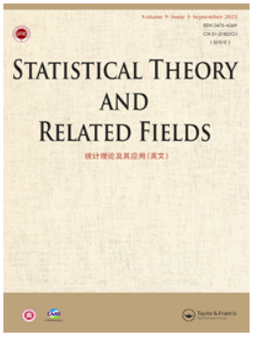

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Comment: Inference after covariate-adaptive randomisation: aspects of methodology and theory

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We thank the editor for the opportunity to write this commentary on the paper by Jun Shao. The author's paper gives an excellent review of methods developed for statistical inference when considering covariate-adaptive, randomised trial designs.

We would like to mention how the results from our paper (Wang et al., 2020) fit into those described by Jun Shao. Our paper focused on stratified permuted block randomisation (Zelen, 1974) and also biased coin randomisation (Efron, 1971), which are categorised as Type 1 randomisation schemes in the author's paper. According to a survey by Lin et al. (2015) on 224 randomised clinical trials published in leading medical journals in 2014, stratified permuted block randomization was used by 70% of trials.

Our goal is to improve precision of statistical inference by combining covariate-adaptive design and covariate adjustment, while providing robustness to model misspecification. In Section 6 of the author's paper, the same goal was discussed and a linear model of potential outcomes given covariates was considered. Our results generalise those given for linear-model-based estimators to all M-estimators (under regularity conditions), which covers many estimators used to analyse data from randomised clinical trials. Examples of M-estimators include estimators based on logistic regression (Moore & van der Laan, 2009), inverse probability weighting (Robins et al., 1994), the doubly-robust weighted-least-squares estimator (Robins et al., 2007), the augmented inverse probability weighted estimator (Robins et al., 1994; Scharfstein et al., 1999), and targeted maximum likelihood estimators (TMLE) that converge in 1-step (van der Laan & Gruber, 2012). Our results are able to handle covariate adjustment, various outcome types, repeated measures outcomes and missing outcome data under the missing at random assumption. Using data from three completed trials of substance use disorder treatments, we estimated that the precision gained due to stratified permuted block randomisation and covariate adjustment ranged from 1% to 36%.

Another contribution of our paper is to prove the consistency and asymptotic normality of the Kaplan-Meier estimator under stratified randomization. Its asymptotic variance was also derived. We conjecture that this result can be generalised to cover covariate-adjusted estimators for the survival function, such as estimators by Lu and Tsiatis (2011); Zhang (2015).

Disclosure statement

No potential conflict of interest was reported by the author(s).

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