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Comment: Outcome-Wide Individualized Treatment Strategies

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1. INTRODUCTION

We congratulate VanderWeele, Mathur and Chen (VMC) for their timely and interesting contribution to the emerging field of longitudinal designs for observational studies. Their paper provides intriguing guidelines on evaluating robustness and sensitivity to potential unmeasured confounding in outcome-wide studies. We expand on their discussion and point out another important application of the outcome-wide studies in developing individualized treatment strategies.

2. OVERT AND HIDDEN BIASES

The primary concern in causal inference is bias that does not diminish as the sample size increases. In general, there are two types of biases: overt and hidden. An overt bias is one that can be seen in the data at hand, for example, the imbalance of a measured pre-treatment covariate across the treatment groups. A hidden bias is similar to an overt bias in the sense that both are caused by the imbalance across treatment groups but the former cannot be seen in the available data because the required information was not observed or recorded (Rosenbaum, 2002). One of the core assumptions in causal inference is the no unmeasured confounder assumption which rules out the presence of hidden biases. But even under the no unmeasured confounder assumption, there is no guarantee that the causal inference methods can produce unbiased estimates, in general. Bias can still manifest itself through certain model misspecification.

Assuming that there is no hidden bias, data adaptive techniques can provide powerful tools to reduce the chance of model misspecification thereby reducing the bias in the treatment effect estimation. However, these methods may lead to an estimator with an unknown asymptotic behavior because of slower rate of convergence than root-n rate. For example, an inverse probability weighting estimator is no longer asymptotically linear if the propensity scores are estimated using a data adaptive technique (e.g., random forest (Liaw, Wiener et al., 2002)). This is because the convergence rate of the inverse probability weighting estimator entirely depends on the rate of convergence of the postulated model for the propensity score. Double robust estimators are alternatives that can overcome this shortcoming. Double robust estimators are based on modeling both the propensity score and the outcome processes and are consistent for the target parameter of interest when any one of two models is consistently estimated. The asymptotic linearity of the double robust estimators is guaranteed when both nuisance parameters are consistently estimated with convergence rate faster than $n^{1/4}$ (Van der Laan and Robins, 2003). Although double robust models facilitate the use of data-adaptive techniques for modeling the nuisance parameters, the resulting estimator can be irregular with large bias and slow rate of convergence when one of the nuisance parameters is inconsistently estimated. Undersmoothing and targeting techniques have been proposed to mitigate this issue (van der Laan, 2014, Benkeser et al., 2017, van der Laan, Benkeser and Cai, 2019).

As pointed out by VMC, the analysis results can be considerably biased by investigator choice after looking at the data. This is even more of a concern when data adaptive techniques are used for two reasons. First, these methods often involve multiple tuning parameters that have to be specified using the data. Often, investigators decide to set some of the tuning parameters to the default (i.e., prespecified) values and choose the others using cross-validation. Second, there are many data adaptive techniques that could be used and the concluding results may depend on the method used. These can be a source of bias if the decision is made after seeing the results. Outcome-wide studies can mitigate this problem if the investigator uses the same modeling and tuning approaches for all the outcomes included in the analyses.

Ensemble learning methods (e.g., super learner) seems to be particularly helpful in reducing the chance of bias caused by model misspecification and researcher bias. Ensemble learning methods combine different user specified data-adaptive techniques (e.g., random forest, generalized additive models, support vector regression) in an optimal way to produce a predictive model which is superior to each individual algorithm included in the ensemble learning model (van der Laan, Polley and Hubbard, 2007).

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