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Title: Covariate adjustment in randomized controlled trials: General concepts and practical considerations

Abstract:
There has been a growing interest in covariate adjustment in the analysis of randomized controlled trials in past years. For instance, the US Food and Drug Administration recently issued guidance that emphasizes the importance of distinguishing between conditional and marginal treatment effects. Although these effects may sometimes coincide in the context of linear models, this is not typically the case in other settings, and this distinction is often overlooked in clinical trial practice. Considering these developments, this article provides a review of when and how to use covariate adjustment to enhance precision in randomized controlled trials. We describe the differences between conditional and marginal estimands and stress the necessity of aligning statistical analysis methods with the chosen estimand. In addition, we highlight the potential misalignment of commonly used methods in estimating marginal treatment effects. We hereby advocate for the use of the standardization approach, as it can improve efficiency by leveraging the information contained in baseline covariates while remaining robust to model misspecification. Finally, we present practical considerations that have arisen in our respective consultations to further clarify the advantages and limitations of covariate adjustment.