Sharing information across patient subgroups to draw conclusions from sparse treatment networks

Theodoros Evrenoglou

Silvia Metelli, Johannes-Schreider Thomas, Spyridon Siafis, Stefan Leucht, Anna Chaimani

Université Paris Cité, Research Center of Epidemiology & Statistics (CRESS-UMR1153), Inserm, France

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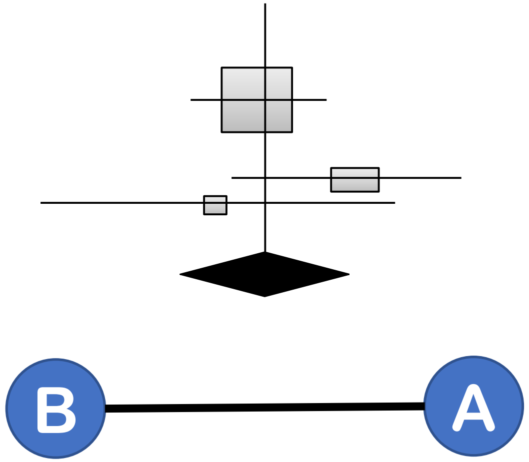
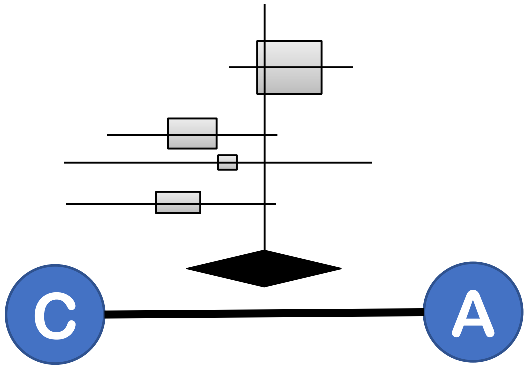
Introduction to Network Meta-Analysis (NMA)



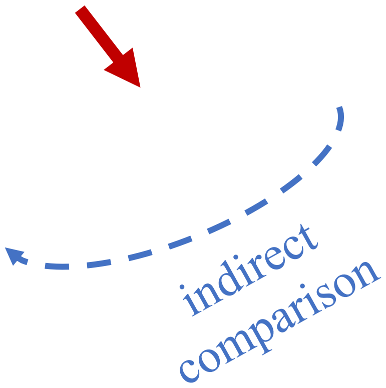


Introduction to Network Meta-Analysis (NMA)

Advantages of NMA

- ✓ Allows the comparison of treatments that have never been compared directly in individual studies.
- ✓ Combines both direct and indirect evidence resulting into estimates with highest precision.
- ✓ Allows for a relative ranking of the competing treatments.

Why to perform a NMA?

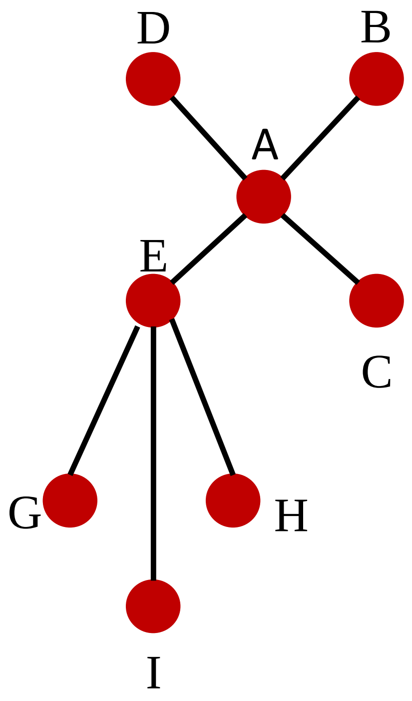


Sparse data in NMA

- The issue refers to poorly connected networks with limited direct comparisons and few studies to inform them

- Statistical challenges in the case of sparse networks
  - large sample approximations fail
  - NMA estimates are expected to be imprecise and biased
  - the formal evaluation of NMA assumptions (transitivity, consistency) is challenging

An example of a sparse network



Aim of our work

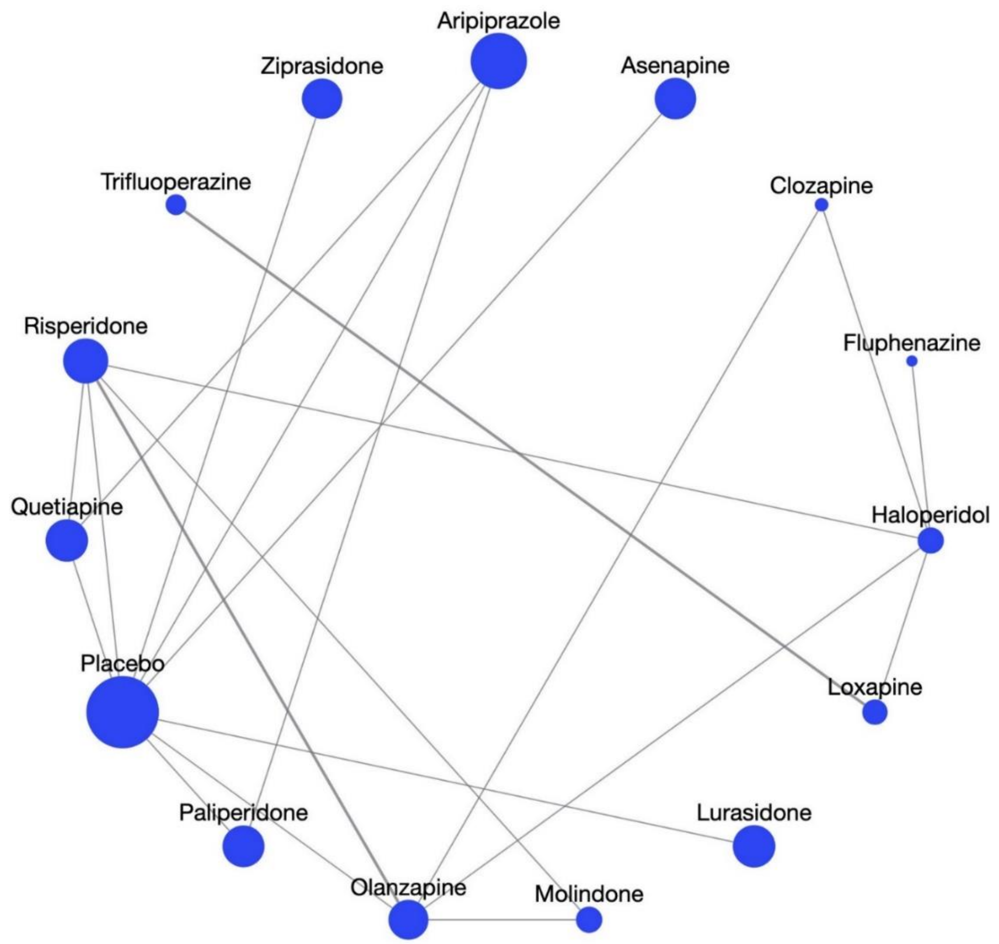
- To propose a framework suitable for NMA of sparse networks in order to
  - improve the precision in the estimation
  - increase the reliability of the final NMA estimates

- Our idea is to use external evidence and to construct informative priors for the analysis of the sparse network

Motivating dataset

- A sparse network of 14 antipsychotics and Placebo
  - **Population of interest**: Children and adolescents (CA)
  - **Outcome of interest**: Reduction in overall schizophrenia symptoms (continuous outcome)

- 21 direct comparisons 19 studies in the network
  - 90% of the direct comparisons are informed by 1 study



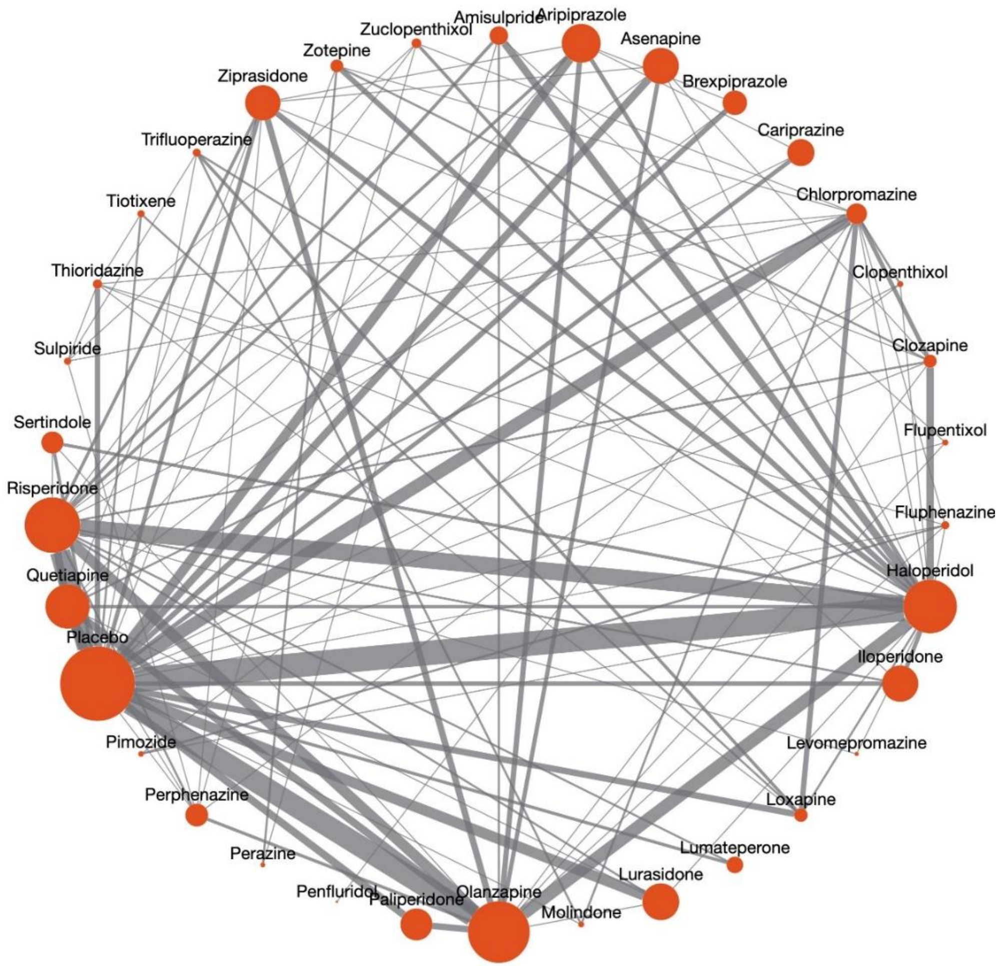
Objective:
Obtain reliable NMA estimates for the effectiveness of the antipsychotics in the population of CA

Krause M, Zhu Y, Huhn M, et al. Efficacy, acceptability, and tolerability of antipsychotics in children and adolescents with schizophrenia: A network meta-analysis. Eur Neuropsychopharmacol J Eur Coll Neuropsychopharmacol. 2018;28(6):659-674. doi:10.1016/j.euroneuro.2018.03.008

The dense network of general patients

- An informative network of 33 antipsychotics and Placebo
  - **<u>Population of interest</u>**: General patients (GP)
  - **<u>Outcome of interest</u>**: Reduction in overall schizophrenia symptoms (continuous outcome)

- 116 direct comparisons and 255 studies in the network
  - No common studies between the two networks



<u>Main goal</u>

Borrow strength from the network of GP to analyze the network of CA

Huhn M, Nikolakopoulou A, Schneider-Thoma J, et al. Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. Lancet Lond Engl. 2019;394(10202):939-951. doi:10.1016/S0140-6736(19)31135-3

How to borrow strength?

Naïve synthesis:

1. Analyze the 2 populations together, or
2. Use **directly** NMA estimates of GP as prior information for CA

Assumptions

- We assume no population difference
- We assume that they are equivalent sources

implausible assumptions

We use a two stage approach:

✓ At the first stage we extrapolate the results of the dense network of GP to CA

✓ At the second stage we use the predictions of the extrapolations to form informative priors and we analyze the network of CA

Notation and general settings

- Let y_{ik} denote the observed mean for the treatment k in study i

Within-studies assumption: $y_{ik} \sim N(\theta_{ik}, sd_{ik}^2)$

- Let $\delta_{i,1k} = \frac{\theta_{ik}-\theta_{i1}}{sd_i^{pooled}}$ denote the SMD between treatment k versus the baseline treatment 1 in study i

Across-studies assumption: $\delta_i \sim N_{K_i-1}(\boldsymbol{\mu}, \boldsymbol{\Sigma})$

arms in study i

matrix structure: τ^2 in the diagonal, $\frac{\tau^2}{2}$ in the off diagonal

- Under the consistency assumption, $\mu_{kl} = \mu_{bl} - \mu_{bk}$

1st stage: Extrapolating GP results to the CA

- At this stage we only analyze the network of GP
  - we reduce the network to include only the 15 interventions that exists for CA
  - we use a modified NMA model to analyze GP

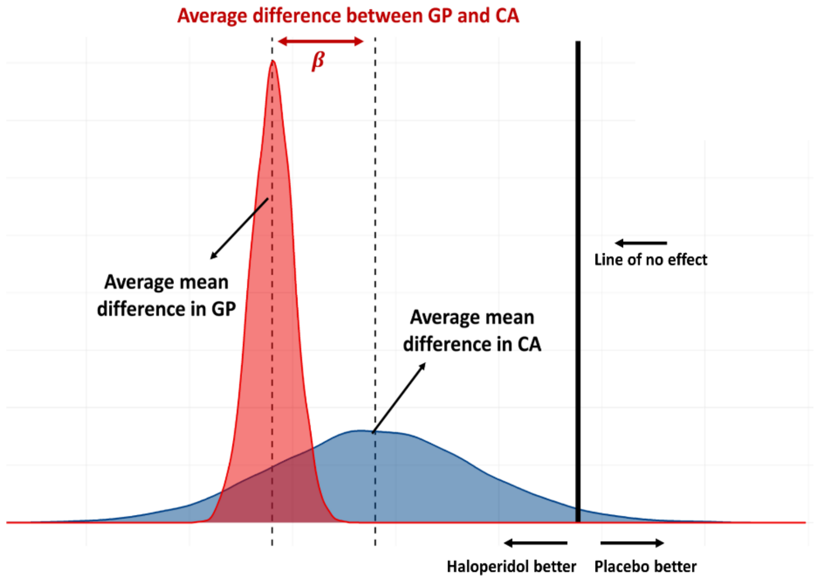
- We add a scale parameter $\boldsymbol{w}$ at the within-studies assumption that inflates the variance of per study mean in GP

NMA assumptions:

$$y_{ik} \sim N\left(\theta_{ik}, sd_{ik}^2\right) \qquad y_{ik} \sim N\left(\theta_{ik}, \frac{sd_{ik}^2}{w_i}\right), \mathrm{w_i} \in (0,1]$$

- We add a location parameter $\boldsymbol{\beta}$ that aims to shift the original distribution of the SMD's in GP towards the distribution of CA

$$\delta_i \sim N_{K_i-1}(\boldsymbol{\mu}, \boldsymbol{\Sigma}) \qquad \delta_i \sim N_{K_i-1}(\boldsymbol{\mu} - \boldsymbol{\beta}, \boldsymbol{\Sigma})$$



Informing the location and the scale parameters

- For the location parameter $\boldsymbol{\beta}$ we consider two approaches

- A data based approach
  - the differences $d_{1k} = \xi_{1k}^{GP} - \xi_{1k}^{CA}$ is used as prior for β_{1k}, $\beta_{1k} \sim \mathrm{N}(\hat{d}_{1k}, var(\hat{d}_{1k}))$

    Pooled result for comparison k vs 1 in GP

    Pooled result for comparison k vs 1 in CA

- Prior elicitation from expert opinion
  - we gave to the experts estimates for the GP and we asked them to provide estimates for the CA
  - they were also asked to give some uncertainty around their responses

- For the scale parameter $\boldsymbol{w}$ the prior distribution is related to the amount of downweight that we want to apply according to a specific criterion (e.g. high risk of bias)
  - usual choices of priors are the $Beta(\varepsilon_1, \varepsilon_2)$ or the $Unif(\varepsilon_1, \varepsilon_2)$

Ibrahim, J. G., Chen, M.-H., Gwon, Y., and Chen, F. (2015) The power prior: theory and applications. Statist. Med., 34: 3724– 3749. doi: 10.1002/sim.6728.

2^{nd} stage: NMA for CA using informative priors

- By fitting the modified NMA model we will obtain extrapolated SMD estimates

- The predictive distributions of the extrapolated SMD's are <u>used as informative prior distributions for CA</u>

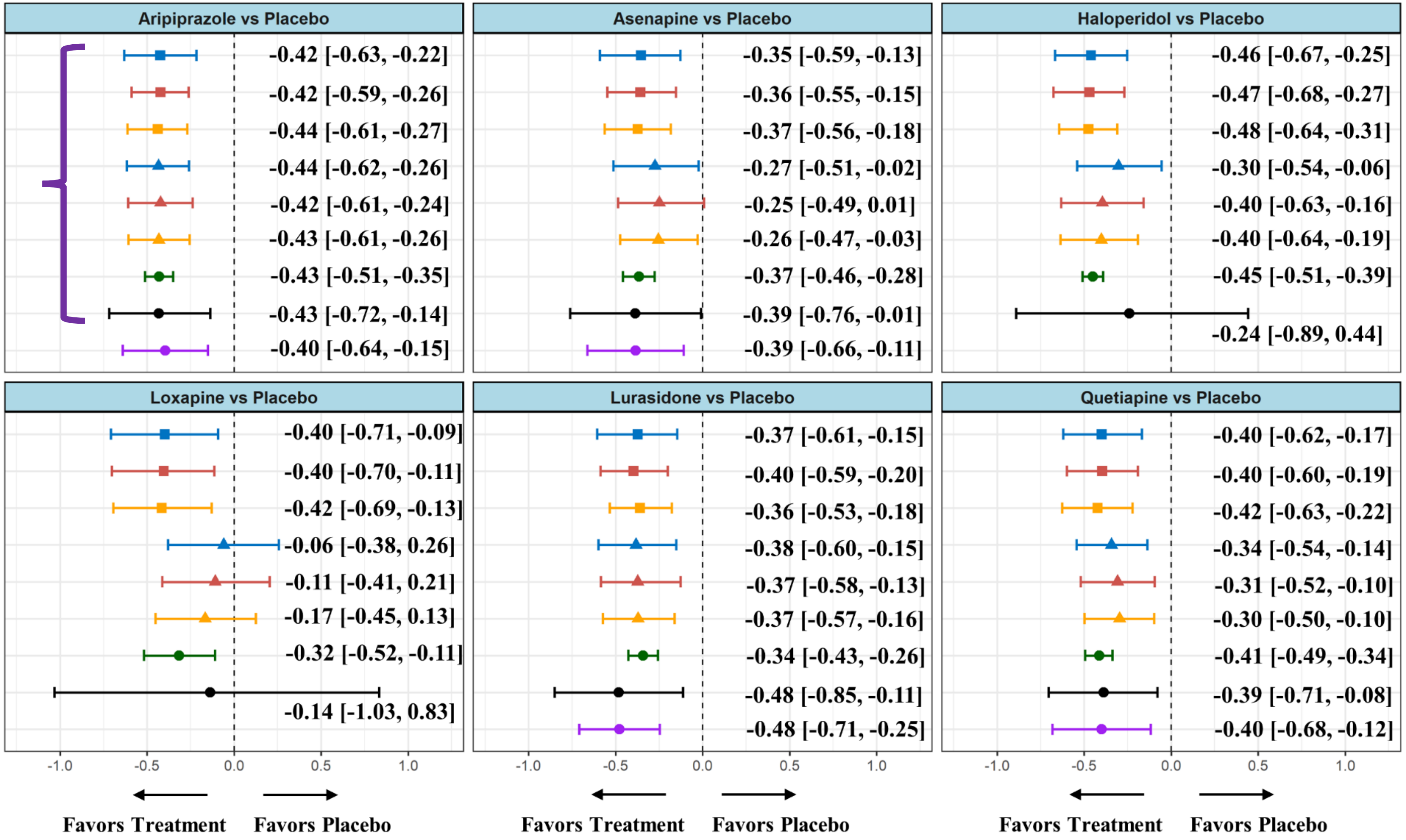
- We compare our approach to the standard NMA model which places non-informative priors for μ's

Results for CA

- Data based $\boldsymbol{\beta}$ – No DW
- Data based $\boldsymbol{\beta}$ – RoB DW
- Data based $\boldsymbol{\beta}$ – NCT DW
- Expert opinion based $\boldsymbol{\beta}$ – No DW
- Expert opinion based $\boldsymbol{\beta}$ – RoB DW
- Expert opinion based $\boldsymbol{\beta}$ – NCT DW
- Naïve pooling
- NMA with non-informative priors
- Direct comparison

Prior for downweight parameter $\boldsymbol{w}$: $\boldsymbol{w \sim Beta(3,3)}$

No-DW: No downweight
RoB-DW: Risk of bias downweight
NCT- Non common treatment downweight



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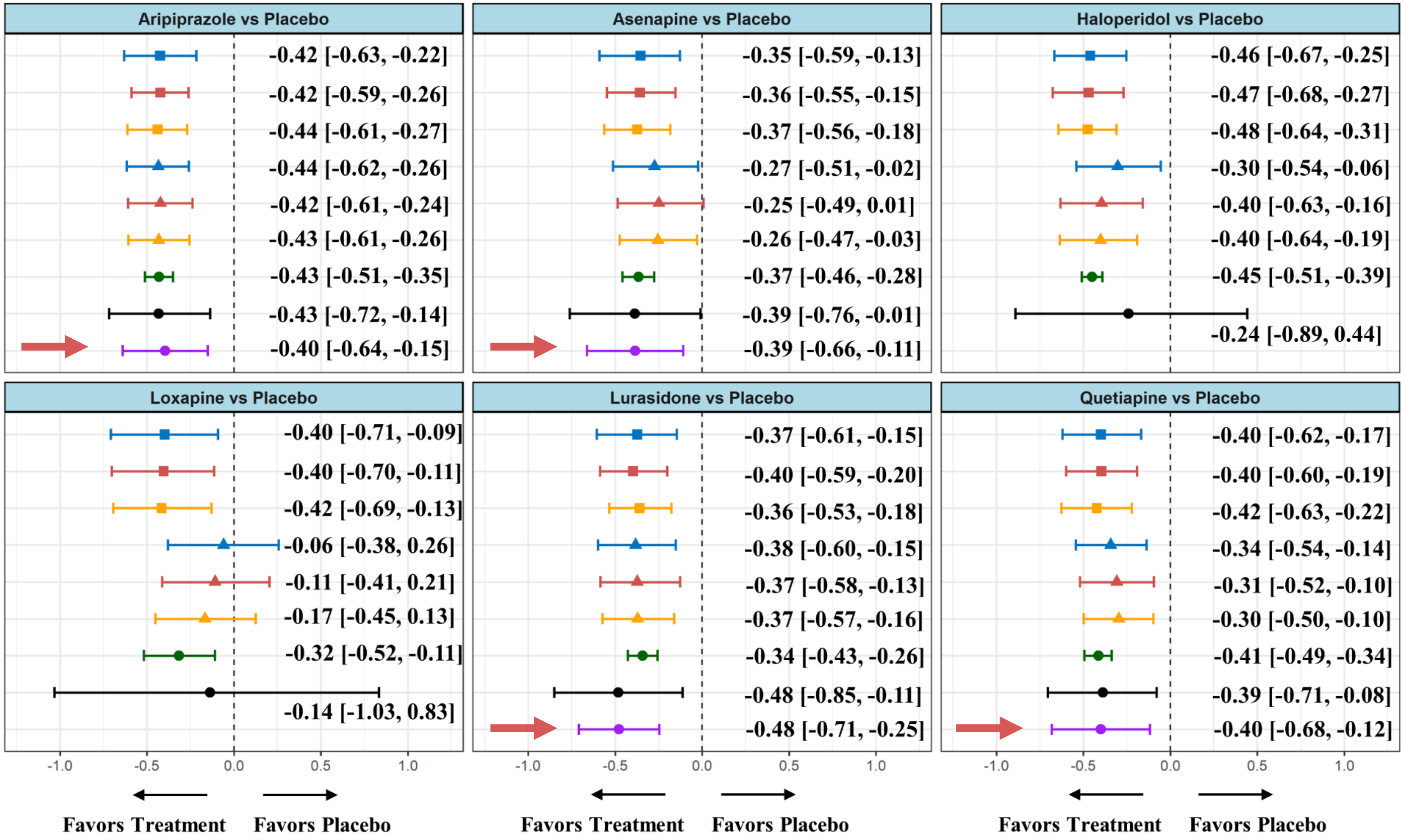
Prior for downweight parameter w: $w \sim Beta(3,3)$

No-DW: No downweight
RoB-DW: Risk of bias downweight
NCT- Non common treatment downweight



Discussion

- In this work we proposed a framework for analyzing sparse networks by using informative priors
  - the precision and the reliability of the estimates is improved as they consider multiple source of evidence
  - our method can applied for sharing information between any dense network P_2 and a sparse network P_1

- There are limitations in our work
  - the heterogeneity estimation is still based on the data coming from the sparse network

- To conclude sharing of information seems to facilitate the estimation of treatment effects in sparse networks
  - Extensive sensitivity analysis across different choices of prior distributions should always take place to investigate the robustness of the results across different analysis schemes

References

1. Chaimani A, Caldwell DM, Li T, Higgins JP, Salanti G. Undertaking network meta-analyses. In: Cochrane Handbook for Systematic Reviews of Interventions. John Wiley & Sons, Ltd; 2019:285-320. doi:10.1002/9781119536604.ch11
2. Krause M, Zhu Y, Huhn M, et al. Efficacy, acceptability, and tolerability of antipsychotics in children and adolescents with schizophrenia: A network meta-analysis. Eur Neuropsychopharmacol J Eur Coll Neuropsychopharmacol. 2018;28(6):659-674. doi:10.1016/j.euroneuro.2018.03.008
3. Huhn M, Nikolakopoulou A, Schneider-Thoma J, et al. Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. Lancet Lond Engl. 2019;394(10202):939-951. doi:10.1016/S0140-6736(19)31135-3
4. Yoon JH, Dias S, Hahn S. A method for assessing robustness of the results of a star-shaped network meta-analysis under the unidentifiable consistency assumption. BMC Med Res Methodol. 2021;21(1):113. doi:10.1186/s12874-021-01290-1
5. Nikolakopoulou A et al. (2014) Characteristics of Networks of Interventions: A Description of a Database of 186 Published Networks. https://doi.org/10.1371/journal.pone.0086754
6. Ibrahim, J. G., Chen, M.-H., Gwon, Y., and Chen, F. (2015) The power prior: theory and applications. Statist. Med., 34: 3724–3749. doi: 10.1002/sim.6728.
7. Dias S, Sutton AJ, Ades AE, Welton NJ. Evidence synthesis for decision making 2: a generalized linear modeling framework for pairwise and network meta-analysis of randomized controlled trials. Med Decis Making. 2013;33(5):607-617.
8. Schmitz, S., Adams, R. and Walsh, C. (2013), Incorporating data from various trial designs into a mixed treatment comparison model. Statist. Med., 32: 2935-2949. https://doi.org/10.1002/sim.5764
9. Turner, RM, Domínguez-Islas, CP, Jackson, D, Rhodes, KM, White, IR. Incorporating external evidence on between-trial heterogeneity in network meta-analysis. Statistics in Medicine. 2019; 38: 1321– 1335. https://doi.org/10.1002/sim.8044

THANK YOU!

QUESTIONS?