University Medical Center Göttingen
Department of Medical Statistics

UNIVERSITÄTSMEDIZIN GÖTTINGEN UMG

Research Seminar Series
Hierarchical / Multilevel Models

Thursday, February 28th 2019
CIP-Raum, Humboldtallee 32, ground floor

Symposium on meta-analysis of rare events

Topic: When rare events are reported in a study (e.g., adverse events in a clinical trial), it is not uncommon that only few or even no events are observed in at least one study arm. Pooling information from several such studies promises to improve precision of effect estimates. However, the proper processing of small event counts still poses a methodological challenge. This symposium intends to present novel approaches suitable in such circumstances.

Program:

14:00	Welcome
14:15	Dankmar Böhning (University of Southampton): *Testing heterogeneity in rare events meta-analysis*
15:15	Coffee break
15:45	Susan Martin (University of Southampton): *Estimating heterogeneity variance under sparsity*
16:30	Burak K. Günhan (University Medical Center Göttingen): *Random effects meta-analysis of few studies involving rare events*
17:00	Discussion and closing remarks

Registration: participants are asked to register with Christian Röver (christian.roever@med.uni-goettingen.de) via email by February 22nd.

This seminar series is financially supported by the *Kooperation der SAS-Anwender in Forschung und Entwicklung (KSFE) e.V.*

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Testing heterogeneity in rare events meta-analysis

Dankmar Böhning
University of Southampton, UK

Abstract:
Analyzing and integrating outcome data arising from several studies is a topic of prominent interest, also frequently entitled meta-analysis. We are interested here in counts of events such as the number of health events or deaths in an intervention compared with a control. We assume that we have several studies available where these outcomes have been determined. Conventionally, effect measures such as the risk ratio, risk difference or the odds ratio are considered as effect measures. In this work, we are specifically concerned with the rare events case, in particular, when studies have no events in at least one or both arms. In these situations, study-specific effect measures can be undefined as well as their associated variances. Whereas using a Mantel-Haenszel approach it is still possible to construct relatively easily a summary measure, the typical chi-square statistic approach for investigating heterogeneity entirely breaks down as does the approach for estimating overall effects under heterogeneity. We here propose a new approach which is based on a conditional likelihood which allows a simple construction of a nonparametric test for heterogeneity. Simulation work shows good performance of the suggested approach.

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Estimating heterogeneity variance under sparsity

Susan Martin
University of Southampton, UK

Abstract:
The random-effects model is generally the preferred method to conduct a meta-analysis, as it incorporates between-study heterogeneity – the variability between study estimates as a result of differences in study characteristics. Many medical meta-analyses are concerned with rare-event data, where zero counts are often observed. In such cases, most pre-existing heterogeneity variance estimators perform poorly, resulting in the incorrect estimation of overall treatment effect. To estimate heterogeneity variance in this scenario, we propose some novel methods based on generalised linear mixed models (GLMMs), in particular the Poisson mixed regression model and conditional logistic mixed regression model. We conducted a simulation study to compare our GLMM-based techniques with pre-existing heterogeneity variance estimators for use in random-effects binary outcome meta-analyses. We found that our GLMM-based methods appear to perform well in terms of the estimation of heterogeneity variance with rare-event data, when compared to pre-existing estimators, especially when sample sizes are unbalanced.

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Random effects meta-analysis of few studies involving rare events

Burak K. Günhan
University Medical Center Göttingen

Abstract:
Meta-analyses of clinical trials targeting rare events face particular challenges when the data lack adequate numbers of events for all treatment arms. Especially when the number of studies is low, standard random effects meta-analysis methods can lead to serious distortions because of such data sparsity. To overcome this, we suggest the use of weakly informative priors (WIP) for the treatment effect parameter of a Bayesian meta-analysis model, which may also be seen as a form of penalization. As a data model, we use a binomial-normal hierarchical model (BNHM) which does not require continuity corrections in case of zero counts in one or both arms. We suggest a normal prior for the log odds ratio with mean 0 and standard deviation 2.82, which is motivated (1) as a symmetric prior centred around unity and constraining the odds ratio to within a range from 1/250 to 250 with 95% probability, and (2) as consistent with empirically observed effect estimates from a set of 37'773 meta-analyses from the *Cochrane Database of Systematic Reviews*. In a simulation study with rare events and few studies, our BNHM with a WIP outperformed a Bayesian method without a WIP and a maximum likelihood estimator in terms of smaller bias and shorter interval estimates with similar coverage. Furthermore, the methods are illustrated by a systematic review in immunosuppression of rare safety events following paediatric transplantation. A publicly available R package, MetaStan, is developed to automate the a Bayesian implementation of meta-analysis models using WIPs.

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