

Cochrane webinar, 13th June 2023

R package '**crossnma**' to synthesize cross-design evidence and cross-format data using network meta-analysis and network meta-regression

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Part I: The theory behind crossnma

The 4 crossnma models:

- Unadjusted (naïve)
- Bias adjustment 1
- Bias adjustment 2
- Use NRS as a prior

Tasnim Hamza

Part II: The crossnma package

- Implementation
- Workflow within crossnma

Tasnim Hamza

Part III: Working example

- Description of the network
- Set up the four different crossnma models
- Run the analysis
- Display the results

Guido Schwarzer

Part IV: Limitations and future plans

- What is missing
- Further details

Guido Schwarzer

Poll: Have you conducted network meta-analysis before?

Poll: Which package do you use to conduct NMA (you can choose more than 1)?

- netmeta
- gemtc
- BUGSnet
- multinma
- write your own code
- others

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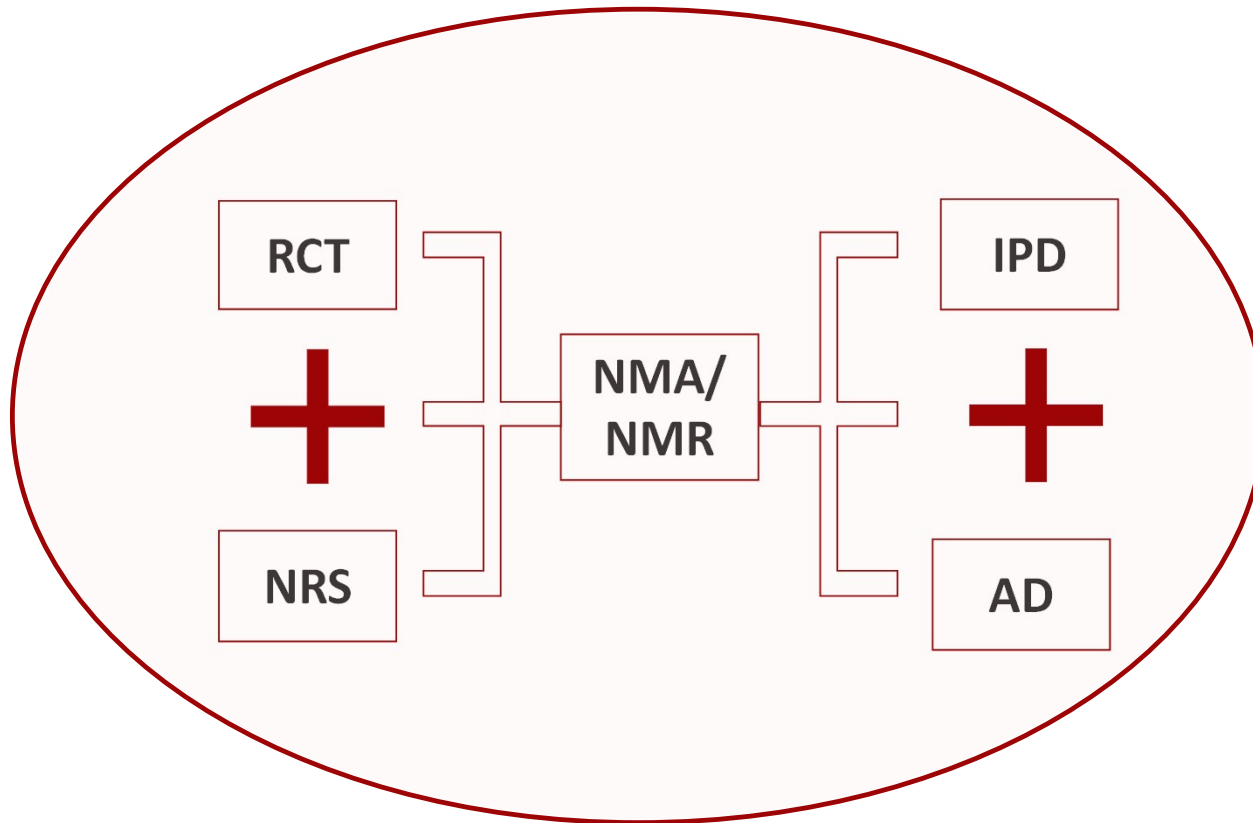
Guido

Part IV: Limitations and future plans

- What is missing
- Further details

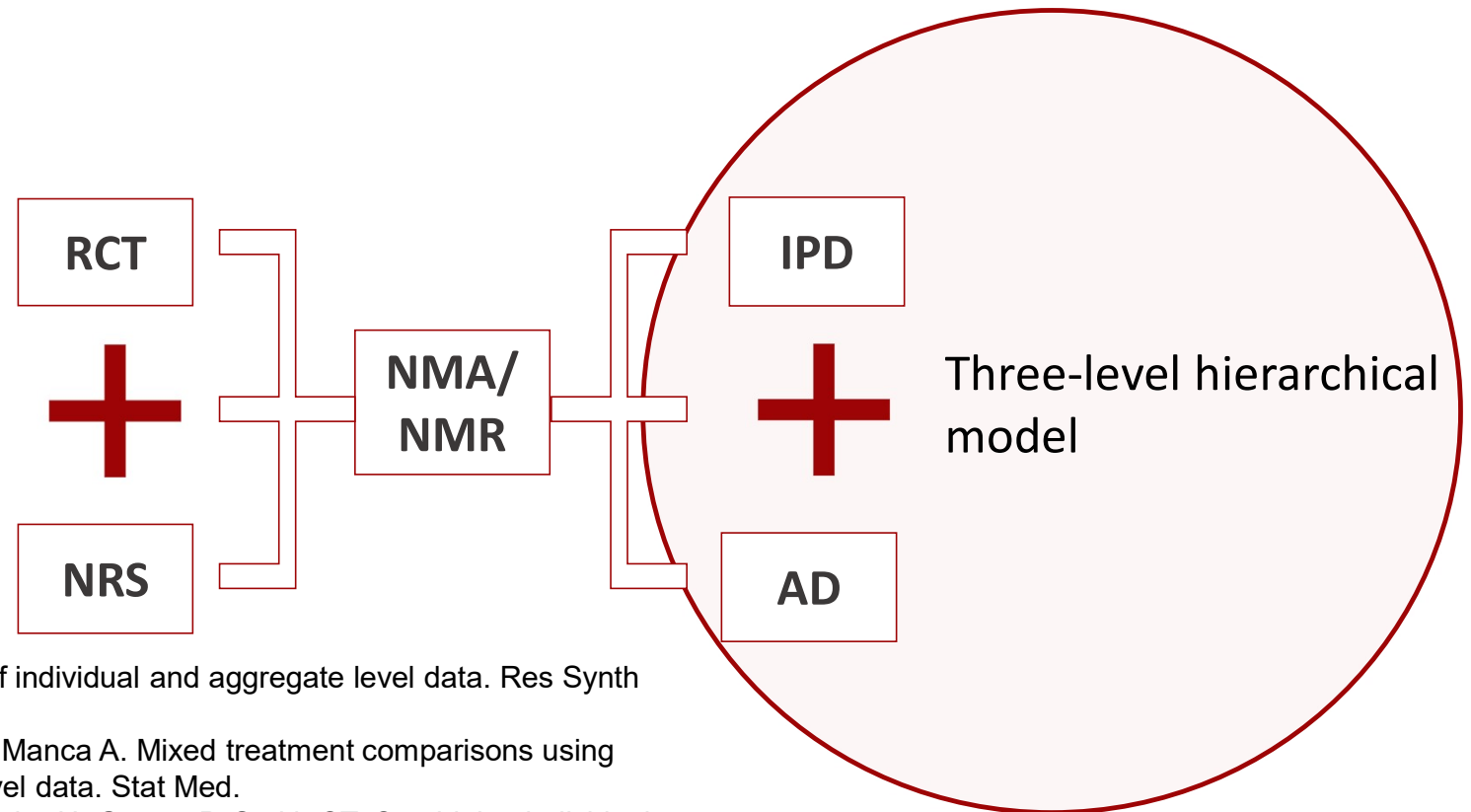
Guido

crossnma model



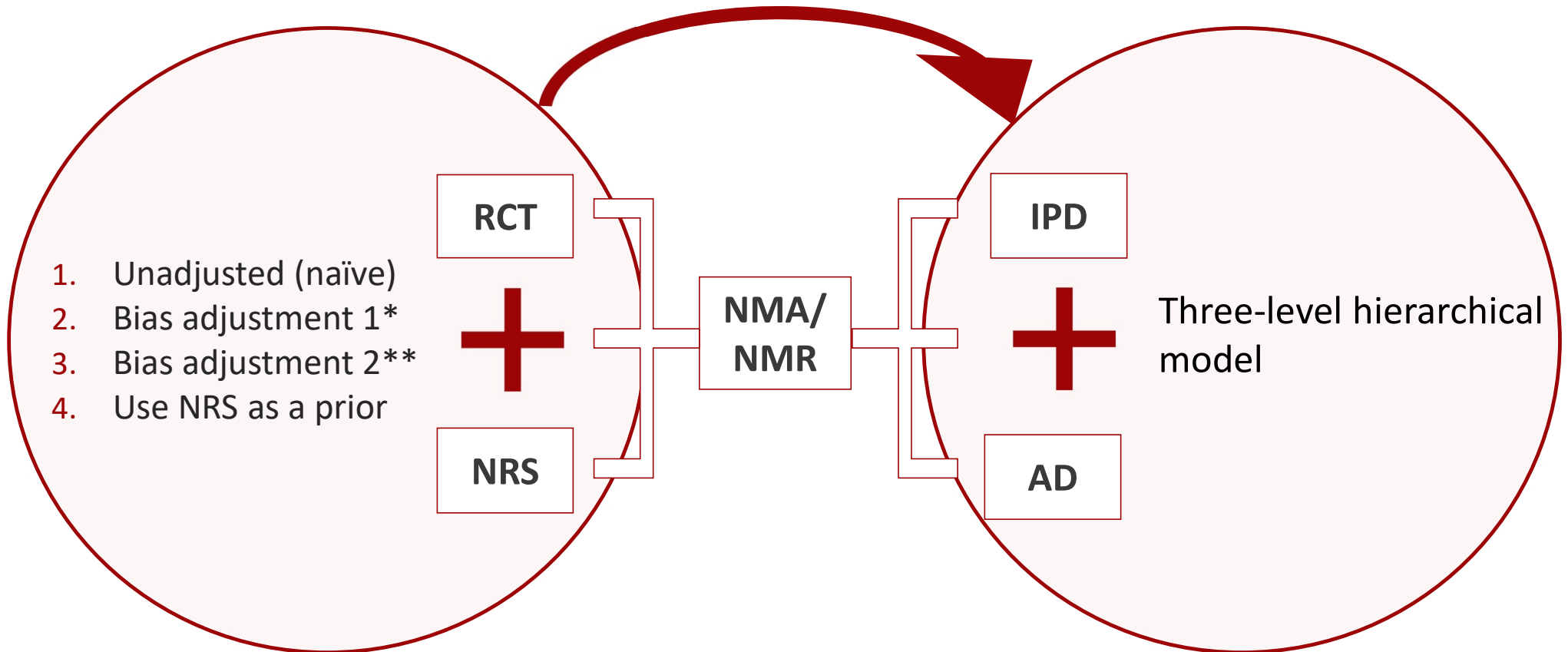
Hamza T, Chalkou K, Pellegrini F, Kuhle J, Benkert P, Lorscheider J, et al. Synthesizing cross-design evidence and cross-format data using network meta-regression. *Res Synth Methods*. 2023;14:283–300.

crossnma model



1. Jansen JP. Network meta-analysis of individual and aggregate level data. Res Synth Methods. 2012
2. Saramago P, Sutton AJ, Cooper NJ, Manca A. Mixed treatment comparisons using aggregate and individual participant level data. Stat Med.
3. Donegan S, Williamson P, D'Alessandro U, Garner P, Smith CT. Combining individual patient data and aggregate data in mixed treatment comparison meta-analysis: Individual patient data may be beneficial if only for a subset of trials. StatMed. 2013

crossnma model



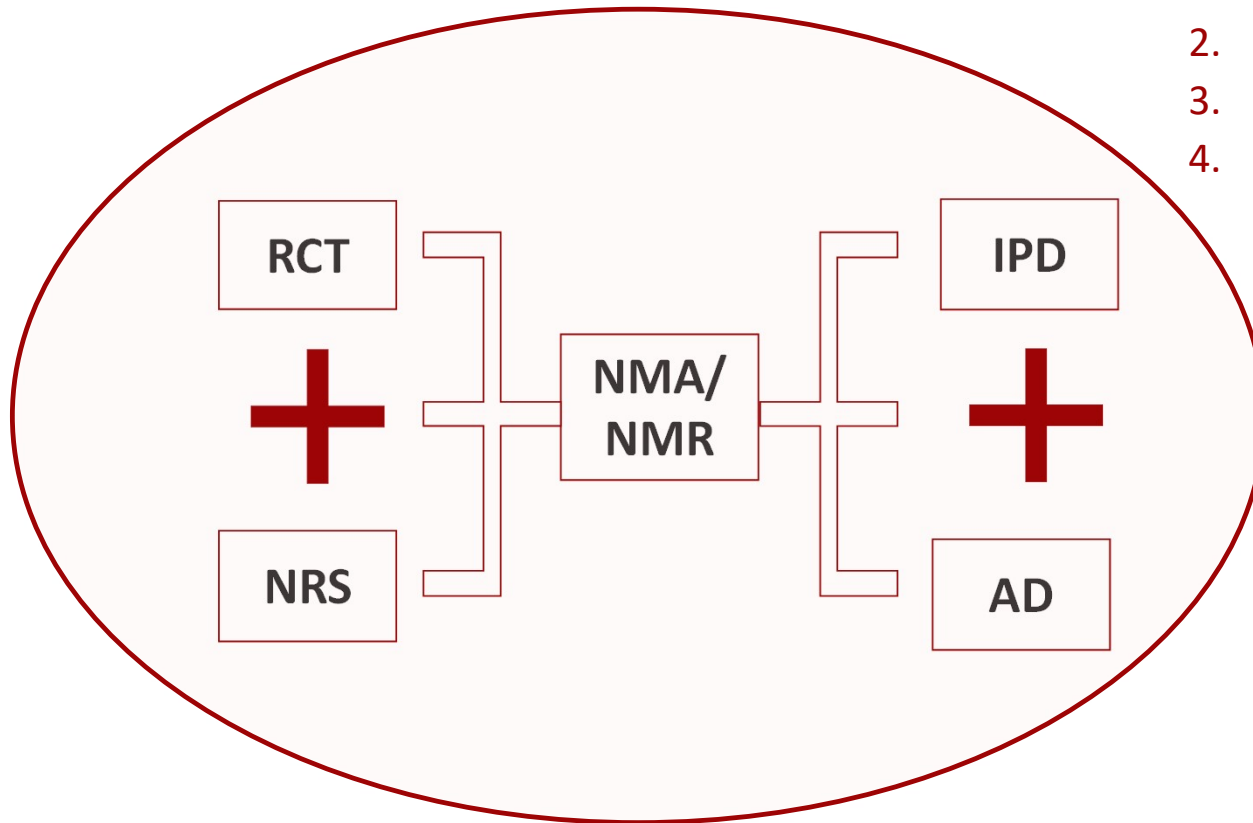
* Dias S, Welton NJ, Marinho VCC, Salanti G, Higgins JPT, Ades AE. Estimation and adjustment of bias in randomized evidence by using mixed treatment comparison meta-analysis. *Journal of the Royal Statistical Society*.

** Verde PE. A bias-corrected meta-analysis model for combining studies of different types and quality. *Biom J*. 2020

crossnma model

Three-level hierarchical model
with

1. Unadjusted (naïve)
2. Bias adjustment 1
3. Bias adjustment 2
4. Use NRS as a prior



IPD+AD three-level hierarchical model

Level 1: NMR model for IPD studies

$$y_{ijk} \sim \text{Bernoulli}(p_{ijk}) \quad \text{Logit}(p_{ijk}) = \begin{cases} u_{jb} + \beta_{0j} x_{ijk} & \text{if } k = b \\ u_{jb} + \delta_{jbk} + \beta_{0j} x_{ijk} + \beta_{1,jbk}^W x_{ijk} + (\beta_{1,jbk}^B - \beta_{1,jbk}^W) \bar{x}_j. & \text{if } k \neq b \end{cases}$$

Level 2: NMR model for AD studies

$$r_{jk} \sim \text{Bin}(p_{jk}, n_{jk}) \quad \text{Logit}(p_{jk}) = \begin{cases} u_{jb} & \text{if } k = b \\ u_{jb} + \delta_{jbk} + \beta_{1,jbk}^B \bar{x}_j & \text{if } k \neq b. \end{cases}$$

Level 3: Combine the evidence from IPD and AD

$$\delta_{jbk} \sim N(d_{Ak} - d_{Ab}, \tau^2), \beta_{1,jbk}^B \sim N(B_{1,Ak}^B - B_{1,Ab}^B, \tau_B^2), \beta_{1,jbk}^W \sim N(B_{1,Ak}^W - B_{1,Ab}^W, \tau_W^2)$$

1. Unadjusted crossnma IPD {RCT+NRS} + AD {RCT+NRS}

Level 1: NMR model for IPD studies for RCT and NRS

$$y_{ijk} \sim \text{Bernoulli}(p_{ijk}) \quad \text{Logit}(p_{ijk}) = \begin{cases} u_{jb} + \beta_{0j} x_{ijk} & \text{if } k = b \\ u_{jb} + \delta_{jbk} + \beta_{0j} x_{ijk} + \beta_{1,jbk}^W x_{ijk} + (\beta_{1,jbk}^B - \beta_{1,jbk}^W) \bar{x}_j & \text{if } k \neq b \end{cases}$$

Level 2: NMR model for AD studies for RCT and NRS

$$r_{jk} \sim \text{Bin}(p_{jk}, n_{jk}) \quad \text{Logit}(p_{jk}) = \begin{cases} u_{jb} & \text{if } k = b \\ u_{jb} + \delta_{jbk} + \beta_{1,jbk}^B \bar{x}_j & \text{if } k \neq b. \end{cases}$$

Level 3: Combine the evidence from IPD and AD

$$\delta_{jbk} \sim N(d_{Ak} - d_{Ab}, \tau^2), \beta_{1,jbk}^B \sim N(B_{1,Ak}^B - B_{1,Ab}^B, \tau_B^2), \beta_{1,jbk}^W \sim N(B_{1,Ak}^W - B_{1,Ab}^W, \tau_W^2)$$

2. Bias-adjusted crossnma1 IPD{RCT+NRS} + AD{RCT+NRS}

Level 1: NMR model for IPD studies for RCT and NRS

$$y_{ijk} \sim \text{Bernoulli}(p_{ijk}) \quad \text{logit}(p_{ijk}) = \begin{cases} u_{jb} + \beta_{0j} x_{ijk} & \text{if } k = b \\ u_{jb} + \underbrace{\delta_{jbk} \gamma_{1,jbk}^{R_j}}_{\text{multiplicative}} + \underbrace{\delta_{jbk} + \gamma_{2,jbk} R_j}_{\text{additive}} & \text{if } k \neq b \\ \beta_{0j} x_{ijk} + \beta_{1,jbk}^W x_{ijk} + (\beta_{1,jbk}^B - \beta_{1,jbk}^W) \bar{x}_j & \end{cases}$$

Level 2: NMR model for AD studies for RCT and NRS

$$r_{jk} \sim \text{Bin}(p_{jk}, n_{jk}) \quad \text{logit}(p_{jk}) = \begin{cases} u_{jb} & \text{if } k = b \\ u_{jb} + \underbrace{\delta_{jbk} \gamma_{1,jbk}^{R_j}}_{\text{multiplicative}} + \underbrace{\delta_{jbk} + \gamma_{2,jbk} R_j}_{\text{additive}} + \beta_{1,jbk}^B \bar{x}_j & \text{if } k \neq b \end{cases}$$

Level 3: Combine the evidence from IPD and AD

$$\delta_{jbk} \sim N(d_{Ak} - d_{Ab}, \tau^2), \beta_{1,ibk}^B \sim N(B_{1,Ak}^B - B_{1,Ab}^B, \tau_B^2), \beta_{1,ibk}^W \sim N(B_{1,Ak}^W - B_{1,Ab}^W, \tau_W^2)$$

$$\gamma_{1,jbk} \sim N(g_{1,bk}, \tau_{1,\gamma}^2), \gamma_{2,jbk} \sim N(g_{2,bk}, \tau_{2,\gamma}^2)$$

2. Bias-adjusted crossnma1 bias indicator

1. Bias indicator R_j

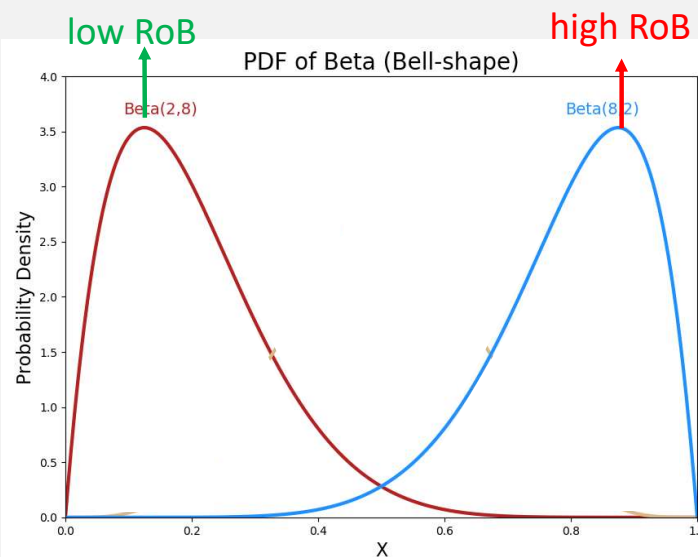
$$R_j = \begin{cases} 1, & \text{if study } j \text{ has high risk of bias} \\ 0, & \text{otherwise} \end{cases}$$

$$R_j \sim \text{Bernoulli}(\pi_j) \text{ and } \pi_j = P(R_j = 1)$$

2. Bias probability π_j

$$I. \pi_j \sim \text{Beta}(a, b)$$

high and low are provided as data based on RoB tools, i.e RoB2 for RCT and ROBINS-I for NRS



II. Use study characteristics'

$$\text{logit}(\pi_j) = a + b * z_j$$

3. Bias-adjusted crossnma2 IPD{RCT+NRS} + AD{RCT+NRS}

Level 1: NMR model for IPD studies for RCT and NRS

$$y_{ijk} \sim \text{Bernoulli}(p_{ijk}) \quad \text{Logit}(p_{ijk}) = \begin{cases} u_{jb} + \beta_{0j} x_{ijk} & \text{if } k = b \\ u_{jb} + \theta_{jbk} + \beta_{0j} x_{ijk} + \beta_{1,jbk}^W x_{ijk} + (\beta_{1,jbk}^B - \beta_{1,jbk}^W) \bar{x}_j & \text{if } k \neq b \end{cases}$$

Level 2: NMR model for AD studies for RCT and NRS

$$r_{jk} \sim \text{Bin}(p_{jk}, n_{jk}) \quad \text{Logit}(p_{jk}) = \begin{cases} u_{jb} & \text{if } k = b \\ u_{jb} + \theta_{jbk} + \beta_{1,jbk}^B \bar{x}_j & \text{if } k \neq b. \end{cases}$$

Level 3: Combine the evidence from IPD and AD

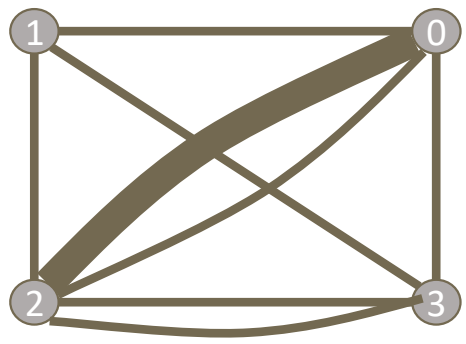
The bias-adjusted relative treatment effect

$$\theta_{jbk} \sim (1 - \pi_j) N(d_{AK} - d_{Ab}, \tau^2) + \pi_j N(d_{AK} - d_{Ab} + \gamma_{jbk}, \tau^2 + \tau_\Gamma^2)_{14}$$

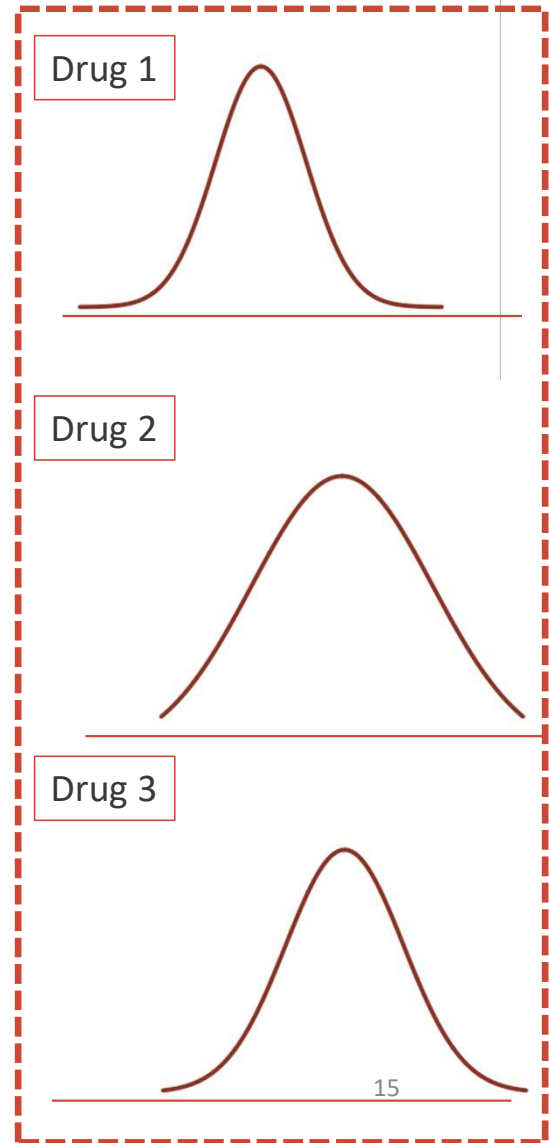
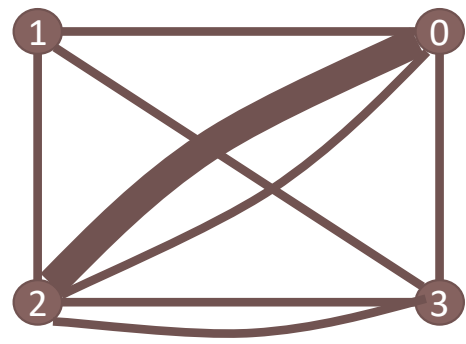
4. Use NRS as a prior in crossnma

$$\text{NRS}\{\text{IPD+AD}\} + \text{RCT}\{\text{IPD+AD}\}$$

2. IPD+AD NMA for RCTs with NRS as prior



1. IPD+AD NMA only with NRS

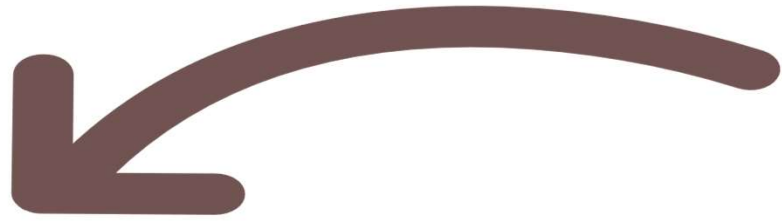
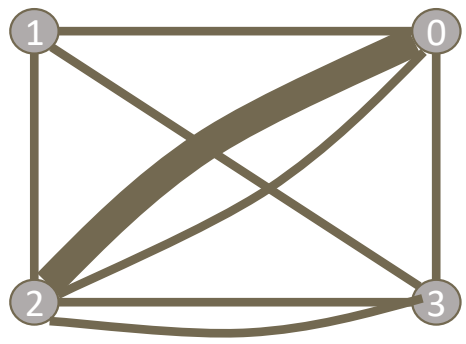


4. Use NRS as a prior in crossnma

NRS{IPD+AD} + RCT{IPD+AD}

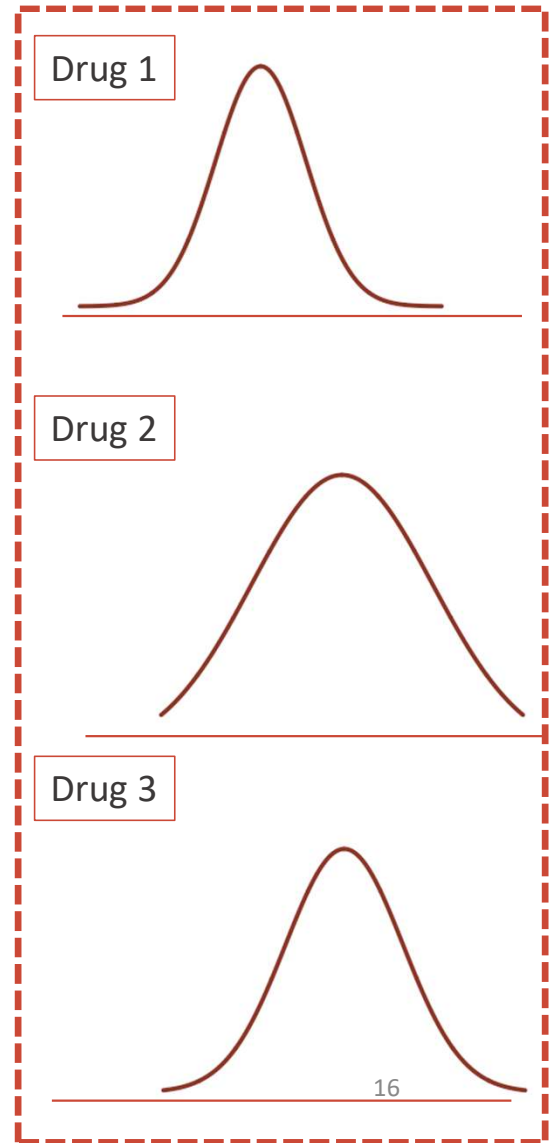
$$d_{Ak}^{RCT} \sim N(\tilde{d}_{Ak}^{NRS}, V_{Ak}^{NRS})$$

2. IPD+AD NMA for RCTs with NRS as prior



Reflect between-NRS heterogeneity,

$$d_{Ak}^{RCT} \sim N(\tilde{d}_{Ak}^{NRS}, \tilde{\tau}_{NRS}^2)$$

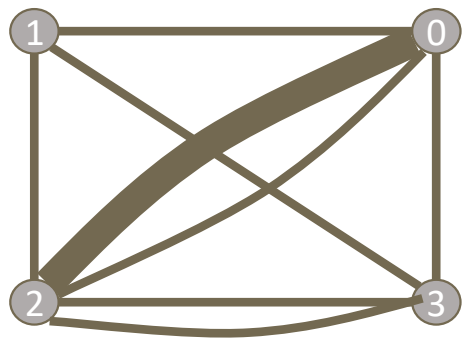


4. Use NRS as a prior in crossnma

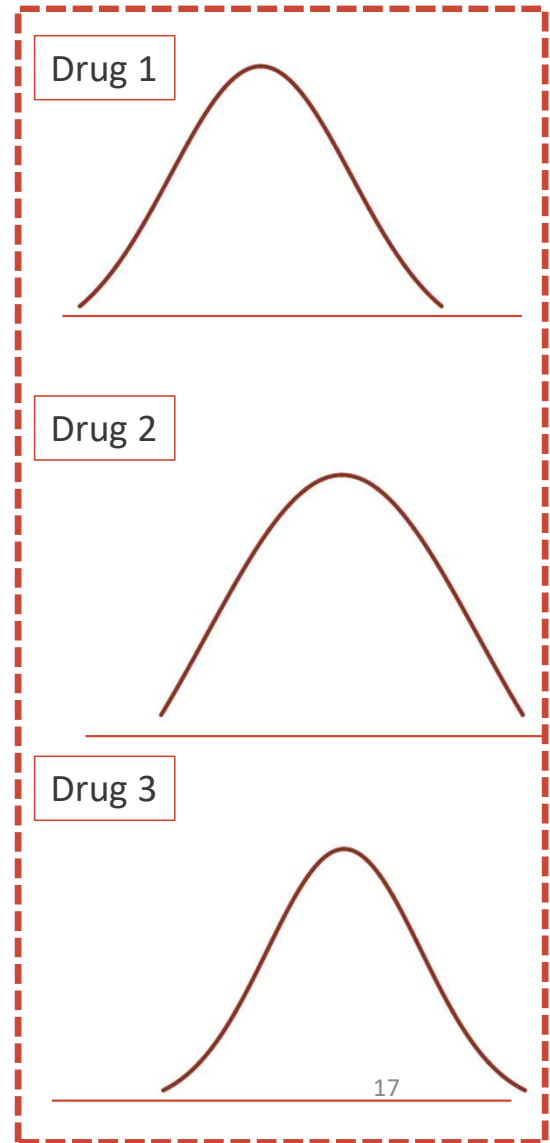
NRS{IPD+AD} + RCT{IPD+AD}

$$d_{Ak}^{RCT} \sim N(\tilde{d}_{Ak}^{NRS} + \varsigma, V_{Ak}^{NRS} / w)$$

2. IPD+AD NMA for RCTs with NRS as prior



- Common inflation factor w , $0 < w < 1$
- Adjust for the over- or under-estimation, ς



More details

Hamza T, Chalkou K, Pellegrini F, Kuhle J, Benkert P, Lorscheider J, et al. Synthesizing cross-design evidence and cross-format data using network meta-regression. *Res Synth Methods*. 2023;14:283–300.

(Open Access)

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Guido

Part IV: Limitations and future plans

- What is missing
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Guido?

crossnma package

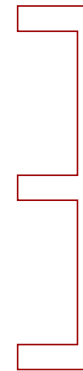
- Implement the four cross-NMA models and more
- Model parameters are estimated in a Bayesian framework using JAGS
- Can run different type of analysis: IPD-NMA, IPD-MA, IPD+AD NMA, AD-NMA, PMA, ...
- Network meta-regression with 3 covariates
- The package supports analyzing OR, RR, MD and SMD
- Default prior distribution*, as *gemtc*

Study design

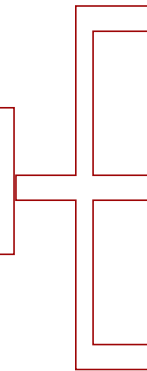
RCT

+

NRS



NMA/
NMR



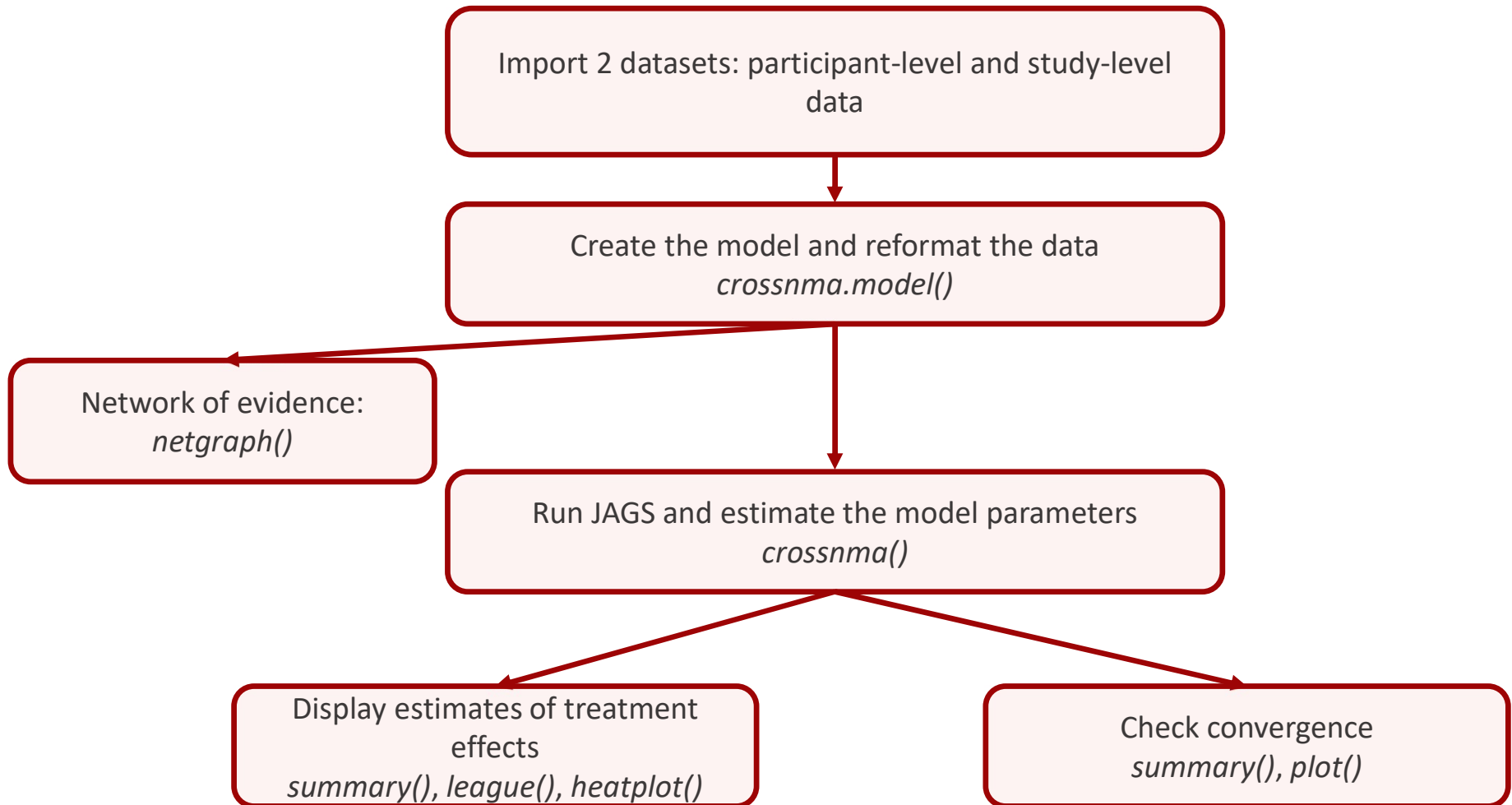
Data type

IPD

+

AD

Workflow in crossnma package



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Guido?

Example dataset

```
head(ipddata)
```

```
##   id relapse treat design age sex rob unfavored bias.group year
## 1  1      0    D    rct  22  1 low          1           1 2002
## 2  1      0    D    rct  31  1 low          1           1 2002
## 3  1      0    D    rct  34  1 low          1           1 2002
## 4  1      0    D    rct  38  0 low          1           1 2002
## 5  1      0    D    rct  46  0 low          1           1 2002
## 6  1      0    D    rct  45  0 low          1           1 2002
```

```
stddata
```

```
##   id  n relapse treat design  age sex  rob unfavored bias.group year
## 1  1  25      19    A    rct 34.3 0.2 high          0           1 2010
## 2  1  25      11    C    rct 34.3 0.3 high          1           1 2010
## 3  2 126      97    A    rct 30.0 0.4 high          0           1 2015
## 4  2 125      89    C    rct 30.0 0.5 high          1           1 2015
```

Set up your crossnma model JAGS code and formatted data

IPD and AD Network meta-analysis model

```
mod1 <- crossnma.model(  
  treat, id, relapse, n, design,  
  prt.data = ippdata, std.data = stddata,  
  sm = "OR",  
  trt.effect = "random",  
  #----- bias adjustment -----  
  method.bias = "naive",  
  #----- assign a prior -----  
  prior.tau.trt = "dunif(0,3)")
```

Column names

Set up your crossnma model JAGS code and formatted data

IPD and AD Network meta-analysis model

```
mod1 <- crossnma.model(  
  treat, id, relapse, n, design,  
  prt.data = ipddata, std.data = stddata  
  sm = "OR",  
  trt.effect = "random",  
  #----- bias adjustment -----  
  method.bias = "naive",  
  #----- assign a prior -----  
  prior.tau.trt = "dunif(0,3)")
```

Your IPD and AD datasets

Set up your crossnma model JAGS code and formatted data

IPD and AD Network meta-analysis model

```
mod1 <- crossnma.model(  
  treat, id, relapse, n, design,  
  prt.data = ippdata, std.data = stddata  
  sm = "OR",  
  trt.effect = "random",  
  #----- bias adjustment -----  
  method.bias = "naive",  
  #----- assign a prior -----  
  prior.tau.trt = "dunif(0,3)")
```

Summary of measure: OR, RR, MD and
SMD

Set up your crossnma model JAGS code and formatted data

IPD and AD Network meta-analysis model

```
mod1 <- crossnma.model(  
  treat, id, relapse, n, design,  
  prt.data = ippdata, std.data = stddata,  
  sm = "OR",  
  trt.effect = "random",  
  #----- bias adjustment -----  
  method.bias = "naive",  
  #----- assign a prior -----  
  prior.tau.trt = "dunif(0,3)")
```

Synthesize relative treatment effects
across studies

Set up your crossnma model JAGS code and formatted data

IPD and AD Network meta-analysis model

```
mod1 <- crossnma.model(  
  treat, id, relapse, n, design,  
  prt.data = ippdata, std.data = stddata,  
  sm = "OR",  
  trt.effect = "random",  
  #----- bias adjustment -----  
  method.bias = "naive",  
  #----- assign a prior -----  
  prior.tau.trt = "dunif(0,3)")
```

1. Unadjusted (naïve)
2. Bias adjustment 1
3. Bias adjustment 2
4. Use NRS as a prior

Set up your crossnma model JAGS code and reformat data

IPD and AD Network meta-regression

```
mod2 <- crossnma.model(treat, id, relapse, n, design,  
  prt.data = ipddata, std.data = stddata, sm = "OR",  
  trt.effect = "random",  
  #----- bias adjustment -----  
  method.bias = "naive",  
  #----- meta-regression -----  
  cov1 = age, split.regcoef = FALSE)
```

Set up your crossnma model JAGS code and formatted data

IPD and AD Network meta-regression model using NRS as prior

```
mod3 <- crossnma.model(treat, id, relapse, n, design,
  prt.data = ipddata, std.data = stddata, sm = "OR",
  reference = "D", trt.effect = "random",
  #----- meta-regression -----
  cov1 = age, split.regcoef = FALSE,
  #----- bias adjustment -----
  method.bias = "prior",
  run.nrs.trt.effect = "common", run.nrs.var.infl = 0.6,
  run.nrs.mean.shift = 0, run.nrs.n.iter = 100000,
  run.nrs.n.burnin = 40000, run.nrs.n.thin = 5,
  run.nrs.n.chains = 2)
```

1. Unadjusted (naïve)
2. Bias adjustment 1
3. Bias adjustment 2
4. Use NRS as a prior

Set up your crossnma model JAGS code and formatted data

IPD and AD network meta-analysis model using bias-adjustment model 1

```
mod4 <- crossnma.model(treat, id, relapse, n, design, bias = rob,  
  prt.data = ipddata, std.data = stddata, sm = "OR",  
  trt.effect = "random",  
  #----- bias adjustment -----  
  method.bias = 'adjust1',  
  bias.type = 'add', bias.effect = 'common',  
  unfav = unfavored, bias.group = bias.group,  
  bias.covariate = year)
```

1. Unadjusted (naïve)
2. Bias adjustment 1
3. Bias adjustment 2
4. Use NRS as a prior

Set up your crossnma model JAGS code and formatted data

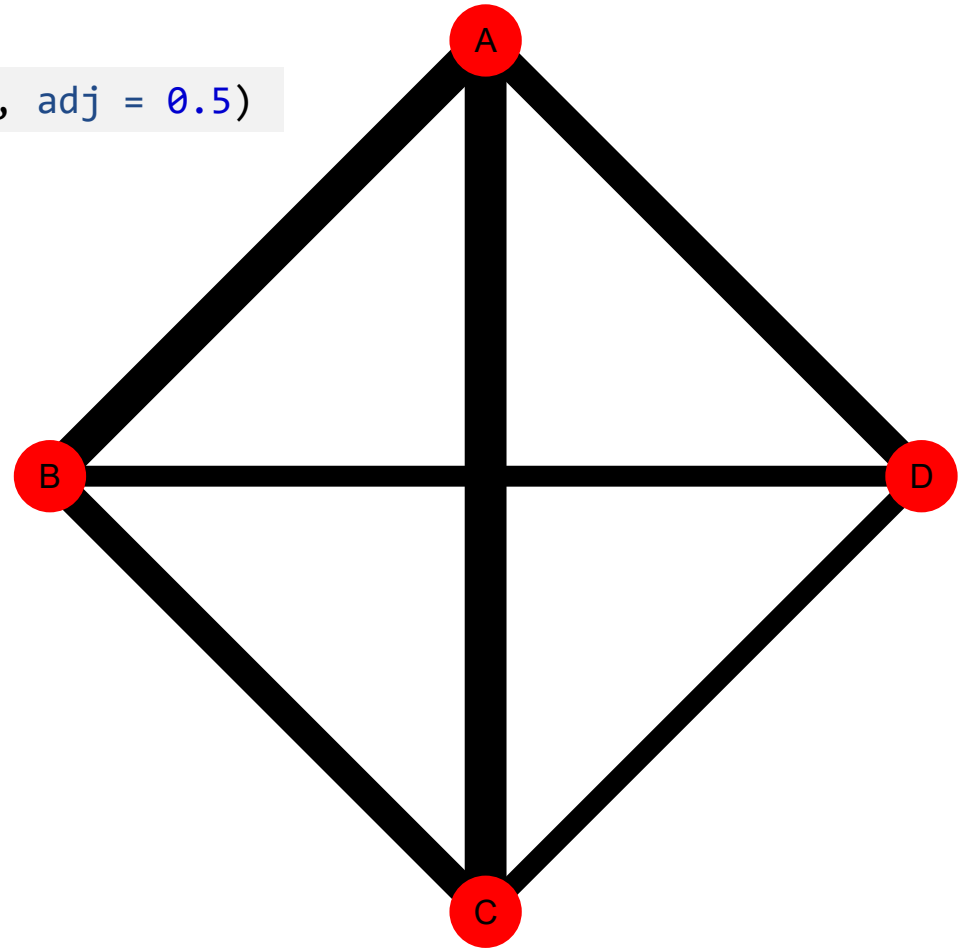
IPD and AD network meta-analysis model using bias-adjustment model 2

```
mod5 <- crossnma.model(treat, id, relapse, n, design, bias = rob,  
  prt.data = ipddata, std.data = stddata, sm = "OR",  
  trt.effect = "random",  
  #----- bias adjustment -----  
  method.bias = 'adjust2',  
  bias.type = 'add', bias.effect = 'common',  
  unfav = unfavored, bias.group = bias.group,  
  bias.covariate = year)
```

1. Unadjusted (naïve)
2. Bias adjustment 1
3. Bias adjustment 2
4. Use NRS as a prior

Network plot

```
netgraph(mod1, plastic = FALSE, cex.points = 7, adj = 0.5)
```



Fit the crossnma model

```
jagsfit3 <- crossnma(mod3, n.iter = 100000, n.burnin = 40000,  
  n.thin = 5, n.chains = 2)
```

Then, get the results by the command `jagsfit3`

	Mean	SD	2.5%	50%	97.5%	Rhat	n.eff
exp(d.D)
exp(d.A)	2.412	0.403	1.091	2.422	4.901	1.191	6548
exp(d.B)	0.999	0.425	0.414	1.023	2.315	1.049	13531
exp(d.C)	1.495	0.454	0.634	1.493	3.776	1.086	12005
tau	0.331	0.281	0.016	0.255	1.072	1.064	14987
exp(b_1)	1.020	0.061	0.917	1.023	1.117	1.114	3905
tau.b_1	0.049	0.093	0.002	0.018	0.340	1.160	4134

League Table

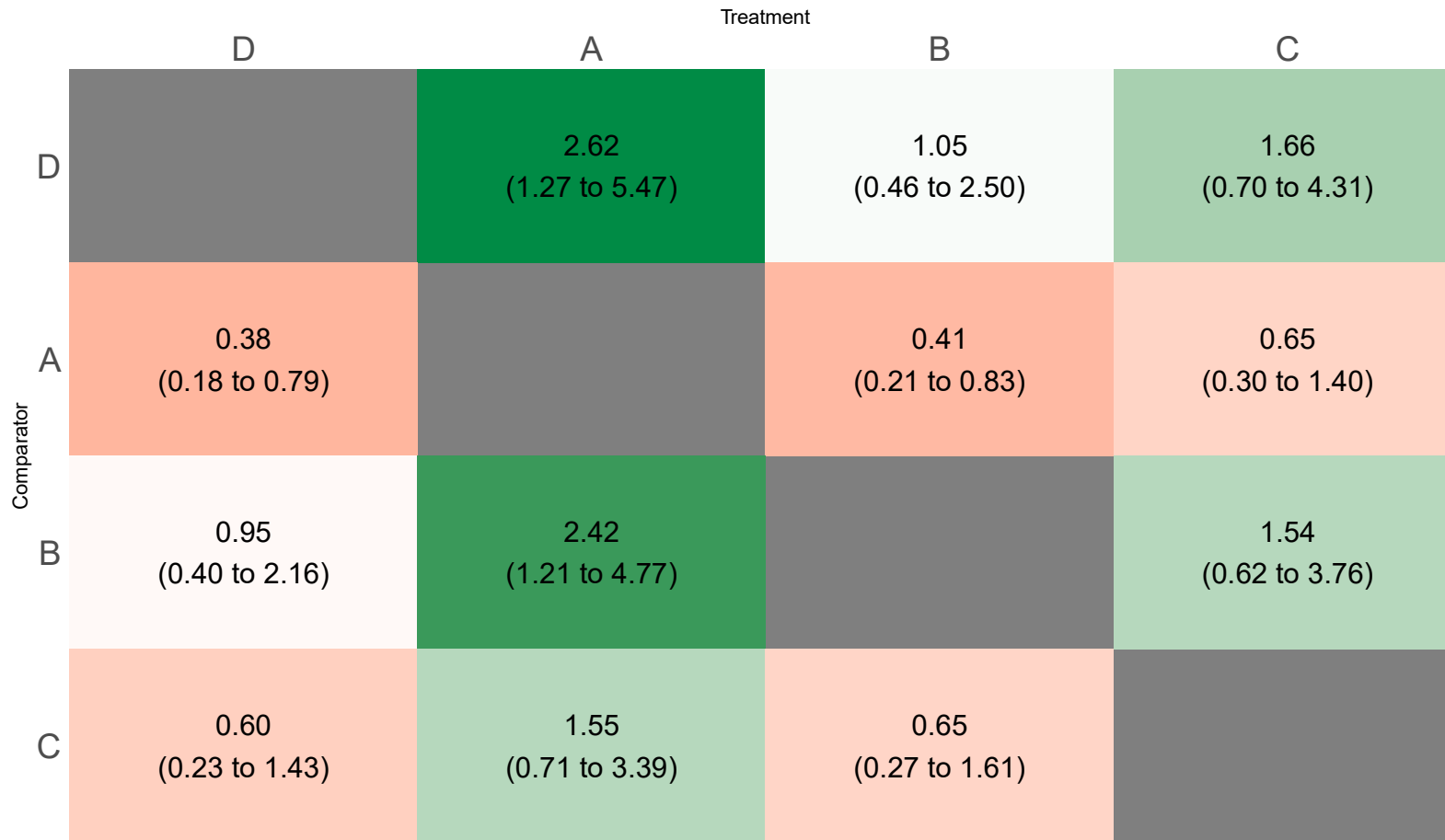
```
league(jagsfit3, cov1.value = 38, direction = "long")
```

```
Treatment Comparator median 2.5% 97.5%
```

<i>A</i>	<i>D</i>	<i>2.618</i>	<i>1.273</i>	<i>5.471</i>
<i>B</i>	<i>D</i>	<i>1.053</i>	<i>0.464</i>	<i>2.503</i>
<i>C</i>	<i>D</i>	<i>1.656</i>	<i>0.701</i>	<i>4.308</i>
<i>D</i>	<i>A</i>	<i>0.382</i>	<i>0.183</i>	<i>0.786</i>
<i>B</i>	<i>A</i>	<i>0.413</i>	<i>0.209</i>	<i>0.828</i>
<i>C</i>	<i>A</i>	<i>0.645</i>	<i>0.295</i>	<i>1.401</i>
<i>D</i>	<i>B</i>	<i>0.950</i>	<i>0.399</i>	<i>2.156</i>
<i>A</i>	<i>B</i>	<i>2.421</i>	<i>1.207</i>	<i>4.775</i>
<i>C</i>	<i>B</i>	<i>1.544</i>	<i>0.623</i>	<i>3.763</i>
<i>D</i>	<i>C</i>	<i>0.604</i>	<i>0.232</i>	<i>1.426</i>
<i>A</i>	<i>C</i>	<i>1.549</i>	<i>0.714</i>	<i>3.386</i>
<i>B</i>	<i>C</i>	<i>0.648</i>	<i>0.266</i>	<i>1.606</i>

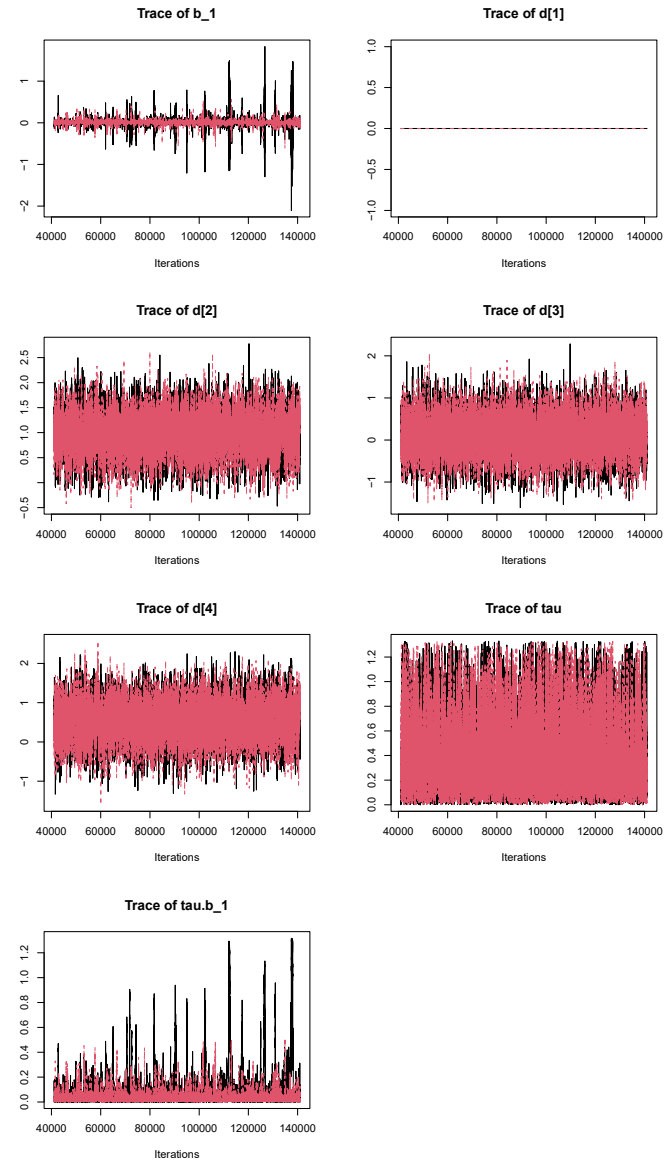
League table heatmap

```
heatplot(jagsfit3, cov1.value = 38)
```



Trace plot

```
par(mfrow = c(4, 2))  
plot(jagsfit3)
```



Part I: The theory behind crossnma

The 4 crossnma models:

- Unadjusted (naïve)
- Bias adjustment 1
- Bias adjustment 2
- Use NRS as a prior

Tasnim Hamza

Part II: The crossnma package

- Implementation
- Workflow within crossnma

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Part III: Worked example

- Description of the network
- Set up the four different crossnma models
- Run the analysis
- Display the results

Guido

Part IV: Limitations and future plans

- What is missing
- Further details

Guido Schwarzer

Limitations and future plans

- Methods for evaluating local or global inconsistency
- Ranking methods, such as SUCRA scores
- Support of count and time-to-event outcomes

Further details

- ***crossnma 1.1.0*** is available on CRAN (`install.packages("crossnma")`)
- Latest version can be accessed from GitHub at [htx-r/crossnma](https://github.com/htx-r/crossnma)
- With help files (`help("crossnma-package")`) and a vignette (`vignette("crossnma")`)
- A manuscript under revision to illustrate the use of functions in ***crossnma***
- Any comments/suggestions can be directed to
Tasnim Hamza (hamza.a.tasnim@gmail.com) or
Guido Schwarzer (guido.schwarzer@uniklinik-freiburg.de)

Which new features should we add to
'crossnma'?