Network meta-analysis of rare events using penalised likelihood regression

Theodoros Evrenoglou

Ian R. White, Dimitris Mavridis, Anna Chaimani

Université de Paris, Research Center of Epidemiology & Statistics (CRESS-UMR1153),

Inserm, France

MRC Clinical Trials Unit, University College London, London, UK

Department of Primary Education, University of Ioannina, Greece

A day with….Statistical Methods Group
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Background

- Lack of a concrete definition of what constitutes a rare event
  - ✓ Roughly, when a small number of events (even zero) is observed in the studies at hand
  - ✓ Usually, outcome risks<5% are considered subject to the issue of rare events
- Meta-analysis of rare events requires special attention
  - ✓ Individual studies are often underpowered to detect any treatment effects
  - ✓ Conventional statistical models (e.g. inverse variance model) are problematic and inappropriate
- Common issue for safety outcomes (e.g. different types of adverse effects)

19.1 Introduction to issues in addressing adverse effects #section-19-1

Every healthcare intervention comes with the risk, great or small, of harmful or adverse effects. A Cochrane Review that considers only the favourable outcomes of the interventions that it examines, without also assessing the adverse effects, will lack balance and may make the intervention look more favourable than it should. All reviews should try to consider the adverse aspects of interventions.

This chapter addresses special issues about adverse effects in Cochrane Reviews. It focuses on methodological differences when assessing adverse effects compared with other outcomes.

The Issue of Rare Events in Cochrane Reviews

- In a sample of 500 Cochrane reviews:
  - ✓ about 50% having (safety) outcomes with rare events
  - ✓ about 30% having at least one study with zero events in one arm
  - ✓ Most common synthesis methods:
    1. Inverse-variance (IV) method
    2. Mantel-Haenszel (MH) method
    3. Peto method
  - ✓ i.e. methods available in RevMan

Statistical Methods in Medical Research 2009; **18**: 421–432

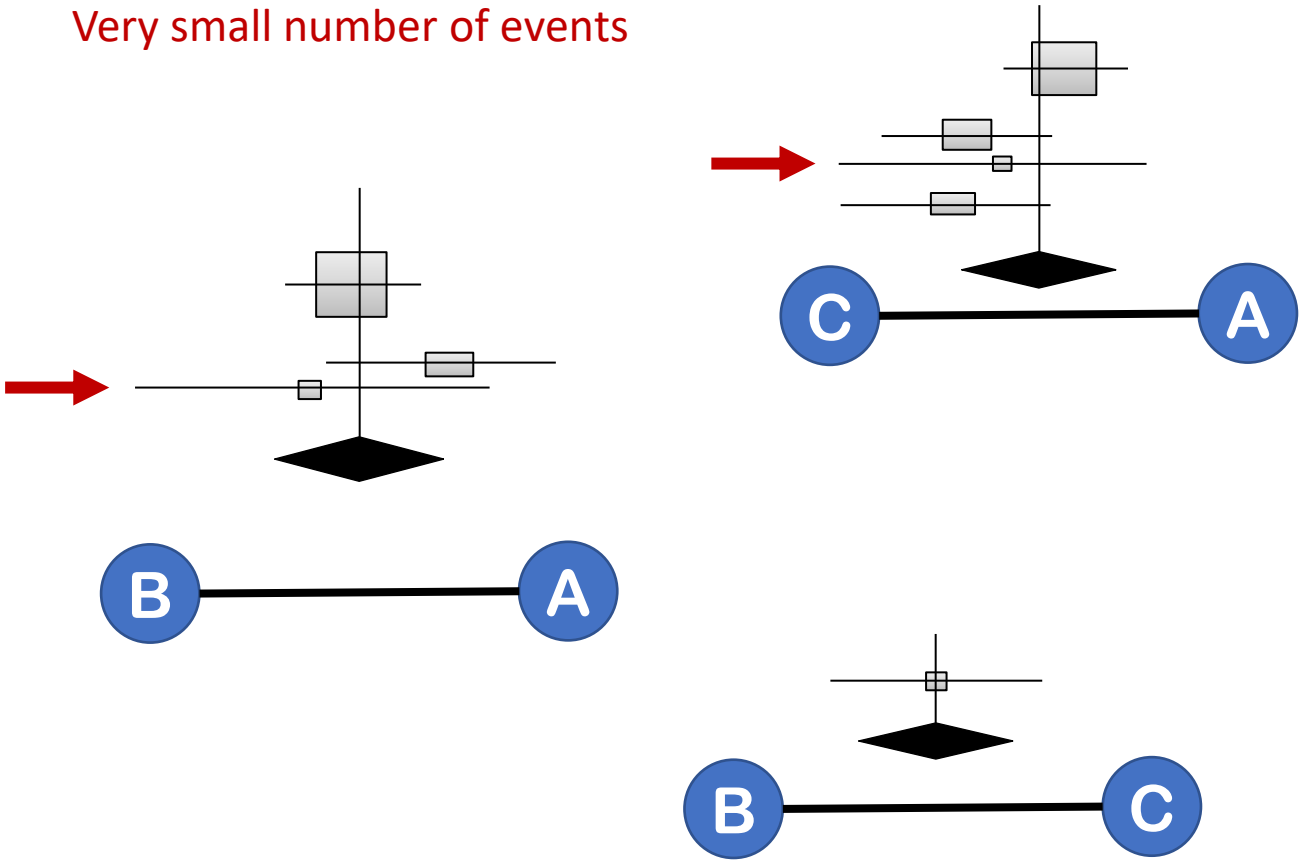
Meta-analyses of safety data: a comparison of exact versus asymptotic methods

Ben Vandermeer, Liza Bialy, Nicola Hooton, Lisa Hartling, Terry P Klassen, University of Alberta Evidence Based Practice Centre, Alberta Research Centre for Health Evidence, **Bradley C Johnston** University of Alberta, Department of Medicine and **Natasha Wiebe** University of Alberta Clinical Nephrology Research Group

The objectives of this study were to establish and describe a database of Cochrane and non-Cochrane meta-analyses of safety data and to determine under what conditions exact methods differ from asymptotic methods in meta-analyses of safety data. A sample of Cochrane ($n = 500$) and non-Cochrane ($n = 200$) systematic reviews was randomly selected and a database of safety meta-analyses established. Point estimates and confidence intervals for each meta-analysis were recalculated using exact methods and compared to the results of asymptotic methods. Cochrane reviews were nearly four times as likely as non-Cochrane reviews to contain meta-analyses of safety data (35% compared to 9%). More than 50% of safety meta-analyses contained an outcome with a rare event rate (<5%) and 30% contained at least one study with no events in one arm of the study. For rare event meta-analyses, exact point estimates differed substantially from asymptotic estimates 46% of the time, compared to 17% for those without rare events. Exact confidence intervals differed substantially from asymptotic ones 67% of the time compared to only 19% for those without rare events. The magnitude of differences was also correlated with the number of studies and the summary statistic used to combine the data. Asymptotic methods will not always be a good approximation for exact methods in safety meta-analyses. Event rates and number of studies should be closely examined when choosing the statistical method for combining rare event data.

Network Meta-Analysis of rare events

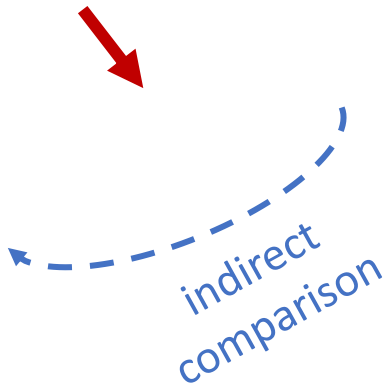
Very small number of events



Network Meta-Analysis of rare events

- IV model
  - ✓ large sample approximations invalid for rare events
  - ✓ requires continuity correction (e.g. adding 0.5) for 0 events
- MH and Non-Central Hypergeometric (NCH) NMA models
  - ✓ usually perform better than IV
  - ✓ only common-effect models
  - ✓ exclusion of only-zero event studies
  - ✓ examined in one simulation study with few scenarios
- Bayesian methods
  - ✓ even vague priors may strongly influence the results

How to analyse these data?



Efthimiou O. Evid Based Ment Health 2018
Efthimiou O, et al. Stat Med. 2019
Stijnen T, et al. Stat Med. 2010

Penalised likelihood NMA (PL-NMA) approach

- Aim: To suggest a new NMA model appropriate for the synthesis of studies with rare events that would
  - ✓ reduce bias in the estimation of treatment effects in comparison to existing methods
  - ✓ be applicable also in extreme cases with very small - even zero - numbers of events

- We extend a logistic regression model with penalised likelihood function proposed by Firth (1993) into the context of NMA.

- We allow the incorporation of heterogeneity using an overdispersion parameter in a two-stage approach

- We compare our method with other NMA models using an extensive simulation study and a real example on the safety of different drugs for chronic plaque psoriasis

Firth D. Biometrika 1993.

The common-effect PL-NMA model

- Binomial distribution:

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

Number of events in arm k of study i

Total participants in arm k of study i

Probability of an event in arm k of study i

- Logistic regression for NMA

$$logit(p_{ik}) = a_i + X_{ik}\delta_{bk}$$

0 for k=b, 1 for k≠b

relative effect of k vs b in study i

baseline risk of the event in study i

reference treatment

- **Penalised** Likelihood function:

$$L^{*}(p_{ik}|r_{ik}, n_{ik}) = \prod_{i=1}^{N}\prod_{k=1}^{K}\binom{n_{ik}}{r_{ik}} p_{ik}{}^{rik}(1-p_{ik})^{rik}\,|I(p_{ik})|^{\frac{1}{2}}$$

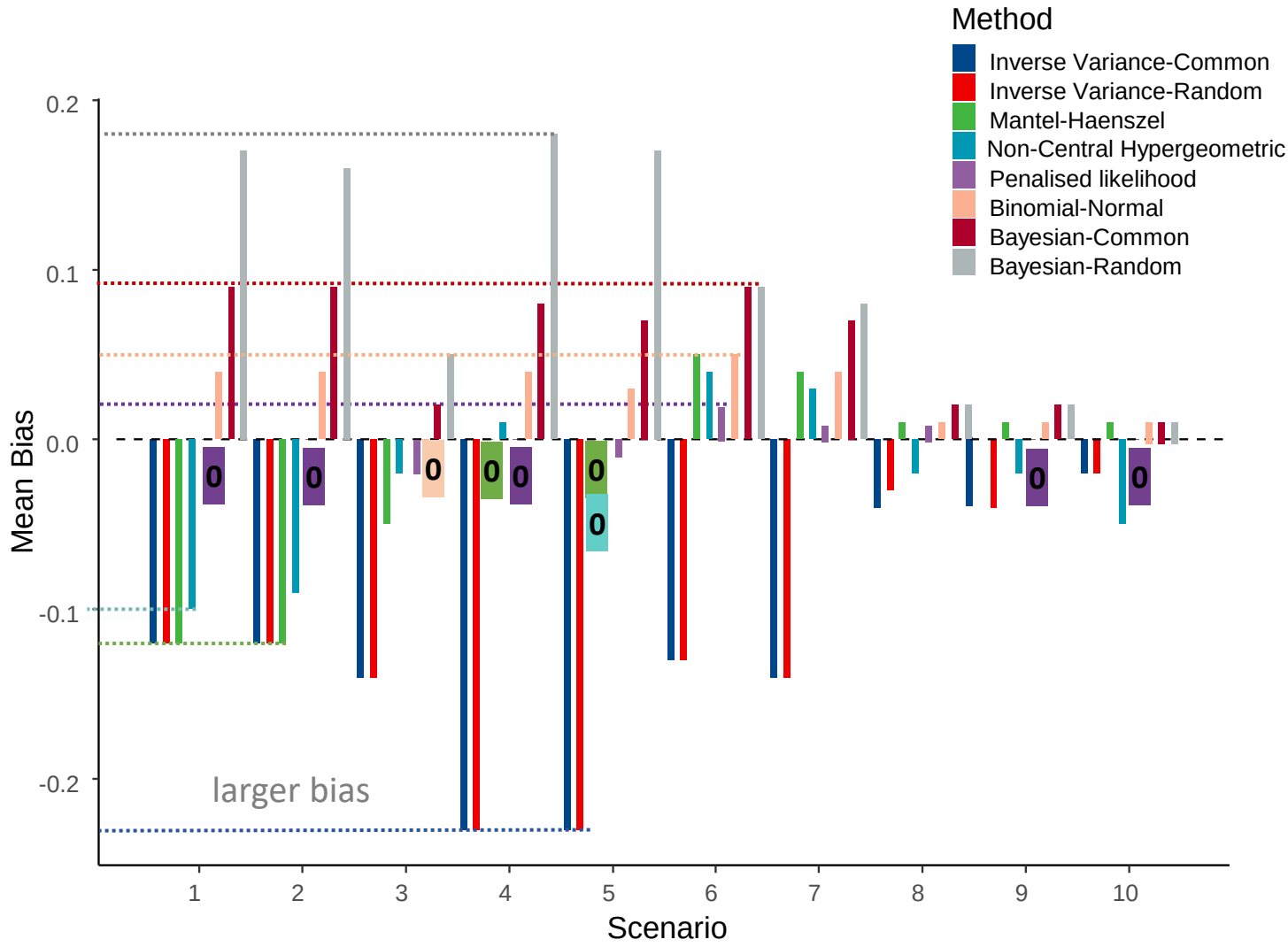
$|I(p_{ik})|^{\frac{1}{2}}$ → Jeffrey's prior

$I(p_{ik})$ → Fisher's matrix

Firth D. Biometrika 1993.
Dias S, et al. Med Decis Making 2013.

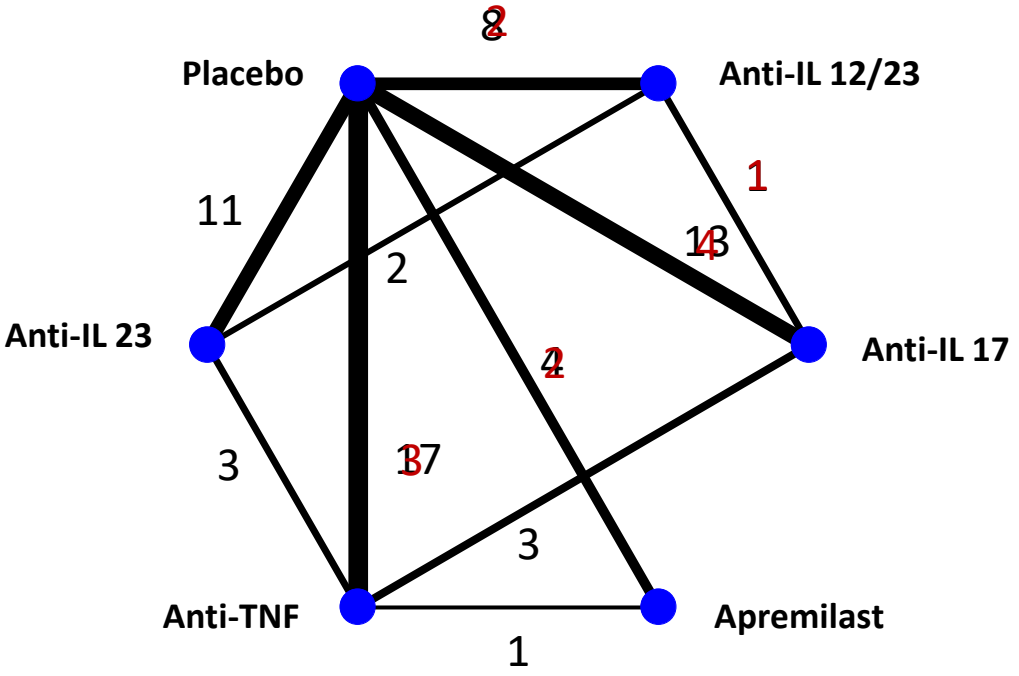
Simulation Results

- Inverse-Variance model
  - ✓ a suboptimal choice - important bias under certain scenarios
- Mantel-Haenszel and Non-Central Hypergeometric models
  - ✓ generally good performance
  - ✓ may suffer from important bias in the presence of very low event rates and many treatments
- Binomial-Normal (BN) model
  - ✓ consistent performance across scenarios
- Bayesian models
  - ✓ The common-effects model was less biased than the random effects model.
  - ✓ Both are highly biased in many scenarios
- Penalised likelihood model
  - ✓ overall the best performance in terms of bias
  - ✓ much more consistent across the different scenarios



Illustrative Example

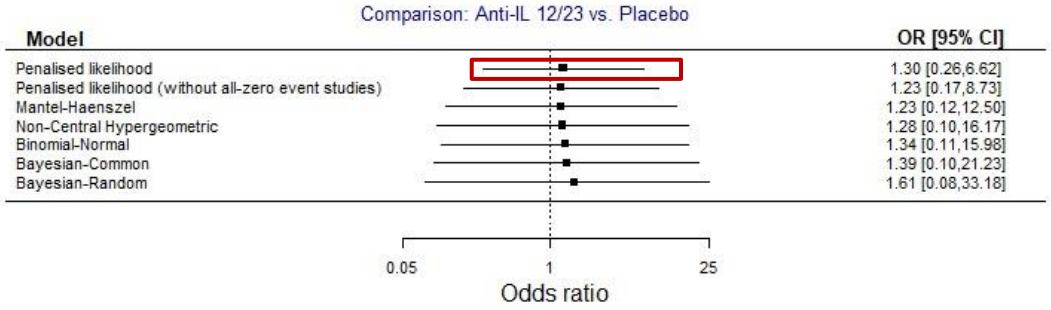
- A network comparing the safety of different drugs for chronic plaque psoriasis.
- Outcome: Number of malignancies
- Network characteristics:
  - ✓ 6 classes of treatments
  - ✓ 43 studies
  - ✓ Range of risks: 0-1%
  - ✓ Mean sample size per arm: 226
  - ✓ 31 zero event trials

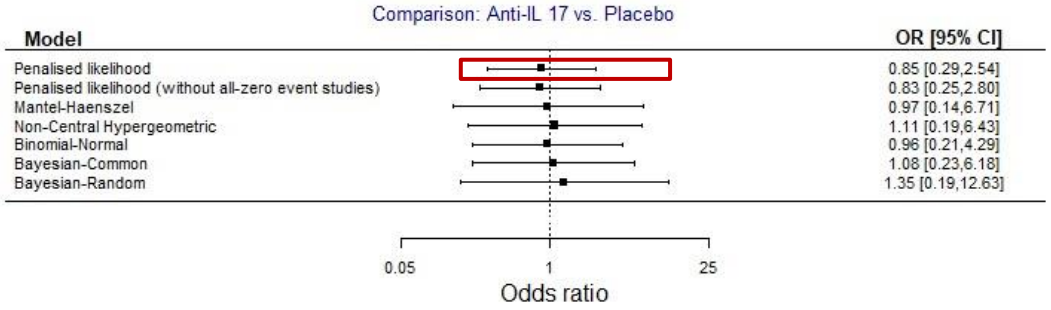


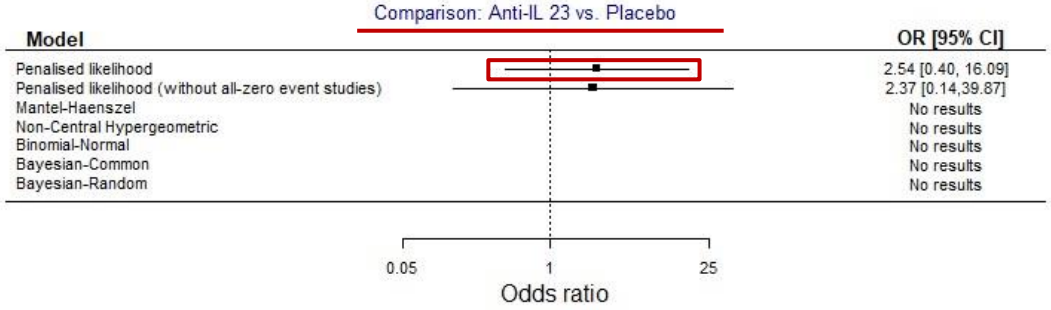
12 studies are available after the exclusion.

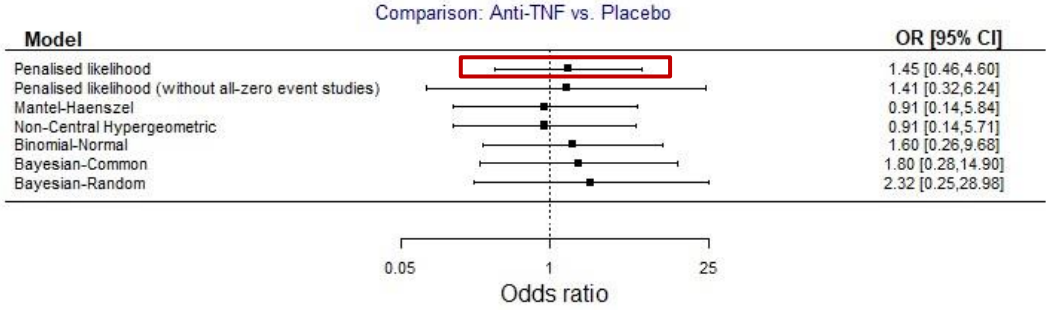
Afach S et al. Br J Dermatol 2020.

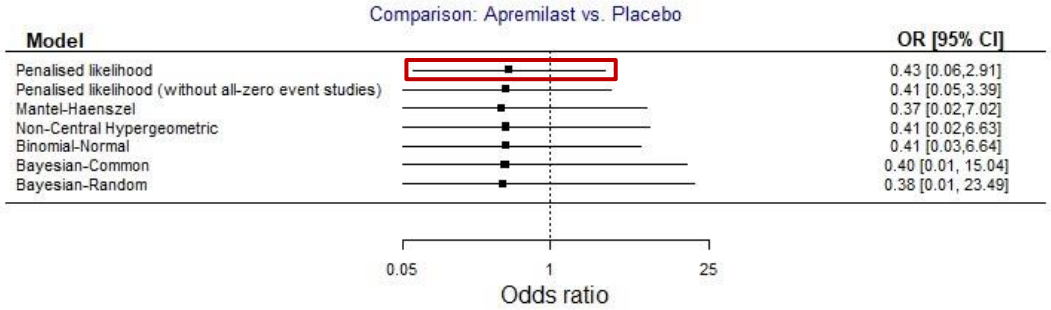
Results











Favours Treatment **Favours Placebo**

All analyses performed in R v3.6.3

Discussion

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

- Our PL-NMA model provides a promising alternative for NMA of rare events
  - ✓ good performance in terms of bias based on the simulation results
  - ✓ works even under extreme scenarios and preserves the connectivity of the network by avoiding study exclusion
  - ✓ under certain conditions gives more precise results

- In principle a common-effects model
  - ✓ Incorporation of heterogeneity takes place in a non-standard way.

- No meta-analytic method is uniquely best in the presence of rare events

- Sensitivity analysis should always take place to investigate the robustness of results under different analysis schemes

- We plan to implement the method in an R-package (e.g. netmeta)

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Thank you!