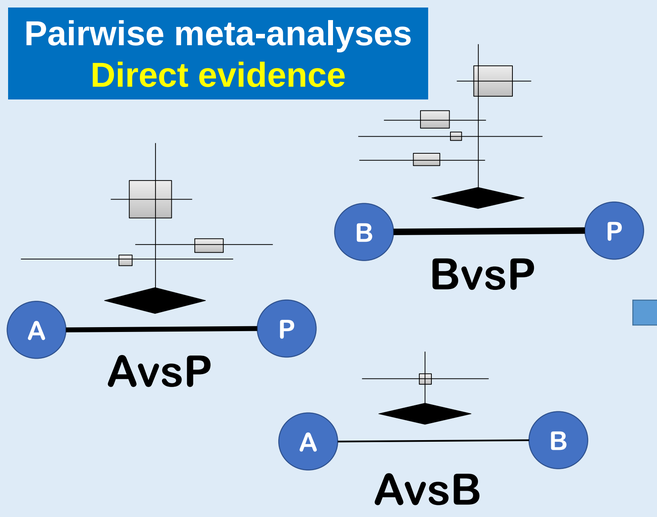
Network meta-analysis of rare events using penalized likelihood regression

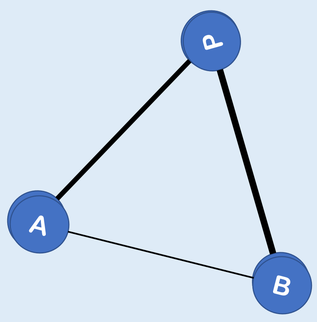
Theodoros Evrenoglou, Dimitris Mavridis, Anna Chaimani
Université de Paris, Research Center of Epidemiology & Statistics (CRESS-UMR1153), Inserm, Paris, France

Background

Pairwise meta-analyses
Direct evidence



Network meta-analysis
Direct + indirect evidence



- ✓ Any number of treatments
- ✓ Comparison of treatments never compared in individual studies.
- ✓ Estimation of relative effects with highest precision.
- ✓ Estimation of treatment relative ranking.

NMA with rare events

large sample approximations & normality assumption implausible → **biased results**

exclusion of double-zero studies → **loss of information**

Few existing NMA methods:

- **poor performance with many treatments and very low event rates**
- **cannot handle double-zero studies**

Objectives & Methods

- ✓ To develop a **new NMA model** appropriate for rare events which will
  - **reduce bias** and improve the accuracy and precision of relative effect estimates
  - allow inclusion of double zero studies and **preserve the connectivity** of the networks
- ✓ To provide a **user-friendly R package** to allow researchers routinely using our method in NMAs with rare events

We adapt and extend well-established methodology from the analysis of individual studies → Based on **penalized likelihood logistic regression** → Removes the 1st order term of maximum likelihood bias expansion – the largest amount of bias

NMA as logistic regression

Binonial likelihood: $r_{ik} \sim Bin(n_{ik}, p_{ik})$

where r_{ik},: # events, n_{ik}: # participants,

p_{ik}: probability of event per study (i) arm (k)

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

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

Standard NMA likelihood function

$$L(p_{ik}|r_{ik}, n_{ik}) = \prod_{i=1}^{N} \prod_{k \in A_i} \binom{n_{ik}}{r_{ik}} {p_{ik}}^{rik} (1 - p_{ik})^{rik}$$

Penalized NMA likelihood function

$$L^*(p_{ik}|r_{ik}, n_{ik}) = L(p_{ik}|r_{ik}, n_{ik}) |I(p_{ik})|^{\frac{1}{2}}$$

Jeffrey's prior

Design of simulations (10 different scenarios – 1000 draws each)

• Participants per arm: 100 - 200 • Treatments in the network: 3 - 5 • Studies per comparison: 2 - 8	• Range of event rate: 0.5% - 10% • With and without heterogeneity

All analyses performed in R v3.6.3

Incorporation of heterogeneity

through a multiplicative term φ:

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

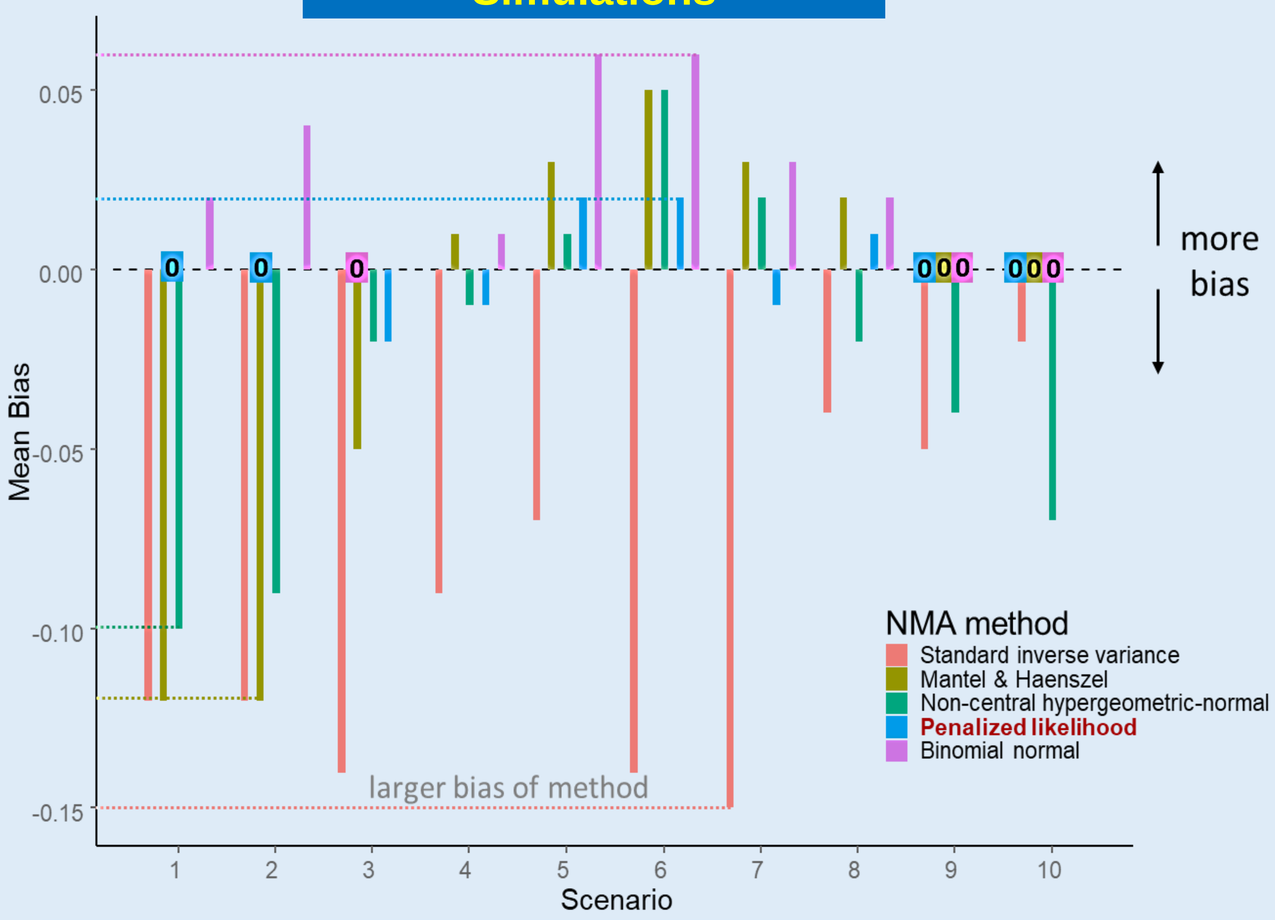
$\varphi > 1$ indicates presence of heterogeneity

'enriched' estimate specific for rare events:

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

Results

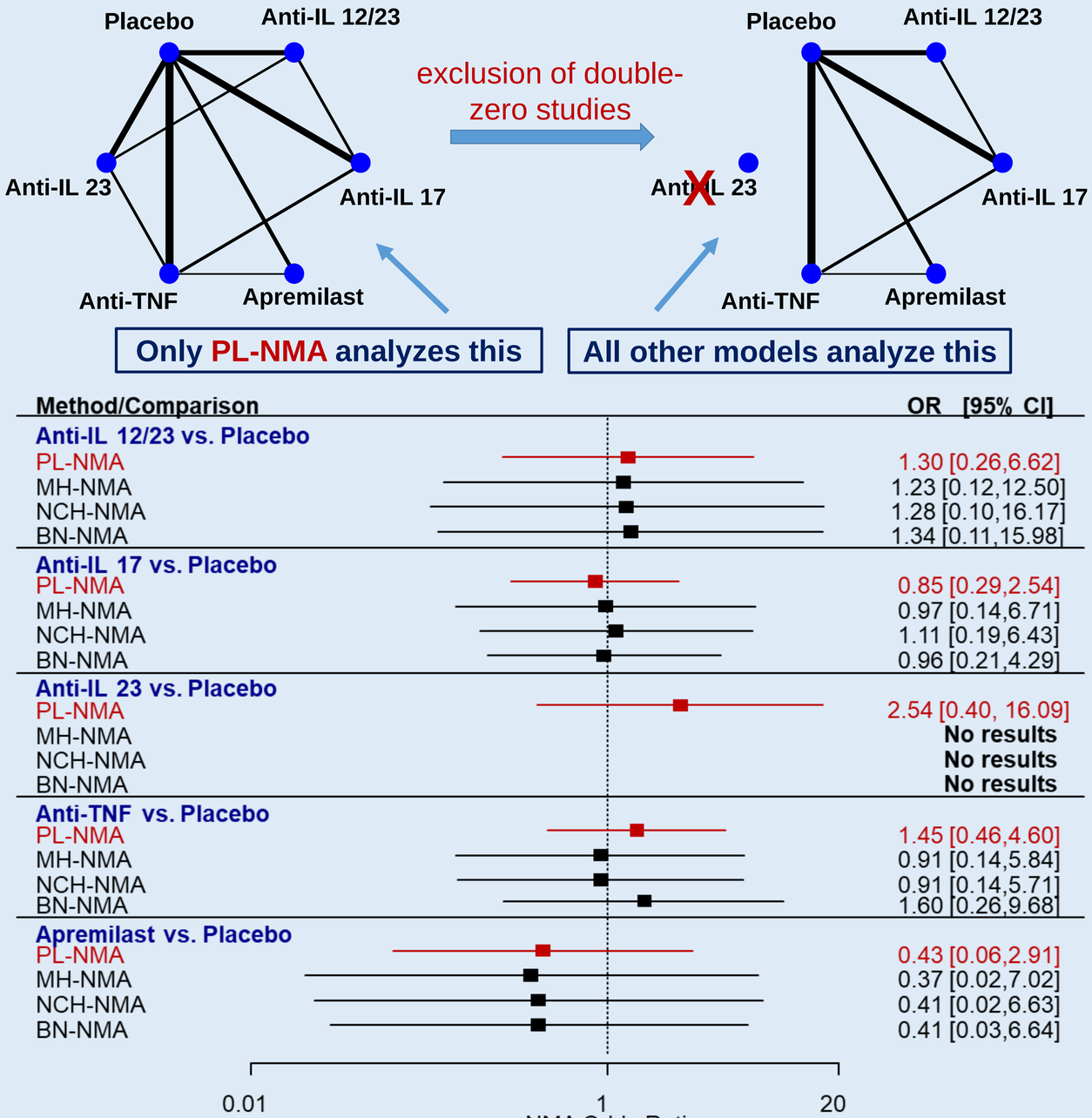
Simulations



- **IV model:** a suboptimal choice with important bias under certain scenarios
- **MH, NCH models:** generally good performance
  important bias with very low event rates/many treatments
- **BN-NMA model:** somewhat consistent performance across scenarios
- **PL-NMA model:** overall the best performance in terms of bias
  much more consistent across the different scenarios

Clinical example

Safety of different drugs for chronic plaque psoriasis
Outcome: incidence of malignancies



Discussion

- NMA of rare events is a challenging field with only few methods available to date
- Our PL-NMA model provides a promising alternative to existing methods
- There is no unique best method – sensitivity analysis is always necessary to assess the robustness of results