On Statistical Inference for Direct and Indirect Multiple Treatment Comparisons

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Outline

Introduction

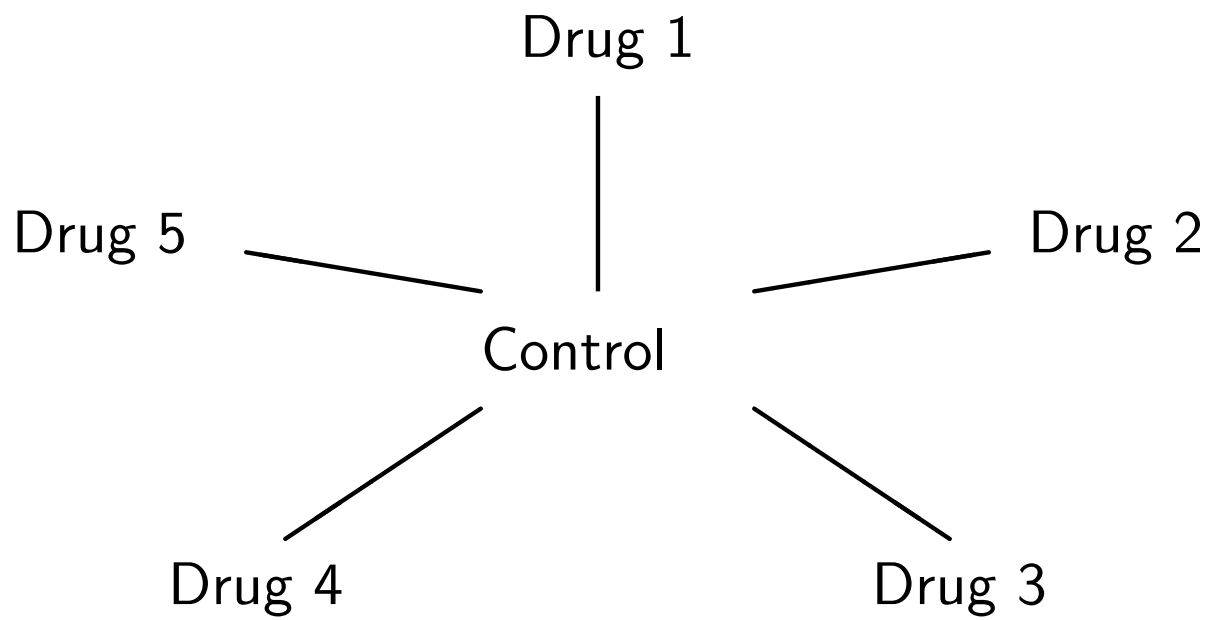
- Scenario 1: Assume that we have results from meta-analyses comparing treatments **A vs. C** and **B vs. C**. What can we conclude from these meta-analyses for the indirect treatment comparison **A vs. B**?
- Scenario 2: Assume that we have results from meta-analyses comparing treatments **A vs. B**, **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

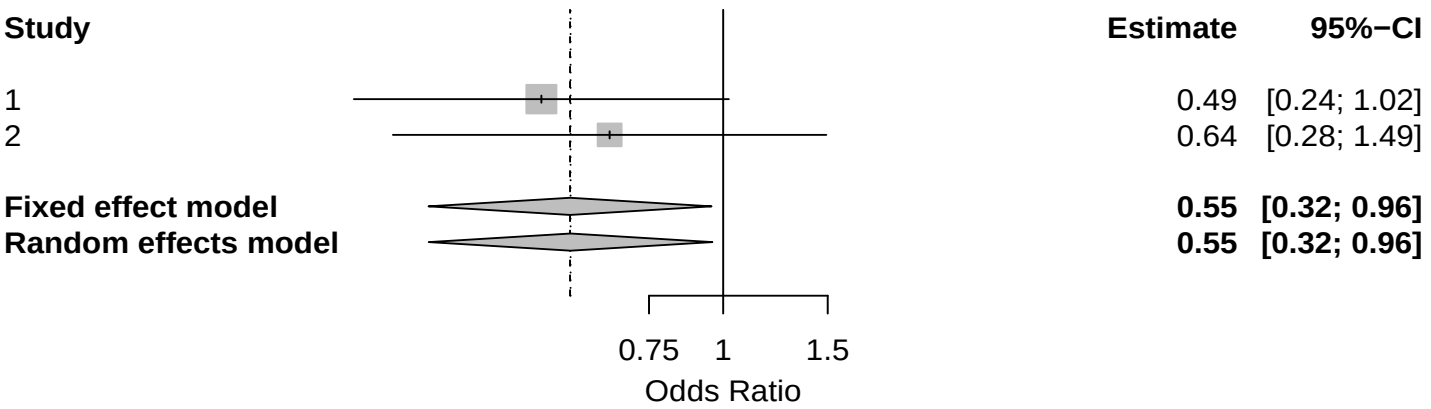


Goal: Inference for Drug i – Drug j, $1 \leq i < j \leq 4$

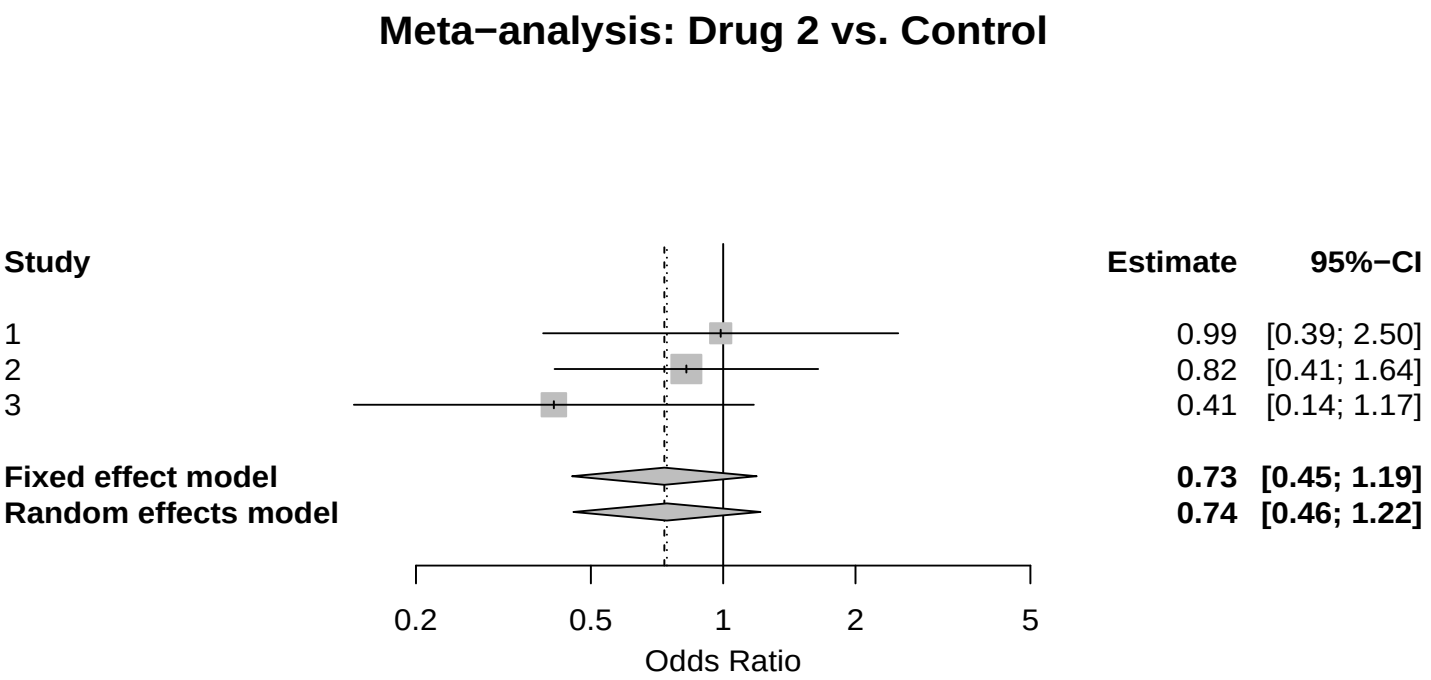
Drug versus Control

- 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



Results in the Example



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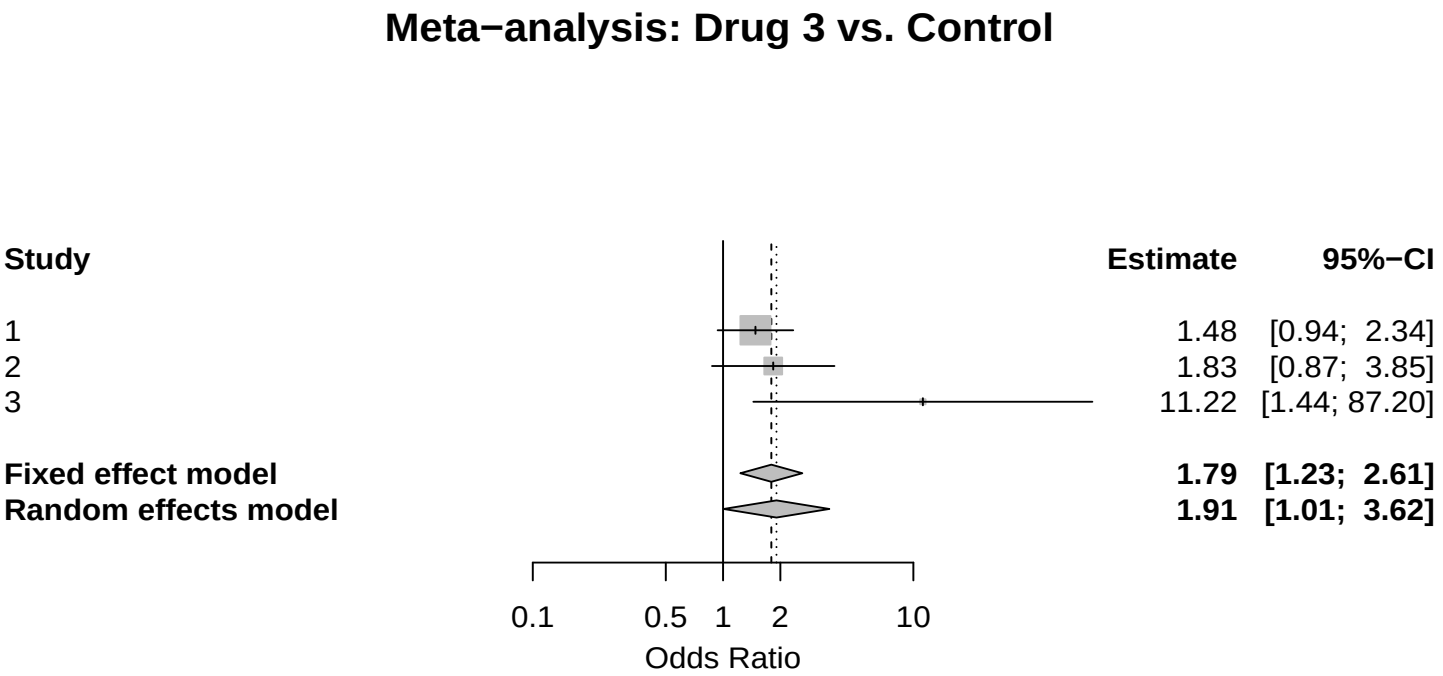
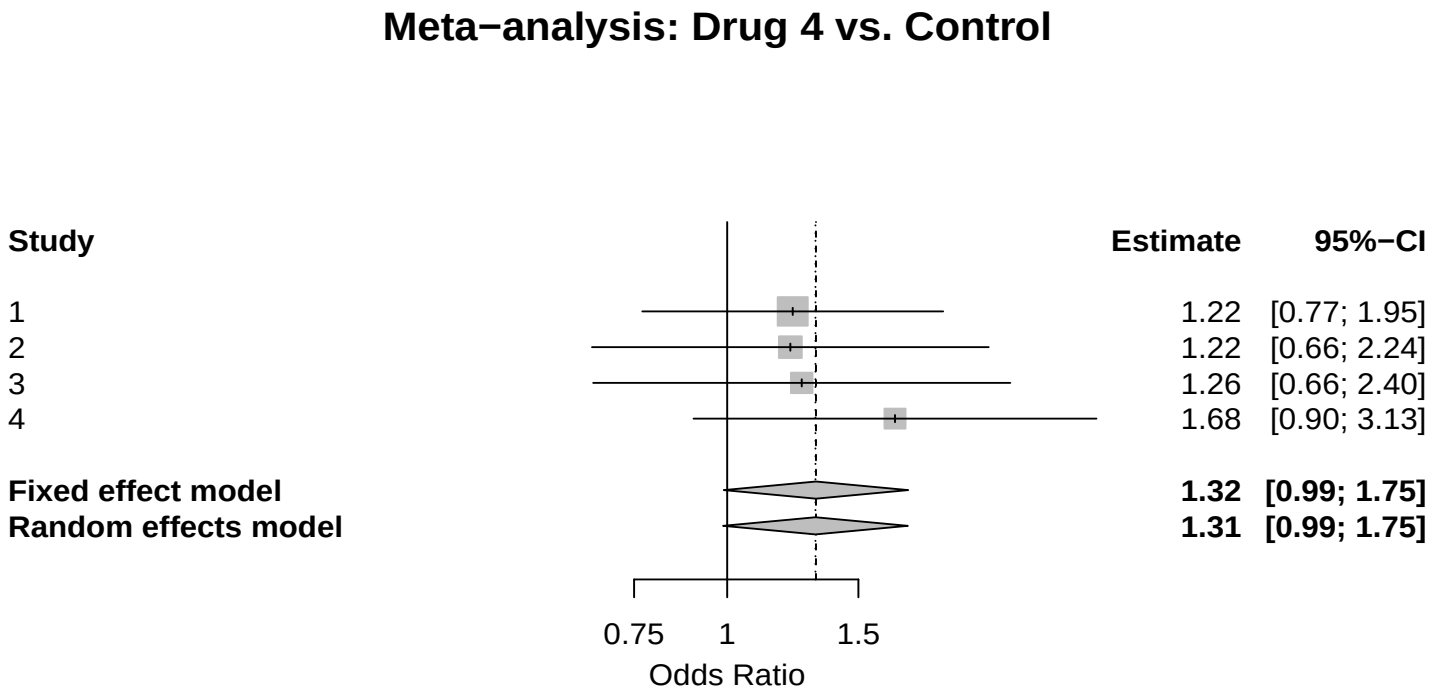


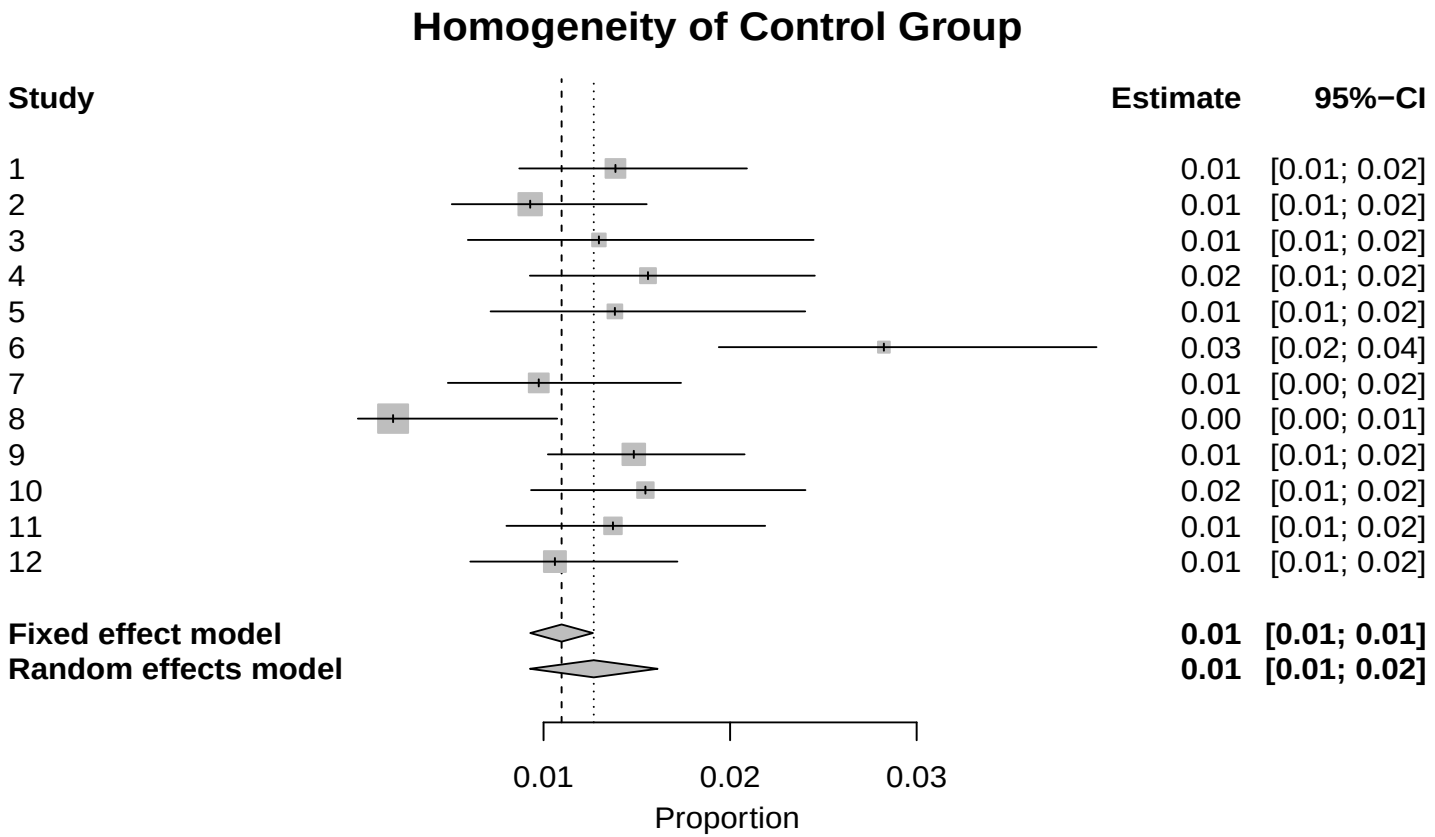
Results in the Example



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 δ_{AC} denote the common effect size (on an additive scale) for comparing treatment A vs C and δ_{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 δ_{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 then 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 ith study.

Simple Adjusted Indirect Comparisons

What about random effects models?

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

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

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

$$\delta_{ACi} \sim \mathcal{N}(\delta_{AC}, \tau^2_{AC}) \qquad \delta_{BCj} \sim \mathcal{N}(\delta_{BC}, \tau^2_{BC})$$

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

$$\hat{\delta}_{ACi} \sim \mathcal{N}(\delta_{AC}, \tau^2_{AC} + \sigma^2_{ACi}) \qquad \hat{\delta}_{BCj} \sim \mathcal{N}(\delta_{BC}, \tau^2_{BC} + \sigma^2_{BCj})$$

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, . . . , 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 ℓ 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 jth study
- $\hat{\beta}_\ell$ estimates the log odds ratio of the kth treatment effect relative to the control
- Same assumption like in fixed effect meta-analysis model: constant log odds ratio over the studies.

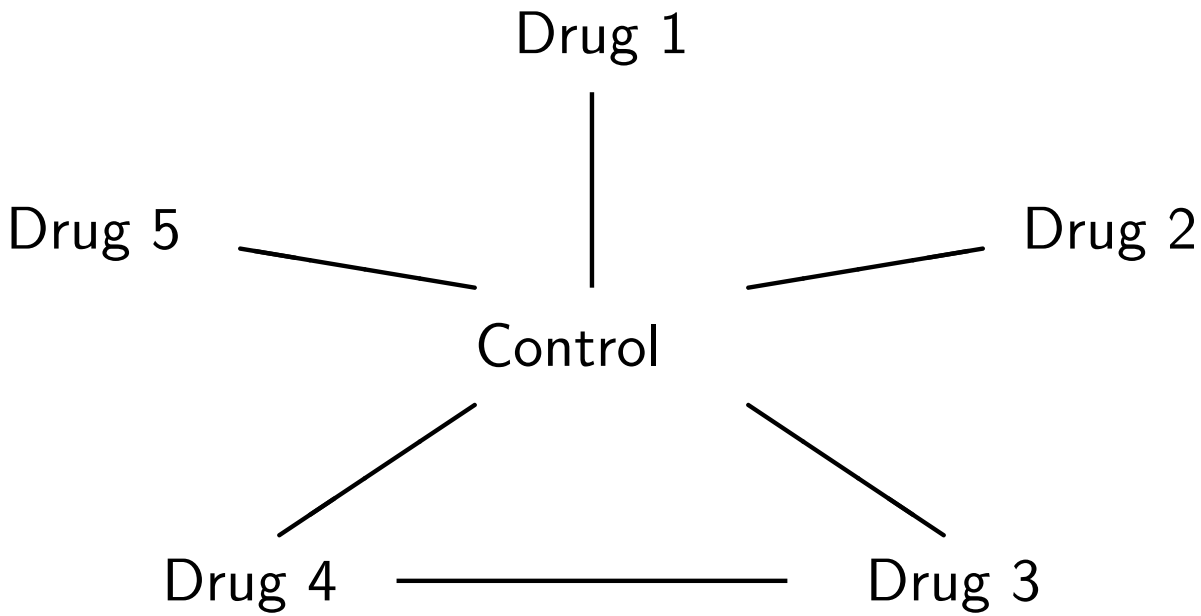
Logistic Regression Approach

- 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 ϵ_i is a realization from a standard normal random variable.
- θ^2 can be interpreted as the variability between the studies.
- Model can be fitted, for instance, with SAS PROC NLMIXED.

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 $\ell, m = 1, \ldots, r$) and k independent studies (indexed with $i = 1, \ldots, k$).
- Let $\hat{\delta}_{\ell m,i}$ be the effect size estimator of treatment ℓ compared to control m in the ith 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

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

and

$$\begin{aligned} a_i &\sim \mathcal{N}(0, \tau^2) \\ b_{\ell m} &\sim \mathcal{N}(0, \omega^2) \\ e_{\ell m,i} &\sim \mathcal{N}\left(0, \hat{\sigma}^2(\hat{\delta}_{\ell m,i})\right) \end{aligned}$$

Lumley's (2002) model

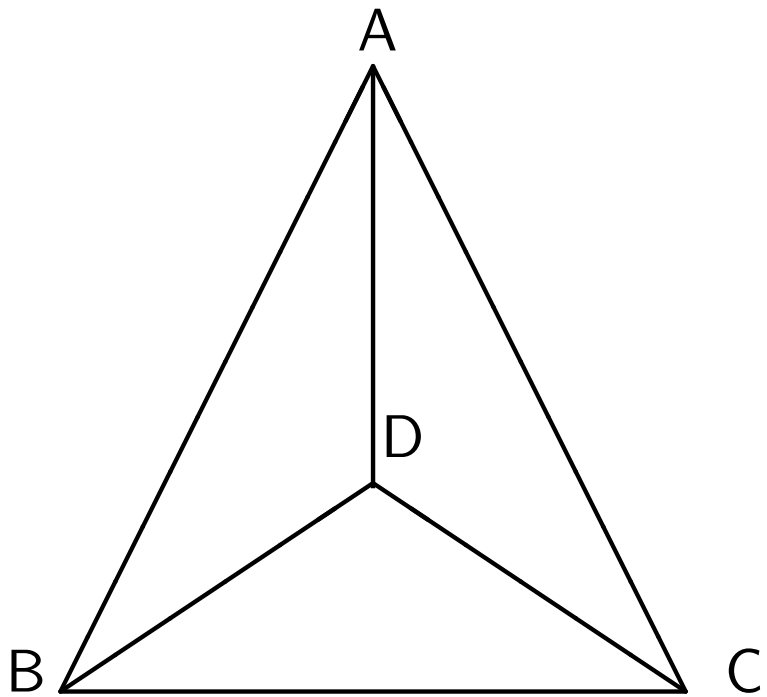
- Recall the model:

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

- Heterogeneity parameter: τ^2, inconsistency parameter: ω^2
- $b_{\ell m}$ represents a change in the effect of treatment ℓ when it is compared to treatment m.
- In order to combine different treatment comparisons we need the effect of treatment ℓ 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:

$$\begin{aligned} \delta_{BC} &= \delta_{BA} - \delta_{CA} \\ \delta_{BD} &= \delta_{BA} - \delta_{DA} \\ \delta_{CD} &= \delta_{CA} - \delta_{DA} \end{aligned}$$

- 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 $\ell \in \mathcal{T}_i \backslash \{b(i)\}$, 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 μ_i and the hyperparameters in the random effects model $\Longrightarrow$ Bayesian network meta-analysis.

Lu and Ades (2006)

Statistical model under inconsistency

- Consider the above example:

$$\begin{aligned} \delta_{BC} &= \delta_{BA} - \delta_{CA} + w_{ABC} \\ \delta_{BD} &= \delta_{BA} - \delta_{DA} + w_{ABD} \\ \delta_{CD} &= \delta_{CA} - \delta_{DA} + w_{ACD} \end{aligned}$$

- 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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