



# NETWORK META ANALYSIS (NMA)

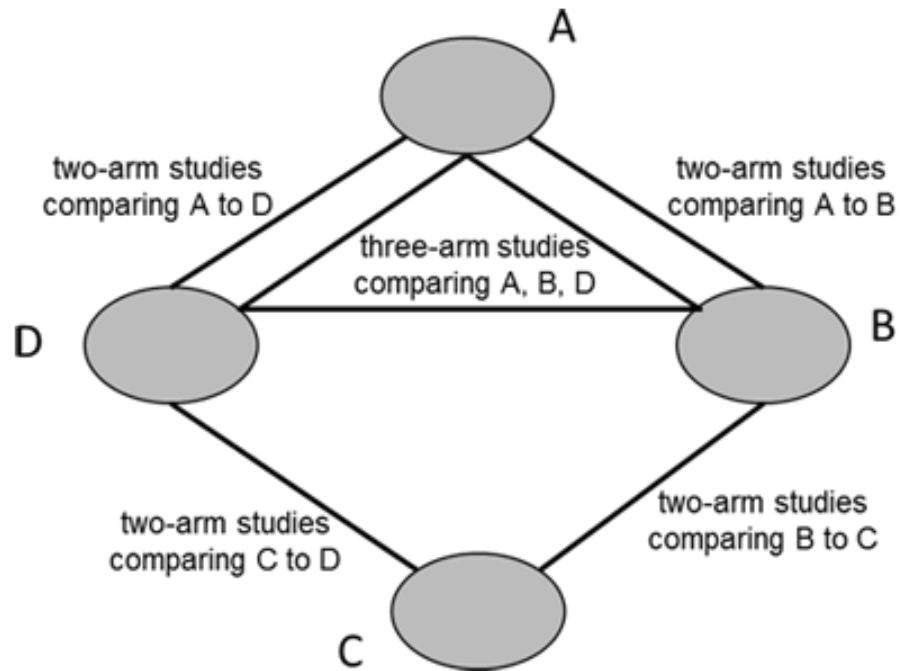
STAT3622  
Data Visualization

# META-ANALYSIS | LIMITATIONS

- ❑ The conventional meta-analysis approach can only
  - compare **pairs** of interventions at a time
  - evaluate **direct** treatment effect (interventions A vs B) in **head-to-head** trials (fail to include multi-arm trials)
- ❑ Sometimes, only few randomized controlled trials (RCTs) have compared the effects of two interventions **directly**
- ❑ In real cases, usually there would exist **more than two interventions** for one specific disease, and RCTs that simultaneously compare all interventions of interest are almost never available
- ❑ How to compare three or more interventions **simultaneously** in a single analysis?
- ❑ How to incorporate **indirect** evidence? (e.g., A vs B by A vs C and B vs C)

# NMA | INTRODUCTION

□ Network meta-analysis is a technique for comparing **three or more interventions simultaneously** in a single analysis by combining both **direct** and **indirect** evidence across a **network** of studies

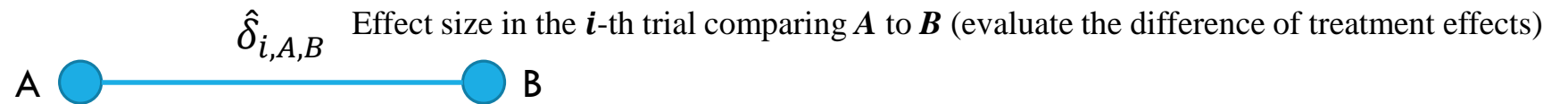


## □ Evidence of *A vs B*

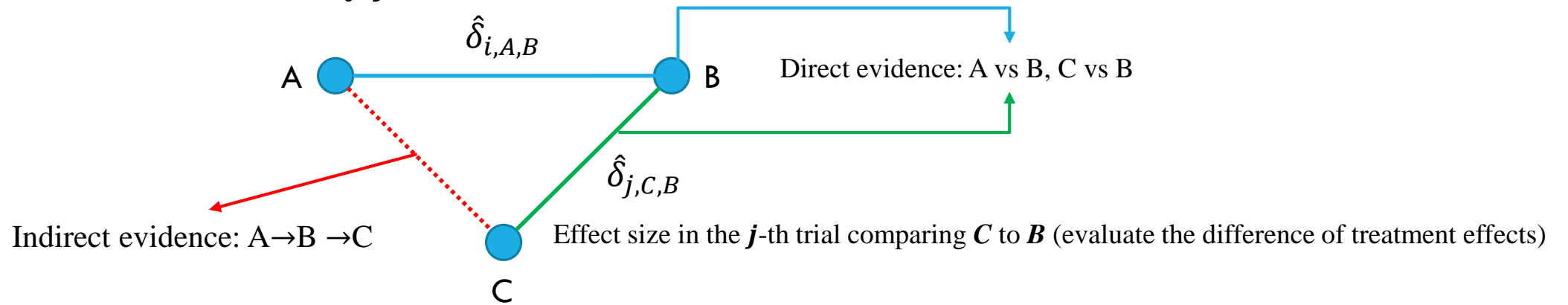
- Direct: two-arm studies comparing *A to B*
- Indirect: loop of evidence, e.g., *A to D to B* (both two-arm studies comparing *A to D* and three-arm studies comparing *A,B,D*), *A to D to C to B*

# NMA | INDIRECT COMPARISON

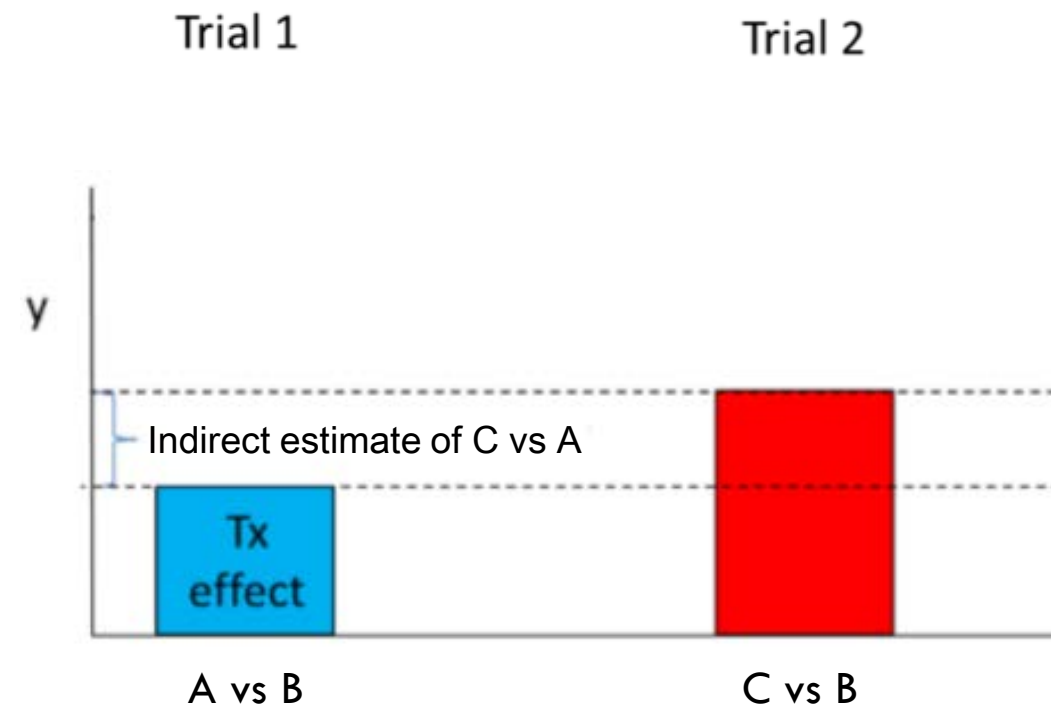
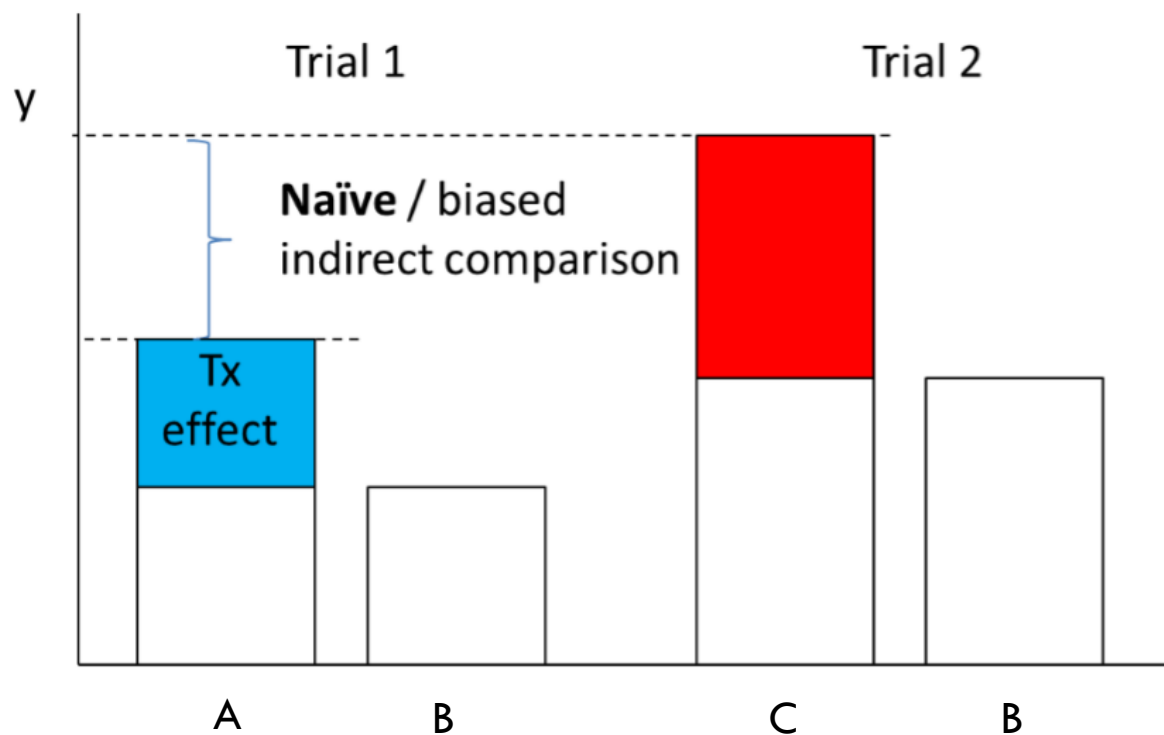
- Head-to-head trial  $i$  for A vs B



- Include another study  $j$  for C vs B

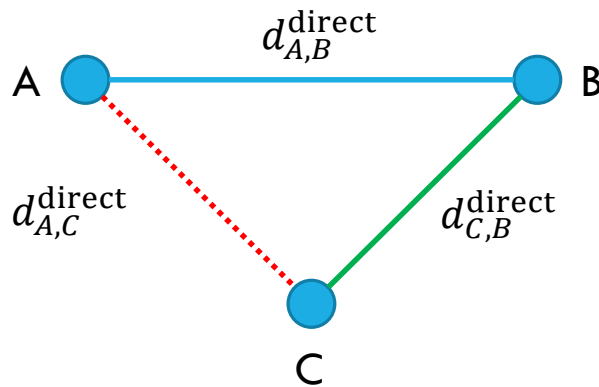


# NMA | INDIRECT COMPARISON



# NMA | INDIRECT COMPARISON

- Assume that we only have RCTs comparing A to B and C to B (no A to C)
- We can obtain aggregate effect size estimates from direct comparisons as  $d_{A,B}^{\text{direct}}, d_{C,B}^{\text{direct}}$
- Nodes A and C are indirectly connected by  $A \rightarrow B, B \rightarrow C$
- Effect between A and C:  $d_{A,C}^{\text{direct}} = d_{A,B}^{\text{direct}} + d_{B,C}^{\text{direct}} = d_{A,B}^{\text{direct}} - d_{C,B}^{\text{direct}}$



# NMA | ASSUMPTIONS: TRANSITIVITY

$$d_{A,C}^{\text{direct}} = d_{A,B}^{\text{direct}} + d_{B,C}^{\text{direct}} = d_{A,B}^{\text{direct}} - d_{C,B}^{\text{direct}}$$

□ Transitivity: **validity** of **indirect** evidence

□ Requirements: we can compare interventions A and C via B

➔ there is **no difference in patient and study characteristics** that may **modify treatment effect** in the **direct** comparisons (e.g., A vs B, B vs C) that form the basis for the indirect estimate of effect of the comparison of interest (A vs C)

□ **Imbalance** in the distribution of patient and study characteristics among trials may **bias** treatment effect estimates

□ For example, if patients included in trials comparing A vs B were all  $\geq 50$  years and those for B vs C were all  $\leq 30$  years, then these two direct effect estimates cannot be compared and combined to estimate the indirect effect between A and C

# NMA | ASSUMPTIONS: CONSISTENCY

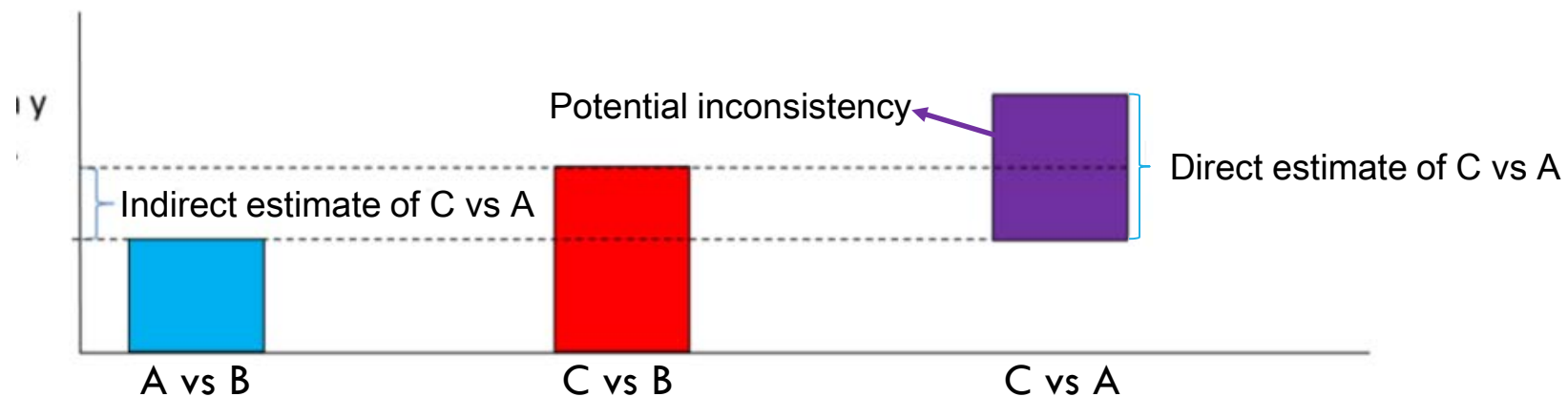
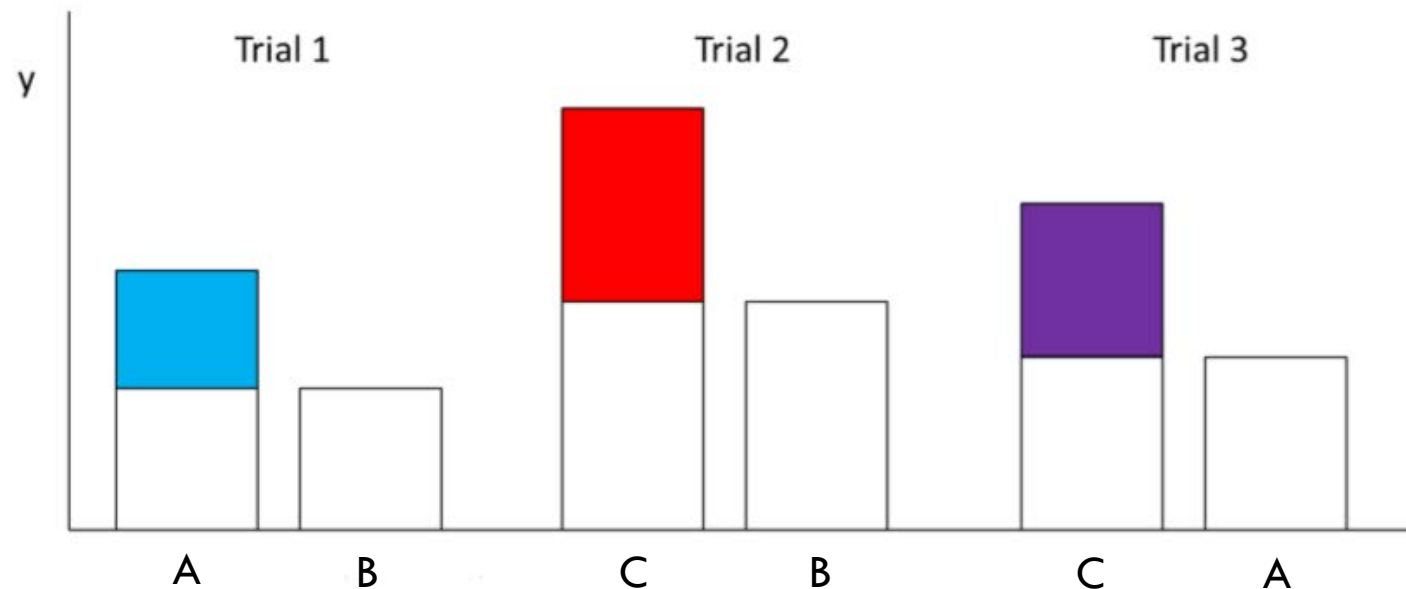
- ❑ In the network meta-analysis, we might obtain both direct (head-to-head comparisons) and indirect (connected by other interventions in the graph) evidence
- ❑ Consistency: the **direct** evidence in a network for the effect size between two treatments (e.g. A vs B) does **not differ** from the **indirect** evidence calculated for that same comparison

$$d_{A,B}^{\text{indirect}} = d_{A,B}^{\text{direct}}$$

- ❑ Global and local statistical approaches to check consistency



# NMA | ASSUMPTIONS: CONSISTENCY



# NMA | FREQUENTIST FRAMEWORK

- Assume that data consist of **only two-arm studies**
- Suppose that NMA includes  $n$  interventions and  $K$  two-arm trials
- For the  $i$ -th trial, we observe the treatment difference estimate  $\hat{\delta}_{i,a_i,b_i}$  comparing intervention  $a_i$  to  $b_i$  and its standard error  $s_{i,a_i,b_i}$ ,  $i = 1, \dots, K$ .
- For arm-level data, we can choose a summary measure and calculate the treatment differences as well as their standard errors.
- We use a  $n \times 1$  vector  $\boldsymbol{\theta} = (\theta_1, \dots, \theta_n)$  to denote the treatment effect of  $n$  interventions
- The *fixed effects model* has the form,

$$\hat{\delta}_{i,a_i,b_i} \sim N(\theta_{a_i} - \theta_{b_i}, s_{i,a_i,b_i}^2), i = 1, \dots, n$$

# NMA | FREQUENTIST FRAMEWORK

- In the matrix form,

$$\hat{\delta} = X\theta + \epsilon$$

- $\hat{\delta} = (\hat{\delta}_{1,a_1,b_1}, \dots, \hat{\delta}_{K,a_K,b_K})$
- $X$  is a  $K \times n$  design matrix for which the rows represent treatment comparisons with  $X_{i,a_i} = 1, X_{i,b_i} = -1$
- $\epsilon \sim N(0, \Sigma), \Sigma = \text{diag}(s^2_{1,a_1,b_1}, \dots, s^2_{K,a_K,b_K})$

# NMA | FREQUENTIST FRAMEWORK

$$\hat{\delta} = X\theta + \epsilon$$

- The design matrix  $X$  might not be of full rank  $\Rightarrow$  Its inverse does not exist
- A *weighted least squares* approach can be utilized to estimate  $\theta$ ,

$$\begin{aligned} L &= X^T W X, \\ W &= \text{diag} \left( \frac{1}{s_{1,a_1,b_1}^2}, \dots, \frac{1}{s_{K,a_K,b_K}^2} \right) \\ L^+ &= \left( L - \frac{J_n}{n} \right)^{-1} + \frac{J_n}{n} \\ \hat{\theta}^{\text{nma}} &= L^+ X^T W \hat{\delta} \end{aligned}$$

where  $J_n$  is the  $n \times n$  matrix whose elements are all one,  $L^+$  is the Moore–Penrose pseudoinverse of  $L$  ( $L$  is not invertible).

# NMA | FREQUENTIST FRAMEWORK

- Predicted values of observed treatment difference:

$$\hat{\delta}^{\text{nma}} = \mathbf{X}\mathbf{L}^+ \mathbf{X}^T \mathbf{W} \hat{\delta}$$

$$\text{Var}(\hat{\delta}^{\text{nma}}) = \mathbf{X}\mathbf{L}^+ \mathbf{X}^T$$

The predicted values  $\hat{\delta}^{\text{nma}}$  are linear combinations of the elements of  $\hat{\delta}$

- Variance of the treatment difference comparing intervention  $i$  to  $j$

$$V_{ij} = L_{ii}^+ + L_{jj}^+ - 2L_{ij}^+$$

# NMA | MULTI-ARM STUDY

- ❑ Multi-arm studies can be included in the NMA as a series of two-arm comparisons
- ❑ For a  $p$ -arm trial, there are  $p(p - 1)/2$  possible comparisons
- ❑ The comparisons within a multi-arm study are **correlated**
- ❑ We need to **adjust the standard error** of each two-arm comparison for the existence of **correlation**
- ❑ Rücker and Schwarzer (2014) **inflated** the standard errors for comparisons within each multi-arm study by back-calculation.

## Research Article

Statistics  
in Medicine

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**Reduce dimension or reduce weights?  
Comparing two approaches to multi-arm  
studies in network meta-analysis**

Gerta Rücker\*<sup>†</sup> and Guido Schwarzer

# NMA | HETEROGENEITY

- Generalized Cochran's Q

$$Q_{\text{total}} = (\hat{\delta} - \hat{\delta}^{\text{nma}})^T W (\hat{\delta} - \hat{\delta}^{\text{nma}})$$

- Each  $p$ -arm study contributes  $p - 1$  degrees of freedom to  $Q_{\text{total}}$

- $df = \sum_{k=1}^K (p_k - 1) - (n - 1)$

- Generalized Higgin's & Thompson's  $I^2$

$$I^2 = \max \left\{ 0, \frac{Q_{\text{total}} - df}{Q_{\text{total}}} \right\}$$

# NMA | RANDOM EFFECTS MODEL

- The *random effects model* has the form,

$$\begin{aligned}\hat{\delta}_{i,a_i,b_i} &\sim N(d_{i,a_i,b_i}, s_{i,a_i,b_i}^2) \\ d_{i,a_i,b_i} &\sim N(\theta_{a_i} - \theta_{b_i}, \tau^2), i = 1, \dots, n\end{aligned}$$

- The estimated heterogeneity  $\hat{\tau}^2$  is added to the variances of each comparison  $i$ :  $s_{i,a_i,b_i}^2 + \hat{\tau}^2$

- The generalized DerSimonian–Laird estimator can be used to estimate  $\tau^2$

$$\hat{\tau}^2 = \max\left(\frac{Q_{total} - df}{tr((I - \mathbf{X}\mathbf{L}^+\mathbf{X}^T\mathbf{W})\mathbf{U}\mathbf{W})}, 0\right)$$

where  $\mathbf{U}$  is a block diagonal matrix from  $\mathbf{X}\mathbf{X}^T/2$  by selecting the diagonal  $p_k \times p_k$  block for  $k = 1, \dots, K$ .

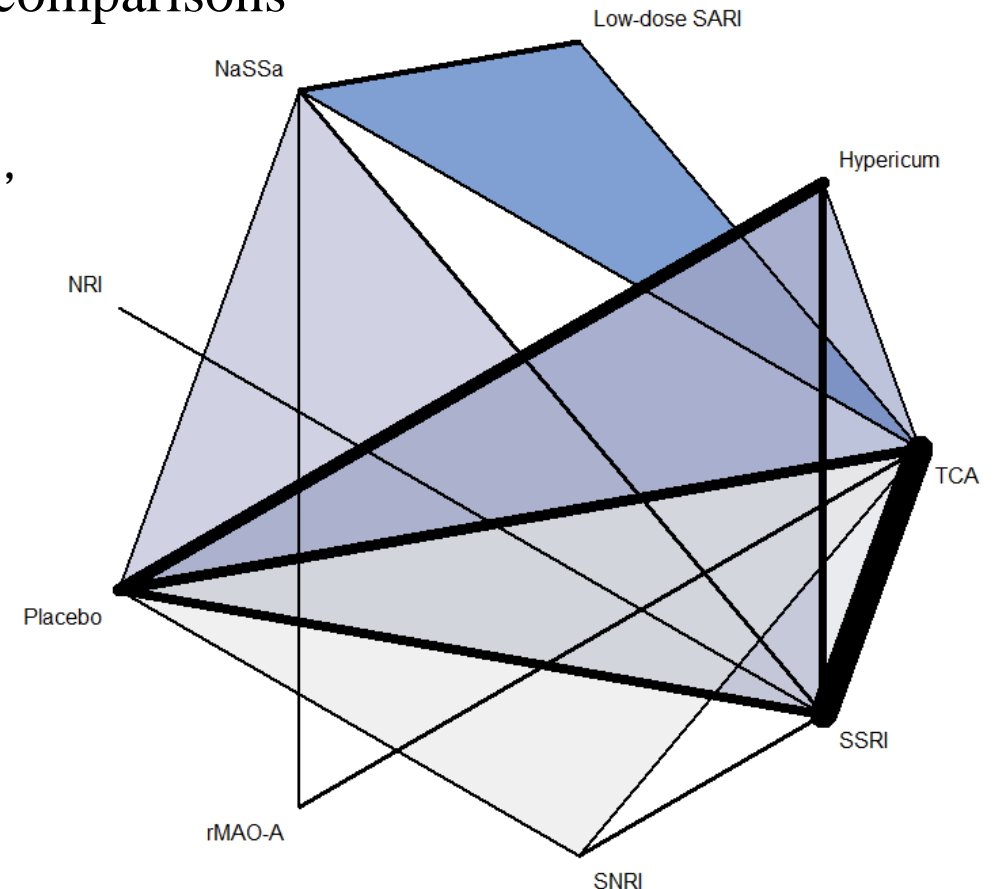


# LINDE2015 | NETWORK PLOT

- The observations of a network-meta analysis can be viewed as a graph
- Nodes are treatments, edges are head-to-head comparisons

```
netgraph(Linde.net, plastic = F,  
         thickness = "number.of.studies",  
         col = 'black')
```

- The width of edges is proportional to the number of studies
- Multi-arm studies are represented as colored polygon (triangles for Linde2015 because it contains only two-arm and three-arm studies)

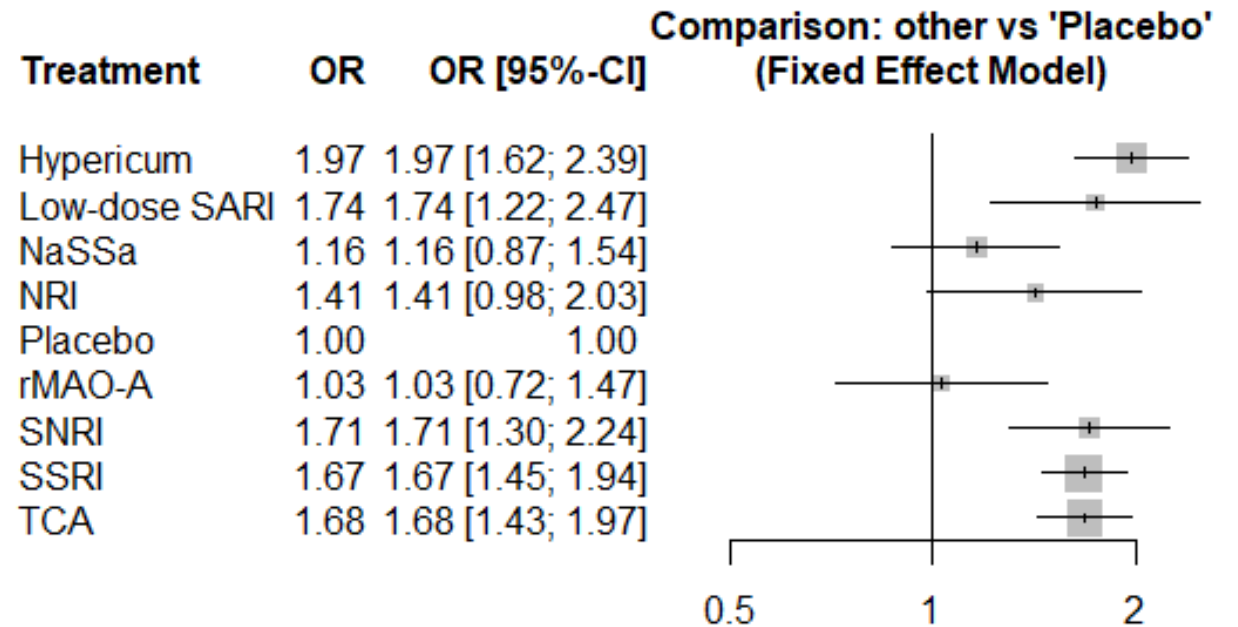


# LINDE2015 | FOREST PLOT

## Fixed effects model

(Placebo as reference)

```
forest(Linde.net,  
       reference.group = 'Placebo',  
       pooled = 'fixed',  
       leftcols = c('studlab',  
                    'effect', 'effect.ci'),  
       rightcols = F)
```



Each row in the forest plot represents the NMA estimates of treatment effect comparing the specific treatment to placebo

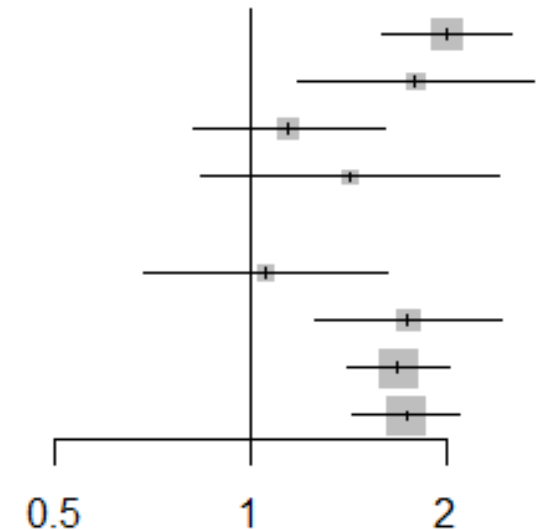
# LINDE2015 | FOREST PLOT

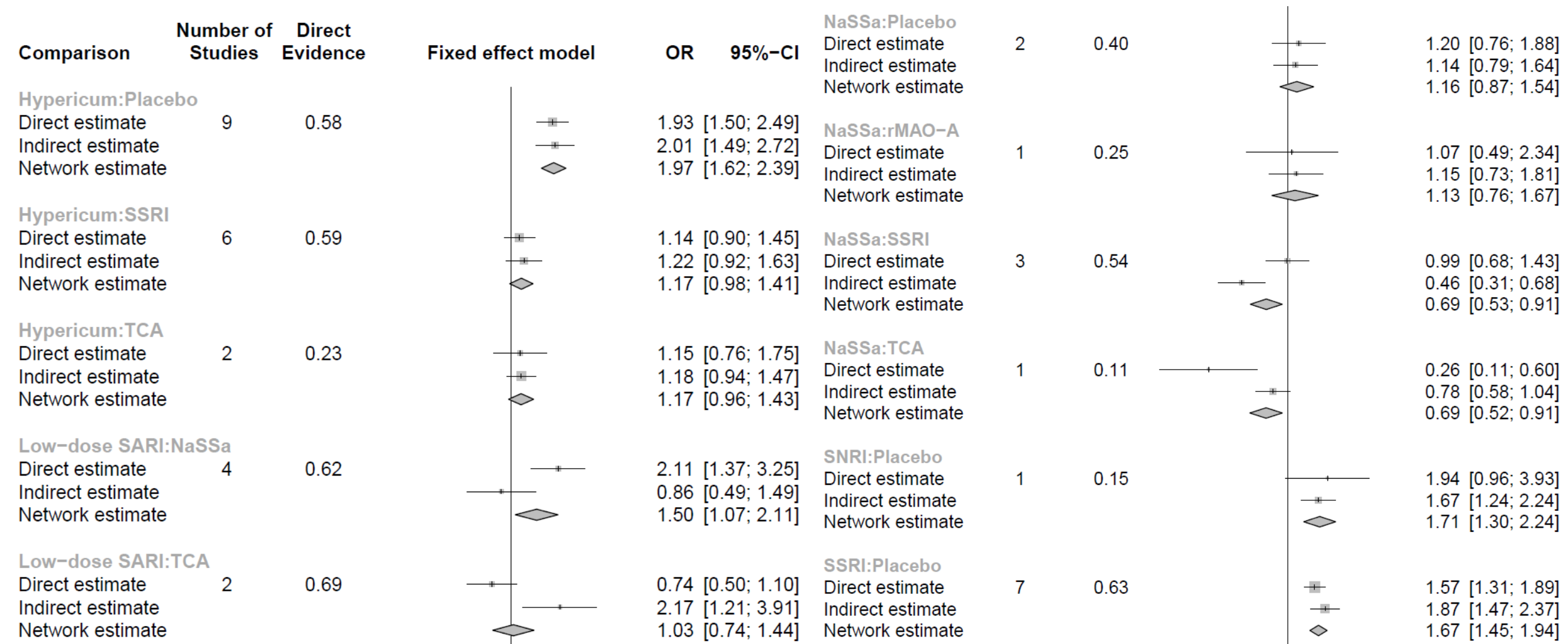
## ❑ Random effects model

(Placebo as reference)


































```
forest(Linde.net,  
       reference.group = 'Placebo',  
       pooled = 'random',  
       leftcols = c('studlab',  
                    'effect', 'effect.ci'),  
       rightcols = F)
```

Treatment	OR	OR [95%-CI]	Comparison: other vs 'Placebo' (Random Effects Model)
Hypericum	1.99	1.99 [1.58; 2.49]	
Low-dose SARI	1.78	1.78 [1.18; 2.70]	
NaSSa	1.14	1.14 [0.82; 1.60]	
NRI	1.42	1.42 [0.84; 2.40]	
Placebo	1.00	1.00	
rMAO-A	1.05	1.05 [0.69; 1.62]	
SNRI	1.74	1.74 [1.25; 2.42]	
SSRI	1.68	1.68 [1.40; 2.01]	
TCA	1.72	1.72 [1.42; 2.09]	





##Results truncated

Comparison	Number of Studies	Direct Evidence	Random effects model	OR	95%-CI	NaSSa:Placebo				
						Direct estimate	2	0.38		1.21 [0.70; 2.08]
						Indirect estimate				1.10 [0.72; 1.69]
						Network estimate				1.14 [0.82; 1.60]
<b>Hypericum:Placebo</b>										
Direct estimate	9	0.61		1.97	[1.47; 2.62]					
Indirect estimate				2.02	[1.40; 2.91]					
Network estimate				1.99	[1.58; 2.49]					
						NaSSa:rMAO-A				
Direct estimate	1	0.29		1.07	[0.45; 2.54]					
Indirect estimate				1.09	[0.63; 1.88]					
Network estimate				1.08	[0.68; 1.72]					
<b>Hypericum:SSRI</b>										
Direct estimate	6	0.58		1.14	[0.85; 1.52]					
Indirect estimate				1.25	[0.89; 1.75]					
Network estimate				1.18	[0.95; 1.47]					
						NaSSa:SSRI				
Direct estimate	3	0.52		0.98	[0.63; 1.52]					
Indirect estimate				0.46	[0.29; 0.73]					
Network estimate				0.68	[0.50; 0.93]					
<b>Hypericum:TCA</b>										
Direct estimate	2	0.23		1.15	[0.70; 1.88]					
Indirect estimate				1.15	[0.88; 1.51]					
Network estimate				1.15	[0.91; 1.46]					
						NaSSa:TCA				
Direct estimate	1	0.13		0.26	[0.11; 0.65]					
Indirect estimate				0.76	[0.54; 1.07]					
Network estimate				0.66	[0.48; 0.91]					
<b>Low-dose SARI:NaSSa</b>										
Direct estimate	4	0.67		2.09	[1.30; 3.36]					
Indirect estimate				0.87	[0.44; 1.70]					
Network estimate				1.56	[1.06; 2.30]					
						SNRI:Placebo				
Direct estimate	1	0.17		1.94	[0.88; 4.30]					
Indirect estimate				1.70	[1.18; 2.45]					
Network estimate				1.74	[1.25; 2.42]					
<b>Low-dose SARI:TCA</b>										
Direct estimate	2	0.66		0.72	[0.45; 1.16]					
Indirect estimate				2.09	[1.07; 4.07]					
Network estimate				1.03	[0.70; 1.52]					
						SSRI:Placebo				
Direct estimate	7	0.59		1.56	[1.23; 1.97]					
Indirect estimate				1.86	[1.41; 2.46]					
Network estimate				1.68	[1.40; 2.01]					

##Results truncated

# COVID19 | NETWORK PLOT

- ❑ Function *plot.mtc.network* generates a network plot.
- ❑ We can directly call *plot* function and use the *mtc.network* object as the input

# Network plot

```
vertex.size = aggregate(mortality.network$data, ab$sampleSize,
```

```
                        by = list(mortality.network$data, ab$treatment),
```

```
FUN = sum)
```

Use Davidson-Harel algorithm for the network plot.

This algorithm has some randomness

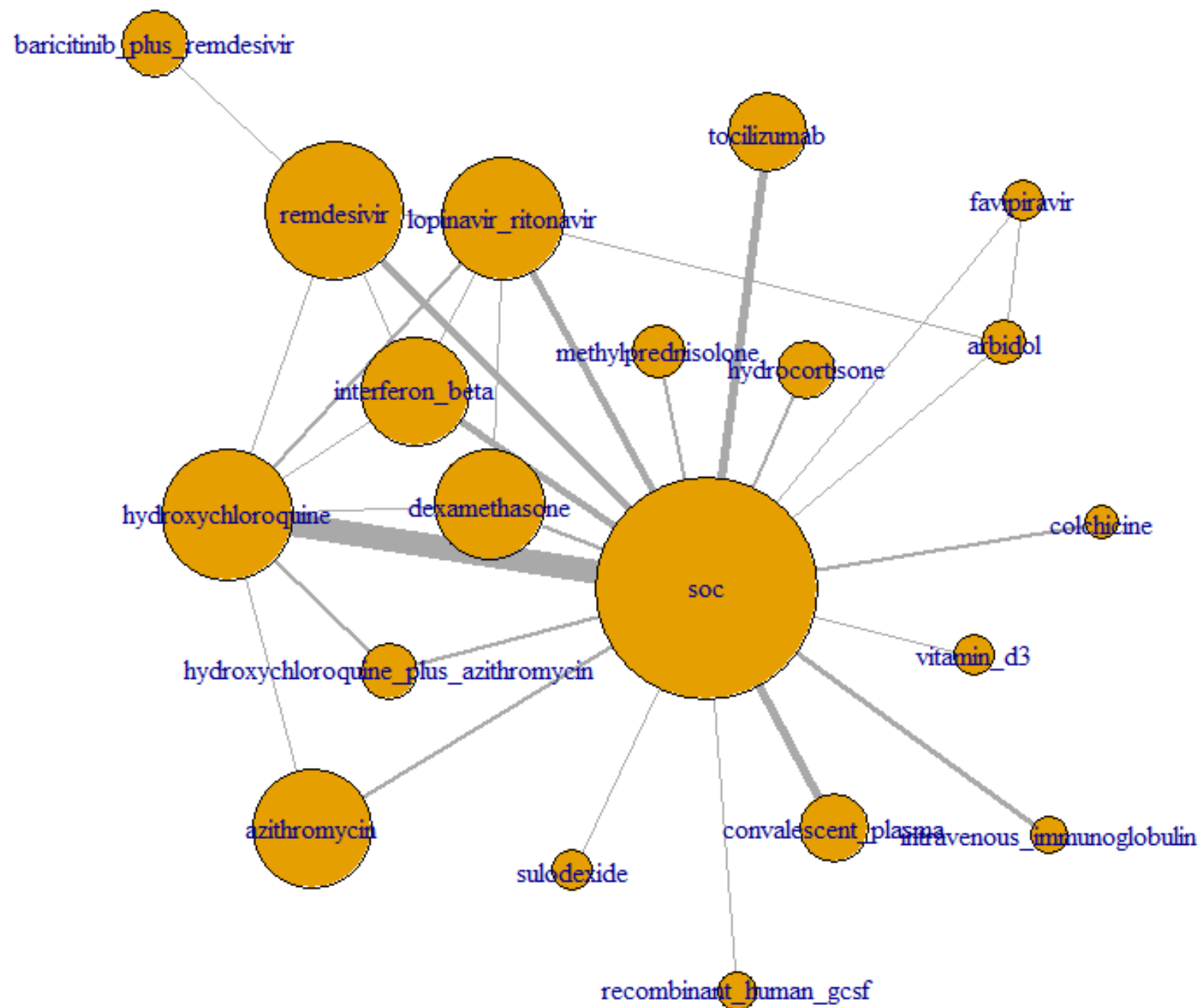
```
plot(mortality.network, layout=igraph::layout.davidson.harel,
```

```
use.description = T, vertex.size = 1.8*(vertex.size$x)**(1/3),
```

```
vertex.label.cex = 1)
```

The size of the node is proportional to the cubic root of the overall number of patients in the treatment group represented by the node

The width of edge between nodes is proportional to the number of head-to-head comparison in the dataset (default setting)



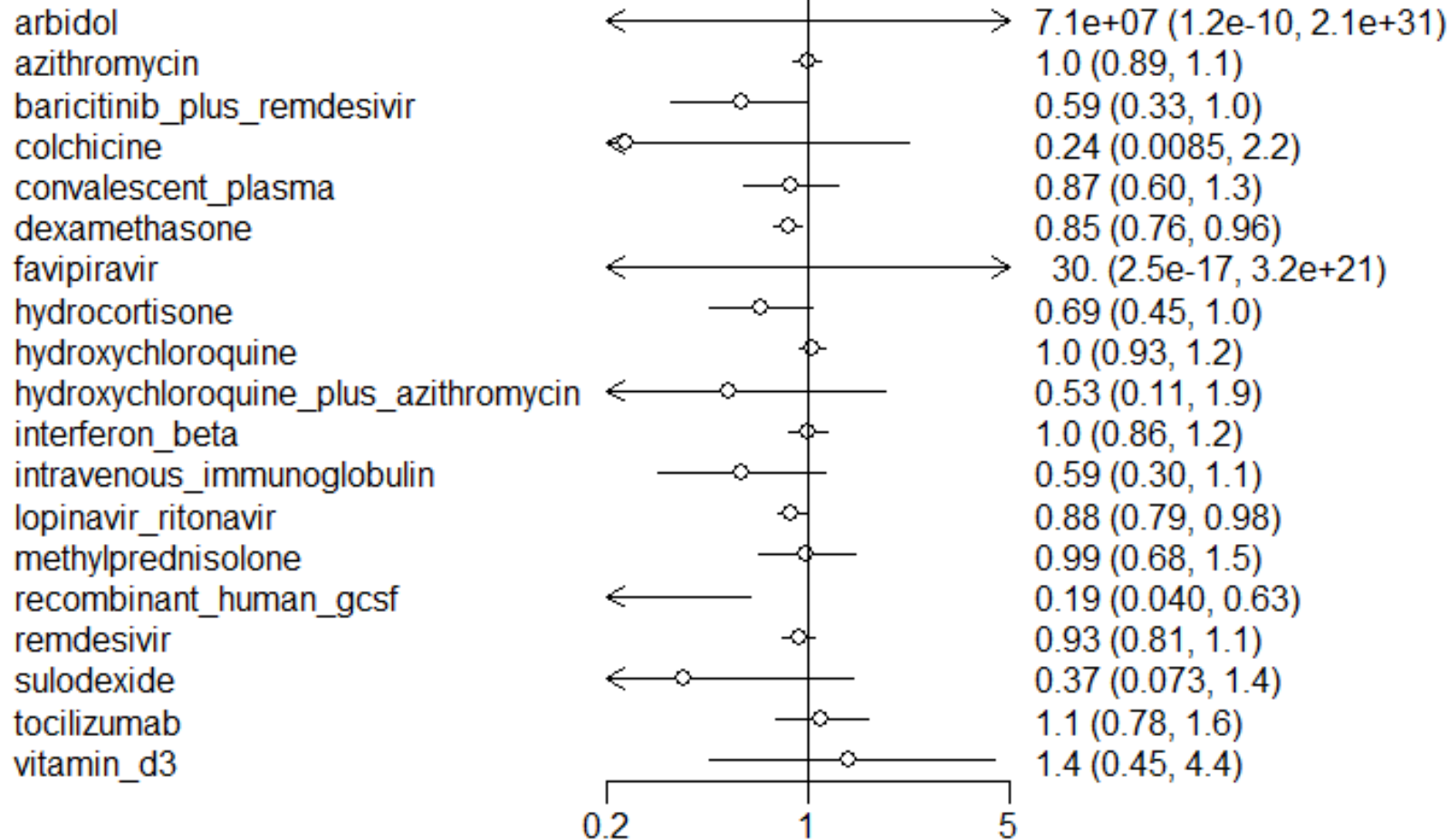
# COVID19 | FOREST PLOT

```
forest(mortality.re,
```

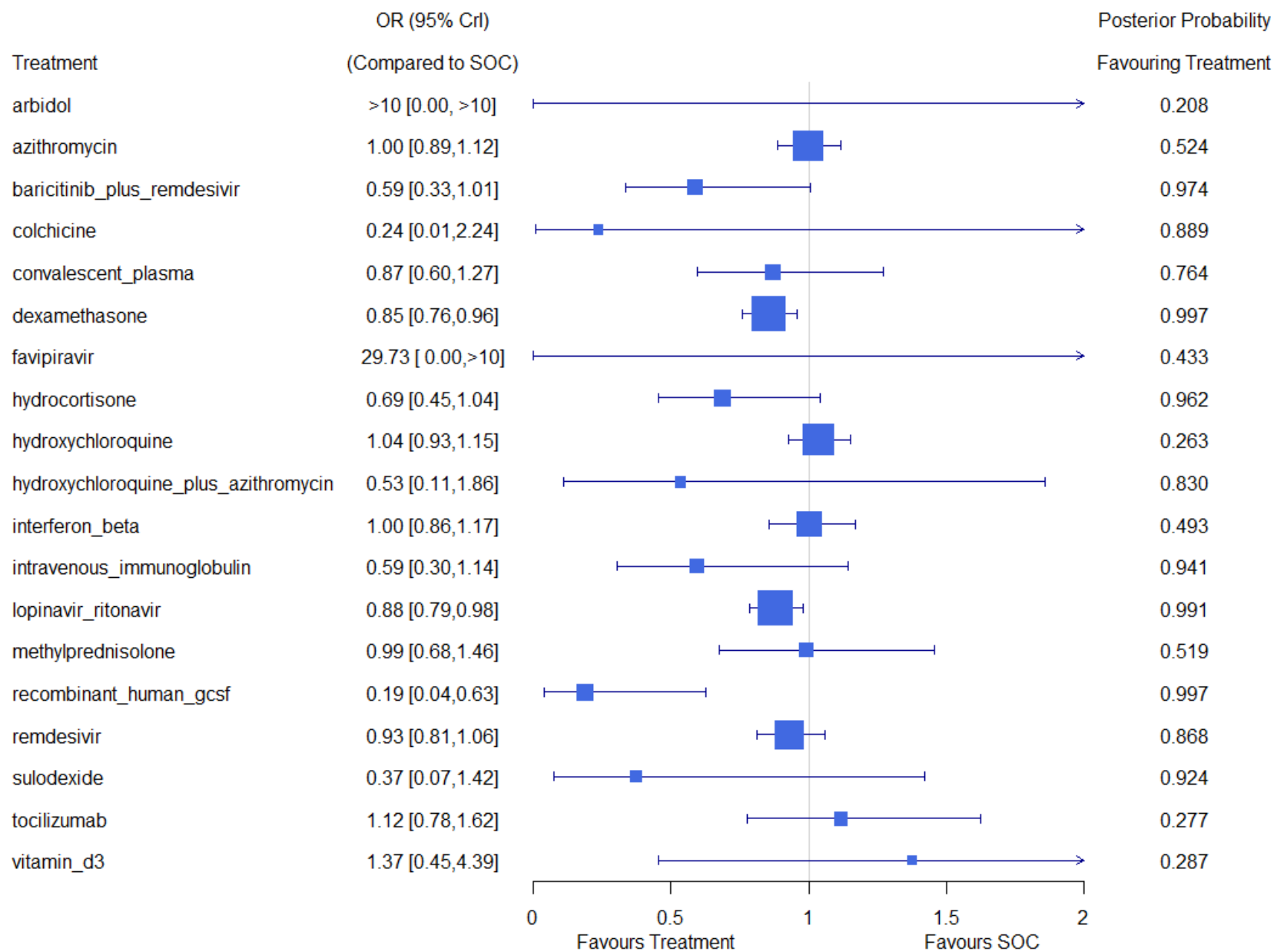
```
  xlim = c(log(0.2), log(5)),
```

```
  digits = 2)
```

## Compared with soc







Or you can generate forest plot by the function *forestplot* in package *forestplot*. See the provided R codes for details.