

## Introduction

Meta-analyses for rare binary (e.g., adverse events or safety) outcomes often include studies that have no events in one (“single-zero”) or even both (“double-zero”) treatment arms. A variety of methods to deal with this problem statistically have been proposed. Most of them rely on adding pseudo-observations to the respective studies, or, in case of “double-zero” studies, simply deleting them. However, simply deleting “double-zero” studies might result in biased treatment effects as those studies (with having equal numbers of outcomes in both arms) point to a null effect.

We recently gave an example of a meta-analysis [1] where ignoring “double-zero” studies missed a clearly significant and clinically relevant advantage of the off-pump technique on post-operative stroke prevalence in bypass surgery [2]. Møller et al. [1] reported a relative risk (RR) of 0.53 [95%-CI: 0.31-0.91] after deleting (27 out of 47!) studies with double-zero cells, and a RR of 0.62 [0.32-1.19] after adding 0.01 to all zero cells. We showed that log-risk regression model with random effects, thereby using *all* studies and adding *no* pseudo-information, finds a RR of 0.45 [0.19-0.71], clearly statistically significant and clinically relevant.

While it has been reported that about 30 % of all meta-analyses contain at least one “single-zero” study [3], there is no evidence on the frequency of meta-analyses with “double-zero” studies.

## Methods

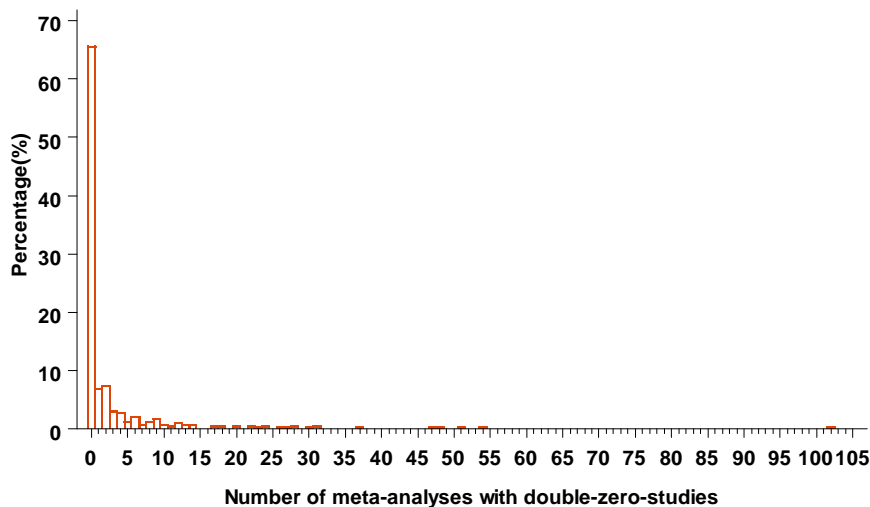
We performed a systematic review on the sample of Cochrane reviews (n = 500) from the Vandermeer et al. [3] study. Two independent reviewers (OK and MW/MK) searched the full text of all reviews. From each systematic review, we extracted 1) the number of meta-analyses containing at least one “double-zero” study and 2) the measure of describing the treatment effect (OR, RR, RD, or Yusuf-Peto). Disagreement was resolved by repeating the search in the respective review and finding consensus.

## Results

Reviewer agreement was very good. For example, for the item „Zero vs. one or more double-zero studies“ we achieved a kappa of 98.7% [97.2,100].

In the 500 Cochrane reviews we found 1394 meta-analyses with at least one “double-zero” study. These 1394 meta-analyses originate from 172 of the 500 (= 34.4 %) reviews. The median number of meta-analyses with at least one “double-zero” study in those 172 reviews was 3.5 (Min: 1, Q1: 1, Q3: 9, Max: 102). Figure 1 gives shows a histogram for the distribution of the number of meta-analyses with double-zero-studies.

In 75 % of these 172 reviews the odds ratio or the relative risk were used for describing the treatment effect. Both measures only allow inclusion of double-zero studies after adding pseudo-observations.



## Conclusion

Meta-analyses with “double-zero” studies occur frequently in Cochrane reviews.

Admittedly we can not check from our data if a correct treatment of double-zero studies (refraining from 1. adding pseudo-observations or 2. simply deleting them) would result in different results, as it was seen in our motivating example.

In ongoing work we are currently collecting and implementing methods for dealing with double-zero studies. Logistic regression models with proper adjustment for correlated responses (GEE, GLMM), the MH-method for risk differences, or the arcsine method [4] are promising candidates.

## References

1. Møller CH, Penninga L, Wetterslev J, Steinbrüchel DA, Gluud C. Clinical outcomes in randomized trials of off- vs. on-pump coronary artery bypass surgery: systematic review with meta-analyses and trial sequential analyses. *Eur Heart J.* 2008 Nov;29(21):2601-16.
2. Kuss O, Börgermann J. Meta-analyses with rare outcomes should use adequate methods – A case study from cardiac surgery. *Deutsche Gesellschaft für Medizinische Informatik, Biometrie und Epidemiologie. 53. Jahrestagung der Deutschen Gesellschaft für Medizinische Informatik, Biometrie und Epidemiologie (gmds).* Stuttgart, 15.-19.09.2008.
3. Vandermeer B, Bialy L, Hooton N, Hartling L, Klassen TP, Johnston B, Wiebe N. Meta-analyses of safety data: a comparison of exact versus asymptotic methods. *Stat Methods Med Res.* 2009 Aug;18(4):421-32.
4. Rucker G, Schwarzer G, Carpenter J, Olkin I. Why add anything to nothing? The arcsine difference as a measure of treatment effect in meta-analysis with zero cells. *Stat Med.* 2009 Feb 28;28(5):721-38.