Title: Methods for estimating covariate-adjusted relative risks: a simulation evaluation

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Introduction

Binary outcomes are widespread in clinical trials. The odds ratio is a common and established approach for estimating covariate-adjusted binary treatment effects when comparing a treatment and control group. Its popularity is primarily because of its stability and robustness to model mis-specification. However, the situation is different for the relative risk; there is no equivalent, widely acceptable approach to estimate an adjusted relative risk (aRR) when conducting clinical trials. This lack of consistency in practice is partly due to the need for a comprehensive evaluation of available candidate methods to identify optimal approaches for estimating aRRs.

Methods

A literature review was performed, and a simulation study was designed to evaluate the performance of several candidate methods for estimating aRR that represent parametric and non-parametric estimation approaches. We consider the log-binomial, generalised linear models with iteratively re-weighted least-squares (IRWLS) and model-based standard errors (SE); log-binomial with convex optimisation and Hessian SEs; modified-Poisson IRWLS and robust SEs; log-binomial and Poisson generalised estimation equations with robust SEs; marginal standardisation with delta method SEs and permutation test SEs.

Independent and identically distributed datasets are simulated from a randomised controlled trial to evaluate these candidate methods. Performance measures (bias, empirical and mean square errors, relative efficiency and convergence rates) are considered across scenarios. Simulations are replicated 10 000 times for each scenario across all combinations of sample sizes (100, 200, 500, 1000, and 5000), outcomes (5%, 20%, 50% and 80%), and covariates (ranging from -0.05 to -0.02 on the log scale) with main and interaction effects. The treatment effect of 0 (on the log scale) under the null (H0) hypothesis is used to evaluate coverage and power. Subsequently, candidate methods are assessed using datasets with correlated covariates (correlation coefficients ranging from 0.0 to 0.25 on the log scale) and mis-specified models to illustrate the behaviour of candidate methods under these settings.

Potential Results

Several methods for estimating aRR work better than others, and differences in coverage probabilities, efficiency, or power have been observed. Findings from this work comprehensively summarise their performance. The empirical results will provide overarching recommendations on the best method(s) to use in different situations. Following FDA recommendations, it will improve the estimation of treatment effects that provide complementary evidence from adjusted relative risks pertinent to policymaking and public health communications.