The inclusion of the estimated inter-study variation into forest plots for random effects meta-analyses – a suggestion for a graphical representation

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Background

Meta-analyses are widely used to combine the results of clinical studies by calculating statistics for overall treatment effects. Basically, two different models exist for meta-analyses. The fixed effects model (FEM) assumes each study is measuring the same treatment effect θ. Different estimations for θ are expected to arise from sampling error only. In contrast, the random effects model (REM) incorporates an inter-study variation τ^2, taking heterogeneous true effects into account [1]. Usually, it is assumed that the true treatment effects are normally distributed. Although these two approaches estimate different parameters (true effect vs. expectation of the distribution of true effects), in practice, the results are represented in the same way. The point and interval estimation of θ is commonly drawn in a forest plot as a diamond, irrespective of the chosen model, e. g., by the software RevMan [2], which is as a rule used in Cochrane Reviews. The estimation of the inter-study variation τ^2 is therefore ignored in the representation of the results of REMs.
It may be helpful for readers to distinguish between the results of fixed and random effects models in forest plots.

Objectives

To suggest a graphical approach for including the estimated inter-study variation into forest plots when representing the results of random effects meta-analyses.

Methods

Assuming a REM, the effect size θi of study i is normally distributed with expectation θ and inter-study variance τ^2. In contrast to a FEM, this approach provides an estimation $\hat{\tau}$ of the inter-study variance and hence, important information about the heterogeneity between the study effect sizes. Different methods exist for estimating τ^2 [3]. The DerSimonian & Laird estimator is used here.
Following the REM, the interval $[\hat{\theta} - 1.96\hat{\tau}; \hat{\theta} + 1.96\hat{\tau}]$ provides an interval in which about 95% of the true study effects are to be expected. We searched for a graphical approach to include this interval into forest plots without impairing the established layout.

Extension of the forest plot

We include two rows for the summary statistics in the forest plot in the case of REMs: As usual, the row “total expectation (95% CI)” represents the point and interval estimation for θ. A new row, “total heterogeneity (95% CI)”, is included into the forest plot. This “heterogeneity interval”, where 95% of the true study effects are to be expected, represents the amount of heterogeneity. The following example illustrates the graphical implementation into forest plots. Figure 1 shows the result of a random effects meta-analysis of eight studies investigating the effect of amatadine for preventing influenza [4]. The estimated overall effect measured by the odds ratio for cases of influenza is 0.34 (95% CI [0.22; 0.53]). However, it is wrong to conclude that the effect of a newly conducted study will be observed within an interval of 0.22 and 0.53 with 95% probability. In contrast to FEM, this interval is just a measure of the precision of the expectation of the distribution of true effects. It depends heavily on the number of studies included in the meta-analysis. However, the heterogeneity interval (red rectangle) delivers information about the distribution of effects. In this example the results are heterogeneous with $\hat{\tau}$ = 0.4.

The effect of a new study will be observed within an interval of 0.15 and 0.74 with 95% probability. In contrast to the confidence interval for θ, the width of this interval does not depend on the number of studies (apart from the precision of the estimation of the boundaries).
Remark: The heterogeneity interval does not provide any information about the statistical significance of θ.

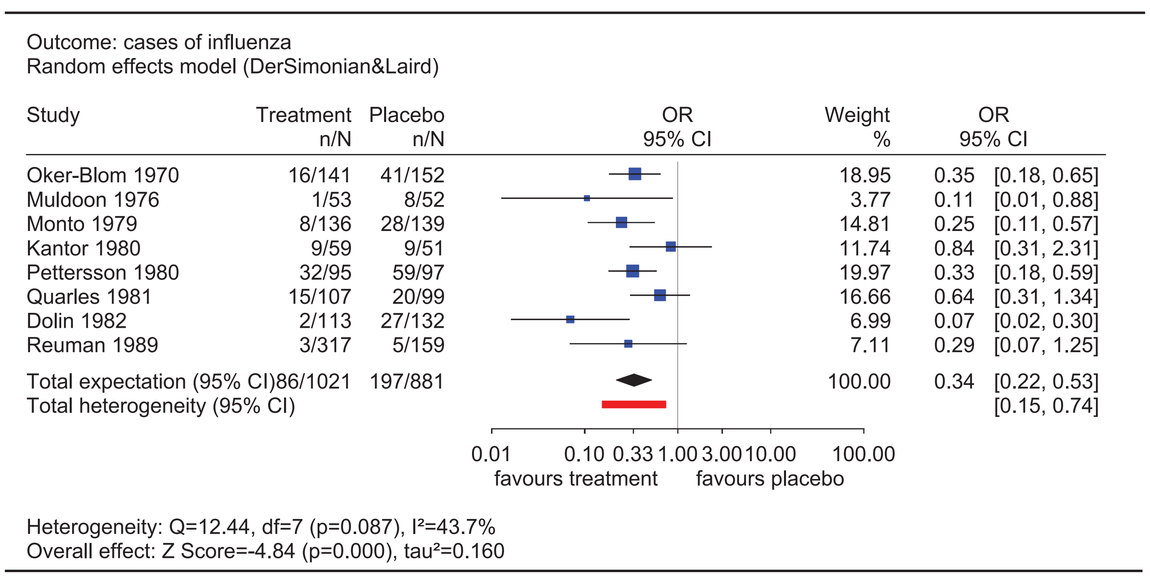

Fig. 1: Meta-Analysis of eight trials of amantadine for prevention of influenza [4]

Discussion

The investigation of potential heterogeneity is an important task in meta-analysis. Various measures and statistical tests for heterogeneity have been suggested in the past years [1,5]. Unfortunately, the commonly used forest plots do not graphically display any items regarding heterogeneous effects. Additionally, representing the results of FEMs and REMs in the same way may lead to the (wrong) impression that both models measure the same thing.
The implementation of the heterogeneity interval into the graphical representation of meta-analyses provides additional information about the variation in treatment effects.

Summary points

The proposed extension of the forest plot may be helpful to

- accurately distinguish the results of meta-analyses with FEMs and REMs,
- graphically illustrate the amount of heterogeneity.

References

1. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002; 21(11): 1539-1558.
2. Review Manager (RevMan) [computer program]. Version 4.2 for Windows. Oxford, England: The Cochrane Collaboration; 2002.
3. Brockwell SE, Gordon IR. A comparison of statistical methods for meta-analysis. Stat Med 2001; 20: 825-840.
4. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003; 327(7414): 557-560.
5. Mittlboeck M, Heinzl H. A simulation study comparing properties of heterogeneity measures in meta-analyses. Stat Med 2006; (in press)

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