Network meta-analysis of rare events using penalized likelihood regression

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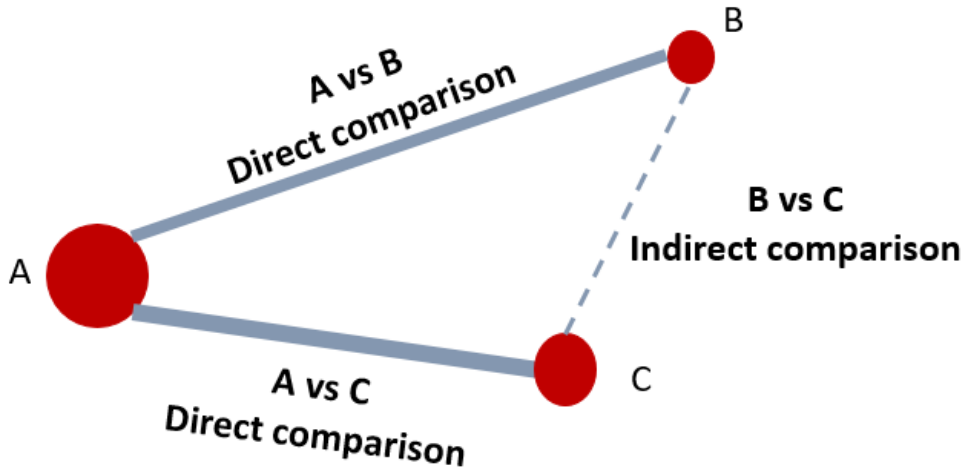
Introduction to Network Meta-Analysis (NMA)

- NMA is an extension of pairwise meta-analysis which allows for the comparison of 3 or more treatments simultaneously.
- Advantages
  - ✓ 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.



Chaimani A et al. Chapter 11, Cochrane Handbook for Systematic Reviews of Interventions 2019

The Issue of Rare Events in Meta-Analysis

- Standard meta-analytical methods (i.e. Inverse-Variance model) are unsuitable for rare events.
  - ✓ They rely on large sample approximations (approximation of binomial distribution from normal requires an adequate number of observed events).
  - ✓ In the presence of studies with zero-events calculation of relative treatment effects is impossible.

- Results are prone to substantial amounts of bias.

- In extreme cases where most studies report zero events meta-analysis can be pointless.

Efthimiou O. Evid Based Ment Health 2018

Available methods in meta-analysis

- Standard IV with a constant number added to tackle zero-event studies (e.g. 0.5 correction)
- Mantel & Haenszel (MH) and Peto methods which are non-parametric fixed effects models.
- Models with exact binomial distribution.
  - Logistic regression model
  - Binomial-Normal model

extended to NMA

- Models with different distributional assumptions.
  - Beta-Binomial model.
  - Non Central Hypergeometric-Normal (NCH) model.
- Bayesian methods (sometimes not suitable for rare events as even vague priors may strongly influence the results.

Stijnen T, et al. Stat Med. 2010
Kulinskaya E. Stat Model. 2014
Efthimiou O, et al. Stat Med. 2019

NMA as a logistic regression model

- Binomial distribution: $r_{ik} \sim Bin(n_{ik}, p_{ik})$,
- Logistic regression for NMA:

$$logit(p_{ik}) = a_i + X_{ik} d_{b(i)k}$$

where $X_{ik} = \begin{cases} 1, if \ \ k \neq b(i) \\ 0, if \ \ k = b(i) \end{cases}$

$d_{b(i)k}$: reference treatment

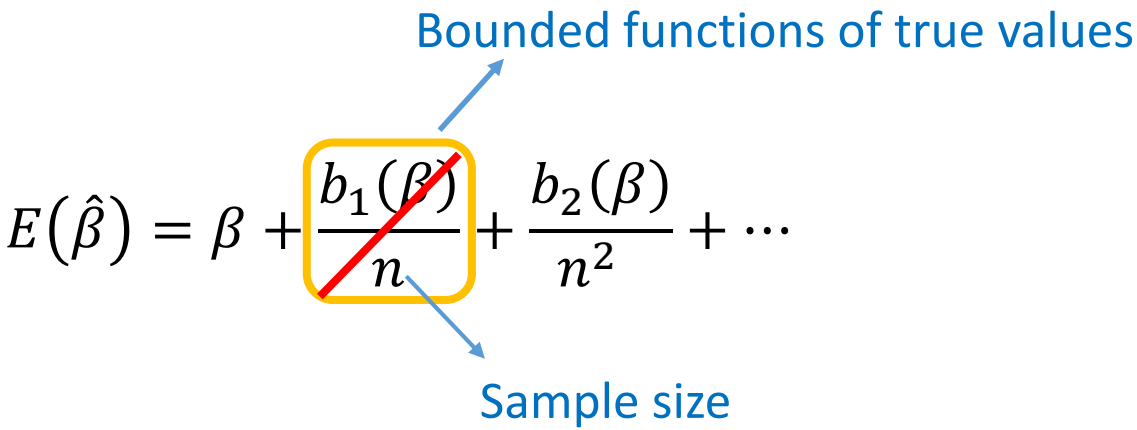
- ✓ The model relies on maximum likelihood estimates (MLE) that are biased when large sample approximations are not valid.
- ✓ Logistic regression cannot handle studies with zero events.
- ✓ For individual studies a common way to analyze rare events for logistic regression models is to use a penalty to the likelihood function.

Dias S, et al. Med Decis Making 2013.
Nemes S, et al. BMC Med Res Methodol. 2009.

Penalized logistic regression

- A modification was proposed by Firth (1993) in order to improve the performance MLE's in terms of bias.

- The method modifies the binomial likelihood function by penalizing it with Jeffrey's prior.



- Mathematical properties:
  - The modified likelihood provides improved estimates in terms of bias.
  - It can handle zero-event trials.

Firth D. Biometrika 1993.
Mansournia MA, et al. Am J Epidemiol. 2018.
Heinze G and Schemper M. Stat Med. 2002.

Penalized Likelihood NMA model

- Likelihood function for logistic regression NMA: $L(p_{ik}|r_{ik}, n_{ik}) = \prod_{i=1}^{N} \prod_{k \in A_i} \binom{n_{ik}}{r_{ik}} p_{ik}^{rik} (1 - p_{ik})^{rik}$

$A_i = \{$all indices of treatments compared in study i$\}$

✓ The inner product 'searches' for the treatments within each study.

✓ The outer product summarizes all the information across the set of studies.

✓ Both within and across studies comparisons are taken into account.

Penalized Likelihood → $L^*(p_{ik}|r_{ik}, n_{ik}) = L(p_{ik}|r_{ik}, n_{ik}) \, |I(p_{ik})|^{\frac{1}{2}}$ → Jeffrey's prior

Modified likelihood for NMA

Extension to random effects

- We incorporate heterogeneity using a multiplicative term

- The variance of the fixed effects model estimates is multiplied by a constant number φ

$$V_{random} = V_{fixed} * \varphi$$

- The estimation of the unknown parameter φ is usually implemented using Pearson's statistic

- An enriched estimate with better performance according to simulations has been proposed in the literature for the case of rare events (*Fletcher DJ. Biometrika 2012*)

$$\hat{\varphi} = \frac{\hat{\varphi}_{\mathrm{P}}}{1+\bar{s}} \, , s_{ik} = \frac{\widehat{V_{ik}'}}{\widehat{V_{ik}}} (r_{ik} - \hat{E}(r_{ik}))$$

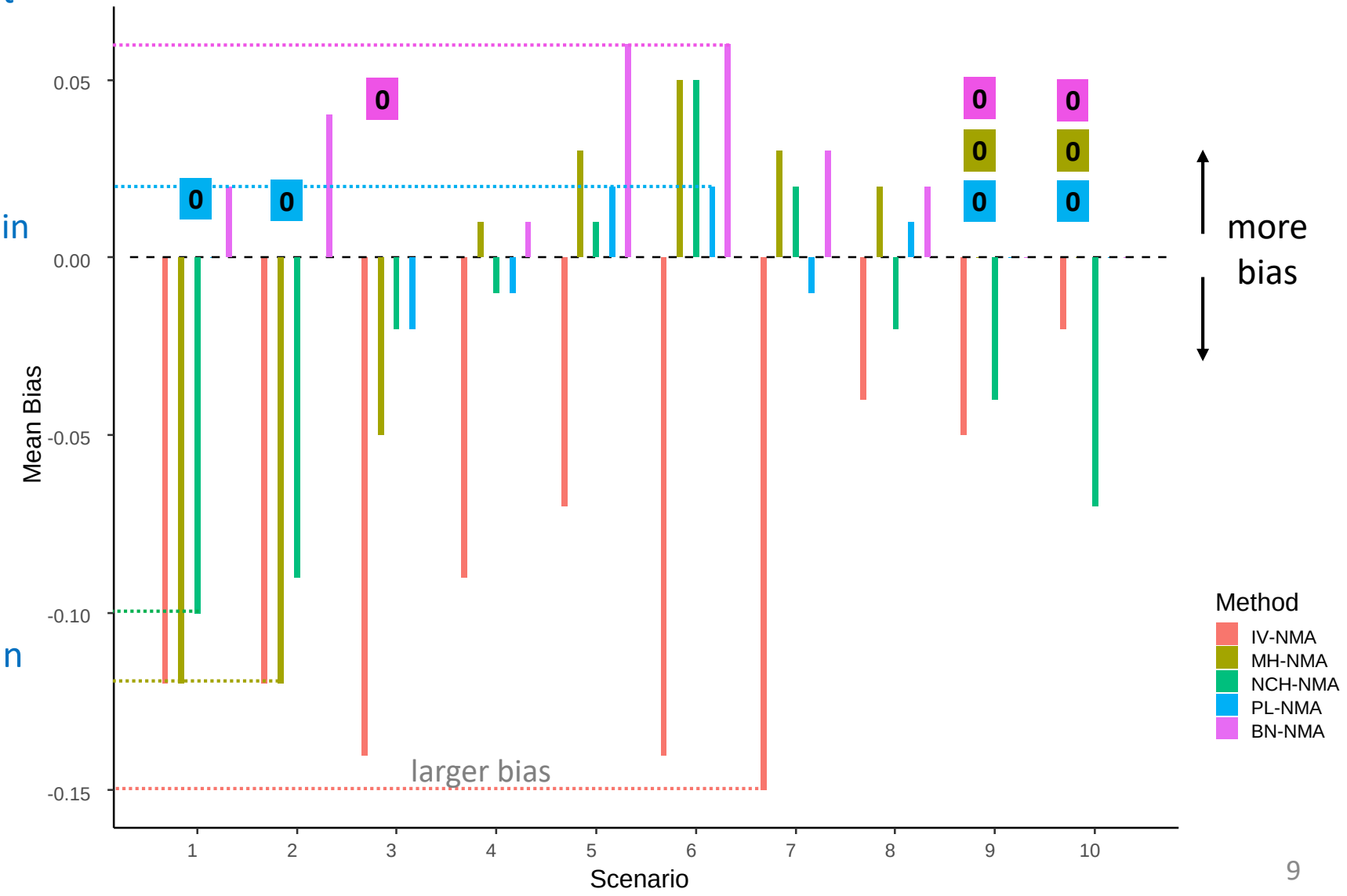
Thompson SG and Sharp SJ. Stat Med 1999
McCullagh P. Generalized Linear Models. Routledge 2018.
Fletcher DJ. Biometrika 2012

Simulation Scenarios

Scenario	Treatments in the network	Participants per arm	No studies per comparison	Heterogeneity (τ)	Event rate (%)
1	5	100-200	2	0	0.5-1%
2	5	100-200	2	0.1	0.5-1%
3	5	100-200	4	0	0.5-1%
4	3	100-200	8	0	1-2%
5	3	100-200	8	0.1	1-2%
6	3	100-200	8	0	0.5-1%
7	3	100-200	8	0.1	0.5-1%
8	3	100-200	8	0	0.5-5%
9	3	100-200	8	0.1	0.5-5%
10	3	100-200	8	0.1	0.5-10%

Simulation Results

- IV model
  - ✓ a suboptimal choice - important bias under certain scenarios.
- MH and NCH models
  - ✓ generally good performance
  - ✓ may suffer from important bias in the presence of very low event rates and many treatments.
- BN-NMA model
  - ✓ consistent performance across scenarios.
- PL-NMA
  - ✓ overall the best performance in terms of bias
  - ✓ much more consistent across the different scenarios

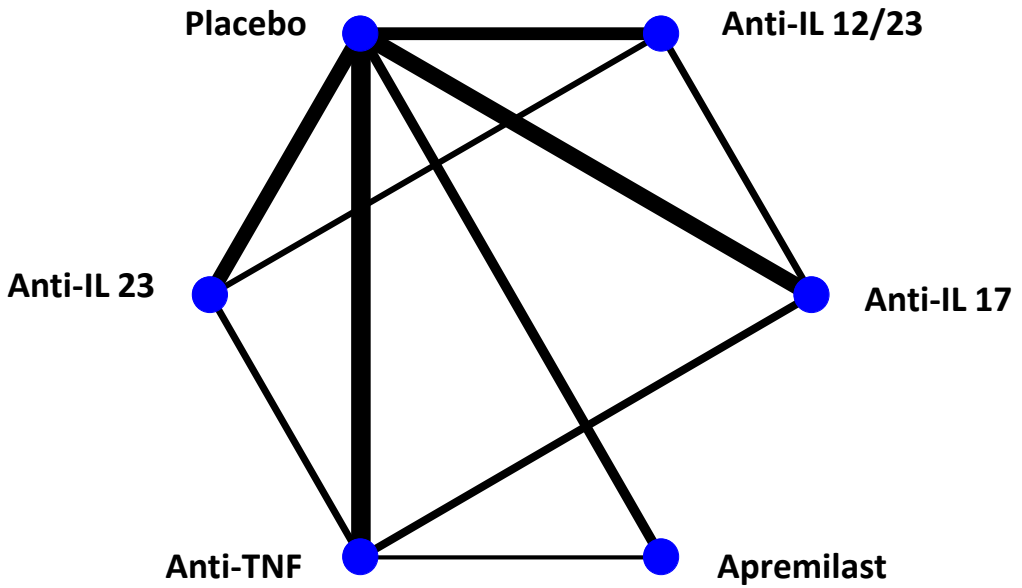


Illustrative Example

- A network comparing the safety of different drugs for chronic plaque psoriasis.

- Outcome: Adverse event of malignancies

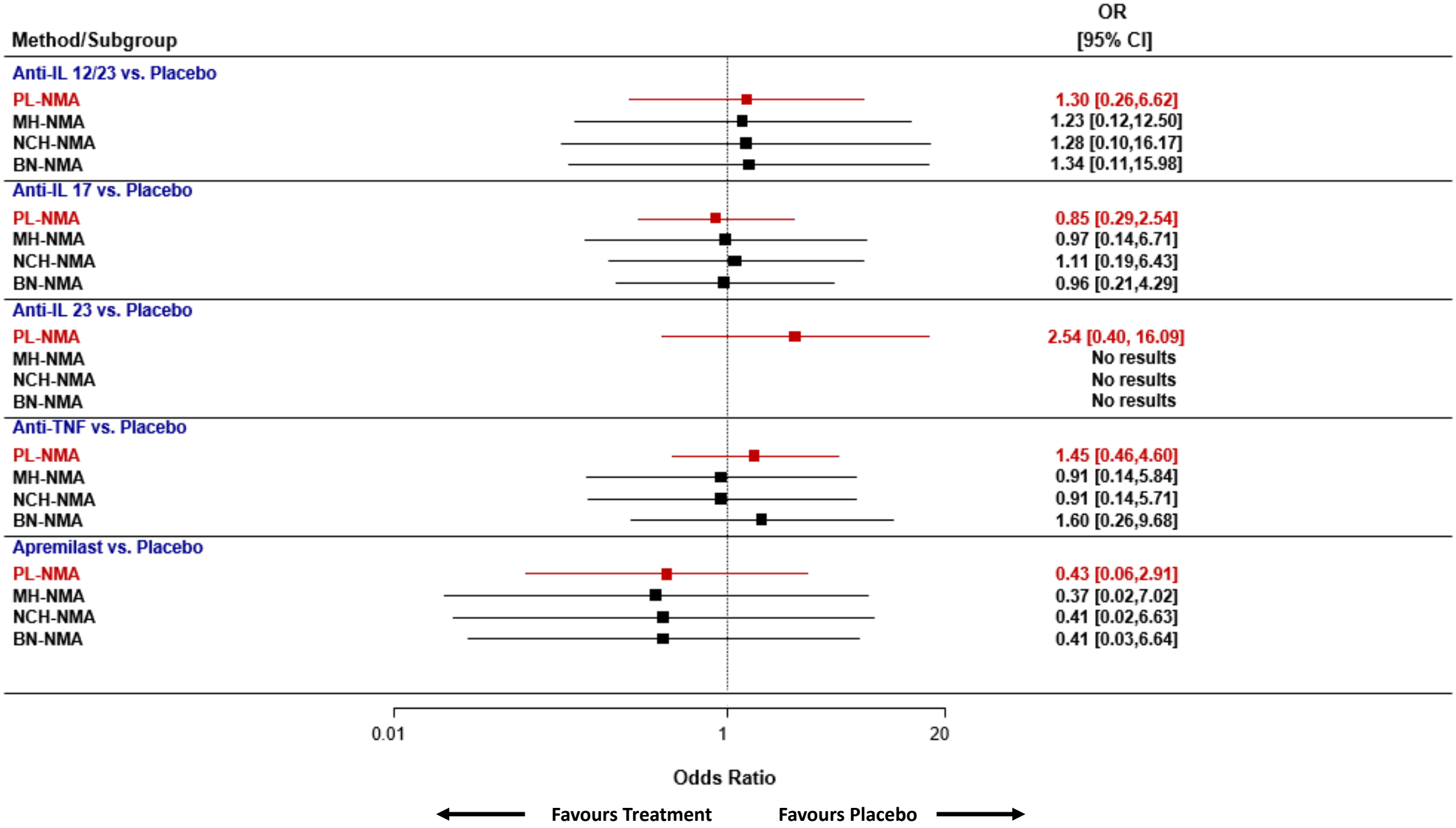
- Network characteristics:
  - ✓ 6 treatments
  - ✓ 43 studies and 63 comparisons
  - ✓ Range of event rate: 0-1%
  - ✓ Mean sample size per arm: 226
  - ✓ 31 zero event trials



12 studies and 12 comparisons are available after the exclusion.

Afach S et al. Br J Dermatol 2020.

Results


Method/Subgroup
OR
[95% CI]
Anti-IL 12/23 vs. Placebo
PL-NMA
1.30 [0.26,6.62]
MH-NMA
1.23 [0.12,12.50]
NCH-NMA
1.28 [0.10,16.17]
BN-NMA
1.34 [0.11,15.98]
Anti-IL 17 vs. Placebo
PL-NMA
0.85 [0.29,2.54]
MH-NMA
0.97 [0.14,6.71]
NCH-NMA
1.11 [0.19,6.43]
BN-NMA
0.96 [0.21,4.29]
Anti-IL 23 vs. Placebo
PL-NMA
2.54 [0.40, 16.09]
MH-NMA
No results
NCH-NMA
No results
BN-NMA
No results
Anti-TNF vs. Placebo
PL-NMA
1.45 [0.46,4.60]
MH-NMA
0.91 [0.14,5.84]
NCH-NMA
0.91 [0.14,5.71]
BN-NMA
1.60 [0.26,9.68]
Apremilast vs. Placebo
PL-NMA
0.43 [0.06,2.91]
MH-NMA
0.37 [0.02,7.02]
NCH-NMA
0.41 [0.02,6.63]
BN-NMA
0.41 [0.03,6.64]
0.01
1
20
Odds Ratio
Favours Treatment
Favours Placebo

Conclusions

- NMA of rare events is a challenging field and only a few methods have been proposed to date for analyzing such data.

- Our penalized likelihood NMA model provides a promising alternative for NMA of rare events
  - ✓ Good performance in terms of bias based on the simulation results
  - ✓ Preserves the connectivity of the network by avoiding study exclusion (i.e. 0-0 studies)
  - ✓ Under certain conditions gives more precise results

- No meta-analytic method is uniquely best in the presence of studies with low event rates

- Sensitivity analysis should always take place to investigate the robustness of results under 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. Efthimiou O. Practical guide to the meta-analysis of rare events. *Evid Based Ment Health*. 2018;21(2):72. doi:10.1136/eb-2018-102911
3. Stijnen T, Hamza TH, Özdemir P. Random effects meta-analysis of event outcome in the framework of the generalized linear mixed model with applications in sparse data. *Stat Med*. 2010;29(29):3046-3067
4. Kulinskaya E, Olkin I. An overdispersion model in meta-analysis. *Stat Model*. 2014;14(1):49-76.
5. Efthimiou O, Rücker G, Schwarzer G, Higgins JP, Egger M, Salanti G. Network meta-analysis of rare events using the Mantel-Haenszel method. *Stat Med*. 2019;38(16):2992-3012.
6. 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.
7. Nemes S, Jonasson JM, Genell A, Steineck G. Bias in odds ratios by logistic regression modelling and sample size. *BMC Med Res Methodol*. 2009;9(1):56.
8. Firth D. Bias reduction of maximum likelihood estimates. *Biometrika*. Published online 1993:27-38.
9. Mansournia MA, Geroldinger A, Greenland S, Heinze G. Separation in logistic regression: causes, consequences, and control. *Am J Epidemiol*. 2018;187(4):864-870.
10. Heinze G, Schemper M. A solution to the problem of separation in logistic regression. *Stat Med*. 2002;21(16):2409-2419.
11. Thompson SG, Sharp SJ. Explaining heterogeneity in meta-analysis: a comparison of methods. *Stat Med*. 1999;18(20):2693-2708.
12. McCullagh P. *Generalized Linear Models*. Routledge; 2018.
13. Fletcher DJ. Estimating overdispersion when fitting a generalized linear model to sparse data. *Biometrika*. 2012;99(1):230-237.
14. Afach S, Chaimani A, Evrenoglou T, et al. Meta-analysis results do not reflect the real safety of biologics in psoriasis. *Br J Dermatol*. Published online 2020.

Thank you!