Empirical Likelihood Weighted Estimation of Average Treatment Effects
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Abstract

There has been growing attention on how to effectively and objectively use covariate information when the primary goal is to estimate the average treatment effect (ATE) in randomized clinical trials (RCTs). In this paper, we propose an effective weighting approach to extract covariate information based on the empirical likelihood (EL) method. The resulting two-sample empirical likelihood weighted (ELW) estimator includes two classes of weights, which are obtained from a constrained empirical likelihood estimation procedure, where the covariate information is effectively incorporated into the form of general estimating equations. Furthermore, this ELW approach separates the estimation of ATE from the analysis of the covariate-outcome relationship, which implies that our approach maintains objectivity. In theory, we show that the proposed ELW estimator is semiparametric efficient. We extend our estimator to tackle the scenarios where the outcomes are missing at random (MAR), and prove the double robustness and multiple robustness properties of our estimator. Furthermore, we derive the semiparametric efficiency bound of all regular and asymptotically linear semiparametric ATE estimators under MAR mechanism and prove that our proposed estimator attains this bound. We conduct simulations to make comparisons with other existing estimators, which confirm the efficiency and multiple robustness property of our proposed ELW estimator. An application to the AIDS Clinical Trials Group Protocol 175 (ACTG 175) data is conducted.

Keywords: Missing outcomes, missing at random, double robustness, multiple robustness, semiparametric efficiency bound

1 Introduction

The RCTs aim to compare various treatments when the subjects are randomized to enter different treatment groups. The ATE is commonly used in RCTs as it measures the difference in the mean outcomes between two treatment groups. A natural estimator of ATE is the difference in the empirical average outcomes between the treatment group and the control group; it is unbiased due to randomization. When there exists possible association between the primary outcome and the extensively collected baseline covariates in RCTs, the precision of the ATE estimator may be improved by adjusting for the effect of covariates. There exists a voluminous literature dealing with covariate adjustment [1, 2, 3, 4, 5, 6] to improve the precision of the estimator and increase statistical power. However, it also contains considerable debate regarding the appropriateness of covariate adjustment [7, 8]. Concerns mainly focus on the potential bias in treatment effect estimation, which is caused by post hoc selection of covariates and by allowing investigators to go on a “fish expedition” to find models with the most significant estimate of treatment effect. To address such concerns, a certain number of approaches are proposed to maintain objectivity when adjusting covariates in randomized trials. By utilizing the semiparametric theory, Tsiasist al. [6] proposed a systematic method to objectively incorporate covariate effects while exploiting the relationship between covariates and response outcomes, by positing two separate working regression models for the data from the two treatment groups, leading to an increase in precision. Besides, Shen et al. [9] and Williamson et al. [10] put forward two two-stage estimation procedures for covariate adjustment based on the inverse probability weighting (IPW) method. They tried to adjust for covariates by estimating the propensity score without using outcome data to ensure objectivity.

The empirical likelihood (EL) method is also an appealing method to adjust for baseline covariates in the estimation of ATE [11, 12]. Since Owen [13] first proposed the EL method as a nonparametric likelihood procedure to construct confidence intervals for the mean and other parameters, there have been numerous advances bringing the application of EL to many research areas. We refer interested readers to Owen’s 2001 monograph [14] for further details. An important work done by Qin and Lawless [15] showed that the EL method can effectively incorporate side information in the form of general estimating equations (GEE) into inference through constrained maximization of the empirical likelihood function. Their work inspired some researchers to utilize EL to make covariate adjustments in RCTs and related clinical designs. Zhang [11] considered two unbiased estimating functions that automatically decouple the estimation of ATE from the regression modeling of covariate-outcome relationship and their resulting estimator can reach...
the same efficiency as the existing efficient adjusted estimators do [6]. Considering the estimation of ATE in pretest-posttest studies, Huang et al. [12] proposed an empirical likelihood-based estimation procedure that can incorporate the common baseline covariate information to improve efficiency.

When the outcome is missing in some of the observations in RCTs, great uncertainty and possible bias in the estimation of ATE may exist. Here, we mainly focus on situations with data missing at random (MAR), i.e., conditioning on the covariates and responses, the missing outcomes depend only on the covariates [16]. In order to correct for the bias caused by missingness, various methods have been proposed, including the weighting methods originated by Horvitz and Thompson [17]. In the context of the pretest-posttest study with missing data, Davidian et al. [5] studied a class of consistent semiparametric estimators for the treatment effect and identified the most efficient one based on the semiparametric theory. However, the construction of the semiparametric efficient estimator depends on whether the underlying relationship between the outcome and covariates is correctly specified. This estimator can be much less efficient if the “working regression model” and the true regression model are not close to each other, especially when the dimension of covariates is high.

Recently, empirical likelihood methods have been received growing attention to missing data problems for its attractive data-driven feature and nice robustness property. Qin and Zhang [18] proposed an empirical likelihood-based approach to estimate the mean response under the MAR assumption, the resulting estimators enjoy the double-robustness property, i.e., the estimator of the mean response is asymptotically unbiased if either the underlying propensity score or the underlying regression function is correctly specified. Huang et al. [12] applied the EL method to estimate the treatment effect in the pretest-posttest setting with missing data; they considered counterfactual missing data to estimate EL weights which were not considered by Qin and Zhang [18]. Chen et al. [19] proposed an imputation-based empirical likelihood approach to adjust for baseline information and dealt with the responses in pretest-posttest studies which are missing by design. However, none of their work defines the estimator of ATE as the difference of two weighted outcomes with two separate classes of weights obtained from constrained maximization of the empirical likelihood function.

In this article, we propose a new approach to incorporate covariate information into the estimation of ATE using the EL method. Inspired by the work of Wu and Yan [20], we construct our estimator by separately weighting the outcomes of two samples, where the weights are estimated to carry covariate information through moment constraints which implicitly utilize randomization inherited in RCTs. These constraints focus solely on covariates and treatment assignments but not on the outcomes. To exploit the relationship between the covariates and the outcomes, we posit two models for each treatment group through parametric regression or identity function, then use them in the moment constraints. Therefore, we separate the modeling of the covariate-outcome relationship from the ATE estimation, making the covariate adjustment procedure objective. Also, we extend our approach to the scenarios where the outcomes are partly missing. In this case, we prove the double robustness, multiple robustness and semiparametric efficiency for our proposed estimator.

Zhang’s [11] recent work focused on estimating the ATE by adding the parameter of interest and the covariate information in the estimating functions and deriving the asymptotic form of the ATE estimator using the empirical likelihood theory. In contrast, we first construct the two-sample ELW estimator for ATE with the estimated weights, which are designed to carry the covariate information based on the EL method; then we discuss the asymptotic property for the proposed estimators. Furthermore, Zhang’s method didn’t consider the possible missingness of the outcome data and the corresponding robustness properties in this case, which we take into account in this paper.

When dealing with missing outcomes, we follow the work of Qin and Zhang [18] by adding two moment constraints to take missing mechanism into account. However, we propose to use the combined information from the treatment group and the control group to construct the two moment constraints for the propensity scores, whereas Qin and Zhang treated the two constraints separately. Intuitively, our estimator is more efficient. In fact, we prove that our estimator is semiparametric efficient. Furthermore, we prove that our estimator is doubly robust and multiply robust [21, 22].

In Section 2, we introduce the proposed weighted empirical likelihood estimator and show the extensions of our method to incorporate missing outcomes and enhance multiple robustness. We show the details of the practical implementation of the proposed method in Section 3. In section 4 the performance of our method is evaluated by a series of simulations and an application to ACTG175 data. We draw conclusions in Section 5. Proofs are presented in the supplementary material.
2 Proposed Methodology

In Section 2.1 we describe our method in the standard RCTs where there is no missingness in the outcomes. In Section 2.2 we consider the scenario where outcomes are partly missing under the missing at random mechanism. Furthermore, we apply multiple working models to enhance robustness in the estimation, which leads to the multiple robustness property described in Section 2.3.

2.1 RCTs without missing outcomes

Consider a two-arm randomized clinical trial comparing the treatment group and the control group. Let \( W \) be a binary variable with \( W = 1 \) if treated and \( W = 0 \) if controlled. Define \( \delta = P(W = 1) \) to be the probability of being treated and assume \( 0 < \delta < 1 \). Let \( Y_0(Y_1) \) be the outcome of a subject from the control (treatment) group. We define the outcome for each subject in a unified way as \( Y = WY_1 + (1 - W)Y_0 \). Denote \( X_{1 \times 1} \) to be a \( 1 \)-dimensional vector of baseline covariates. Under randomization in the RCTs, treatment assignment and baseline covariates are independent, i.e., \( W \perp X \). Therefore, \( X|W = 1 \) and \( X|W = 0 \) have the same distribution as that of the covariate \( X \) in the entire sample, i.e., \( p_1(x) = p_0(x) = \rho(x) \) where we define \( p_1(x) \) and \( p_0(x) \) as the probability density function of the covariate \( X \) in the treatment group and the control group, respectively, and \( \rho(x) \) as that of the covariate \( X \) in the entire sample. The observed data of the treatment group \( \{(X_{1i}, Y_{1i}), i = 1, \cdots, m\} \) are independent and identically distributed (i.i.d.). Likewise, the observed data of the control group \( \{(X_{0j}, Y_{0j}), j = 1, \cdots, n\} \) are i.i.d.. Let \( N = m + n \) be the total size of the two samples. Denote \( \mu_1 = E(Y_1) \) and \( \mu_0 = E(Y_0) \). We are interested in estimating ATE, given by \( \theta = \mu_1 - \mu_0 = E(Y_1) - E(Y_0) \), from the observed data.

We introduce an empirical likelihood method to effectively incorporate covariate information when estimating ATE. Let \( f_1(x, y_1) \) be the joint density function of \( (X, Y_1) \) and \( f_0(x, y_0) \) be the joint density function of \( (X, Y_0) \). Let \( p_i = f_1(X_{1i}, Y_{1i}) \) for \( i = 1, \cdots, m \), and \( q_j = f_0(X_{0j}, Y_{0j}) \) for \( j = 1, \cdots, n \), be the probability mass at point \( (X_{1i}, Y_{1i}) \) and \( (X_{0j}, Y_{0j}) \), respectively. The nonparametric likelihood for the observed data is

\[
\prod_{i=1}^{m} p_i \prod_{j=1}^{n} q_j.
\]

We propose to obtain the estimators of the \( p_i \)'s and \( q_j \)'s, by maximizing the likelihood (1) subject to the following constraints

\[
\sum_{i=1}^{m} p_i = 1, \quad p_i \geq 0, \quad i = 1, \cdots, m, \tag{2}
\]
\[
\sum_{j=1}^{n} q_j = 1, \quad q_j \geq 0, \quad j = 1, \cdots, n, \tag{3}
\]
\[
\sum_{i=1}^{m} p_i g(X_{1i}) = \bar{g}, \tag{4}
\]
\[
\sum_{j=1}^{n} q_j h(X_{0j}) = \bar{h}, \tag{5}
\]

where \( \bar{g} = \frac{1}{m} \left\{ \sum_{i=1}^{m} g(X_{1i}) + \sum_{j=1}^{n} g(X_{0j}) \right\} \) and \( h(x) = \frac{1}{n} \left\{ \sum_{i=1}^{m} h(X_{1i}) + \sum_{j=1}^{n} h(X_{0j}) \right\} \). The \( g(x) \) and \( h(x) \) are arbitrary \( r_1 \)-dimensional and \( r_0 \)-dimensional functions, respectively. We take \( r_1 \geq 1 \) and \( r_0 \geq 1 \) as two integers. The constraints (2) and (3) ensure that \( p_i \)'s and \( q_j \)'s are the empirical probabilities. The latter two constraints (4) and (5) are the empirical versions of two equations \( E\{g(X)|W = 1\} = E\{g(X)\} \) and \( E\{h(X)|W = 0\} = E\{h(X)\} \), which utilize the fact that the two groups have identical baseline covariate distributions due to the randomization procedure in the RCTs. Since the constraints for the \( p_i \)'s do not involve any of the \( q_j \)'s and vice versa, we can estimate the \( p_i \)'s and the \( q_j \)'s separately as two optimization problems. Note that \( g(x) \) and \( h(x) \) are known functions, for instance, they can be identity functions, linear functions of the covariates, etc.

Since the above optimization problem is a strictly convex problem, there exists an unique global maximum under some mild conditions, including the convex hull condition that \( \bar{g} \) and \( \bar{h} \) are inside the convex hull of
\{g(X_{1i}), i = 1, \cdots, m\} and \{h(X_{0j}), j = 1, \cdots, n\}$, respectively [14]. The solutions can be obtained by using the method of Lagrange multipliers (details are shown in Section 3):

$$\hat{\beta}_i = \frac{1}{m} \frac{1}{1 + \lambda_1^i} \left\{ g(X_{1i}) - \bar{g} \right\}, \quad i = 1, \cdots, m,$$

$$\hat{q}_j = \frac{1}{n} \frac{1}{1 + \lambda_2^j} \left\{ h(X_{0j}) - \bar{h} \right\}, \quad j = 1, \cdots, n,$$

where $\lambda_1$ and $\lambda_2$ are the Lagrange multipliers determined by

$$\frac{1}{m} \sum_{i=1}^{m} \frac{g(X_{1i}) - \bar{g}}{1 + \lambda_1^i \left\{ g(X_{1i}) - \bar{g} \right\}} = 0, \quad \frac{1}{n} \sum_{j=1}^{n} \frac{h(X_{0j}) - \bar{h}}{1 + \lambda_2^j \left\{ h(X_{0j}) - \bar{h} \right\}} = 0,$$

respectively. Our proposed two-sample empirical likelihood weighted (ELW) estimator is

$$\hat{\theta} = \sum_{i=1}^{m} \hat{\beta}_i Y_{1i} - \sum_{j=1}^{n} \hat{q}_j Y_{0j},$$

which is consistent for the ATE under suitable regularity conditions due to the following theorem.

**Theorem 1.** As $N \to \infty$, $m/N \to \delta > 0$ and $n/N \to 1 - \delta > 0$, $\hat{\theta}$ is a consistent estimator for $\theta$.

The regularity conditions and the proofs of Theorem 1 and other theorems in the article are provided in the supplementary material.

Usually, we take $g(x)$ and $h(x)$ as two parametric outcome regression models $\bar{g}(x; \beta_1)$ and $h(x; \beta_0)$ to approximate $\bar{g}(x) = E(Y|W = 1, X = x)$ and $h(x) = E(Y|W = 0, X = x)$. Note that taking $g(x)$ and $h(x)$ as the identity functions can be seen as adding multiple moment constraints for multiple parametric outcome regression models, each of which only involves one covariate. In practice, we estimate $\beta_1$ and $\beta_0$ by their corresponding estimators $\hat{\beta}_1$ and $\hat{\beta}_0$, which are obtained by fitting two parametric outcome regression models $\bar{g}(x; \beta_1)$ and $h(x; \beta_0)$ separately using the least square method. According to White [23], under suitable regularity conditions, $\hat{\beta}_1 \to \beta_{1*}$ and $\hat{\beta}_0 \to \beta_{0*}$ in probability as $N \to \infty$ where $*$ denote the corresponding values of the parameters that minimizes the Kullback-Leibler distance from the probability distribution function based on the postulated model to the true one that generates the data. Generally, $\bar{g}(x; \beta_{1*}) \neq E(Y|W = 1, X = x)$ unless $\bar{g}(x; \beta_1)$ is correctly specified and $h(x; \beta_{0*}) \neq E(Y|W = 0, X = x)$ unless $h(x; \beta_0)$ is correctly specified. In addition, we have $\bar{g}(\hat{\beta}_1) \to E(\bar{g}(\beta_{1*}))$ and $h(\hat{\beta}_0) \to E(h(\beta_{0*}))$ in probability as $N \to \infty$. Here, we set $g(x)$ and $h(x)$ in [14] and [15] to be $g(x) = \bar{g}(x; \hat{\beta}_1)$ and $h(x) = h(x; \hat{\beta}_0)$. The following theorem gives the asymptotic distribution for $\hat{\theta}$ in this case.

**Theorem 2.** As $N \to \infty$, $N^{1/2}(\hat{\theta} - \theta)$ follows an asymptotically normal distribution with mean $\theta$ and variance $\text{var}\{\varphi(Y, X, W)\}$ with the influence function

$$\varphi(Y, X, W) = \frac{W}{\delta} (Y - \mu_1) - \frac{W - \delta}{\delta} C_1 D_1^{-1} [\bar{g}(X; \beta_{1*}) - E(\bar{g}(X; \beta_{1*}))]$$

$$- \frac{1 - W}{1 - \delta} (Y - \mu_0) + \frac{W - \delta}{1 - \delta} C_0 D_0^{-1} \left[ h(X; \beta_{0*}) - E(h(X; \beta_{0*})) \right],$$

where

$$C_1 = E \left( \frac{W}{\delta} (Y - \mu_1) [\bar{g}(X; \beta_{1*}) - E(\bar{g}(X; \beta_{1*}))] \right),$$

$$C_0 = E \left( \frac{1 - W}{1 - \delta} (Y - \mu_0) [h(X; \beta_{0*}) - E(h(X; \beta_{0*}))] \right),$$

$$D_0 = E \left( \left[ h(X; \beta_{0*}) - E(h(X; \beta_{0*})) \right] \otimes 2 \right),$$

$$D_1 = E \left( \left[ \bar{g}(X; \beta_{1*}) - E(\bar{g}(X; \beta_{1*})) \right] \otimes 2 \right).$$
When \( \tilde{g}(x; \beta_1) \) and \( \tilde{h}(x; \beta_0) \) are correctly specified; namely, \( \tilde{g}(x; \beta_1) = \tilde{g}(x) = E(Y|W = 1, X = x) \) and \( \tilde{h}(x; \beta_0) = \tilde{h}(x) = E(Y|W = 0, X = x) \), we have

\[
\varphi_{opt}(Y, X, W) = \frac{W}{\delta} (Y - \mu_1) - \frac{W - \delta}{\delta} \{E(Y|X, W = 1) - \mu_1\}
- \frac{1 - W}{1 - \delta} (Y - \mu_0) - \frac{W - \delta}{1 - \delta} \{E(Y|X, W = 0) - \mu_0\},
\]

which is the efficient influence function for regular and asymptotically linear (RAL) estimators of \( \theta \) in RCTs described by Tsai et al [24]. In this case, \( \text{var} \{ \varphi_{opt}(Y, X, W) \} \) is the asymptotic variance of \( N^{1/2}(\hat{\theta} - \theta) \), which equals to the semiparametric efficiency bound. This observation leads to the following theorem on the efficiency of \( \hat{\theta} \).

**Theorem 3.** When \( \tilde{g}(x; \beta_1) \) is correctly specified for \( E(Y|W = 1, X = x) \) and \( \tilde{h}(x; \beta_0) \) is correctly specified for \( E(Y|W = 0, X = x) \), the asymptotic variance of \( \hat{\theta} \) attains the semiparametric efficiency bound.

According to Theorem 2 \( \hat{\theta} \) is still consistent even if \( \tilde{g}(x; \beta_1) \) and \( \tilde{h}(x; \beta_0) \) are not correctly specified, but it is not semiparametric efficient due to Theorem 3. Details for the proofs are shown in the supplementary material.

### 2.2 RCTs with missing outcomes

In this section, we follow the work of Qin and Zhang [18] to take missing outcomes into account. However, their work tackled the one-sample case; we extend their work to the RCT data and take randomization into account when we construct our empirical likelihood estimator. Suppose \( Y \) is missing for some subjects, and the baseline covariates \( X \) are always observed. Let \( R_1 \) (\( R_0 \)) be the missing indicator for treatment group (control group) that takes value 0 if \( Y_1 \) (\( Y_0 \)) is missing and 1 otherwise. The observed data are \( \{(R_{1i}Y_{1i}, R_{1i}, X_{1i}), i = 1, \ldots, m; (R_{0j}Y_{0j}, R_{0j}, X_{0j}), j = 1, \ldots, n\} \). We reformulate the data into a two-sample setting as

\[
\{(Y_{1i}, X_{1i}); i = 1, \ldots, m_0\}, \text{ \ Y_{1i} \ is \ observed \ in \ the \ treatment \ group;}
\{(?, X_{1i}); i = m_0 + 1, \ldots, m\}, \text{ W_{1i} \ is \ missing \ in \ the \ treatment \ group;}
\{(Y_{0j}, X_{0j}); j = 1, \ldots, n_0\}, \text{ \ Y_{0j} \ is \ observed \ in \ the \ control \ group;}
\{(?, X_{0j}); j = n_0 + 1, \ldots, n\}, \text{ \ Y_{0j} \ is \ missing \ in \ the \ control \ group.}
\]

For unified notation, we define \( R = WR_1 + (1 - W)R_0, Y = WR_{1Y} + (1 - W)R_{0Y} \). Then the observed data can be written as \( \{(Y_k, X_k, R_k, W_k), k = 1, \ldots, N\} \). We impose the common MAR mechanism[19]: that is, \( P(R = 1|Y, X, W) = P(R = 1|X, W) \). Denote the missing probabilities for the treatment and control groups as \( \pi_1(x) = P(R = 1|W = 1, X = x) \) and \( \pi_0(x) = P(R = 1|W = 0, X = x) \), respectively. We specify \( \pi_1(x; \alpha_1) \) as a parametric model to approximate \( \pi_1(x) \), likewise, \( \pi_0(x; \alpha_0) \) is a parametric model to approximate \( \pi_0(x) \). The \( \alpha_1 \) and \( \alpha_0 \) are given as unknown vector parameters. In practise, we usually model model the propensity scores \( \pi_{w}(x), w = 0, 1 \), with logistic regression models.

Our interest is still to estimate \( \theta = E(Y_1) - E(Y_0) \) in the presence of missingness in the outcomes. Here our proposed estimator is \( \hat{\theta}_{\text{min}} = \sum_{i=1}^{m_0} \hat{p}_iY_{1i} - \sum_{j=1}^{n_0} \hat{q}_jY_{0j} \) where \( \hat{p}_i \)'s and \( \hat{q}_j \)'s are obtained by maximizing the following nonparametric likelihood

\[
\prod_{i=1}^{m_0} p_i \prod_{j=1}^{n_0} q_j
\]  

(6)
subject to

\[ \sum_{i=1}^{m_0} p_i = 1, \quad p_i \geq 0, \quad i = 1, \ldots, m_0, \]
\[ \sum_{j=1}^{n_0} q_j = 1, \quad q_j \geq 0, \quad j = 1, \ldots, n_0, \]
\[ \sum_{i=1}^{m_0} p_i \pi_1(X_{1i}; \hat{\alpha}_1) = \pi_1, \quad \text{(7)} \]
\[ \sum_{j=1}^{n_0} q_j \pi_0(X_{0j}; \hat{\alpha}_0) = \pi_0, \quad \text{(8)} \]
\[ \sum_{i=1}^{m_0} p_i g(X_{1i}) = \tilde{g}, \quad \text{(9)} \]
\[ \sum_{j=1}^{n_0} q_j h(X_{0j}) = \tilde{h}, \quad \text{(10)} \]

where \( \pi_1 = \frac{1}{N} \left\{ \sum_{i=1}^{m_0} \pi_1(X_{1i}; \hat{\alpha}_1) + \sum_{j=1}^{n_0} \pi_1(X_{0j}; \hat{\alpha}_1) \right\}, \) \( \pi_0 = \frac{1}{N} \left\{ \sum_{i=1}^{m_0} \pi_0(X_{1i}; \hat{\alpha}_0) + \sum_{j=1}^{n_0} \pi_0(X_{0j}; \hat{\alpha}_0) \right\}. \) The first two constraints guarantee that \( p_i \)'s and \( q_j \)'s are empirical probabilities. The constraints (7) and (8) reflect the selection bias according to Qin and Zhang [18]. Similarly, the latter two constraints (9) and (10) utilize covariate information through functions \( g(x) \) and \( h(x) \). As described in Section 2.3, we set \( \hat{\pi}(x) = \bar{g}(x; \hat{\beta}_1) \) and \( \tilde{h}(x) = \bar{h}(x; \hat{\beta}_0) \), which are the parametric estimations for \( \bar{g}(x) = E(Y|W = 1, X = x) \) and \( \bar{h}(x) = E(Y|W = 0, X = x) \), respectively. Here, we have the following result on the consistency of \( \hat{\theta}_{\text{mis}} \).

**Theorem 4.** \( \hat{\theta}_{\text{mis}} \) is consistent for \( \theta \) as \( N \to \infty \) if both the following conditions are satisfied: i) either \( \pi_1(x; \alpha_1) \) is correctly specified for \( \pi_1(x) \) or \( \bar{g}(x; \beta_1) \) is correctly specified for \( E(Y|W = 1, X = x) \); ii) either \( \pi_0(x; \alpha_0) \) is correctly specified for \( \pi_0(x) \) or \( \bar{h}(x; \beta_0) \) is correctly specified for \( E(Y|W = 0, X = x) \).

The property indicated by Theorem 4 is known as double robustness [25]. Since double robustness is a special case for multiple robustness which we discuss in Section 2.3, the proof for double robustness is shown in the supplementary material where we prove the multiple robustness. Furthermore, \( \hat{\theta}_{\text{mis}} \) is asymptotically normal distributed if both \( \pi_1(x; \alpha_1) \) and \( \pi_0(x; \alpha_0) \) are correctly specified. The asymptotic distribution for \( \hat{\theta}_{\text{mis}} \) is shown in the next section, where we describe our method in a more general way by allowing multiple models for each of \( \pi_1(x), \pi_0(x), E(Y|W = 1, X = x) \) and \( E(Y|W = 0, X = x) \), but not only one model for each.

For comparison, we consider an alternative estimator for \( \theta \), which is \( \hat{\theta}_{\text{mis}} = \sum_{i=1}^{m_0} \tilde{p}_i Y_{1i} - \sum_{j=1}^{n_0} \tilde{q}_j Y_{0j} \) where \( \tilde{p}_i \)'s and \( \tilde{q}_j \)'s are obtained by the same optimization problem mentioned above except that the constraints (7) - (10) are replaced by

\[ \sum_{i=1}^{m_0} p_i \pi_1(X_{1i}; \hat{\alpha}_1) = \frac{1}{m} \sum_{i=1}^{m} \pi_1(X_{1i}; \hat{\alpha}_1), \quad \text{(11)} \]
\[ \sum_{j=1}^{n_0} q_j \pi_0(X_{0j}; \hat{\alpha}_0) = \frac{1}{n} \sum_{j=1}^{n} \pi_0(X_{0j}; \hat{\alpha}_0), \quad \text{(12)} \]
\[ \sum_{i=1}^{m_0} p_i g(X_{1i}) = \frac{1}{m} \sum_{i=1}^{m} g(X_{1i}), \quad \text{(13)} \]
\[ \sum_{j=1}^{n_0} q_j h(X_{0j}) = \frac{1}{n} \sum_{j=1}^{n} h(X_{0j}). \quad \text{(14)} \]

Clearly, \( \hat{\theta}_{\text{mis}} \) is obtained by directly applying the method proposed in Qin and Zhang [18] which is originally designed for the one-sample case. Since our method considers the randomization procedure for the two samples in each constraint of (7) - (10), while each one of (11) - (14) only focuses on the information from one of the two samples, \( \hat{\theta}_{\text{mis}} \) is intuitively more efficient, which is confirmed by our simulation results in Section 4.
2.3 Multiple robustness

Following the work of Han and Wang [21] and Han [26], we postulate multiple working parametric models $P_1 = \{\pi_i^1(x; \alpha_i^1); c = 1, \ldots, C\}$ for $\pi_1(x)$, $P_0 = \{\pi_0^d(x; \alpha_0^d); d = 1, \ldots, D\}$ for $\pi_0(x)$, $G = \{g^e(x; \beta_0^e); e = 1, \ldots, E\}$ for $E(Y|W = 1, X = x)$ and $H = \{h^f(x; \beta_0^f); f = 1, \ldots, F\}$ for $E(Y|W = 0, X = x)$. The $\alpha_i^1, \alpha_0^d, \beta_0^e, \beta_0^f$ are the corresponding empirical average of the two entire samples, which consistently estimates the population mean. Unlike the postulated parametric function, which is evaluated at one biased sample with missing outcomes, to the corresponding empirical average of $\pi_1(x)$ for $c = 1 \cdots C$, and $\alpha_0^d$ for $d = 1 \cdots D$, are taken to be the maximizer of the corresponding binomial likelihoods

\[
\prod_{i=1}^{m_1} \left\{ \pi_i^1(\alpha_i^1; X_{1i}) \right\}^{R_{1i}} \left\{ 1 - \pi_i^1(\alpha_i^1; X_{1i}) \right\}^{1 - R_{1i}}, \quad c = 1, \ldots, C,
\]

\[
\prod_{j=1}^{n_0} \left\{ \pi_0^d(\alpha_0^d; X_{0j}) \right\}^{R_{0j}} \left\{ 1 - \pi_0^d(\alpha_0^d; X_{0j}) \right\}^{1 - R_{0j}}, \quad d = 1, \ldots, D.
\]

Our proposed estimator is $\hat{\theta}_{mr} = \sum_{i=1}^{m_1} \hat{p}_i Y_{1i} - \sum_{j=1}^{n_0} \hat{q}_j Y_{0j}$ with the estimated weights $\{(\hat{p}_i, \hat{q}_j); i = 1, \ldots, m_0, j = 1, \ldots, n_0\}$ obtained by maximizing the empirical likelihood $\prod_{i=1}^{m_1} \prod_{j=1}^{n_0} \hat{q}_j$ in (19) with the same constraints except that (7) - (10) are changed to

\[
\sum_{i=1}^{m_0} p_i \pi_i^1(X_{1i}; \hat{\alpha}_i^1) = \pi_1 \quad (c = 1, \ldots, C),
\]

\[
\sum_{j=1}^{n_0} q_j \pi_0^d(X_{0j}; \hat{\alpha}_0^d) = \pi_0 \quad (d = 1, \ldots, D),
\]

\[
\sum_{i=1}^{m_0} p_i g^e(X_{1i}; \hat{\beta}_i^e) = g^e \quad (e = 1, \ldots, E),
\]

\[
\sum_{j=1}^{n_0} q_j h^f(X_{0j}; \hat{\beta}_0^f) = h^f \quad (f = 1, \ldots, F),
\]

where $\pi_1 = \frac{1}{N} \left\{ \sum_{i=1}^{m_1} \pi_i^1(X_{1i}; \hat{\alpha}_i^1) + \sum_{j=1}^{n_0} \pi_0^d(X_{0j}; \hat{\beta}_0^d) \right\}$, $\pi_0 = \frac{1}{N} \left\{ \sum_{i=1}^{m_1} \pi_i^0(X_{1i}; \hat{\alpha}_i^0) + \sum_{j=1}^{n_0} \pi_0^d(X_{0j}; \hat{\beta}_0^d) \right\}$, $g^e = \frac{1}{N} \left\{ \sum_{i=1}^{m_0} g^e(X_{1i}; \hat{\beta}_i^e) + \sum_{j=1}^{n_0} g^e(X_{0j}; \hat{\beta}_0^e) \right\}$, $h^f = \frac{1}{N} \left\{ \sum_{i=1}^{m_0} h^f(X_{1i}; \hat{\beta}_i^f) + \sum_{j=1}^{n_0} h^f(X_{0j}; \hat{\beta}_0^f) \right\}$ with $c = 1, \ldots, C$, $d = 1, \ldots, D$, $e = 1, \ldots, E$, $f = 1, \ldots, F$. The first two constraints ensure that $p_i$’s and $q_j$’s are empirical probabilities as mentioned in Section 2.2. The latter four constraints calibrate the weighted average of each postulated parametric function, which is evaluated at one biased sample with missing outcomes, to the corresponding empirical average of the two entire samples, which consistently estimates the population mean. Unlike the previous setting in Section 2.2, there are more than one postulated models for each of $\pi_1(x)$, $\pi_0(x)$, $E(Y|W = 1, X = x)$ and $E(Y|W = 0, X = x)$ to incorporate information from covariates. In this case, we have the following theorem on the consistency of $\hat{\theta}_{mr}$.

**Theorem 5.** $\hat{\theta}_{mr}$ is consistent for $\theta$ as $N \to \infty$ if the following two conditions are satisfied: i) $P_1$ contains a correctly specified model for $\pi_1(x)$ or $G$ contains a correctly specified model for $E(Y|W = 1, X = x)$; ii) $P_0$ contains a correctly specified model for $\pi_0(x)$ or $H$ contains a correctly specified model for $E(Y|W = 0, X = x)$.

Therefore, $\hat{\theta}_{mr}$ is a multiple robust estimator of $\theta$. Next, we introduce the asymptotic distribution and efficiency of $\hat{\theta}_{mr}$. The following theorem gives the asymptotic distribution of $\hat{\theta}_{mr}$.

**Theorem 6.** When $\pi_1(x; \alpha_1^1)$ is a correctly specified model for $\pi_1(x)$ and $\pi_0^d(x; \alpha_0^d)$ is a correctly specified model for $\pi_0(x)$. $N^{1/2}(\hat{\theta}_{mr} - \theta)$ is asymptotically normal distributed with mean 0 and variance $\text{var}(\varphi(Y, X, R, W))$ with the influence function for $\theta$

\[
\varphi(Y, X, R, W) = Z_1 - Z_0 - \frac{W}{\delta} E(Z_1 S_1^T) \{E(S_1^{\otimes 2})\}^{-1} S_1 - \frac{1 - W}{1 - \delta} E(Z_0 S_0^T) \{E(S_0^{\otimes 2})\}^{-1} S_0,
\]
where

\[
Z_1 = \frac{W}{\pi_1(X)} (Y - \mu_1) - \frac{W - \delta \pi_1(X)}{\delta \pi_1(X)} L_1^1 G_1^{-1} U_1(X),
\]

\[
Z_0 = \frac{1 - W}{1 - \delta} \frac{R}{\pi_0(X)} (Y - \mu_0) - \frac{W - \delta \pi_0(X)}{\delta \pi_0(X)} L_0^1 G_0^{-1} U_0(X),
\]

\[
S_1 (X_1, R_1, \alpha_1) = \frac{R_1 - \pi_1^0 (\alpha_1; X_1)}{\pi_1^0 (\alpha_1; X_1)} \frac{\partial \pi_1 (\alpha_1; X_1)}{\partial \alpha_1},
\]

\[
S_0 (X_0, R_0, \alpha_0) = \frac{R_0 - \pi_0^0 (\alpha_0; X_0)}{\pi_0^0 (\alpha_0; X_0)} \frac{\partial \pi_0 (\alpha_0; X_0)}{\partial \alpha_0}.
\]

Here, \(S_1 (X_1, R_1, \alpha_1)\) and \(S_0 (X_0, R_0, \alpha_0)\) are the corresponding score functions of the binomial likelihoods in \([13]\) and \([10]\), respectively.

To show that our proposed estimator \(\hat{\theta}_{mr}\) attains the semiparametric efficiency bound, we derive the semiparametric efficiency bound for ATE estimator in RCTs with missing outcomes, which is given by the following theorem.

**Theorem 7.** The efficient influence function for the RAL estimators of \(\theta\) in RCTs with missing outcomes is given by

\[
\varphi_{opt}(Y, X, R, W) = \frac{W R}{\delta \pi_1(X)} \{Y - E(Y|W = 1, X)\} - \frac{(1 - W) R}{(1 - \delta) \pi_0(X)} \{Y - E(Y|W = 0, X)\}
\]

\[
+ E(Y|W = 1, X) - E(Y|W = 0, X) - \theta,
\]

which leads to the semiparametric efficiency bound \(\text{var} \{\varphi_{opt}(Y, X, R, W)\}\).

Following the techniques used in Han and Wang [21], we prove that the asymptotic variance \(\text{var} \{\varphi(Y, X, R, W)\}\) in Theorem 6 can reach the semiparametric efficiency bound defined in Theorem 7, which leads to the following result on the efficiency of \(\hat{\theta}_{mr}\) (proofs are given in the supplementary material).

**Theorem 8.** When \(\mathcal{P}_1\) contains a correctly specified model for \(\pi_1(x)\), \(\mathcal{P}_0\) contains a correctly specified model for \(\pi_0(x)\), \(\mathcal{G}\) contains a correctly specified model for \(E(Y|W = 1, X = x)\) and \(\mathcal{H}\) contains a correctly specified model for \(E(Y|W = 0, X = x)\), the asymptotic variance of \(\hat{\theta}_{mr}\) attains the semiparametric efficiency bound.

For comparison, the alternative estimator, which is based on the work of Han and Wang [21], is denoted as \(\tilde{\theta}_{hw} = \sum_{i=1}^{m} p_i Y_{1i} - \sum_{j=1}^{n} q_j Y_{0j}\) where \(p_i\)’s and \(q_j\)’s are obtained from the same optimization problem with the same constraints as in Section 2.2 except that (17) - (20) are replaced by

\[
\sum_{i=1}^{m} p_i \pi_1^c (X_{1i}; \hat{\alpha}_1^c) = \frac{1}{n} \sum_{i=1}^{m} \pi_1^c (X_{1i}; \hat{\alpha}_1^c) \quad (c = 1, \ldots, C),
\]

\[
\sum_{j=1}^{n} q_j \pi_0^d (X_{0j}; \hat{\alpha}_0^d) = \frac{1}{n} \sum_{j=1}^{n} \pi_0^d (X_{0j}; \hat{\alpha}_0^d) \quad (d = 1, \ldots, D),
\]

\[
\sum_{i=1}^{m} p_i g^e (X_{1i}; \hat{\beta}_1^e) = \frac{1}{n} \sum_{i=1}^{m} g^e (X_{1i}; \hat{\beta}_1^e) \quad (e = 1, \ldots, E),
\]

\[
\sum_{j=1}^{n} q_j h^f (X_{0j}; \hat{\beta}_0^f) = \frac{1}{n} \sum_{j=1}^{n} h^f (X_{0j}; \hat{\beta}_0^f) \quad (f = 1, \ldots, F).
\]

As mentioned in Section 2.2, our method takes randomization for the two samples into account, as indicated by each of the constraints (17) - (20), while each of the constraints (21) - (24) only involves one of the two samples. Therefore, \(\hat{\theta}_{mr}\) is intuitively more efficient than \(\tilde{\theta}_{hw}\), which is confirmed by our simulation results in Section 4.

### 3 Optimization Details

In Section 5.1, we introduce the computation details of solving the aforementioned optimization problem to obtain our proposed estimators, based on data with or without missing outcomes. Besides, we illustrate how to tackle the convex hull constraint problem in Section 3.2.
3.1 Numerical implementation

As mentioned in Section 2, the proposed optimization problem actually can be split into two optimization problems to estimate $p_j$’s and $q_j$’s separately. Now we demonstrate the method to estimate $p_j$’s, the estimation of $q_j$’s follows the same procedure. We only need to maximize

$$\prod_{i=1}^{m} p_i,$$

subject to (2) and (4). To simplify the notation, we write $\hat{U}_1 = g(X_{1i}) - \bar{g}$. Applying the standard Lagrange multiplier method, the solution of $p_i$ can be written as

$$\hat{p}_i = \frac{1}{m} \frac{1}{1 + \lambda_1^i U_{1i}},$$

(26)

where $\lambda_1$ is the $r_1$-dimensional Lagrange multipliers satisfying

$$\frac{1}{m} \sum_{i=1}^{m} \frac{\hat{U}_{1i}}{1 + \lambda_1^i \hat{U}_{1i}} = 0.$$

(27)

In order to search for the solution of $\lambda_1$, we define

$$\hat{l}(\lambda_1) = \sum_{i=1}^{m} \log \left(1 + \lambda_1^i \hat{U}_{1i}\right)$$

(28)

as our maximizer over $\lambda_1$, which is a strictly convex function. The maximum point $\hat{\lambda}_1$ of (28) satisfies (2) and the $\hat{p}_i$ given by (26) is subject to (2). Note that the existence of the solution of $\lambda_1$ requires some conditions including the convex hull constraint that the convex hull of $\{\hat{U}_{1i}\}_{i=1}^{m}$ retains the zero point. Here, we use a modified Newton–Raphson algorithm to do the numerical search for $\lambda_1$, which is similar to the method discussed by Chen et al. [27].

**Algorithm 1: Modified Newton–Raphson algorithm**

Step 0. Let $\hat{\lambda}_1^{(0)} = 0$. Set $t = 0$, $\gamma_0 = 1$ and $\varepsilon = 10^{-8}$.

Step 1. Calculate $\Delta_1 \left(\hat{\lambda}_1^{(t)}\right) = \partial \hat{l}/\partial \lambda_1$ and $\Delta_2 \left(\hat{\lambda}_1^{(t)}\right) = \left\{\partial^2 \hat{l}/ \left(\partial \lambda_1 \partial \lambda_1^\top\right)\right\}^{-1} \Delta_1 \left(\hat{\lambda}_1^{(t)}\right)$; that is

$$\Delta_1(\lambda_1) = \sum_{i=1}^{m} \frac{\hat{U}_{1i}}{1 + \lambda_1^i \hat{U}_{1i}},$$

$$\Delta_2(\lambda_1) = \left\{- \frac{\sum_{i=1}^{m} \hat{U}_{1i} \hat{U}_{1i}^\top}{\left(1 + \lambda_1^i \hat{U}_{1i}\right)^2}\right\}^{-1} \Delta_1(\lambda_1).$$

If $||\Delta_2 \left(\hat{\lambda}_1^{(t)}\right)|| < \varepsilon$, stop the algorithm and report $\hat{\lambda}_1^{(t)}$; otherwise go to Step 1.

Step 2. Calculate $\delta^{(t)} = \gamma^{(t)} \Delta_2 \left(\hat{\lambda}_1^{(t)}\right)$. If $1 + \left(\hat{\lambda}_1^{(t)} - \delta^{(t)}\right)^\top \hat{U}_{1i} \leq 0$ for some $i$ or $\hat{l} \left(\hat{\lambda}_1^{(t)} - \delta^{(t)}\right) < \hat{l} \left(\hat{\lambda}_1^{(t)}\right)$, let $\gamma^{(t)} = \gamma^{(t)}/2$ and repeat Step 2.

Step 3. Set $\hat{\lambda}_1^{(t+1)} = \hat{\lambda}_1^{(t)} - \delta^{(t)}$, $t = t + 1$ and $\gamma^{(t+1)} = (t + 1)^{-1/2}$. Go to Step 1.

Similarly, to obtain the $\hat{p}_i$’s by solving the optimization problems described in Section 2.2 or 2.3, we only have to take $m = m_0$ in (25) and define $\hat{U}_{1i} = \{\pi_1(X_{1i}; \hat{\alpha}_i) - \pi_1, g(X_{1i}; \hat{\beta}_i) - \bar{g}\}$ or $\hat{U}_{1i} = \{\pi_1(X_{1i}; \hat{\alpha}_i) - \pi_1, \pi_1 \hat{C}_1(X_{1i}; \hat{\beta}_i) - \pi_1, g(X_{1i}; \hat{\beta}_i) - \bar{g}\}$, respectively.
3.2 Convex hull constraint problem

When we try to solve the constrained maximization problem depicted in Section 2, a major problem encountered frequently in practise is that the convex hull condition, i.e., the zero vector is an interior point of the convex hull spanned by \( \hat{U}_{1i} \) for \( i = 1, \ldots, m \), may not be satisfied. The violation of the convex hull condition causes the solution for Lagrange multipliers may not exist, leading to the non-convergence of the algorithm.

This convex hull constraint may be easily violated when the samples are small or the constraints are high-dimensional. Some significant efforts have been made to solve this problem. For instance, Emerson and Owen [28] proposed a balanced augmented empirical likelihood (BAEL) method, which aims to augment the sample with two artificial data points leading to an expanded convex hull with the zero vector inside while preserving the mean of augmented data as the same. Nguyen et al. [29] extended Emerson and Owen’s method [28] to the general estimating equations. Following their work, we define two artificial points added in \( \hat{U}_{1i} \) as

\[
\hat{U}_{1(m+1)} = -sc_{u_1}^* \bar{u}_1, \\
\hat{U}_{1(m+2)} = 2 \bar{U}_1 + sc_{u_1}^* \bar{u}_1,
\]

where \( \bar{U}_1 = \frac{1}{m} \sum_{i=1}^{m} \hat{U}_{1i} \) is in the direction of \( \bar{u}_1 = \frac{\bar{U}_1}{|| \bar{U}_1 ||} \), \( c_{u_1}^* \) is defined as the inverse Mahalanobis distance of a unit vector from \( \bar{U}_1 \) given by

\[
c_{u_1}^* = (\bar{u}_1^\top S^{-1} \bar{u}_1)^{-1/2},
\]

where \( S \) is the sample covariance matrix, \( s \) is an additional parameter set to tune the calibration of the resulting statistic. Note that the sample mean for \( \hat{U}_{1i} \) is maintained by adding these two points, i.e., \( \frac{1}{m} \sum_{i=1}^{m} \hat{U}_{1i} = \sum_{i=1}^{m+2} \hat{U}_{1i} = \bar{U}_1 \).

After augmenting the sample as \( \{\hat{U}_{1i}\}_{i=1}^{m+2} \) and \( \{\hat{U}_{0j}\}_{j=1}^{n+2} \), the empirical likelihood function for estimation of \( \theta \) can be adjusted as

\[
\prod_{i=1}^{m+2} p_i \prod_{j=1}^{n+2} q_j
\]

subject to

\[
\sum_{i=1}^{m+2} p_i = 1, \quad p_i \geq 0, \quad i = 1, \ldots, m,
\]

\[
\sum_{j=1}^{n+2} q_j = 1, \quad q_j \geq 0, \quad j = 1, \ldots, n,
\]

\[
\sum_{i=1}^{m+2} p_i \hat{U}_{1i} = 0,
\]

\[
\sum_{j=1}^{n+2} q_j \hat{U}_{0j} = 0.
\]

In this case, the solution for the weights is given by

\[
\hat{p}_i^* = \frac{1}{(m + 2)} \cdot \frac{1}{(1 + \lambda_1^i \hat{U}_{1i})},
\]

and the \( \hat{\lambda}_1^* \) is obtained by solving

\[
\frac{1}{m + 2} \sum_{i=1}^{m+2} \frac{\hat{U}_{1i}}{1 + \lambda_1^i \hat{U}_{1i}} = 0.
\]

Then our maximizer over \( \lambda_1 \) changed to

\[
\tilde{T}^* (\lambda_1) = \sum_{i=1}^{m+2} \log \left( 1 + \lambda_1^i \hat{U}_{1i} \right).
\]

Therefore, we provide another modified Newton–Raphson algorithm with an augmented sample in Algorithm 2 to avoid violation of the convex hull constraint when searching for \( \hat{\lambda}_1^* \). Since Algorithm 2 only has one more
Algorithm 2: Modified Newton–Raphson algorithm with an augmented sample

Step 0. Let $\lambda_1^{(0)} = 0$. Set $t = 0$, $\gamma_0 = 1$ and $\varepsilon = 10^{-8}$.

Step 1. Generate two artificial points:

\[
\begin{align*}
\tilde{U}_{1(m+1)} &= -s c_u \tilde{u}_1, \\
\tilde{U}_{1(m+2)} &= 2 \tilde{U}_1 + s c_u \tilde{u}_1.
\end{align*}
\]

Step 2. Calculate $\Delta_1 \left( \lambda_1^{(t)} \right) = \partial^2 \hat{\lambda} / \partial \lambda_1$ and $\Delta_2 \left( \lambda_1^{(t)} \right) = \left\{ \partial^2 \hat{\lambda} / \left( \partial \lambda_1 \right) \right\}^{-1} \Delta_1 \left( \lambda_1^{(t)} \right)$, that is

\[
\Delta_1(\lambda_1) = \sum_{i=1}^{m+2} \frac{\tilde{U}_{1i}}{1 + \lambda_1^{(t)} \tilde{U}_{1i}},
\]

\[
\Delta_2(\lambda_1) = \left\{ -\sum_{i=1}^{m+2} \frac{\tilde{U}_{1i} \tilde{U}_{1i}^\top}{\left( 1 + \lambda_1^{(t)} \tilde{U}_{1i} \right)^2} \right\}^{-1} \Delta_1(\lambda_1).
\]

If $||\Delta_2 \left( \lambda_1^{(t)} \right)|| < \varepsilon$, stop the algorithm and report $\lambda_1^{(t)}$; otherwise go to Step 2.

Step 3. Calculate $\delta^{(t)} = \gamma^{(t)} \Delta_2 \left( \lambda_1^{(t)} \right)$. If $1 + \left( \lambda_1^{(t)} - \delta^{(t)} \right)^\top \tilde{U}_{1i} \leq 0$ for some $i$ or

$\hat{\lambda}_i^{(t)} - \delta^{(t)} < \hat{\gamma}_i^{(t)} \left( \lambda_1^{(t)} \right)$, let $\gamma^{(t)} = \gamma^{(t)} / 2$ and repeat Step 2.

Step 4. Set $\lambda_1^{(t+1)} = \lambda_1^{(t)} - \delta^{(t)}$, $t = t + 1$ and $\gamma^{(t+1)} = (t + 1)^{-1/2}$. Go to Step 2.

step of generating two artificial points to build an augmented sample compared to Algorithm 1; these two algorithms have almost the same computational speed.

In the simulations implemented in Section 4.1.1, we use Algorithm 2 only in the Simulation 3 where we apply our method on the simulated missing data by solving the optimization problem in Section 2.2. Recall that this optimization problem has two more moment constraints involving propensity score models, which can easily cause a high-dimension problem especially when we take the functions $g(x)$ and $h(x)$ as the identity functions.

### 4 Simulation and Real Data Analysis

In this section, we report the results of several simulation experiments and a real data analysis for ACTG175 data to evaluate the performance of our proposed estimators.

#### 4.1 Simulation

We present four simulation studies to demonstrate the performance of our proposed method based on 1000 Monte Carlo data sets.

**Simulation 1.** Similar to the simulation studies reported by Tsiatis et al. [6], we conduct a simulation experiment based on ACTG175 data analysis in Section 1.2. In each simulated data set, we generate five continuous baseline covariates ($X_1, X_2, X_3, X_4, X_5$) from a multivariate normal distribution with empirical mean and covariance matrix of the same variables in the ACTG175 data. Besides, we generate each binary covariate in ($X_6, X_7, X_8, X_9, X_{10}, X_{11}$) from an independent Bernoulli distribution with their own data proportion in the ACTG175 data as parameters. Independent of all the other variables, the treatment indicator $W$ is derived from Bernoulli($\delta$) with $\delta$ as the treatment assignment probability. Finally, according to the covariates and the treatment assignment, the outcome variable CD4 count at 20 ± 5 weeks is generated from a normal distribution with the conditional mean $\mu_{1,2}$ and conditional variance given after (20).

In each data set, we use our proposed method and the competing methods mentioned in Tsiatis et al. [6] to estimate $\theta$, including “Unadjusted” estimator $\bar{Y}_1 - \bar{Y}_0$, “Change score” estimator $\bar{Y}_1 - \bar{Y}_0 - (X_1 - X_0)$, two semiparametric estimators proposed by Tsiatis et al. [6] with variable selection procedure “Forward-1”
and “Forward-2” estimators, and two classical estimators “ANCOVA” estimator [3] and “KOCH” estimator [2]. Details for these competing estimators are shown in the supplementary material.

Table I shows the results of two cases: \( N = 2139 \) and \( \delta = 0.75 \); \( N = 400 \) and \( \delta = 0.5 \). ELW-Identity and ELW-Linear are both our proposed two-sample ELW estimators. A “benchmark” estimator of \( \theta \), which uses the true treatment-specific regression models, is also included for comparison. The former estimator takes \( g(x) \) and \( h(x) \) as identity functions, while the latter one sets \( g(x) \) and \( h(x) \) as linear regression functions that fitted separately by data from each treatment group. Table I shows that all adjusted estimators including our proposed ones have better performance in all evaluation metrics compared to the unadjusted estimator, e.g. they all have smaller bootstrap standard error, which implies covariate information incorporation can lead to an efficiency improvement. Furthermore, the result indicates our proposed ELW estimators can achieve a significant efficiency gain as they enjoy the smallest bootstrap standard error and mean square error among all estimates.

### Table 1: Results for simulation based on ACTG175 data

| Estimator      | Bias   | Ave.Boot.SE | Cov.prob.boot. | MSE     |
|---------------|--------|-------------|----------------|---------|
| \( n = 2139, \delta = 0.75 \) |        |             |                |         |
| Unadjusted    | -0.127 | 6.736       | 0.955          | 43.942  |
| Change scores | -0.155 | 5.627       | 0.954          | 30.368  |
| Forward-1     | -0.157 | 5.159       | 0.954          | 25.139  |
| Forward-2     | -0.112 | 5.281       | 0.961          | 25.574  |
| ANCOVA        | -0.175 | 5.179       | 0.954          | 25.331  |
| KOCH          | -0.162 | 5.147       | 0.954          | 25.034  |
| ELW-Identity  | -0.141 | 5.146       | 0.957          | 25.001  |
| ELW-Linear    | -0.140 | 5.133       | 0.956          | 25.028  |
| Benchmark     | -0.139 | 5.113       | 0.954          | 24.850  |
| \( n = 400, \delta = 0.5 \) |        |             |                |         |
| Unadjusted    | 0.004  | 13.756      | 0.939          | 202.402 |
| Change scores | -0.563 | 11.665      | 0.954          | 132.685 |
| Forward-1     | -0.439 | 10.985      | 0.948          | 121.313 |
| Forward-2     | -0.412 | 14.409      | 0.962          | 124.378 |
| ANCOVA        | -0.533 | 10.939      | 0.950          | 120.614 |
| KOCH          | -0.523 | 10.941      | 0.949          | 120.795 |
| ELW-Identity  | -0.344 | 10.971      | 0.945          | 120.466 |
| ELW-Linear    | -0.381 | 11.008      | 0.945          | 120.794 |
| Benchmark     | -0.353 | 10.801      | 0.949          | 115.672 |

Bias is the mean difference between the estimator between \( \hat{\theta} \) and the true value of \( \theta \); Ave.Boot.SE is the average bootstrap standard error calculated as the average of 1000 bootstrap standard error estimates, each of which involves 500 bootstrap replicates; Cov.prob.boot. is the coverage probability of a 95% Wald confidence interval using the average bootstrap standard error as standard error; MSE is the mean squared error calculated as the mean squared difference between \( \hat{\theta} \) and the true value of \( \theta \). Details for each competing estimator are shown in the supplementary material.

### Simulation 2.

The above simulation design assumes that there is a linear relationship between the outcome variable and covariates, which may not be true in most cases. Next, we consider a nonlinear case to check the performance of our proposed method. This simulation uses three continuous variables, \( X = (X_1, X_2, X_3)^\top \sim N(\mu, \Sigma) \), where \( \mu = (1, 2, 3)^\top \) and \( \Sigma_{3x3} = \begin{pmatrix} 1 & 1 & 1 \\ 1 & 2 & 2 \\ 1 & 2 & 3 \end{pmatrix} \). We generate the outcome for each treatment group using \( Y_n = \beta_{n0}^{(w)} + \beta_{n1}^{(w)} \sin(X_1) + \beta_{n2}^{(w)} X_2 + \beta_{n3}^{(w)} X_3 + \epsilon_1^{(w)} \), where \( w \) is the treatment assignment indicator that takes 1 for the treatment group and 0 for the control group. For comparison, we generate a similar linear outcome variable \( Y_1 \), where \( Y_1 = \beta_{l0}^{(l)} + \beta_{l1}^{(l)} X_1 + \beta_{l2}^{(l)} X_2 + \beta_{l3}^{(l)} X_3 + \epsilon_2^{(l)} \), \( w = 0, 1 \). The only difference between the above two cases lies in the relationship between \( Y \) and \( X_1 \). Let \( (\epsilon_1^{(1)}, \epsilon_1^{(0)}, \epsilon_2^{(1)}, \epsilon_2^{(0)})^\top \sim N(0, \Sigma_e) \),
where $\Sigma_\epsilon$ is a diagonal matrix with diagonal entries \{4^2, 6^2, 4^2, 6^2\}. By setting $\beta_{m(1)} = (12, 11.756, 10, 9)$, $\beta_{m(2)} = (9, 19.593, 13, 10)$, $\beta_{l(1)} = (3, 10, 13, 10)$ and $\beta_{l(2)} = (5, 7, 10, 9)$, we control the true value of treatment effect $\theta$ between two treatment groups to be 10. The sample size $N$ and the probability of treatment assignment $\delta$ for this simulation are set to be 400 and 0.5.

As shown in Table 2, all estimators have better performance in the linear case than in the nonlinear case, as we note that the mean squared error for each estimator in the nonlinear case is nearly twice of the mean squared error in the linear case except the unadjusted estimator and Forward-2 estimator. Although all the estimators have very close results in the nonlinear case, which is indicated by the mean squared error, our proposed ELW estimators still achieve better precision than the others, but not as good as the Forward-2 estimator.

### Simulation 3.

To evaluate the performance of our proposed estimator $\hat{\theta}_{\text{mis}}$ in Section 2.1, which considers missing outcomes, we design a simulation experiment to compare it with $\hat{\theta}_{qz}$, the estimator proposed by Qin and Zhang [18]. This simulation involves four mutually independent variables, $X_1 \sim \text{Normal}(1, 3)$, $X_2 \sim \text{Normal}(2, 3)$, $X_3 \sim \text{Normal}(3, 1)$ and $X_4 \sim \text{Bernoulli}(0.5)$. The outcome is generated by $Y_m = \beta_m \top X + \epsilon_m$, where $\epsilon_m \sim N(0, \Sigma)$ and $\Sigma$ is a 2 x 2 diagonal matrix with diagonal entries \{4^2, 6^2\}. The true treatment effect is controlled to be 10 by setting $\beta_{m(2)} = (10, 8, 11, 10, 4)$ and $\beta_{l(2)} = (5, 7, 10, 9, 6)$. The missingness mechanism is set by logistic regression models $\text{logit}\{\pi_{w}(X, \alpha(\theta))\} = \alpha_0(w) + \alpha_1(w) X_1 + \alpha_2(w) X_2 + \alpha_3(w) X_3 + \alpha_4(w) X_4$, $w = 0, 1$. We use different set of $\alpha(w)$ to change the missing proportion of the outcomes. For example, we set $\alpha^{(1)} = (-5.147, -0.3, 0.8, 0.5, 0.3)$ and $\alpha^{(0)} = (-3.247, 0.2, -0.3, 0.4, 0.5)$ for a missing proportion of approximate 10%.

Table 3 reports the results of 1000 Monte Carlo data sets, in which we set $N = 400$ and $\delta = 0.5$. The bootstrap standard error in each Monte Carlo data set is based on 500 replicates. For each data set, we estimate $\theta$ using $\hat{\theta}_{\text{mis}}$ and $\hat{\theta}_{qz}$ for comparison. Results for estimators using the true model are included as the “benchmark” estimator. The evaluation metrics in Table 3 are the same as those in the previous experiments, noting that “qz” indicates this metric is for Qin and Zhang’s method [18].

As shown in Table 3 as the missing proportion increases, though all the estimators perform worse, our proposed estimators are still significantly better than Qin and Zhang’s. We note that $\hat{\theta}_{\text{mis}}$ and $\hat{\theta}_{qz}$ have close efficiency judging from their close average bootstrap standard error and mean squared error when the missing proportion is low. However, when the missing proportion is large, the performance of both $\hat{\theta}_{\text{mis}}$ and $\hat{\theta}_{qz}$ using identity functions deteriorates dramatically while those using a linear regression model, which is the correctly

### Table 2: Results for simulation comparing nonlinear and linear cases

| Estimator         | Bias  | Ave.Boot.SE | Cov.prob.boot. | MSE   |
|-------------------|-------|-------------|----------------|-------|
| **Nonlinear Case**|       |             |                |       |
| Unadjusted        | 0.230 | 3.589       | 0.943          | 13.180|
| Forward-1         | 0.056 | 0.907       | 0.944          | 0.862 |
| Forward-2         | 0.006 | 0.722       | 0.945          | 0.514 |
| ANCOVA            | 0.059 | 0.906       | 0.938          | 0.863 |
| KOCH              | 0.057 | 0.905       | 0.940          | 0.861 |
| Identity          | 0.046 | 0.908       | 0.947          | 0.856 |
| Linear model      | 0.050 | 0.922       | 0.946          | 0.861 |
| Benchmark         | 0.016 | 0.660       | 0.949          | 0.433 |
| **Linear Case**   |       |             |                |       |
| Unadjusted        | 0.217 | 3.789       | 0.944          | 15.229|
| Forward-1         | 0.028 | 0.650       | 0.949          | 0.400 |
| Forward-2         | 0.028 | 0.653       | 0.950          | 0.403 |
| ANCOVA            | 0.026 | 0.652       | 0.949          | 0.401 |
| KOCH              | 0.028 | 0.651       | 0.953          | 0.400 |
| ELW-Identity      | 0.028 | 0.649       | 0.952          | 0.400 |
| ELW-Linear        | 0.029 | 0.651       | 0.950          | 0.400 |
| Benchmark         | 0.027 | 0.650       | 0.952          | 0.398 |

All entries are as in Table 1.
specified model, can maintain good performance. This demonstrates a growing sensitivity to the model specified with a growing missing proportion no matter using our proposed method or Qin and Zhang’s.

Table 3: Results for simulation with different missing proportion

| Metric         | Estimator | Mean Missing Proportion |
|----------------|-----------|-------------------------|
|                |           |                         |
|                |           | 0.138 | 0.242 | 0.333 | 0.417 | 0.501 |
| Bias           | Identity  | -0.174 | -0.187 | -0.223 | -0.341 | -1.150 |
|                | Linear    | -0.140 | -0.120 | -0.115 | -0.088 | -0.018 |
|                | Benchmark | -0.140 | -0.123 | -0.111 | -0.090 | -0.022 |
| Bias.qz        | Identity  | -0.170 | -0.186 | -0.226 | -0.387 | -1.186 |
|                | Linear    | -0.139 | -0.119 | -0.109 | -0.090 | -0.013 |
|                | Benchmark | -0.139 | -0.121 | -0.111 | -0.091 | -0.020 |
| Ave.Boot.SE    | Identity  | 0.603  | 0.647  | 0.771  | 1.965  | 5.960  |
|                | Linear    | 0.574  | 0.625  | 0.689  | 0.762  | 0.862  |
|                | Benchmark | 0.576  | 0.625  | 0.687  | 0.760  | 0.857  |
| Ave.Boot.SE.qz | Identity  | 2.238  | 2.244  | 2.299  | 3.154  | 6.422  |
|                | Linear    | 2.243  | 2.251  | 2.264  | 2.283  | 2.312  |
|                | Benchmark | 2.247  | 2.253  | 2.266  | 2.283  | 2.311  |
| Cov.prob.boot  | Identity  | 0.939  | 0.934  | 0.946  | 0.988  | 0.984  |
|                | Linear    | 0.930  | 0.943  | 0.934  | 0.938  | 0.943  |
|                | Benchmark | 0.928  | 0.945  | 0.937  | 0.945  | 0.944  |
| Cov.prob.boot.qz| Identity | 0.957  | 0.958  | 0.958  | 0.977  | 0.981  |
|                | Linear    | 0.954  | 0.958  | 0.954  | 0.955  | 0.958  |
|                | Benchmark | 0.959  | 0.961  | 0.960  | 0.957  | 0.960  |
| MSE            | Identity  | 0.383  | 0.443  | 0.546  | 1.054  | 18.427 |
|                | Linear    | 0.368  | 0.418  | 0.514  | 0.581  | 0.743  |
|                | Benchmark | 0.365  | 0.418  | 0.502  | 0.573  | 0.717  |
| MSE.qz         | Identity  | 4.722  | 4.738  | 4.892  | 5.689  | 23.610 |
|                | Linear    | 4.714  | 4.739  | 4.874  | 5.015  | 5.005  |
|                | Benchmark | 4.711  | 4.734  | 4.899  | 5.009  | 5.005  |

All metrics are as in Table 1 except that metrics with no suffix are for our proposed estimator while those with “.qz” are for Qin and Zhang’s method.

Simulation 4. Table 4 and Table 5 summarize the performance of $\hat{\theta}_{mr}$, which described in Section 2.3 based on data with and without missing outcomes, respectively.

When considering data without missing outcomes, we estimate the ATE under a similar setting as in the last simulation. The outcome variable is generated by $Y = \beta_{\theta}^{(w)} + \beta_{c1}^{(w)} X_1 + \beta_{c2}^{(w)} X_2 + \beta_{c3}^{(w)} X_3 + \beta_{c4}^{(w)} X_4 + \epsilon_{1}^{(w)}$, $w = 0, 1$. The four mutually independent variables $X_1, X_2, X_3, X_4$ are set to have the same distribution as in the last simulation. Here, we set $\beta_{c1}^{(1)} = (10, 10, 0, 0, 0)^T$ and $\beta_{c1}^{(0)} = (3, 7, 0, 0, 0)^T$, which lead to a true value of $\theta = 10$ and a true linear model only including $X_1$ to describe the true relationship between outcome and covariates. In this way, a series of identity functions used in the estimation can be regarded as multiple models, one of which correctly specifies the true model, as shown in the first row in Table 4. The second row is related to another estimator using two linear regression models, each of which involves all 4 variables. The third estimator based on two linear regression models, both of which include only $X_1$, uses the exactly correct-specified model. The results show a very close performance for these three estimators, which indicates the multiple robustness of the proposed estimator.

When we consider data with missing outcomes, we use a similar simulation setting as in Han [22], which is originally designed to estimate the parameters in regression models. Denote four mutually independent covariates to be $X_1 \sim \text{Normal}(5, 1), X_2 \sim \text{Bernoulli}(0.5), X_3 \sim \text{Normal}(0, 1)$ and $X_4 \sim \text{Normal}(0, 1)$. The outcome is generated by $Y = \beta_{\theta}^{(w)} + \beta_{c1}^{(w)} X_1 + \beta_{c2}^{(w)} X_2 + \beta_{c3}^{(w)} X_3 + \beta_{c4}^{(w)} X_4 + \epsilon_{1}^{(w)}, w = 0, 1$, where $\beta_{c1}^{(1)} = (10, 8, 12, 10, 4)$ and $\beta_{c1}^{(0)} = (6, 7, 10, 9, 6)$ leading to a true value of $\theta = 10$. There are three auxiliary variables involved: $S_1 = 1 + X_1 - X_2 + \epsilon_1$, $S_2 = \mathcal{I} \{S_1 + 0.3 \epsilon_2 > 5.8\}$, and $S_3 = \exp \left\{ (S_1 / 9)^2 \right\} + \epsilon_3$. Here, $\mathcal{I}(\cdot)$ represents the indicator function, $(\epsilon_Y, \epsilon_1, \epsilon_2, \epsilon_3)^T \sim \text{Normal}(0, \Sigma)$ where $\Sigma$ is a $4 \times 4$ matrix with diagonal entries 2, 2, 1.
where all the models are correctly specified. 0 or 1 to the corresponding digit.

and “EL W-11101110” already have very similar efficiency performance compared to “EL W-10101010” estimator. The efficiency performance of our proposed estimators are consistently better than except “EL W-01010101” is well demonstrated since they all have ignorable bias. The efficiency performance of all the eight models are used to estimate θ in the optimization problem with the constraints depicted in Section 2.3. We consider the sample size to be N = 400, and the results are summarized based on 1000 replications. In order to distinguish the estimators of different models, we assign a name for each in the form of “EL W-00000000”, where the eight digits, from left to right, indicate whether ZDV + zalcitabine, and ddI monotherapy.

and now all of them to 4 different antiretroviral regimens: zidovudine (ZDV) monotherapy, ZDV + didanosine (ddI), ZDV + zalcitabine, and ddI monotherapy.

### 4.2 Real data analysis

Firstly, we demonstrate and compare our proposed method with the other 5 competing methods by applying all of them to ACTG 175 data, which is collected from 2139 HIV-infected individuals and equally randomizes all of them to 4 different antiretroviral regimens: zidovudine (ZDV) monotherapy, ZDV + didanosine (ddI), ZDV + zalcitabine, and ddI monotherapy.

| Estimator            | Bias   | Ave.BootSE | Cov.prob.boot | MSE   |
|----------------------|--------|------------|---------------|-------|
| Identity             | -0.029 | 0.573      | 0.937         | 0.331 |
| Linear               | -0.029 | 0.572      | 0.944         | 0.330 |
| Linear(correct)      | -0.029 | 0.570      | 0.945         | 0.331 |

| Estimator            | Bias   | Bias.hw | MSE   | MSE.hw |
|----------------------|--------|---------|-------|--------|
| ELW-10101010         | -0.007 | 0.033   | 0.087 | 2.261  |
| ELW-01010101         | 0.110  | 0.134   | 6.966 | 6.912  |
| ELW-11111111         | -0.009 | 0.033   | 0.090 | 2.266  |
| ELW-10011001         | 0.119  | 0.122   | 6.693 | 6.576  |
| ELW-10101001         | 0.006  | 0.030   | 2.554 | 4.009  |
| ELW-10011010         | 0.106  | 0.126   | 3.169 | 4.689  |
| ELW-10111111         | -0.008 | 0.034   | 0.090 | 2.260  |
| ELW-01100110         | 0.003  | 0.043   | 0.088 | 2.260  |
| ELW-10100110         | -0.002 | 0.038   | 0.090 | 2.272  |
| ELW-01101010         | -0.001 | 0.039   | 0.085 | 2.250  |
| ELW-11101110         | 0.003  | 0.043   | 0.088 | 2.260  |

All metrics are as in Table 1 except that metrics with no suffix are for our proposed estimator while those with “.hw” are for Han and Wang’s method.
Simplifying the experiment setting as Tsiatis et al. did, we regard the \( m = 532 \) individuals receiving ZDV monotherapy as the treatment group, while the rest of \( n = 1607 \) individuals receiving any other antiretroviral regimens were classified as the control group. Accordingly, we have \( \delta = \frac{m}{m+n} \approx 0.75 \).

We focus on the analysis of mean differences in CD4 count (cells/mm\(^3\)) at 20 ± 5 weeks post-baseline (CD420), denoted as \( Y \), between the above 2 groups. For potential use in covariate adjustment, we consider the following 5 continuous baseline variables: \( X_1 = \text{CD4 count (cells/mm}\(^3\)), \( X_2 = \text{CD8 count (cells/mm}\(^3\)), \( X_3 = \text{age(years)}, X_4 = \text{weight (kg)}, X_5 = \text{Karnofsky score (scale of 0–100)}, \) and 7 indicator variables: \( X_6 = \text{hemophilia,} \) \( X_7 = \text{homosexual activity,} \) \( X_8 = \text{history of intravenous drug use,} \) \( X_9 = \text{race (0=white, 1=nonwhite),} \) \( X_{10} = \text{gender (0=female, 1=male),} \) \( X_{11} = \text{antiretroviral history (0=naive, 1=experienced),} \) and \( X_{12} = \text{symptomatic status (0=asymptomatic, 1=symptomatic).} \)

Now we apply the optimization algorithm in Section 2 to obtain the proposed ELW estimators. We assume \( g(X) \) and \( h(X) \) to be linear regression functions or identity functions of covariates in two different scenarios. In the first scenario, we develop two treatment-specific linear models for \( E(Y|W = w, X) \), \( w = 0, 1 \), with 12 baseline covariates by fitting separate linear models to the observed data in each treatment arm. The fitted treatment-specific linear regression models are

\[
g(X; \hat{\beta}_1) = 98.900 + 0.689X_1 - 0.019X_2 - 0.362X_3 + 0.133X_4 \\
+ 1.107X_5 - 17.337X_6 + 6.542X_7 + 12.026X_8 \\
- 23.343X_9 - 13.301X_{10} - 40.456X_{11} - 20.545X_{12},
\]

\[
h(X; \hat{\beta}_0) = 126.771 + 0.719X_1 - 0.022X_2 - 0.432X_3 - 0.455X_4 \\
+ 0.607X_5 - 58.747X_6 - 19.672X_7 - 10.567X_8 \\
- 5.818X_9 + 18.900X_{10} - 41.816X_{11} - 11.039X_{12},
\]

(29)

with estimated treatment-specific variances \( \widehat{\text{Var}}(Y|W = 1, X) = (96.305)^2 \) and \( \widehat{\text{Var}}(Y|W = 0, X) = (116.864)^2 \), and the treatment-specific coefficients of determination \( R^2 = 0.3687 \) for \( W = 1 \) and \( R^2 = 0.4592 \) for \( W = 0 \). Applying these models to the optimization procedure proposed in Section 2, we obtain the proposed ELW-Linear estimator. In the second scenario, we replace linear functions with identity functions in the above models to obtain the ELW-Identity estimator. Here, \( X \) denote the \( l \times 1 \) covariate vector with \( l = 12 \).

Table 6: Estimate of \( \theta \) for the ACTG 175 data based on CD420

| Estimator       | Estimate | Boot.SE | Test.stat. | Rel. |
|-----------------|----------|---------|------------|------|
| Unadjusted      | 46.810   | 7.055   | 6.924      | 1.000|
| Change scores   | 50.409   | 5.693   | 9.150      | 1.506|
| Forward-1       | 49.895   | 5.439   | 9.716      | 1.733|
| Forward-2       | 51.589   | 5.700   | 10.183     | 1.780|
| ANCOVA          | 49.694   | 5.451   | 9.680      | 1.734|
| KOCH            | 49.758   | 5.458   | 9.641      | 1.716|
| ELW-Identity    | 50.006   | 5.288   | 10.057     | 1.849|
| ELW-Linear      | 49.824   | 5.200   | 9.776      | 1.760|

Boot.SE is the bootstrap-based standard error; Test.stat. is the Wald test statistic; and Rel. eff. \( = (\text{SE for the unadjusted estimator})^2/(\text{SE for the indicated estimator})^2 \).

Given the results in Table 6, all different estimators indicate the same evidence of treatment difference. The performance of all methods seems to be similar except that the unadjusted estimator has a lower estimate due to a mild imbalance for baseline CD4 between two treatment groups. However, the bootstrap standard errors of our proposed ELW estimators are both smaller than that of the others, which indicates a better performance of our proposed method.

Table 7 shows the results for the estimates of \( \theta \) based on the missing outcome CD496, approximately 37% of which are missing. Here, we only calculate the standard error using bootstrapping method. As shown in the Table 7, our proposed ELW estimators have higher estimates of \( \theta \) but consistently smaller bootstrap-based standard errors than those based on Qin and Zhang’s method, which indicates a better efficiency for our proposed ELW estimators.
Table 7: Estimate of $\theta$ for the ACTG 175 data based on CD496

| Estimator       | Estimate | Boot.SE | Test stat. |
|-----------------|----------|---------|------------|
| ELW-Identity    | 64.623   | 9.082   | 7.116      |
| ELW-Linear      | 64.038   | 9.065   | 7.064      |
| Qz-Identity     | 61.223   | 10.316  | 5.935      |
| Qz-Linear       | 60.981   | 10.159  | 6.003      |

ELW-Identity and ELW-Linear are our proposed estimators using identity functions and linear functions, respectively. Similarly, Qz-Identity and Qz-Linear are the corresponding estimators based on Qin and Zhang’s method[18].

5 Conclusion

We have proposed a two-sample empirical likelihood weighted estimator to effectively incorporate covariate information into the estimation of the average treatment effect in randomized clinical trials. Namely, we obtain two classes of estimated weights through constrained empirical likelihood estimation, where the constraints are designed to carry side information from covariates. Besides, our proposed estimator maintains objectivity since it separates the estimation of ATE from analysis of the covariate outcome relationship.

Furthermore, we apply the proposed estimator to the common problem of missing outcome data in RCTs under the assumption of missing at random. Theoretically, we have proved that our proposed estimator maintains double robustness and multiple robustness properties.

To evaluate the efficiency of our estimator, we demonstrate the proposed estimator is semiparametric efficient given data without or with missingsness. Various simulation experiments and an application to ACTG175 have been conducted to compare our proposed estimator with the others and the results indicates a better performance of our proposed method.

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