Model Based Network Meta-Analysis:

A framework for evidence synthesis of dose-response models in randomised controlled trials

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Sofia Dias

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BayesPharma, Leuven, 18 May 2016

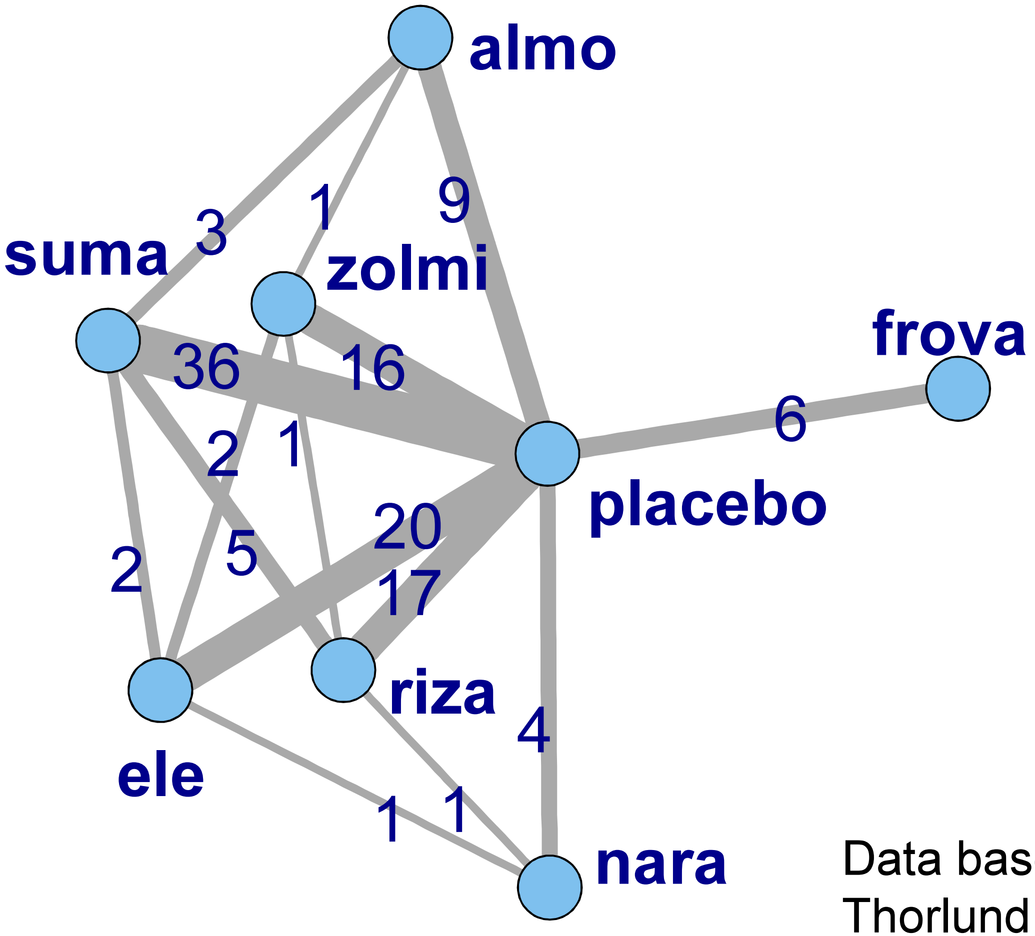
Motivation

- Network meta-analysis (NMA) lets us compare many treatments and assess consistency of treatment effects in a connected network
- Model based meta-analysis (MBMA) incorporates dose and/or time course information in a meta-analysis
- We propose a framework to combine both – MBNMA

Structure

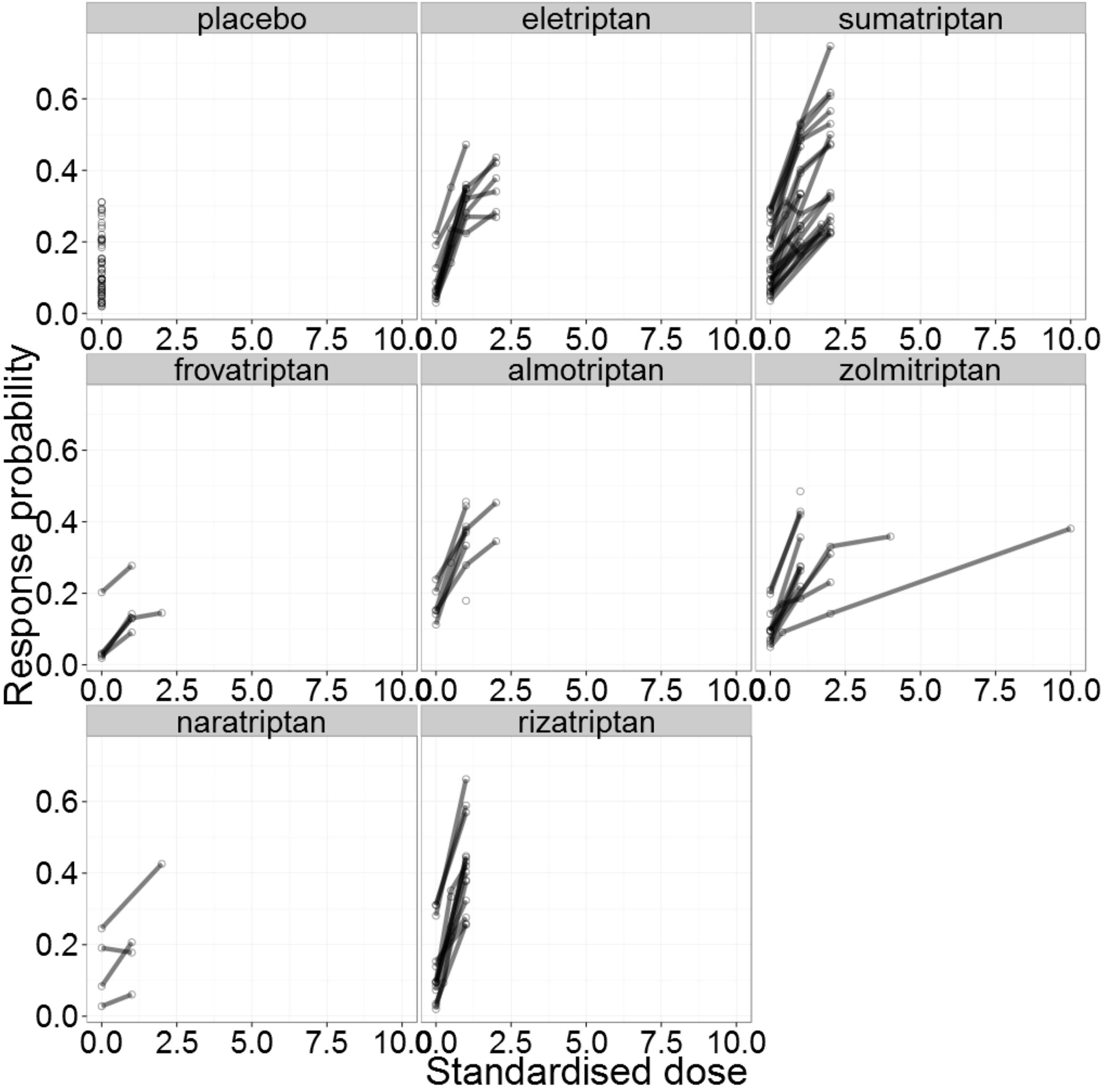
- Example data
- Dose in NMA
- Dose response models
- MBNMA methodology
- Evidence consistency

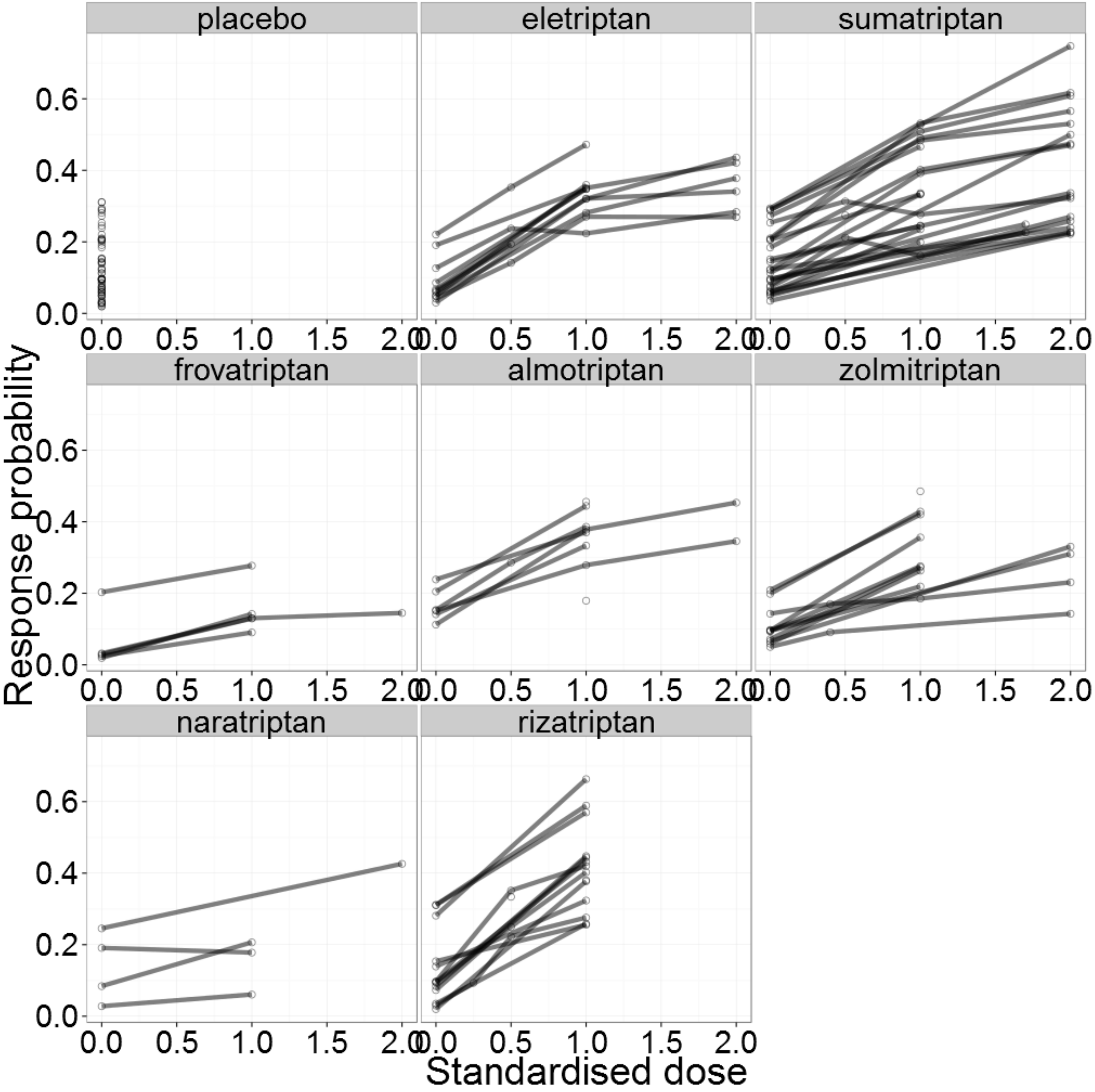
Triptans for migraine relief



Outcome: proportion of patients headache free at 2 hours

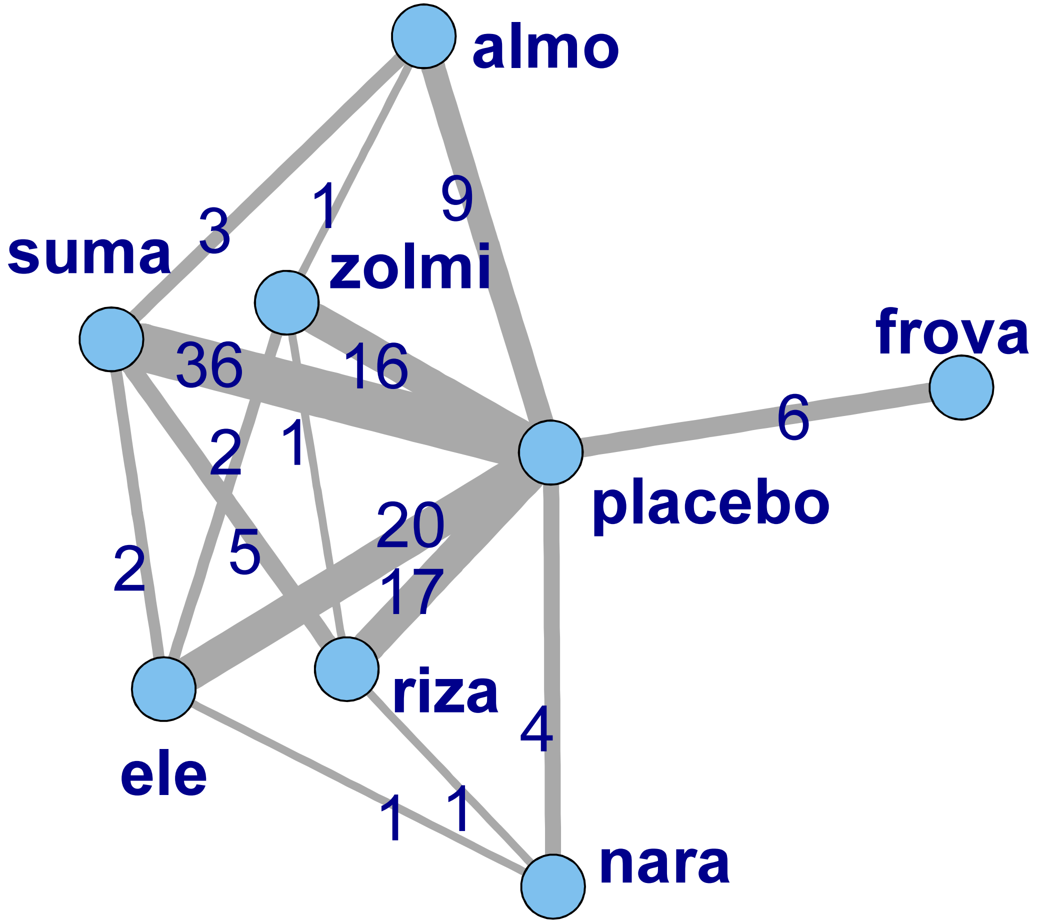
Data based on:
Thorlund (2014), Cephalagia (34) 258-67


placebo
eletriptan
sumatriptan
frovatriptan
almotriptan
zolmitriptan
naratriptan
rizatriptan
Response probability
0.0
0.2
0.4
0.6
0.0
2.5
5.0
7.5
10.0
Standardised dose


placebo
eletriptan
sumatriptan
frovatriptan
almotriptan
zolmitriptan
naratriptan
rizatriptan
Response probability
Standardised dose
0.0
0.2
0.4
0.6
0.0
0.5
1.0
1.5
2.0

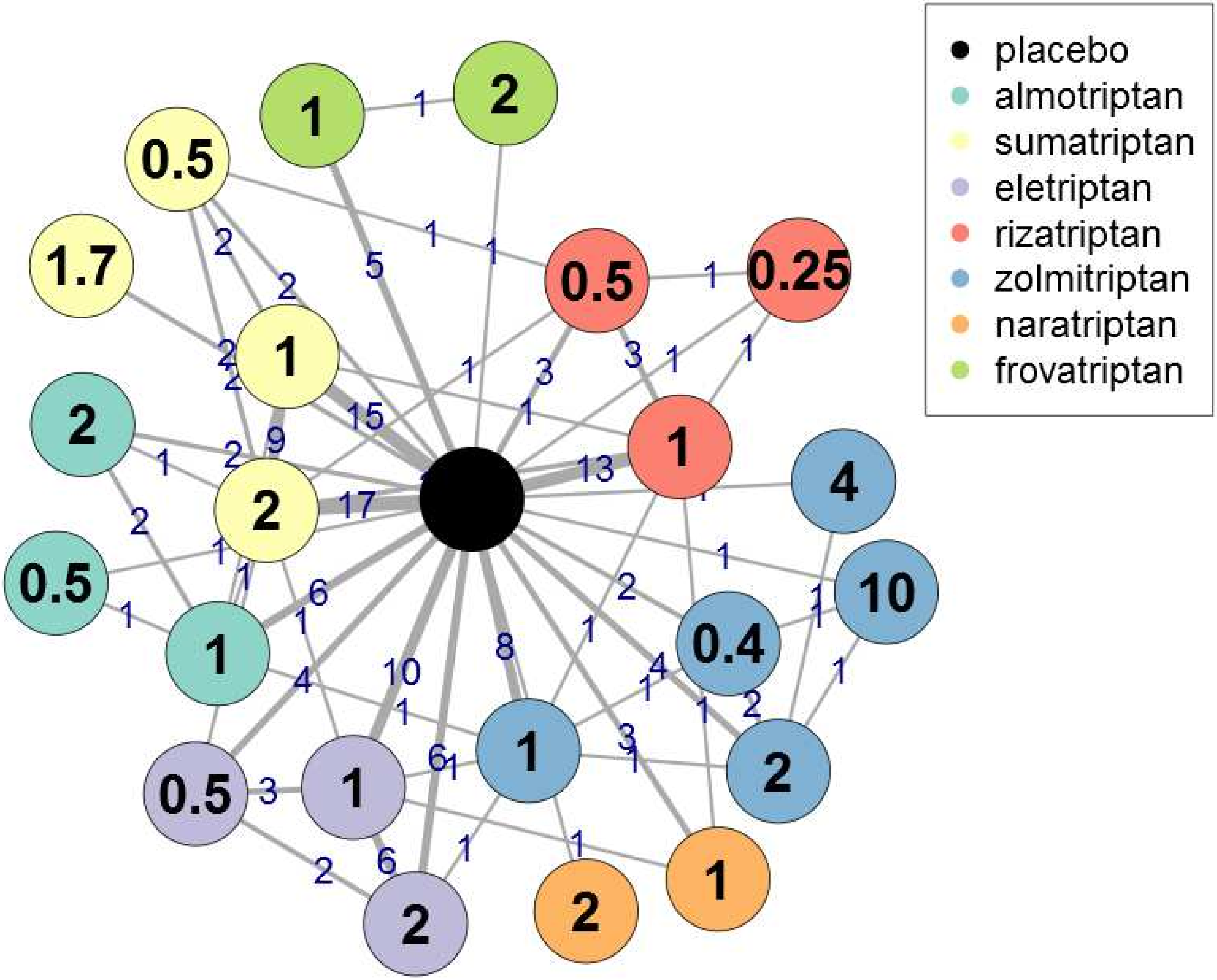
Modelling approaches in NMA

- Single dose for each treatment
    - Does not use all available information
- “Lump” doses?
    - Ignores dose response
    - Risk of inconsistency and heterogeneity
    - How to interpret?


almo
suma
zolmi
frova
placebo
ele
riza
nara
3
1
9
36
16
6
2
1
20
17
2
5
4
1
1

Modelling approaches in NMA

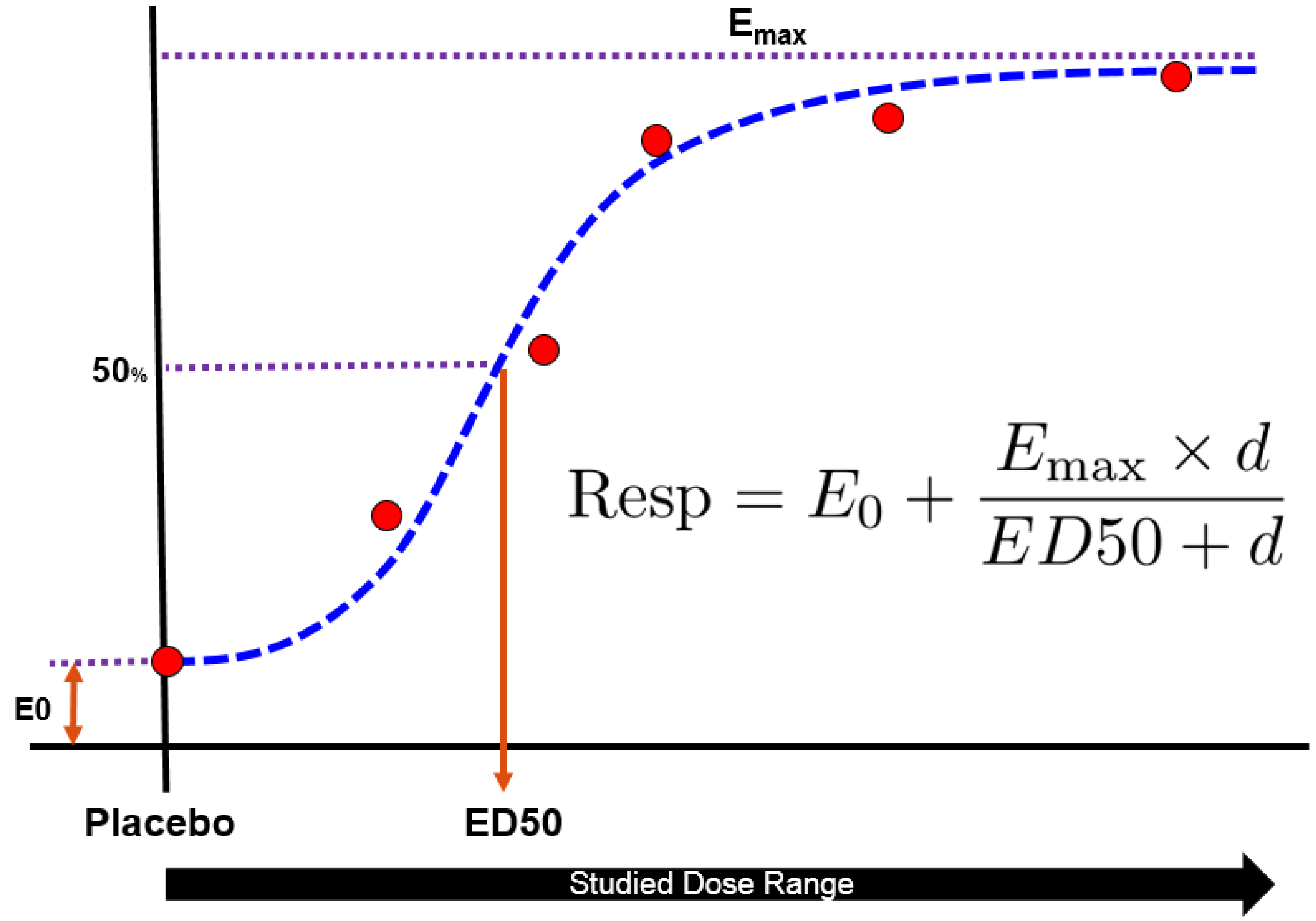
- Treat each agent-dose combination as a separate treatment?
  - Sparse network. Ignores dose-response


● placebo
● almotriptan
● sumatriptan
● eletriptan
● rizatriptan
● zolmitriptan
● naratriptan
● frovatriptan
1
2
0.5
1.7
1
0.5
0.25
2
1
2
1
4
0.5
10
1
0.4
0.5
1
1
2
2
2
1
5
1
1
2
2
2
1
3
3
1
1
2
2
15
9
1
2
1
13
17
2
1
1
1
1
6
1
2
1
1
1
8
1
4
10
4
1
1
2
1
3
6
1
1
3
1
1
2
6
1

Modelling approaches in NMA

- Treat each treatment dose combination as a separate treatment?
  - Sparse network. Ignores dose-response
- Model dose response curve.

Emax models



$$\text{Resp} = E_0 + \frac{E_{\text{max}} \times d}{ED50 + d}$$

Model-based NMA

- Extend NMA framework

$$r_{ik} \sim \text{Binomial}(\theta_{ik}, n_{ik})$$

$$\begin{aligned} \text{logit}(\theta_{ik}) &= \mu_i & \text{when } k = 1 \\ &= \mu_i + \delta_{ik} & \text{otherwise} \end{aligned}$$

Higgins P T et al (1996) Borrowing Strength from External Trials in a Meta-Analysis *Stats. in Medicine 15(24), 2733-2749*
Dias, S et al. (2013). Evidence synthesis for decision making 2: a generalized linear modeling framework … *Medical Decision Making 33*(5), 607–17.

$$f(x,t) = \frac{\mathrm{Emax}_t \cdot x}{\mathrm{ED50}_t + x}$$

- Apply consistency equation at the level of the dose response curve:
  - For a 2 arm trial:

$$\delta_{i,k} \sim \mathrm{N}(f(x_{ik}, t_{ik}) - f(x_{i1}, t_{i1}), \sigma^2)$$

  - Apply multi-arm correction for >2 arm trials (see Dias et al.)
- Can consider other dose-response models

Model fitting

- Models fitted using JAGS
- Vague priors used throughout
- Model ED50 on log scale
- Assume class effects on Emax and ED50
  - ED50 class effect required for parameter estimation (requires dose standardisation)
  - Emax class effect improved model fit

Plummer (2003). JAGS: A Program for Analysis of Bayesian Graphical Models Using Gibbs Sampling, Proceedings of the 3rd International Workshop on Distributed Statistical Computing (DSC 2003)

Methods

- Compare:
  - Lumped NMA
  - Split NMA
  - Linear model-based NMA
  - Emax model-based NMAs
    - Emax and ED50 class effect
- Assess goodness of fit using DIC, residual deviance and heterogeneity

Results

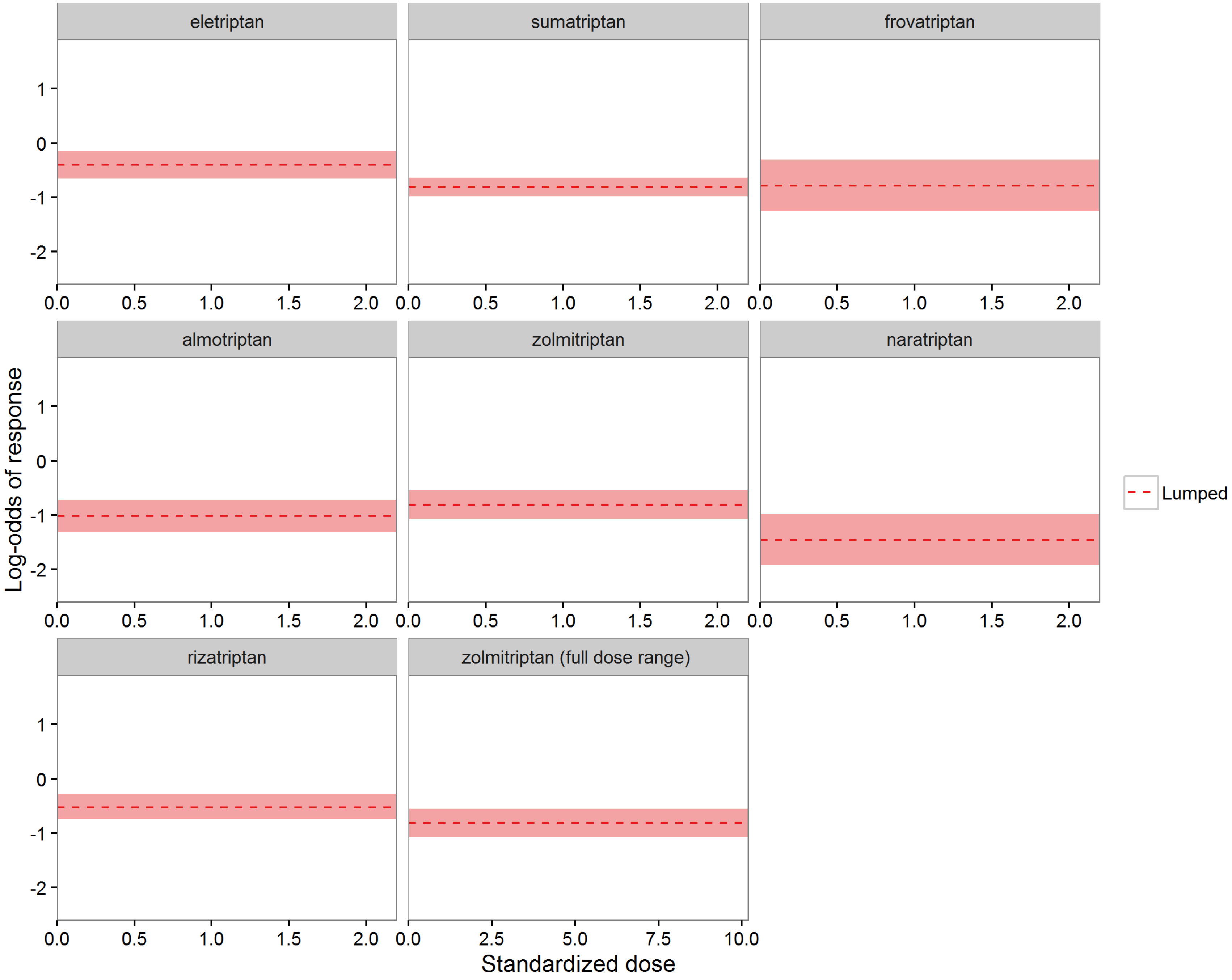
Model	DIC	Residual Deviance	σ
Lumped NMA	330.5	189.0	0.373 (0.289 to 0.469)
Split NMA	325.2	189.6	0.270 (0.178 to 0.376)

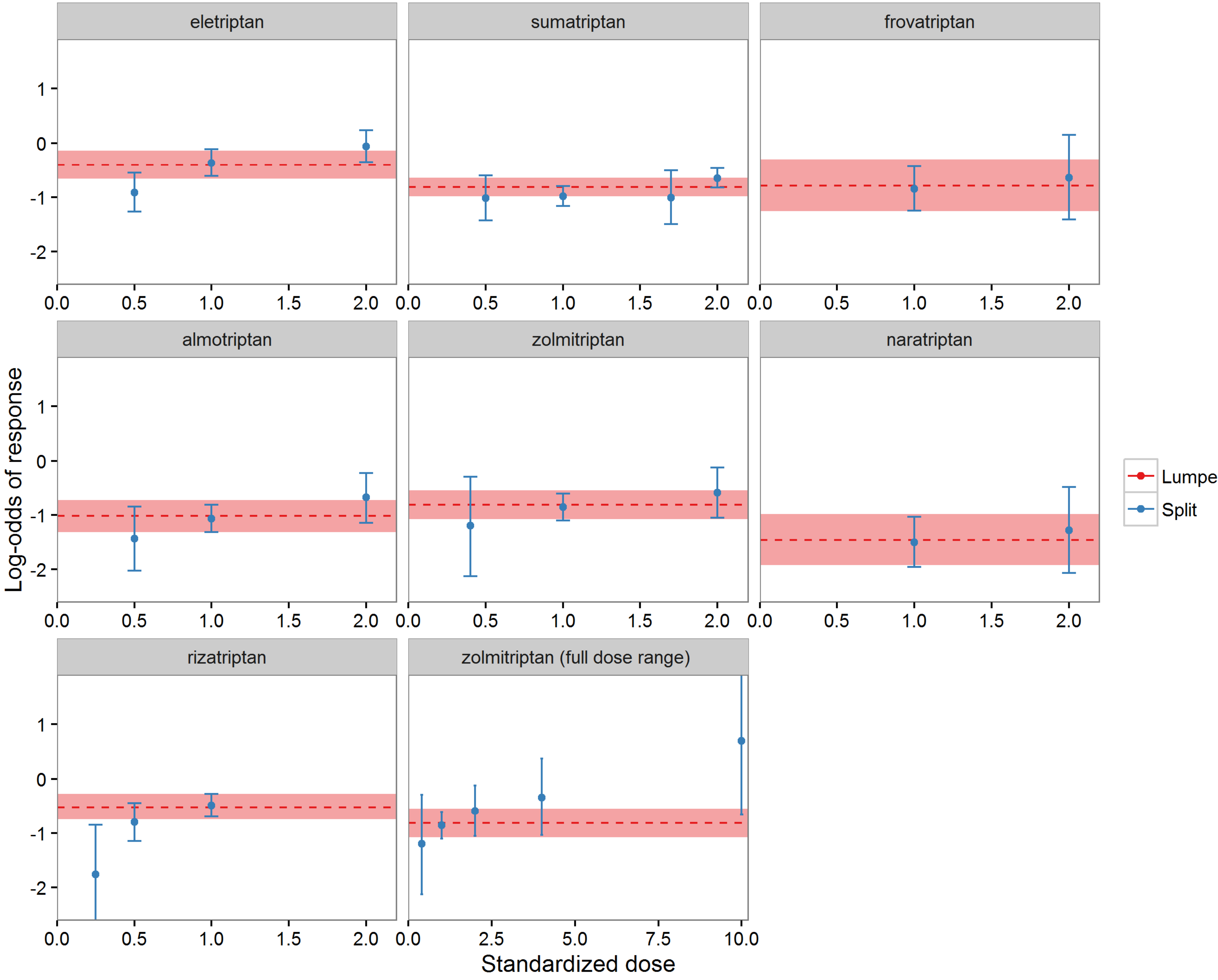
182 data points

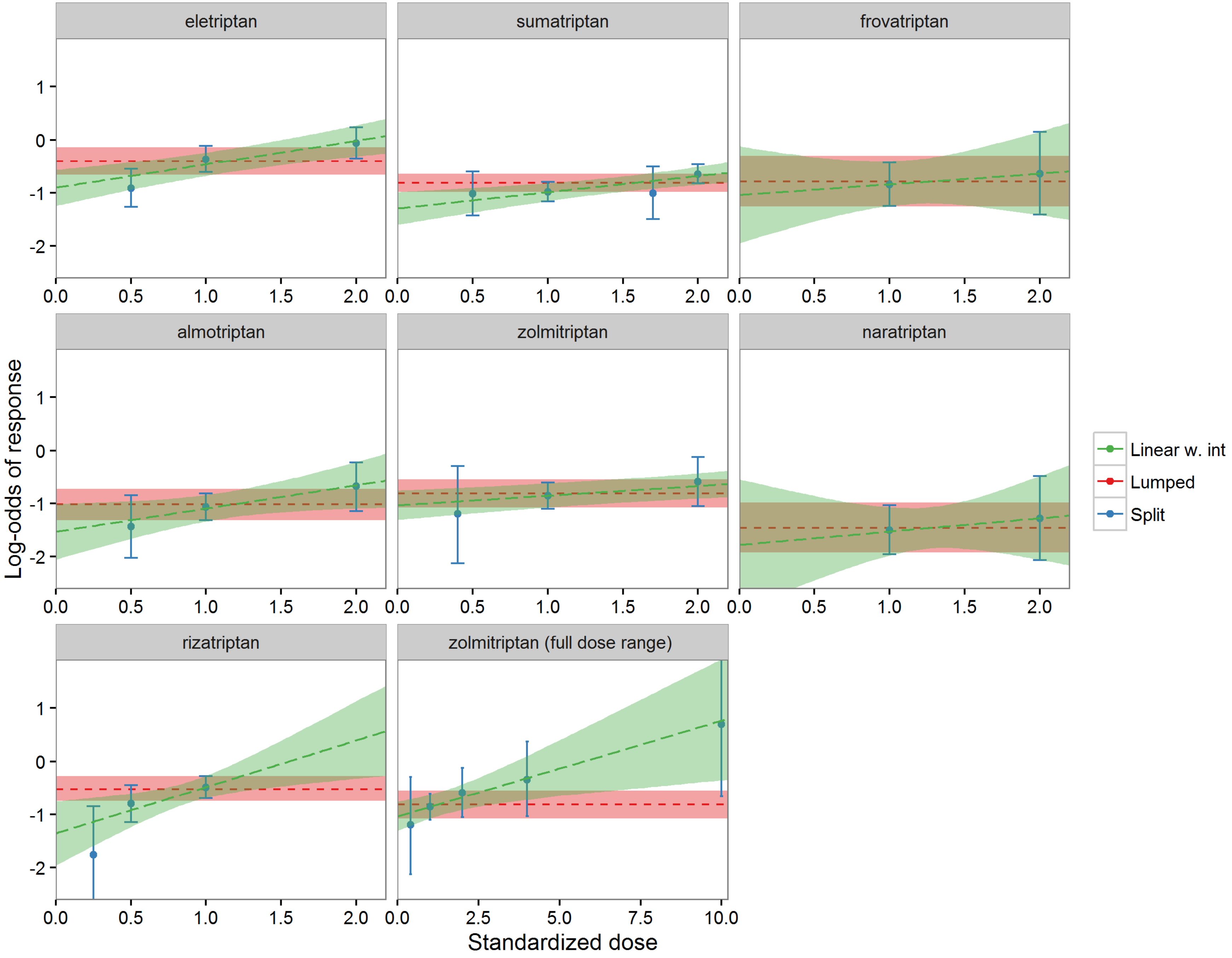
Results

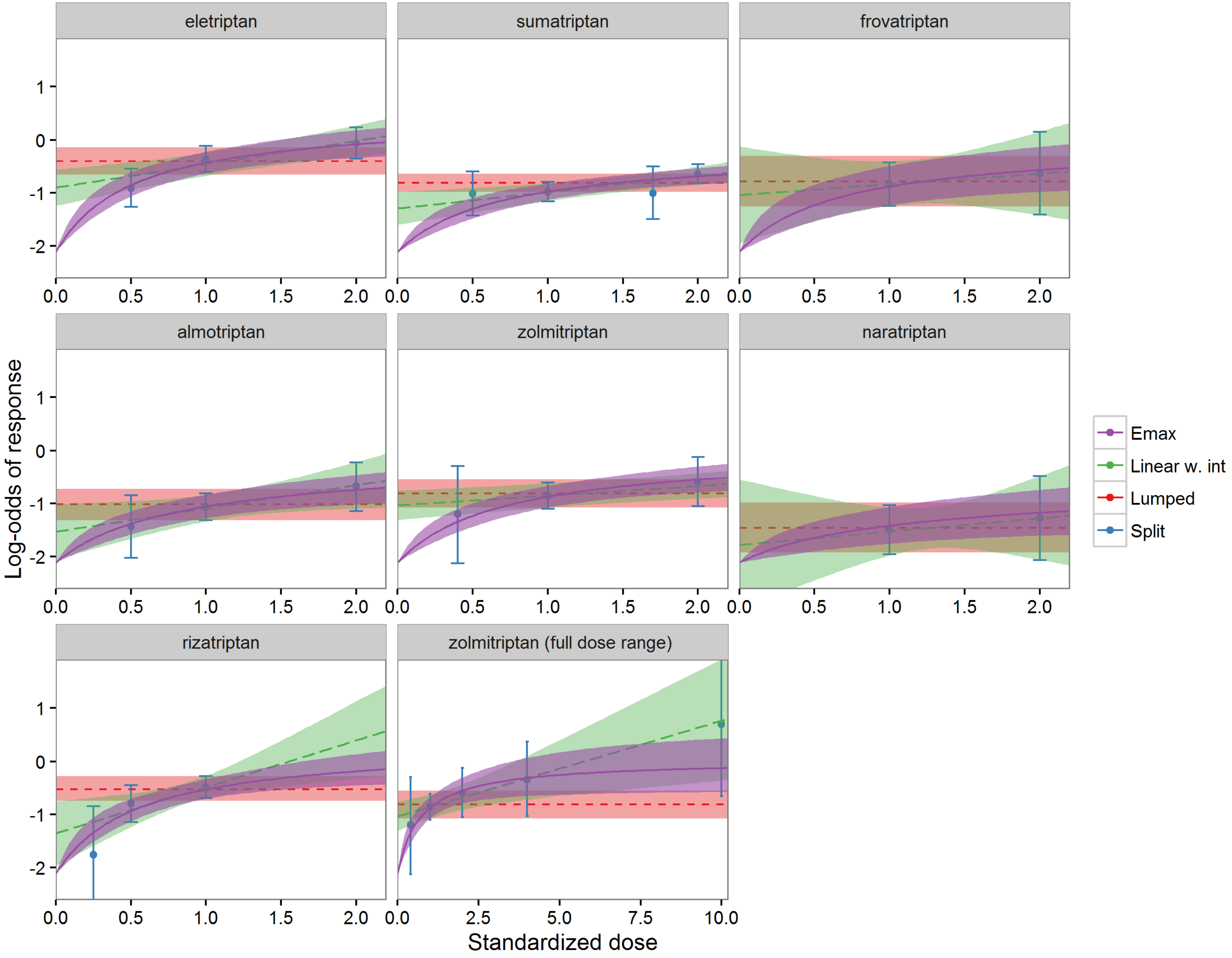
Model	DIC	Residual Deviance	σ
Lumped NMA	330.5	189.0	0.373 (0.289 to 0.469)
Split NMA	325.2	189.6	0.270 (0.178 to 0.376)
Linear MBNMA (w. int)	321.0	188.7	0.274 (0.192 to 0.371)
Emax (ED50 class)	321.8	191.5	0.249 (0.159 to 0.350)
Emax (2x class effects)	318.7	191.9	0.242 (0.160 to 0.335)

182 data points


eletriptan
sumatriptan
frovatriptan
almotriptan
zolmitriptan
naratriptan
rizatriptan
zolmitriptan (full dose range)
Log-odds of response
1
0
-1
-2
0.0
0.5
1.0
1.5
2.0
2.5
5.0
7.5
10.0
Standardized dose
Lumped


eletriptan
sumatriptan
frovatriptan
almotriptan
zolmitriptan
naratriptan
rizatriptan
zolmitriptan (full dose range)
Log-odds of response
Standardized dose
1
0
-1
-2
0.0
0.5
1.0
1.5
2.0
2.5
5.0
7.5
10.0
Lumped
Split


eletriptan
sumatriptan
frovatriptan
almotriptan
zolmitriptan
naratriptan
rizatriptan
zolmitriptan (full dose range)
Log-odds of response
Standardized dose
1
0
-1
-2
0.0
0.5
1.0
1.5
2.0
2.5
5.0
7.5
10.0
Linear w. int
Lumped
Split

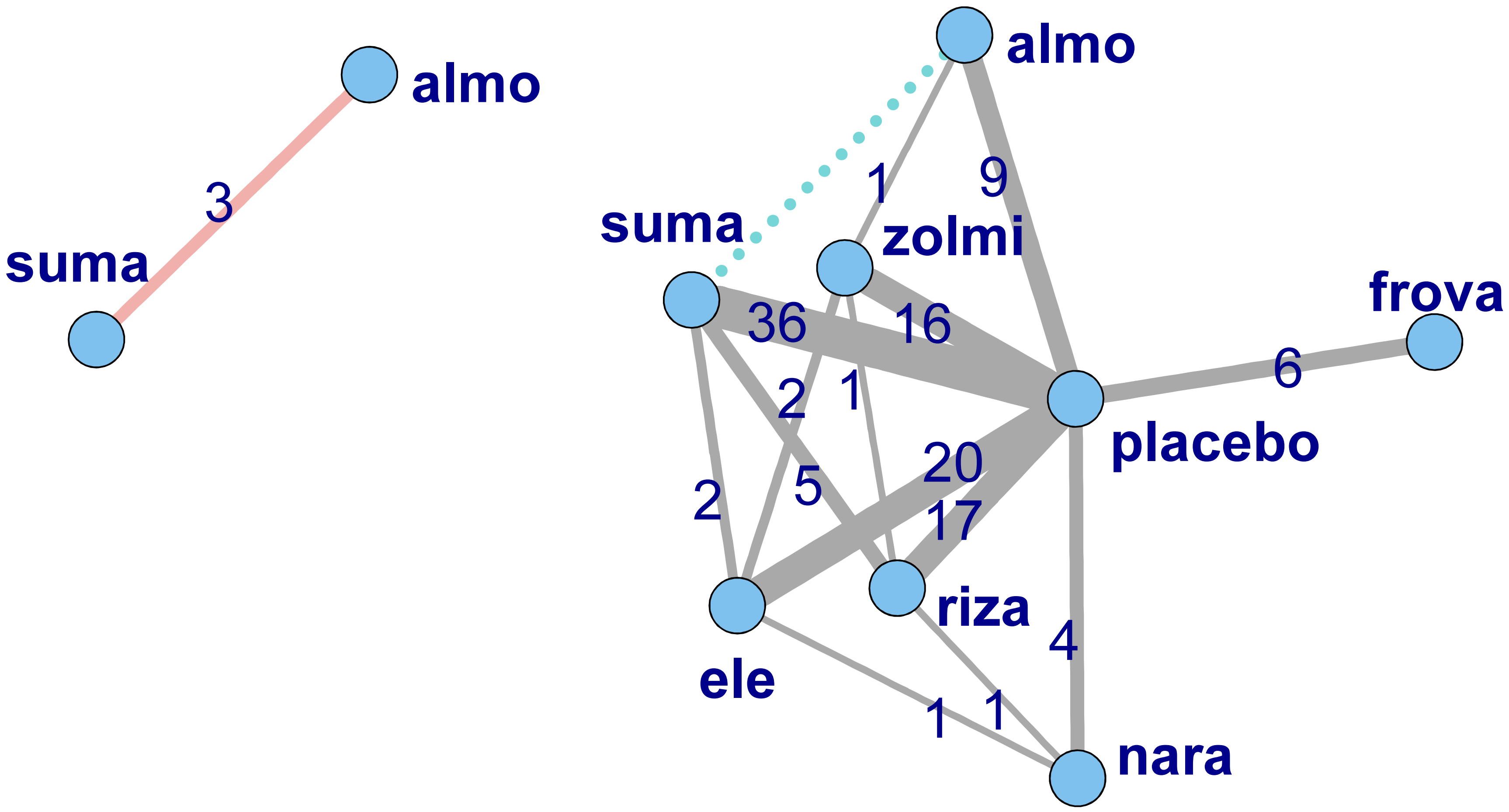

eletriptan
sumatriptan
frovatriptan
almotriptan
zolmitriptan
naratriptan
rizatriptan
zolmitriptan (full dose range)
Log-odds of response
Standardized dose
1
0
-1
-2
0.0
0.5
1.0
1.5
2.0
2.5
5.0
7.5
10.0
Emax
Linear w. int
Lumped
Split

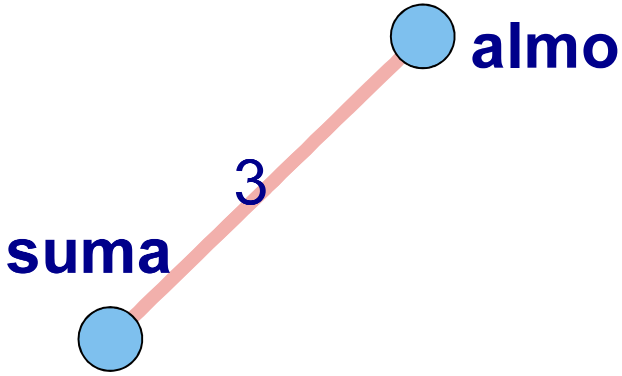
Comparison to NMA and MBMA

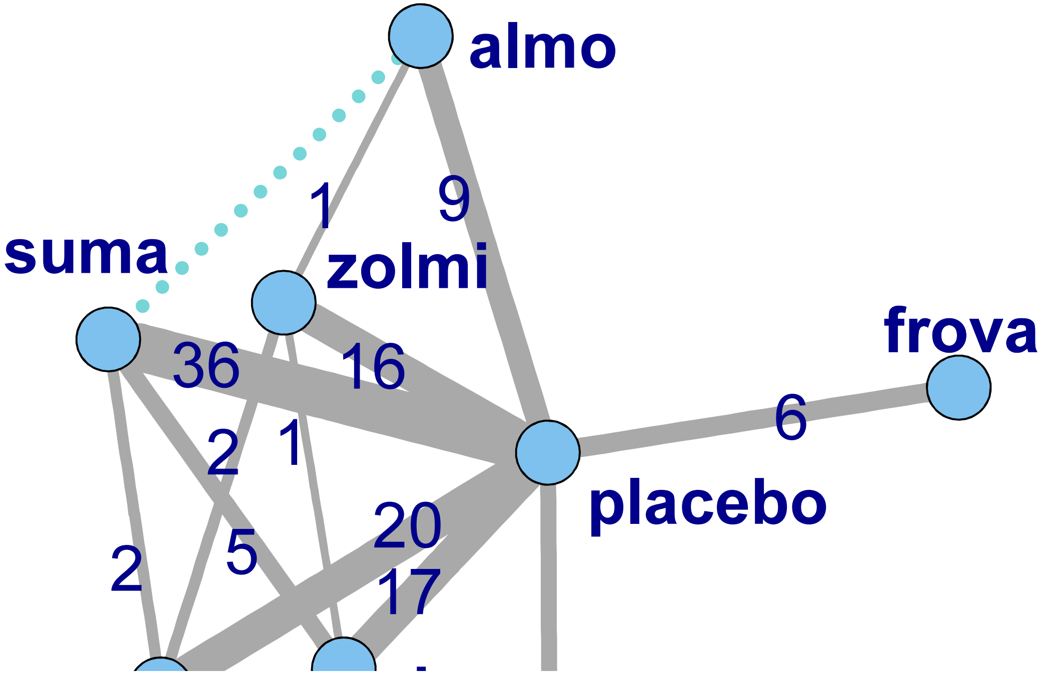
- Avoids lumping doses and/or times
- Makes full use of data
- Allows comparisons in absence of direct evidence
- Interpretable results
- Consistency equations
  - Ensure self consistent estimates
  - Direct and indirect evidence may be in conflict

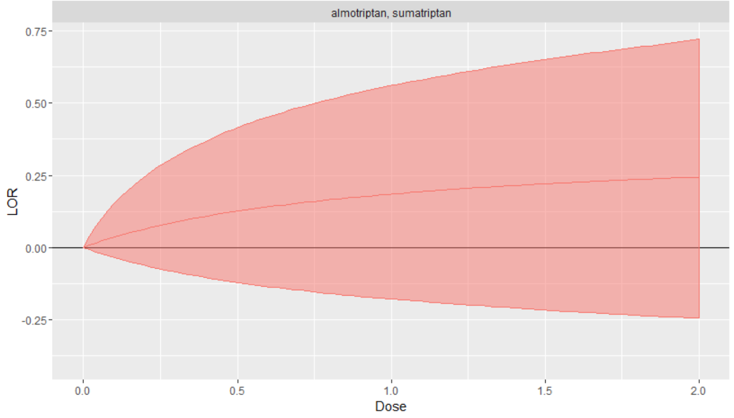
Evidence consistency

- Where direct and indirect evidence exist for a contrast:
  - Extract direct evidence for the contrast to separate network
  - Only indirect evidence for contrast remains
- Compare effect estimates for direct and indirect evidence
  - Need to compare across whole dose range
- Similar idea to node splitting in NMA

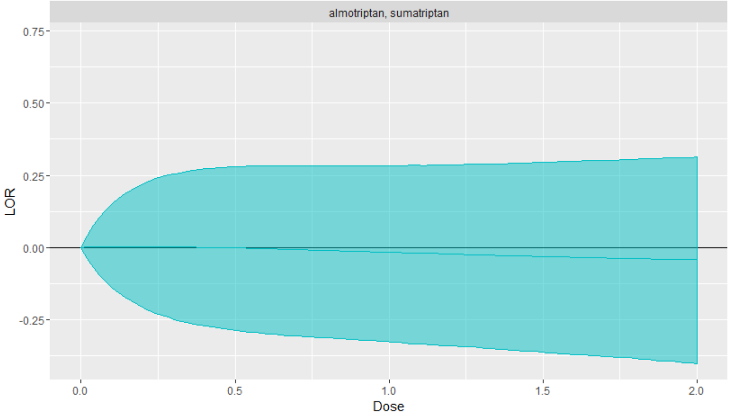

almo
3
suma
almo
1
9
suma
zolmi
frova
36
16
6
2
1
placebo
20
2
5
17
riza
4
ele
1
1
nara



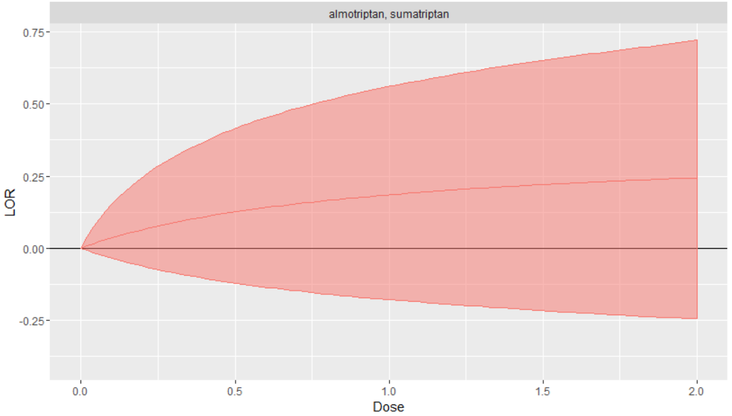




Direct evidence

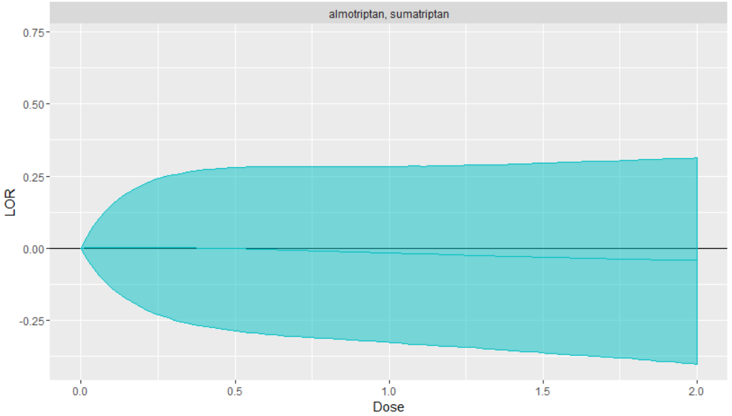


Indirect evidence



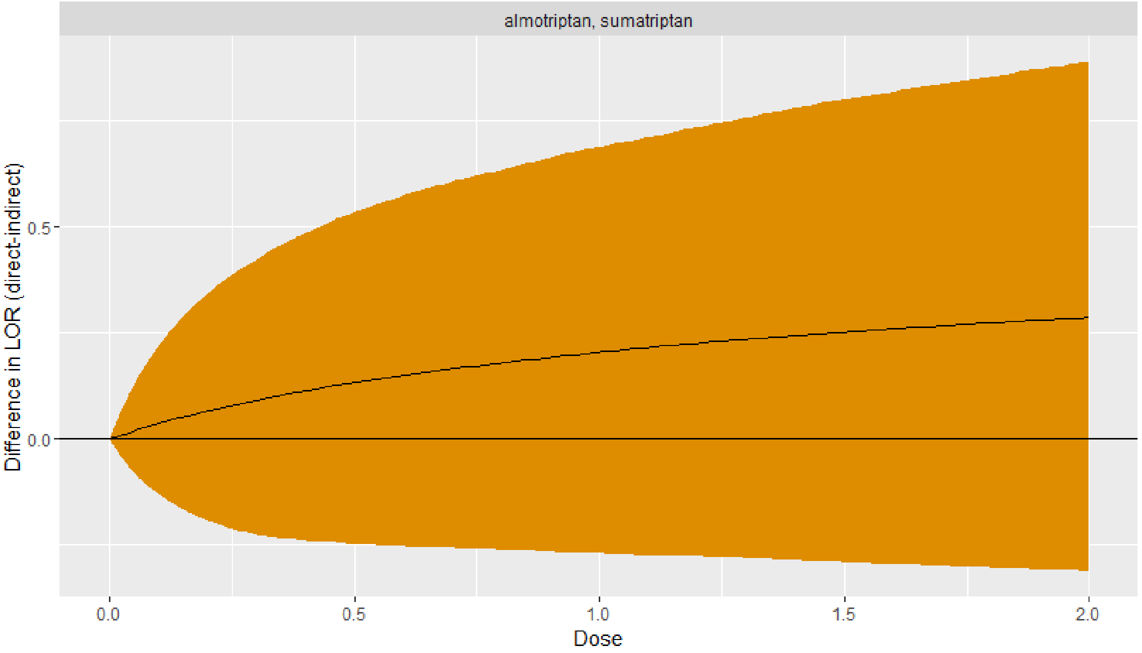
Direct evidence

-



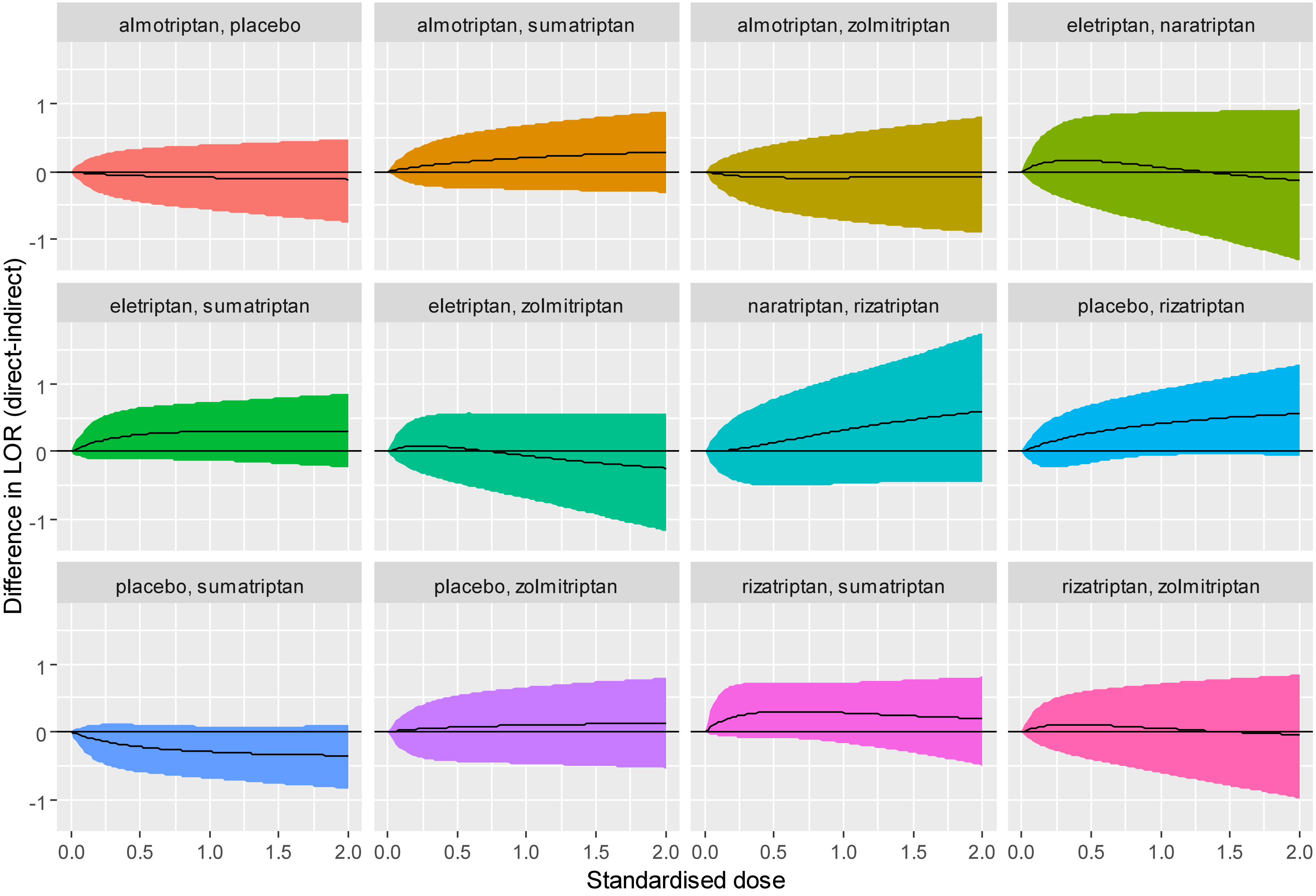
Indirect evidence

=



Evidence consistency

- We fit models for direct and indirect evidence simultaneously
  - Sharing σ
  - Sharing $\overline{ED50}$ and σ_{ED50}, $\overline{Emax}$ and σ_{Emax}
    - Required since limited direct evidence on some contrasts
    - May obscure inconsistency
  - Repeat for each loop of evidence


almotriptan, placebo
almotriptan, sumatriptan
almotriptan, zolmitriptan
eletriptan, naratriptan
eletriptan, sumatriptan
eletriptan, zolmitriptan
naratriptan, rizatriptan
placebo, rizatriptan
placebo, sumatriptan
placebo, zolmitriptan
rizatriptan, sumatriptan
rizatriptan, zolmitriptan
Difference in LOR (direct-indirect)
1
0
-1
0.0
0.5
1.0
1.5
2.0
Standardised dose

Evidence consistency

- 12 Loops of evidence
- No evidence of inconsistency between direct and indirect evidence on any contrast
- Shared class effects may obscure inconsistency since common means assumed

- Developing cross-validation type approach to avoid estimating model for direct evidence

Discussion and Future work

- Simulation study
  - Explore data requirements & model performance
- Cross validation for evidence consistency
- Other functional forms of dose response
- Incorporation of dose and time course information

Acknowledgements

Nicky Welton
Sofia Dias

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Martin Boucher

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ConDuCT Hub

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