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Interval estimation of the overall treatment effect in a meta-analysis of a few small studies with zero events

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ABSTRACT

When a meta-analysis consists of a few small trials that report zero events, accounting for heterogeneity in the (interval) estimation of the overall effect is challenging. Typically, we predefine meta-analytical methods to be employed. In practice, data poses restrictions that lead to deviations from the pre-planned analysis, such as the presence of zero events in at least one study arm. We aim to explore heterogeneity estimators behaviour in estimating the overall effect across different levels of sparsity of events. We performed a simulation study that consists of two evaluations. We considered an overall comparison of estimators unconditional on the number of observed zero cells and an additional one by conditioning on the number of observed zero cells. Estimators that performed modestly robust when (interval) estimating the overall treatment effect across a range of heterogeneity assumptions were the Sidik-Jonkman, Hartung-Makambi and improved Paul-Mandel. The relative performance of estimators did not materially differ between making a predefined or data-driven choice. Our investigations confirmed that heterogeneity in such settings cannot be estimated reliably. Estimators whose performance depends strongly on the presence of heterogeneity should be avoided. The choice of estimator does not need to depend on whether or not zero cells are observed.

1. Introduction

Meta-analyses (MAs) techniques are commonly employed in order to obtain a more precise and more general effect estimate of a treatment. Heterogeneity (τ) of treatment effects measured in multiple Randomized Controlled Trials (RCTs) is a crucial part of the estimation [1].

In MAs of RCTs, methodological challenges arise when the disease under examination is rare and only a few small RCTs are available [2,3]. This is mostly due to the large sample assumptions on which most MA methods are based. In the case of rare diseases with binary endpoints, zero cells are more likely to be observed in at least one of the treatment arms of at least one contributing trial [4–6]. Zero cells in MAs pose challenges as they induce bias in both the estimation of the overall effect and the between-study variance (heterogeneity) [7–14].

When conducting a MA, the estimation method might be adjusted conditionally on observing zero cells. Corrections are typically introduced by adding a number to the zero cells observed; furthermore, the choice of the heterogeneity estimator could change. The latter choice is by itself a challenging task, given the large pool of options [15–24]. Prospective choice of analysis strategies is a fundamental element of statistical inference. The extent to which conditional (on the observed zero cells) analysis choices can affect robustness is of obvious concern.

Especially for dealing with a MA of a few RCTs, there is no straightforward answer to which estimator would be robust across several heterogeneity assumptions [21]. Most estimators face difficulties in case of a limited number of trials; they induce bias in the estimation of τ [25,26] and may result in inappropriate interval estimation of the treatment effect. However, not much is known regarding their behaviour in the presence of zero cells and small populations.

The primary objective of this work is to assess the robustness of heterogeneity estimators in the (interval) estimation of treatment effect across ranges of sparsity of events and assumed heterogeneity. The starting point is the acknowledged poor estimation of heterogeneity in this setting. We evaluate the estimators in case they are predefined (unconditional), as well as when they are chosen depending on the observed zero cells in contributing trials (conditional on the observed

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data, in short: conditional), and explore whether such a retrospective analysis choice can substantially affect inference.

The paper is organized as follows. First we describe the standard random-effects (RE) model and introduce the heterogeneity estimators briefly. Subsequently, we present two motivating examples and their analysis. Then we describe the simulation study and evaluate the two distinct approaches. We conclude with recommendations on evidence synthesis for a sparse-events MA in small populations.

2. Methods

We consider a set of k trials with binary outcomes that compare an experimental treatment to a control. Patients are randomized between two groups: treatment (T) and control (C).

By Y_i we denote the log odds ratio (logOR) in the i^{th} trial. Following standard theory (e.g. Ref. [1]), we assume:

$$Y_i|\theta_i \sim N(\theta_i, \sigma_i^2),\ i = 1, ..., k \quad (1)$$

The study-specific treatment effect estimates are $\hat{\theta}_i = log\left(\frac{r_{Ti}\cdot(n_{Ci}-r_{Ci})}{r_{Ci}\cdot(n_{Ti}-r_{Ti})}\right)$, while their variances are $s_i^2 = \frac{1}{r_{Ti}} + \frac{1}{n_{Ti}-r_{Ti}} + \frac{1}{r_{Ci}} + \frac{1}{n_{Ci}-r_{Ci}}$, where r_i and n_i denote the number of responders and the total number of subjects in each trial, respectively.

Assuming a fixed-effects (FE) model, θ is common for all studies ($\theta_i = \theta$). Assuming a RE model, the θ_i are considered exchangeable and follow a normal distribution, that is,

$$\theta_i|\theta, \tau^2 \sim N(\theta, \tau^2) \quad (2)$$

where θ is the overall effect and τ^2 is the between-study variance. When $\tau^2 = 0$, then the RE model reduces to the FE model. The pooled effect estimate is calculated as a weighted average $\hat{\theta} = \sum_i w_i Y_i / \sum_i w_i$. The inverse variance (IV) weights are then defined as $w_{i,RE} = 1/(s_i^2 + \hat{\tau}^2)$ for the RE model and as $w_{i,FE} = 1/s_i^2$ for the FE model.

A standard confidence interval is calculated as, $\hat{\theta} \pm \hat{\sigma}_\theta\, z_{1-a/2}$, where $z_{1-a/2}$ is the $(1-a/2)$ quantile of the standard normal distribution and $\hat{\sigma}_\theta = \sqrt{1/\sum_i w_i}$.

To apply the RE model, estimation of heterogeneity is required. In the presence of zero cells, heterogeneity estimators entail the addition of a small continuity correction (CC) on zero cells in order to provide finite estimates. Several methods for estimating τ^2 are proposed in the literature. Table 1 presents a summary of the 15 estimators that are included in this study. For a detailed overview of heterogeneity estimators, we refer the reader to two systematic reviews [27,28].

3. Motivating examples

3.1. Intravenous immunoglobulin (IVIG) for Guillain-Barre syndrome (GBS)

GBS syndrome has a prevalence of 1–9/100.000 [29], the term is used to describe a number of rare post-infection neuropathies. Patients may recover completely, remain unable to walk 6 months after disease onset or have a fatal outcome. A recent Cochrane review and MA summarized four RCTs that compared IVIG to plasma exchange [4]. Treatment discontinuation was reported, as a secondary outcome. Trials which were relatively small either failed to report any event or they only had one in each arm. On the contrary, the largest of these trials reported a considerable number of events in both arms (Fig. 1). For the initial analysis the Mantel-Haenszel (MH) FE risk ratio 0.14 (95% 0.05–0.36) was used. By using the MH, the authors excluded information from trials with no reported event, which resulted in a significant overall effect with moderate estimated heterogeneity.

Table 1
Summary of heterogeneity estimators, including their equation, abbreviation and source.

Methods	Equation	Abbreviation	Source
DerSimonian Laird	$\hat{\tau}^2_{dl} = max(0, (Q_{FE} - (k-1))/c_{FE})$	dl	[15]
Positive DerSimonian Laird	$\hat{\tau}^2_{dlp} = \hat{\tau}^2_{dl}$, $\hat{\tau}^2_{dl} > 0$ and $\hat{\tau}^2_{dl} = 0.01$, $\hat{\tau}^2_{dl} <= 0$	dlp	[17]
Two-step Der Simonian Laird	$\hat{\tau}^2_{dl2} = max\left(0, Q_{RE} - \left(w^2_{i,RE}\ s_i^2 - \frac{\sum_i w^2_{i,RE}\ s_i^2}{\sum_i w_{i,RE}}\right)/c_{RE}\right)$	dl2	[16]
Hedges	$\hat{\tau}^2_{he} = max\left(0, \frac{\sum_i (Y_i - \overline{Y}_{FE})^2}{k-1} - \frac{\sum_i s_i^2}{k}\right)$	he	[24]
Two step Hedges	Similar to DL2 using the Hedges estimator	he2	[16]
Positive Sidik-Jonkman	$\hat{\tau}^2_{sj} = max\left(\frac{\sum_i ((Y_i - \overline{Y_{FE}})^2 / (r_i+1))}{k-1}, 0.01\right)$, $r_i = s_i^2/\hat{\tau}^2_O$	sj	[20]
Model error variance - vc	$\hat{\tau}^2_{mvvc} = \frac{\sum_i ((Y_i - \overline{Y_{FE}})^2 / / r_i^* + 1)}{k-1}$, $r_i^* = s_i^2/\hat{\tau}^2_{HE}$	mvvc	[20]
Paul-Mandel	(τ^2_{pm}), $F(\tau^2) = \sum_i w_{i,RE}[Y_i - Y_w(\tau^2)]^2 - (k-1)$	pm	[18]
Improved Paul-Mandel	(τ^2_{ipm}), $F(\tau^2) = \sum_i w^*_{i,RE}[Y_i - Y_w(\tau^2)]^2 - (k-1)$	Ipm	[19]
Hartung - Makambi	$\hat{\tau}^2_{hm} = \frac{Q^2_{FE}}{[2(k-1)+Q_{FE}]c_{FE}}$	hm	[22]
Hunter-Schmidt	$\hat{\tau}^2_{hs} = max(0, (Q_{FE} - k)/\sum_i w_{i,FE})$	hs	[23]
Maximum Likelihood	$\hat{\tau}^2_{ml} = max(0, \sum_i w^2_{i,RE}((Y_i - \overline{Y}_{ML})^2 - s_i^2)/\sum_i w^2_{i,RE})$	ml	–
Restricted Maximum likelihood	$\hat{\tau}^2_{reml} = max\left(0, \frac{\sum_i w^2_{i,RE}\left((Y_i - \overline{Y}_{ML})^2 - s_i^2\right)}{\sum_i w^2_{i,RE}} + \frac{1}{\sum_i w_{i,RE}}\right)$	reml	–
Rukhin Bayes zero estimator	$\hat{\tau}^2_{rb0} = \frac{\sum_i (Y_i - \overline{Y}_{FE})^2}{k+1} - \frac{\sum_i (n_i - k)(k-1)\sum_i s_i^2}{k(k+1)\sum_i (n_i - k+2)}$	rb0	[21]
Rukhin Bayesian positive	$\hat{\tau}^2_{rbp} = \sum_i (Y_i - \overline{Y}_{FE})^2/(k+1)$	rbp	[21]

$w_{i,RE} = \frac{1}{(s_i^2+\tau^2)}$, $w_{i,FE} = \frac{1}{s_i^2}$, $\overline{Y}_{RE/FE} = \frac{\sum_i w_{i,RE/FE} Y_i}{\sum_i w_{i,RE/FE}}$, $Q_{RE/FE} = \sum_i\ w_{i,RE/FE}(Y_i - \overline{Y}_{RE/FE})^2$, $c_{RE/FE} = \sum_i\ w_{i,RE/FE} - \frac{\sum_i w^2_{i,RE/FE}}{\sum_i w_{i,RE/FE}}$, $w_i^* = \frac{1}{\left(\tau^2 + v^*_{i,ipm}\right)}$, $v_{i,iPM} = \frac{1}{n_{(T,i)}+1}(e^{-Prc_O - \widetilde{Y} + \tau^2/2} + 2 + e^{Prc_O + \widetilde{Y} + \tau^2/2}) + \frac{1}{n_{(Ci)}+1}(e^{-Prc_O} + 2 + e^{Prc_O})$ $Pr_{c,o}$: Observed control event rate, $\tau^2_O = \sum_i (Y_i - \overline{Y_{FE}})/k$. The pm, ipm, ml and reml are iterative estimators.