

Sensitivity to Excluding Treatments in Network Meta-Analysis

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Introduction: Network Meta-Analysis

- The traditional meta-analysis combines study-level results (such as odds ratios) from several independent studies to compare *two* treatments.
- *Network meta-analysis* (NMA) aims to compare *multiple* treatments *simultaneously*.
- Currently, two types of approaches are developed for NMA: *contrast-based* and *arm-based*.
- Mills et al. (2013) found that excluding a treatment may have substantial influence on results by contrast-based NMA.
- How about arm-based NMA?

- A typical NMA dataset with binary outcome: (Lu & Ades, 2006)

Study	Treatment (# Events / # Participants)			
	A	B	C	D
1	9/140		23/140	10/138
2		11/78	12/85	29/170
3	79/702	77/694		
4	18/671	21/535		
5	8/116	19/146		
6	75/731		363/714	
⋮	⋮	y_{ik}/n_{ik}	⋮	⋮

- Suppose an NMA reviews I studies on K treatments.

Approaches: Network Meta-Analysis

Currently, two types of approaches are developed for NMA:

(1) The contrast-based approach: (Lu & Ades, 2004; 2006)

$$y_{ik} \sim \text{bin}(n_{ik}, p_{ik}) \quad \text{Likelihood}$$

$$\text{logit}(p_{ik}) = \mu_i + X_{ik} \delta_{ibk} \quad \text{Link}$$

$$\delta_{ibk} \sim N(d_{bk}, \sigma_{bk}^2) \quad \text{Random Effect}$$

$$d_{hk} = d_{bk} - d_{bh}$$

where X_{ik} is a dummy variable; = 1 if $k \neq b$ and 0 if $k = b$.

– **cannot** use single-arm trials / estimate treatment-specific event rate p_k without external data source or separate modeling.

(2) The arm-based approach: (Zhang, 2014; Hong, 2015)

$$y_{ik} \sim \text{bin}(n_{ik}, p_{ik}) \quad \text{Likelihood}$$

$$\text{probit}(p_{ik}) = \mu_k + \nu_{ik} \quad \text{Link}$$

$$(\nu_{i1}, \nu_{i2}, \dots, \nu_{iK})^T \sim \text{MVN}(\mathbf{0}, \boldsymbol{\Sigma}_K) \quad \text{Random Effect}$$

– **can** use single-arm trials / estimate treatment-specific event rate.

Sensitivity to Excluding Treatments

(Two-arm study: compares two treatments; Multi-arm study: compares > 2 treatments; Single-arm study: includes only one treatment)

- We used 14 NMA datasets reported in Veroniki et al. (2013), containing 567 randomized clinical trials with a total of 389,361 participants.
- For each dataset, performed both contrast- and arm-based NMA for the full network.
- For each treatment in the above dataset, removed it from the network and applied NMA to the remaining dataset (the reduced network).

Note:

- (i) If a two-arm study includes the removed treatment, it becomes a single-arm study. The whole study must be deleted when using a contrast-based NMA; it is kept when using an arm-based NMA.
- (ii) If a multi-arm study includes the removed treatment, the study still compares ≥ 2 treatments; it is kept for both contrast- and arm-based NMA.

Result: Change of Event Rate

- Contrast-based NMA cannot estimate population-averaged event rate without external data source or separate modeling.
- Only report results for arm-based NMA.
- $\hat{\pi}_f$: estimated population-averaged event rate based on the full network; $\hat{\pi}_r$: based on the reduced network.
- Fold change is defined as $\max\{\hat{\pi}_f/\hat{\pi}_r, \hat{\pi}_r/\hat{\pi}_f\}$; always ≥ 1 .

Result: Change of Event Rate (cont'd)

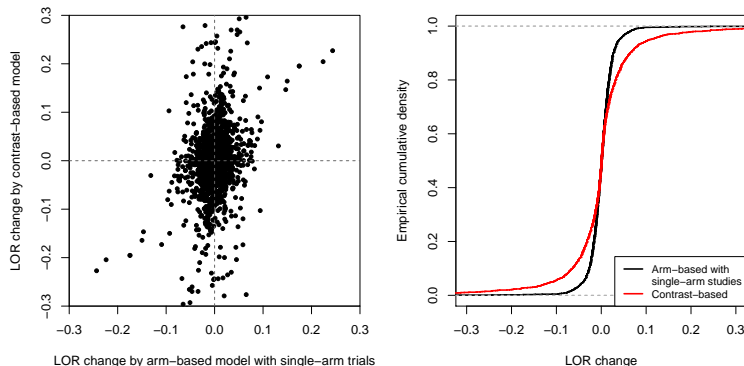
Fold change: < 1.03 minor; > 1.10 large; > 1.20 substantial. (Mills et al., 2013)

Network	Fold change		Network	Fold change	
	Average	Maximum		Average	Maximum
Ballesteros 2005	1.00	1.01	Puhan 2009	1.02	1.05
Ara 2009	1.03	1.09	Lu 2009	1.01	1.04
Bucher 1997	1.02	1.06	Picard 2000	1.01	1.05
Middleton 2010	1.01	1.04	Eisenberg 2008	1.00	1.01
Elliott 2007	1.01	1.06	Trikalinos 2009	1.05	1.39
Thijs 2008	1.01	1.08	Mills 2009	1.01	1.05
Lu 2006	1.01	1.03	Cipriani 2009	1.00	1.03

– Arm-based NMA is fairly robust.

Result: Change of Log Odds Ratio (LOR)

LOR change = LOR based on the reduced network – LOR based on the full network, for *both* contrast- and arm-based NMA.



Used bootstrap resampling to calculate p -value = 0.005 for H_0 : Contrast-based = Arm-based.
– Single-arm trials, which can be used by the arm-based NMA, provide valuable information.

Thank you!