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NIHR CRSU

Complex Reviews Support Unit

Network Meta-Analysis

CRSU & Cochrane Workshop
22nd November 2019
GCU London

Nicola Cooper and Yiqiao Xin

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Outline

- Network Meta-analysis
  - Key points from the Cochrane Handbook*
  - Advantages

- MetaInsight App
  - Overview
  - New features

*Chaimani et al. Chapter 11: Undertaking network meta-analyses. In: Higgins et al.(editors). *Cochrane Handbook for Systematic Reviews of Interventions* version 6.0 (updated July 2019). Cochrane, 2019. Available from www.training.cochrane.org/handbook.

Network Meta-Analysis: Key points

- **A technique for comparing 3 or more interventions simultaneously in a single analysis**
- Produces estimates of the relative effects between any pair of interventions in the network
- Relies of the assumption that the different sets of studies included in the analysis are similar, on average, in all important factors that may affect the relative effects (i.e. transitivity)
- Incoherence (inconsistency) occurs when different sources of information about a particular intervention comparison disagree
- Grading confidence in evidence from Network Meta-analysis begins by evaluating confidence in each direct comparison

Chapter 11: Cochrane Handbook

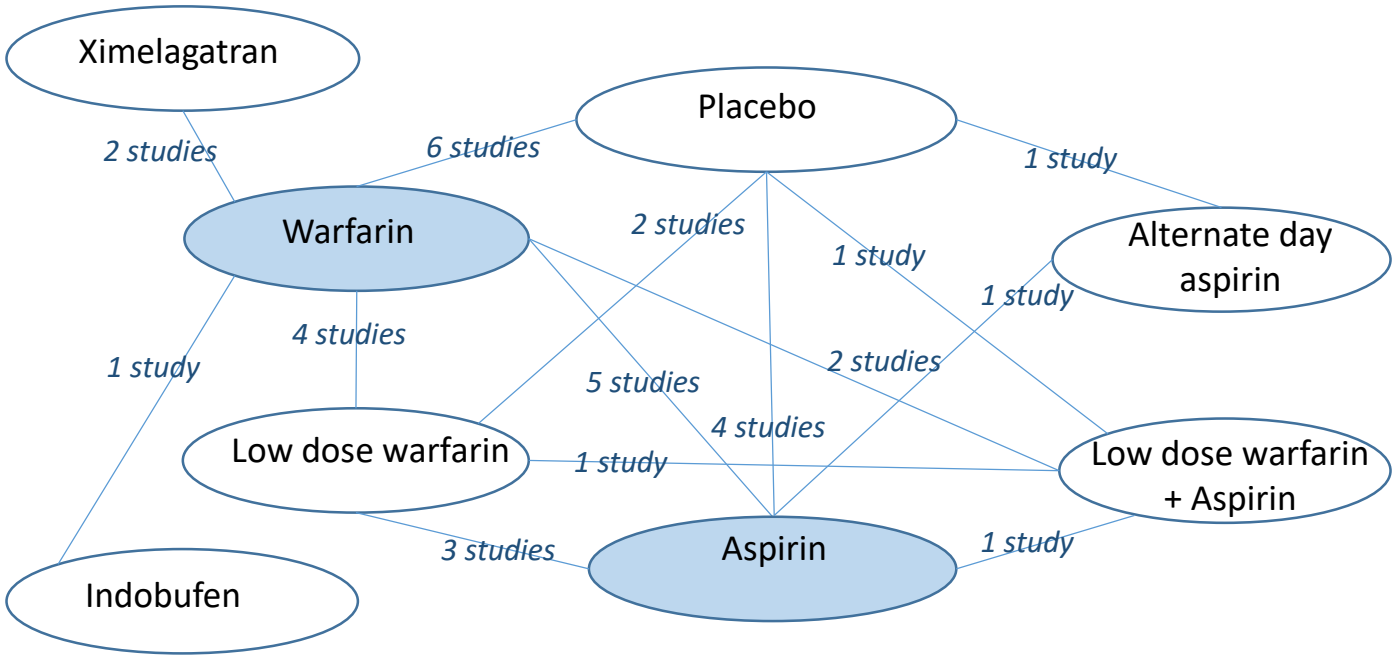
www.training.cochrane.org/handbook

Comparing 2 interventions

- Historically reviews present comparisons between pairs of interventions.
  - *For example, Warfarin versus Aspirin for preventing stroke in individuals with atrial fibrillation*

Comparing 3 or more interventions

- However, often there are numerous competing interventions available for any given condition
- Therefore, decision makers and clinicians must decide between multiple alternative interventions
  - *For example, interventions for preventing stroke in individuals with atrial fibrillation*



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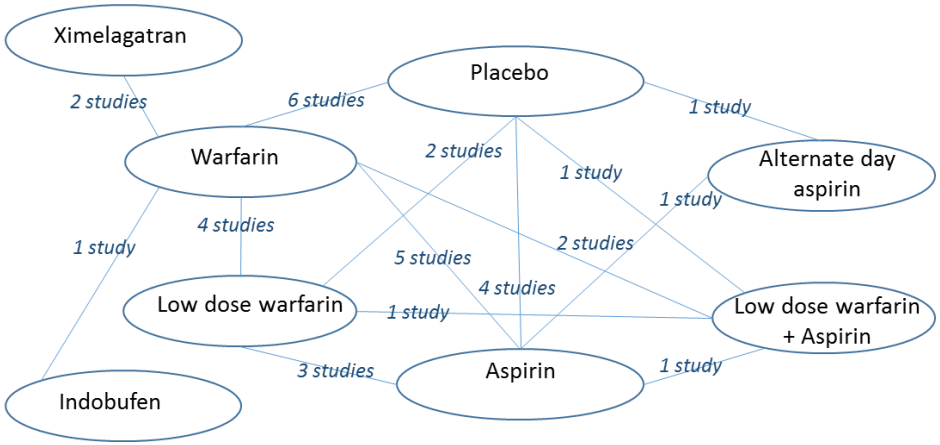
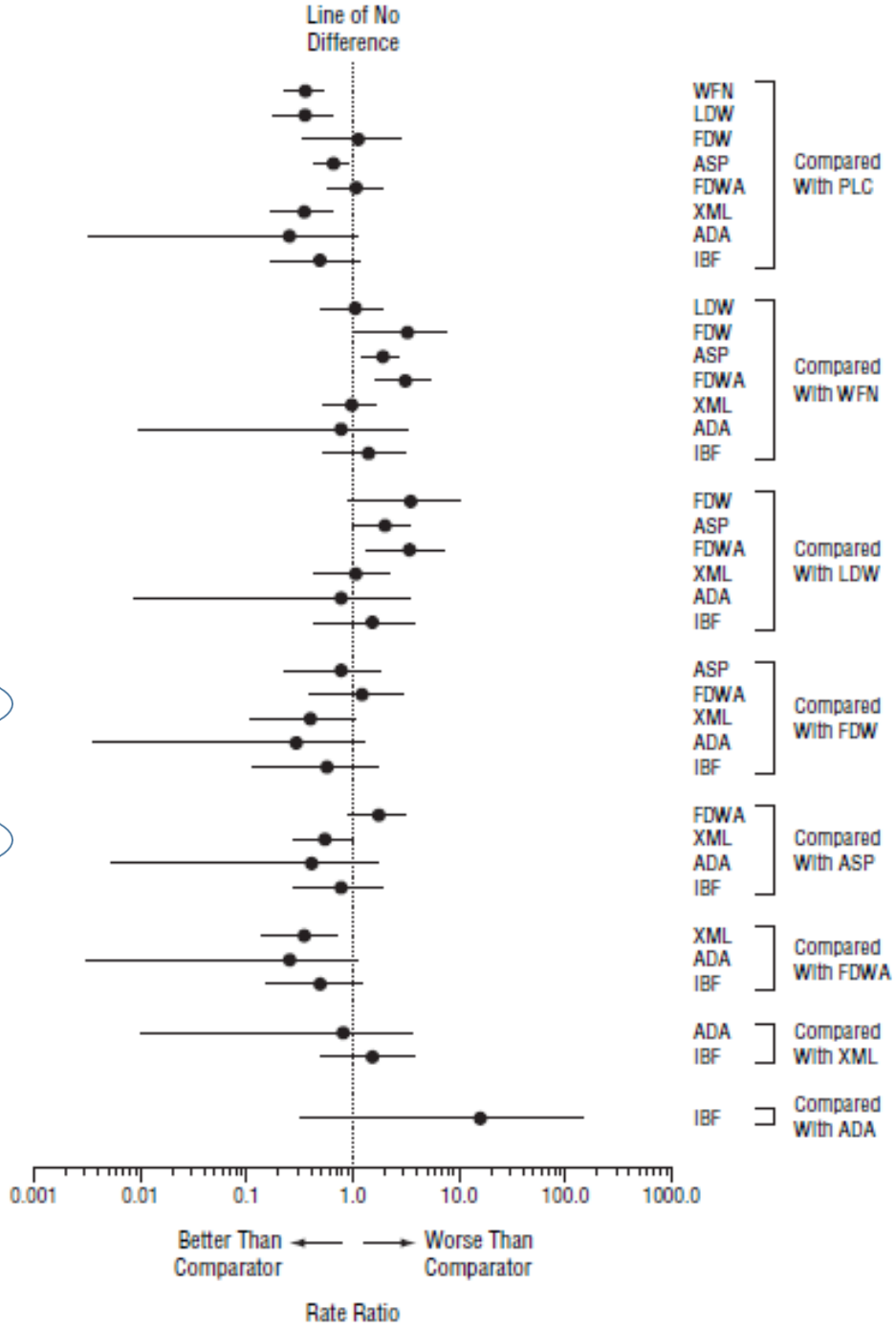
Estimates of the relative effects between any pair of interventions in the network





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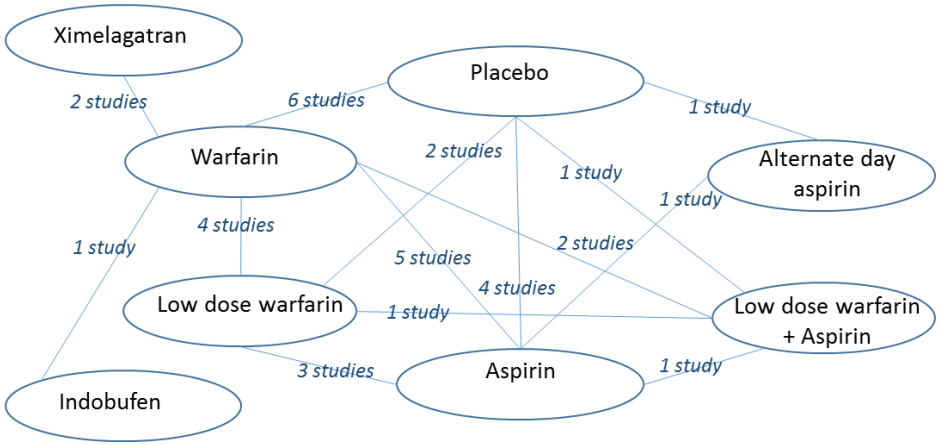

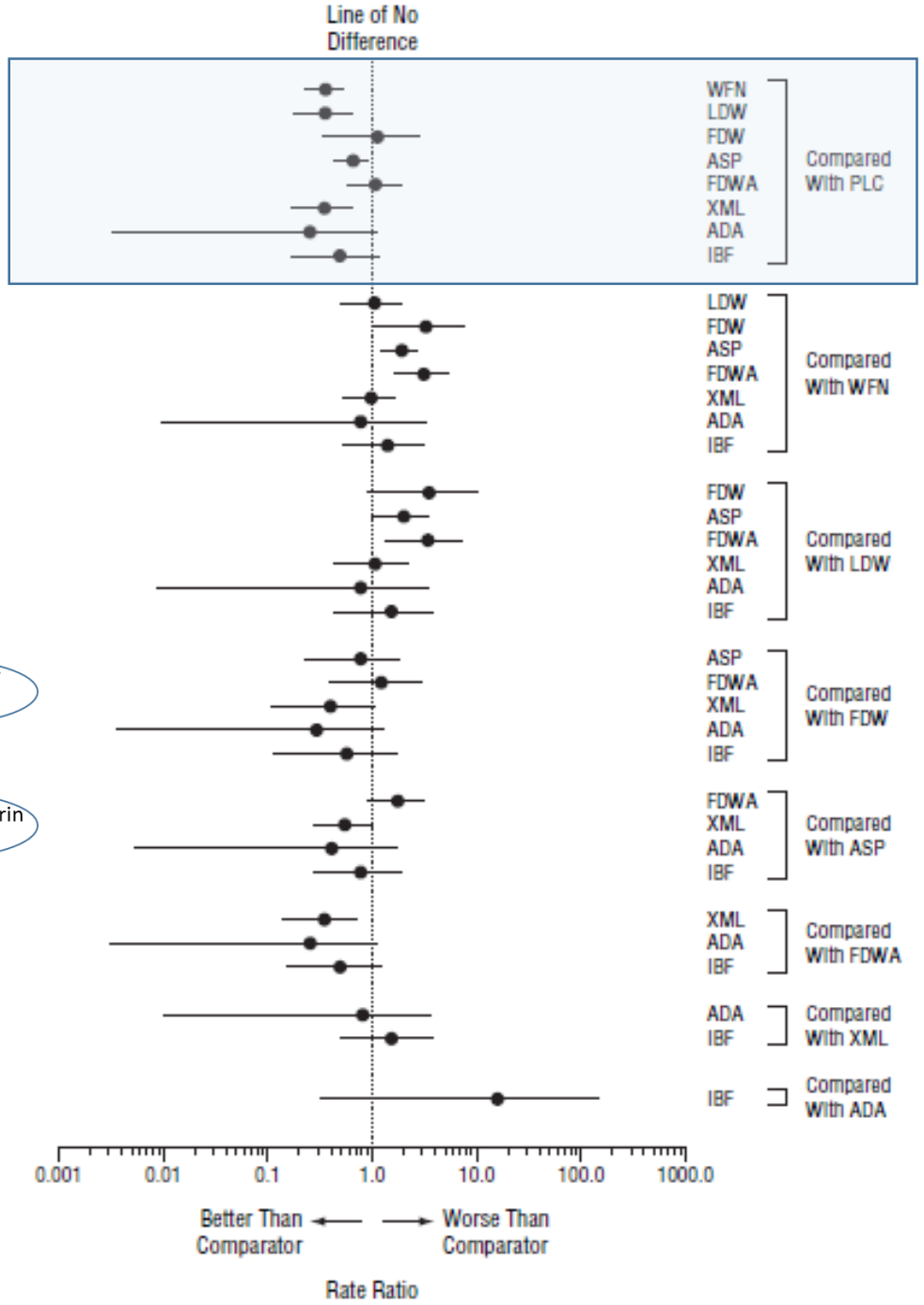

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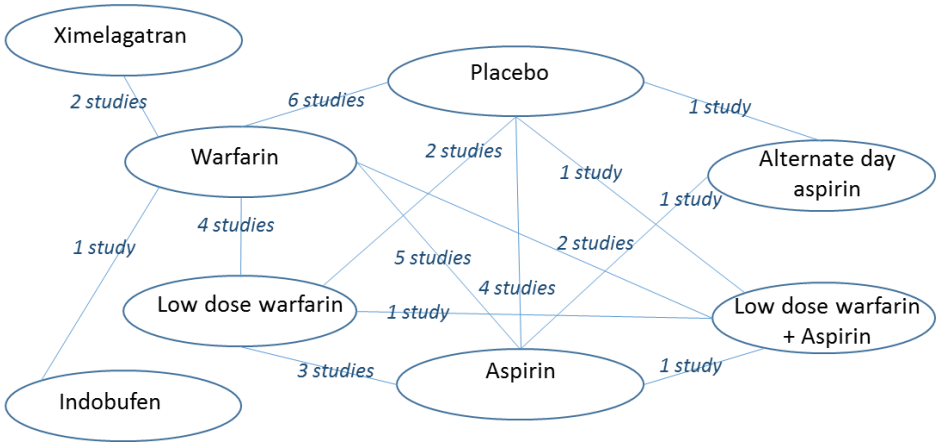

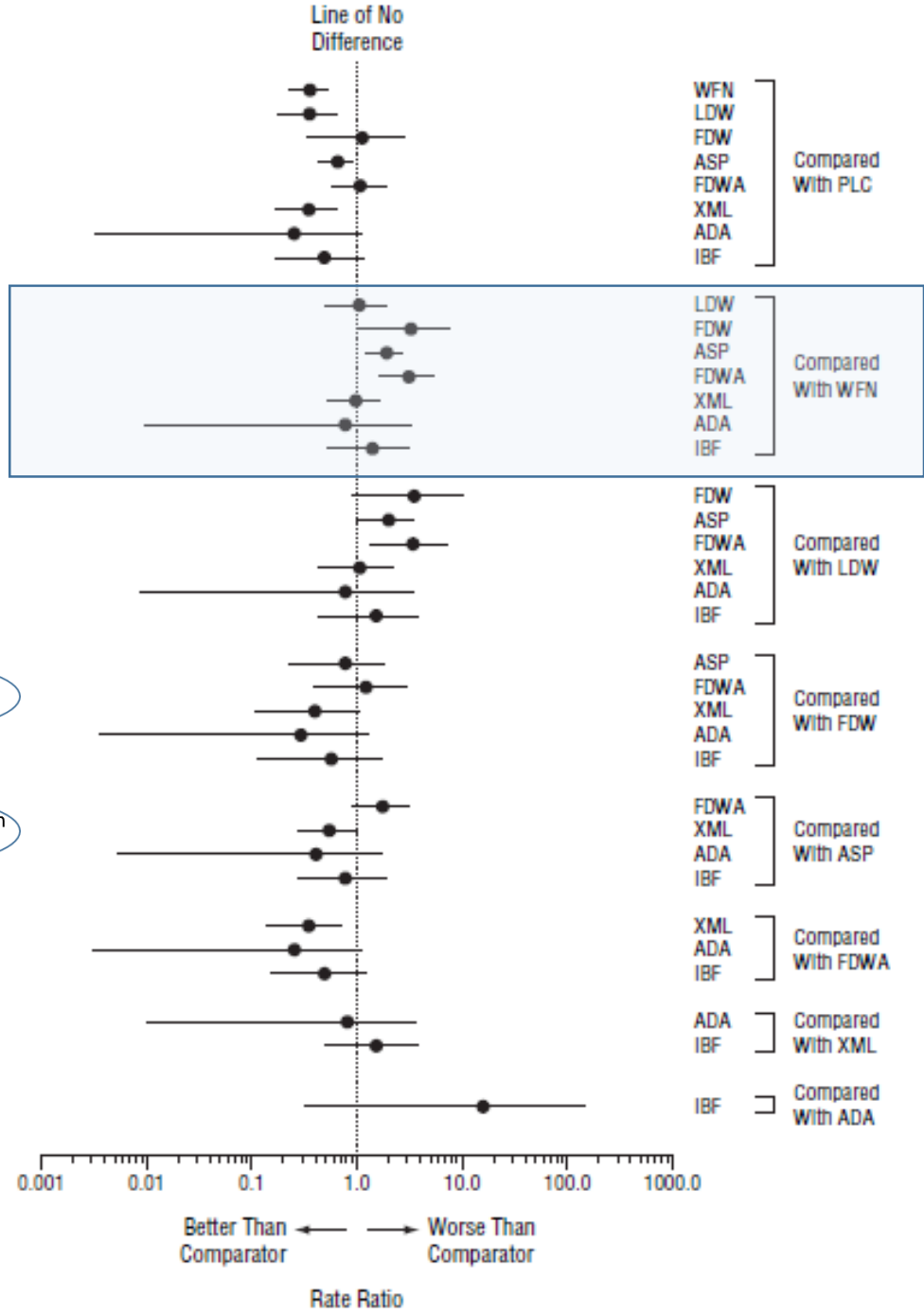

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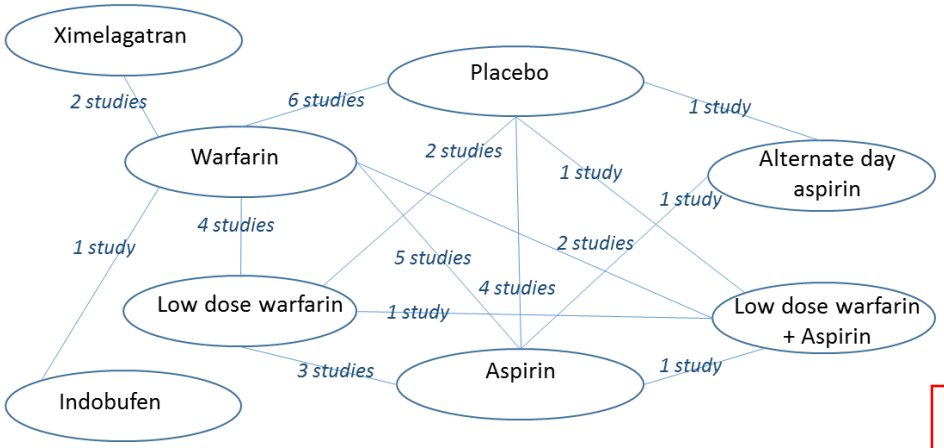
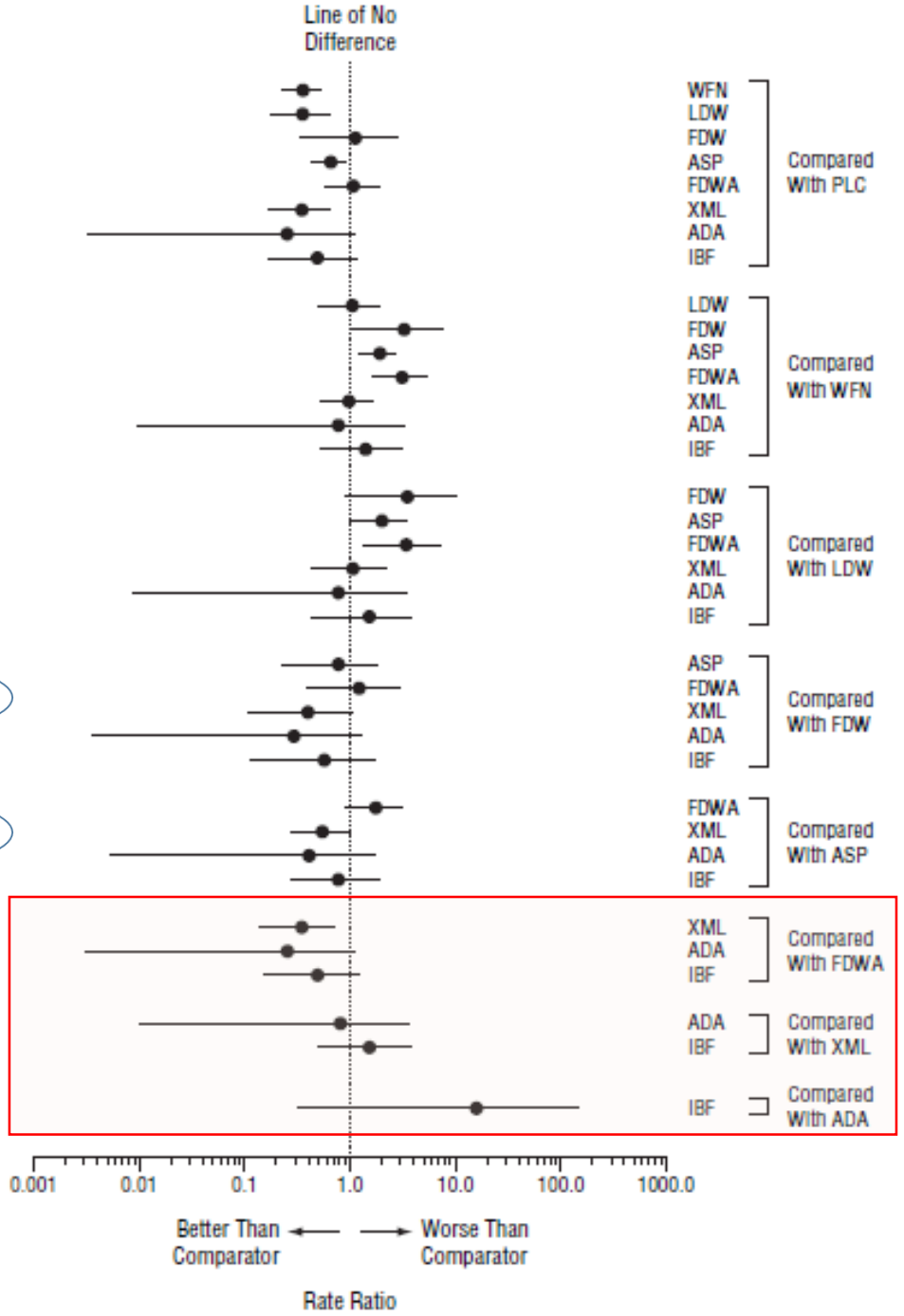


Not previously compared in trials



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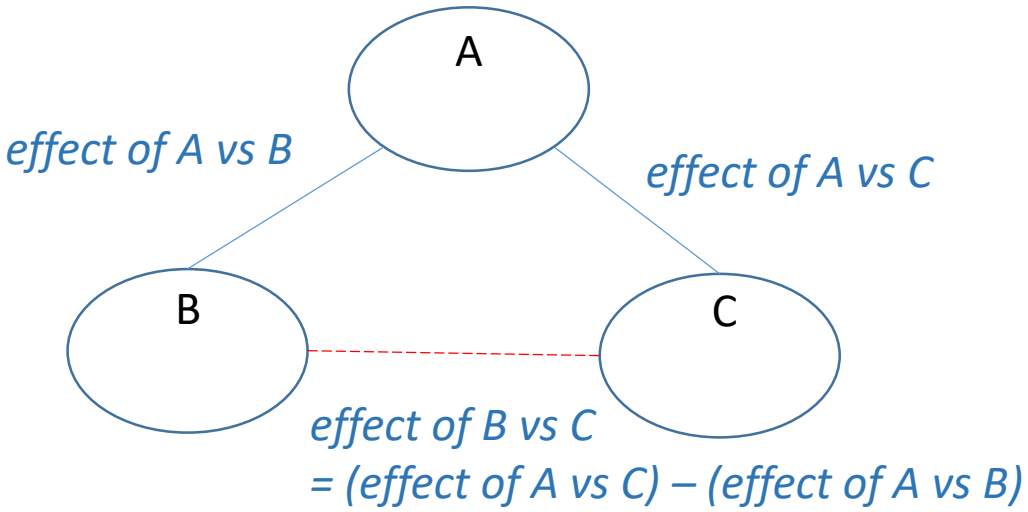
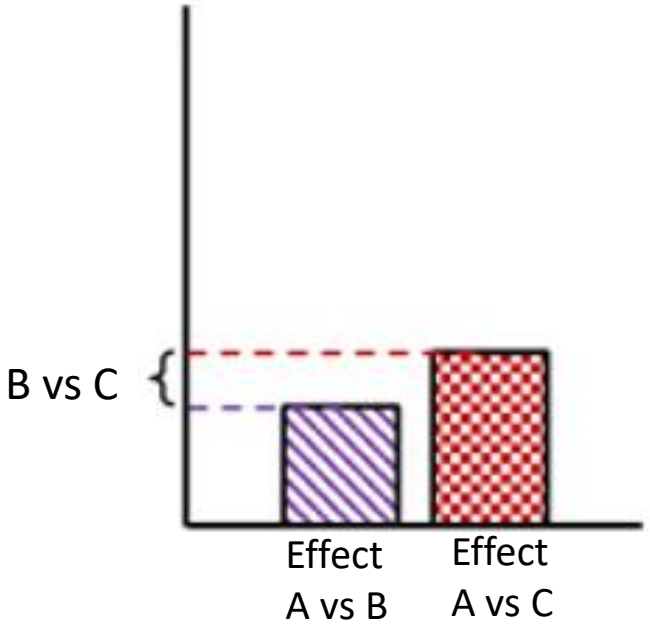
Transitivity

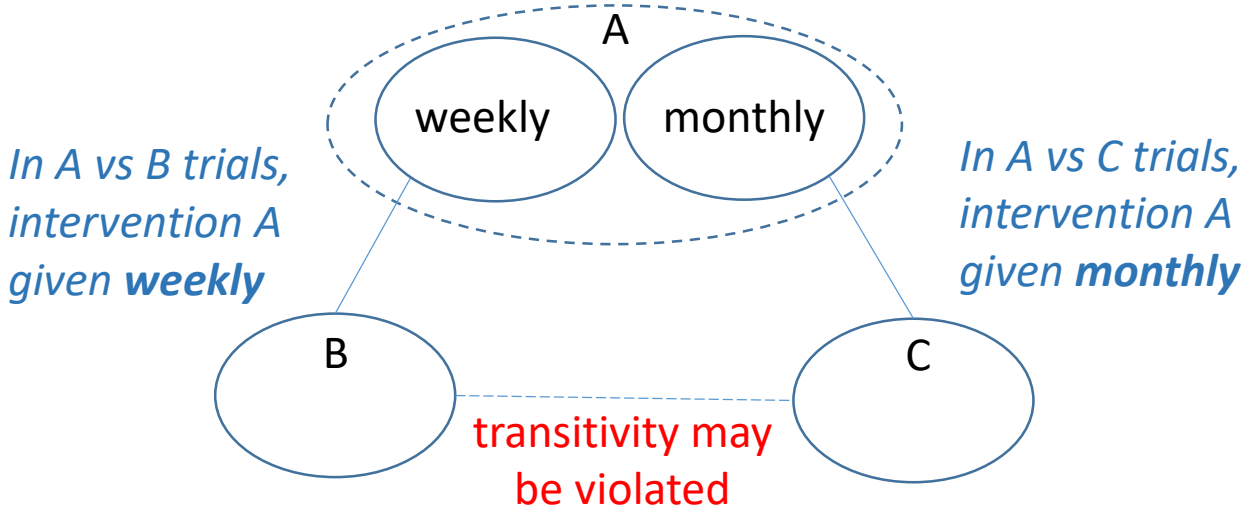
- **Example:** Consider a 3 intervention network, **transitivity** assumes that we can learn about the true relative effect of B vs C via intervention A by combining the true relative effects A vs B and A vs C.
- That is, *effect of B vs C = (effect of A vs C) – (effect of A vs B)*





Violation of transitivity

- Studies comparing different interventions may differ in a range of characteristics
- If these characteristics are associated with the effect of an intervention, they are referred to as *effect modifiers*
- Transitivity requires that intervention A is similar in the A vs B trials and A vs C trials with respect to characteristics (effect modifiers) that may affect the 2 relative effects
- For example,



Effect of B vs C ≠ (effect of A vs C) – (effect of A vs B)

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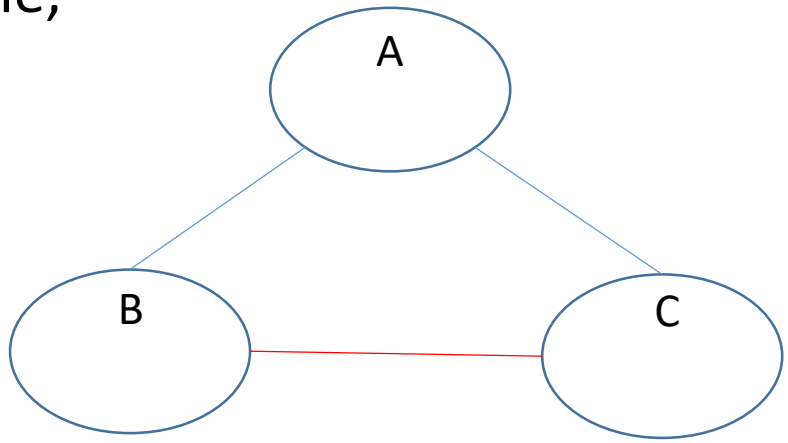
Incoherence / Inconsistency

- Coherence is measured as the **absolute difference between the direct and indirect summary estimates** for any of the pairwise comparisons in the loop
- For example,



$(effect\ of\ B\ vs\ C)_{direct} = (effect\ of\ B\ vs\ C)_{indirect} = (effect\ of\ A\ vs\ C) - (effect\ of\ A\ vs\ B)$

- Coherence should hold in every loop of evidence in the network

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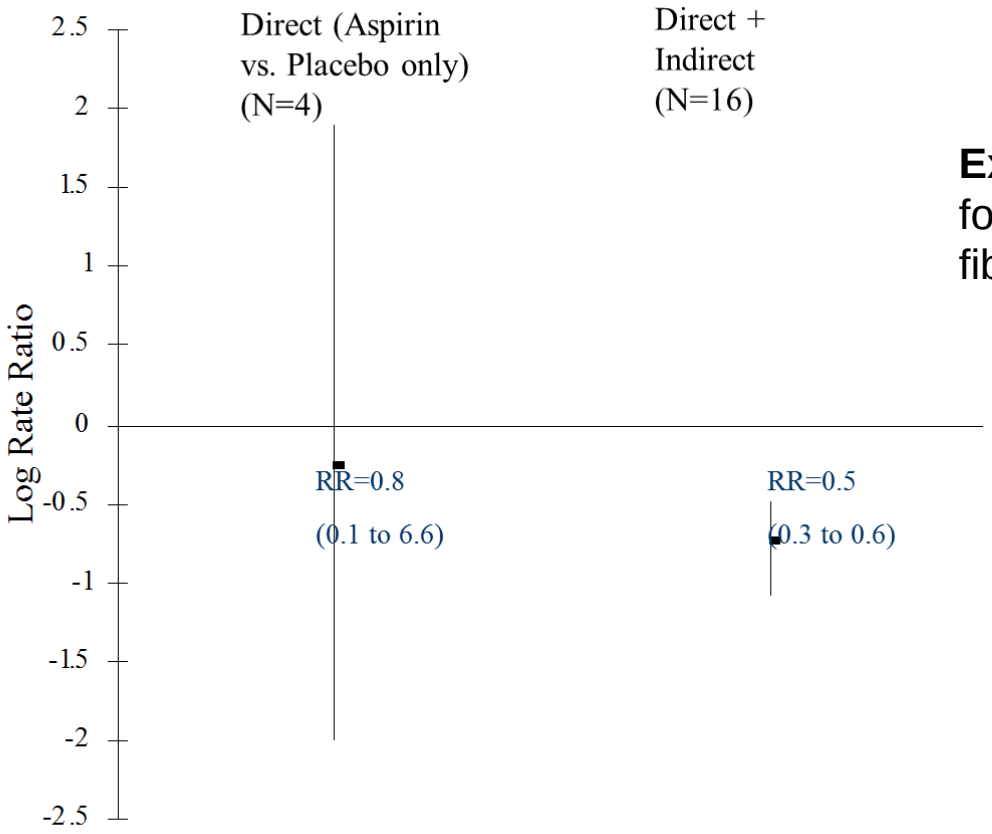
Grading confidence in evidence

- Two approaches proposed to evaluate confidence in evidence in Network Meta-analysis
  - Salanti G, Del Giovane C, Chaimani A, Caldwell DM, Higgins JPT. Evaluating the quality of evidence from a network meta-analysis. *PloS One* 2014; **9**: e99682
  - Puhan MA, Schünemann HJ, Murad MH, Li T, Brignardello-Petersen R, Singh JA, Kessels AG, Guyatt GH; GRADE Working Group. A GRADE Working Group approach for rating the quality of treatment effect estimates from network meta-analysis. *BMJ* 2014; **349**: g5630.
- Both approaches modify the standard GRADE domains to fit Network Meta-analysis and provide a **qualitative** evaluation of the quality of evidence.
- Recently proposed threshold method enables **quantification** of the robustness of the network meta-analysis results to potentially biased evidence.
  - Phillippo et al. Sensitivity of treatment recommendations to bias in network meta-analysis. *Royal Statistical Society Series A* 2018; 181(3): 843-867.

Advantages of Network Meta-Analysis

- Maximises use of the available evidence
- May yield more precise estimates of the intervention of effects in comparison with a single direct estimate



Example: Effectiveness of aspirin for prevention of stroke in atrial fibrillation compared to placebo

Advantages of Network Meta-Analysis

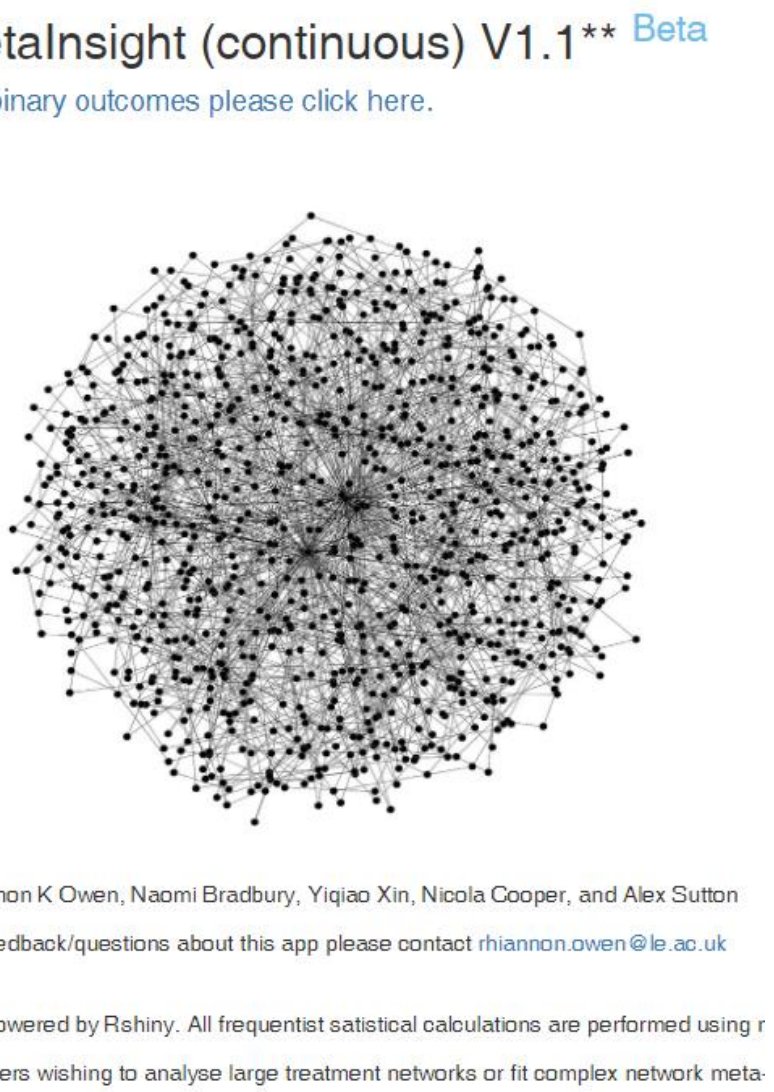
- Maximises use of the available evidence
- May yield more precise estimates of the intervention of effects in comparison with a single direct estimate
- Can provide information for comparisons between pairs of interventions that have not previously been evaluated within a single randomised trial
- Simultaneous comparison of all interventions within a single analysis enables estimation of their relative *ranking* and *hierarchy of interventions*

MetaInsight App - Overview

- **MetaInsight:** an interactive web-based tool for analysing and visualising network meta-analyses

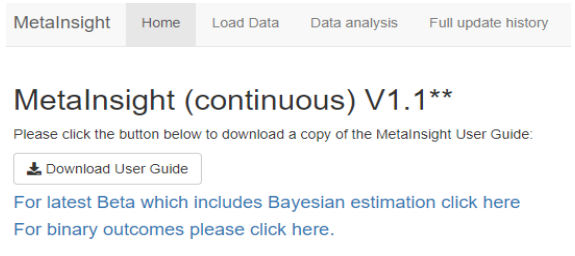
- freely available
- no specialist software required
- ‘point and click’

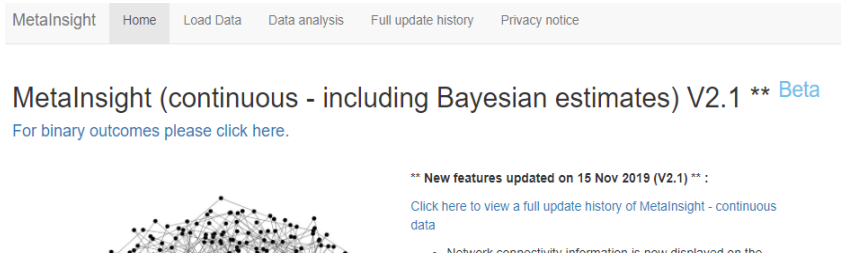
- Rhiannon K Owen, Naomi Bradbury, Yiqiao Xin, Nicola Cooper, and Alex Sutton

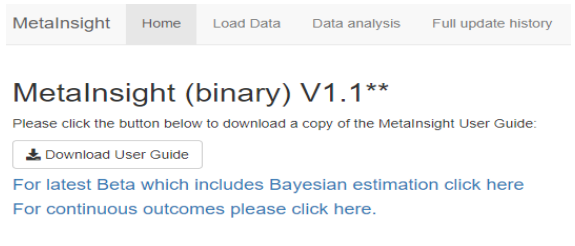


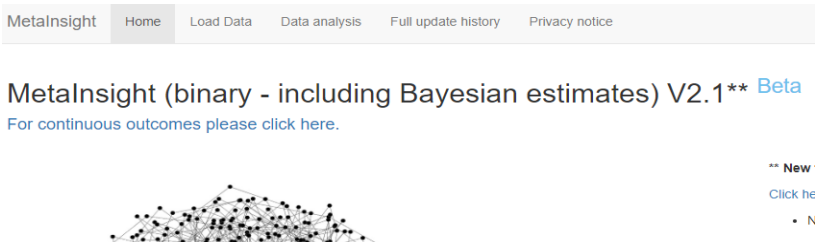
MetaInsight App - versions

	Frequentist	Frequentist + Bayesian
Continuous outcome	https://crsu.shinyapps.io/metainsightc/	https://crsu.shinyapps.io/metainsight_continuous2/
Binary outcome	https://crsu.shinyapps.io/metainsightb/	https://crsu.shinyapps.io/metainsight_binary2/









MetaInsight App V2.1

MetaInsight App features - summary

Features	V1.1 Freq (netmeta)	V2.1 Baye (GEMTC)
Forest plot of each intervention vs. reference	✔	✔
Estimates between all treatment pairs from NMA	✔	✔
Pairwise MA estimates	✔	✔
Treatment ranking	✔	✔[1]
Inconsistency	✔	✔[2]
Model fit	✗	✔[3]
Model details	-	✔

Key new features with MetaInsight V2.1 – 1. ranking

Frequentist

P-score calculated from point estimates and standard error

Rimonbant	.	-1.73 [-3.24; -0.22]	.	.	.
-1.72 [-3.66; 0.22]	Orli_Sibut	.	-0.71 [-1.82; 0.40]	-1.48 [-2.55; -0.41]	-1.94 [-2.92; -0.95]
-1.73 [-3.24; -0.22]	-0.01 [-1.23; 1.21]	Metformin	0.70 [-0.94; 2.34]	-1.40 [-2.45; -0.35]	-1.10 [-2.77; 0.57]
-2.12 [-3.88; -0.35]	-0.40 [-1.27; 0.47]	-0.39 [-1.30; 0.53]	Sibutramine	-0.46 [-1.01; 0.10]	-1.69 [-1.98; -1.39]
-2.66 [-4.41; -0.92]	-0.95 [-1.83; -0.06]	-0.93 [-1.81; -0.06]	-0.55 [-0.96; -0.13]	Orlistat	-1.17 [-1.61; -0.73]
-3.76 [-5.52; -1.99]	-2.04 [-2.89; -1.18]	-2.03 [-2.94; -1.12]	-1.64 [-1.93; -1.35]	-1.09 [-1.48; -0.70]	Placebo

Bayesian

Probability of the treatment at each rank over the N iterations (currently 20000)

Ranking table for all studies - Probability for each treatment to be the best

	Rank 1	Rank 2	Rank 3	Rank 4	Rank 5	Rank 6
Metformin	0.00717	0.49140	0.33644	0.14300	0.02190	0.00009
Orli_Sibut	0.03736	0.42260	0.36844	0.14555	0.02587	0.00017
Orlistat	0.00003	0.00035	0.00439	0.05166	0.94358	0.00000
Placebo	0.00000	0.00000	0.00000	0.00001	0.00030	0.99969
Rimonbant	0.95252	0.03270	0.00866	0.00389	0.00217	0.00005
Sibutramine	0.00291	0.05295	0.28208	0.65589	0.00617	0.00000

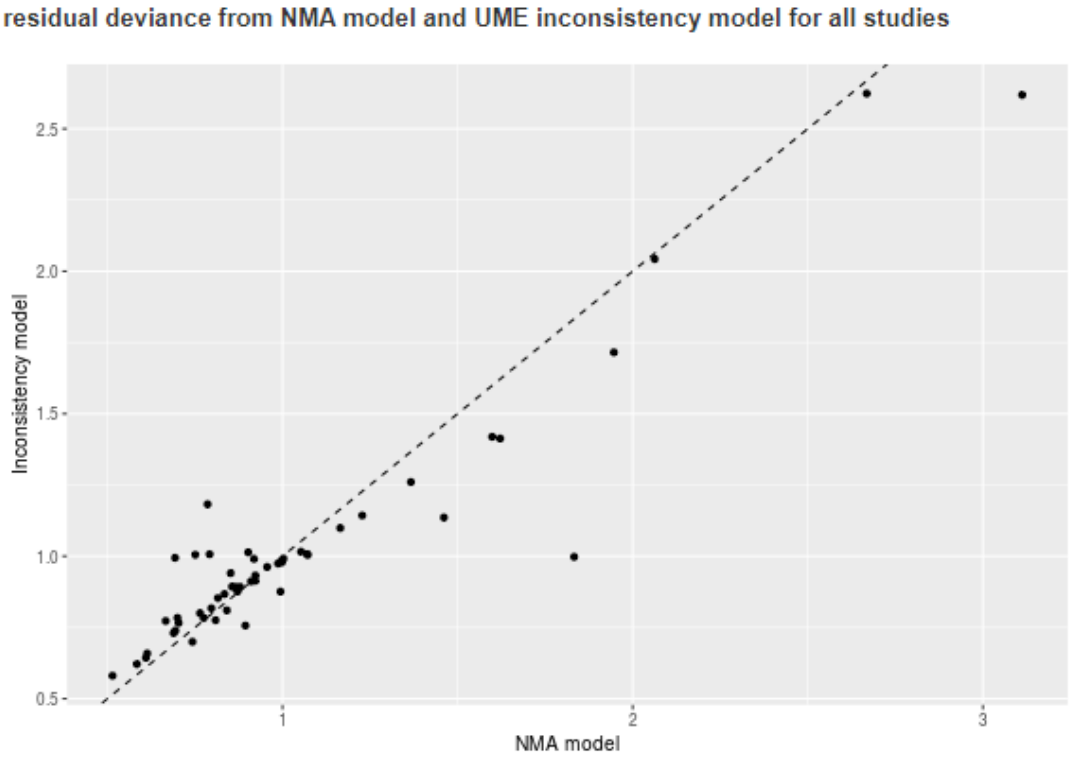
Download

Ranking with all studies - network meta-analysis median rank chart

Rank	Intervention
1	Rimonbant
2	
3	Metformin Orli_Sibut
4	Sibutramine
5	Orlistat
6	Placebo

Key new features with MetaInsight V2.1 – 2. inconsistency plot

- Bayesian NMA provides a plot of residual deviance of ume model and NMA model to visualise the degree of inconsistency

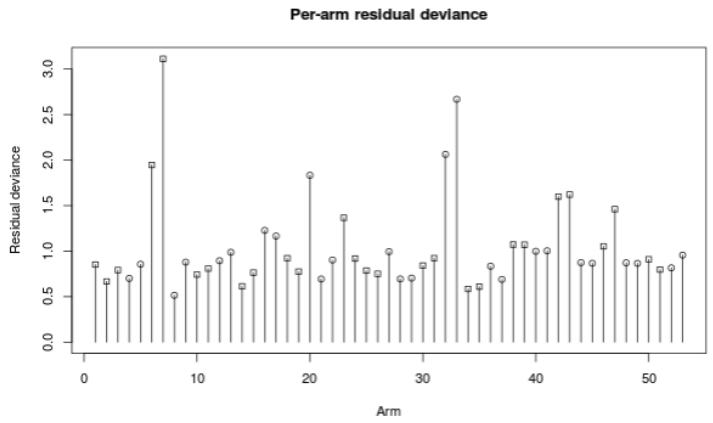


This plot represents each data points' contribution to the residual deviance for the NMA with consiste with the line of equality. The points on the equality line means there is no improvement in model fit w above the equality line means they have a better fit in the ume inconsistency model and points belov unrelated mean effects model may not handle multi-arm trials correctly. (Further reading: Dias S, Ad Model fit, model comparison and outlier detection. @2018 John Wiley & Sons Ltd.)

Key new features with MetaInsight V2.1 – 3. model deviance

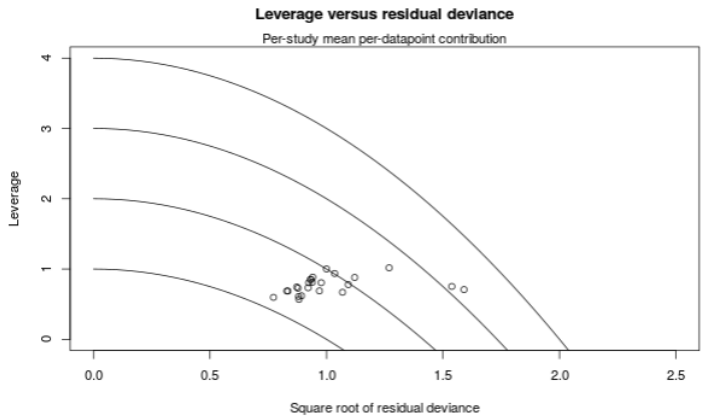
- Bayesian NMA provides two plots for users to check model fit in terms of individual data points. Users can use these plots to identify outliers and conduct sensitivity analyses excluding them to assess the impact.

Per-arm residual deviance for all studies



This stem plot represents the posterior residual deviance per study arm. The total number of stems equal each study in the deviance results below ($dev.ab) (through which you can identify which stem correspon data point. (Further reading: Dias S, Ades AE, Welton NJ, Jansen JP, Sutton AJ. Network meta-anlaysis f

Leverage plot for all studies



This leverage plot shows the leverage for each data point ($lev.ab) versus the square root of the residu deviance, minus the deviance at the posterior mean of the fitted values. The leverage plot may be usec the overall model fit and DIC. Curves of the form x2 + y = c, c = 1, 2, 3, ., where x represents square ro

‘Insight’ by MetaInsight

- The addition of the Bayesian analysis improves the app’s ability to estimate complex models and fully reflect the uncertainty in estimating heterogeneity.
- It facilitates the interrogation of data and investigation of the variability in results from frequentist and Bayesian approaches.
- It aims to increase capacity by empowering informed non-specialists to be able to conduct more NMAs, and also provide an efficient solution even for those who are familiar with the necessary coding.
- It allows decision makers to scrutinize presented results visually and in real-time and facilitates understanding and interpretation of NMA results to broader stakeholder groups.

More to come …

- More details during the MetaInsight demonstration session in the afternoon
- Cochrane Training: NMA webinar series

Cochrane Training

Trusted evidence.
Informed decisions.
Better health.

Online learning | Learning events | Guides and handbooks | T

Network meta-analysis: Learning Live webinar series

December 3, 2019

MetaInsight: The Complex Review Support Unit (CRSU) network meta-analysis (NMA) web-based app

Alex Sutton & Yiqiao Xin, members of the NIHR Complex Review Support Unit

[more info and sign up] link

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Dr Yiqiao Xin Yiqiao.xin@glasgow.ac.uk
NIHR Complex Review Support Unit (CRSU)