

# On Statistical Inference for Direct and Indirect Multiple Treatment Comparisons

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# Outline

- 1 Introduction
- 2 Meta-Analysis
- 3 Indirect Comparisons
- 4 Direct and Indirect Comparisons
- 5 Concluding Remarks

## Introduction

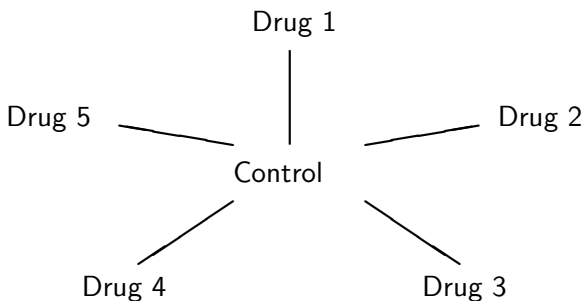
- Scenario 1: Assume that we have results from meta-analyses comparing treatments **A vs. C** and **B vs. C**. What can we conclude from these meta-analyses for the indirect treatment comparison **A vs. B**?
- Scenario 2: Assume that we have results from meta-analyses comparing treatments **A vs. B**, **A vs. C**, and **B vs. C**. Can we improve the comparison of **treatment A vs. treatment B** by using the results from the meta-analyses comparing treatments A vs. C and B vs. C? Are the results from the direct and indirect comparison consistent?
- Of course, much more complicated networks of multiple treatment comparisons can be considered.

## Motivating Example

Endpoint: Adverse Event (# Events / Sample Sizes)

Study	Control	Drug 1	Drug 2	Drug 3	Drug 4
1	22 / 1588	11 / 1596			
2	14 / 1508	9 / 1501			
3	9 / 694		9 / 703		
4	18 / 1154		15 / 1163		
5	12 / 868		5 / 871		
6	32 / 1133			47 / 1140	
7	11 / 1129			20 / 1128	
8	1 / 517			11 / 517	
9	33 / 2224				40 / 2209
10	19 / 1229				23 / 1228
11	17 / 2139				21 / 1220
12	16 / 1508				27 / 1526

# Star-Network



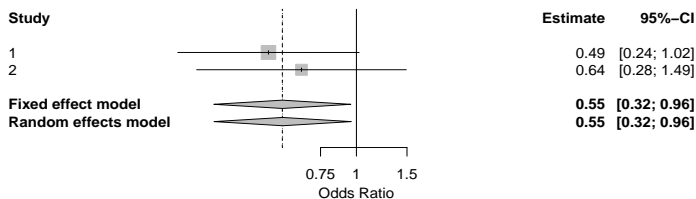
Goal: Inference for Drug  $i$  – Drug  $j$ ,  $1 \leq i < j \leq 4$

## Drug versus Control

- Effect size: **Risk Difference** or (log) **Odds Ratio**?
- Model: **Fixed effect** or **random effects** model? Is heterogeneity present? How can we measure heterogeneity?
- Homogeneity of effect size estimates  $\Rightarrow$  fixed effect model: Inverse variance method, Mantel-Haenszel method, or Peto method (only for log odds ratio available)

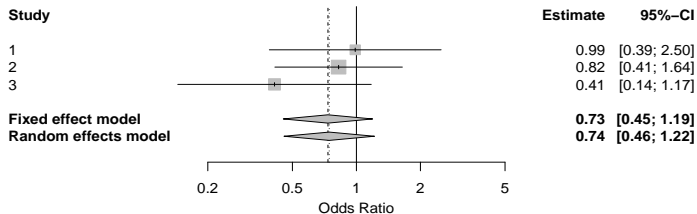
# Results in the Example

## Meta-analysis: Drug 1 vs. Control



# Results in the Example

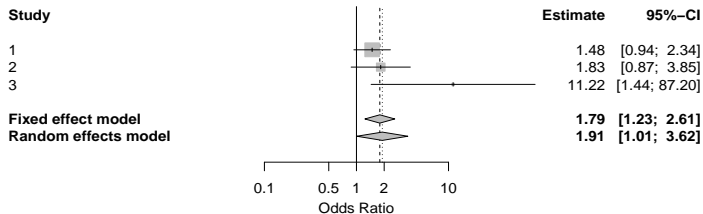
## Meta-analysis: Drug 2 vs. Control





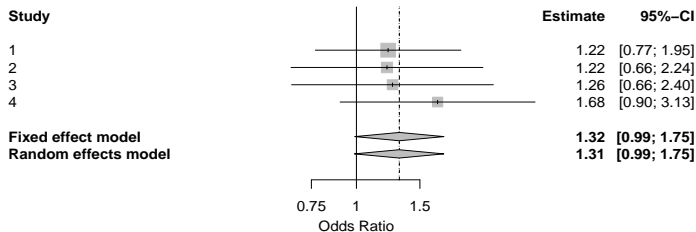
# Results in the Example

## Meta-analysis: Drug 3 vs. Control



# Results in the Example

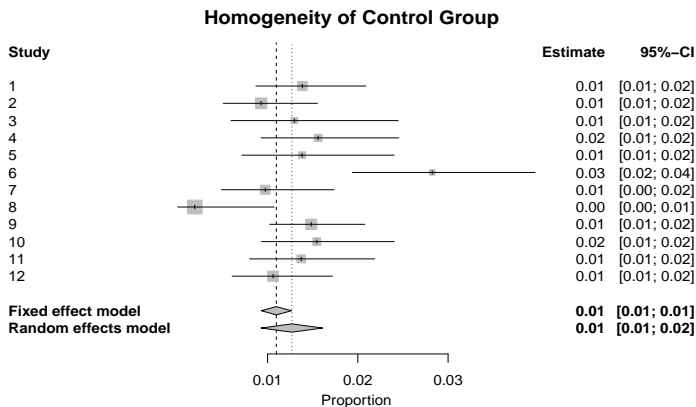
## Meta-analysis: Drug 4 vs. Control



## Summary: Drug versus Control

- Interpretation of the results is the same for both effect sizes (risk difference and log odds ratio).
- Drug 1 and 2 better than control; drug 3 and 4 worse than control.
- Heterogeneity only observed for drug 3 versus control.
- Are the results for the control group homogeneous? NO!

# Homogeneity of control group



## Simple Adjusted Indirect Comparisons

Bucher et al. (1997):

- Let  $\delta_{AC}$  denote the common effect size (on an additive scale) for comparing treatment A vs C and  $\delta_{BC}$  denote the common effect size for comparing treatment B vs C. Then, the common effect size for comparing treatment A vs C is  $\delta_{AB} = \delta_{AC} - \delta_{BC}$ .
- Fixed effect meta-analysis model is appropriate to obtain the common effect size estimators  $\hat{\delta}_{AC}$  and  $\hat{\delta}_{BC}$ .
- The estimate of  $\delta_{AB}$  is then

$$\hat{\delta}_{AB} = \hat{\delta}_{AC} - \hat{\delta}_{BC}$$

with

$$\widehat{\text{Var}}(\hat{\delta}_{AB}) = \widehat{\text{Var}}(\hat{\delta}_{AC}) + \widehat{\text{Var}}(\hat{\delta}_{BC}).$$

## Simple Adjusted Indirect Comparisons

- Bucher's method requires fixed effect model assumption in all meta-analyses and is limited to two-arm trials.
- The method can be applied for effect sizes on an additive scale like risk difference or log odds ratio and for all combining methods, that is, inverse variance, Mantel-Haenszel (variance is estimated on log scale), or Peto method.
- Using the inverse variance method, the improved variance estimators of the meta-analysis estimators proposed by Hartung and Knapp (2001) can be used.

## Simple Adjusted Indirect Comparisons

- Applying Bucher's et al. method to the example (independent of chosen effect size and method):
  - Drug 1 and 2 are not different; drug 3 and 4 are not different.
  - Drug 1 and 2 are better than drug 3 and 4.
- Incorporating three-arm trials in this method needs a specification of the covariance of two effect size estimators, say  $\text{Cov}(\hat{\delta}_{ACi}, \hat{\delta}_{BCi})$ , from the  $i$ th study.

## Simple Adjusted Indirect Comparisons

What about random effects models?

Observational models ( $i = 1, \dots, k; j = 1, \dots, m$ ):

$$\hat{\delta}_{ACi} \sim \mathcal{N}(\delta_{ACi}, \sigma_{ACi}^2) \quad \hat{\delta}_{BCj} \sim \mathcal{N}(\delta_{BCj}, \sigma_{BCj}^2)$$

Structural models ( $i = 1, \dots, k; j = 1, \dots, m$ ):

$$\delta_{ACi} \sim \mathcal{N}(\delta_{AC}, \tau_{AC}^2) \quad \delta_{BCj} \sim \mathcal{N}(\delta_{BC}, \tau_{BC}^2)$$

Random effects models ( $i = 1, \dots, k; j = 1, \dots, m$ ):

$$\hat{\delta}_{ACi} \sim \mathcal{N}(\delta_{AC}, \tau_{AC}^2 + \sigma_{ACi}^2) \quad \hat{\delta}_{BCj} \sim \mathcal{N}(\delta_{BC}, \tau_{BC}^2 + \sigma_{BCj}^2)$$

What does the difference of the meta-analysis estimators  $\hat{\delta}_{AC} - \hat{\delta}_{BC}$  estimate?



## Logistic Regression Approach

- Data from the motivating example can be seen as individual patient data (IPD)
- Hasselblad (1998): logistic regression approach for multitreatment studies
- Model for each arm:  $k$  studies indexed by  $i$ , ( $i=1, \dots, k$ ) and  $r$  treatments (not including the control  $\ell = 0$ )

$$\ln \left( \frac{p_{i\ell(x)}}{1 - p_{i\ell(x)}} \right) = \sum_{j=1}^k \alpha_j x_{ij} + \sum_{\ell=1}^r \beta_{\ell} x_{i\ell}$$

where  $p_{i\ell(x)}$  is the probability of response,  $x_{ij} = 1$  if  $i = j$  and  $x_{ij} = 0$  otherwise, and  $x_{i\ell} = 1$  if the arm received treatment  $\ell$  and  $x_{i\ell} = 0$  otherwise.

## Logistic Regression Approach

- Recall the model

$$\ln \left( \frac{p_{i\ell(x)}}{1 - p_{i\ell(x)}} \right) = \sum_{j=1}^k \alpha_j x_{ij} + \sum_{\ell=1}^r \beta_{\ell} x_{i\ell}$$

- $\hat{\alpha}_j$  estimates the log odds of the event rate with control for the  $j$ th study
- $\hat{\beta}_{\ell}$  estimates the log odds ratio of the  $k$ th treatment effect relative to the control
- Same assumption like in fixed effect meta-analysis model: constant log odds ratio over the studies.

## Logistic Regression Approach

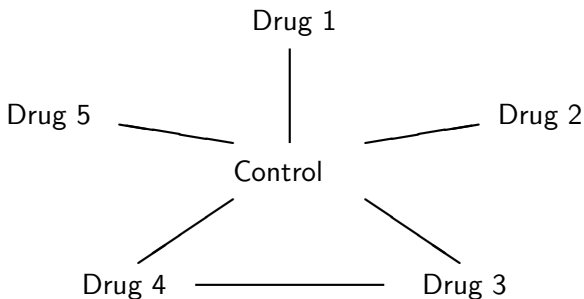
- Random effects model used in Hasselblad:

$$\ln \left( \frac{p_{i\ell(x)}}{1 - p_{i\ell(x)}} \right) = \sum_{j=1}^k \alpha_j x_{ij} + \sum_{\ell=1}^r \beta_{\ell} x_{i\ell} + \theta \epsilon_i$$

and  $\epsilon_i$  is a realization from a standard normal random variable.

- $\theta^2$  can be interpreted as the variability between the studies.
- Model can be fitted, for instance, with SAS PROC NL MIXED.

## A slightly modified network



Goal 1: Inference for Drug  $i$  – Drug  $j$ ,  $1 \leq i < j \leq 4$

Goal 2: Measuring or modeling (in)consistency between direct and indirect comparisons.

## Inconsistency or incoherence

- In the above network, we have a direct comparison between drug 3 and drug 4.
- We have still the indirect comparison between drug 3 and 4 via the control.
- Consequently, we have two separate sources of information about the difference between drug 3 and 4.
- If these sources agree, we should be more confident about the result; if they disagree we should be less confident.

## Lumley's (2002) model

- Consider a network of  $r$  treatment (indexed with  $\ell, m = 1, \dots, r$ ) and  $k$  independent studies (indexed with  $i = 1, \dots, k$ ).
- Let  $\hat{\delta}_{\ell m, i}$  be the effect size estimator of treatment  $\ell$  compared to control  $m$  in the  $i$ th study for the true effect size  $\delta_{\ell m}$ .
- Model:

$$\hat{\delta}_{\ell m, i} = \delta_{\ell m} + a_i + b_{\ell m} + e_{\ell m, i}$$

with

$$E(\hat{\delta}_{\ell m, i}) = \delta_{\ell m}$$

and

$$a_i \sim \mathcal{N}(0, \tau^2)$$

$$b_{\ell m} \sim \mathcal{N}(0, \omega^2)$$

$$e_{\ell m, i} \sim \mathcal{N}\left(0, \hat{\sigma}^2(\hat{\delta}_{\ell m, i})\right)$$

## Lumley's (2002) model

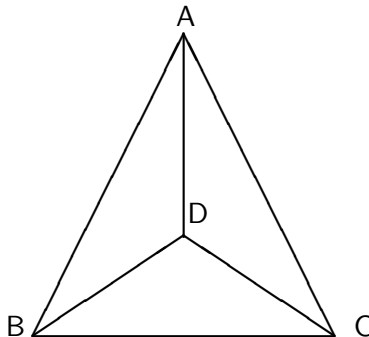
- Recall the model:

$$\hat{\delta}_{\ell m, i} = \delta_{\ell m} + a_i + b_{\ell m} + e_{\ell m, i}$$

- Heterogeneity parameter:  $\tau^2$ , inconsistency parameter:  $\omega^2$
- $b_{\ell m}$  represents a change in the effect of treatment  $\ell$  when it is compared to treatment  $m$ .
- In order to combine different treatment comparisons we need the effect of treatment  $\ell$  to be the same no matter what it is compared against, that is, we need  $b_{\ell m}$  to be close to zero.

## Multi-treatment comparisons

Assumption: We have direct comparisons of all treatments!  
We can handle multi-arm studies with this approach.





## Lu and Ades (2006)

- Goal: Estimate the log odds ratio of  $\delta_{\ell m}$ ,  $\ell, m \in \{A, B, C, D\}$ . Here: 6 parameters!
- Define *basic parameters* with respect to a control treatment, say *A* here,

$$\delta_{BA}, \delta_{CA}, \delta_{DA}$$

- Functional parameters:

$$\delta_{BC} = \delta_{BA} - \delta_{CA}$$

$$\delta_{BD} = \delta_{BA} - \delta_{DA}$$

$$\delta_{CD} = \delta_{CA} - \delta_{DA}$$

- Each relation corresponds to a cycle of edges in the graph.
- Any statistical model based on the above relations may be called *model under evidence consistency*.

## Lu and Ades (2006)

### Statistical model:

- Let  $\mathcal{T}_i$  denote the set of treatments in study  $i$  and  $\mathcal{T}$  the set of all treatments.
- Let  $b(i)$  the baseline (control) treatment in study  $i$  and

$$\mu_i = \text{logit}(\pi_{b(i)i}) = \ln \left( \frac{\pi_{b(i)i}}{1 - \pi_{b(i)i}} \right)$$

- Let be  $\ell \in \mathcal{T}_i \setminus \{b(i)\}$ , then

$$\text{logit}(\pi_\ell) = \mu_i + \delta_{\ell b(i),i}$$

- If  $\delta_{\ell b(i),i} = \delta_{\ell b(i)}$ , then we have a fixed effect model; otherwise a random effects model.
- Prior distributions for  $\mu_i$  and the hyperparameters in the random effects model  $\implies$  Bayesian network meta-analysis.

## Lu and Ades (2006)

### Statistical model under inconsistency

- Consider the above example:

$$\delta_{BC} = \delta_{BA} - \delta_{CA} + w_{ABC}$$

$$\delta_{BD} = \delta_{BA} - \delta_{DA} + w_{ABD}$$






$$\delta_{CD} = \delta_{CA} - \delta_{DA} + w_{ACD}$$

- $w_{ABC}$ ,  $w_{ABD}$  und  $w_{ACD}$  are called inconsistency factors.
- The inconsistency factors represent the discrepancy between the evidence supporting the functional parameters on the left side and the difference between the basic parameters in the right side.
- Bayesian model as above with additional prior distributions for the inconsistency factors.

## Concluding Remarks

- The motivating example comes from a project where the four drugs were compared to the control with respect to two variables for effectiveness (efficacy) and two variables for safety. Based on the indirect comparisons, a ranking of the drugs including the control with respect to effectiveness and safety together should be carried out.
- A new reference: Lu, G., Welton, N.J., Higgins, J.P.T., White, I.R, Ades, A.E. (2011). Linear inference for mixed treatment comparison meta-analysis: A two-stage approach. *Research Synthesis Methods*, **2**, 43–60.

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