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Methods for evidence synthesis in the case of very few studies

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Research Synthesis Methods

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Methods for evidence synthesis in the case of very few studies

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Introduction

Situation

- Common-effect (CE) model (usually called **fixed-effect** model!)
  - Assumption: No true heterogeneity → strong assumption
- Random-effects (RE) model
  - Assumption: True heterogeneity
  - Problem: In the case of very few studies τ cannot be estimated reliably
- How to synthesize the results?

Generic models

- **Common-effect (CE) model** (Usually called **fixed-effect** model)
  - $y_i = \theta_{CE} + \varepsilon_i \ , \ \varepsilon_i \sim N(0, v_i) \ , \ Var(y_i) = v_i$
  - Assumption: No heterogeneity, same true effect in all studies
  - Parameter of interest: True common treatment effect θ_{CE}
- **Fixed-effects (FE) model** (Laird & Mosteller, 1990)
  - $y_i = \theta_i + \varepsilon_i \ , \ \varepsilon_i \sim N(0, v_i) \ , \ Var(y_i) = v_i$
  - Assumption: Different true (fixed) effects in all studies
  - Parameter of interest: Appropriate function of the θ_i, e.g. the unweighted average $\theta_{FE} = \frac{1}{k} \sum_{i=1}^{k} \theta_i$
  - Use of weights possible
- **Random-effects (RE) model**
  - $y_i = \theta_i + \varepsilon_i, \theta_i = \theta_{RE} + \delta_i, \varepsilon_i \sim N(0, v_i) \ , \delta_i \sim N(0, \tau^2), Var(y_i) = v_i + \tau^2$
  - Assumption: Heterogeneity, distribution of true effects
  - Parameter of interest: Mean of the true treatment effects θ_{RE}

Qualitative evidence synthesis

- If heterogeneity too large → no meta-analysis
- Only choice: Qualitative evidence synthesis
- Nevertheless, clear statements possible
- Example:
  2 studies with significant beneficial results in the same direction
- → Proof of benefit
- But quantification of the effect size is not possible

Meta-analysis with common effect

- Inverse variance approach for continuous endpoints
- Effect estimate: $\hat{\theta}_{CE} = \frac{\sum_{i=1}^{k} y_i w_{i,CE}}{\sum_{i=1}^{k} w_{i,CE}}$, with $w_{i,CE} = 1/\hat{v}_i$
- 95% CI: $\hat{\theta}_{CE} \pm z_{1-\frac{\alpha}{2}} \sqrt{\frac{1}{\sum_{i=1}^{k} w_{i,CE}}}$, z_q q-quantile of normal distribution
- For binary endpoints also applicable but not recommended

Meta-analysis with fixed effects

- Advantage: No assumption of homogeneity required
- In the case of equal importance of all studies:
  Simple unweighted average of the estimated study effects
  (Laird & Mosteller, 1990)
- Effect estimate: $\hat{\theta}_{FE} = \frac{1}{k}\sum_{i=1}^{k} y_i$
- 95% CI: $\hat{\theta}_{FE} \pm z_{1-\frac{\alpha}{2}} \frac{1}{k^2}\sqrt{\sum_{i=1}^{k} \hat{v}_i}$, z_q q-quantile of normal distribution
- Use of weighted average possible but problematic
- **FE meta-analysis has not gained acceptance in medical statistics**

Meta-analysis with random effects

- DerSimonian & Laird (DSL) method criticized (Cornell et al., 2014)
- DSL ignores estimation uncertainty of τ
- Knapp-Hartung (KH) method recommended (Veroniki et al., 2015)
- Effect estimate: $\hat{\theta}_{RE} = \frac{\sum_{i=1}^{k} y_i w_{i,RE}}{\sum_{i=1}^{k} w_{i,RE}}$, with $w_{i,RE} = 1/(\hat{v}_i + \hat{\tau}^2)$
- τ estimated by using the iterative Paule-Mandel method
- 95% CI:

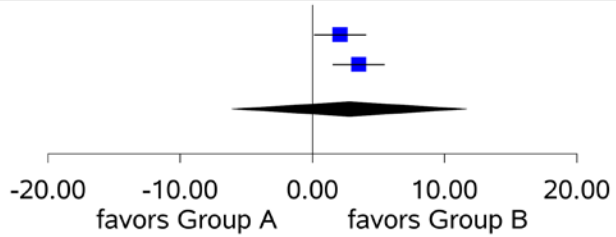
$$\hat{\theta}_{RE} \pm t_{k-1,1-\frac{\alpha}{2}} \sqrt{\frac{\sum_{i=1}^{k} w_{i,RE}(y_i - \hat{\theta}_{RE})^2}{(k-1)\sum_{i=1}^{k} w_{i,RE}}}$$

, $t_{m,q}$ q-quantile of t-distribution

($z_{0.975}$ =**1.96**, $t_{1;0.975}$ =**12.7**, $t_{2;0.975}$ =**4.3**, $t_{3;0.975}$ =**3.2**, $t_{4;0.975}$ =**2.8**)

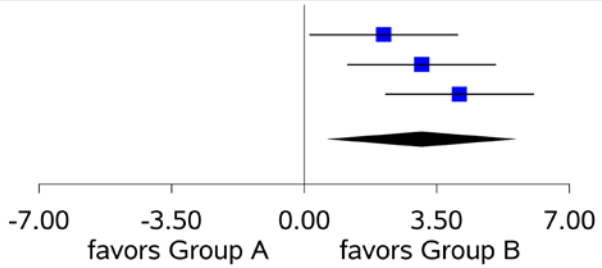
Example 1: Knapp-Hartung method

Study	effect	SE	effect (95% CI)	weight	effect	95% CI
Study A	2.10	1.00		50.0	2.10	[0.14, 4.06]
Study B	3.50	1.00		50.0	3.50	[1.54, 5.46]
Total				100.0	2.80	[-6.09, 11.69]



Heterogeneity: Q=0.98, df=1, p=0.322, I²=0%
Overall effect: Z Score=4.00, p=0.156, Tau(Paule-Mandel)=0

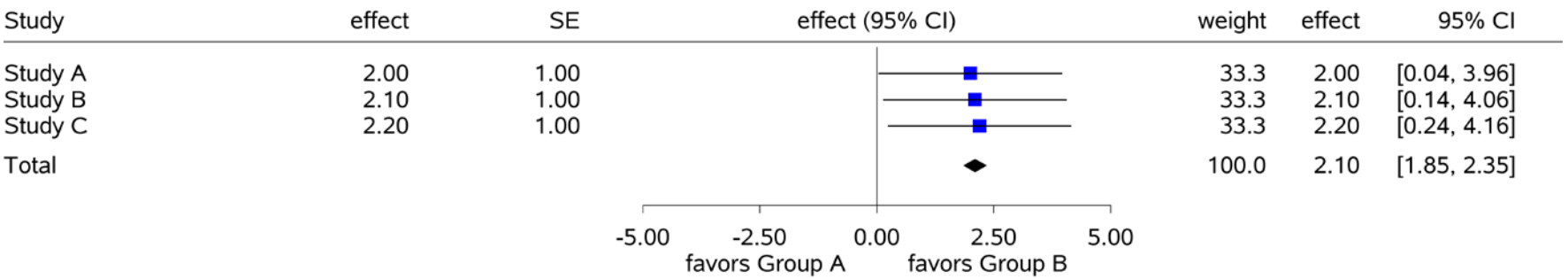
Study	effect	SE	effect (95% CI)	weight	effect	95% CI
Study A	2.10	1.00		33.3	2.10	[0.14, 4.06]
Study B	3.10	1.00		33.3	3.10	[1.14, 5.06]
Study C	4.10	1.00		33.3	4.10	[2.14, 6.06]
Total				100.0	3.10	[0.62, 5.58]



Heterogeneity: Q=2.00, df=2, p=0.368, I²=0%
Overall effect: Z Score=5.37, p=0.033, Tau(Paule-Mandel)=0

Knapp-Hartung method + less than 5 studies → very imprecise

Example 2: Knapp-Hartung method



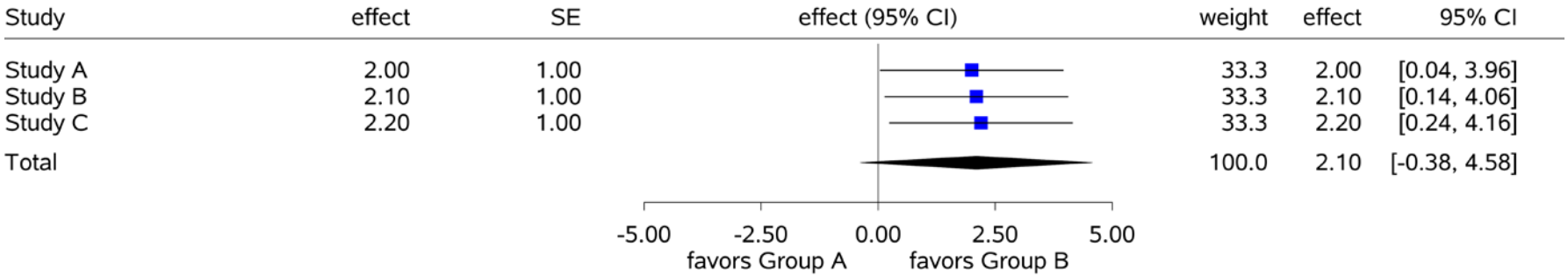
Heterogeneity: Q=0.02, df=2, p=0.990, I^2=0%
Overall effect: Z Score=36.37, p<0.001, Tau(Paule-Mandel)=0

$$\hat{\theta}_{RE} \pm t_{k-1,1-\frac{\alpha}{2}} \sqrt{\frac{\sum_{i=1}^{k} w_{i,RE}(y_i - \hat{\theta}_{RE})^2}{(k-1)\sum_{i=1}^{k} w_{i,RE}}}$$

Knapp-Hartung method + very homogenous results
→ CI misleadingly narrow

Meta-analysis with random effects

- Ad hoc variance correction (Knapp & Hartung, 2003)
- $Var(\hat{\theta}_{RE}) = max\left[\frac{1}{\sum_{i=1}^{k} w_{i,RE}}, \frac{\sum_{i=1}^{k} w_{i,RE}(y_i - \hat{\theta}_{RE})^2}{(k-1)\sum_{i=1}^{k} w_{i,RE}}\right]$
- Misleadingly narrow CIs avoided
- Use of variance correction recommended for very few studies (Röver et al., 2015)



Meta-analysis with random effects

- Ad hoc variance correction (Knapp & Hartung, 2003)
- $Var(\hat{\theta}_{RE}) = max\left[\frac{1}{\sum_{i=1}^{k} w_{i,RE}}, \frac{\sum_{i=1}^{k} w_{i,RE}(y_i - \hat{\theta}_{RE})^2}{(k-1)\sum_{i=1}^{k} w_{i,RE}}\right]$
- Misleadingly narrow CIs avoided
- Use of variance correction recommended for very few studies (Röver et al., 2015)
- In the case of few studies very imprecise (not helpful)
- **Situation of k=2 studies unsolved**
  (Gonnermann et al., 2015)

Methods for binary endpoints

- Standard inverse variance approach can perform very poorly
- Alternative well-established procedures:
  - Mantel-Haenszel method
  - Peto method (for very rare events)
- Frequently overlooked:
  If 2 × 2 tables are given you have full IPD
- Methods for IPD can be used!
- Class of logistic regression models for correlated data (Simmonds & Higgins, 2016)
- Beta-binomial models seem to have favorable properties (Kuss, 2015)
- First investigations available for the situation with very few studies (Mathes & Kuss, 2018) → work in progress

Bayesian methods

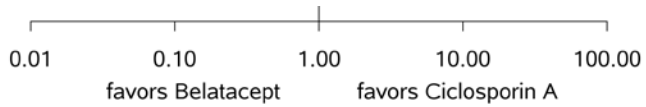
- Competitive alternative to frequentist methods of meta-analysis is given by Bayesian methods
- Usually non-informative prior distributions are chosen for the unknown parameters
- Bayesian methods allow the inclusion of prior knowledge about the heterogeneity parameter in the form of (weakly) informative prior distributions (Friede et al., 2017)
- Reliable information on the prior distribution of the unknown parameters is required
- It may be possible to use empirical data from the Cochrane Database of Systematic Reviews
- A general scientific agreement is required which distribution for the heterogeneity parameter is valid for which situation

Belatacept after kidney transplant (2 significant studies)

- Belatacept vs ciclosporin A for prophylaxis of graft rejection in adults receiving a renal transplant
- Endpoint "renal insufficiency in chronic kidney disease stage 4/5"

Figure 1
Belatacept vs. Ciclosporin A
Renal insufficiency in chronic kidney disease

Study	log(HR)	SE	HR (95% CI)	weight (DSL)	HR	95% CI
BENEFIT	-0.82	0.17		44.6	0.44	[0.32, 0.61]
BENEFIT-EXT	-0.51	0.13		55.4	0.60	[0.46, 0.78]
DSL				100.0	0.52	[0.39, 0.71]
CE IV					0.53	[0.43, 0.65]
KH					0.52	[0.07, 3.71]



Heterogeneity: Q=2.06, df=1, p=0.151, I^2=51.5%
Overall effect: Z Score=-4.21, p<0.001, Tau=0.157

→ **Bayesian approach requires the decision of the "right" prior**

Discussion

- No satisfactory standard method is currently available to perform meta-analyses in the case of very few studies
- CE model in practice possible, but has limitations
- In general, whenever heterogeneity cannot be excluded, the CE model should not be used
- However, in situations with only 1 single study, results of this study are interpreted and conclusions are made for the considered population
- In the case of 2 or more studies we can technically investigate heterogeneity and we try to assess heterogeneity even if heterogeneity cannot reliably estimated
- Thus, in the situation with very few studies, the simple CE model should be applied more frequently

Conclusions

- If heterogeneity is too large for a meaningful pooling of the available study results, apply **qualitative evidence synthesis**
- If the CE assumption does not seem to be violated too strongly, apply **CE meta-analysis** (especially in the case of 2 studies)
- In the case where the pooling of study results seems to be meaningful despite of heterogeneity, apply **RE meta-analysis** by using the **KH method,** otherwise a **special method** (see below)

Special methods:

- For **binary data** apply alternative approaches based on logistic regression models for correlated data (e.g. **beta-binomial model**)
- In the case of reliable prior information regarding the heterogeneity parameter, apply **Bayesian methods** with (weakly) informative prior distributions

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