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Title: A Unified Inference Framework for Risk Difference and Risk Ratio: Enhanced Performance in Small-Sample, Low-Incidence Binary Endpoints

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Abstract

Binary endpoints in clinical trials are commonly summarized using the risk difference (RD) or risk ratio (RR), with RD more frequently used in regulatory settings and RR more common in HTA. Some concerns arise in practice: statistical significance may disagree between confidence intervals and hypothesis tests due to non-duality of the employed estimation and testing procedures, and conclusions may differ between RD and RR even when based on the same data and stratification factors. Small samples due to ethical, operational, or rare-disease constraints, and low or zero incidence in safety analyses, further complicate inference. Current practices vary from pragmatic continuity corrections to more complex approaches such as Firth correction or penalized likelihood. We investigate the extent of the incoherence issues above, examine the statistical properties of several commonly used procedures for estimation and/or testing across diverse data settings, and introduce an innovative modeling framework that unifies inference on RD and RR while employing Blaker's exact method for confidence intervals and tests. The framework also handles zero-incidence settings via a Bayesian correction that generalizes continuity corrections by assigning Beta priors to event probabilities. Simulations show improved estimation accuracy and near-nominal confidence interval coverage in small-sample and low-incidence settings. Extensive numerical experiments provide practical guidance for selecting appropriate inference strategies across data conditions. An R package facilitates implementation, with code and materials available at: https://github.com/hta-pharma/brm-plus.