Component network meta-analysis compared to a matching method in a disconnected network: a case study

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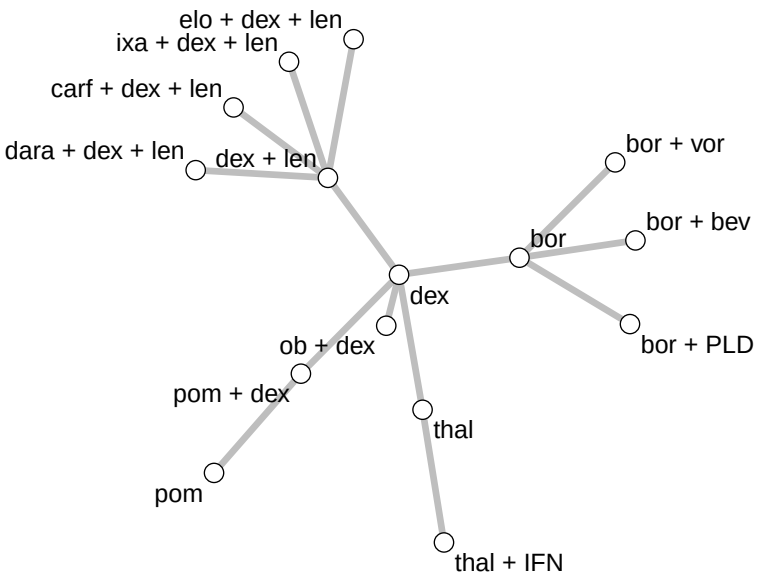
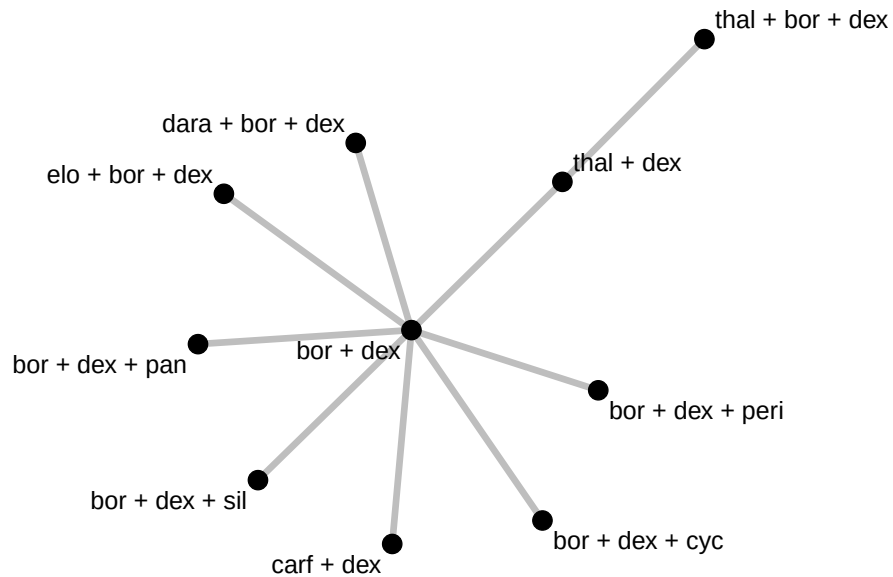
Outline

A disconnected network

- Network meta-analysis (NMA) of 25 trials investigating treatments and treatment combinations for multiple myeloma [Schmitz et al., 2018]
- Outcome: Progression-free survival, relative effects measured as hazard ratios (HR)
- Encountered two separate networks, the ”white network” (left, 15 treatments) and the ”black network” (right, 10 treatments)





A disconnected network

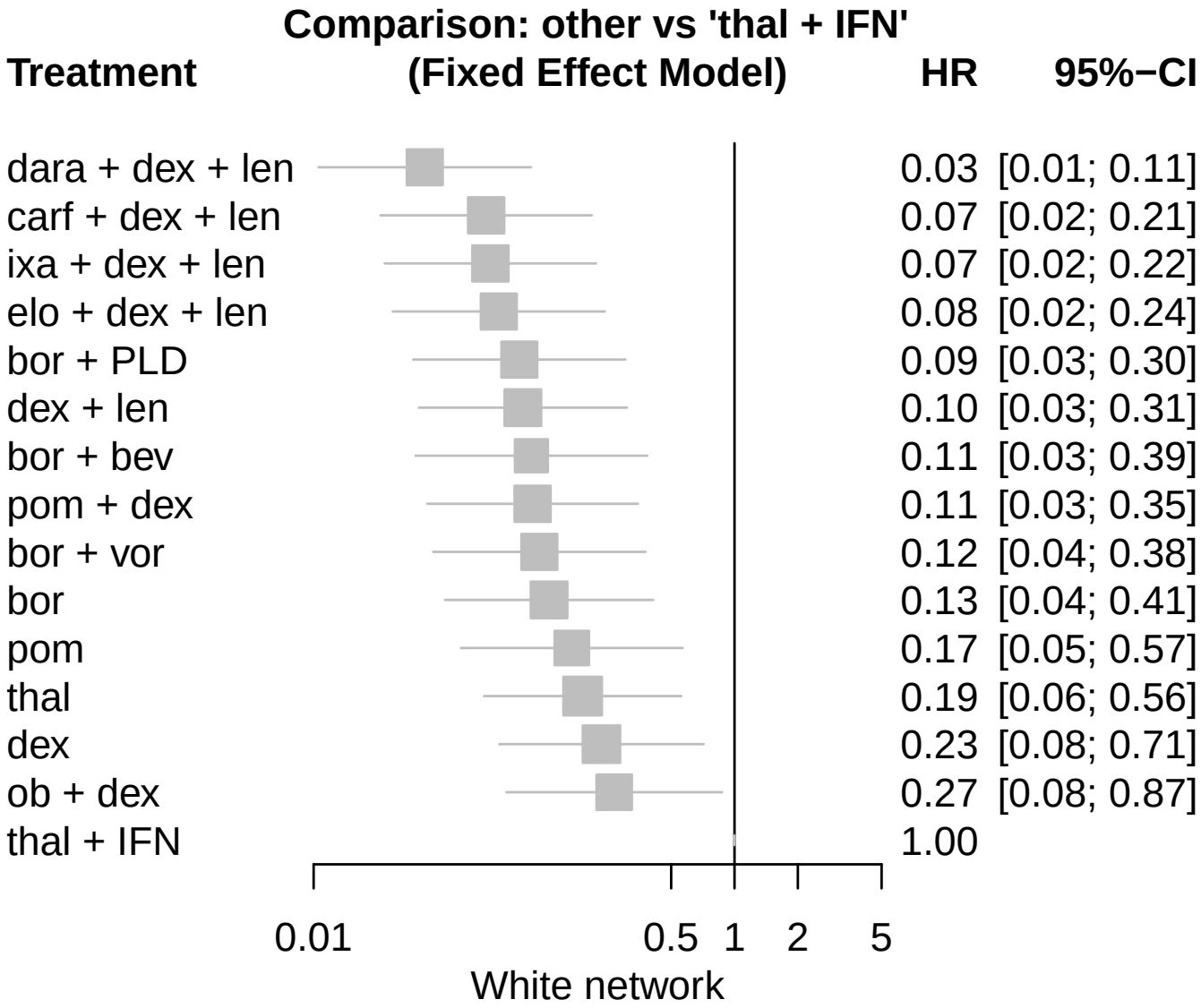
The ”white network” and the ”black network” have no treatments in common

How to deal with that in a network meta-analysis?

- Separate NMA analyses
- Matching method [Schmitz et al., 2018]
- Component network meta-analysis
  [Welton et al., 2009, Rücker et al., 2019b]

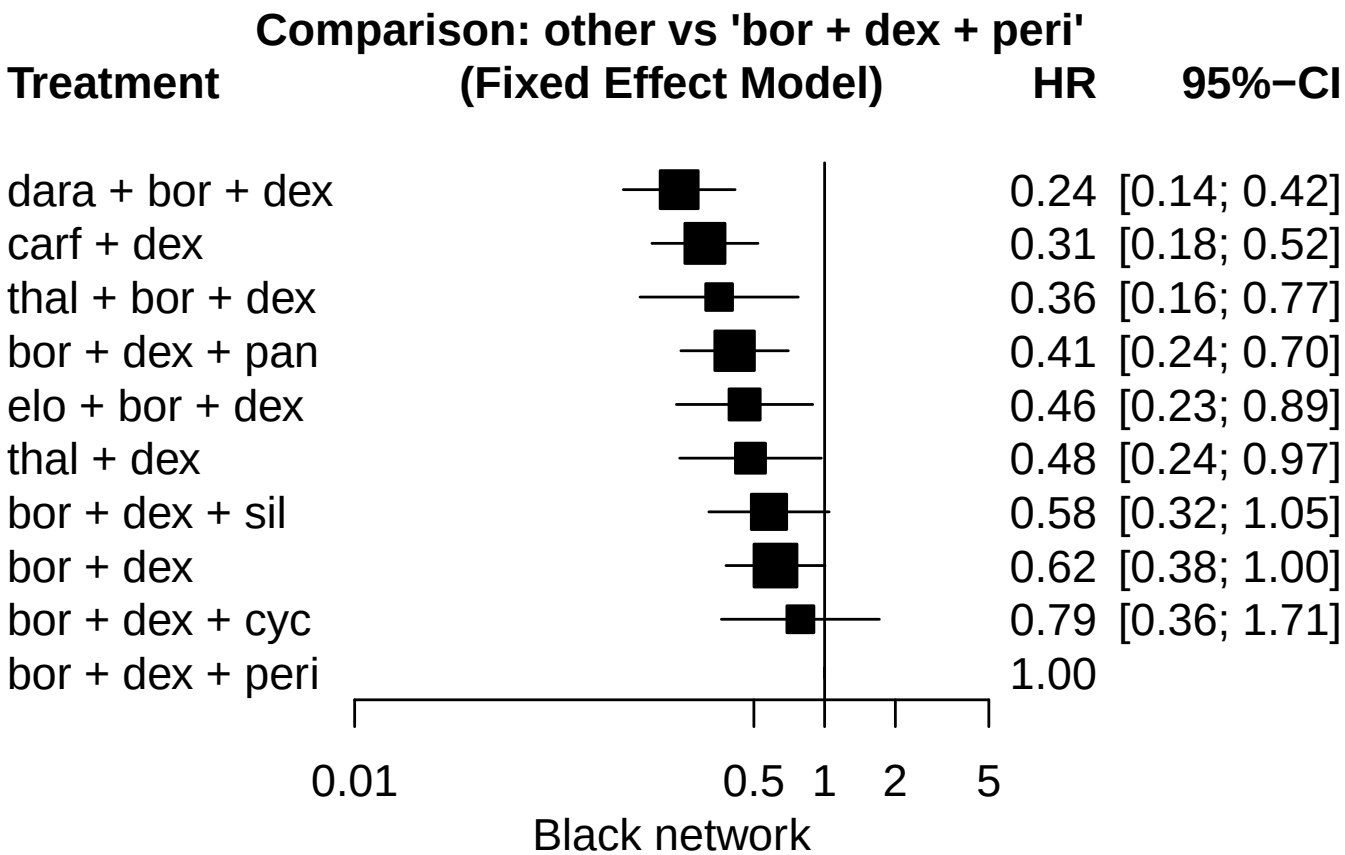
Separate network meta-analyses

”White network”



Separate network meta-analyses

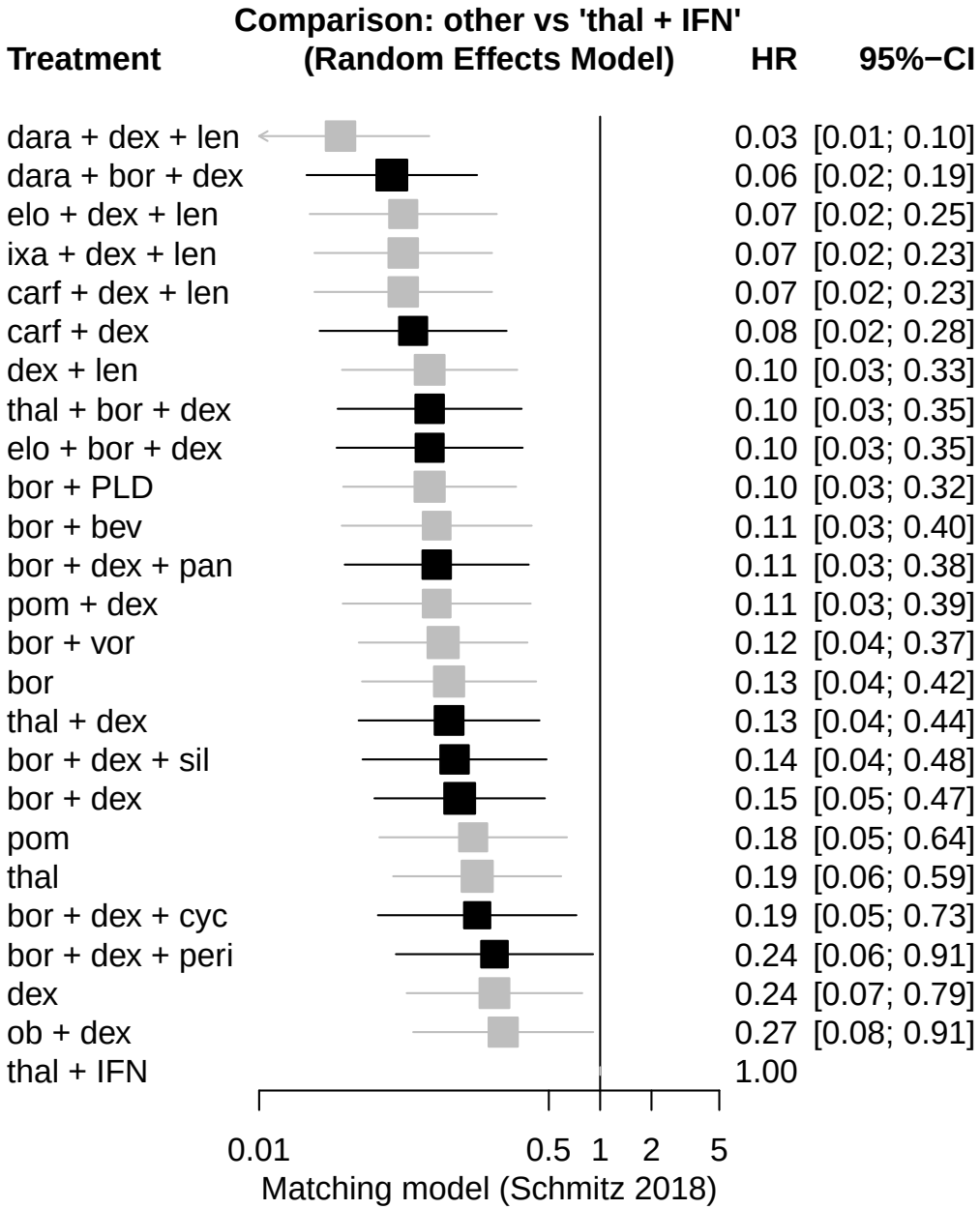
”Black network”



Matching method [Schmitz et al., 2018]

- Sought evidence from observational studies to connect the disconnected network
- In the absence of comparative observational studies, single-arm studies were considered
- Distance metric based on covariate profiles allowed measuring similarity between studies (treatment history, age, baseline stage, gender)
- Five matches between the networks could be identified
- Models fitted in `WinBUGS` using the R package `R2WinBUGS` [R Core Team, 2019, Sturtz et al., 2005]

Matching method



Component network meta-analysis

- Standard model of network meta-analysis:
  Each treatment is represented by one node in the network
- However, treatments may be complex, for example, combinations of other treatments (multicomponent interventions)
- This was observed in the Multiple Myeloma case study
  - White network: dara + dex + len, carf + dex + len, bor + bev, thal + IFN, …
  - Black network: dara + bor + dex, carf + dex, bor + dex, thal + dex, …
- $\Rightarrow$ Component network meta-analysis (CNMA)
  [Welton et al., 2009, Rücker et al., 2019b]

Additive CNMA Model [Rücker et al., 2019b]

- Consider two **active components:**
  - pom pomalidomide
  - dex dexamethasone
- Three possible **treatment combinations**:
  1. pom
  2. dex
  3. pom + dex
- **Additive model:** The effect of the combined treatment is an additive sum of its components
  - This means that 'equal components cancel out':
    pom + dex vs. dex estimates pom
  - Example for three components:
    carf + dex + len vs. dex + len estimates carf

Additive 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 pom, dex, pom+dex

study 1:	pom	vs	dex
study 2:	pom + dex	vs	dex
study 3:	pom + dex	vs	pom
study 4:	pom	vs	dex

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

- $\mathbf{B}$ is the design matrix of the standard NMA model
- For sake of simplicity of presentation, we ignore that there may be multi-arm studies

Additive CNMA model

- $n \times c$ **combination structure matrix** $\mathbf{C}$ describes how the $n = 3$ treatments (here pom, dex, pom + dex) are composed of the $c = 2$ components pom and dex

treatment 1: pom
treatment 2: dex
treatment 3: pom + dex

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

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

study 1: pom vs dex
study 2: pom + dex vs dex
study 3: pom + dex vs pom
study 4: pom vs dex

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

Interaction CNMA model

- $n \times c$ **combination structure matrix** $\mathbf{C}^*$ describes how the $n = 3$ treatments (here pom, dex, pom + dex) are composed of the $c = 3$ components pom, dex and pom+dex:

treatment 1: pom
treatment 2: dex
treatment 3: pom+dex

$$\mathbf{C}^* = \begin{pmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 1 & 1 & 1 \end{pmatrix}$$

- The **design matrix of the interaction model** is

study 1: pom vs dex
study 2: pom + dex + pom+dex vs dex
study 3: pom + dex + pom+dex vs pom
study 4: pom vs dex

$$\mathbf{X} = \mathbf{B}\mathbf{C}^* = \begin{pmatrix} 1 & -1 & 0 \\ 1 & 0 & 1 \\ 0 & 1 & 1 \\ 1 & -1 & 0 \end{pmatrix}$$

General CNMA model

The component NMA model (CNMA model) is

$$\mathbf{d} = \mathbf{X}\beta + \epsilon$$

where

- $\mathbf{d} \in \mathbb{R}^m$ is the vector of observed relative effects (differences) from the studies
- $\mathbf{X} = \mathbf{BC}$ is the design matrix
  (based on $\mathbf{C}$ with an additive or $\mathbf{C}^*$ with an interaction structure)
- $\beta \in \mathbb{R}^c$ is a parameter vector representing the components
- $\epsilon \in \mathbb{R}^m$ is a multivariate normally distributed error

Estimation via weighted least squares [Rücker et al., 2019b]

Heterogeneity statistic for the CNMA model

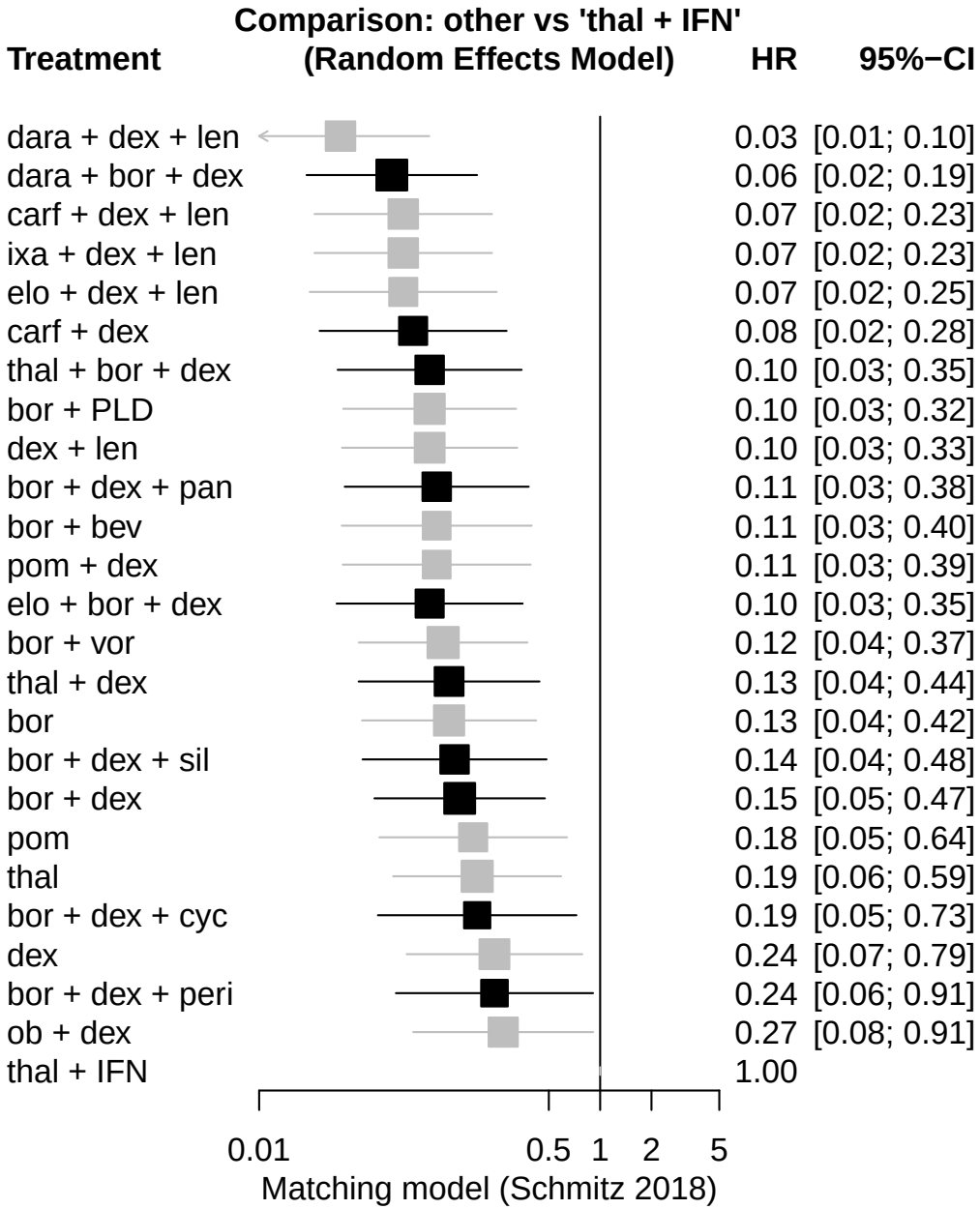
The heterogeneity statistic for the CNMA model is

$$Q = (\mathbf{d} - \hat{\delta})^\top \mathbf{W}(\mathbf{d} - \hat{\delta})$$

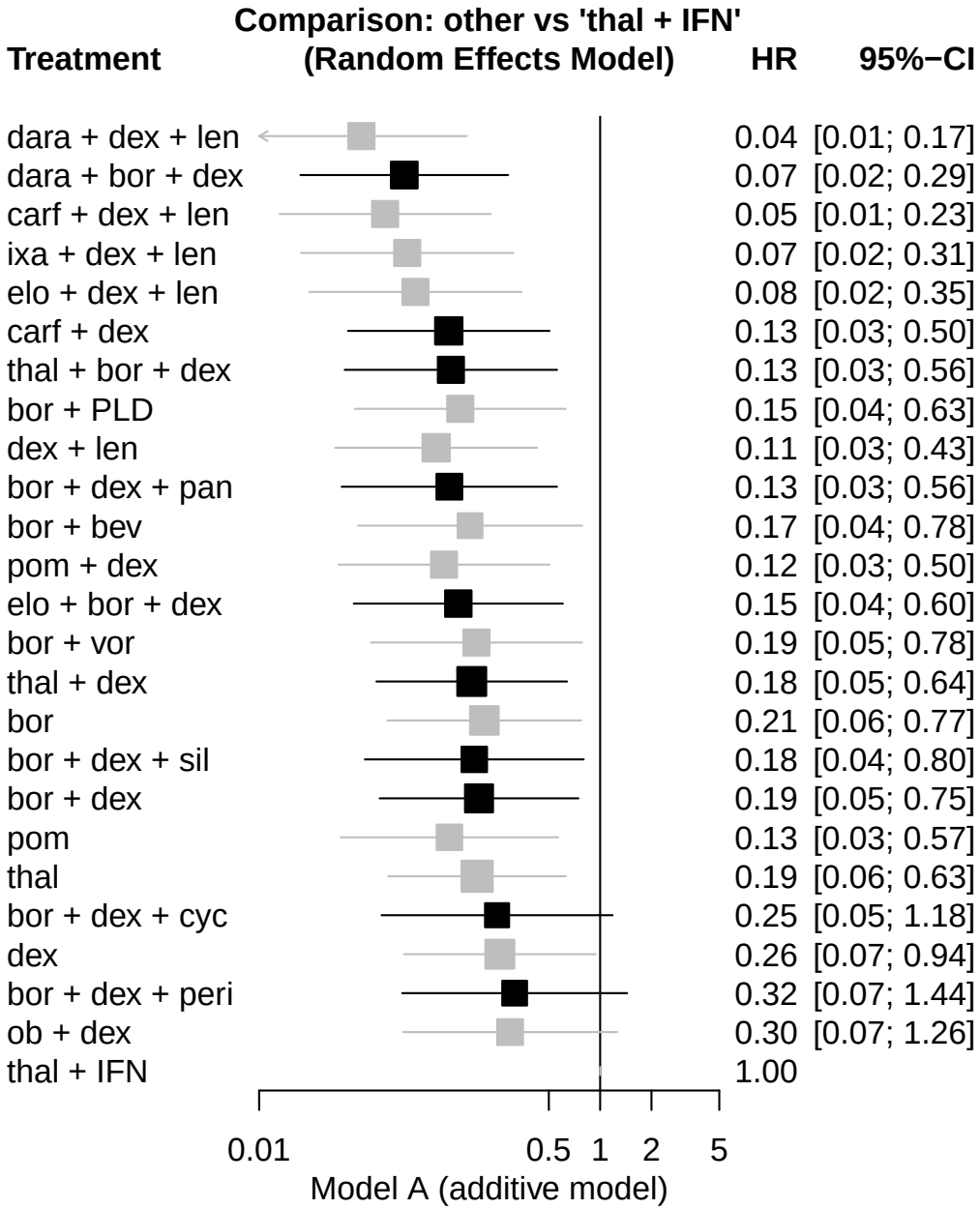
where

- $\hat{\delta}$ denotes the vector of estimates based on the CNMA model
- $\mathbf{W}$ is a $m \times m$ weight matrix derived of inverse variances of the observed effects
- Q approximately follows a χ^2 distribution with $df = n_a - k - r$ degrees of freedom where
  - n_a is the total number of arms in the network
  - k is the total number of studies in the network
  - r is the rank of the design matrix $\mathbf{X}$

Compare models: Matching method



Compare models: Additive model



Interaction CNMA models: Model selection

Starting from the additive model, add interaction terms in a systematic model selection procedure
Note:

- Only interactions corresponding to combinations observed in the data can be estimated
- Some interaction terms cannot be estimated (we'll come back to this in the discussion)

First idea: Find a sparse model that fits the data well!

Interaction CNMA models: Model selection

Sparse or not sparse?

- Usually, we want to avoid overfitting
- However, in a connected network, the standard NMA uses **all** interactions (all treatment combinations)!
- We cannot do this in a disconnected network
- But, why shouldn't we try to include in a disconnected network as many interactions as possible, before the network breaks up?

Two possible procedures

- Forward selection: Starting from the (sparse) additive model, add interactions
- Backward selection: Starting from the (rich, but impossible) NMA model, separate single components

Interaction CNMA models: Model selection

Forward selection

- Start from the additive model (no interactions)
- Add (in turn) each two-way interaction that was observed in the data to the additive model
- Add (in turn) each three-way interaction that was observed in the data to the additive model
- Further candidate models by combining each two, three, … interaction terms
- Select the final model based on comparing Cochran's Q statistic between nested models
- Ideally, Q reduces to the sum of the Qs from the subnetworks

Interaction CNMA models: Model selection

- Separate CNMA
  - White network (Q = 0.30, df = 2, p = 0.8595)
  - Black network (Q = 0, df = 0)
- Additive model (Q = 27.78, df = 7, p = 0.0002)
- 10 two-way interactions with data
  - Three of them led to a reduction of the degrees of freedom and a reduction of Q (bor*dex, pom*dex, thal*dex)
  - Best: bor*dex (Q = 9.40, df = 6, p = 0.1523)
- 11 three-way interactions with data
  - Only carf*dex*len considerably improved the model fit (Q = 9.47, df = 6, P = 0.1487)
- Combining two (2-way or 3-way) interaction terms
  - Best: bor*dex + carf*dex*len (Q = 0.91, df = 5, p = 0.9699)

Interaction CNMA models: Model selection

Best models with more than two interaction terms

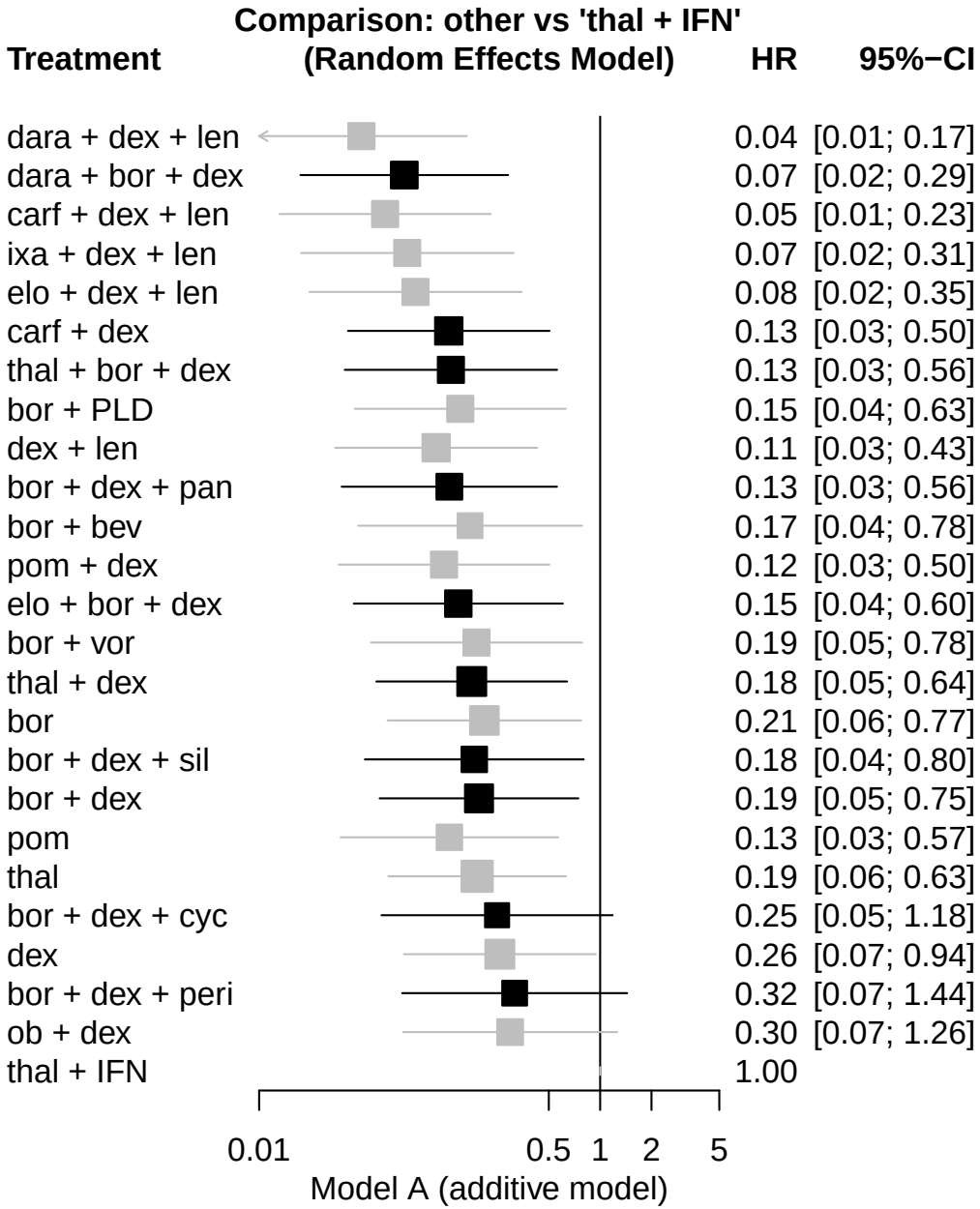
- Combining three interaction terms
  - bor*dex + carf*dex*len + thal*bor*dex
    (Q = 0.86, df = 4, p = 0.9301)
- Combining four interaction terms
  - bor*dex + carf*dex*len + thal*bor*dex + dara*bor*dex
    (Q = 0.33, df = 3, p = 0.9553)
- Combining five interaction terms
  - bor*dex + carf*dex*len + thal*bor*dex + dara*bor*dex + elo*bor*dex
    (Q = 0.30, df = 2, p = 0.8595)
  - This is a saturated model as it achieves the fit of the white network (Q = 0.30, df = 2, p = 0.8595) $\Rightarrow$ No further improvement possible
  - The saturated model is not significantly better than the sparser model bor*dex + carf*dex*len
    (Q test for difference: Q_{diff} = 0.60, df = 3, p = 0.8959)

Interaction CNMA models: Model selection

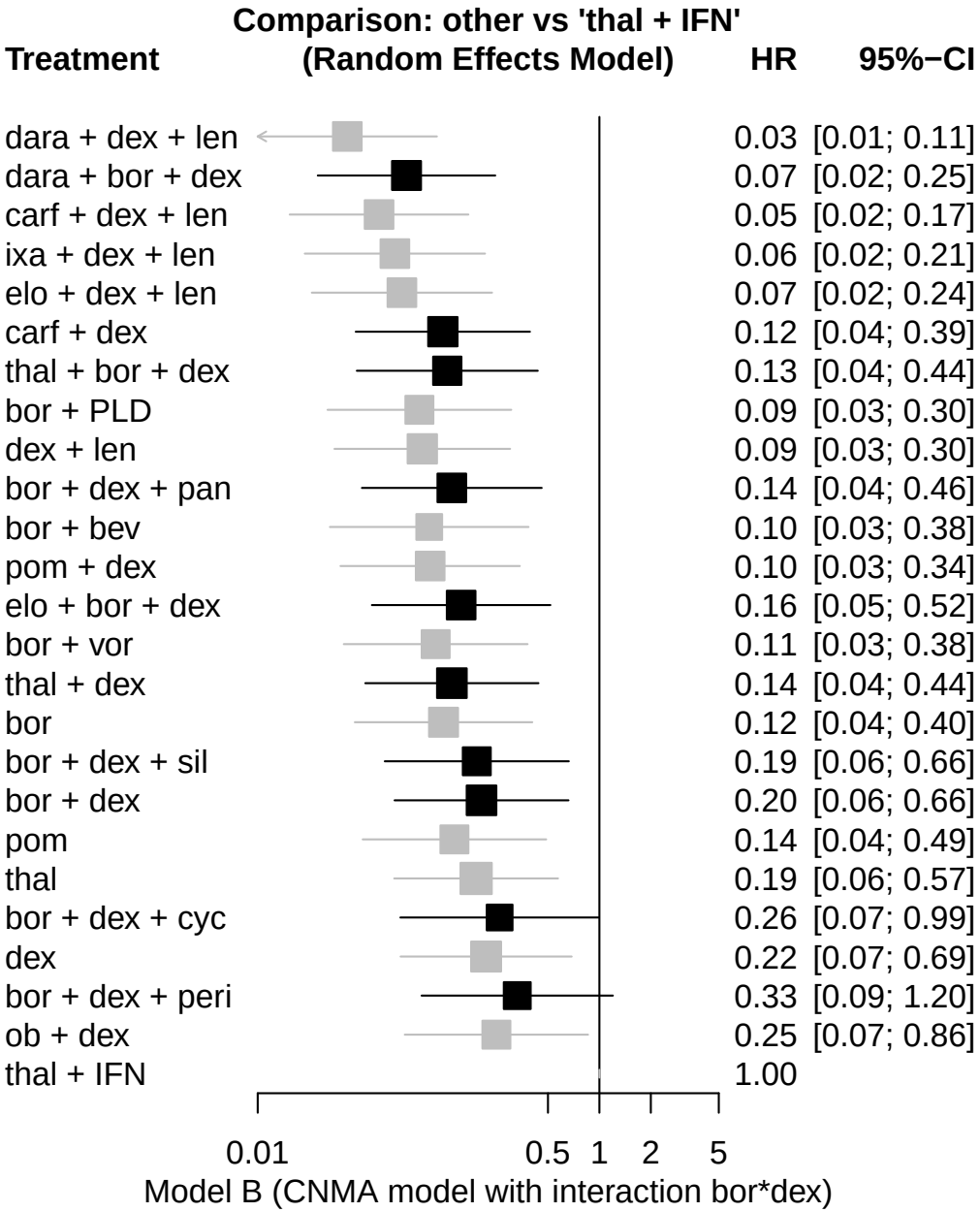
Backward selection

- Start with isolating only one component, for example thal
- Technically, define a matrix $\mathbf{C}^{**}$ with all combinations and replace column thal with a column with ones for all treatment combinations that contain thal as a component
- thal is in the white network, but thal + dex is in the black network
  $\Rightarrow$ sufficient to connect the subnetworks
- Surprisingly, this (rich) model corresponds to another saturated model, but with slightly different estimates (Q = 0.30, df = 2, p = 0.8595)
- Same works with bor, carf, dara, or elo

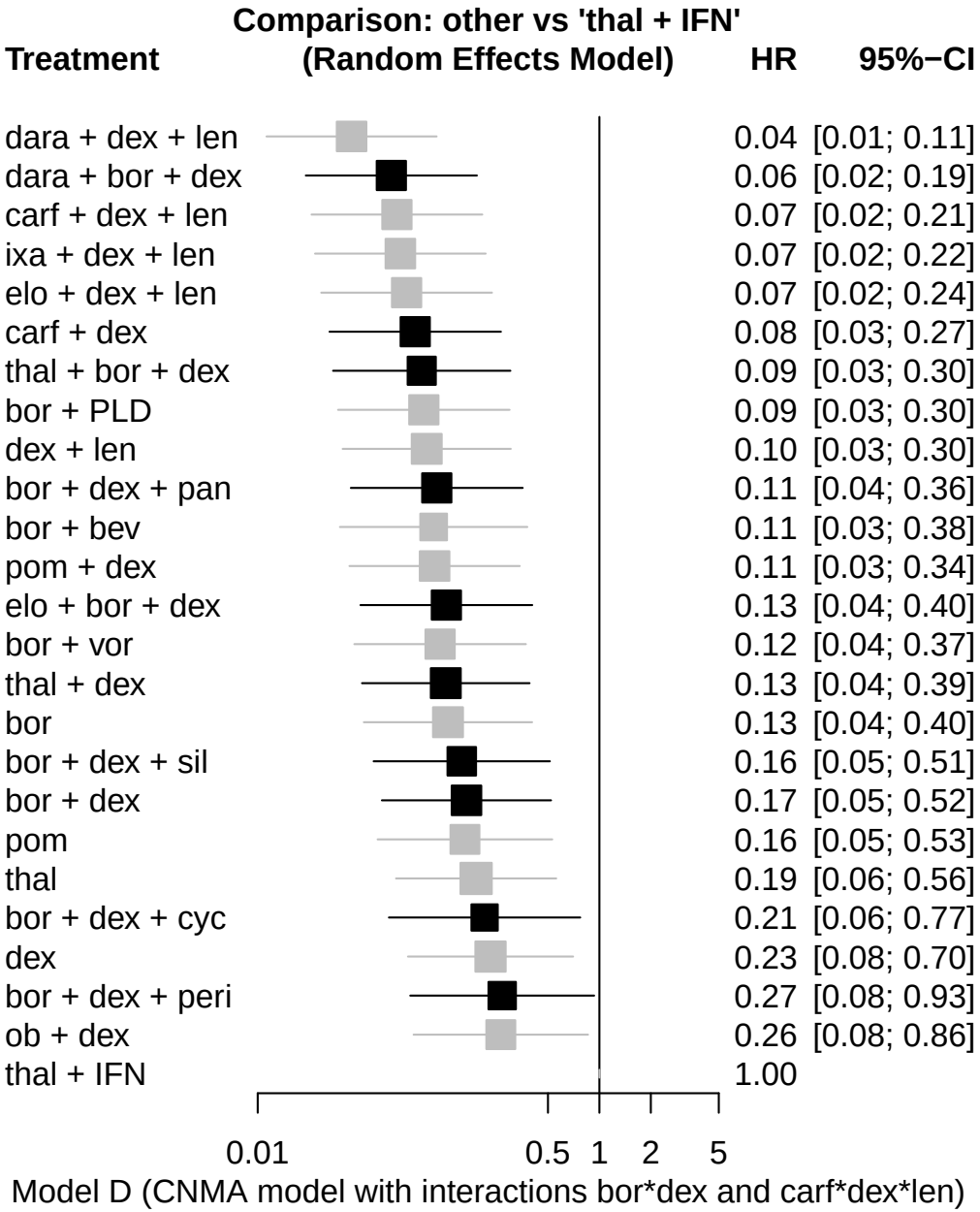
Additive model (Q = 27.78, df = 7, p = 0.0002)



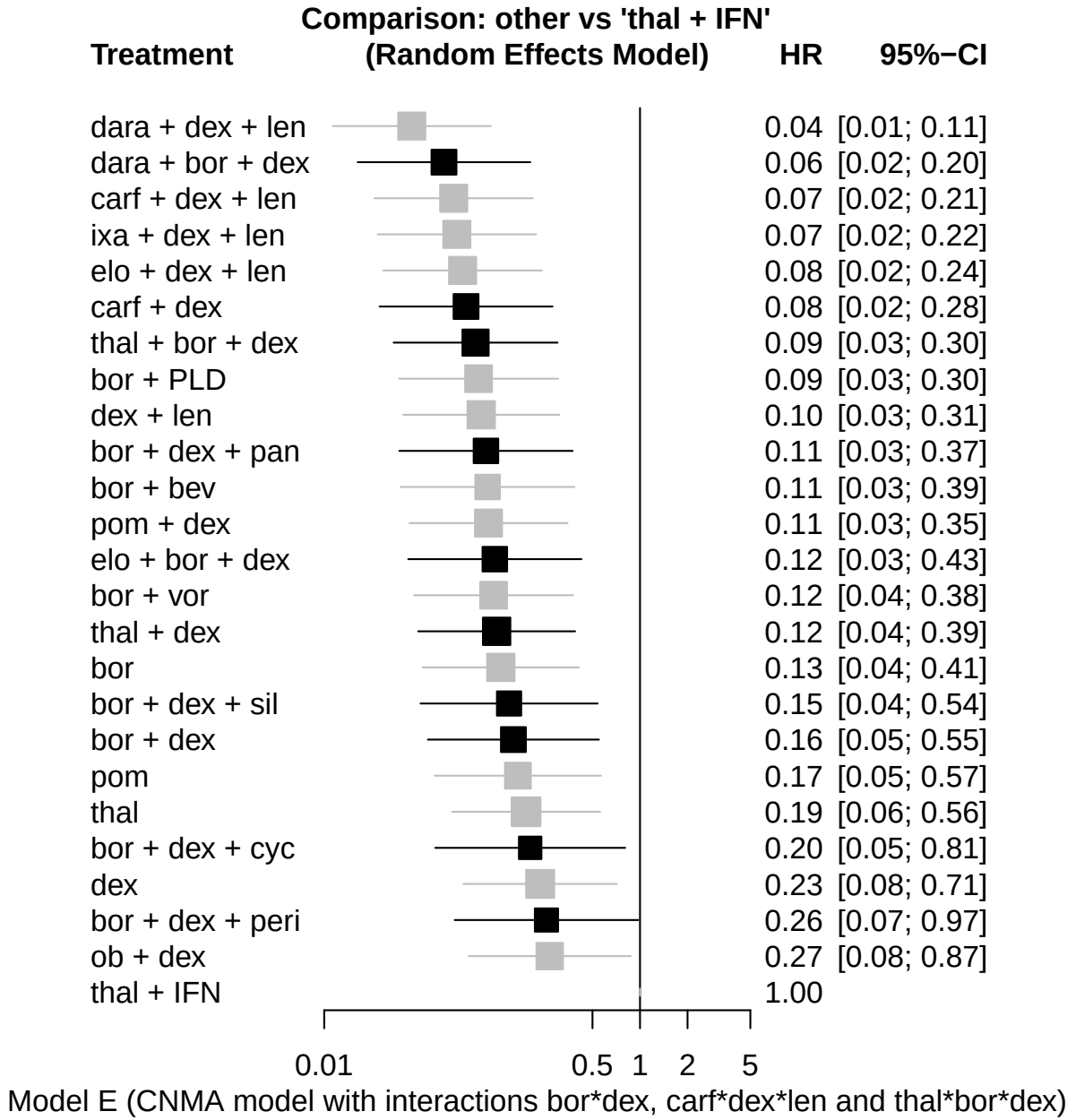
Model with bor*dex (Q = 9.40, df = 6, p = 0.152)



bor*dex + carf*dex*len (Q = 0.91, df = 5, p = 0.970)

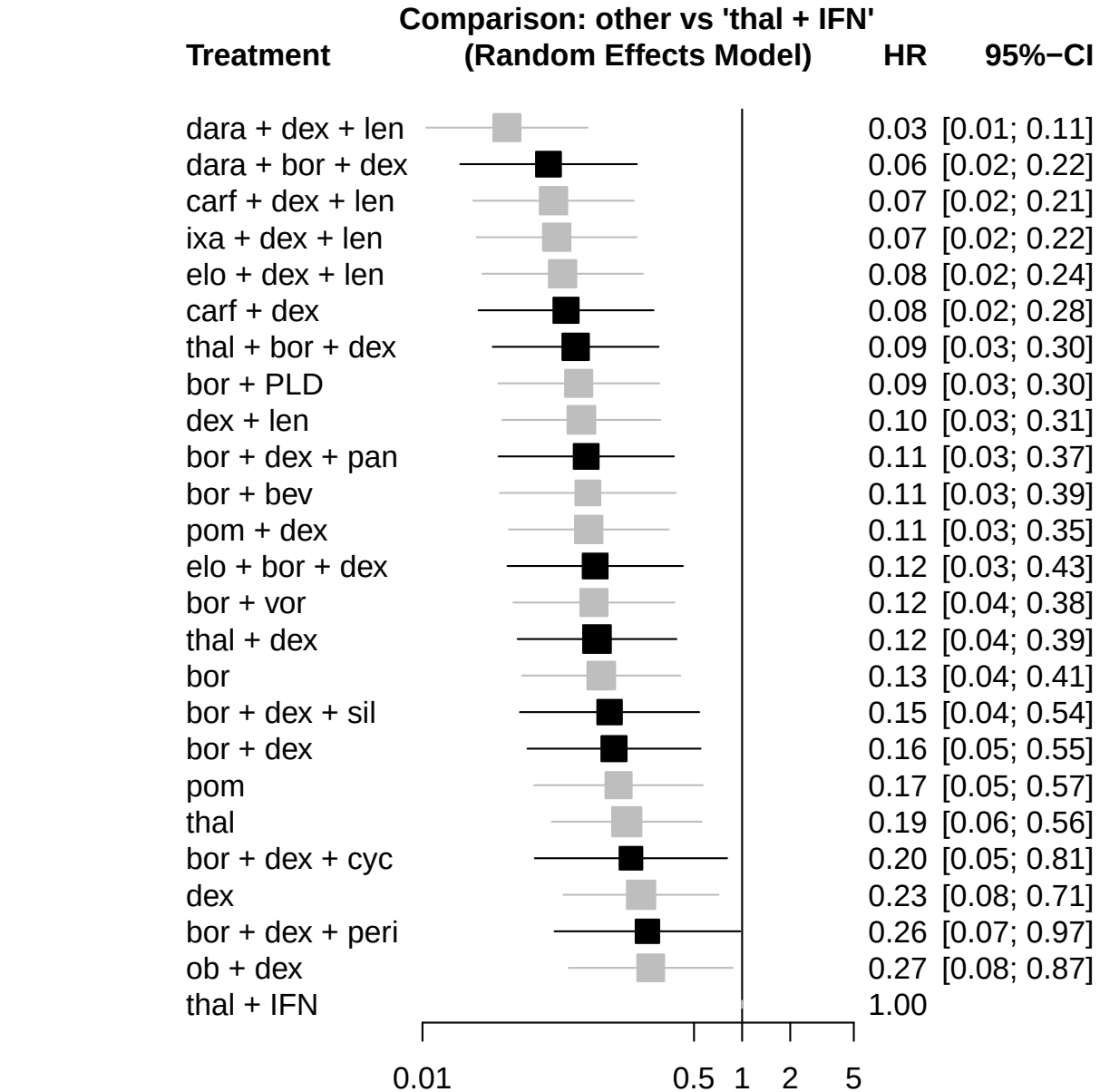


Three interactions (Q = 0.86, df = 4, p = 0.930)



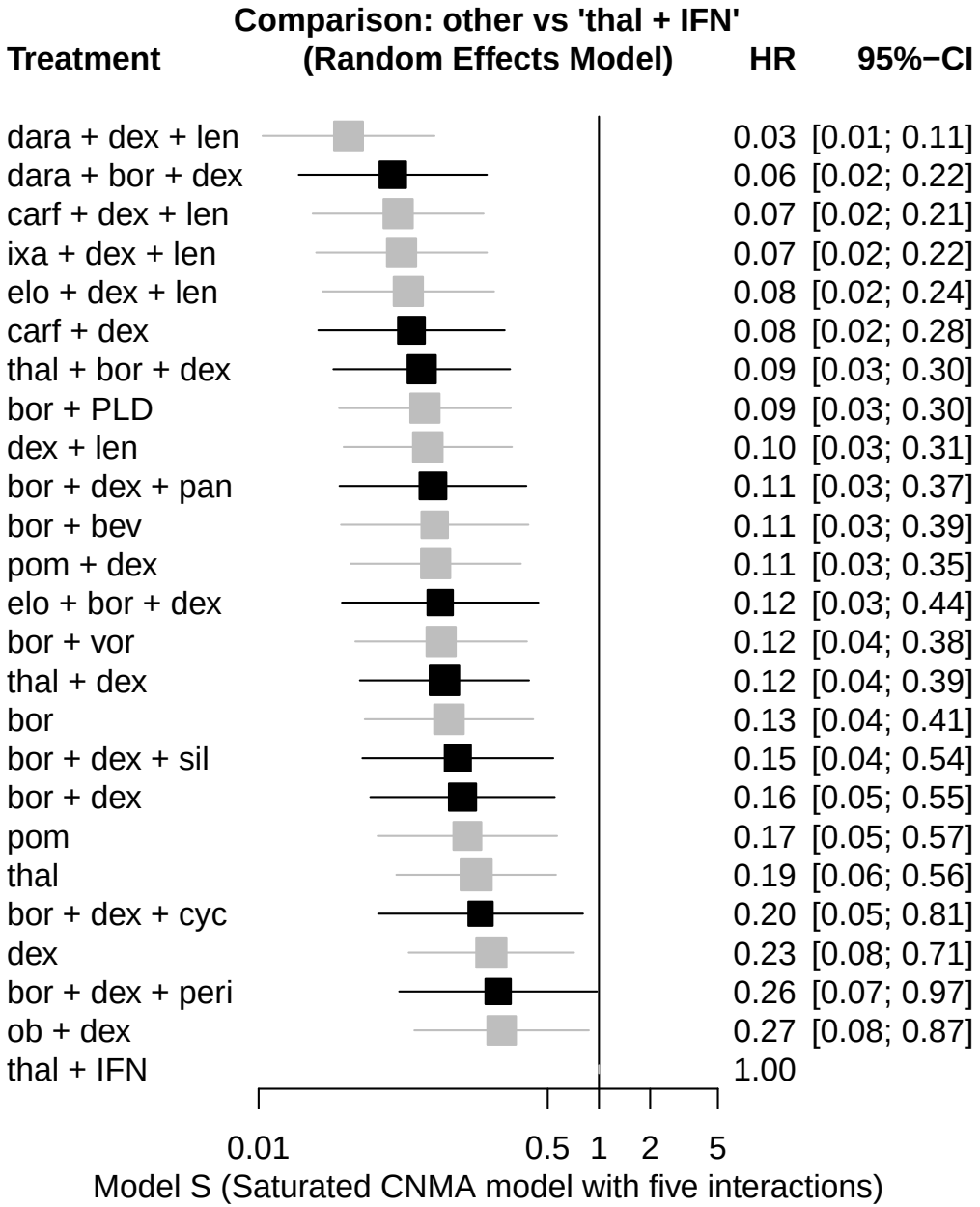
Model E (CNMA model with interactions bor*dex, carf*dex*len and thal*bor*dex)

Four interactions (Q = 0.33, df = 3, p = 0.955)

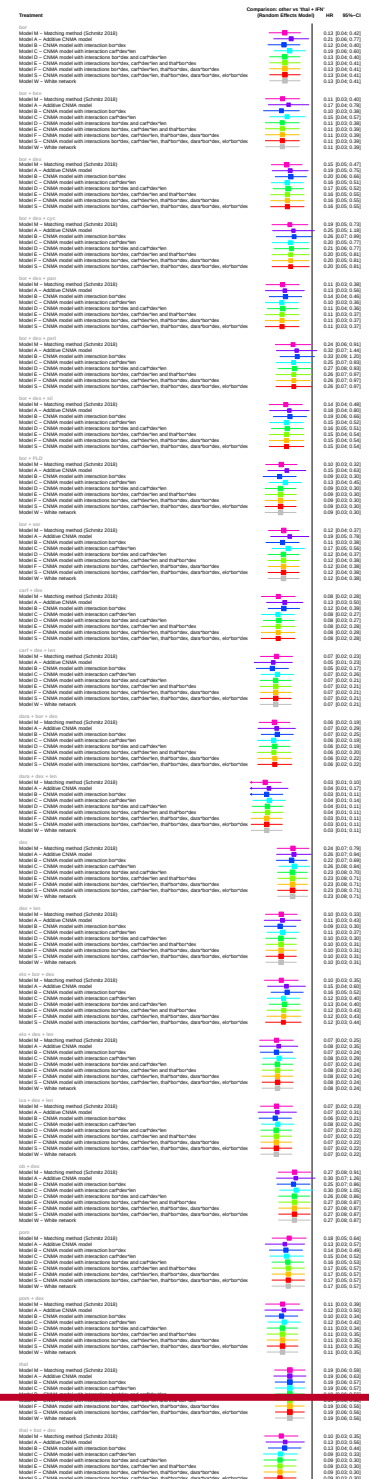


Model F (CNMA model with interactions bor*dex + carf*dex*len + thal*bor*dex + dara*bor*dex)

Saturated model (Q = 0.30, df = 2, p = 0.860)



Compare all models: Forest plot



carf + dex

Model M − Matching method (Schmitz 2018)	0.08	[0.02; 0.28]
Model A − Additive CNMA model	0.13	[0.03; 0.50]
Model B − CNMA model with interaction bor*dex	0.12	[0.04; 0.39]
Model C − CNMA model with interaction carf*dex*len	0.08	[0.02; 0.27]
Model D − CNMA model with interactions bor*dex and carf*dex*len	0.08	[0.03; 0.27]
Model E − CNMA model with interactions bor*dex, carf*dex*len and thal*bor*dex	0.08	[0.02; 0.28]
Model F − CNMA model with interactions bor*dex, carf*dex*len, thal*bor*dex, dara*bor*dex	0.08	[0.02; 0.28]
Model S − CNMA model with interactions bor*dex, carf*dex*len, thal*bor*dex, dara*bor*dex, elo*bor*dex	0.08	[0.02; 0.28]

carf + dex + len

Model M − Matching method (Schmitz 2018)	0.07	[0.02; 0.23]
Model A − Additive CNMA model	0.05	[0.01; 0.23]
Model B − CNMA model with interaction bor*dex	0.05	[0.02; 0.17]
Model C − CNMA model with interaction carf*dex*len	0.07	[0.02; 0.26]
Model D − CNMA model with interactions bor*dex and carf*dex*len	0.07	[0.02; 0.21]
Model E − CNMA model with interactions bor*dex, carf*dex*len and thal*bor*dex	0.07	[0.02; 0.21]
Model F − CNMA model with interactions bor*dex, carf*dex*len, thal*bor*dex, dara*bor*dex	0.07	[0.02; 0.21]
Model S − CNMA model with interactions bor*dex, carf*dex*len, thal*bor*dex, dara*bor*dex, elo*bor*dex	0.07	[0.02; 0.21]
Model W − White network	0.07	[0.02; 0.21]

dara + bor + dex

Model M − Matching method (Schmitz 2018)	0.06	[0.02; 0.19]
Model A − Additive CNMA model	0.07	[0.02; 0.29]
Model B − CNMA model with interaction bor*dex	0.07	[0.02; 0.25]
Model C − CNMA model with interaction carf*dex*len	0.06	[0.02; 0.19]
Model D − CNMA model with interactions bor*dex and carf*dex*len	0.06	[0.02; 0.19]
Model E − CNMA model with interactions bor*dex, carf*dex*len and thal*bor*dex	0.06	[0.02; 0.20]
Model F − CNMA model with interactions bor*dex, carf*dex*len, thal*bor*dex, dara*bor*dex	0.06	[0.02; 0.22]
Model S − CNMA model with interactions bor*dex, carf*dex*len, thal*bor*dex, dara*bor*dex, elo*bor*dex	0.06	[0.02; 0.22]

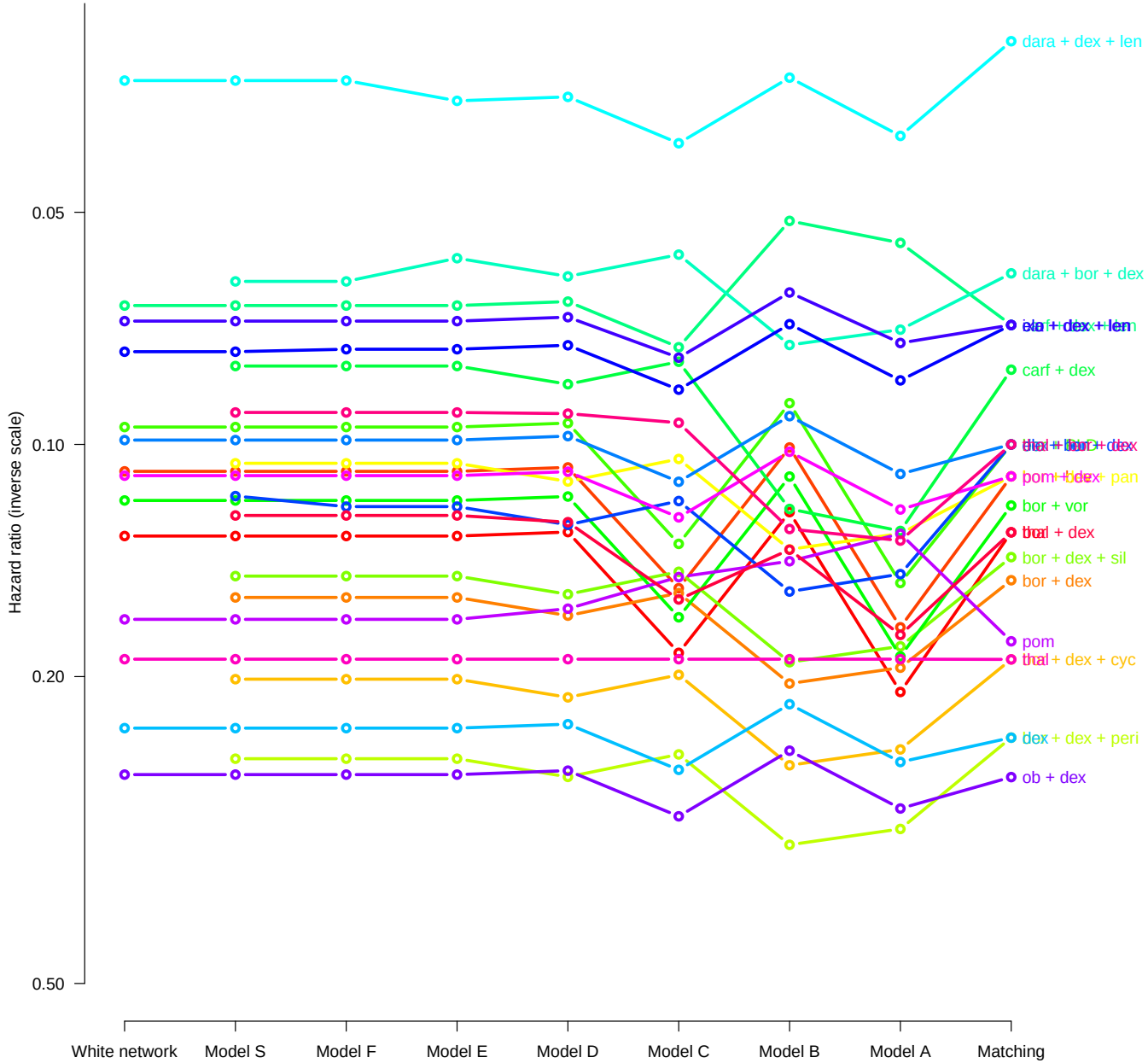
dara + dex + len

Model M − Matching method (Schmitz 2018)	0.03	[0.01; 0.10]
Model A − Additive CNMA model	0.04	[0.01; 0.17]
Model B − CNMA model with interaction bor*dex	0.03	[0.01; 0.11]
Model C − CNMA model with interaction carf*dex*len	0.04	[0.01; 0.14]
Model D − CNMA model with interactions bor*dex and carf*dex*len	0.04	[0.01; 0.11]
Model E − CNMA model with interactions bor*dex, carf*dex*len and thal*bor*dex	0.04	[0.01; 0.11]
Model F − CNMA model with interactions bor*dex, carf*dex*len, thal*bor*dex, dara*bor*dex	0.03	[0.01; 0.11]
Model S − CNMA model with interactions bor*dex, carf*dex*len, thal*bor*dex, dara*bor*dex, elo*bor*dex	0.03	[0.01; 0.11]
Model W − White network	0.03	[0.01; 0.11]

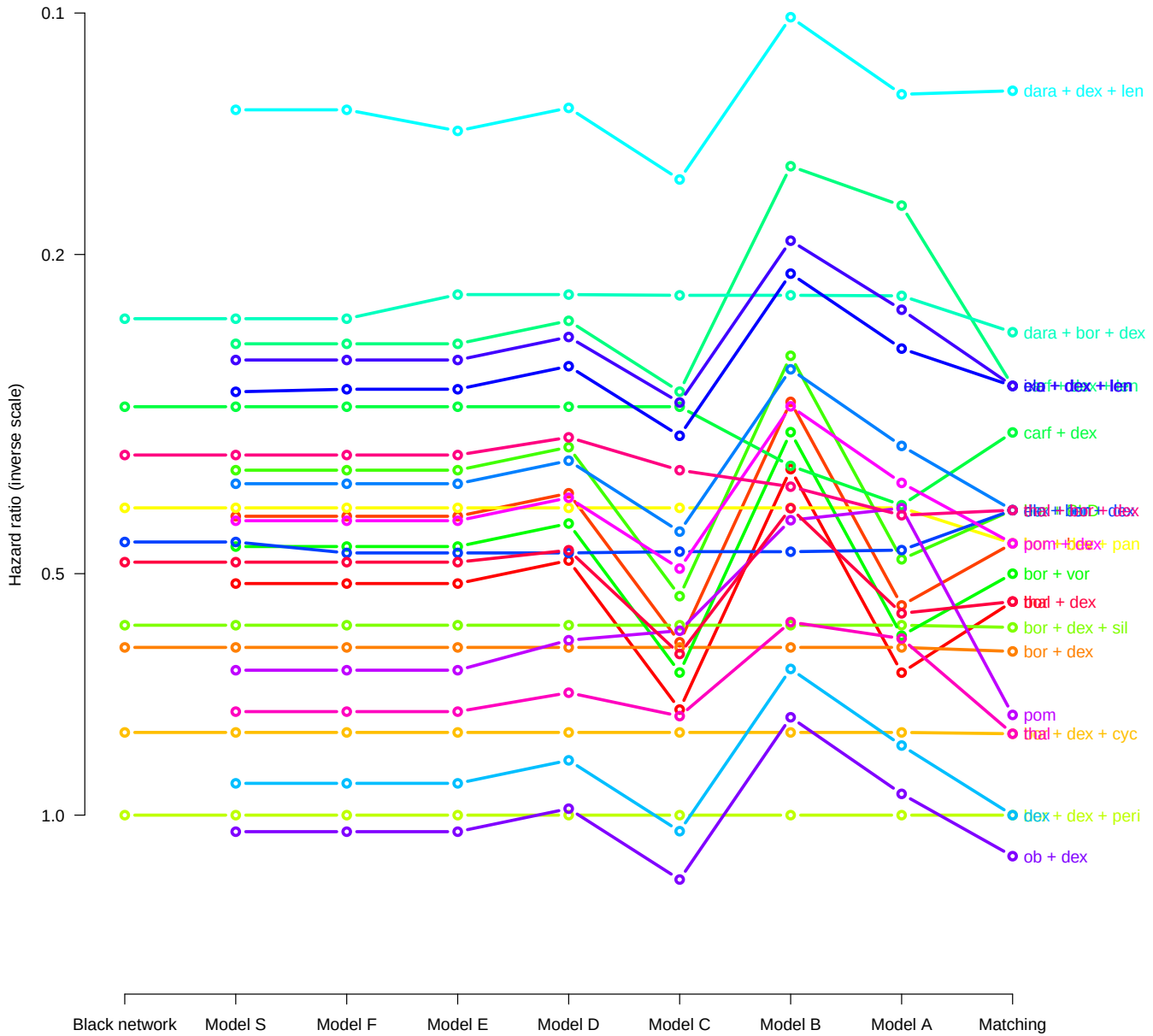
dex

Model M − Matching method (Schmitz 2018)	0.24	[0.07; 0.79]

Compare all models to the white network: Line plot

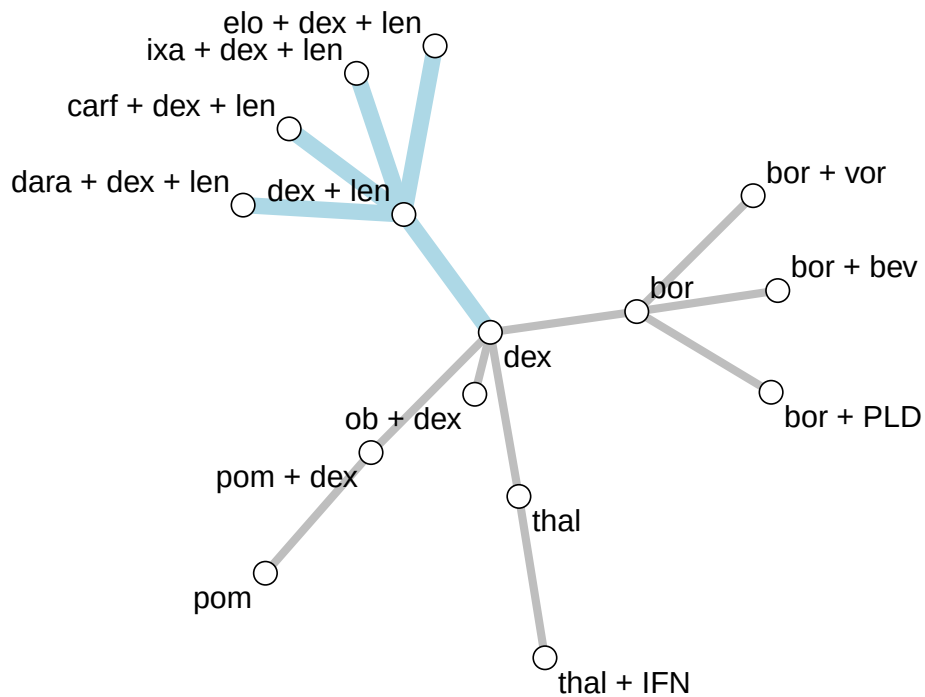


Compare all models to the black network: Line plot



Possible overparameterization in CNMA models

- In a CNMA model only observed interactions can be tested
- Some observed interactions can be formally included, but do not add to the model because they are not estimable
  - Example dex + len:
    Either compared to X + dex + len (estimates X) or to dex alone (such that dex*len cannot be separated from len alone)



Discussion I

- All models rely on assumptions
  - Matching method assumes no unmeasured confounders
  - CNMA assumes no unmeasured interactions
    - Forward selection - from sparse to rich: stepwise mitigate the additivity assumptions
    - Backward selection - from rich to sparse: isolate only a single component (or a small number of components) and thus avoid assumptions of additivity as far as possible
  - All models make the usual assumptions of NMA, such as transitivity of effect moderators across different studies
- Limitation of matching method
  - Relies on external evidence from observational studies
  - Time-consuming

Discussion II

- Aims of CNMA
  - To fit the model to the given data
- This case study
  - allowed to fit an overarching model to both networks
    - while perfectly reproducing (via interactions) the analyses of the separate networks
  - compared the results to those of the matching method
    - not necessarily to reproduce them, but
    - finding wide agreement with the matching method results
- Ideally, clinical knowledge should be incorporated to inform the model and critically assess the results

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 R package **netmeta** [Rücker et al., 2019a]
  - `netcomb()` for connected networks
  - `discomb()` for disconnected networks
- Similar (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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Connecting networks by isolating a component (thal)