UNIVERSITÄTS KLINIKUM FREIBURG

Netzwerkmetaanalyse (Teil 2)

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Seminar “Statistische Auswertung medizinischer Daten mit R”

Outline

1. **Inconsistency diagnostics**
2. **Ranking interventions (one outcome)**
3. **Multicomponent interventions**
4. **Summary**
5. **Ranking with more outcomes; Disconnected networks**

Example 1 (Part of R package netmeta)

Diabetes data

Network of 10 diabetes treatments including 26 studies, where the outcome was HbA1c (measured as mean change or mean post treatment value) (Senn et al., 2013)

Splitting direct and indirect evidence in network meta-analysis

Each network meta-analysis estimate is a weighted mean of the direct estimate and the indirect estimate

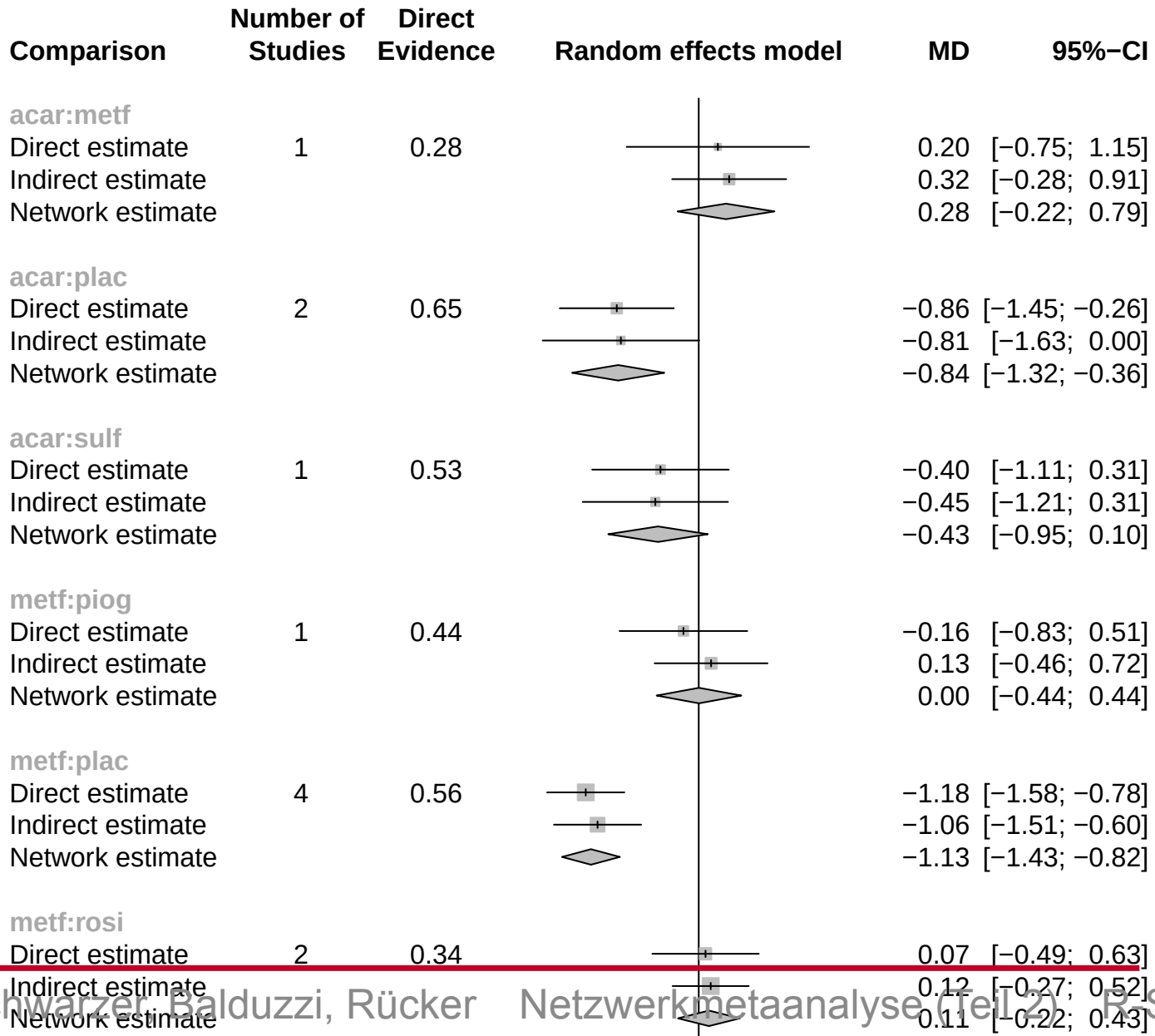
- $\hat{\theta}_{AB}^{direct}$ (the direct estimate) from a pairwise meta-analysis of all studies that compare A and B directly
- $\hat{\theta}_{AB}^{indirect}$ (the indirect estimate) from all paths leading from A to B via other treatments nodes in the network
- Either direct or indirect evidence may be missing

Diabetes Dataset – Splitting the Evidence

```
ns1 <- netsplit(net1); print(ns1, comb.fixed = FALSE, digits = 2)

## Separate indirect from direct evidence (SIDE) using back-calculation method
##
## Random effects model:
##
##  comparison k prop   nma direct indir.  Diff     z p-value
##   acar:benf 0    0 -0.11      .  -0.11     .     .       .
##   acar:metf 1 0.28  0.28   0.20   0.32 -0.12 -0.21  0.8368
##   acar:migl 0    0  0.11      .   0.11     .     .       .
##   acar:piog 0    0  0.29      .   0.29     .     .       .
##   acar:plac 2 0.65 -0.84  -0.86  -0.81 -0.04 -0.08  0.9338
##   *** Output truncated ***
##
## Legend:
##  comparison - Treatment comparison
##  k          - Number of studies providing direct evidence
##  prop       - Direct evidence proportion
##  nma        - Estimated treatment effect (MD) in network meta-analysis
##  direct     - Estimated treatment effect (MD) derived from direct evidence
##  indir.     - Estimated treatment effect (MD) derived from indirect evidence
##  Diff       - Difference between direct and indirect treatment estimates
##  z          - z-value of test for disagreement (direct versus indirect)
##  p-value    - p-value of test for disagreement (direct versus indirect)
```

Diabetes Dataset – Forest Plot – Direct and Indirect

```
forest(netsplit(net1))
```



Diabetes Dataset – Decomposition of Q

```
# Decompose total Q statistics into parts from designs
decomp.design(net1)

## Q statistics to assess homogeneity / consistency
##
##                      Q df  p-value
## Total            96.99 18 < 0.0001
## Within designs   74.46 11 < 0.0001
## Between designs  22.53  7   0.0021
##
## Design-specific decomposition of within-designs Q statistic
##
##     Design     Q df  p-value
##  benf:plac  4.38  1   0.0363
##  metf:plac 42.16  2 < 0.0001
##  metf:rosi  0.19  1   0.6655
##  migl:plac  6.45  2   0.0398
##  plac:rosi 21.27  5   0.0007
##
## ...
```

Diabetes Dataset – Decomposition of *Q*

```
## ...
##
##  Detached design     Q df p-value
##        acar:plac 22.44  6  0.0010
##        acar:sulf 22.52  6  0.0010
##        metf:piog 17.13  6  0.0088
##        metf:plac 22.07  6  0.0012
##        metf:rosi 22.52  6  0.0010
##        metf:sulf  7.51  6  0.2760   ***
##        piog:plac 17.25  6  0.0084
##        piog:rosi 22.48  6  0.0010
##        plac:rosi 16.29  6  0.0123
##        rosi:sulf  6.77  6  0.3425   ***
##   acar:metf:plac 22.38  5  0.0004
##
## ...
```

Explanation: Detaching a design means relaxing the consistency assumption for this design. If Q decreases markedly after detaching a design (*** added for the purpose of this talk), we conclude that this design contributed to between-design inconsistency. If Q does not decrease markedly, the design is not thought to contribute to between-design inconsistency.

Diabetes Dataset – Decomposition of Q

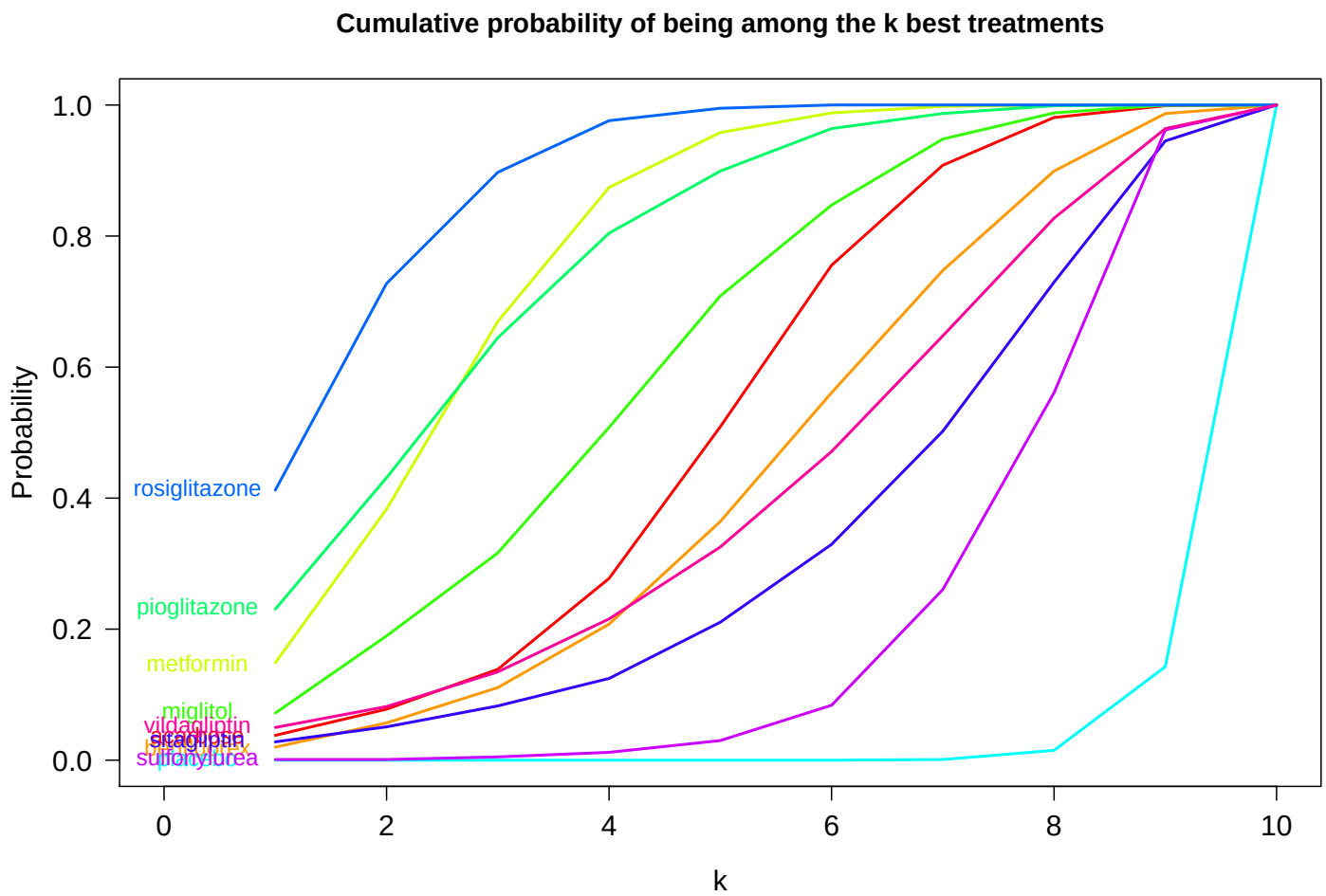
```
## ...
## Q statistic to assess consistency under the assumption of
## a full design-by-treatment interaction random effects model
##
##                    Q df p-value tau.within tau2.within
## Between designs 2.19  7  0.9483     0.3797      0.1442
```

Explanation: If all designs are allowed to provide different treatment effects, residual inconsistency should be reduced. This is the case here.

Ranking treatments: Diabetes data

Bayesian framework:

Treatments may be ranked by the surface under the cumulative ranking curve (SUCRA) (Salanti et al., 2011)



P-scores

Frequentist framework:

We introduced a quantity, called P-score, as an analogue to SUCRA (Rücker and Schwarzer, 2015)

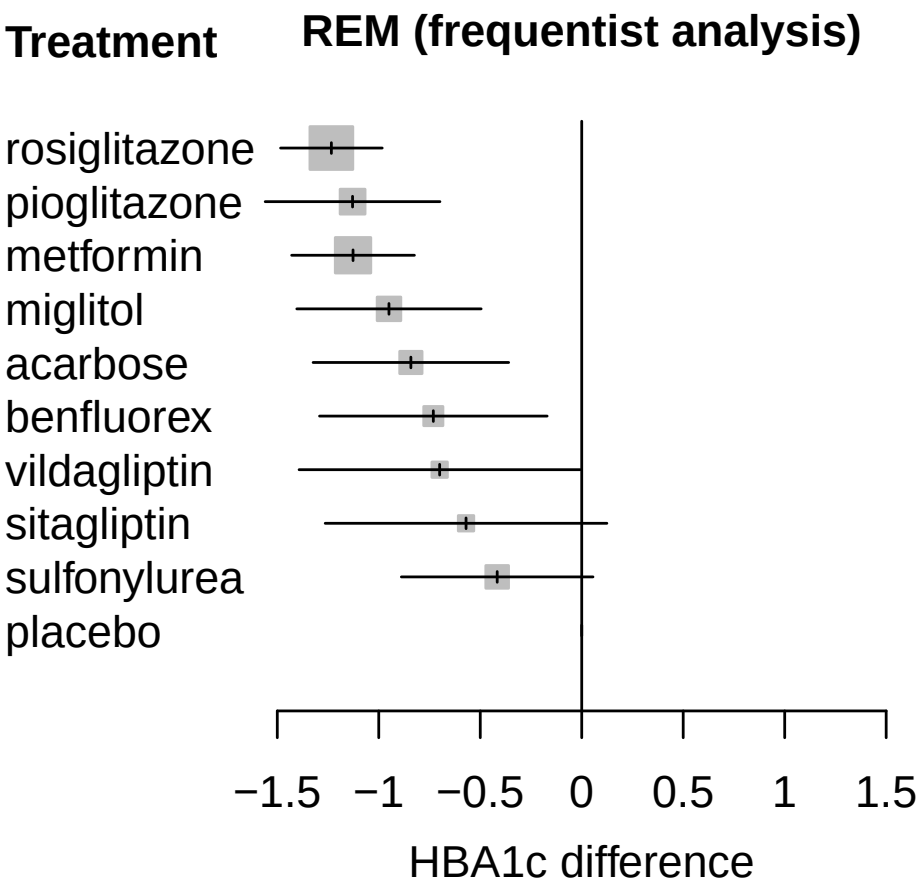
- P-scores allow ranking the treatments on a continuous 0-1 scale (0 means worst, 1 best)
- Derived from the p-values of all pairwise comparisons, without resampling methods
- Linear transformation of mean rank
- Frequentist analogue and numerically similar to SUCRA values (for known probabilities, both rankings are equal)

Diabetes Dataset – Ranking Treatments using P-Scores

```
# Small values are "good" here (which is the default), otherwise "bad"
netrank(net1, small.value = "good")

##      P-score (fixed) P-score (random)
## rosi          0.9789           0.8934
## metf          0.8513           0.7818
## piog          0.7686           0.7746
## migl          0.6200           0.6137
## acar          0.4792           0.5203
## benf          0.5727           0.4358
## vild          0.3512           0.4232
## sita          0.2386           0.3331
## sulf          0.1395           0.2103
## plac          0.0000           0.0139
```

Ranking treatments using P-scores: Diabetes data

Compare forest plot, point estimates, SUCRA values and P-scores



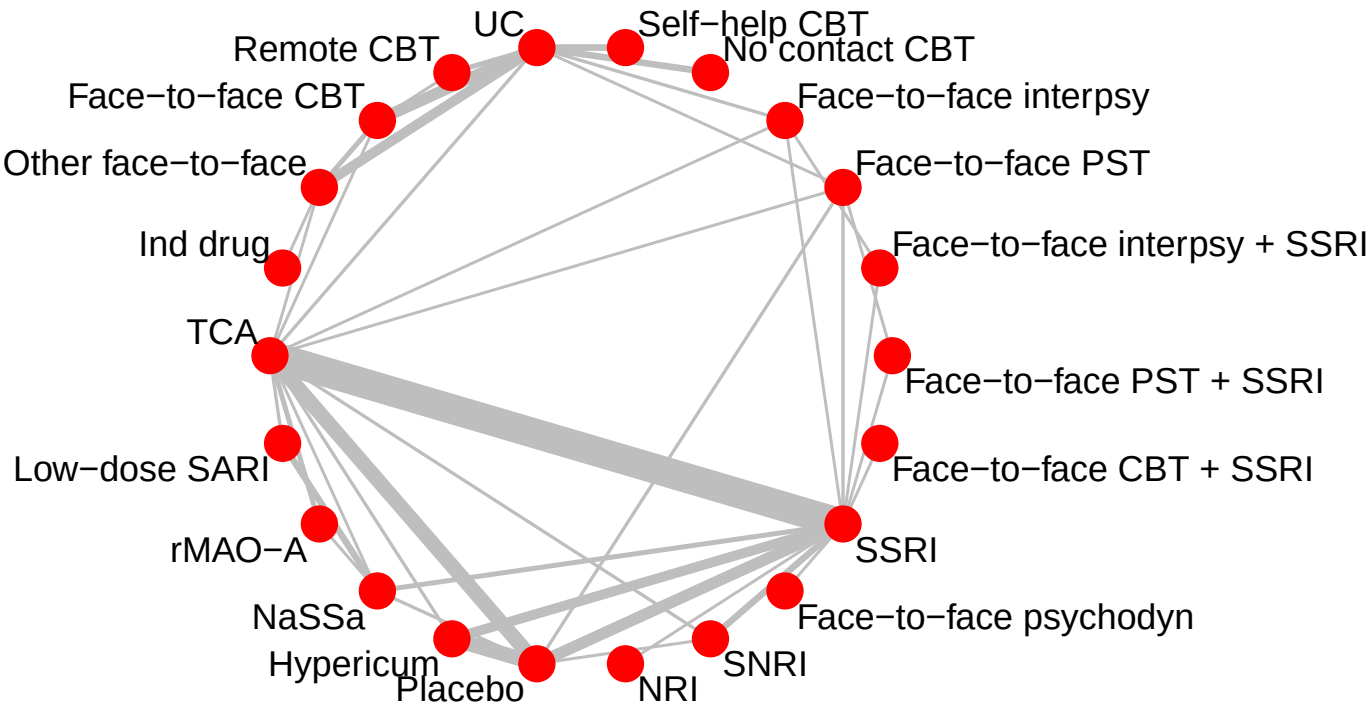
	Frequentist	SUCRA	P-score
rosi	-1.23	0.890	0.893
metf	-1.13	0.780	0.782
piog	-1.13	0.773	0.775
migl	-0.95	0.620	0.614
acar	-0.84	0.520	0.520
benf	-0.73	0.439	0.436
vild	-0.70	0.413	0.423
sita	-0.57	0.334	0.333
sulf	-0.42	0.213	0.210
plac	0	0.018	0.014

Multicomponent Interventions

- Standard model:
  Each treatment is represented by one node in the network
- However, treatments may be complex, for example, combinations of other treatments (multicomponent interventions)
- How to deal with that in a network meta-analysis?
- $\Rightarrow$ Component network meta-analysis (CNMA)
  (Welton et al., 2009)

Example 2: Depression Data (Linde et al., 2016)

- Network of 22 treatments of depression in primary care
- 100 trials with 21,298 patients in 217 treatment arms
- 19 treatment components, including placebo and usual care
- 3 treatments are combinations of others in the network
- Primary outcome: Response (binary, odds ratio as effect measure)



Additive CNMA Model (Rücker et al., 2020b)

- Consider two **active components:**
  - CBT Face-to-face cognitive behavioural therapy
  - SSRI Selective serotonin reuptake inhibitors
- Three possible **treatment combinations**:
  1. CBT
  2. SSRI
  3. CBT + SSRI
- **Additive model:** The effect of the combined treatment is an additive sum of its components
  - This means that 'equal components cancel out':
    CBT + SSRI vs. SSRI estimates CBT
- **Interaction model:** Treatment components interact in a synergistic or antagonistic way

Additive component NMA model (CNMA model)

Introductory example:

- $n = 3$ **treatments**, interpreted as additive combinations from
- $c = 2$ **components**
- $m = 4$ **pairwise comparisons** of treatments
- $m \times n$ **structure matrix** $\mathbf{B}$ describes the structure of the network
  - rows correspond to the observed pairwise comparisons (studies)
  - columns represent treatments CBT, SSRI, CBT + SSRI

study 1:	CBT	*vs*	SSRI
study 2:	CBT + SSRI	*vs*	SSRI
study 3:	CBT + SSRI	*vs*	CBT
study 4:	CBT	*vs*	SSRI

$$\mathbf{B} = \begin{pmatrix} 1 & -1 & 0 \\ 0 & -1 & 1 \\ -1 & 0 & 1 \\ 1 & -1 & 0 \end{pmatrix}$$

(For sake of simplicity of presentation we ignore that there may be multi-arm studies)

Additive component NMA model (CNMA model)

- $n \times c$ **combination structure matrix** $\mathbf{C}$ describes how the $n = 3$ treatments (here CBT, SSRI, CBT + SSRI) are composed of the $c = 2$ components CBT and SSRI (in case of interaction, $c = 3$):

CBT
SSRI
CBT + SSRI

$$\mathbf{C} = \begin{pmatrix} 1 & 0 \\ 0 & 1 \\ 1 & 1 \end{pmatrix} \qquad \mathbf{C}_{int} = \begin{pmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 1 & 1 & 1 \end{pmatrix}$$

- The **design matrix of the additive model** is the $m \times c$ matrix $\mathbf{X}$:

study 1:	CBT	*vs*	SSRI
study 2:	CBT + SSRI	*vs*	SSRI
study 3:	CBT + SSRI	*vs*	CBT
study 4:	CBT	*vs*	SSRI

$$\mathbf{X} = \mathbf{BC} = \begin{pmatrix} 1 & -1 \\ 1 & 0 \\ 0 & 1 \\ 1 & -1 \end{pmatrix}$$

Additive component NMA model (CNMA model)

The component NMA model (CNMA model) is

$$\boldsymbol{\delta} = \mathbf{X}\boldsymbol{\beta}$$

where

- $\boldsymbol{\delta} \in \mathbb{R}^m$ is the vector of true relative effects (differences) from the studies
- $\mathbf{X} = \mathbf{BC}$ is the design matrix
  (based on $\mathbf{C}$ with an additive or $\mathbf{C}_{int}$ with an interaction structure)
- $\boldsymbol{\beta} \in \mathbb{R}^c$ is a parameter vector representing the components

Estimation via weighted least squares (Rücker et al., 2020b)

Standard NMA model with R

```
## Load dataset Linde2016 (part of R package netmeta)
data(Linde2016)

# Standard NMA model (with Placebo as reference treatment)
net2 <- netmeta(lnOR, selnOR, treat1, treat2, id,
                data = Linde2016, reference.group = "Placebo",
                sm = "OR", comb.fixed = FALSE, comb.random = TRUE)

# Print summary
print(summary(net2), digits = 2)

## Number of studies: k = 93
## Number of treatments: n = 22
## Number of pairwise comparisons: m = 124
## Number of designs: d = 40
##
## Random effects model
##
## Treatment estimate (sm = 'OR', comparison: other treatments vs 'Placebo'):
##                                  OR          95%-CI
## Face-to-face CBT               2.05 [1.26;   3.36]
## Face-to-face CBT + SSRI       30.86 [4.94; 192.81]
## *** Output truncated ***
```

Additive CNMA model with R

```
# Additive CNMA model (with Placebo as inactive component)
nc2 <- netcomb(net2, inactive = "Placebo")

# Print summary
print(summary(nc2), digits = 2)

## Number of studies: k = 93
## Number of treatments: n = 22
## Number of active components: c = 18
## Number of pairwise comparisons: m = 124
##
## Results for combinations (additive model, random effects model):
##                               OR       95%-CI    z        p
## Face-to-face CBT            2.31 [1.44; 3.70] 3.48   0.0005
## Face-to-face CBT + SSRI     3.91 [2.32; 6.59] 5.12 < 0.0001
## *** Output truncated ***
##
## Results for components (random effects model):
##                          OR       95%-CI    z        p
## Face-to-face CBT       2.31 [1.44; 3.70] 3.48   0.0005
## *** Output truncated ***
## SSRI                   1.69 [1.45; 1.97] 6.81 < 0.0001
## *** Output truncated ***
```

Additive CNMA model with R

```
## ...
##
## Quantifying heterogeneity / inconsistency:
## tau^2 = 0.0208; tau = 0.1441; I^2 = 17.5% [0.0%; 37.1%]
##
## Heterogeneity statistics:
##                       Q df.Q   pval
## Additive model   109.12   90 0.0832
## Standard model   102.45   87 0.1234
## Difference         6.67    3 0.0831
```

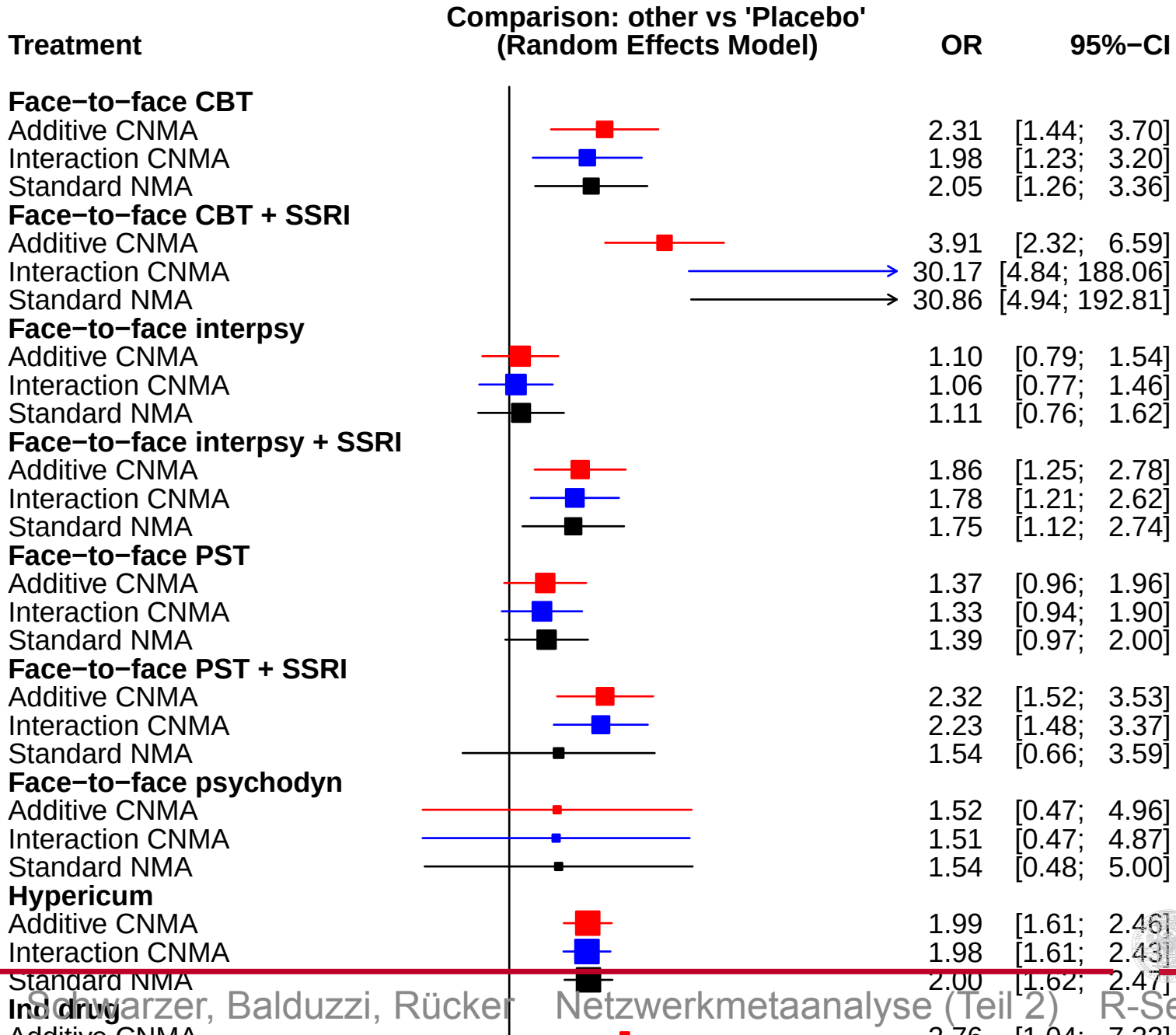
Interaction CNMA model with R

```
# Interaction CNMA model (with Placebo as inactive component)
C <- nc2$C.matrix
CBT.SSRI <- C[,"Face-to-face CBT"] * C[,"SSRI"]
C2 <- cbind(C, CBT.SSRI)
nc2.int <- netcomb(net2, C.matrix = C2, inactive = "Placebo")
# Print summary
print(summary(nc2.int), digits = 2)

## Number of studies: k = 93
## Number of treatments: n = 22
## Number of active components: c = 19
## Number of pairwise comparisons: m = 124
##
## Results for combinations (additive model, random effects model):
##                                OR          95%-CI    z        p
## Face-to-face CBT             1.98 [1.23;   3.20] 2.81   0.0050
## Face-to-face CBT + SSRI     30.17 [4.84; 188.06] 3.65   0.0003
## *** Output truncated ***
##
## Heterogeneity statistics:
##                      Q df.Q   pval
## Additive model 103.61   89 0.1379
## Standard model 102.45   87 0.1234
## Difference       1.16    2 0.5593
```

CNMA models with R – Forest Plot

```
# Combine results of standard NMA and CNMAs
nb2 <- netbind(nc2, nc2.int, net2,
               name = c("Additive CNMA", "Interaction CNMA",
                        "Standard NMA"),
               col.study = c("red", "blue", "black"),
               col.square = c("red", "blue", "black"))


# Forest plot comparing standard NMA and CNMAs
forest(nb2, xlim = c(0.45, 30), at = c(0.5, 1, 2, 5, 10),
       col.by = "black", addrow.subgroups = FALSE,
       fontsize = 10, spacing = 0.7, squaresize = 0.9,
       label.left = "Favours Placebo",
       label.right = "Favours other")
```

Compare models: Detail of Forest Plot



Summary

- CNMA models allow
  - estimating effects of treatment components of multicomponent interventions
  - comparing estimates and model fit to the standard NMA using likelihood ratio statistics
  - borrowing strength from studies with common components
  - bridging the gap between disconnected networks
- Implemented in the functions `netcomb` and `discomb` of R package netmeta (Rücker et al., 2020a)
- For choosing between additive and interaction CNMA models, model selection strategies are recommended (Rücker et al., 2020c)
- Bayesian approaches (Welton et al., 2009; Mills et al., 2012)
- Applications (Caldwell and Welton, 2016; Freeman et al., 2017; Pompoli et al., 2018)

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Example 3: Chemotherapy for nasopharyngeal carcinoma (Ribassin-Majed et al., 2017)

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

What Is the Best Treatment of Locally Advanced Nasopharyngeal Carcinoma? An Individual Patient Data Network Meta-Analysis

Laureen Ribassin-Majed, Sophie Marguet, Anne W.M. Lee, Wai Tong Ng, Jun Ma, Anthony T.C. Chan, Pei-Yu Huang, Guopei Zhu, Daniel T.T. Chua, Yong Chen, Hai-Qiang Mai, Dora L.W. Kwong, Shie-Lee Cheah, James Moon, Yuk Tung, Kwan-Hwa Chi, George Fountzilas, Jean Bourhis, Jean Pierre Pignon, and Pierre Blanchard

See accompanying article doi:10.1200/JCO.2016.70.4775

Author affiliations appear at the end of this article.

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A B S T R A C T

Purpose

The role of adjuvant chemotherapy (AC) or induction chemotherapy (IC) in the treatment of locally advanced nasopharyngeal carcinoma is controversial. The individual patient data from the Meta-Analysis of Chemotherapy in Nasopharynx Carcinoma database were used to compare all available treatments.

Methods

All randomized trials of radiotherapy (RT) with or without chemotherapy in nonmetastatic nasopharyngeal carcinoma were considered. Overall, 20 trials and 5,144 patients were included. Treatments were grouped into seven categories: RT alone (RT), IC followed by RT (IC-RT), RT followed by AC (RT-AC), IC followed by RT followed by AC (IC-RT-AC), concomitant chemoradiotherapy (CRT), IC followed by CRT (IC-CRT), and CRT followed by AC (CRT-AC). P-score was used to rank the treatments. Fixed- and random-effects frequentist network meta-analysis models were applied.

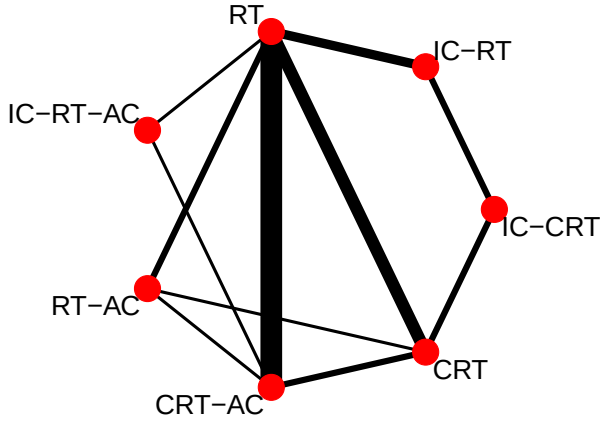
Example 3: Chemotherapy for nasopharyngeal carcinoma (Ribassin-Majed et al., 2017)

- Individual patient data network meta-analysis (20 trials, 5144 patients)
- Treatments grouped into seven categories:

RT	radiotherapy alone
IC-RT	induction chemotherapy (IC) followed by RT
RT-AC	RT followed by adjuvant chemotherapy
IC-RT-AC	IC followed by RT followed by AC
CRT	concomitant chemoradiotherapy
IC-CRT	IC followed by CRT
CRT-AC	CRT followed by AC

- P-scores published for all outcomes:

  overall survival (OS)
  progression-free survival (PFS)
  locoregional control (LRC)
  distant control (DC)



P-scores for the chemotherapy data

Treatment	OS	PFS	LRC	DC
IC-CRT	**0.63**	**0.79**	**0.47**	**0.95**
IC-RT	**0.33**	**0.46**	**0.27**	**0.76**
CRT-AC	**0.96**	**0.94**	**0.82**	**0.72**
CRT	**0.70**	**0.52**	**0.37**	**0.48**
RT-AC	**0.28**	**0.36**	**0.58**	**0.32**
IC-RT-AC	0.45	0.39	0.90	0.10
RT	**0.15**	**0.04**	**0.09**	**0.16**

- Note:
  - **IC-CRT** > **IC-RT** > **RT** (all outcomes)
  - **CRT-AC** > **CRT** > **RT** (all outcomes)
  - **CRT-AC** > **RT-AC** > **RT** (all outcomes)
- However, there are also conflicting outcomes: IC-RT-AC is worst with respect to DC, but best with respect to LRC

Chemotherapy data: P-scores

```r
# Chemotherapy data (Ribassin-Majed et al., 2017, J. Clin. Oncol.)
outcomes <- c("OS", "PFS", "LRC", "DC")
treatments <- c("RT", "IC-RT", "IC-CRT", "CRT",
                "CRT-AC", "RT-AC", "IC-RT-AC")
```

```r
# P-scores (from Ribassin-Majed 2017, Table 1)
pscore.os  <- c(15, 33, 63, 70, 96, 28, 45) / 100
pscore.pfs <- c( 4, 46, 79, 52, 94, 36, 39) / 100
pscore.lrc <- c( 9, 27, 47, 37, 82, 58, 90) / 100
pscore.dc  <- c(16, 76, 95, 48, 72, 32, 10) / 100
```

```r
# Construct matrix with P-scores
pscore.matrix <- data.frame(pscore.os, pscore.pfs, pscore.lrc, pscore.dc)
rownames(pscore.matrix) <- treatments
colnames(pscore.matrix) <- outcomes
```

Chemotherapy data: Partial ordering and diagrams

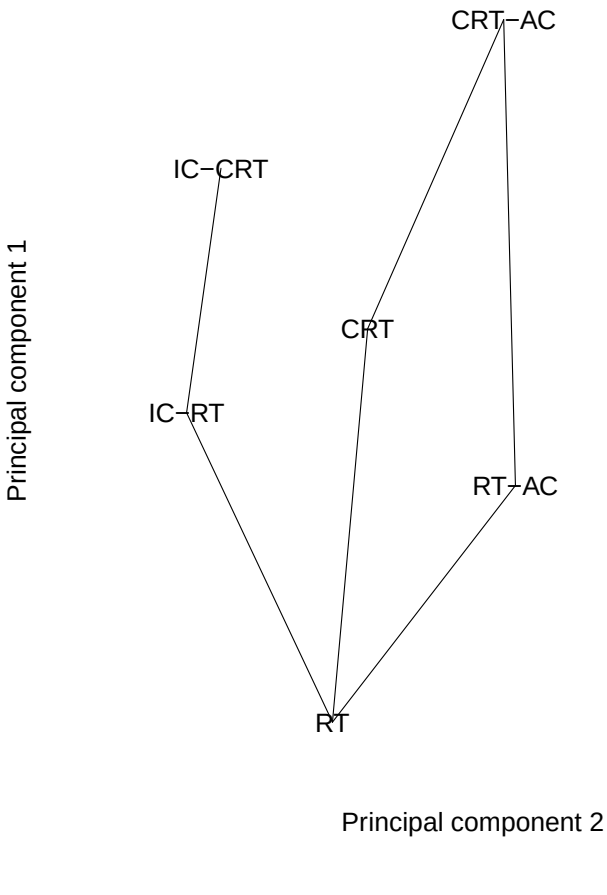
```r
# Partial ordering
np1 <- netposet(pscore.matrix)
# An entry 1 means that the treatment in the row
# is uniformly superior to the treatment in the column
np1
```

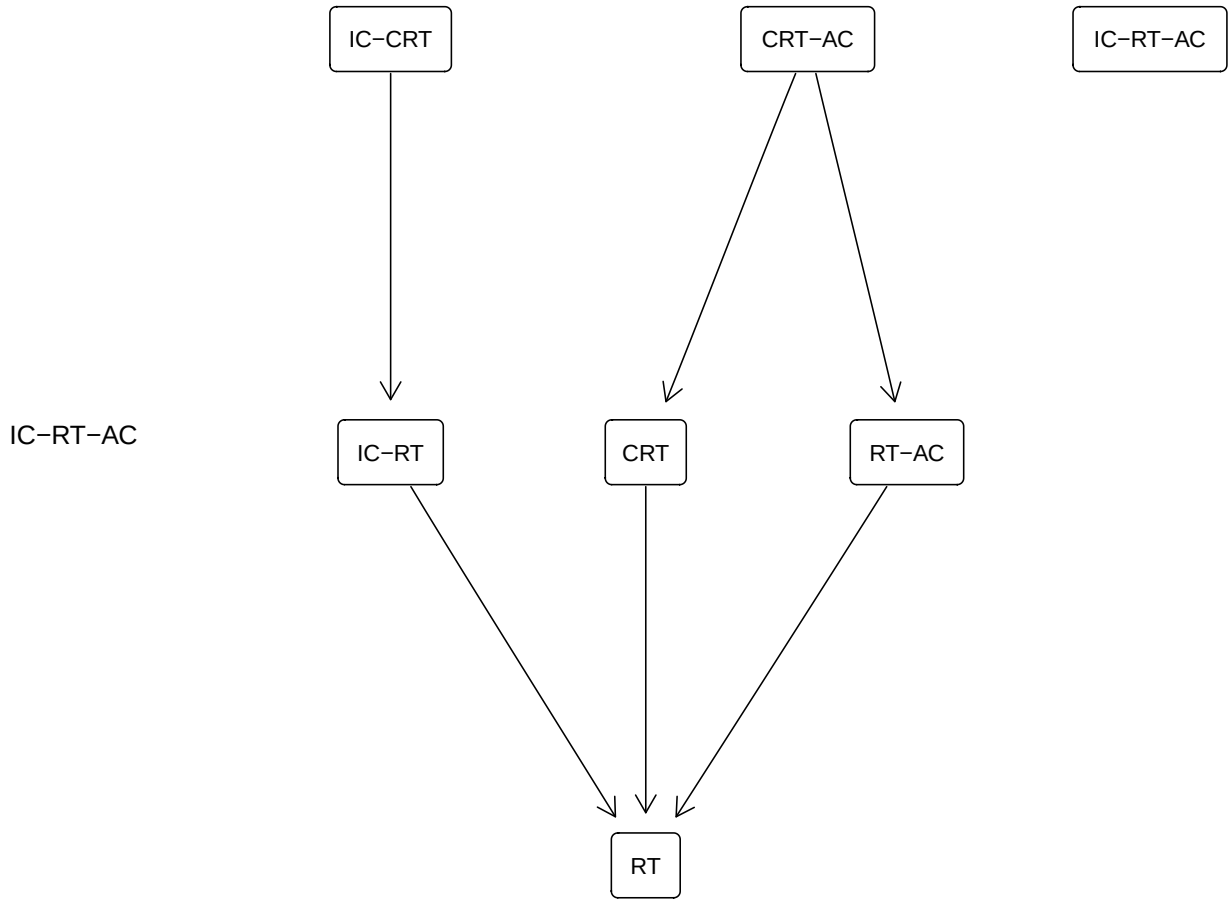
```
##           RT IC-RT IC-CRT CRT CRT-AC RT-AC IC-RT-AC
## RT         0     0      0   0      0     0        0
## IC-RT      1     0      0   0      0     0        0
## IC-CRT     0     1      0   0      0     0        0
## CRT        1     0      0   0      0     0        0
## CRT-AC     0     0      0   1      0     1        0
## RT-AC      1     0      0   0      0     0        0
## IC-RT-AC   0     0      0   0      0     0        0
```

```r
# Biplot (= Figure 3 in Rucker & Schwarzer 2017)
plot(np1, "biplot", axes = FALSE, cex.text = 1.2, cex.lab = 1.2,
     offset.x = -0.05, pch = 16, cex.points = 1.2, xlim = c(1.2, -2.3))
```

```r
# Hasse diagram (= Left panel of Figure 2 in Rucker & Schwarzer 2017)
hasse(np1)
```

Chemotherapy data: Biplot and Hasse diagram (Rücker and Schwarzer, 2017)





The additive CNMA model for disconnected networks

- The additive CNMA model allows 'reconnecting' a disconnected network if the subsets include enough common components (Rücker et al., 2020c)
- Hypothetical example: a network with 3 studies and 6 treatments
  1. $A + B$ vs. A
  2. $A + C$ vs. C
  3. $B + C$ vs. B
- Due to the common components A, B and C this system of equations can be solved!
- We have

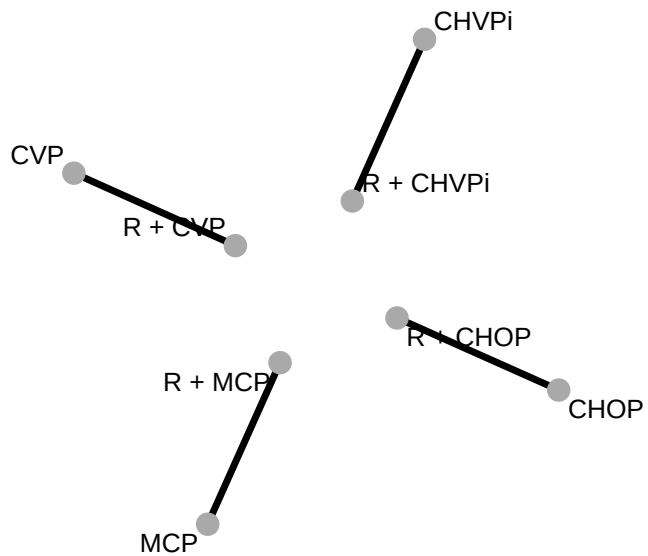
$$\mathbf{X} = \begin{pmatrix} 0 & 1 & 0 \\ 1 & 0 & 0 \\ 0 & 0 & 1 \end{pmatrix}$$

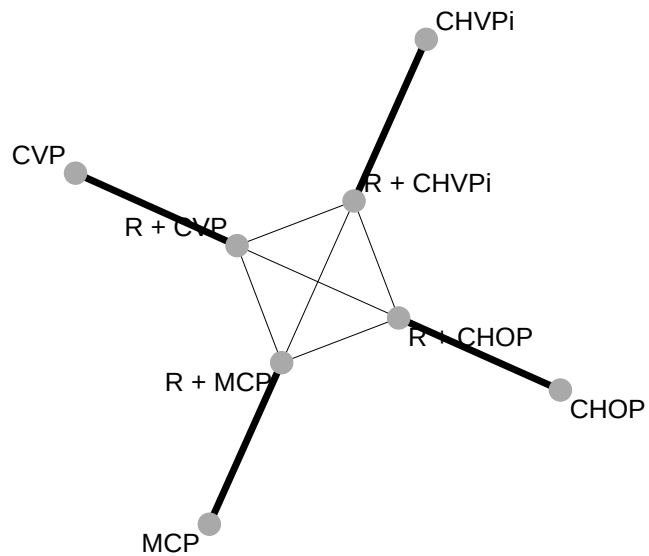
such that all components A, B, C can be uniquely estimated

Rituximab for the first-line treatment of stage III-IV follicular lymphoma (Papaioannou et al., 2011)

The outcome is the proportion of overall survival after 4 or 5 years

study	treat1	treat2	event1	n1	event2	n2
1	CVP	Rituximab (R) + CVP	122	159	134	162
2	CHOP	Rituximab (R) + CHOP	234	278	251	279
3	MCP	Rituximab (R) + MCP	71	96	91	105
4	CHVPi	Rituximab (R) + CHVPi	145	183	147	175





Rituximab for the first-line treatment of stage III-IV follicular lymphoma (Papaioannou et al., 2011)

All combination treatments include rituximab $\Rightarrow$ we may estimate a common log-additive effect of rituximab on the survival proportion from all four studies:

$$\text{RR} = 1.08\ [1.03; 1.13]$$

(Same result obtained with pairwise meta-analysis)