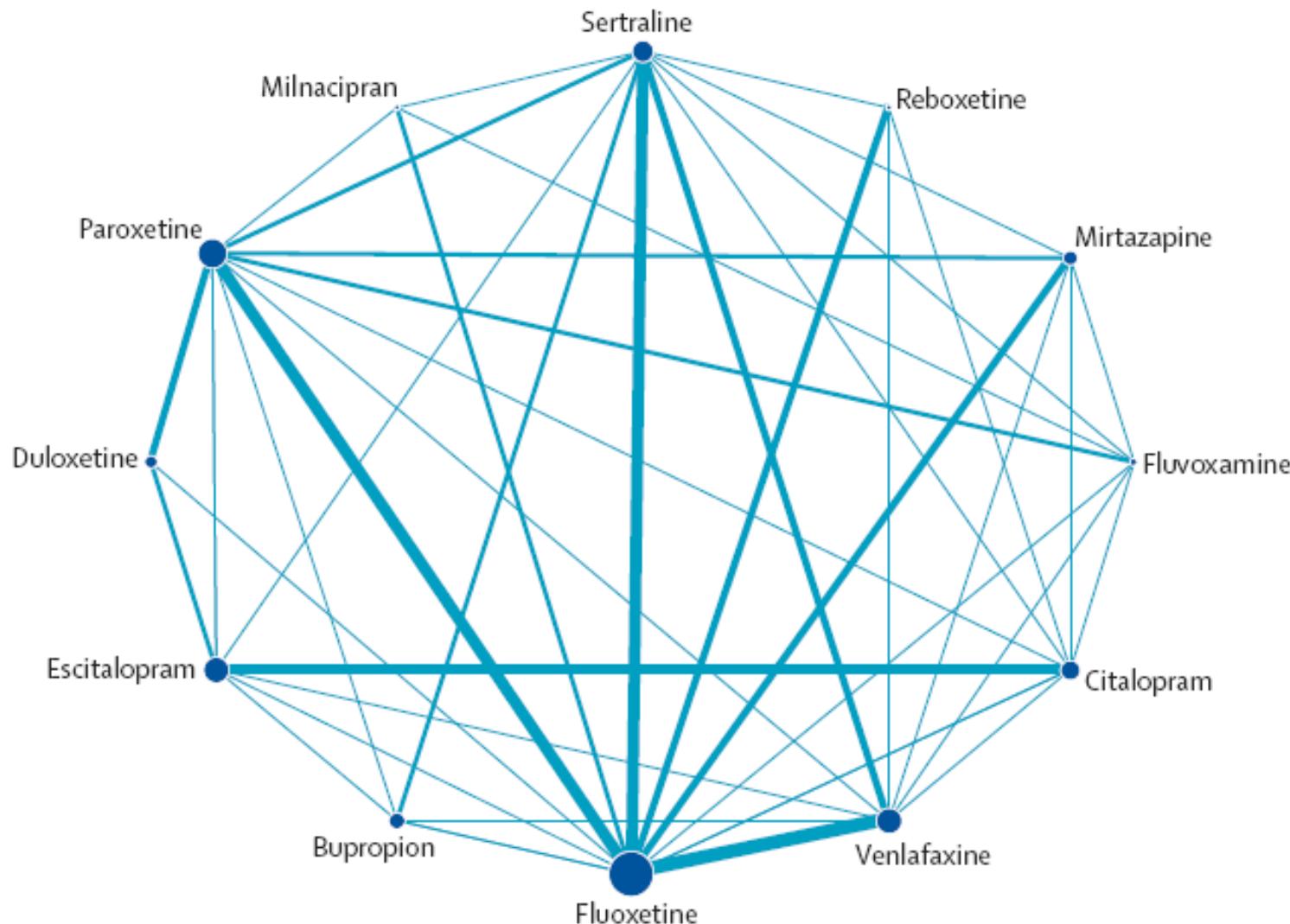
Background

- Clinicians, patients, and health-policy makers need to decide which treatment is “best” and want to use relevant evidence
- Often use meta-analysis to synthesize studies of two treatments
- Many questions involve multiple treatments
- Examples:
 - Behavioral and pharmacological treatments for smoking cessation
 - SSRIs for treatment of depression
 - Oral and intravenous treatments for knee osteoarthritis
- Unfortunately, robustly designed RCTs that simultaneously compare all interventions of interest are almost never available
- Different meta-analyses compare different treatment pairs

Background

- New drugs are often compared with placebo or standard care, but not against each other, in trials aimed to contribute toward obtaining approval for drug licensing
- Commercial disincentive to compare new treatment with active control
- *Indirect treatment comparisons* provide useful evidence
- *Network meta-analysis* extends standard pairwise meta-analysis by including multiple pairwise comparisons across a range of interventions
- Incorporates both *direct* and *indirect* evidence

Example: Antidepressants



Example: Antidepressants

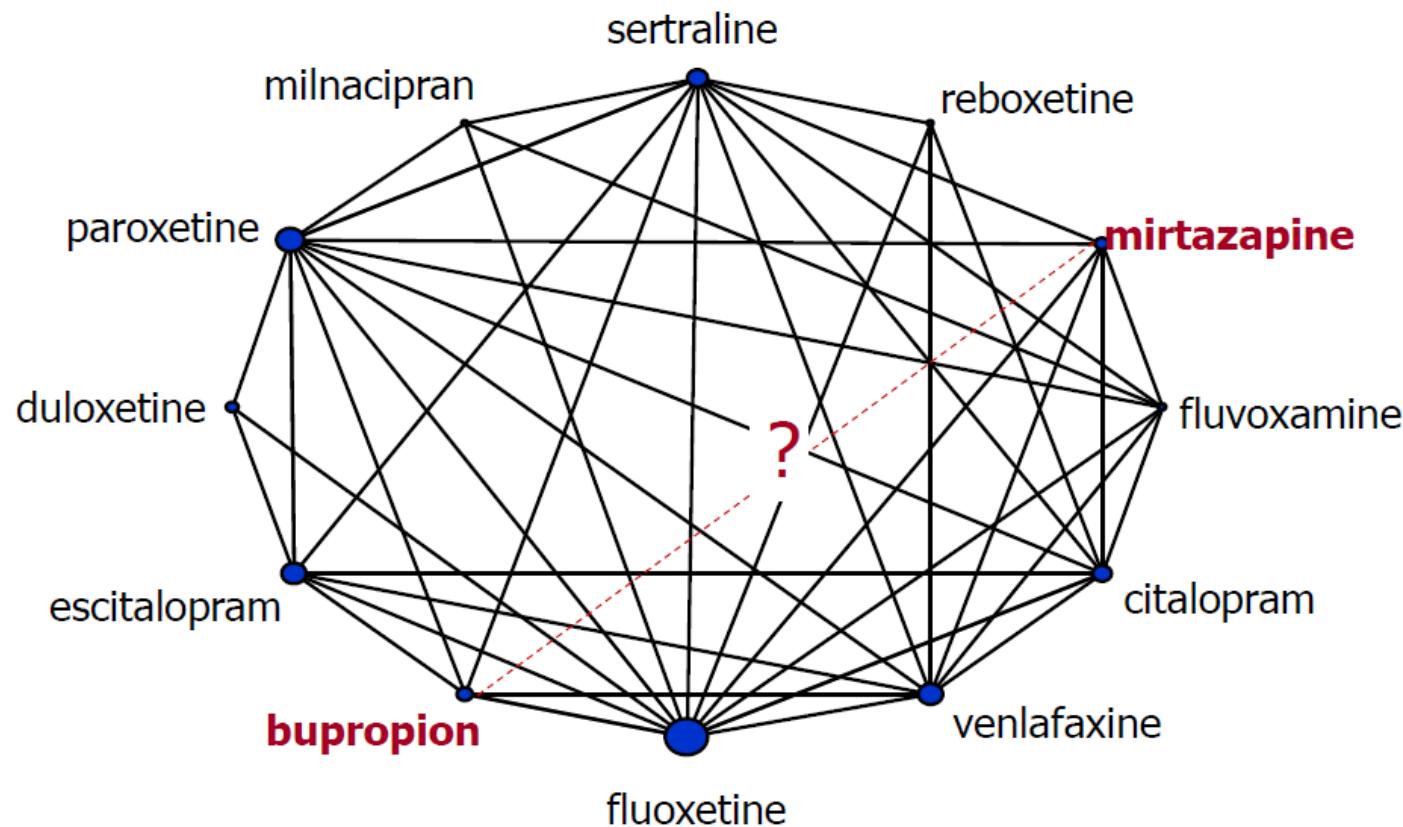
Source data. New-generation antidepressants for major depression, dropouts

Study	fluoxetine		bupropion		citalopram		duloxetine		escitalopram		fluvoxamine		milnacipran		mirtazapine		paroxetine		reboxetine		sertraline		venlafaxine		
	r	n	r	n	r	n	r	n	r	n	r	n	r	n	r	n	r	n	r	n	r	n	r	n	
2906/421	45	119															50	123							
29060/365	27	70															21	68							
29060/785					43	207											41	199							
Aberg-Wisted, 2000																	26	177					33	176	
Agren, 1999							8	133								18	137								
Auguglia, 1993	31	56																				17	52		
AK130939			45	204																				46	198
Akkaya, 2003																					7	57		7	50
Alves, 1999	9	47																						10	40
Amini, 2005	3	18															2	18							
Annseaaau, 1993																23	64						16	56	
Annseau, 1994	18	93															23	97							
Baldwin, 2005																15	166						14	159	
Benkert, 1999	—	—																							
Bennie, 1995	23	144																						24	142
	—	—	—	—	—	—																			
Detke, 2004																21	188						10	86	
Zanardi, 1996																								0	24

Source: For complete dataset see Cipriani et al., 2009; r refers to dropouts; n refers to number of patients.

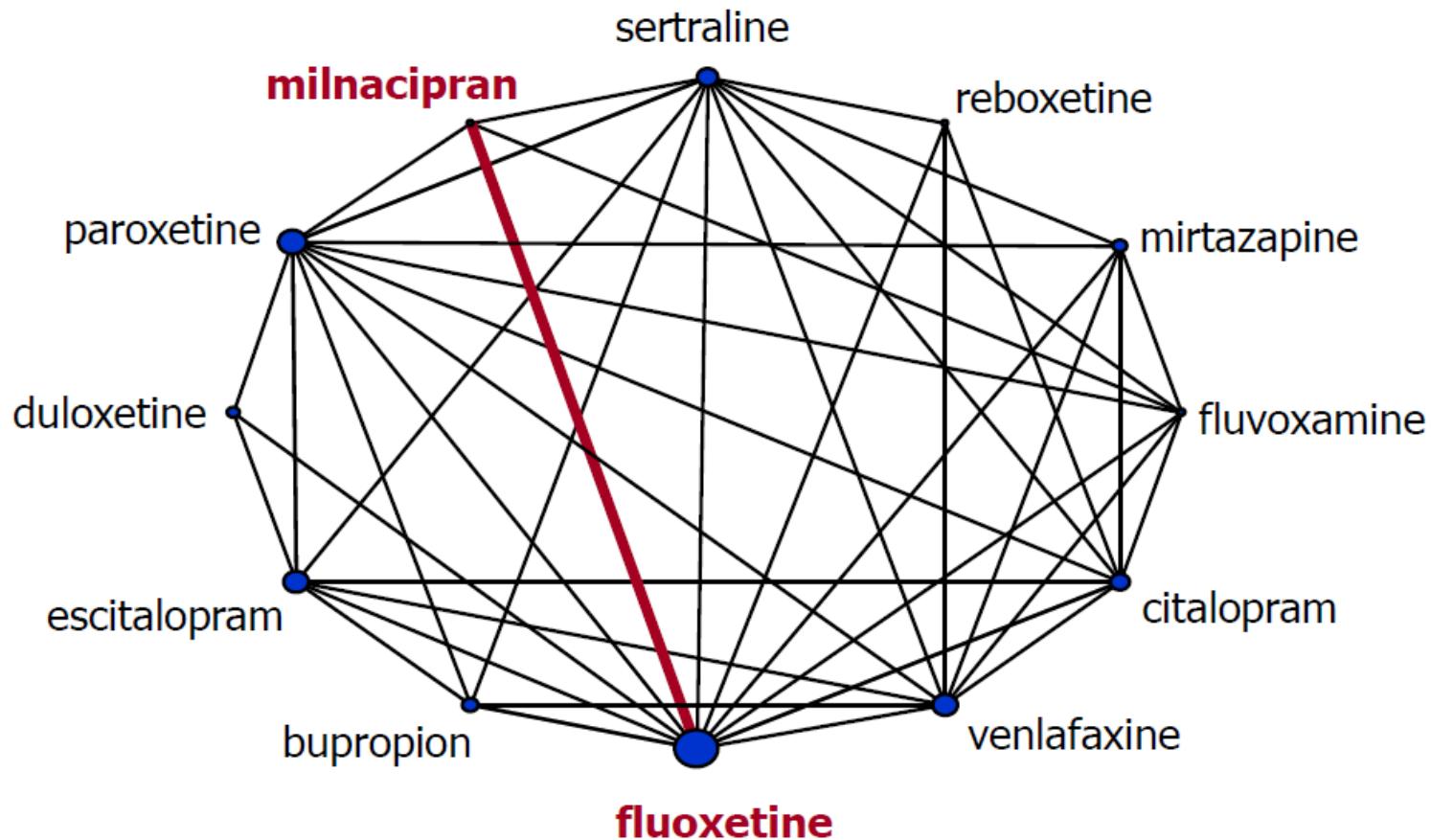


Treatments Without Direct Comparison



OR(B vs M)= 0.79 (0.72, 1)

Improved Precision



Fluoxetine vs Milnacipran (response to treatment)

Meta-analysis: 1.15 (0.72, 1.85)

MTM: 0.97 (**0.69, 1.32**)

Ranking Treatments

■ Efficacy (response rate) (95% CI)

■ Comparison

□ Acceptability (dropout rate) (95% CI)

BUP	1.00 (0.78-1.28)	0.75 (0.55-1.01)	1.06 (0.86-1.32)	0.89 (0.74-1.08)	0.73 (0.53-1.00)	0.87 (0.58-1.24)	0.87 (0.66-1.14)	0.81 (0.65-1.00)	0.62 (0.45-0.86)	1.01 (0.82-1.27)	0.84 (0.68-1.02)
0.98 (0.78-1.23)	CIT	0.75 (0.55-1.02)	1.07 (0.86-1.31)	0.90 (0.73-1.09)	0.73 (0.54-0.99)	0.87 (0.60-1.24)	0.87 (0.66-1.15)	0.81 (0.65-1.01)	0.62 (0.45-0.84)	1.02 (0.81-1.28)	0.84 (0.67-1.06)
1.09 (0.83-1.43)	1.12 (0.87-1.44)	DUL	1.43 (1.09-1.85)	1.19 (0.91-1.57)	0.98 (0.67-1.41)	1.16 (0.77-1.73)	1.16 (0.83-1.61)	1.08 (0.84-1.40)	0.83 (0.57-1.22)	1.36 (1.01-1.83)	1.12 (0.84-1.50)
0.82 (0.67-1.01)	0.84 (0.70-1.01)	0.75 (0.60-0.93)	ESC	0.84 (0.70-1.01)	0.69 (0.50-0.94)	0.81 (0.55-1.15)	0.81 (0.62-1.07)	0.76 (0.62-0.93)	0.58 (0.43-0.81)	0.95 (0.77-1.19)	0.78 (0.64-0.97)
1.08 (0.90-1.29)	1.10 (0.93-1.31)	0.99 (0.79-1.24)	1.32 (1.12-1.55)	FLU	0.82 (0.62-1.07)	0.97 (0.69-1.32)	0.97 (0.77-1.21)	0.91 (0.79-1.05)	0.70 (0.53-0.92)	1.14 (0.96-1.36)	0.94 (0.81-1.09)
1.10 (0.83-1.47)	1.13 (0.86-1.47)	1.01 (0.74-1.38)	1.35 (1.02-1.76)	1.02 (0.81-1.30)	FVX	1.18 (0.76-1.75)	1.18 (0.87-1.61)	1.10 (0.84-1.47)	0.85 (0.57-1.26)	1.38 (1.03-1.89)	1.14 (0.86-1.54)
1.07 (0.77-1.48)	1.09 (0.78-1.50)	0.97 (0.69-1.38)	1.30 (0.95-1.78)	0.99 (0.74-1.31)	0.97 (0.68-1.37)	MIL	0.99 (0.69-1.53)	0.94 (0.68-1.31)	0.72 (0.48-1.10)	1.17 (0.84-1.72)	0.97 (0.69-1.40)
0.79 (0.72-1.00)	0.80 (0.63-1.01)	0.72 (0.54-0.94)	0.96 (0.76-1.19)	0.73 (0.60-0.88)	0.71 (0.55-0.92)	0.74 (0.53-1.01)	MIR	0.93 (0.75-1.17)	0.72 (0.51-1.03)	1.17 (0.91-1.51)	0.97 (0.76-1.23)
1.06 (0.87-1.30)	1.08 (0.90-1.30)	0.97 (0.78-1.20)	1.30 (1.10-1.53)	0.98 (0.86-1.12)	0.96 (0.76-1.23)	1.00 (0.74-1.33)	1.35 (1.11-1.64)	PAR	0.77 (0.56-1.05)	1.25 (1.04-1.52)	1.03 (0.86-1.24)
1.60 (1.20-2.16)	1.63 (1.25-2.14)	1.46 (1.05-2.02)	1.95 (1.47-2.59)	1.48 (1.16-1.90)	1.45 (1.03-2.02)	1.50 (1.03-2.18)	2.03 (1.52-2.78)	1.50 (1.16-1.98)	REB	1.63 (1.19-2.24)	1.34 (0.99-1.83)
0.87 (0.72-1.05)	0.88 (0.72-1.07)	0.79 (0.62-1.01)	1.06 (0.88-1.27)	0.80 (0.69-0.93)	0.79 (0.61-1.01)	0.81 (0.60-1.11)	1.10 (0.90-1.36)	0.82 (0.69-0.96)	0.54 (0.41-0.71)	SER	0.82 (0.67-1.00)
0.85 (0.70-1.01)	0.86 (0.71-1.05)	0.77 (0.60-0.99)	1.03 (0.86-1.24)	0.78 (0.68-0.90)	0.77 (0.59-0.99)	0.79 (0.58-1.08)	1.08 (0.87-1.33)	0.79 (0.67-0.94)	0.53 (0.40-0.69)	0.98 (0.82-1.16)	VEN

OR>1 means the treatment in top-left is better

Network Meta-Analysis

- Combine direct + indirect estimates of multiple treatment effects
- Internally consistent set of estimates that respects randomization
- Estimate effect of each intervention relative to every other
whether or not there is direct comparison in studies
- Calculate probability that each treatment is most effective
- Compared to conventional pair-wise meta-analysis:
 - Greater precision in summary estimates
 - Ranking of treatments according to effectiveness or safety

Indirect Comparisons

Trial

1 A B

- Want to compare A vs. B
Direct evidence from trials 1, 2 and 7

2 A B

Indirect evidence from trials 3, 4, 5, 6 and 7

3 B C

4 B C

- Combining all “A” arms and comparing with all “B” arms destroys randomization

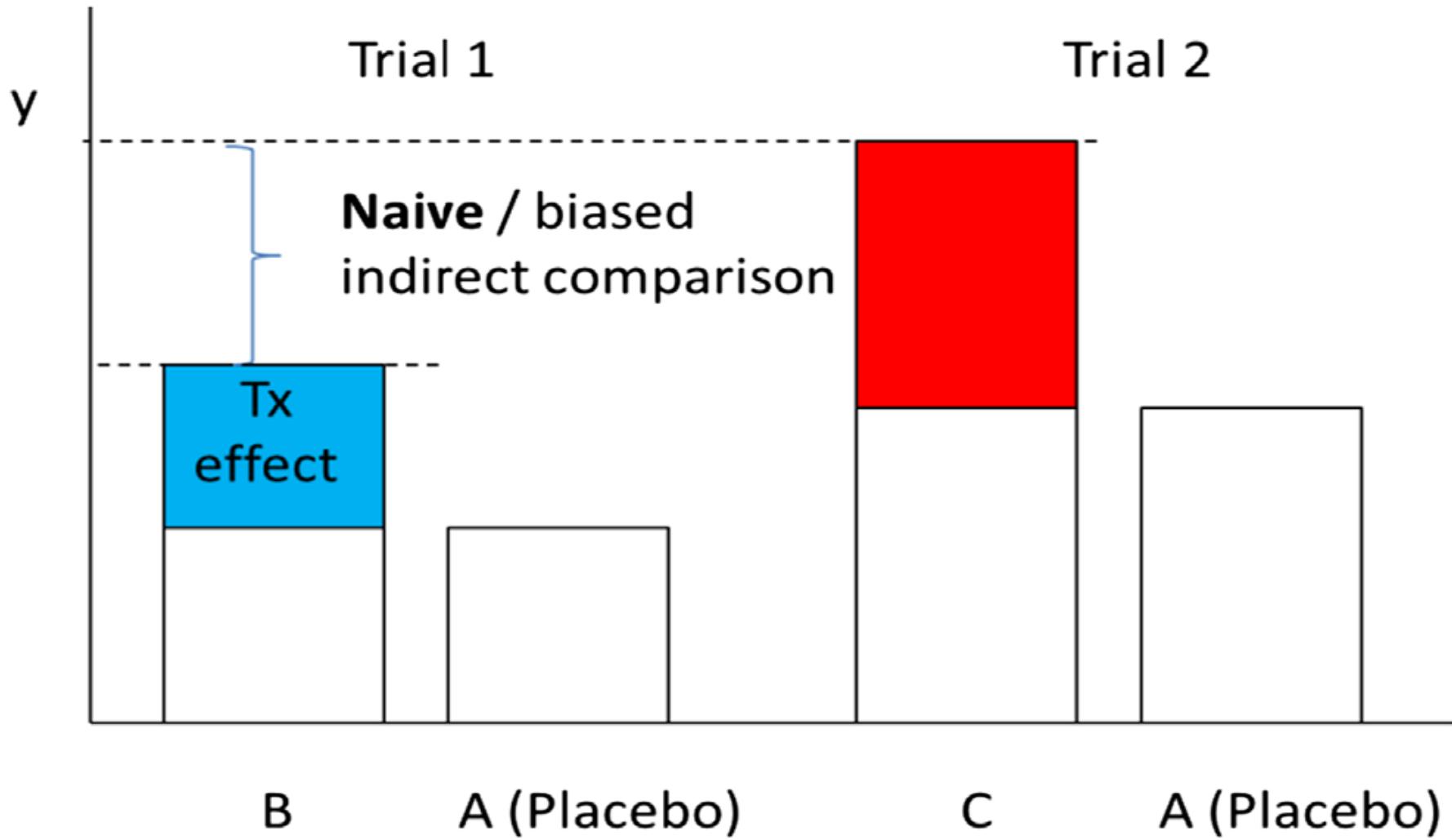
5 A C

6 A C

7 A B C

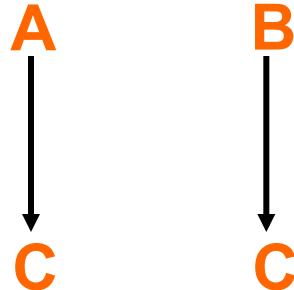
- Use indirect evidence of A vs. C and B vs. C comparisons as additional evidence to preserve randomization and within-study comparison

Naive indirect comparison



- Invalid because study effect differences not acknowledged

Indirect comparison



Two studies A vs C and B vs C

Want to compare A vs B

Indirect comparison



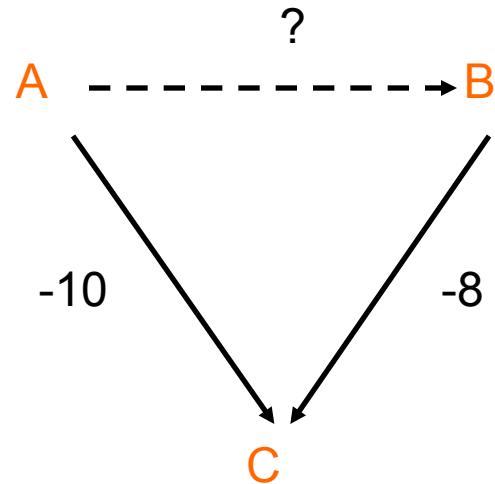
Can do this through common comparator C
(under certain conditions)

Indirect comparison

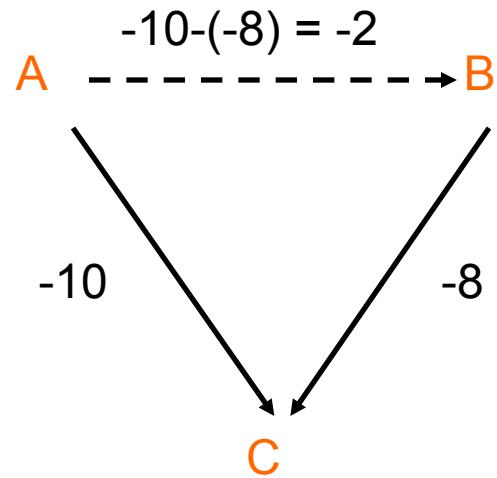


$$A - B = (A - C) - (B - C)$$

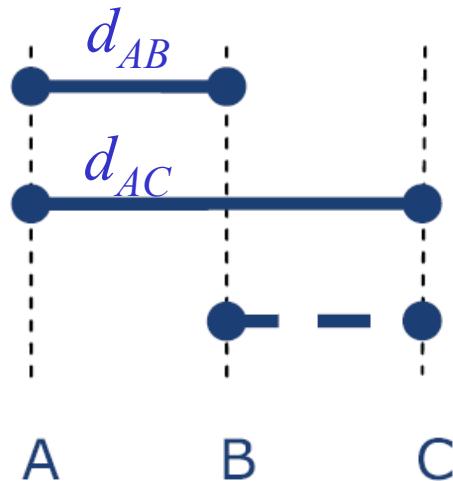
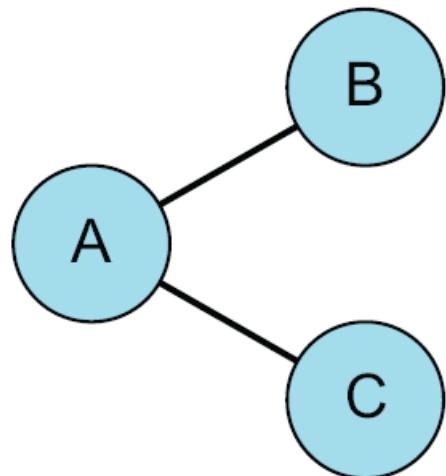
Indirect comparison



Indirect comparison



Indirect comparison



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



Direct comparison

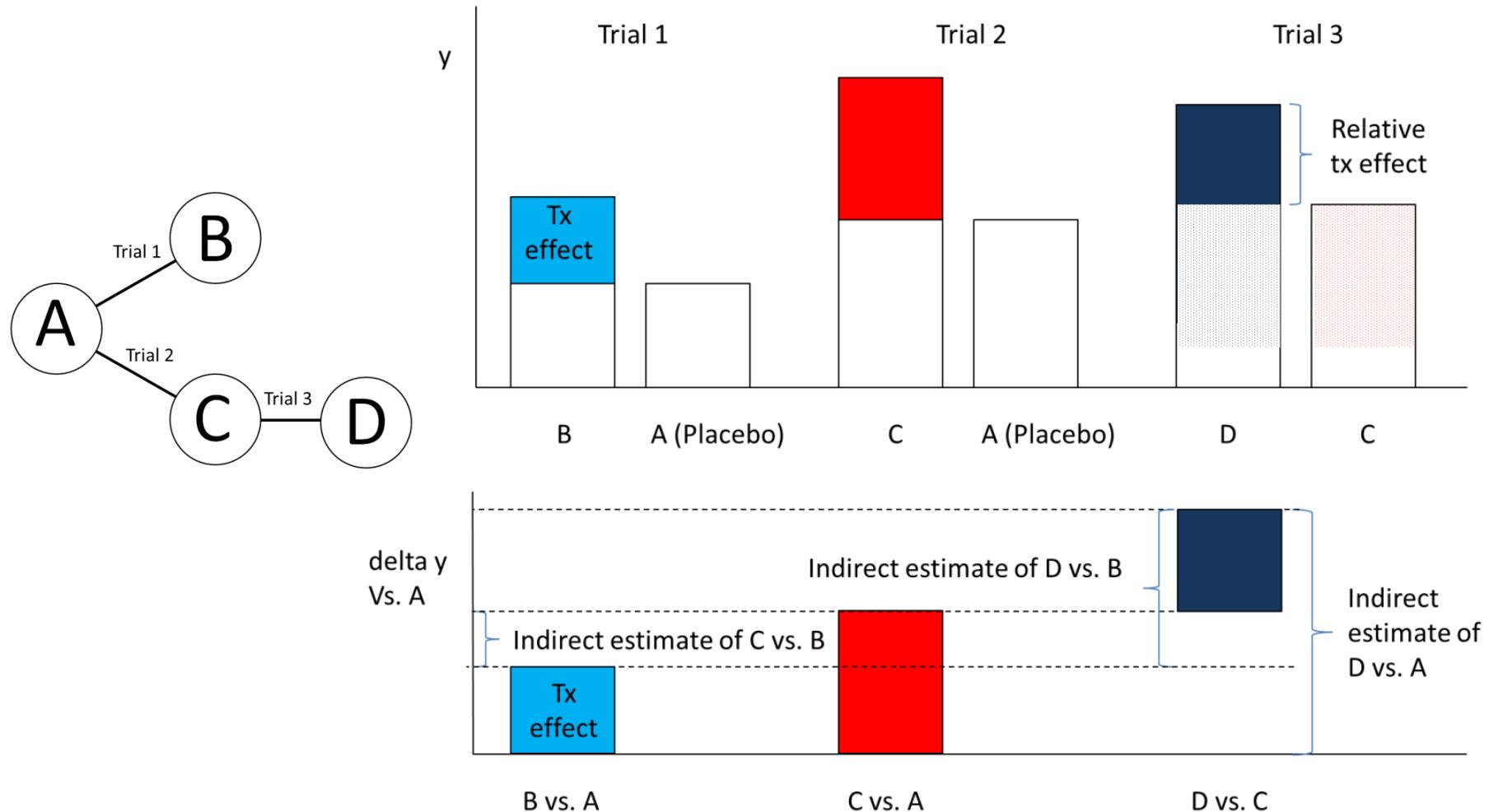


Indirect comparison

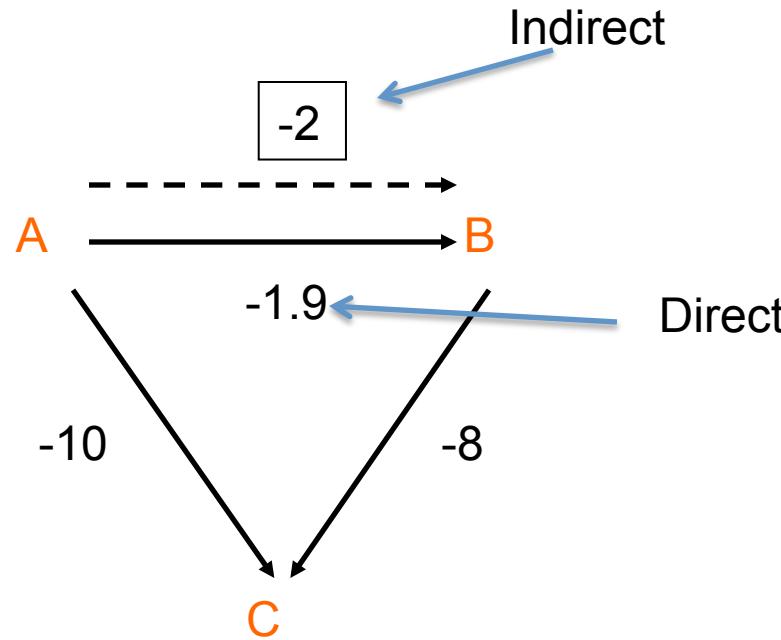
Source: Jansen P, Fleurence R, Devine B, et al. Interpreting indirect treatment comparisons & network meta-analysis for health care decision-making: Report of the ISPOR Task Force on indirect treatment comparisons good research practices—Part 1. Value Health 2011;14:



Indirect comparison

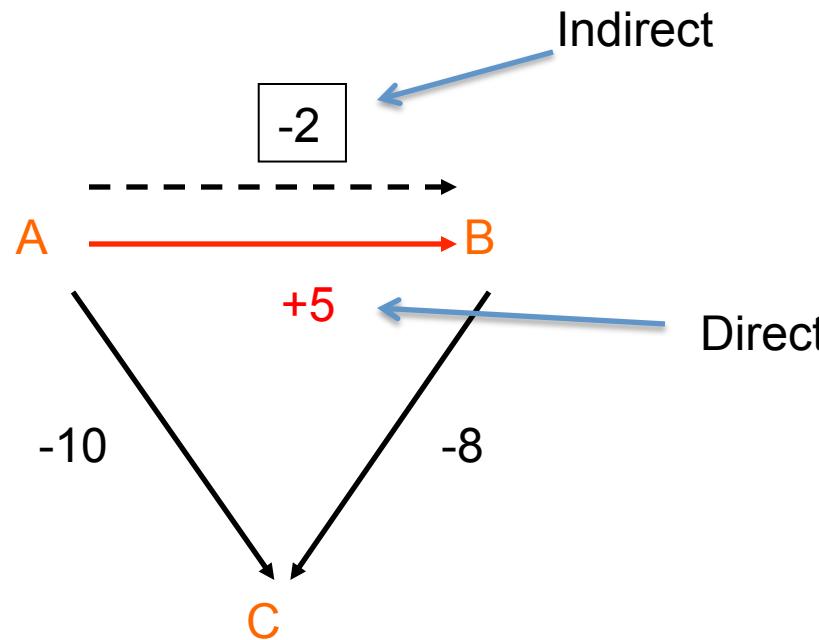


Consistency



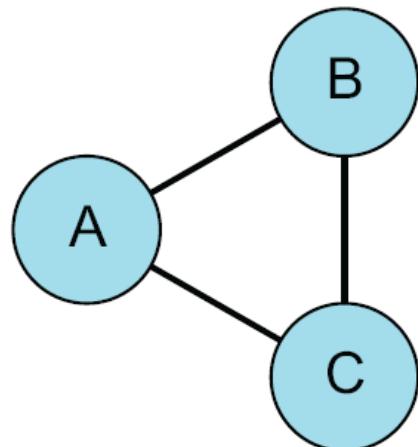
Little difference between direct and indirect estimates

Inconsistency



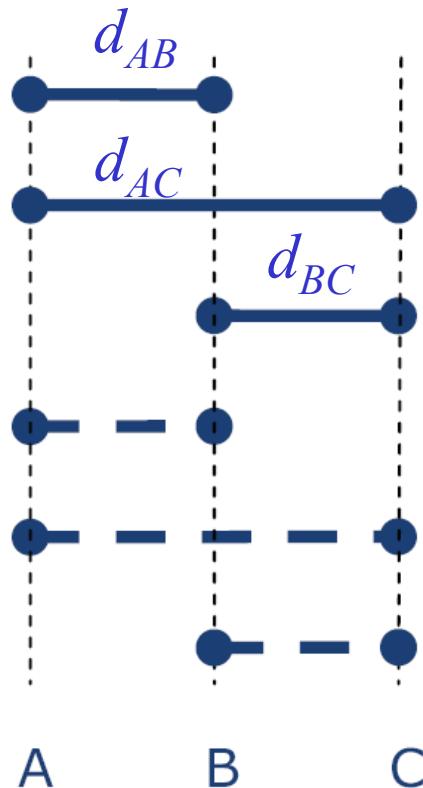
Big difference between direct and indirect estimates

Mixed Treatment Comparison



Direct comparison

Indirect comparison



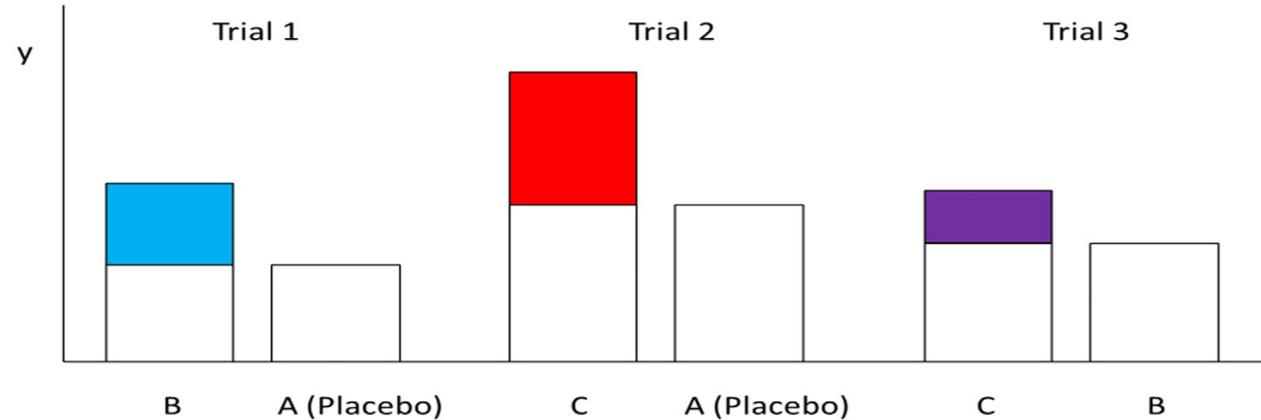
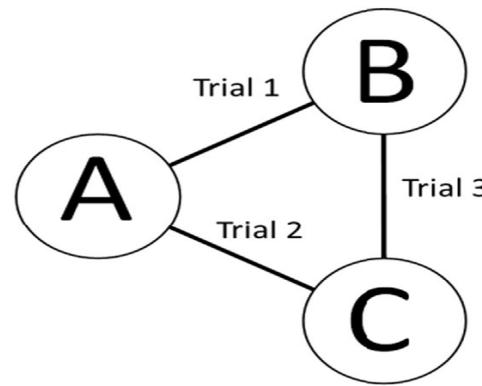
k treatments

A total of $k(k-1)/2$ contrasts

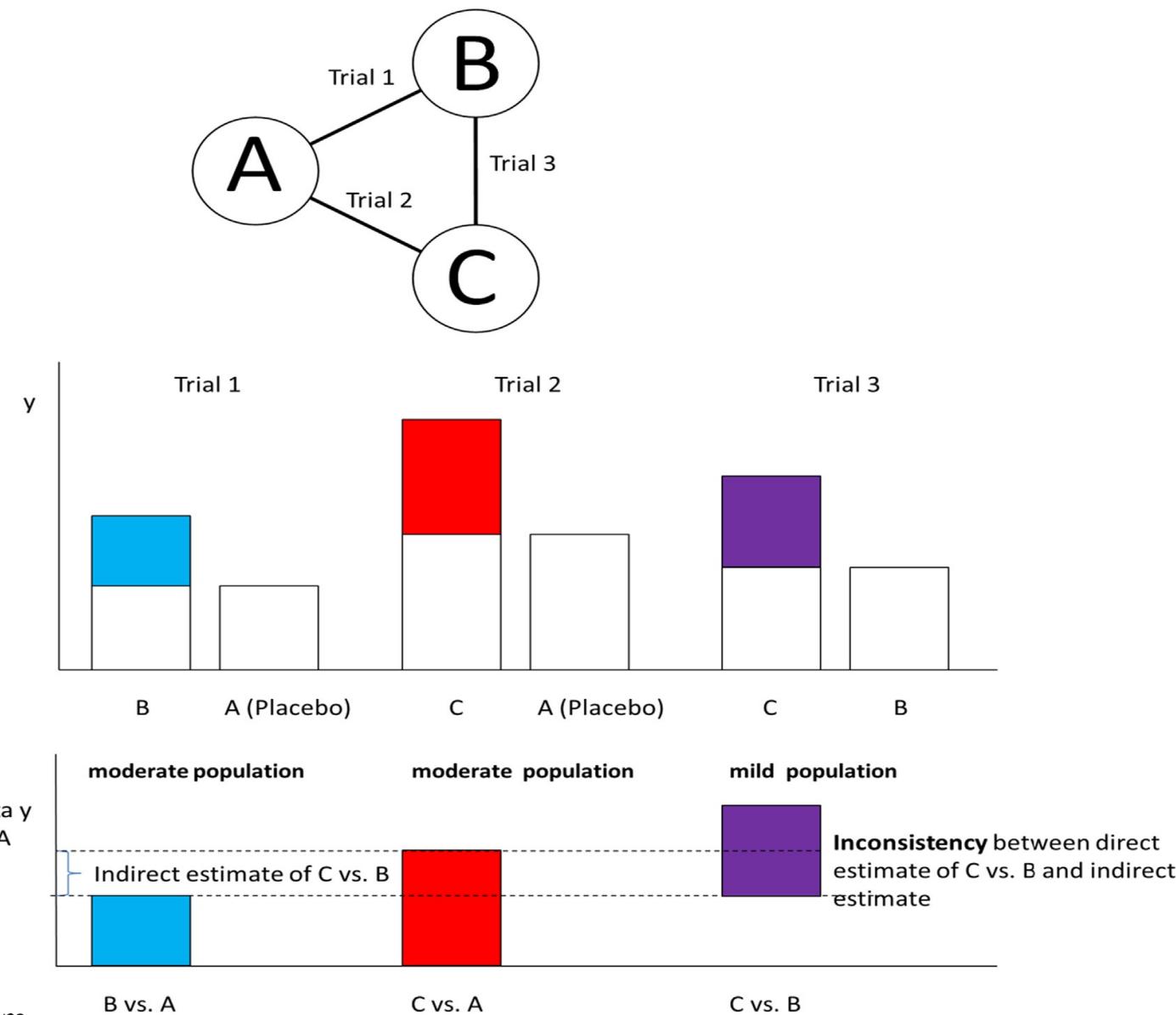
Source: Jansen P, Fleurence R, Devine B, et al. Interpreting indirect treatment comparisons & network meta-analysis for health care decision-making: Report of the ISPOR Task Force on indirect treatment comparisons good research practices—Part 1. *Value Health* 2011;14:



Consistent Closed Loop Network



Inconsistent Closed Loop Network



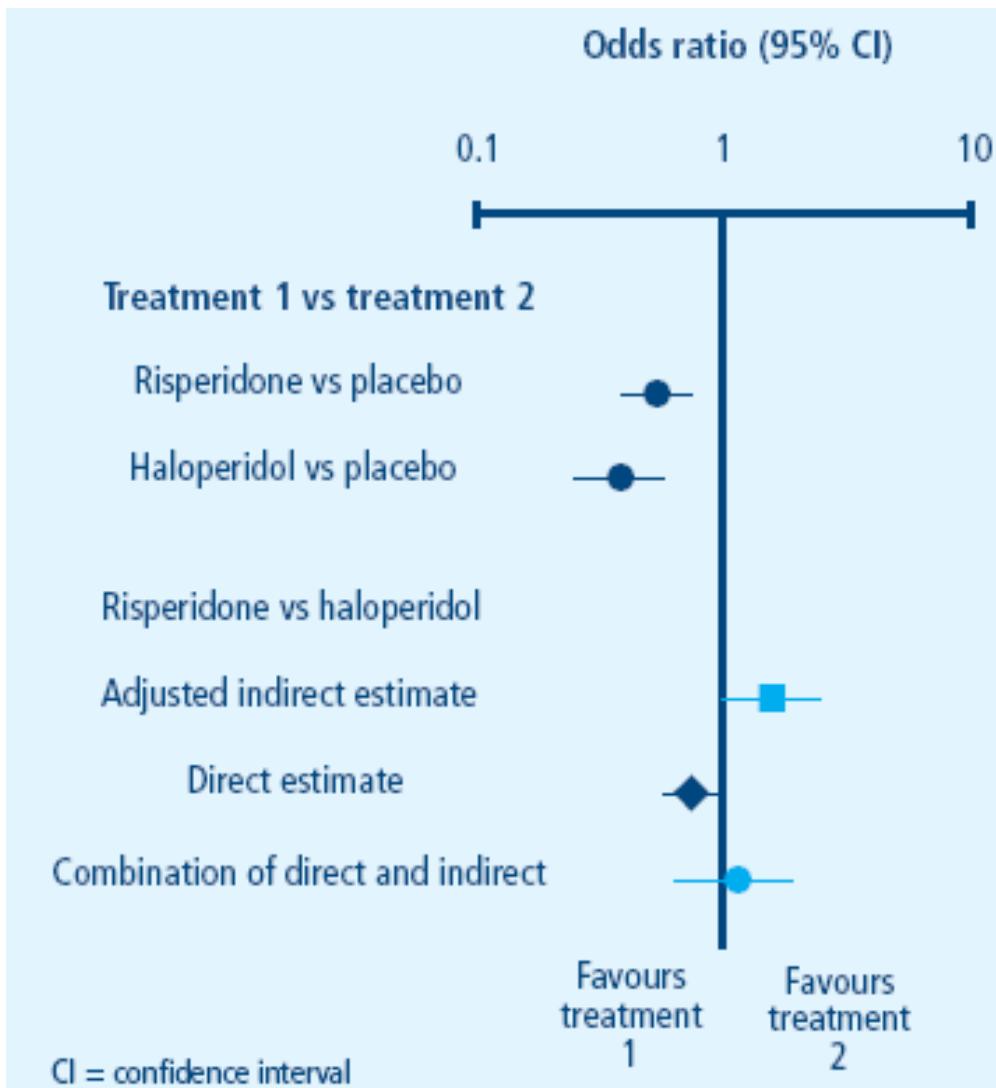
Inconsistent Network

Comparison	Number of trials	Log odds ratio (SE)	Odds ratio (95% CI)	I ² %
Placebo controlled trials				
Risperidone vs placebo	3	-0.909 (0.218)	0.40 (0.26, 0.62)	37%
Haloperidol vs placebo	9	-1.707 (0.318)	0.18 (0.10, 0.34)	11%
Risperidone vs haloperidol				
Direct comparison	10	-0.262 (0.142)	0.77 (0.58, 1.02)	14%
Adjusted indirect comparison	3/9	0.798 (0.386)	2.22 (1.04, 4.72)	
Combination of direct and indirect estimates	10+(3/9)	0.207 (0.527)	1.23 (0.44, 3.45)	85%

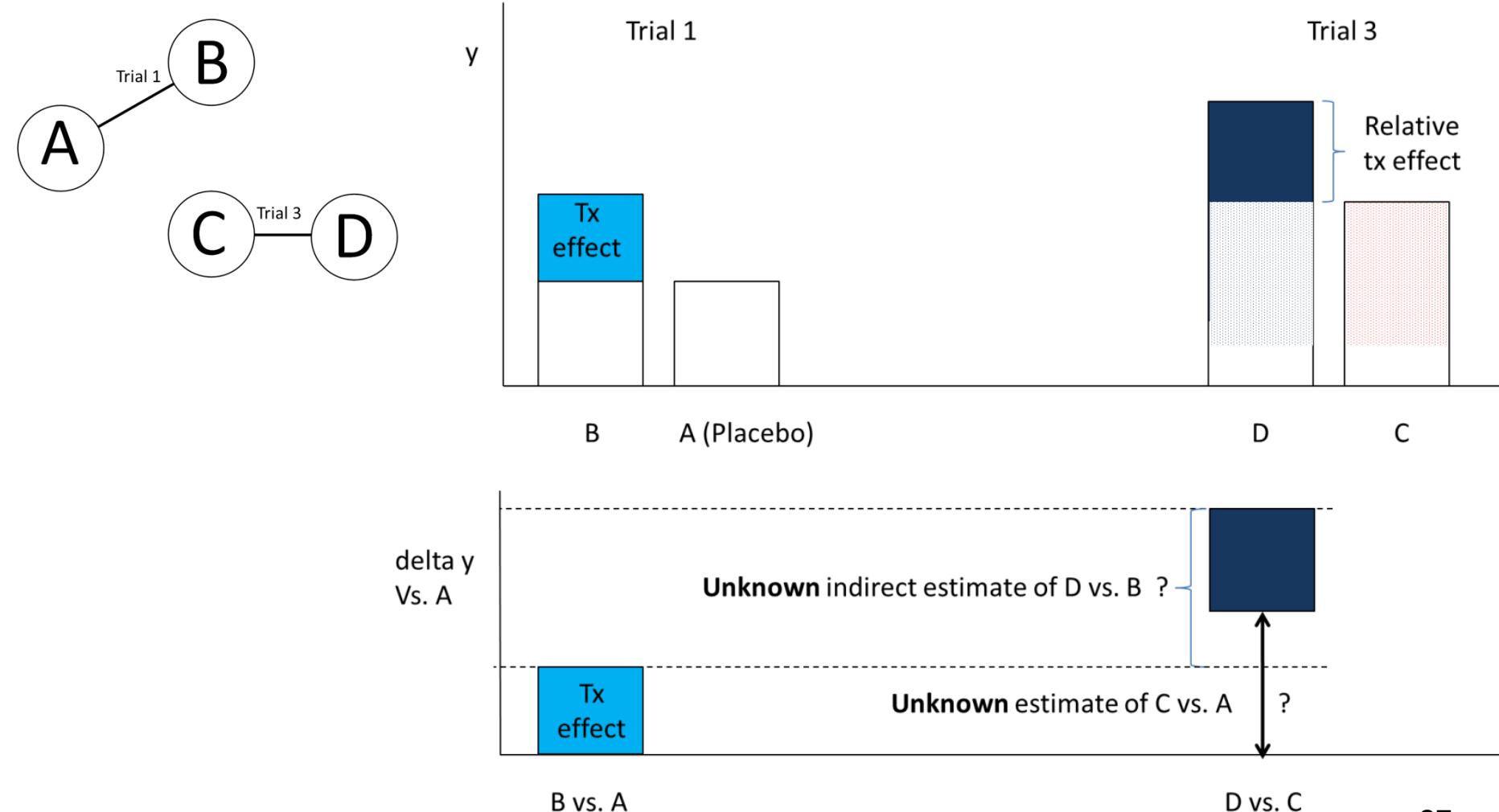
NB Random-effects model was used in meta-analyses of trials and for the combination of the direct and indirect estimates. Odds ratio = EXP(log odds ratio).

CI: confidence interval; SE: standard error

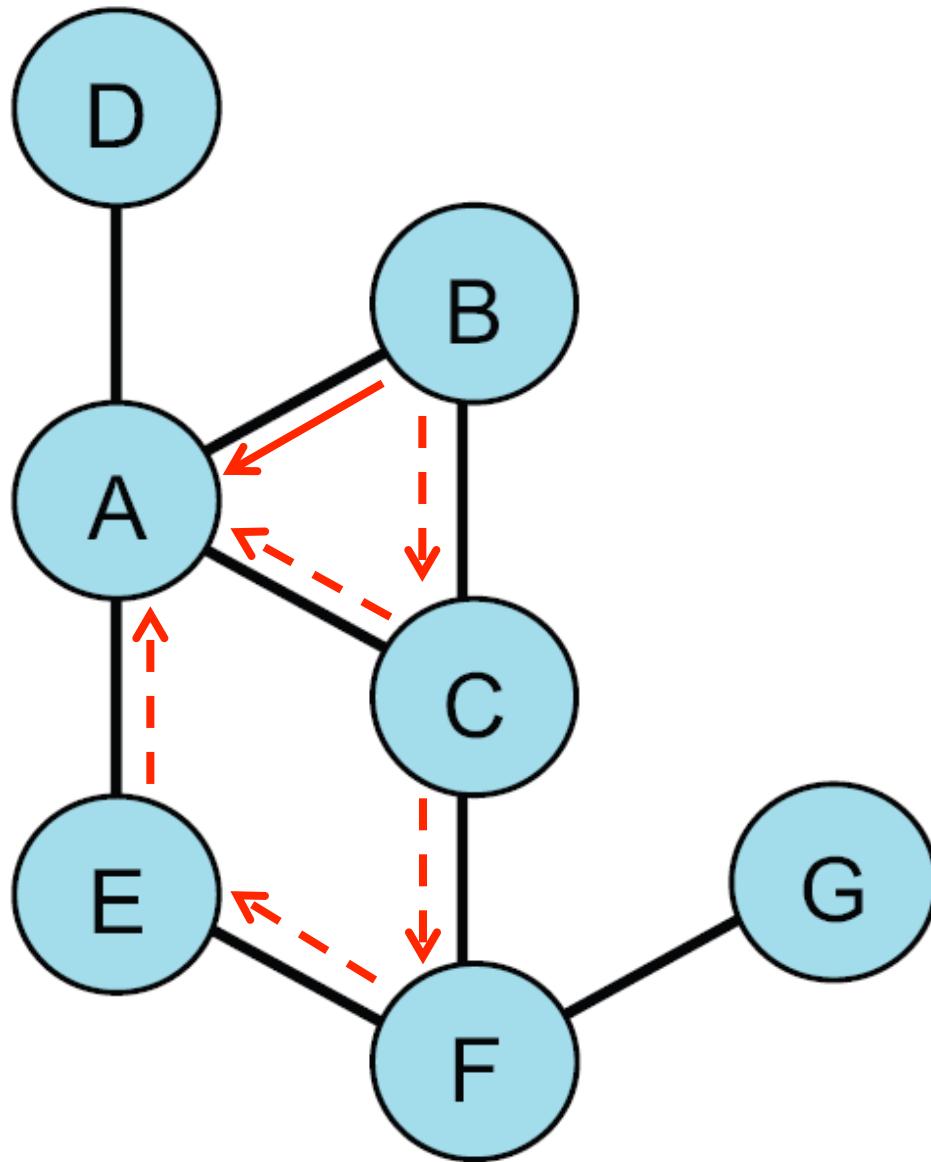
Inconsistent Network



Need for a network



Mixed Treatment Comparisons



- Network of direct and indirect evidence contributing to contrast estimates.
- AB studies provide direct evidence for d_{AB}
- Other studies provide indirect evidence for this contrast.



How Do We Choose Treatments?

- Relevance depends on research question and analysis plan
- Requires collaboration among methods and subject matter experts
- Rankings may be affected by inclusion criteria
- Consider including placebo, older and legacy treatments
- Lump or split?
 - Different treatments within class
 - Different doses within treatment
 - Different comparison groups
- Size of network, comparability, heterogeneity, precision

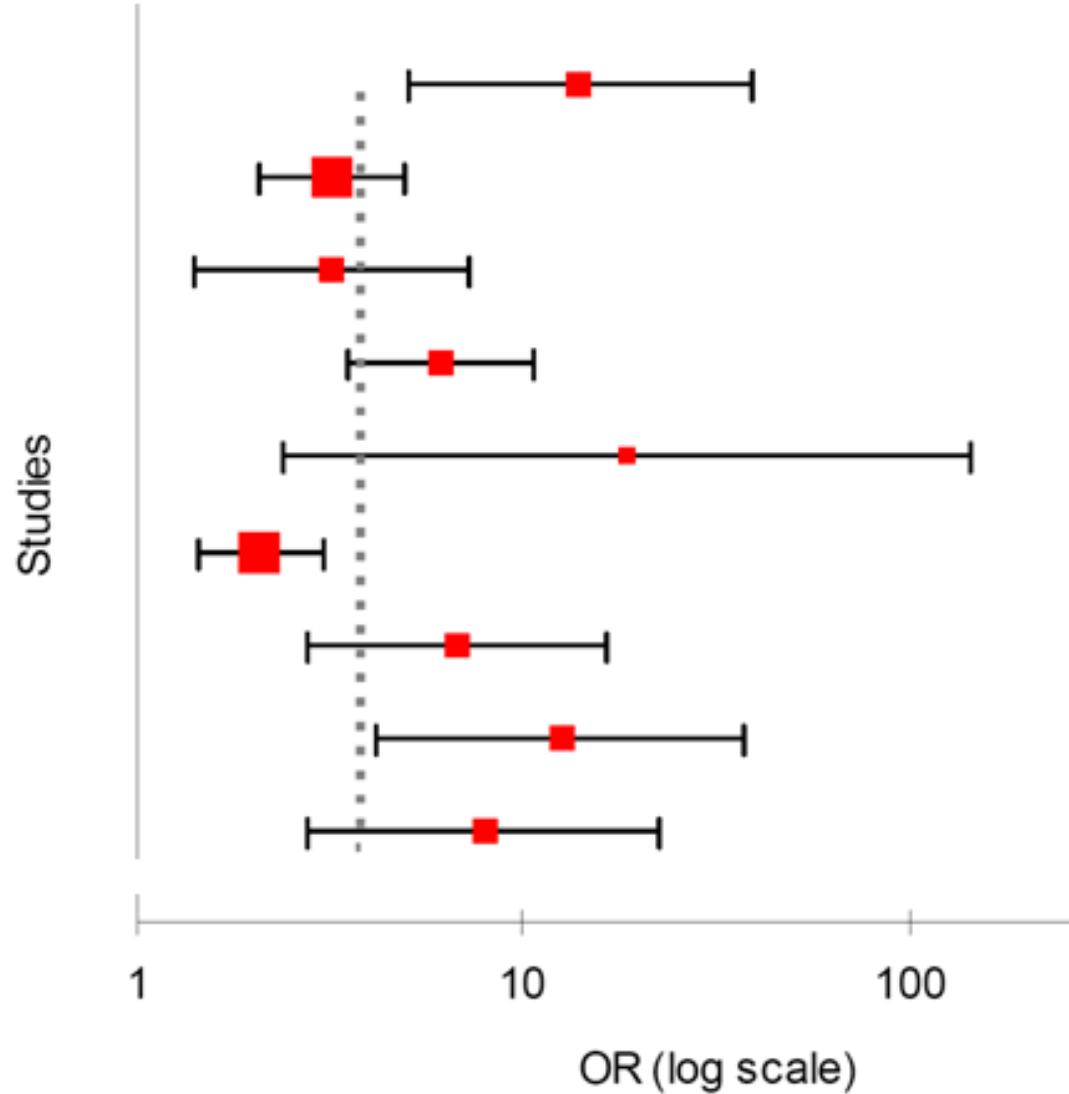
Basic Assumptions

- **Exchangeability** of Treatment Effects Between Studies
Needed for valid combining of estimates
- **Exchangeability** of Treatment Comparisons Between Studies
Needed for valid indirect comparison estimates
- **Consistency:** Direct and indirect estimates give same answer
Needed for valid mixed treatment comparison estimates

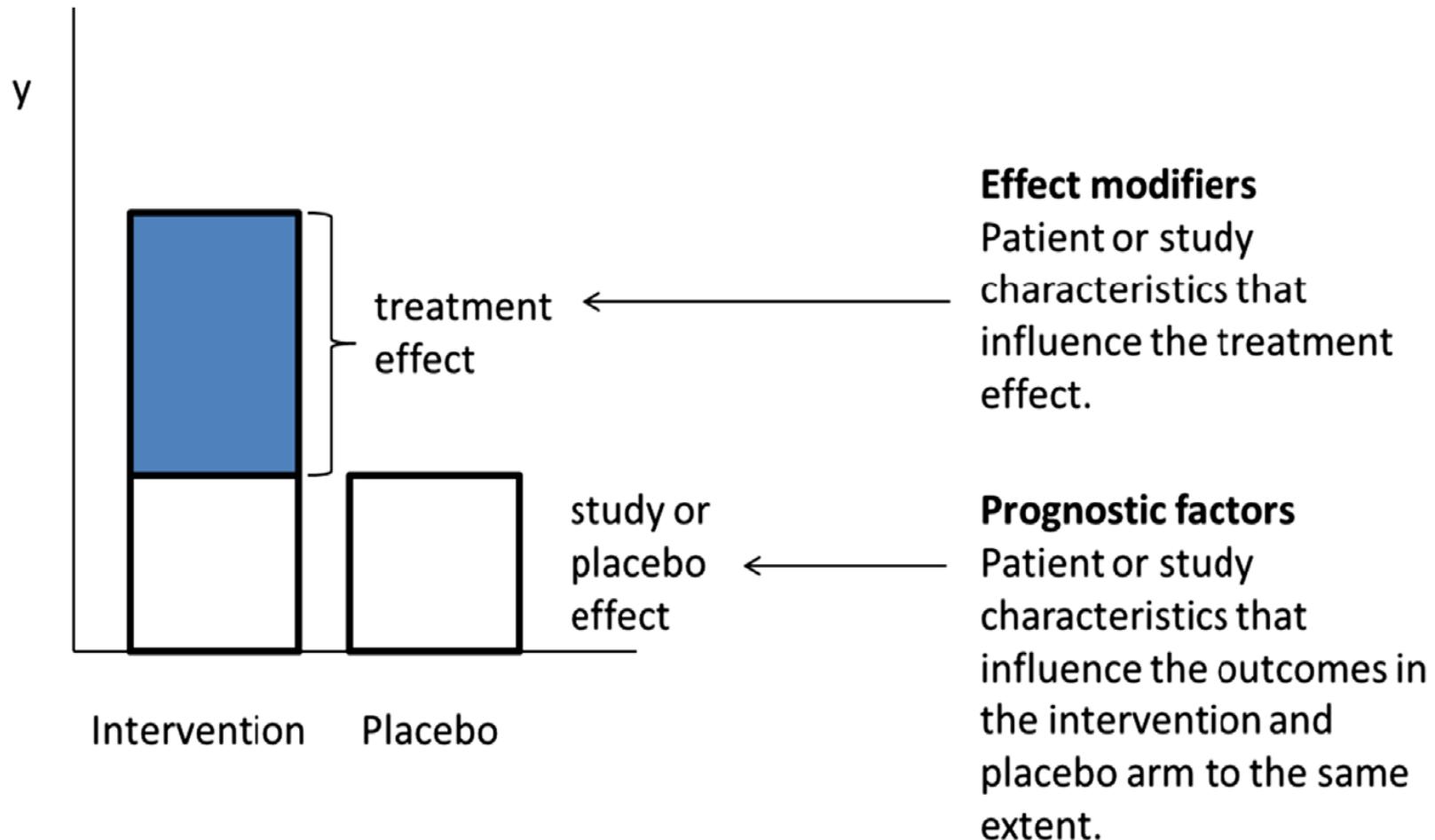
Heterogeneity

- Extent to which *true* treatment effect varies with different populations/ patient characteristics, treatment characteristics (such as dose or duration) or study characteristics.
- Known as *interaction* or *effect modification*
- Caused by variation in (un)measured effect-modifiers of relative treatment effect.

Heterogeneity across studies



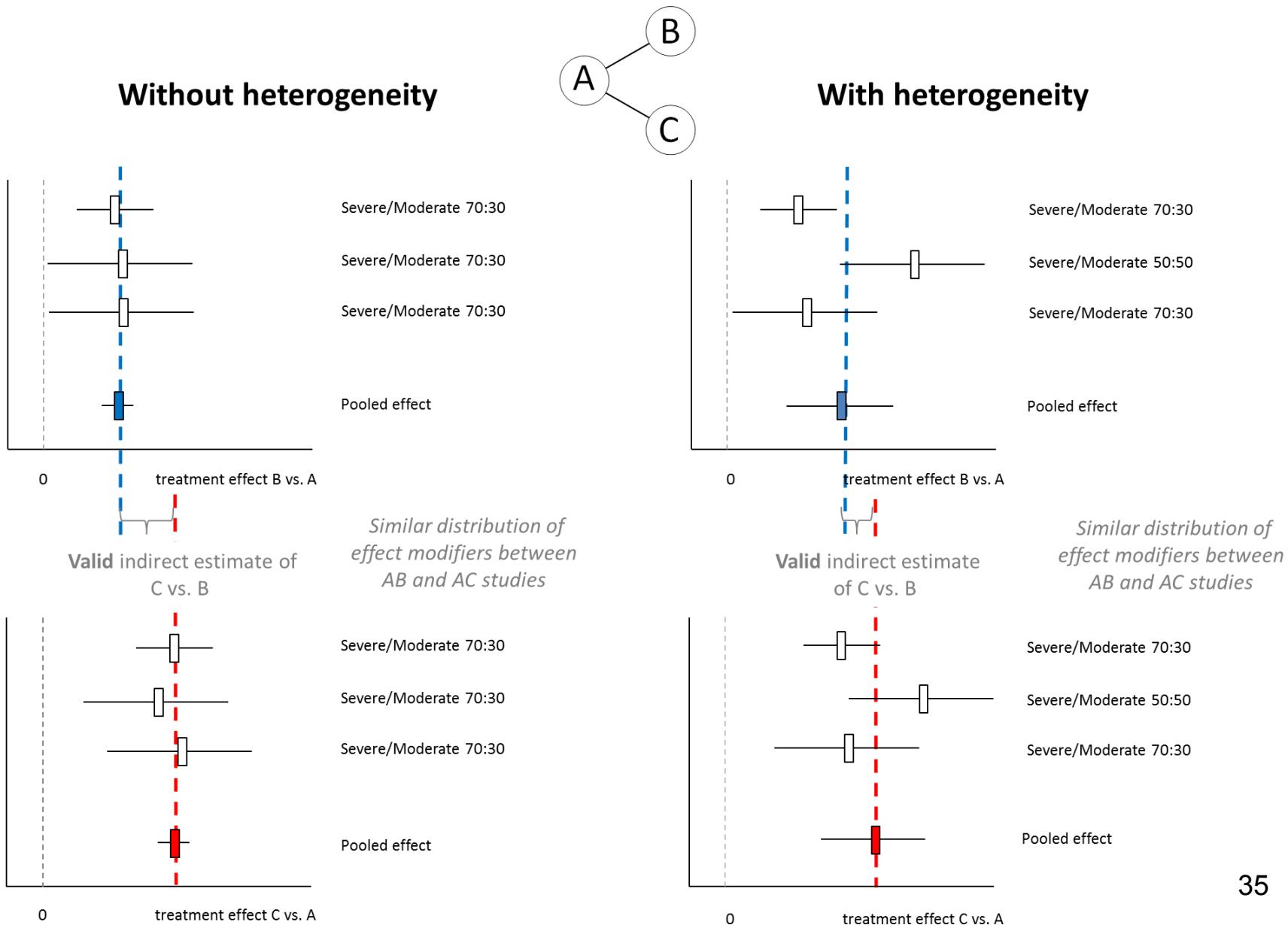
Prognostic Factors and Effect Modifiers



Heterogeneity and Inconsistency

- **Heterogeneity** occurs within direct treatment comparisons
 - Effect modification(treatment effects vary by study characteristics)
- **Inconsistency** occurs across different treatment comparisons
 - Interaction with study design (e.g. 3-arm vs. 2-arm) or within loops of treatments
 - Consistency can be checked by model extensions when direct and indirect evidence is available

Heterogeneity in a network



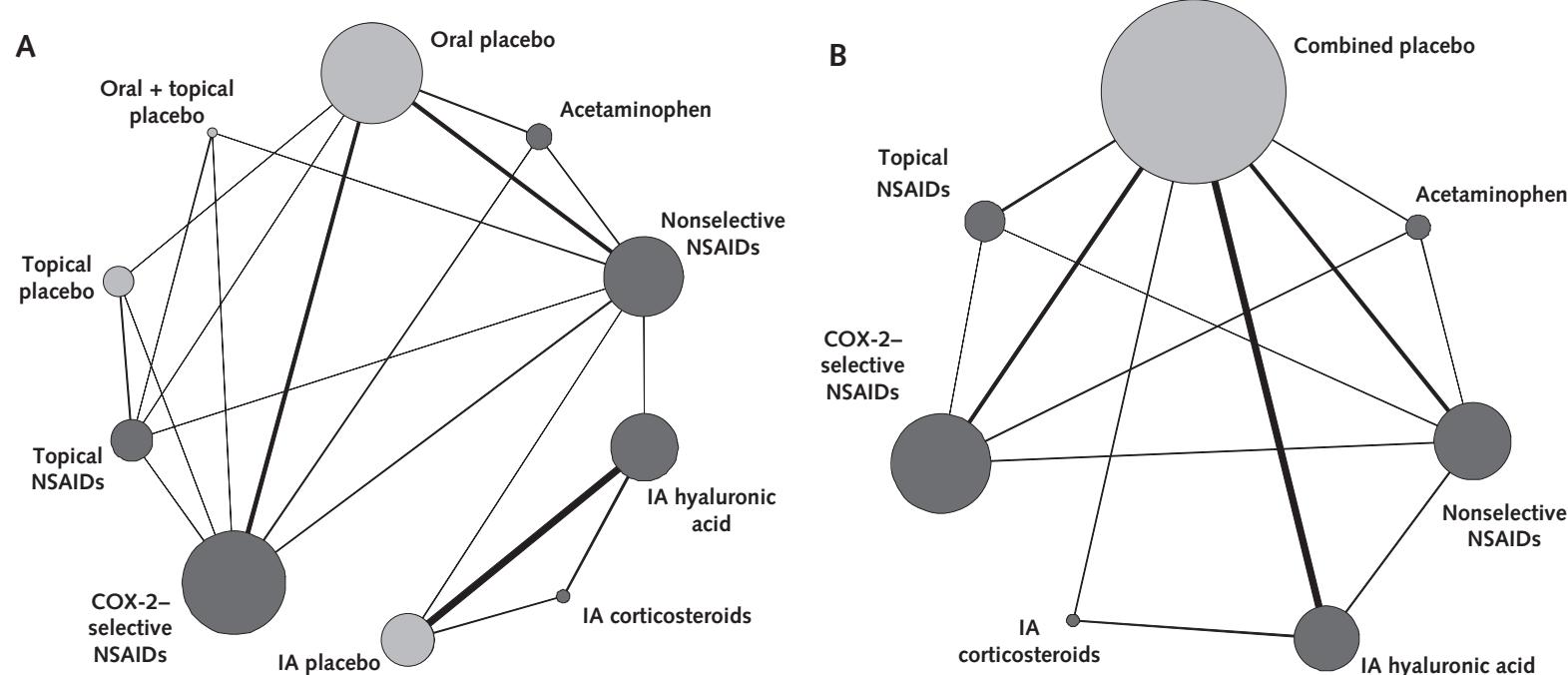
Exchangeability

- Treatment C is similar when it appears in AC and BC studies
What if C is standard care and A and B are different generations of drugs
- AC and BC trials have similar distribution of effect modifiers
What if AC studies have higher proportion of very ill patients than BC studies
- Participants could be randomized to any of treatments A, B, C
What if C can only be given to certain types of patients
- ‘Missing’ treatment in each trial is missing (completely) at random

Salanti, *Research Synthesis Methods*, 2012

Two Placebos in One Network

Figure 1. Network of different placebo comparisons.

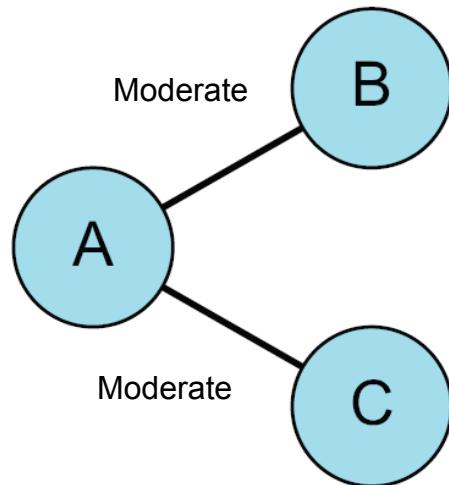


A. Differential placebo effects model. B. Nondifferential combined placebo effects model. Combined placebo = all 4 placebo groups (oral, topical, IA, and oral plus topical) are combined into a single group. Circle size reflects number of participants, and the line width reflects number of direct comparisons. No connecting line between 2 circles indicates that there was no direct comparison between the 2 treatments. COX = cyclooxygenase; IA = intra-articular; NSAID = nonsteroidal anti-inflammatory drug.

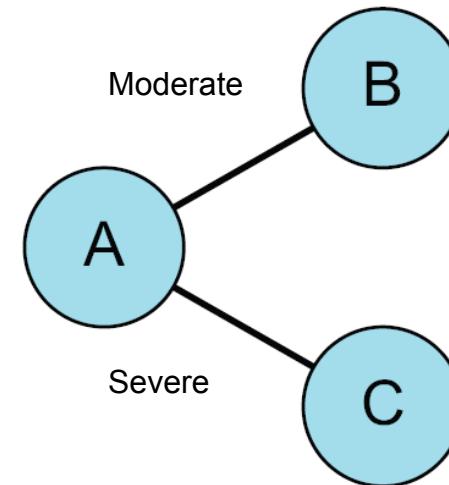
Bannuru et al. Effectiveness and Implications of Alternative Placebo Treatments. *Annals of Internal Medicine* 2015; 163:365-372

(Un)biased indirect treatment comparison

Unbiased indirect comparison



Biased indirect comparison



Disease severity modifies AB and AC effect

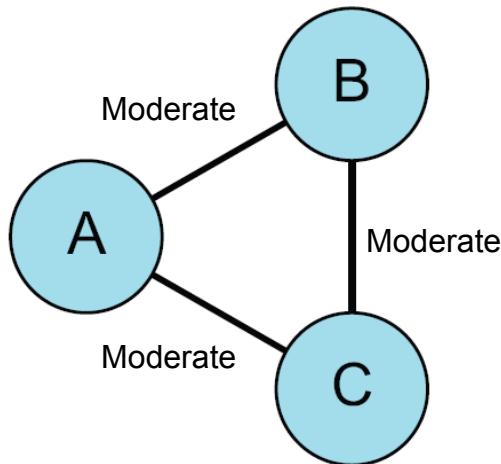
Transitivity assumption holds

$$d_{BC}^{indirect} = d_{AC}^{direct} - d_{AB}^{direct}$$

Transitivity assumption fails

AB, AC have different distribution of effect modifiers
BC estimate affected by confounding bias from differences in effect-modifiers across comparisons

Consistency in MTC



$$d_{BC}^{direct} = d_{BC}^{indirect} = d_{AC}^{direct} - d_{AB}^{direct}$$

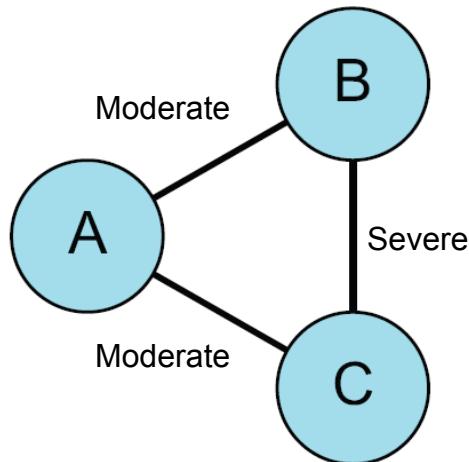
$$d_{AC}^{direct} = d_{AC}^{indirect} = d_{AB}^{direct} + d_{BC}^{direct}$$

No inconsistency, no bias

$$d_{AB}^{direct} = d_{AB}^{indirect} = d_{AC}^{direct} - d_{BC}^{direct}$$



Inconsistency in MTC



$$d_{BC}^{direct} \neq d_{BC}^{indirect} = d_{AC}^{direct} - d_{AB}^{direct}$$

Severe Moderate Moderate Moderate

BC: unbiased indirect estimate is different from direct estimate.
Inconsistency does not result in biased BC estimates. (Only variation in BC estimates, in similar fashion as heterogeneity in pairwise meta-analysis)

$$d_{AC}^{direct} \neq d_{AC}^{indirect} = d_{AB}^{direct} + d_{BC}^{direct}$$

Moderate Biased Moderate Severe

AC: Biased indirect estimate because effect modifiers different for AB and BC. Biased indirect estimate is different from direct AC. Inconsistency in network results in biased AC estimate

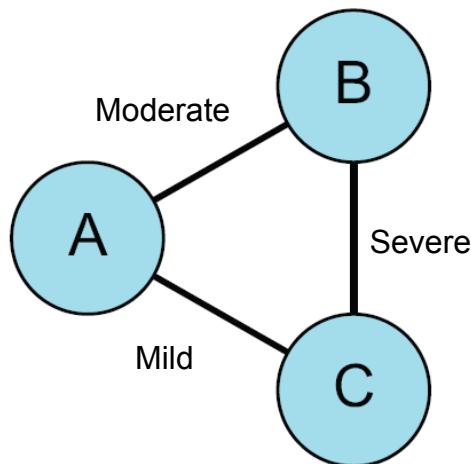
$$d_{AB}^{direct} \neq d_{AB}^{indirect} = d_{AC}^{direct} - d_{BC}^{direct}$$

Moderate Biased Moderate Severe

AB: Biased indirect estimate because effect modifiers different for AC and BC. Biased indirect estimate is different from direct AB. Inconsistency in network results in biased AB estimate



Inconsistency in MTC



$$d_{BC}^{direct} \neq d_{BC}^{indirect} = d_{AC}^{direct} - d_{AB}^{direct}$$

Severe Biased Mild Moderate

$$d_{AC}^{direct} \neq d_{AC}^{indirect} = d_{AB}^{direct} + d_{BC}^{direct}$$

Mild Biased Moderate Severe

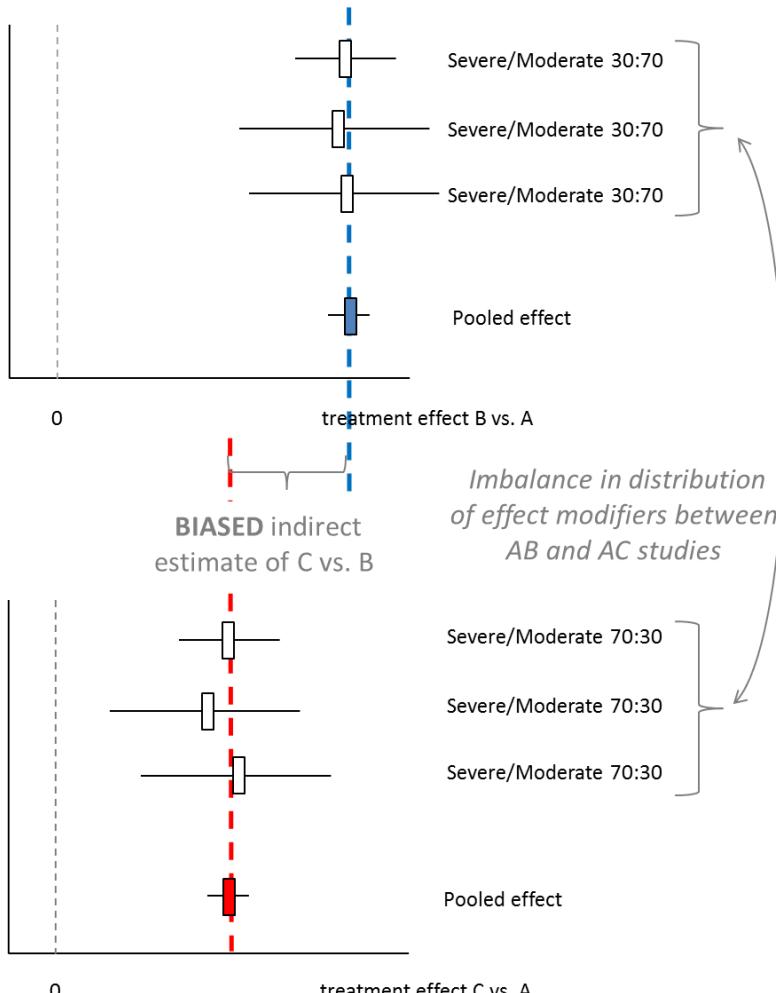
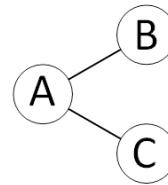
$$d_{AB}^{direct} \neq d_{AB}^{indirect} = d_{AC}^{direct} - d_{BC}^{direct}$$

Moderate Biased Mild Severe

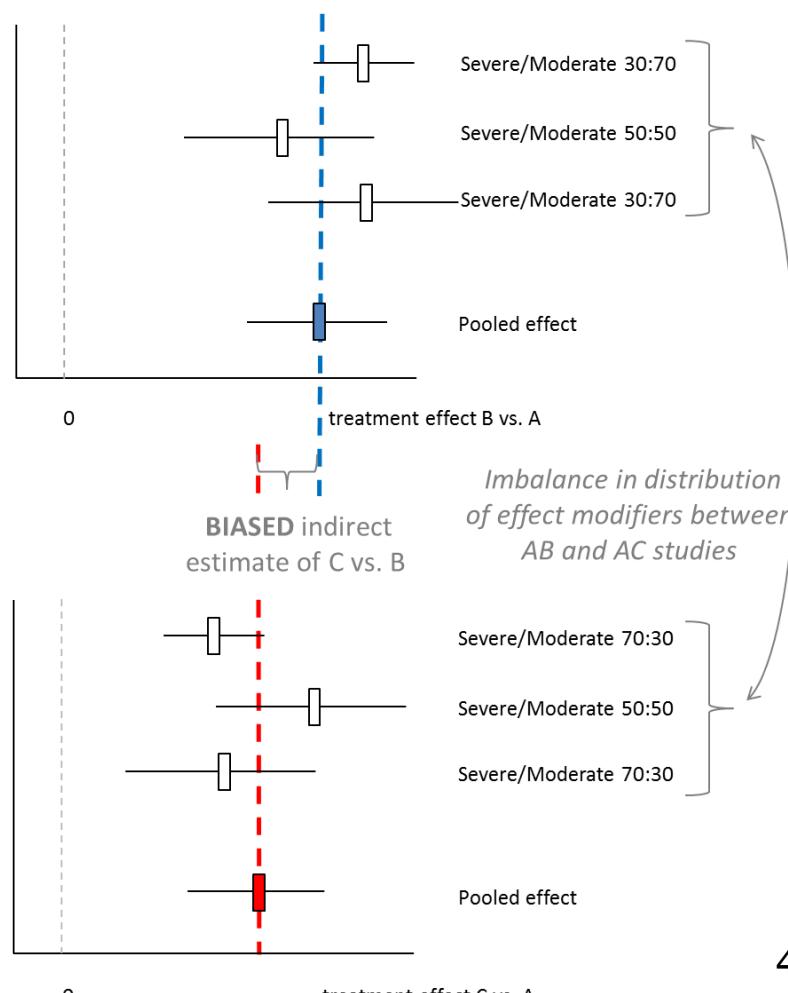
Inconsistency, all estimates biased

Biased network meta-analysis

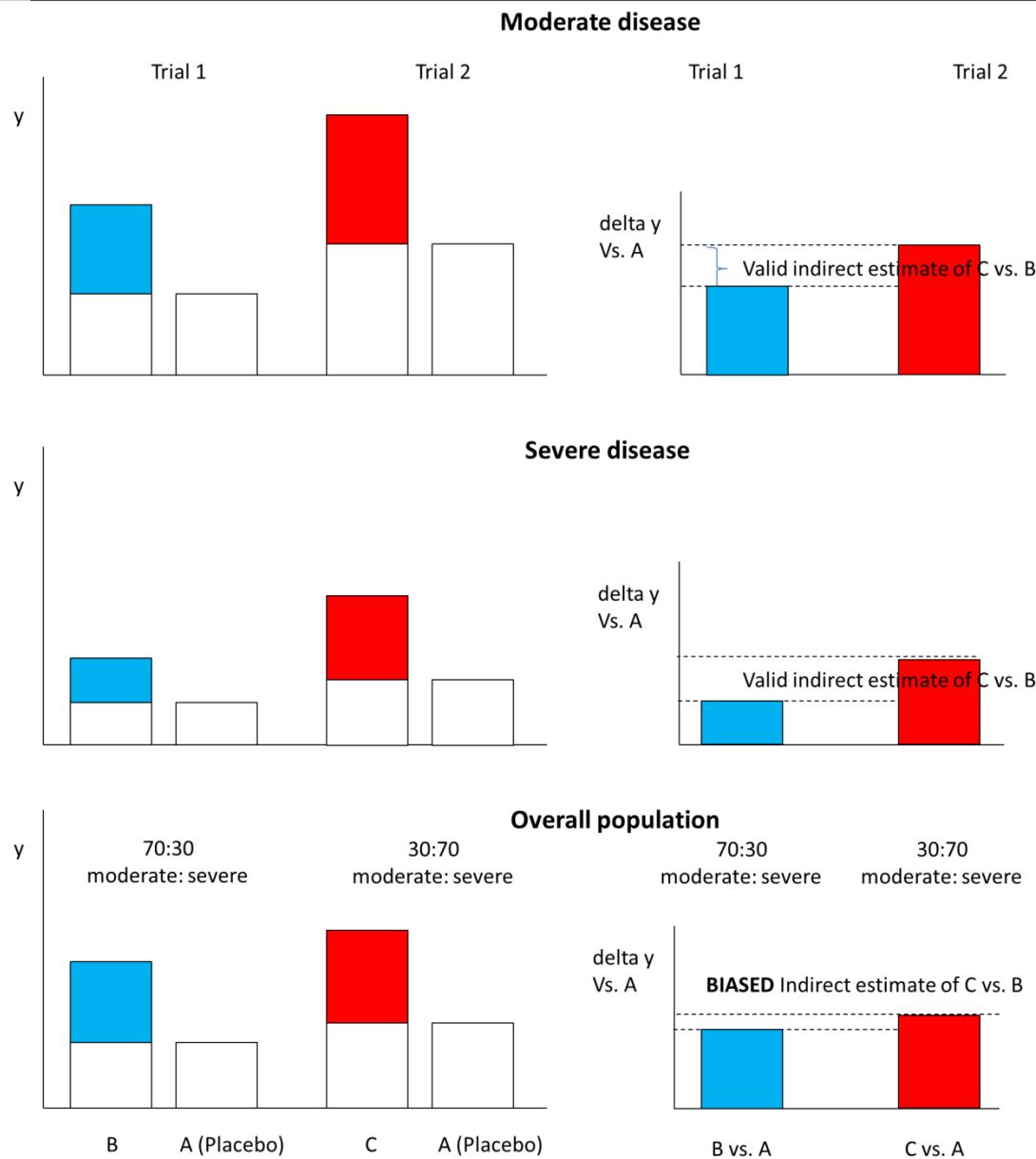
Without heterogeneity



With heterogeneity



Indirect comparison with Effect Modifier Imbalance



- Disease severity is effect modifier
- Valid indirect comparisons for moderate and severe disease
- Invalid indirect comparison for overall population
 - distribution of severity differs for AB and AC studies



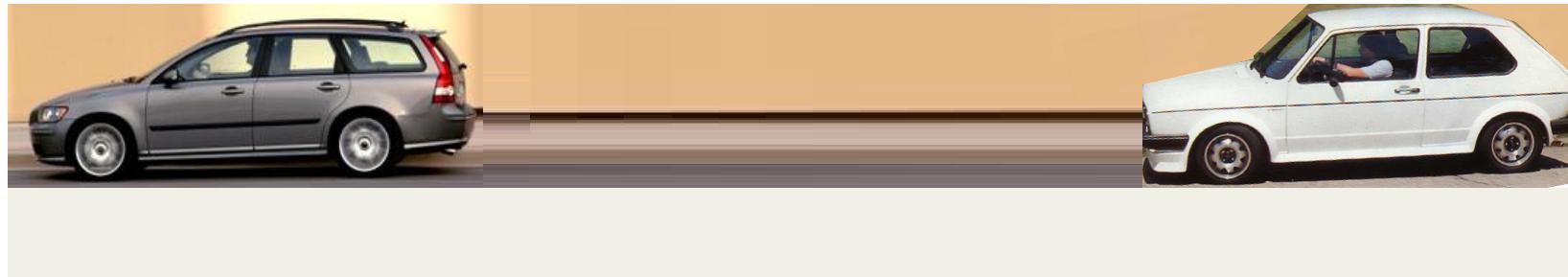
Imbalanced Effect Modification

‘Trial 1: Porsche versus Golf’

Porsche - Golf = 2s

‘Trial 2: Volvo versus Golf’

Volvo - Golf = 8s



→ Volvo versus Porsche: 8-2=6s (Indirect comparison)

Is a Volvo faster than a Porsche?

$Ce^{-\beta n}$

No, biased indirect estimate due to
imbalance in treatment effect modifier
(snow) across comparisons



Trials of HAART regimes for HIV

A: 2 NRTIs

B: 2 NRTIs + PI

C: 2 NRTIs + NNRTI

- Indirect B vs C evidence inconsistent with direct evidence from B vs C trials

Conclusion: Indirect Comparisons unreliable for complex interventions like HAART

Trials of HAART regimes for HIV

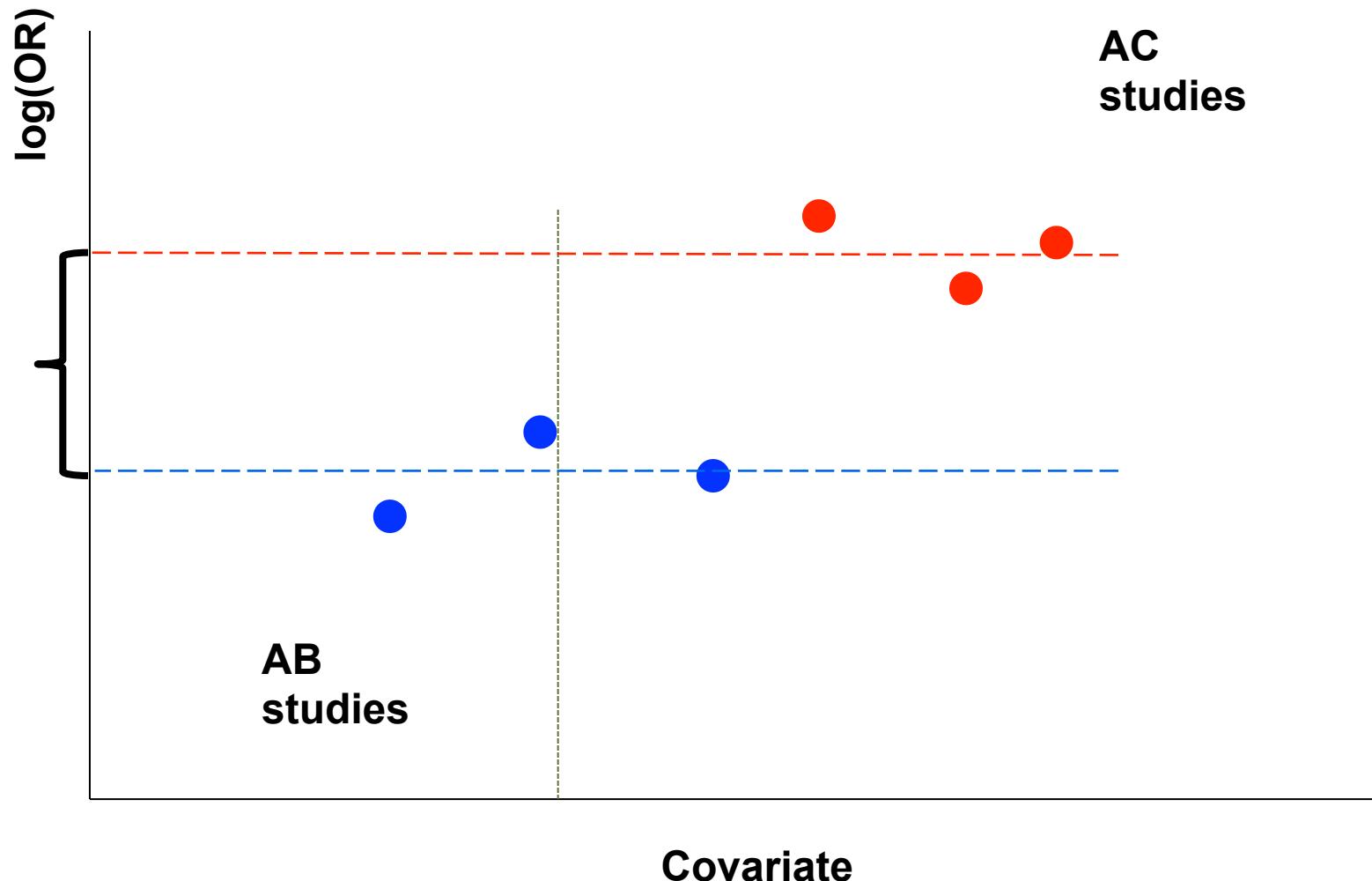
A: 2 NRTIs

B: 2 NRTIs + PI

C: 2 NRTIs + NNRTI

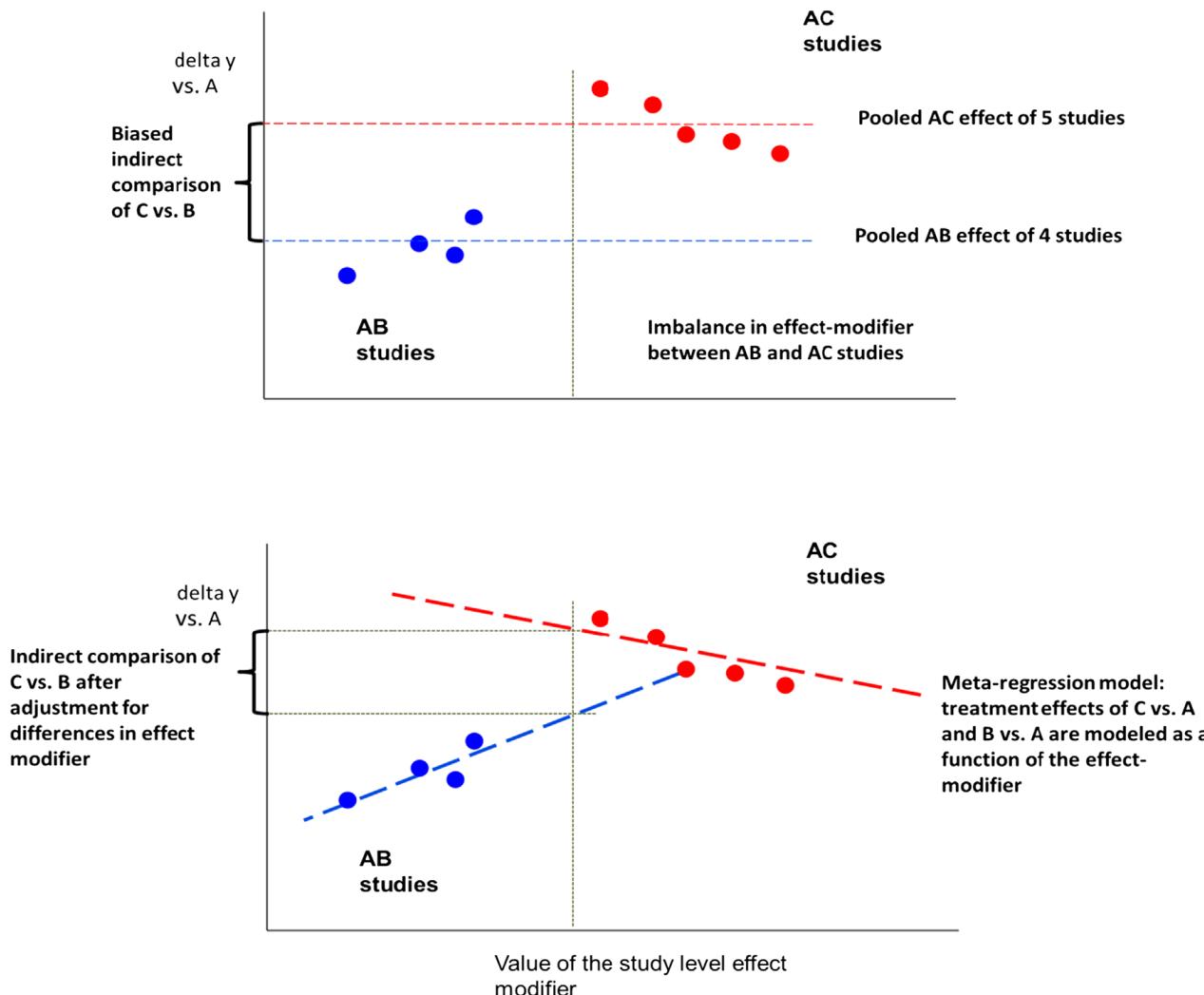
- BUT the NRTIs in A vs B trials were DIFFERENT from NRTIs in B vs C trials
- When comparison restricted to trials with SAME NRTI regimes, inconsistency no longer statistically significant

Indirect Comparison: No Adjusting for Covariate



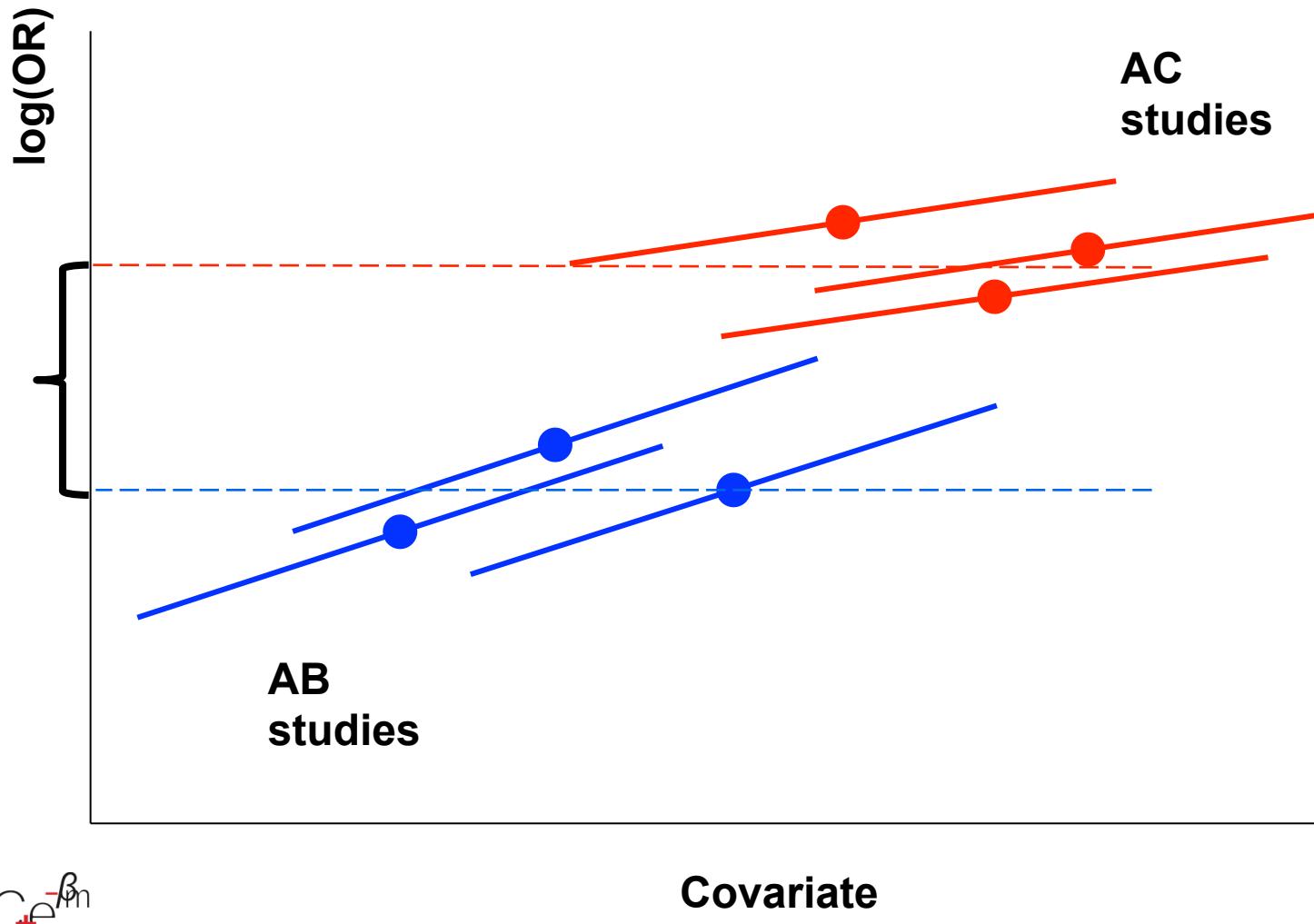
Source: Jansen JP. Network meta-analysis of individual and aggregate level data. Research Synthesis Methods 2012;3:177–90

Adjusting for Imbalance with Meta-regression

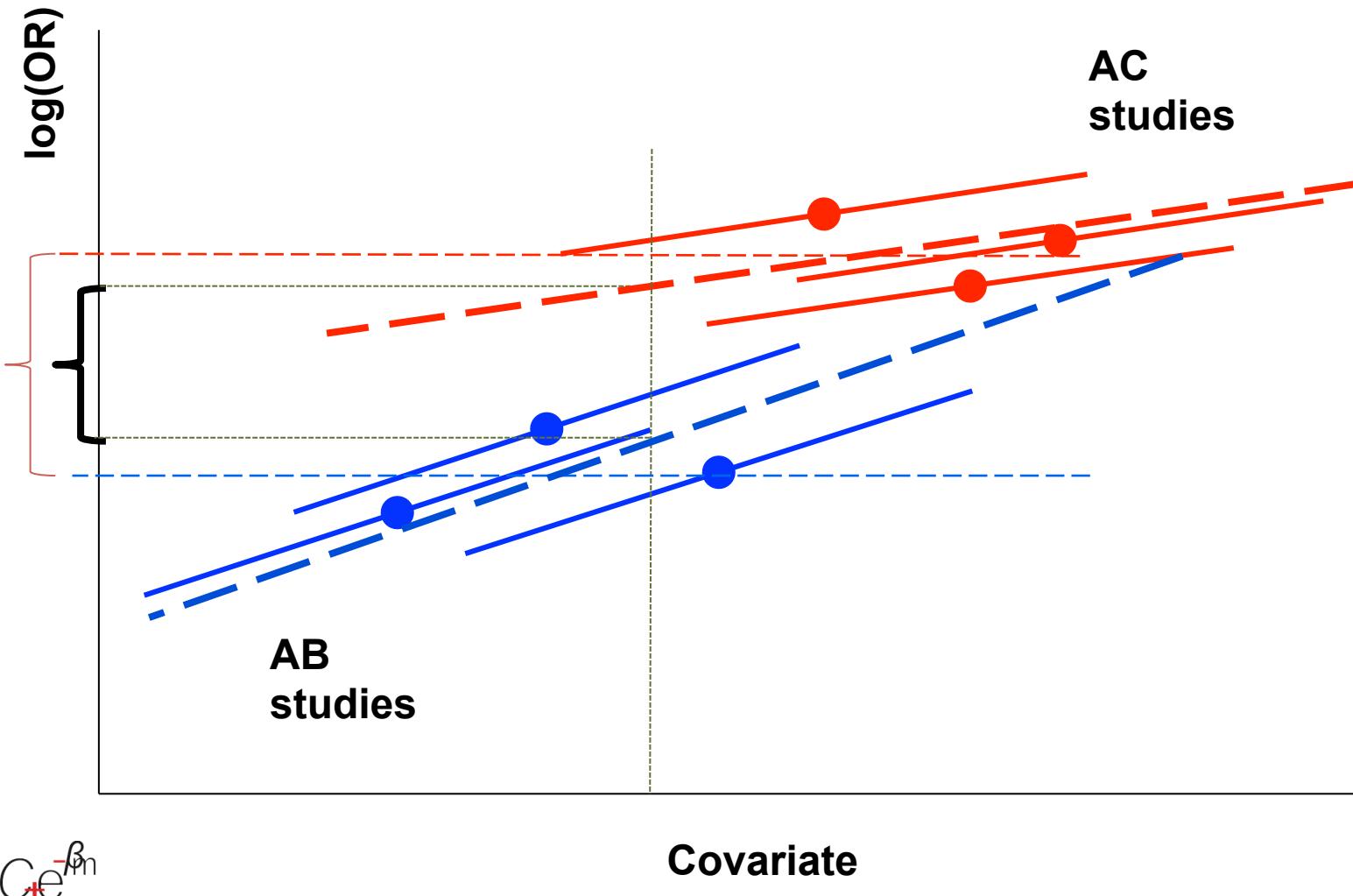


- Treatment effects depend on the value of effect modifier

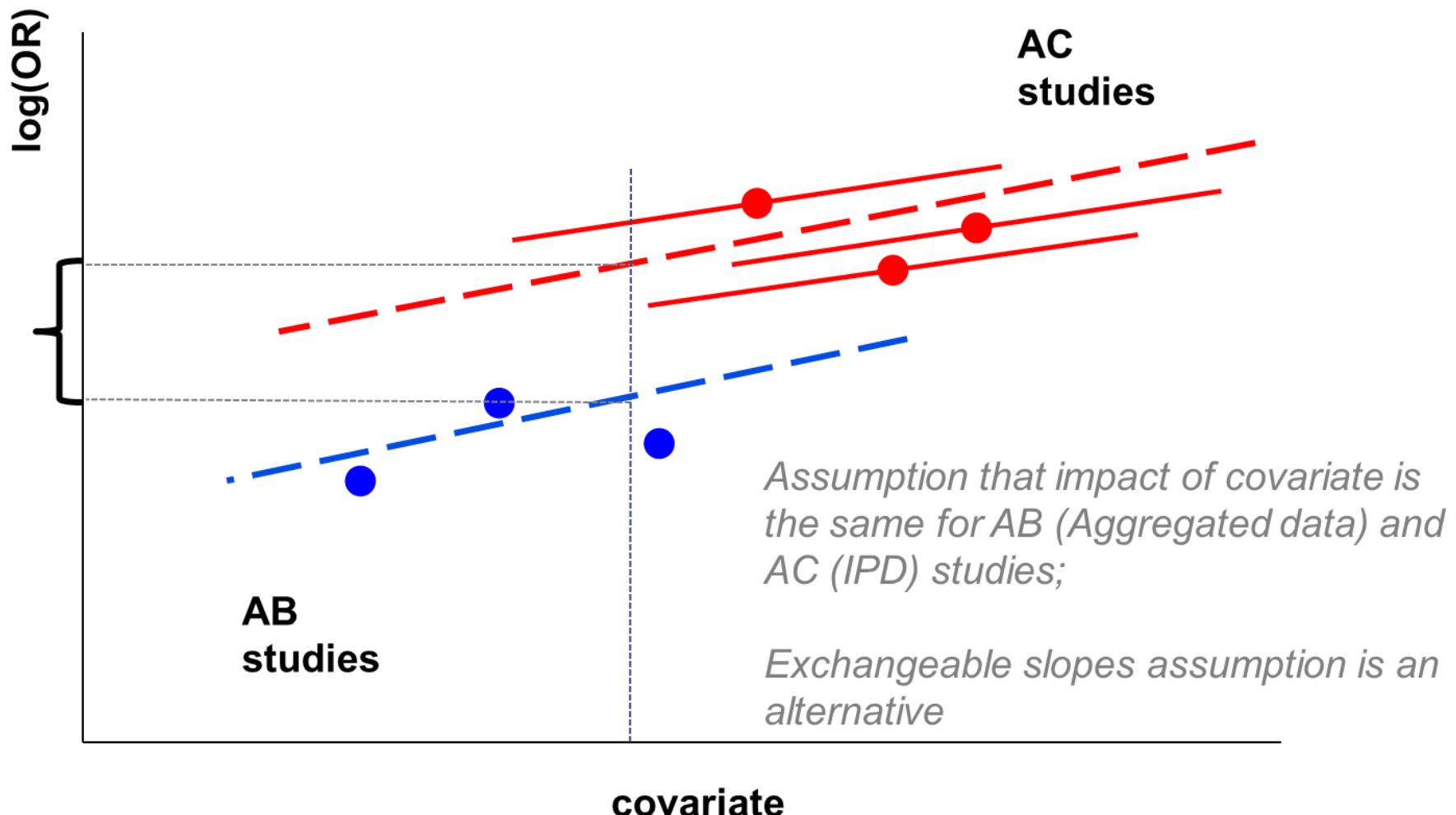
Biased Indirect Treatment Comparison



Correcting Bias Using IPD



Adjustment with IPD and AD



MODELS

Ce^{-β_n}



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Basic and Functional Parameters

- Three treatments with treatment A as reference
- Relative treatment effects (log odds ratios) of B, C relative to A are the **basic** parameters

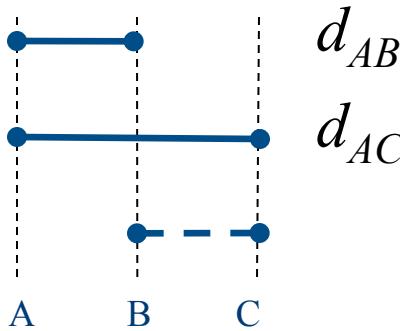
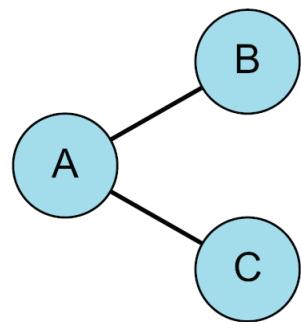
$$\Delta_{AB}, \Delta_{AC}$$

- Remaining contrasts are **functional** parameters

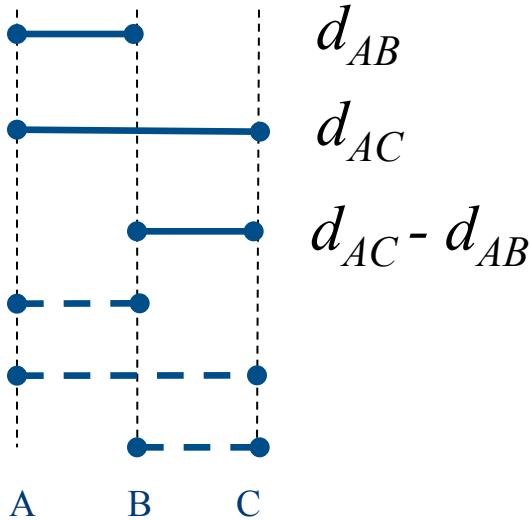
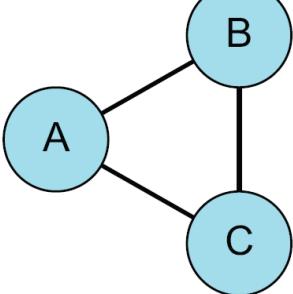
$$\Delta_{BC} = \Delta_{AC} - \Delta_{AB}$$

- Basic parameters determine functional parameters
- Functional parameters inform indirectly about basic parameters
- Could also model treatment arms rather than contrasts

Basic and Functional Parameters



k treatments
 $k(k-1)/2$ contrasts



k-1 basic parameters: d_{AB} , d_{AC}

(Priors needed for these in Bayesian model)

Functional parameter: d_{BC}

(to relate data back to basic parameters)

Consistency relation: $d_{BC} = d_{AC} - d_{AB}$

$Ce^{-\beta n}$ Direct comparison



Indirect comparison



Expressing Network by Meta-Regression

Contrast	X1	X2
AC	1	0
BC	0	1
AB	1	-1

$$\begin{pmatrix} y_{1,AB} \\ y_{2,AC} \\ y_{3,BC} \end{pmatrix} = \begin{pmatrix} 1 & 0 \\ 0 & 1 \\ -1 & 1 \end{pmatrix} \begin{pmatrix} \mu_{AB} \\ \mu_{AC} \end{pmatrix} + \begin{pmatrix} \beta_1 \\ \beta_2 \\ \beta_3 \end{pmatrix} + \begin{pmatrix} \varepsilon_1 \\ \varepsilon_2 \\ \varepsilon_3 \end{pmatrix}$$

Observed

Fixed Random Error

Ce^{- β_0}



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Multi-Arm Trials

$$\begin{pmatrix} y_{1,AB} \\ y_{2,AC} \\ y_{3,BC} \\ y_{4,AB} \\ y_{4,AC} \end{pmatrix} = \begin{pmatrix} 1 & 0 \\ 0 & 1 \\ -1 & 1 \\ 1 & 0 \\ 0 & 1 \end{pmatrix} \begin{pmatrix} \mu_{AB} \\ \mu_{AC} \end{pmatrix} + \begin{pmatrix} \beta_{1,1} \\ \beta_{2,1} \\ \beta_{3,1} \\ \beta_{4,1} \\ \beta_{4,2} \end{pmatrix} + \begin{pmatrix} \varepsilon_{1,1} \\ \varepsilon_{2,1} \\ \varepsilon_{3,1} \\ \varepsilon_{4,1} \\ \varepsilon_{4,2} \end{pmatrix}$$

$y_{4,AB}$ and $y_{4,AC}$ are correlated

Random effects b and observed error e are correlated

$$\varepsilon \sim N(0, V)$$

$$\beta \sim N(0, T)$$

$$Ce^{-\beta_n} Y \sim N(X\mu, T+V)$$



Multi-Arm Trials

$$\begin{pmatrix} y_{1,AB} \\ y_{2,AC} \\ y_{3,BC} \\ y_{4,AB} \\ y_{4,AC} \end{pmatrix} = \begin{pmatrix} 1 & 0 \\ 0 & 1 \\ -1 & 1 \\ 1 & 0 \\ 0 & 1 \end{pmatrix} \begin{pmatrix} \mu_{AB} \\ \mu_{AC} \end{pmatrix} + \begin{pmatrix} \beta_{1,1} \\ \beta_{2,1} \\ \beta_{3,1} \\ \beta_{4,1} \\ \beta_{4,2} \end{pmatrix} + \begin{pmatrix} \varepsilon_{1,1} \\ \varepsilon_{2,1} \\ \varepsilon_{3,1} \\ \varepsilon_{4,1} \\ \varepsilon_{4,2} \end{pmatrix}$$

$$\begin{pmatrix} \varepsilon_{1,1} \\ \varepsilon_{2,1} \\ \varepsilon_{3,1} \\ \varepsilon_{4,1} \\ \varepsilon_{4,2} \end{pmatrix} \sim N \left(\begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}, \begin{pmatrix} v_{1,1} & 0 & 0 & 0 & 0 \\ 0 & v_{2,1} & 0 & 0 & 0 \\ 0 & 0 & v_{3,1} & 0 & 0 \\ 0 & 0 & 0 & v_{4,1} & c_{4,1:4,2} \\ 0 & 0 & 0 & c_{4,1:4,2} & v_{4,2} \end{pmatrix} \right)$$

Correlation in observed values

$$\begin{pmatrix} \beta_{1,1} \\ \beta_{2,1} \\ \beta_{3,1} \\ \beta_{4,1} \\ \beta_{4,2} \end{pmatrix} \sim N \left(\begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \tau_{AB}^2 & 0 & 0 & 0 & 0 \\ 0 & \tau_{AC}^2 & 0 & 0 & 0 \\ 0 & 0 & \tau_{BC}^2 & 0 & 0 \\ 0 & 0 & 0 & \tau_{AB}^2 & \text{cov}(\beta_{4,1}, \beta_{4,2}) \\ 0 & 0 & 0 & \text{cov}(\beta_{4,1}, \beta_{4,2}) & \tau_{AC}^2 \end{pmatrix} \right)$$

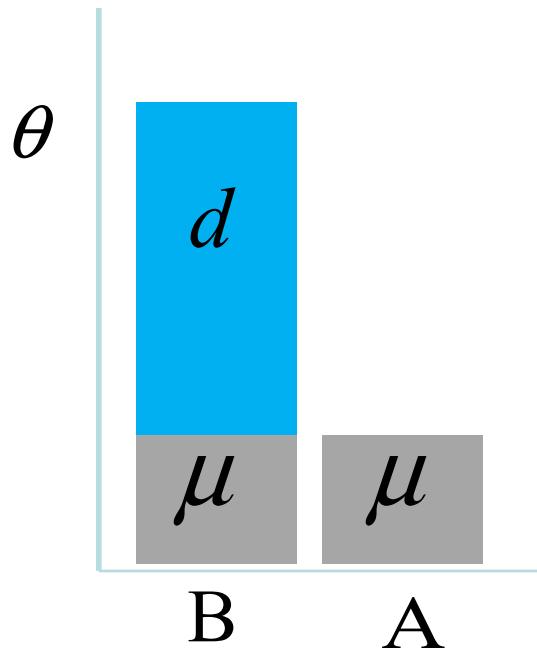
Correlation in random effects

Correlations of random effects are $\frac{1}{2}$ if equivariant effects

Fit using mixed models

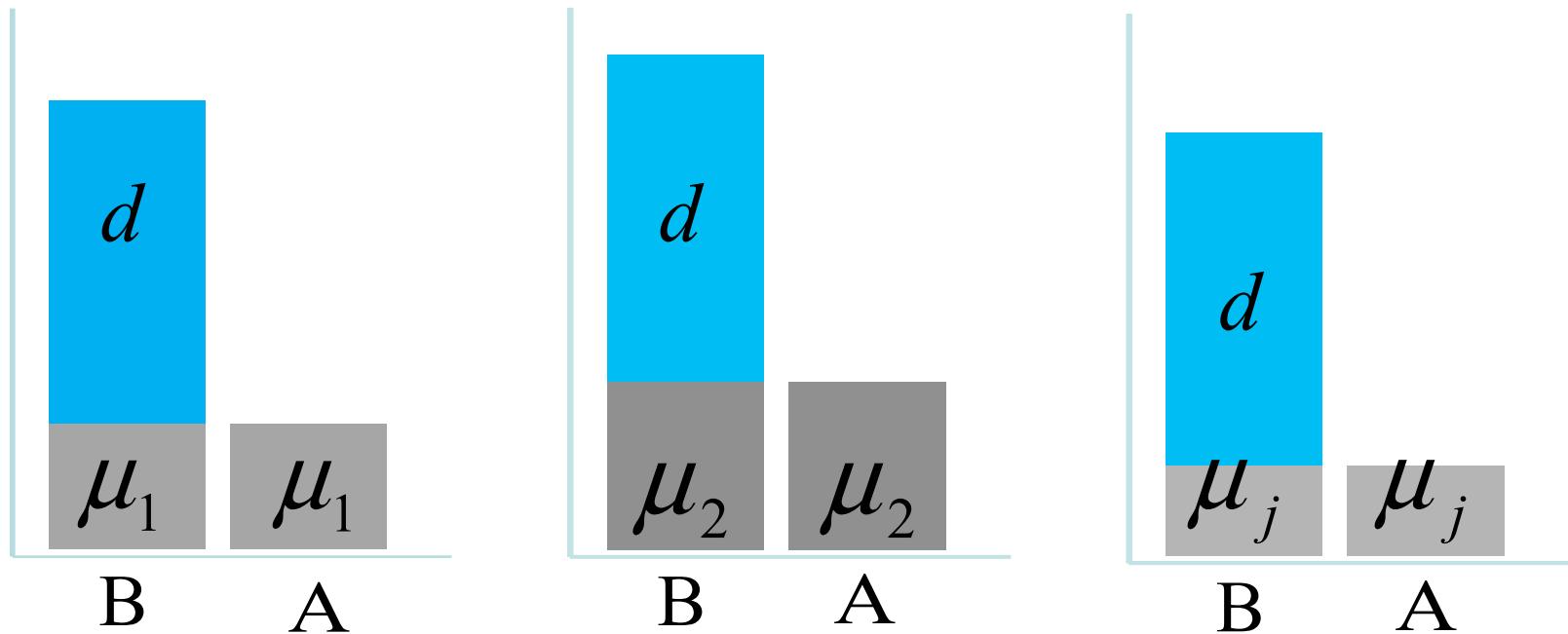


Modeling by Arms: Single AB study



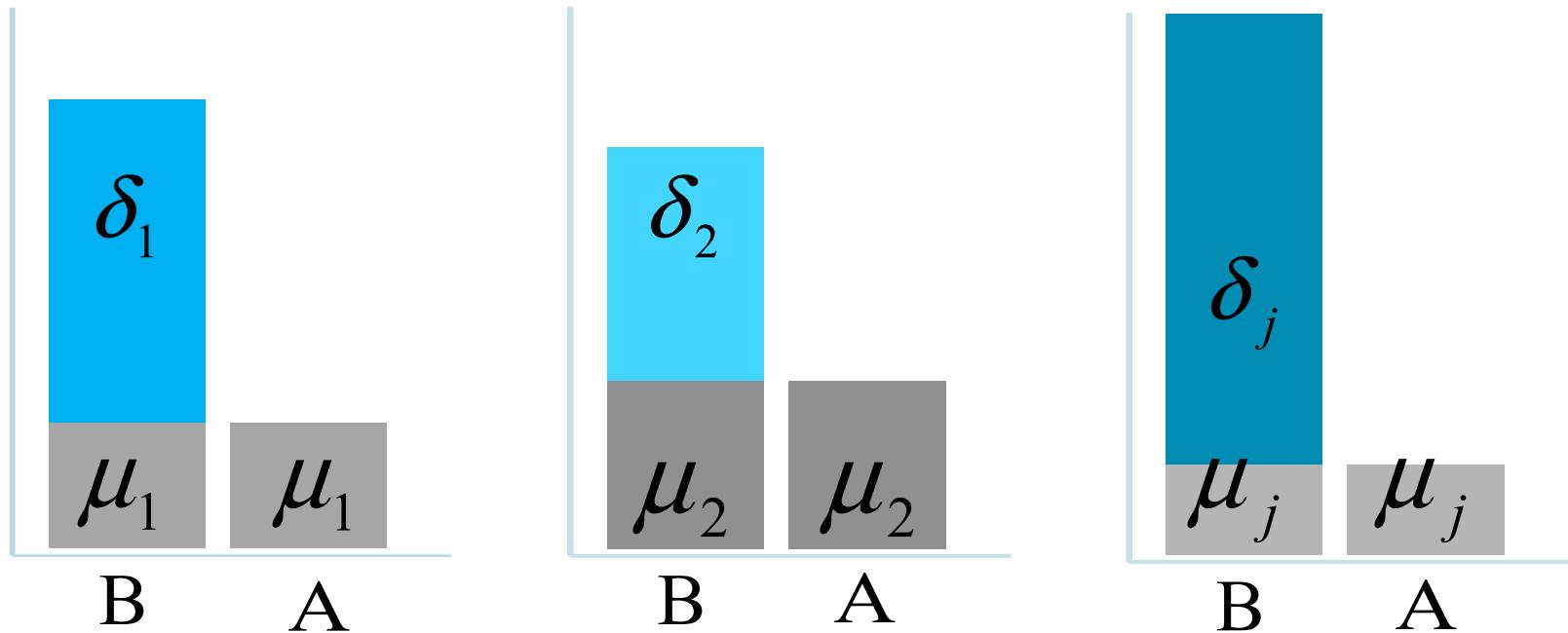
$$\theta_k = \begin{cases} \mu & k = A \\ \mu + d & k = B \end{cases}$$

Equal (Fixed) Effects model



$$\theta_{jk} = \begin{cases} \mu_j & k = A \\ \mu_j + d & k = B \end{cases}$$

Random Effects Model



$$\theta_{jk} = \begin{cases} \mu_j & k = A \\ \mu_j + \delta_j & k = B \end{cases}$$

$$\delta_j \sim Normal(d, \sigma_{\delta}^2)$$

Arm-based FE & RE NMA Models

Fixed effects

$$\theta_{jk} = \begin{cases} \mu_{jb} & b = A, B, C, \dots \text{ if } k = b \\ \mu_{jb} + d_{bk} = \mu_{jb} + d_{Ak} - d_{Ab} & \text{if } k \text{ 'after' } b \end{cases}$$

$$d_{AA} = 0$$

$$d_{bk} = d_{Ak} - d_{Ab}$$

Random effects

$$\theta_{jk} = \begin{cases} \mu_{jb} & b = A, B, C, \dots \text{ if } k = b \\ \mu_{jb} + \delta_{jbk} & \text{if } k \text{ 'after' } b \end{cases}$$

$$\delta_{jbk} \sim Normal(d_{bk}, \sigma_{\delta}^2) = Normal(d_{Ak} - d_{Ab}, \sigma_{\delta}^2)$$

$$d_{AA} = 0$$

Ce^{-β₀}



MA and NMA Models

Fixed effects meta-analysis

$$\theta_{jk} = \begin{cases} \mu_j & k = A \\ \mu_j + d & k = B \end{cases}$$

Fixed effects network meta-analysis

$$\theta_{jk} = \begin{cases} \mu_{jb} & b = A, B, C, \dots \text{ if } k = b \\ \mu_{jb} + d_{bk} = \mu_{jb} + d_{Ak} - d_{Ab} & \text{if } k \text{ 'after' } b \end{cases}$$

$$d_{AA} = 0$$

Random effects meta-analysis

$$\theta_{jk} = \begin{cases} \mu_j & k = A \\ \mu_j + \delta_j & k = B \end{cases}$$

$$\delta_j \sim N(d, \sigma^2)$$

Random effects network meta-analysis

$$\theta_{jk} = \begin{cases} \mu_{jb} & b = A, B, C, \dots \text{ if } k = b \\ \mu_{jb} + \delta_{jbk} & \text{if } k \text{ 'after' } b \end{cases}$$

$$\delta_{jbk} \sim N(d_{bk}, \sigma^2) = N(d_{Ak} - d_{Ab}, \sigma^2)$$

$$d_{AA} = 0$$

Models for Binary Outcomes

$$r_{jk} \sim \text{binomial}(n_{jk}, p_{jk})$$

$$\text{logit}(p_{jk}) = \begin{cases} \mu_{jb} & b = A, B, C, \dots \text{ if } k = b \\ \mu_{jb} + \delta_{jbk} & \text{if } k \text{ 'after' } b \end{cases}$$

$$\delta_{jbk} \sim N(d_{bk}, \sigma^2) = N(d_{Ak} - d_{Ab}, \sigma^2)$$

$$d_{AA} = 0$$

NMA model for IPD and AD

IPD

$$y_{ijk} \sim \text{Bernoulli}(p_{ijk})$$

$$\text{logit}(p_{ijk}) = \begin{cases} \mu_{jb} + \beta_{0j} x_{ij} & b = \text{A, B, C,} \quad \text{if } k = b \\ \mu_{jb} + \beta_{0j} x_{ij} + \delta_{jbk} + (\gamma_{Ak} - \gamma_{Ab}) x_{ij} & \text{if } k \text{ 'alphabetically after' } b \end{cases}$$

AgD

$$r_{jk} \sim \text{binomial}(q_{jk}, n_{jk})$$

$$\text{logit}(q_{jk}) = \begin{cases} \lambda_{jb} & b = \text{A, B, C,} \quad \text{if } k = b \\ \lambda_{jb} + \delta_{jbk} + (\gamma_{Ak} - \gamma_{Ab}) m_j & \text{if } k \text{ 'alphabetically after' } b \end{cases}$$

$$\delta_{jbk} \sim N(d_{bk}, \tau^2) = N(d_{Ak} - d_{Ab}, \tau^2)$$

$$d_{AA} = 0, \gamma_{AA} = 0$$

Ce^{-βn}

Source: Jansen JP. Network meta-analysis of individual and aggregate level data. Research Synthesis Methods 2012 (in press)



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Analysis of inconsistency

- Bucher method
- Inconsistency models / Independent means models
- Network models with inconsistency factors
- Edge splitting

Bucher Method for Testing Inconsistency

Suppose we have AB, AC, BC direct evidence

Indirect estimate $\hat{d}_{BC}^{indirect} = \hat{d}_{AC}^{direct} - \hat{d}_{AB}^{direct}$

Measure of inconsistency: $\hat{\omega}_{BC} = \hat{d}_{BC}^{indirect} - \hat{d}_{BC}^{direct}$

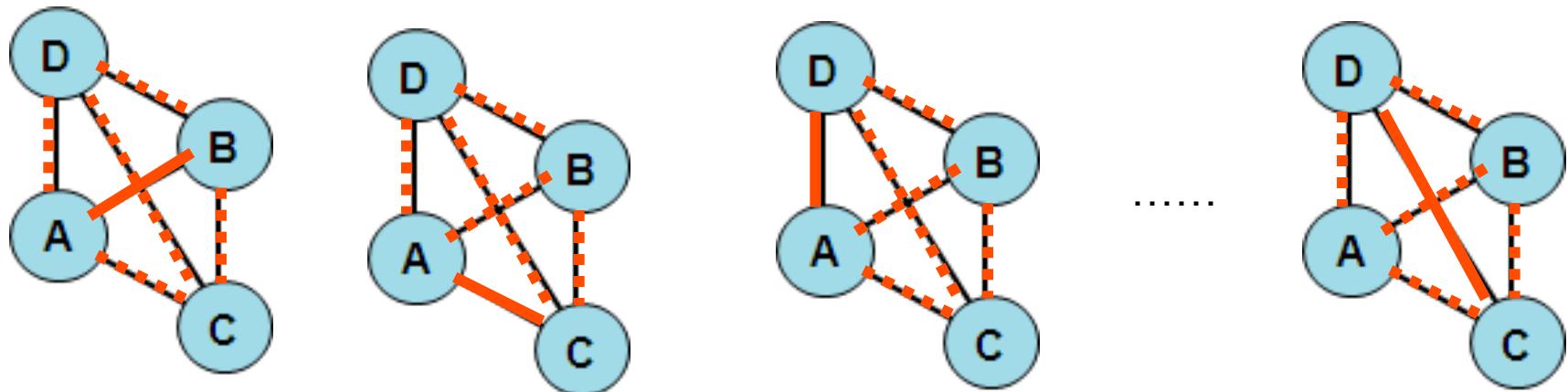
Approximate test (normal distribution): $z_{BC} = \frac{\hat{\omega}_{BC}}{\sqrt{V(\hat{\omega}_{BC})}}$

with variance $V(\hat{\omega}_{BC}) = V(d_{BC}^{direct}) + V(d_{AC}^{direct}) + V(d_{AB}^{direct})$

Cannot include 3-arm trials

Source: Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. J Clin Epidemiol 1997;50:683-91.

Edge splitting



Treatments		MTC		Direct		Indirect		Inconsistency estimate	
X	Y	Mean	se	Mean	se	Mean	se	Mean	se
A	B	0.493	0.406	0.342	0.55	0.706	0.635	-0.365	0.840
A	C	0.844	0.240	0.845	0.254	0.673	0.679	0.171	0.716
A	D	1.106	0.442	1.360	0.829	1.108	0.539	0.253	0.983
B	C	0.352	0.416	-0.052	0.702	0.519	0.503	-0.571	0.853
B	D	0.613	0.488	0.676	0.698	0.511	0.684	0.165	0.966
C	D	0.261	0.419	-0.085	0.479	1.708	0.893	-1.793	1.009

$$\delta_{jxy} \sim \text{Normal}\left(d_{xy}^{\text{Direct}}, \sigma^2\right)$$

$$\delta_{jkb} \sim \text{Normal}\left(d_{bk}, \sigma^2\right)$$

$$\omega_{XY} = d_{XY}^{\text{direct}} - d_{XY}^{\text{indirect}}$$

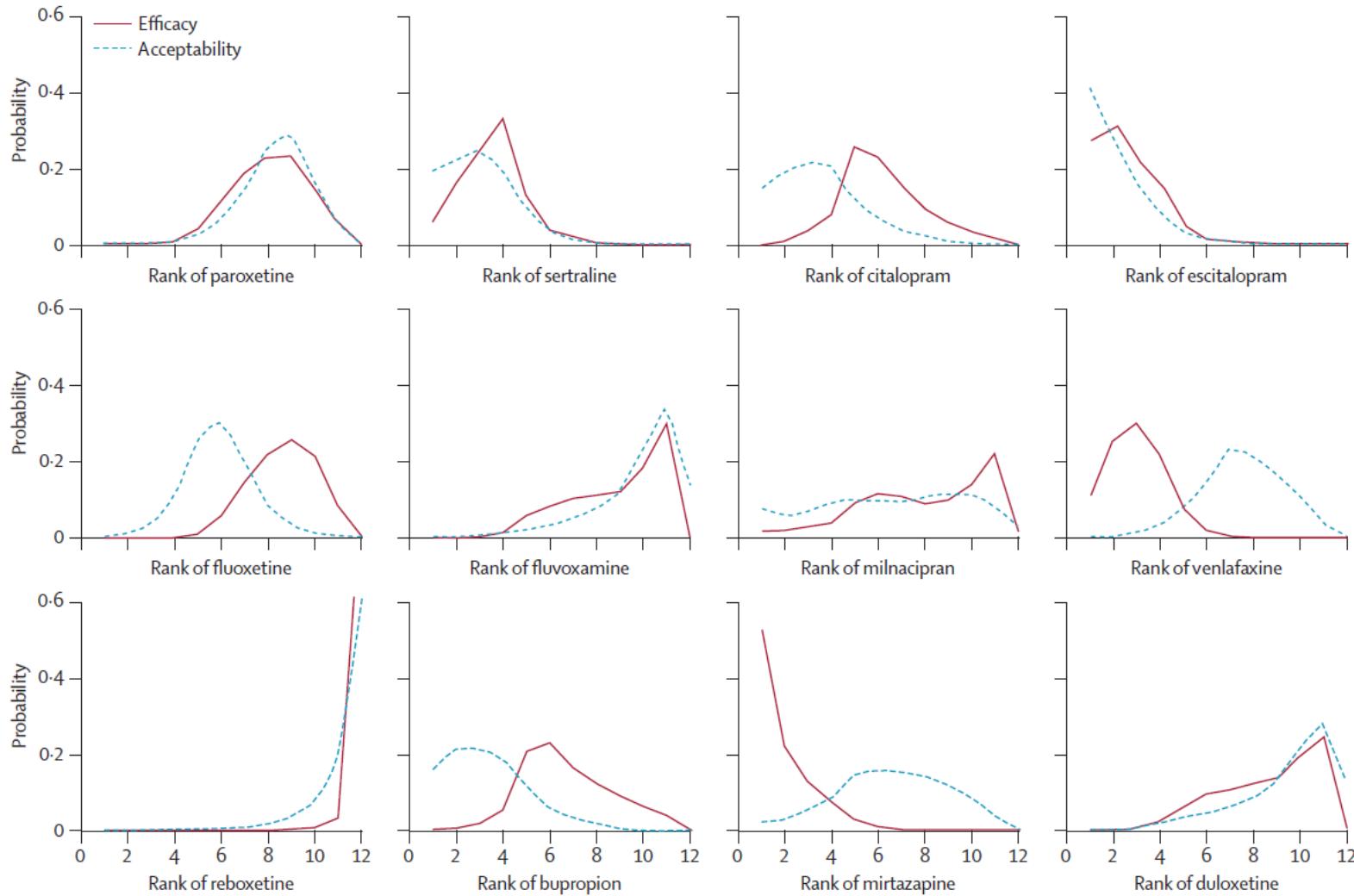
$$= \text{Normal}\left(d_{Ak} - d_{Ab}, \sigma^2\right)$$

$$d_{AA} = 0$$

$$(b, k) \neq (X, Y)$$



Probabilistic interpretation of the findings



Source: Cipriani A, Furukawa TA, Salanti G, et al. Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. Lancet 2009;373:746-58.

Software

- Specialized meta-analysis software cannot handle multivariate models
- Facilities in standard packages for weighted least squares regression and maximum likelihood but requires fix-ups
- Stata has a suite of meta-analysis programs including MVMETA for fitting multivariate normal models
- BUGS and STAN can fit arbitrary Bayes models
- R package metafor
- Open Meta-Analyst (from our shop) provides GUI over metafor

Summary

- Network meta-analysis extends traditional meta-analysis
- Includes multiple different pairwise comparisons across a range of different interventions to allow for multiple treatment comparisons including direct and indirect effects
- Networks can be analyzed with regression models relying on consistency relations
- Individual patient level data will improve the validity of a network meta-analysis

Caveats

- Randomization does not hold across trials
- Risk of imbalance in (unmeasured) effect-modifiers across comparisons which causes heterogeneity and inconsistency
- Imbalance in effect-modifiers across comparisons gives biased indirect estimates and invalid mixed estimates
- Inconsistency in a closed loop network can be investigated by comparing direct with indirect estimates
- Extension of network meta-analysis models with treatment-by-covariate interactions can help explore heterogeneity and improve consistency



Thank You

Ce^{-βn}



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