Propensity Score Weighting for Covariate Adjustment in Randomized Clinical Trials

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ABSTRACT

Imbalance in baseline characteristics due to chance is common in randomized clinical trials. Regression adjustment such as the analysis of covariance (ANCOVA) is often used to account for imbalance and increase precision of the treatment effect estimate. An objective alternative is through inverse probability weighting (IPW) of the propensity scores. Although IPW and ANCOVA are asymptotically equivalent, the former may demonstrate inferior performance in finite samples. In this article, we point out that IPW is a special case of the general class of balancing weights, and propose the overlap weighting (OW) method for covariate adjustment. The OW approach has a unique advantage of completely removing chance imbalance when the propensity score is estimated by logistic regression. We show that the OW estimator attains the same semiparametric variance lower bound as the most efficient ANCOVA estimator and the IPW estimator with a continuous outcome, and derive closed-form variance estimators for OW when estimating additive and ratio estimands. Through extensive simulations, we demonstrate OW consistently outperforms IPW in finite samples and improves the efficiency over ANCOVA and augmented IPW when the degree of treatment effect heterogeneity is moderate or when the outcome model is incorrectly specified. We apply the proposed OW estimator to the Best Apnea Interventions for Research (BestAIR) randomized trial to evaluate the effect of continuous positive airway pressure on patient health outcomes.

KEY WORDS: analysis of covariance, covariate balance, inverse probability weighting, overlap weighting, randomized controlled trials, variance reduction

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1 Introduction

Randomized controlled trials are the gold standard for evaluating the efficacy and safety of new treatments and interventions. Statistically, randomization ensures the optimal internal validity and balances both measured and unmeasured potential confounders in expectation. This allows the simple unadjusted difference-in-means estimator to provide an unbiased estimate of the intervention effect (Rosenberger and Lachin, 2002). Frequently, important patient characteristics are collected at baseline; although over repeated experiments, they will be balanced across treatment arms, chance imbalance often arises in a single trial due to the random nature in allocating the treatment (e.g. Senn, 1989; Ciolino et al., 2015), especially when the sample size is limited (Thompson et al., 2015). If any of the baseline covariates are prognostic risk factors that are predictive of the outcome, adjusting for the imbalance of these factors in the analysis can improve the statistical power and provide a greater chance of identifying the treatment signals when they actually exist (e.g. Ciolino et al., 2015; Pocock et al., 2002; Hernández et al., 2004).

There are two general streams of methods for covariate adjustment in randomized trials: (outcome) regression adjustment (e.g. Yang and Tsiatis, 2001; Kahan et al., 2016; Leon et al., 2003; Tsiatis et al., 2008; Zhang et al., 2008) and the inverse probability of treatment weighting (IPW) based on propensity scores (e.g. Williamson et al., 2014; Shen et al., 2014; Colantuoni and Rosenblum, 2015). For regression adjustment with continuous outcomes, the analysis of covariance (ANCOVA) model is often used, where the outcome is regressed on the treatment, covariates and possibly their interactions (Tsiatis et al., 2008). The treatment effect is estimated by the coefficient of the treatment variable. With binary outcomes, a generalized linear model can be postulated to estimate the adjusted risk ratio or odds ratio, with the caveat that the regression coefficient of treatment may not represent the marginal effect potentially due to non-collapsability (Williamson et al., 2014). By appealing to the semiparametric theory, Tsiatis and colleagues (e.g. Yang and Tsiatis, 2001; Leon et al., 2003; Tsiatis et al., 2008) developed a suite of broadly applicable ANCOVA estimators that improves efficiency over the unadjusted analysis in randomized trials. Lin (2013) further clarified that it is critical to incorporate a full set of covariate-by-treatment interaction terms in regression adjustment for efficiency gain. The finite-sample performance
of these ANCOVA estimators has been examined by previous simulations (Tsiatis et al., 2008). An attractive feature of the ANCOVA estimators is that the point estimates as well as the standard error estimates when the randomization probability is $1/2$ remain consistent even if the outcome model is misspecified (e.g. Yang and Tsiatis, 2001; Lin, 2013; Wang et al., 2019). However, misspecification of the outcome model can decrease precision in unbalanced experiments with heterogeneity (Freedman, 2008). An additional limitation of regression adjustment is the potential for inviting a fishing expedition to search for an outcome model that gives the most dramatic treatment effect estimate, and thus jeopardizes the objectivity of causal inference with randomized trials (e.g. Tsiatis et al., 2008; Shen et al., 2014).

Originally developed in the context of survey sampling and observational studies (Lunceford and Davidian, 2004), IPW has been advocated as an objective alternative to ANCOVA in randomized trials (Williamson et al., 2014). To implement a typical IPW estimator, one first fits a logistic “working” model to estimate the propensity scores, defined as the conditional probability of receiving the treatment given the baseline covariates (Rosenbaum and Rubin, 1983). With the weights constructed as the inverse of the estimated propensity scores, the treatment effect is estimated by the weighted outcome difference between the treatment arms. In randomized trials, the allocation process of the treatment is completely controlled and the true propensity score is known. Therefore, the working model for the propensity scores is always correctly specified, and the IPW estimator is consistent to the marginal treatment effect. Moreover, with a continuous outcome, the IPW estimator under a logistic working model has the same large-sample variance as the efficient ANCOVA estimator (e.g. Shen et al., 2014; Williamson et al., 2014), but offers several advantages. First, IPW separates the design and analysis (Rubin, 2008) in that the propensity score model only involves baseline covariates and the treatment indicator; it does not require the access to the outcome and hence avoids the fishing expedition. As such, arguably IPW offers better transparency and objectivity in pre-specifying the analytical adjustment during the design stage. Second, IPW preserves the marginal treatment effect estimand with non-continuous outcomes, while the interpretation of the outcome regression coefficient may change according to different covariate specifications (e.g. Hauck et al., 1998; Robinson and Jewell, 1991). Third, IPW can easily obtain treatment
effect estimates for rare binary or categorical outcomes whereas outcome regression models often fail to converge in such situations (Williamson et al., 2014). This is particularly the case when the target parameter is a risk ratio, where log-binomial models are known to have unsatisfying convergence properties (Zou, 2004). On the other hand, a major limitation of IPW is that it may be inefficient compared to ANCOVA in scenarios with limited sample sizes and unbalanced treatment allocations, as demonstrated in a recent simulation study (Raad et al., 2020).

In this paper, we point out that IPW is a special case of the general class of propensity score weights, called the balancing weights (Li et al., 2018), many members of which could be used for covariate adjustment in randomized trials. Within this class, we advocate to use a new weighting method, the overlap weighting (OW), which has been shown previously, in the context of observational studies, to offer theoretical and empirical gain in variance estimation compared to IPW (Li et al., 2019). In the context of randomized trials, a particularly attractive feature of OW is that, if the propensity score is estimated from a logistic regression “working” model, then OW leads to exact mean balance of any baseline covariate in the logistic model, and consequently remove the chance imbalance of that covariate. As a propensity score method, OW retains the aforementioned advantages of IPW while offers better finite-sample operating characteristics in terms of variance reduction (Section 2). Specifically, in Section 3 we demonstrate that the OW estimator, similar as IPW, achieves the same semiparametric variance lower bound and hence is asymptotically equivalent to the efficient ANCOVA estimator for continuous outcomes. For binary outcomes, we further provide closed-form variance estimators of the OW estimator for estimating marginal risk difference, risk ratio and odds ratio, which incorporates the uncertainty in estimating the propensity scores and achieves close to nominal coverage in finite samples. Through extensive simulations in Section 4 we demonstrate the efficiency advantage of OW under small to moderate sample sizes, and also validate the proposed variance estimator for OW. Finally, in Section 5 we apply the proposed method to the Best Apnea Interventions for Research (BestAIR) randomized trial and evaluate the treatment effect of continuous positive airway pressure (CPAP) on clinical outcomes.
2 Propensity score weighting for covariate adjustment

2.1 The Balancing Weights

We consider a randomized trial with two arms and \( N \) patients, where \( N_1 \) and \( N_0 \) patients are randomized into the treatment and control arm, respectively. Let \( Z_i = z \) be the binary treatment indicator, with \( z = 1 \) indicates treatment and \( z = 0 \) control. Under the potential outcome framework (Rubin 1974), each unit has a pair of potential outcomes \( \{ Y_i(1), Y_i(0) \} \), mapped to the treatment and control condition, respectively, of which only the one corresponding to the actual treatment assigned is observed. We maintain the consistency assumption (Hernan and Robins 2010) so that the observed outcome \( Y_i = Z_i Y_i(1) + (1 - Z_i) Y_i(0) \). In randomized trials, a collection of \( p \) baseline variables could be recorded for each patient, denoted by \( X_i = (X_{i1}, \ldots, X_{ip})^T \). Denote \( \mu_z = E\{ Y_i(z) \} \) and \( \mu_z(x) = E\{ Y_i(z)|X_i = x \} \) as the marginal and conditional expectation of the outcome in arm \( z \) \((z = 0, 1)\), respectively. A common estimand on the additive scale is the average treatment effect (ATE):

\[
\tau = E\{ Y_i(1) - Y_i(0) \} = \mu_1 - \mu_0.
\] (1)

We assume that the treatment \( Z \) is randomly assigned to patients, where \( \Pr(Z_i = 1|X_i, Y_i(1), Y_i(0)) = \Pr(Z_i = 1) = r \), and \( 0 < r < 1 \) is the randomization probability. The most typical study design ensures balanced assignment so that \( r = 1/2 \). Other values of \( r \) may be possible, for example, when there is a perceived benefit of the treatment, and a larger proportion of patients are randomized to the intervention.

Under randomization of treatment and the consistency assumption, we have \( \tau = E(Y_i|Z_i = 1) - E(Y_i|Z_i = 0) \), and thus an unbiased estimator for \( \tau \) is the unadjusted difference-in-means estimator:

\[
\tau^{UNADJ} = \frac{\sum_{i=1}^{N} Z_i Y_i}{\sum_{i=1}^{N} Z_i} - \frac{\sum_{i=1}^{N} (1 - Z_i) Y_i}{\sum_{i=1}^{N} (1 - Z_i)}.
\] (2)

Below we generalize the ATE to a class of weighted average treatment effect (WATE) estimands to construct alternative weighting methods. Assume the study sample is drawn from a probability density \( f(x) \), and let \( g(x) \) denote the covariate distribution density of a target population, possibly different from the one represented by the observed sample. The ratio \( h(x) = g(x)/f(x) \) is called a tilting function.
(Li and Li, 2019b), which re-weights the distribution of the baseline characteristics of the study sample to represent the target population. We can represent the ATE on the target population $g$ by a WATE estimand:

$$\tau^h = E_g[Y_i(1) - Y_i(0)] = \frac{E\{h(x)(\mu_1(x) - \mu_0(x))\}}{E\{h(x)\}}.$$  \hspace{1cm} (3)

In practice, we usually pre-specify $h(x)$ instead of $g(x)$. Most commonly $h(x)$ is specified as a function of the propensity score or simply a constant. The propensity score (Rosenbaum and Rubin, 1983) is the conditional probability of treatment given the covariates, $e(x) = \Pr(Z_i = 1 | X_i = x)$. Under the randomization assumption, $e(x) = \Pr(Z_i = 1) = r$ for any baseline covariate value $x$, and therefore as long as $h(x)$ is a function of the propensity score $e(x)$, different $h$ corresponds to the same target population $g$, and the WATE reduces to ATE, i.e. $\tau^h = \tau$. This is distinct from observational studies, where the propensity scores are usually unknown and vary between units, and consequently different $h(x)$ corresponds to different target populations and estimands. This special feature under randomized trials provides the basis for considering alternative weighting strategies to achieve better finite-sample performances.

In the context of confounding adjustment in observational studies, [Li et al.] (2018) proposed a class of propensity score weights, named the balancing weights, to estimate WATE. Specifically, given any $h(x)$, the balancing weights for patients in the treatment and control arm are defined as:

$$w_1(x) = h(x)/e(x), \quad w_0(x) = h(x)/\{1 - e(x)\},$$  \hspace{1cm} (4)

which balances the distributions of the covariates between treatment and control arms in the target population, so that $f_1(x)w_1(x) = f_0(x)w_0(x) = f(x)h(x)$, where $f_z(x)$ is the conditional distribution of covariates in treatment arm $z$ (e.g. Wallace and Moodie, 2015; Li et al., 2018). Then, one can use the following Hájek-type estimator to estimate $\tau^h$:

$$\hat{\tau}^h = \hat{\mu}_1^h - \hat{\mu}_0^h = \frac{\sum_{i=1}^N w_1(x_i)Z_i Y_i}{\sum_{i=1}^N w_1(x_i)Z_i} - \frac{\sum_{i=1}^N w_0(x_i)(1 - Z_i) Y_i}{\sum_{i=1}^N w_0(x_i)(1 - Z_i)}.$$  \hspace{1cm} (5)

Though the function $h(x)$ can take any form, we restrict our discussion to the following special cases relevant to randomized trials. For example, when $h(x) = 1$, the balancing weights become the inverse
probability weights, \((w_1, w_0) = (1/e(x), 1/\{1 − e(x)\})\); when \(h(x) = e(x)(1 − e(x))\), we have the overlap weights \(\text{Li et al., 2018}\), \((w_1, w_0) = (1 − e(x), e(x))\). Other examples of the balancing weights include the average treatment effect among treated (ATT) weights \(\text{Hirano and Imbens, 2001}\) and the matching weights \(\text{Li and Greene, 2013}\).

IPW is the most well-known case of the balancing weights. Specific to covariate adjustment in randomized trials, \(\text{Williamson et al., 2014}\) and \(\text{Shen et al., 2014}\) suggested the following IPW estimator of \(\tau\):

\[
\hat{\tau}_{\text{IPW}} = \frac{\sum_{i=1}^{N} Z_i Y_i / \hat{e}_i}{\sum_{i=1}^{N} Z_i / \hat{e}_i} - \frac{\sum_{i=1}^{N} (1 − Z_i) Y_i / (1 − \hat{e}_i)}{\sum_{i=1}^{N} (1 − Z_i) / (1 − \hat{e}_i)}.
\]

We will point out in Section \(3\) that their findings on IPW are generally applicable to the balancing weights as long as \(h(x)\) is a smooth function of the true propensity score. The choice of \(h(x)\), however, will affect the finite-sample operating characteristics of the weighting estimator. In particular, below we will closely examine the overlap weights.

### 2.2 The Overlap Weights

The overlap weights, \((w_1, w_0) = (1−e(x), e(x))\), weigh each patient by its probability of being assigned to the opposite group, and thus gradually down-weigh the patients whose propensity scores are away from the center (0.5). In contrast to IPW, the patients with extreme (close to 0 and 1) propensity scores contribute the least in the estimation of the treatment effect. In observational studies, the overlap weights correspond to a target population with the most overlap in the baseline characteristics, and have been shown theoretically to give the smallest asymptotic variance of \(\hat{\tau}^h\) among all balancing weights \(\text{Li et al., 2018}\) as well as empirically reduce the variance of \(\tau^h\) in finite samples \(\text{Li et al., 2019}\). In randomized trials, as discussed before, because the true propensity score is constant, the overlap weights and IPW target the same estimand \(\tau^h\), but their finite-sample operating characteristics can be markedly different, as elucidated below.

The OW estimator for the ATE in randomized trials is

\[
\hat{\tau}_{\text{OW}} = \hat{\mu}_1 − \hat{\mu}_0 = \frac{\sum_{i=1}^{N} (1 − \hat{e}_i) Z_i Y_i}{\sum_{i=1}^{N} (1 − \hat{e}_i) Z_i} − \frac{\sum_{i=1}^{N} \hat{e}_i (1 − Z_i) Y_i}{\sum_{i=1}^{N} \hat{e}_i (1 − Z_i)},
\]

\(7\)
where \( \hat{e}_i = e(X_i; \hat{\theta}) \) is the estimated propensity score from a logistic regression model:

\[
e_i = e(X_i; \theta) = \frac{\exp(\theta_0 + X_i^T \theta_1)}{1 + \exp(\theta_0 + X_i^T \theta_1)},
\]

with parameters \( \theta = (\theta_0, \theta_1^T)^T \) and \( \hat{\theta} \) is the maximum likelihood estimate of \( \theta \). Regarding the selection of covariates in the propensity score model, the previous literature suggests to include stratification variables as well as a small number of key prognostic factors pre-specified in the design stage (e.g., Raab et al., 2000; Williamson et al., 2014). These guidelines are also applicable to the OW estimator.

The logistic propensity score model fit underpins a unique exact balance property of OW. Specifically, the overlap weights estimated from model (8) lead to exact mean balance of any predictor included in the model (Theorem 3 in Li et al. (2018)):

\[
\frac{\sum_{i=1}^N (1 - \hat{e}_i) Z_i X_{ji}}{\sum_{i=1}^N (1 - \hat{e}_i) Z_i} - \frac{\sum_{i=1}^N \hat{e}_i (1 - Z_i) X_{ji}}{\sum_{i=1}^N \hat{e}_i (1 - Z_i)} = 0, \quad \text{for } j = 1, \ldots, p.
\]

This property has important practical implications in randomized trials, namely, for any baseline covariate included in the propensity score model, the associated chance imbalance in a single randomized trial vanishes once the overlap weights are applied. If one reports the weighted mean differences in baseline covariates between arms (frequently included in the standard “Table 1” in primary trial reports), those differences are identically zero. Thus the application of OW enhances the face validity of the randomized study.

More importantly, the exact mean balance property translates into better efficiency in estimating \( \tau \).

To illustrate the intuition, consider the following simple example. Suppose the true outcome surface is

\[ Y_i = \alpha + Z_i \tau + X_i^T \beta_0 + \varepsilon_i \] with \( E(\varepsilon_i | Z_i, X_i) = 0 \). Denote the weighted chance imbalance in the baseline covariates by

\[ \Delta_X(w_0, w_1) = \frac{\sum_{i=1}^N w_1(X_i) Z_i X_i}{\sum_{i=1}^N w_1(X_i) Z_i} - \frac{\sum_{i=1}^N w_0(X_i)(1 - Z_i) X_i}{\sum_{i=1}^N w_0(X_i)(1 - Z_i)}, \]

and the weighted difference in random noise by

\[ \Delta_\varepsilon(w_0, w_1) = \frac{\sum_{i=1}^N w_1(X_i) Z_i \varepsilon_i}{\sum_{i=1}^N w_1(X_i) Z_i} - \frac{\sum_{i=1}^N w_0(X_i)(1 - Z_i) \varepsilon_i}{\sum_{i=1}^N w_0(X_i)(1 - Z_i)}. \]
For the unadjusted estimator, substituting the true outcome surface in equation (2) gives \( \hat{\tau}_{UNADJ} - \tau = \Delta_X(1, 1)^T \beta_0 + \Delta_{\varepsilon}(1, 1) \), where \( \Delta_X(1, 1) \) measures the chance imbalance in a single random allocation, and \( \Delta_{\varepsilon}(1, 1) \) is pure noise. This expression implies that the estimation error of \( \hat{\tau}_{UNADJ} \) is a sum of the chance imbalance and random noise, and becomes large when imbalanced covariates are highly prognostic (i.e. large magnitude of \( \beta_0 \)). Similarly, if we substitute the true outcome surface in (6), we can show that the estimation error of IPW is \( \hat{\tau}_{IPW} - \tau = \Delta_X(1/\hat{e}, 1/(1 - \hat{e}))^T \beta_0 + \Delta_{\varepsilon}(1/\hat{e}, 1/(1 - \hat{e})) \). Intuitively, IPW controls for chance imbalance because we usually have \( \| \Delta_X(1/\hat{e}, 1/(1 - \hat{e})) \| < \| \Delta_X(1, 1) \| \), which reduces the variation of the estimation error over repeated experiments. However, because \( \Delta_X(1/\hat{e}, 1/(1 - \hat{e})) \) is not zero, the estimation error remains sensitive to the magnitude of \( \beta_0 \). In contrast, because of the exact mean balance property of OW, we have \( \Delta_X(1 - \hat{e}, \hat{e}) = 0 \); consequently, substituting the true outcome surface in (7), we can see that the estimation error of OW equals \( \hat{\tau}_{OW} - \tau = \Delta_{\varepsilon}(1 - \hat{e}, \hat{e}) \), which is only noise and free of \( \beta_0 \). This simple example illustrates that, for each realized randomization, OW should have the smallest estimation error, which translates into larger efficiency in estimating \( \tau \) over repeated experiments.

Of note, more flexible models such as machine learning methods are available for estimating the propensity score (Colantuoni and Rosenblum, 2015). In observational studies, these models could be more helpful because they reduce the chance for model misspecification. However, in randomized trials, the true propensity score is known and the propensity score model is merely a “working” model that is never misspecified. Thus, the benefit of more flexible propensity score models in randomized trials is negligible. More importantly, we employ the logistic propensity score model to obtain the overlap weights that achieve the exact mean balance on baseline covariates.

For non-continuous outcomes, besides the additive estimands we also consider ratio estimands. For example, for binary outcomes, the ATE is also known as the causal risk difference, \( \tau = \tau_{RD} \). Two other standard estimands are the causal risk ratio (RR) and the causal odds ratio (OR) on the log scale, defined by

\[
\tau_{RR} = \log \left( \frac{\mu_1}{\mu_0} \right), \quad \tau_{OR} = \log \left\{ \frac{\mu_1/(1 - \mu_1)}{\mu_0/(1 - \mu_0)} \right\}.
\]  

(10)
The OW estimator for risk ratio and odds ratio are $\hat{\tau}_{RR} = \log\{\hat{\mu}_1/\hat{\mu}_0\}$, and $\hat{\tau}_{OR} = \log\{\hat{\mu}_1/(1 - \hat{\mu}_1)\}/\{\hat{\mu}_0/(1 - \hat{\mu}_0)\}$, respectively, with $\hat{\mu}_1$, $\hat{\mu}_0$ being defined in (7).

3 Efficiency Considerations and Variance Estimation

In this section we demonstrate that in randomized trials the OW estimator leads to increased large-sample efficiency in estimating the treatment effect compared to the unadjusted estimator. We further propose a consistent variance estimator for the OW estimator of both the additive and ratio estimands.

3.1 Continuous Outcomes

[Tsiatis et al. (2008) show that the family of regular and asymptotically linear estimators for the additive estimand $\tau$ is

$$I: \frac{1}{N} \sum_{i=1}^{N} \left\{ \frac{Z_i Y_i}{r} - \frac{(1 - Z_i) Y_i}{1 - r} \right\} \{rg_0(X_i) + (1 - r)g_1(X_i)\} + o_p(N^{-1/2}),$$

(11)

where $r$ is the randomization probability, and $g_0(X_i), g_1(X_i)$ are scalar functions of the baseline covariates $X_i$. Several commonly used estimators for the treatment effect are members of the family $I$, with different specifications of $g_0(X_i), g_1(X_i)$. For example, setting $g_0(X_i) = g_1(X_i) = 0$, we obtain the unadjusted estimator $\hat{\tau}_{UNADJ}$. Setting $g_0(X_i) = g_1(X_i) = E(Y_i|X_i)$, we obtain the “ANCOVA I” estimator in Yang and Tsiatis (2001), which is the least-squares solution of the coefficient of $Z_i$ in a linear regression of $Y_i$ on $Z_i$ and $X_i$. Further, setting $g_0(X_i) = E(Y_i|Z_i = 0, X_i)$ and $g_1(X_i) = E(Y_i|Z_i = 1, X_i)$, we obtain the “ANCOVA II” estimator (e.g. Yang and Tsiatis, 2001; Tsiatis et al., 2008; Lin, 2013), which is the least-squares solution of the coefficient of $Z_i$ in a linear regression of $Y_i$ on $Z_i, X_i$ and their interaction terms. This estimator achieves the semiparametric variance lower bound within the family $I$, when the conditional mean functions $g_0(X_i)$ and $g_1(X_i)$ are correctly specified in the ANCOVA model (e.g. Robins et al., 1994; Leon et al., 2003). Another member of $I$ is the target maximum likelihood estimator (e.g. Moore and van der Laan, 2009; Moore et al., 2011; Colantuoni and Rosenblum, 2015), which is asymptotic efficient under correct outcome model specification. The IPW estimator $\hat{\tau}_{IPW}$ is
also a member of \( \mathcal{I} \). Specifically, [Shen et al. (2014)] showed that if the logistic model \( (8) \) is used to estimate the propensity score \( \hat{e}_i \), then the IPW estimator is asymptotically equivalent to the “ANCOVA II” estimator and becomes semiparametric efficient if the true \( g_0(X_i) \) and \( g_1(X_i) \) are linear functions of \( X_i \).

In the following Proposition we show that the OW estimator is also a member of \( \mathcal{I} \) and is asymptotically efficient under the linearity assumption. The proof of Proposition 1 is provided in Web Appendix A.

**Proposition 1** (Asymptotic efficiency of overlap weighting)

(a) If the propensity score is estimated by a parametric model \( e(X; \theta) \) with parameters \( \theta \) that satisfies a set of mild regularity conditions (specified in Web Appendix A), then \( \hat{\tau}_{ow} \) belongs to the class of estimators \( \mathcal{I} \).

(b) Suppose \( X^1 \) and \( X^2 \) are two nested sets of baseline covariates with \( X^2 = (X^1, X^*) \), and \( e(X^1; \theta_1) \), \( e(X^2; \theta_2) \) are nested smooth parametric models. Write \( \hat{\tau}_{ow}^{1} \) and \( \hat{\tau}_{ow}^{2} \) as two OW estimators with the weights defined through \( e(X^1; \hat{\theta}_1) \) and \( e(X^2; \hat{\theta}_2) \), respectively. Then the asymptotic variance of \( \hat{\tau}_{ow}^{2} \) is no larger than that of \( \hat{\tau}_{ow}^{1} \).

(c) If the propensity score is estimated from the logistic regression \( (8) \), then \( \hat{\tau}_{ow} \) is asymptotically equivalent to the “ANCOVA II” estimator, and becomes semiparametric efficient as long as the true \( E(Y_i|X_i, Z_i = 1) \) and \( E(Y_i|X_i, Z_i = 0) \) are linear in \( X_i \).

Proposition 1 summarizes the large-sample properties of the OW estimator in randomized trials, extending those demonstrated for IPW in [Shen et al. (2014)]. In particular, adjusting for the baseline covariates using OW does not adversely affect efficiency in large samples than without adjustment. Further, the asymptotic equivalence between \( \hat{\tau}_{ow} \) and the “ANCOVA II” estimator indicates that OW becomes fully semiparametric efficient when the conditional outcome surface is a linear function of the covariates adjusted in the logistic propensity score model. In the special case where the randomization
probability \( r = 1/2 \), we show in Web Appendix B that the limit of the large-sample variance of \( \hat{\tau}^{\text{OW}} \)

\[
\lim_{N \to \infty} N \text{Var}(\hat{\tau}^{\text{OW}}) = (1 - R^2_{Y \sim X}) \lim_{N \to \infty} N \text{Var}(\hat{\tau}^{\text{UNADJ}}) = 4(1 - R^2_{Y \sim X}) \text{Var}(\tilde{Y}_i),
\]

where \( \tilde{Y}_i = Z_i(Y_i - \mu_1) + (1 - Z_i)(Y_i - \mu_0) \) is the mean-centered outcome and \( R^2_{Y \sim X} \) measures the proportion of explained variance after regressing \( \tilde{Y}_i \) on \( X_i \). Similar definition of \( R \)-squared was also used elsewhere when demonstrating efficiency gain with covariate adjustment (e.g. Moore and van der Laan, 2009; Moore et al., 2011; Wang et al., 2019). The amount of variance reduction is also a direct result from the asymptotic equivalence between the OW, IPW, and “ANCOVA II” estimators. Equation (12) shows that incorporating additional covariates into the propensity score model will not reduce the asymptotic efficiency because \( R^2_{Y \sim X} \) is non-decreasing when more covariates are considered. Although adding covariates does not hurt the asymptotic efficiency, in practice we recommend incorporating the covariates that exhibit severe baseline imbalance and that have large predictive power for the outcome (Williamson et al., 2014).

Perhaps more interestingly, the results in Proposition 1 apply more broadly to the family of balancing weights estimators, formalized in the following Proposition. The proof of Proposition 2 is presented in Web Appendix A.

**Proposition 2 (Extension to balancing weights)**

Proposition 1 holds for the general family of estimators (5) using balancing weights defined in (4), as long as the tilting function \( h(X) \) is a “smooth” function of the propensity score, where “smooth” is defined by satisfying a set of mild regularity conditions (specified in details in Web Appendix A).

### 3.2 Binary Outcomes

For binary outcomes, the target estimand could be the causal risk difference, risk ratio and odds ratio, denoted as \( \tau_{RD} \), \( \tau_{RR} \) and \( \tau_{OR} \), respectively. The discussions in Section 3.1 directly apply to the estimation of the additive estimand, \( \tau_{RD} \). When estimating the ratio estimands, one should proceed with caution in interpreting regression parameters for the ANCOVA-type generalized linear models due to the potential non-collapsibility issue. Additionally, it is well-known that the log-binomial model frequently fails to
converge with a number of covariates, and therefore one may have to resort to less efficient regression methods such as the modified Poisson regression (Zou, 2004). Williamson et al. (2014) showed that IPW can be used to adjust for baseline covariates without changing the interpretation of the marginal treatment effect estimands, $\tau_{RR}$ and $\tau_{OR}$. Because of the asymptotic equivalence between the IPW and OW estimators (Proposition 1), OW shares the advantages of IPW in improving the asymptotic efficiency over the unadjusted estimators for risk ratio and odds ratio without compromising the interpretation of the marginal estimands. In addition, due to its ability to remove all chance imbalance associated with $X_i$, OW is likely to give higher efficiency than IPW in finite samples, which we will demonstrate in Section 4.

### 3.3 Variance Estimation

To estimate the variance of propensity score estimators, it is important to incorporate the uncertainty in estimating the propensity scores (Lunceford and Davidian, 2004). Failing to do so leads to conservative variance estimates of the weighting estimator and therefore reduces power of the Wald test for treatment effect (Williamson et al., 2014). Below we use the M-estimation theory (e.g. Tsiatis, 2007) to derive a consistent variance estimator for OW. Specifically, we cast $\hat{\mu}_1, \hat{\mu}_0$ in equation (7), and $\hat{\theta}$ in the logistic model (8) as the solutions to $\hat{\lambda} = (\hat{\mu}_1, \hat{\mu}_0, \hat{\theta})^T$ to the following joint estimation equations

$$\sum_{i=1}^{N} U_i = \sum_{i=1}^{N} U(Y_i, X_i, Z_i; \hat{\lambda}) = 0,$$

where $\hat{X}_i = (1, X_i^T)^T$ is the augmented covariates with intercept. Here, the first two rows represent estimating functions for $\hat{\mu}_1$ and $\hat{\mu}_0$ and the last rows are the score functions of the logistic model including an intercept and main effects of $X_i$. If $X_i$ is of $p$ dimensions, equation (13) involves $p + 3$ scalar estimating equations for $p + 3$ parameters. Let $A = -E(\partial U_i/\partial \lambda)^T, B = E(U_i U_i^T)$, the asymptotic covariance matrix for $\hat{\lambda}$ can be written as $N^{-1}A^{-1}BA^{-T}$. Extracting the covariance matrix for the first
two components in \( \lambda \), we can show that, as \( N \) goes to infinity,

\[
\sqrt{N} \begin{bmatrix} \hat{\mu}_1 - \mu_1 \\ \hat{\mu}_0 - \mu_0 \end{bmatrix} \to N \left\{ 0, \begin{bmatrix} \Sigma_{11}, \Sigma_{12} \\ \Sigma_{21}, \Sigma_{22} \end{bmatrix} \right\},
\]

where the covariance matrix is defined as the corresponding elements in \( A^{-1}BA^{-T} \),

\[
\Sigma_{11} = [A^{-1}BA^{-T}]_{1,1}, \Sigma_{22} = [A^{-1}BA^{-T}]_{2,2}, \Sigma_{12} = \Sigma_{21} = [A^{-1}BA^{-T}]_{1,2}.
\]

where \([A^{-1}BA^{-T}]_{j,k}\) denotes the \((j,k)\)th element of the matrix \( A^{-1}BA^{-T} \). Using the delta method, we can obtain the asymptotic variance of \( \frac{\delta_{\text{OW}}}{\hat{\tau}_{\text{RD}}} \), \( \frac{\delta_{\text{OW}}}{\hat{\tau}_{\text{RR}}} \), and \( \frac{\delta_{\text{OW}}}{\hat{\tau}_{\text{OR}}} \) as a function of \( \Sigma_{11}, \Sigma_{22}, \Sigma_{12} \). Consistent plug-in estimators can then be obtained by estimating the expectations in the “sandwich” matrix \( A^{-1}BA^{-T} \) by their corresponding sample averages. We summarize the estimators for the asymptotic variance of \( \frac{\delta_{\text{OW}}}{\hat{\tau}_{\text{RD}}}, \frac{\delta_{\text{OW}}}{\hat{\tau}_{\text{RR}}}, \frac{\delta_{\text{OW}}}{\hat{\tau}_{\text{OR}}} \) in the following equations,

\[
\text{Var}(\hat{\tau}_{\text{UNADJ}}) = \frac{1}{N} \hat{V}_{\text{UNADJ}} - \hat{v}_1^T \left\{ \frac{1}{N} \sum_{i=1}^{N} \hat{e}_i(1 - \hat{e}_i)\hat{X}_i\hat{X}_i^T \right\}^{-1} (2\hat{v}_1 - \hat{v}_2),
\]

where

\[
\hat{V}_{\text{UNADJ}} = \left\{ \frac{1}{N} \sum_{i=1}^{N} \hat{e}_i(1 - \hat{e}_i) \right\}^{-1} \left( \frac{\hat{E}_1}{N} \sum_{i=1}^{N} Z_i \hat{e}_i(1 - \hat{e}_i)(Y_i - \hat{\mu}_1)^2 + \frac{\hat{E}_0}{N} \sum_{i=1}^{N} (1 - Z_i)\hat{e}_i(1 - \hat{e}_i)(Y_i - \hat{\mu}_0)^2 \right),
\]

\[
\hat{v}_1 = \left\{ \frac{1}{N} \sum_{i=1}^{N} \hat{e}_i(1 - \hat{e}_i) \right\}^{-1} \left( \frac{\hat{E}_1}{N} \sum_{i=1}^{N} Z_i \hat{e}_i(1 - \hat{e}_i)(Y_i - \hat{\mu}_1)^2 \hat{X}_i + \frac{\hat{E}_0}{N} \sum_{i=1}^{N} (1 - Z_i)\hat{e}_i(1 - \hat{e}_i)(Y_i - \hat{\mu}_0)^2 \hat{X}_i \right),
\]

\[
\hat{v}_2 = \left\{ \frac{1}{N} \sum_{i=1}^{N} \hat{e}_i(1 - \hat{e}_i) \right\}^{-1} \left( \frac{\hat{E}_1}{N} \sum_{i=1}^{N} Z_i \hat{e}_i(1 - \hat{e}_i)^2(Y_i - \hat{\mu}_1)^2 \hat{X}_i + \frac{\hat{E}_0}{N} \sum_{i=1}^{N} (1 - Z_i)\hat{e}_i(1 - \hat{e}_i)^2(Y_i - \hat{\mu}_0)^2 \hat{X}_i \right),
\]

and \( \hat{E}_k \) depends on the choice of estimands. For \( \frac{\delta_{\text{OW}}}{\hat{\tau}_{\text{RD}}} \), we have \( \hat{E}_k = 1 \); for \( \frac{\delta_{\text{OW}}}{\hat{\tau}_{\text{RR}}} \), we set \( \hat{E}_k = \hat{\mu}_k^{-1} \); for \( \frac{\delta_{\text{OW}}}{\hat{\tau}_{\text{OR}}} \), we use \( \hat{E}_k = \hat{\mu}_k^{-1}(1 - \hat{\mu}_k)^{-1} \) with \( k = 0, 1 \). Detailed derivation of the asymptotic variance and its consistent estimator can be found in Web Appendix B.

### 4 Simulation Studies

This section carries out extensive simulations to investigate the finite-sample operating characteristics of OW relative to IPW, direct regression adjustment and an augmented estimator that combined IPW and
outcome regression. The main purpose of the simulation study is to empirically (i) illustrate that OW leads to marked finite-sample efficiency gain compared with IPW in estimating the treatment effect, and (ii) validate the sandwich variance estimator of OW developed in Section 3.3.

4.1 Continuous Outcomes

The first set of simulations involves continuous outcomes. We generate $p = 10$ baseline covariates from the standard normal distribution, $X_{ij} \sim N(0, 1)$, $j = 1, 2, \cdots, p$. Fixing the randomization probability $r$, the treatment indicator is randomly generated from a Bernoulli distribution, $Z_i \sim \text{Bern}(r)$. Given the baseline covariates $X_i = (X_{i1}, \ldots, X_{ip})^T$, we generate the potential outcomes from the following linear model (model 1): for $z = 0, 1$

$$Y_i(z) \sim N(z \alpha + X_i^T \beta_0 + zX_i^T \beta_1, \sigma_y^2), \quad i = 1, 2, \cdots, N$$

where $\alpha$ is the main effect of the treatment, and $\beta_0, \beta_1$ are the effects of the covariates and treatment-by-covariate interactions. The observed outcome is set to be $Y_i = Y_i(Z_i) = Z_i Y_i(1) + (1 - Z_i) Y_i(0)$. In our data generating process, because the baseline covariates have mean zero, the true average treatment effect on the additive scale $\tau = \alpha$. For simplicity, we fix $\tau = 0$ and choose $\beta_0 = b_0 \times (1, 1, 2, 2, 4, 4, 8, 8, 16, 16)^T$, $\beta_1 = b_1 \times (1, 1, 1, 1, 1, 1, 1, 1, 1, 1)^T$. We specify the residual variance $\sigma_y^2 = 2$, and choose the multiplication factor $b_0$ so that the signal-to-noise ratio (due to the main effects) is 1, namely, $\sum_{i=1}^{p} \beta_{0i}^2 / \sigma_y^2 = 1$. This specification mimics a scenario where the baseline covariates can explain up to 50% of the variation in the outcome. We also assign different importance to each covariates. For example, the last two covariates, $X_9, X_{10}$, explain the majority of the variation, mimicking the scenario that one may have access to only a few strong prognostic risk factors at baseline. We additionally vary the value of $b_1 \in \{0, 0.25, 0.5, 0.75\}$ to control the strength of treatment-by-covariate interactions. A larger value of $b_1$ indicates a higher level of treatment effect heterogeneity so that the baseline covariates are more strongly associated with the individual-level treatment contrast, $Y_i(1) - Y_i(0)$. For the randomization probability $r$, we consider two values: $r = 0.5$ represents a balanced design with one-to-one randomization, and $r = 0.7$ an unbalanced assignment where more patients are randomized.
to the treatment arm. Findings under other scenarios with $r = 0.6$ are similar to those with $r = 0.7$ and are omitted for brevity. We also vary the total sample sizes $N$ from 50 to 500, with 50 and 500 mimicking a small and large sample scenario, respectively.

In each simulation scenario, we compare several different estimators for ATE, including the unadjusted estimator $\hat{\tau}^{\text{UNADJ}}$ (UNADJ), the IPW estimator $\hat{\tau}^{\text{IPW}}$, the estimator based on linear regression $\hat{\tau}^{\text{LR}}$ (LR), and the OW estimator $\hat{\tau}^{\text{OW}}$. For the IPW and OW estimators, we estimate the propensity score by logistic regression including all baseline covariates as linear terms, and the final estimator is given by the Hájek-type estimator $\hat{\tau}^{\text{IPW}}$ using the corresponding weights. For the LR estimator, we fit the correctly specified outcome model in (17) (model 1). To explore the performance of various estimators under model misspecification, we repeat the simulations by replacing the potential outcome generating process with the following model (model 2)

$$Y_i(z) \sim \mathcal{N}(z\alpha + X_i^T \beta_0 + zX_i^T \beta_1 + X_{i,\text{int}}^T \gamma, \sigma_y^2), \quad (18)$$

where $X_{i,\text{int}} = (X_{i1}X_{i2}, X_{i2}X_{i3}, \cdots, X_{ip-1}X_{ip})$ represents $p - 1$ interactions between pairs of covariates with consecutive indices and $\gamma = \sqrt{\sigma_y^2/p \times (1, 1, \cdots, 1)^T}$ represents the strength of this interaction effect. The LR estimator omitting these additional interactions is thus considered as misspecified. For IPW and OW, the propensity score model is technically correctly specified (because the true randomization probability is a constant) even though it does not adjust for the interaction term $X_{i,\text{int}}$. With a slight abuse of terminology, we refer to this scenario as “model misspecification”.

In addition to the previous four estimators, we also consider an augmented IPW (AIPW) estimator that augments IPW with an outcome regression [Lunceford and Davidian, 2004], which is also a member of the class $\mathcal{I}$:

$$\hat{\tau}^{\text{AIPW}} = \hat{\mu}_{1}^{\text{AIPW}} - \hat{\mu}_{0}^{\text{AIPW}} = \frac{1}{N} \sum_{i=1}^{N} \left\{ \frac{Z_iY_i}{\hat{e}_i} - \frac{(Z_i - \hat{e}_i)\hat{\mu}_1(X_i)}{\hat{e}_i} \right\} - \left\{ \frac{(1 - Z_i)Y_i}{1 - \hat{e}_i} + \frac{(Z_i - \hat{e}_i)\hat{\mu}_0(X_i)}{1 - \hat{e}_i} \right\}, \quad (19)$$

where $\hat{\mu}_z(X_i) = \hat{E}[Y_i|X_i, Z_i = z]$ is the prediction from the outcome regression. In the context of observational studies, such an estimator is also known as the doubly-robust estimator. Because AIPW hybrids propensity score weighting and outcome regression, it does not retain the objectivity of the
former. Nonetheless, the AIPW estimator is often perceived as an improved version of IPW (Bang and Robins [2005]); therefore, we also compare it in the simulations to understand its operating characteristics in randomized trials.

Figure 1: The relative efficiency of $\hat{\tau}^{\text{IPW}}$, $\hat{\tau}^{\text{AIPW}}$, $\hat{\tau}^{\text{LR}}$ and $\hat{\tau}^{\text{OW}}$ relative to $\hat{\tau}^{\text{UNADJ}}$ for estimating ATE when (a) $r = 0.5$, $b_1 = 0$ and the outcome model is correctly specified (b) $r = 0.5$, $b_1 = 0.75$ and the outcome model is correctly specified (c) $r = 0.7$, $b_1 = 0$ and the outcome model is correctly specified (d) $r = 0.7$, $b_1 = 0$ and the outcome model is misspecified. A larger value of relative efficiency corresponds to a more efficient estimator.

For each scenario, we simulate 2000 replicates, and calculate the bias, Monte Carlo variance and mean squared error for each estimator of $\tau$. Across all scenarios, as expected we find that the bias of all estimators is negligible, and thus the Monte Carlo variance and the mean squared error are almost identical. For this reason, we focus on reporting the efficiency comparisons using the Monte Carlo variance. We define the relative efficiency of an estimator as the ratio between the Monte Carlo variance of that estimator and that of the unadjusted estimator. Relative efficiency larger than one indicates that estimator is more efficient than the unadjusted estimator. We also examine the empirical coverage rate of the associated 95% normality-based confidence intervals. Specifically, the confidence interval of $\hat{\tau}^{\text{LR}}$, $\hat{\tau}^{\text{IPW}}$, and $\hat{\tau}^{\text{OW}}$ is constructed based on the Huber-White estimator in Lin (2013), the sandwich estimator in Williamson et al. (2014), and the sandwich estimator developed in Section 3.3 respectively. Finally,
the confidence interval of $\hat{\tau}^{\text{AIPW}}$ is based on the sandwich variance derived based on the M-estimation theory; the details are presented in Web Appendix C.

Figure 1 presents the relative efficiency of the different estimators in four scenarios. In panel (a), where the outcomes are generated from model 1, with randomization probability $r = 0.5$ and without treatment effect heterogeneity ($b_1 = 0$), it is evident that $\hat{\tau}^{\text{IPW}}$, $\hat{\tau}^{\text{LR}}$, $\hat{\tau}^{\text{AIPW}}$ and $\hat{\tau}^{\text{OW}}$ are consistently more efficient than the unadjusted estimator, and the relative efficiency increases with a larger sample size $N$. However, when the sample size is no larger than 100, OW leads to higher efficiency compared to LR, IPW and AIPW, while IPW is the least efficient among the adjusted estimators. In panel (b), in which we impose strong treatment effect heterogeneity $b_1 = 0.75$, $\hat{\tau}^{\text{LR}}$ and $\hat{\tau}^{\text{AIPW}}$ become slightly more efficient than $\hat{\tau}^{\text{OW}}$; this is expected as the true outcome model is used and the design is balanced. The efficiency advantage decreases for $\hat{\tau}^{\text{LR}}$ and $\hat{\tau}^{\text{AIPW}}$ as $b_1$ moves closer to zero (Table 1). On the other hand, $\hat{\tau}^{\text{OW}}$ becomes more efficient than $\hat{\tau}^{\text{LR}}$ and $\hat{\tau}^{\text{AIPW}}$ when the randomization probability deviates from 0.5. For instance, in panel (c), when the randomization probability is 0.7 and sample size is $N = 50$, $\hat{\tau}^{\text{LR}}$ and $\hat{\tau}^{\text{AIPW}}$ become even less efficient than the unadjusted estimator, while OW demonstrates substantial efficiency gain over the unadjusted estimator. The deteriorating performance of $\hat{\tau}^{\text{LR}}$ under $r = 0.7$ supports the earlier findings in Freedman (2008). These results show that the relative performance between LR and OW is affected by the degree of treatment effect heterogeneity and the randomization probability. In the scenarios with small heterogeneous treatment effect or/and with unbalanced design (Table 1), OW tends to be more efficient than LR. Overall, the LR and OW are generally more comparable when model is correctly specified, both outperforming IPW. But OW becomes more efficient than LR when the outcome model is incorrectly specified. Namely, when the outcomes are generated from model 2, $\hat{\tau}^{\text{OW}}$ becomes the most efficient even if the propensity model omits important interaction terms in the true outcome model, as in panel (d) of Figure 1. In addition, LR and AIPW have almost identical finite-sample efficiency, suggesting that the regression component dominates the AIPW estimator in randomized trials. Throughout, $\hat{\tau}^{\text{OW}}$ is consistently more efficient than $\hat{\tau}^{\text{IPW}}$, regardless of sample size, randomization probability and the degree of treatment effect heterogeneity. These patterns persist when the sample size increases to $N = 500$, although there the differences between methods become smaller.
Table 1: The relative efficiency of each estimator compared to the unadjusted estimator, the ratio between the average estimated variance over Monte Carlo variance (\(\frac{\text{Est Var}}{\text{MC Var}}\)), and 95% coverage rate of IPW, LR, AIPW and OW estimators. The results are based on 2000 simulations with a continuous outcome. In the “correct specification” scenario, data are generated from model 1; in the “misspecification” scenario, data are generated from model 2. For each estimator, the same specification is used throughout, regardless of the data generating model.

| Sample size | Relative efficiency | \(\frac{\text{Est Var}}{\text{MC Var}}\) | 95% Coverage |
|-------------|---------------------|----------------|---------------|
|             | IPW | LR | AIPW | OW | IPW | LR | AIPW | OW | IPW | LR | AIPW | OW |
| \(r = 0.5, b_1 = 0\), correct specification |
| 50          | 1.621 | 2.126 | 2.042 | 2.451 | 1.001 | 0.866 | 0.668 | 1.343 | 0.936 | 0.933 | 0.885 | 0.967 |
| 100         | 2.238 | 2.475 | 2.399 | 2.548 | 0.898 | 0.961 | 0.799 | 1.116 | 0.938 | 0.944 | 0.914 | 0.955 |
| 200         | 2.927 | 2.987 | 2.984 | 3.007 | 0.951 | 0.996 | 0.927 | 1.051 | 0.946 | 0.949 | 0.938 | 0.956 |
| 500         | 2.985 | 3.004 | 2.995 | 3.006 | 0.963 | 0.987 | 0.959 | 1.000 | 0.944 | 0.949 | 0.942 | 0.952 |
| \(r = 0.5, b_1 = 0.25\), correct specification |
| 50          | 1.910 | 2.792 | 2.606 | 2.905 | 1.141 | 0.711 | 0.684 | 1.562 | 0.946 | 0.899 | 0.887 | 0.972 |
| 100         | 2.968 | 3.575 | 3.481 | 3.489 | 0.988 | 0.811 | 0.896 | 1.295 | 0.954 | 0.925 | 0.928 | 0.968 |
| 200         | 3.640 | 3.864 | 3.855 | 3.794 | 0.932 | 0.754 | 0.923 | 1.079 | 0.940 | 0.912 | 0.933 | 0.956 |
| 500         | 3.801 | 3.814 | 3.814 | 3.791 | 0.947 | 0.735 | 0.940 | 0.992 | 0.945 | 0.907 | 0.945 | 0.950 |
| \(r = 0.5, b_1 = 0.5\), correct specification |
| 50          | 1.635 | 2.894 | 2.781 | 2.755 | 1.021 | 0.463 | 0.769 | 1.530 | 0.936 | 0.822 | 0.910 | 0.970 |
| 100         | 3.084 | 3.917 | 3.835 | 3.546 | 0.984 | 0.510 | 0.977 | 1.291 | 0.942 | 0.840 | 0.944 | 0.968 |
| 200         | 3.187 | 3.410 | 3.406 | 3.287 | 0.924 | 0.446 | 0.936 | 1.061 | 0.944 | 0.802 | 0.942 | 0.956 |
| 500         | 3.730 | 3.809 | 3.810 | 3.717 | 1.037 | 0.477 | 1.049 | 1.085 | 0.957 | 0.818 | 0.960 | 0.962 |
| \(r = 0.5, b_1 = 0.75\), correct specification |
| 50          | 1.715 | 3.043 | 2.972 | 2.570 | 0.991 | 0.286 | 0.816 | 1.383 | 0.935 | 0.712 | 0.918 | 0.967 |
| 100         | 2.679 | 3.279 | 3.253 | 3.003 | 0.931 | 0.280 | 0.917 | 1.168 | 0.942 | 0.710 | 0.934 | 0.966 |
| 200         | 2.979 | 3.220 | 3.215 | 3.023 | 0.967 | 0.278 | 0.995 | 1.075 | 0.951 | 0.697 | 0.949 | 0.964 |
| 500         | 3.337 | 3.425 | 3.426 | 3.338 | 0.995 | 0.273 | 1.013 | 1.037 | 0.943 | 0.696 | 0.945 | 0.954 |
Table 1: (Continued) The relative efficiency of each estimator compared to the unadjusted estimator, the ratio between the average estimated variance over Monte Carlo variance (\(\frac{\text{Est Var}}{\text{MC Var}}\)), and 95% coverage rate of IPW, LR, AIPW and OW estimators. The results are based on 2000 simulations with a continuous outcome. In the “correct specification” scenario, data are generated from model 1; in the ”misspecification” scenario, data are generated from model 2. For each estimator, the same specification is used throughout, regardless of the data generating model.

| Sample size | Relative efficiency | \(\frac{\text{Est Var}}{\text{MC Var}}\) | 95% Coverage |
|-------------|---------------------|---------------------------------|-------------|
|             | IPW     | LR     | AIPW  | OW     | IPW     | LR     | AIPW  | OW     | IPW     | LR     | AIPW  | OW     |
| 50          | 1.415   | 1.686  | 1.605 | 2.418  | 1.041   | 0.745  | 0.617 | 1.377  | 0.938   | 0.913  | 0.883 | 0.959 |
| 100         | 2.042   | 2.378  | 2.290 | 2.521  | 0.889   | 0.942  | 0.784 | 1.104  | 0.944   | 0.941  | 0.915 | 0.956 |
| 200         | 2.777   | 2.926  | 2.896 | 2.981  | 0.987   | 1.027  | 0.947 | 1.078  | 0.949   | 0.950  | 0.940 | 0.953 |
| 500         | 2.898   | 2.939  | 2.939 | 2.950  | 0.976   | 0.994  | 0.969 | 1.003  | 0.953   | 0.953  | 0.949 | 0.953 |
|             |         |        |       |        |         |        |       |        |         |        |       |       |
| 50          | 1.056   | 0.036  | 0.036 | 2.270  | 1.060   | 0.014  | 0.026 | 1.184  | 0.938   | 0.779  | 0.816 | 0.931 |
| 100         | 1.825   | 2.439  | 2.311 | 2.935  | 0.914   | 0.858  | 0.717 | 1.039  | 0.946   | 0.921  | 0.897 | 0.923 |
| 200         | 2.474   | 2.706  | 2.679 | 2.874  | 0.971   | 0.931  | 0.857 | 0.963  | 0.948   | 0.944  | 0.927 | 0.935 |
| 500         | 2.641   | 2.743  | 2.738 | 2.809  | 0.922   | 0.912  | 0.887 | 0.925  | 0.940   | 0.936  | 0.934 | 0.938 |
|             |         |        |       |        |         |        |       |        |         |        |       |       |
| 50          | 1.009   | 1.093  | 0.986 | 1.299  | 0.773   | 0.768  | 0.598 | 0.900  | 0.908   | 0.915  | 0.870 | 0.933 |
| 100         | 1.371   | 1.502  | 1.379 | 1.549  | 0.805   | 0.954  | 0.779 | 0.924  | 0.924   | 0.946  | 0.921 | 0.942 |
| 200         | 1.526   | 1.567  | 1.516 | 1.592  | 0.897   | 0.965  | 0.888 | 0.925  | 0.938   | 0.953  | 0.936 | 0.944 |
| 500         | 1.576   | 1.587  | 1.569 | 1.595  | 0.913   | 0.937  | 0.911 | 0.912  | 0.943   | 0.949  | 0.944 | 0.941 |
|             |         |        |       |        |         |        |       |        |         |        |       |       |
| 50          | 0.896   | 0.009  | 0.009 | 1.468  | 0.843   | 0.005  | 0.009 | 0.857  | 0.904   | 0.777  | 0.808 | 0.906 |
| 100         | 1.096   | 1.258  | 1.152 | 1.533  | 0.724   | 0.754  | 0.637 | 0.837  | 0.911   | 0.903  | 0.878 | 0.917 |
| 200         | 1.390   | 1.457  | 1.398 | 1.570  | 0.861   | 0.894  | 0.816 | 0.898  | 0.929   | 0.938  | 0.920 | 0.933 |
| 500         | 1.591   | 1.632  | 1.612 | 1.648  | 0.980   | 1.003  | 0.976 | 0.981  | 0.948   | 0.949  | 0.948 | 0.949 |
as a result of Proposition 1. Additional numerical results on relative efficiency are provided in Table 1.

Table 1 also summarizes the accuracy of the estimated variance and the coverage rate of each interval estimator. The former is measured by the ratio between the average estimated variance and the Monte Carlo variance of the estimator, and a ratio close to 1 indicates adequate performance. In general, we find that estimated variance is close to the truth for both IPW and OW, but less so for the LR and AIPW estimator, especially in small samples such as $N = 50$ or 100. Specifically, the sandwich variance of IPW and our variance for OW tend to adequately quantify the uncertainty, even when the sample size is as small as $N = 50$, when the outcomes are generated from model 1. For these settings, the variance of the Huber-White variance estimator for LR sometimes substantially underestimates the true variance, and leads to under-coverage of the interval estimator. Also, in the case where LR has a slight efficiency advantage ($b_1 = 0.75$), the coverage of LR is only around 70% even when the true linear regression model is fit. This results show that the Huber-White sandwich variance, although known to be robust in large samples to heteroscedasticity, could be severely biased towards zero in finite samples and under treatment effect heterogeneity. This finding provides an additional caveat for using LR. Similar to the Huber-White variance for LR, the sandwich variance of AIPW also frequently underestimates the true variance when $N \leq 100$. On the other hand, when the outcomes are generated from model 2 and the randomization probability $r = 0.7$, all variance estimators tend to underestimate the truth, and the coverage rate slightly deteriorates. However, the coverage of IPW and OW estimators is still closer to nominal than LR and AIPW when sample size $N = 50$, suggesting that the sandwich variance of the propensity score weighting estimators have more stable performance.

4.2 Binary Outcomes

The second set of simulations involves binary outcomes generated from a generalized linear model. Specifically, we assume the potential outcome follows a logistic regression model (model 3): for $z = 0, 1$,

$$\text{logit}\{\Pr(Y_i(z) = 1)\} = \eta + z\alpha + X_i^T \beta_0 + zX_i^T \beta_1, \quad i = 1, 2, \ldots, N, \quad (20)$$
where $X_i$ denotes the vector of $p = 10$ baseline covariates simulated as in Section 4.1 and the parameter $\eta$ to represent the baseline prevalence of the outcomes in the control arm, i.e., $u \approx \Pr(Y_i(0) = 1) = 1/(1 + \exp(-\eta))$. We specify the main effects $\beta_0 = b_0 \times (1, 1, 2, 2, 4, 4, 8, 8, 16, 16)^T$, where $b_0$ is chosen to be the same value used in Section 4.1. For the covariate-by-treatment interactions, we set $\beta_1 = b_1 \times (1, 1, 1, 1, 1, 1, 1, 1)^T$ and examine scenarios with $b_1 = 0$ and $b_1 = 0.75$, with the latter representing strong treatment effect heterogeneity. Similarly, we set the true treatment effect to be zero $\tau = 0$. We vary the sample size $N$ from 50 to 500 to represent both small and moderately large sample sizes. Additionally, we vary the value of $\eta$ such that the baseline prevalence $u \in \{0.5, 0.3, 0.2, 0.1\}$, representing scenarios where the outcome is common and rare. It is expected that the stability of regression adjustment becomes sensitive to the prevalence of outcome, while propensity score weighting estimators are less affected (Williamson et al., 2014). We also consider a data generating process with additional covariate interaction terms (model 4): for $z = 0, 1,$

$$\text{logit}\{\Pr(Y_i(z) = 1)\} = \eta + z\alpha + X_i^T \beta_0 + zX_i\beta_1 + X_i^T\gamma, \quad i = 1, 2, \ldots, N,$$

which can be viewed as the binary analogy of model 2 defined in (18). When the data are generated using model 4, we will examine the performance of a misspecified logistic regression ignoring the interaction terms $X_{i,\text{int}}$. We examine both balanced assignment with $r = 0.5$ and unbalanced assignment with $r = 0.7$, and simulate 2000 data replicates under each scenario.

Under each scenario, we compare five estimators, $\hat{\tau}^{\text{UNADJ}}, \hat{\tau}^{\text{IPW}}, \hat{\tau}^{\text{LR}}, \hat{\tau}^{\text{AIPW}}, \hat{\tau}^{\text{OW}}$, for binary outcomes. The unadjusted estimator is again the nonparametric difference-in-mean estimator. For the IPW and OW estimators, we fit a propensity score model by regressing the treatment on the main effects of the baseline covariates $X_i$. With a slight abuse of acronym, in this Section we will use the abbreviation ‘LR’ to represent logistic regression. For this estimator, we fit the logistic outcome model with main effects of treatment and covariates, along with their interactions, as in $\text{logit}\{\Pr(Y_i = 1)\} = \delta + Z_i\kappa + X_i^T\xi_0 + Z_iX_i^T\xi_1$. The group means $\mu_0, \mu_1$ are estimated by standardization (i.e. the basic form of the g-formula
\begin{equation}
\hat{\mu}_{0}^{LR} = \frac{1}{N} \sum_{i=1}^{N} \frac{\exp(\hat{\delta} + X_i^T \hat{\xi}_0)}{1 + \exp(\hat{\delta} + X_i^T \hat{\xi}_0)}, \quad \hat{\mu}_{1}^{LR} = \frac{1}{N} \sum_{i=1}^{N} \frac{\exp(\hat{\delta} + \hat{\kappa} + X_i^T \hat{\xi}_0 + X_i^T \hat{\xi}_1)}{1 + \exp(\hat{\delta} + \hat{\kappa} + X_i^T \hat{\xi}_0 + X_i^T \hat{\xi}_1)}.
\end{equation}

(Hernan and Robins [2010]),

The estimated group means are then used to calculate risk difference \(\tau_{RD}\), log risk ratio \(\tau_{RR}\) and log odds ratio \(\tau_{OR}\). For the AIPW estimator, we estimate \(\hat{\mu}_{0}^{AIPW}\) and \(\hat{\mu}_{1}^{AIPW}\) as defined in [19], except that \(\hat{\mu}_{z}(X_i) = \hat{E}[Y_i|X_i, Z_i = z]\) is now the prediction from the above logistic outcome model. The ratio estimands are then estimated following equation [10]. Because the bias of all these approaches is close to zero, we focus on the relative efficiency of the adjusted estimator compared to the unadjusted in estimating the three estimands. We also examine the performance of the variance and normality-based confidence interval estimators. For the LR estimator, we use the Huber-White variance, and then derive the large-sample variance of \(\hat{\tau}_{RD}^{LR}, \hat{\tau}_{RR}^{LR}\) and \(\hat{\tau}_{OR}^{LR}\) using the delta method. For IPW, we use the sandwich variance of Williamson et al. (2014); for OW, we use the sandwich variance proposed in Section 3.3.

Details of the variance calculation for the AIPW estimator is given in Web Appendix C.

In general, within the range of sample sizes we considered, the potential efficiency gain using the covariate-adjusted estimators over the unadjusted estimator is at most modest for binary outcomes. Specifically, Figure 2 presents the relative efficiency results. Because the finite-sample performance of AIPW is generally driven by the outcome regression component, we mainly focus on interpreting the comparisons between IPW, LR and OW. In column (a), where the outcome is common and the data are generated from model 3, \(\hat{\tau}_{IPW}, \hat{\tau}_{LR}\) or \(\hat{\tau}_{OW}\) become more efficient than \(\hat{\tau}_{UNADJ}\) only when \(N\) is greater than 80. Because the true outcome model is used in model fitting, LR is slightly more efficient than OW and IPW but the difference quickly diminishes as \(N\) increases. The comparison results are similar when the outcome is generated from model 4 (column (b) and (d)). In addition, when the prevalence of the outcome decreases to around 30% (column (c)), the covariate-adjusted estimators become more efficient than the unadjusted estimator only when \(N\) is greater than 100. In this case, the correctly-specified LR estimator may become unstable in estimating the two ratio estimands when \(N\) is only 50, while both OW and IPW are not subject to such concerns because they do not attempt to estimate an outcome model. As expected, the AIPW estimator also becomes quite inefficient due to the instability of the
Figure 2: The relative efficiency of $\hat{\tau}_{IPW}$, $\hat{\tau}_{LR}$, $\hat{\tau}_{AIPW}$ and $\hat{\tau}_{OW}$ relative to $\hat{\tau}_{UNADJ}$ for estimating $\tau_{RD}$, $\tau_{RR}$, $\tau_{OR}$, when (a) $u = 0.5$ and the outcome model is correctly specified (b) $u = 0.5$ and the outcome model is misspecified (c) $u = 0.3$, and the outcome model is correctly specified (d) $u = 0.3$ and the outcome model is misspecified. A larger value of relative efficiency corresponds to a more efficient estimator.
Figure 3: The relative efficiency of $\hat{\tau}_{IPW}$, $\hat{\tau}_{LR}$, $\hat{\tau}_{AIPW}$ and $\hat{\tau}_{OW}$ relative to $\hat{\tau}_{UNADJ}$ for estimating $\tau_{RD}$, $\tau_{RR}$, $\tau_{OR}$, when (e) $u = 0.5$, $b_1 = 0.75$, $r = 0.5$ and the outcome model is correctly specified (f) $u = 0.5$, $b_1 = 0$, $r = 0.7$ and the outcome model is misspecified (g) $u = 0.2$, $b_1 = 0$, $r = 0.5$, and the outcome model is correctly specified (h) $u = 0.1$, $b_1 = 0$, $r = 0.5$, and the outcome model is correctly specified.
regression component. Figure 3 presents the relative efficiency results in four additional scenarios. In the presence of strong treatment effect heterogeneity (column (e)), the covariate-adjusted estimators, LR and OW, improve over the unadjusted estimator even with extremely small sample size $N = 50$. In this case, the efficiency of LR and OW is almost identical across the range of sample size we examined. In contrast to the continuous outcome simulations, the LR estimator may become more efficient than OW and IPW with unbalanced randomization ($r = 0.7$) and $N \leq 80$ (column (f)). However, when the outcome becomes rare (column (g) and (h)), the OW and IPW estimators are more stable than LR in small samples. In these scenarios, the LR estimates can be quite variable, leading to dramatic efficiency loss even compared with the unadjusted estimator. With further investigation, we found that the LR estimator frequently run into numerical issues and fails to converge under rare outcomes. This non-convergence issue under rare outcomes also adversely affects the efficiency of the AIPW estimator. Table 2 and Web Table 3 summarize the proportion of times that the logistic regression fails to converge as a function of sample size and prevalence of the outcome under the control condition. For instance, when the outcome is rare ($u = 0.1$), the logistic regression fails to converge more than half of the times even when $N = 100$. Finally, for binary outcomes, the difference in efficiency between the adjusted estimators is more pronounced when $N$ does not exceed 200, and becomes trivial when $N = 500$.

To summarize, we conclude that for binary outcomes (i) covariate adjustment improves efficiency most likely when the sample size is at least 100, except in the presence of large treatment effect heterogeneity where there is efficiency gain even with $N = 50$; (ii) the OW estimator is uniformly more efficient in finite samples than IPW and should be the preferred propensity score weighting estimator in randomized trials; (iii) although correctly-specified outcome regression is slightly more efficient than OW in the ideal case with a non-rare outcome, in small samples regression adjustment is generally unstable when the prevalence of outcome decreases; (iv) the efficiency of AIPW is mainly driven by the outcome regression component, and the instability of the outcome model may also lead to an inefficient AIPW estimator in finite-samples.

For $N \in \{50, 100, 200, 500\}$, Web Table 1 and 2 further summarize the accuracy of the variance estimators and the empirical coverage rate of the corresponding interval estimator for each approach,
Table 2: Proportion of times that the logistic regression fails to converge given different outcome prevalence \( u \in \{0.5, 0.3, 0.2, 0.1\} \) and sample sizes

| \( N \) | \( u = 0.5 \) | \( u = 0.3 \) | \( u = 0.2 \) | \( u = 0.1 \) |
|-------|------------|------------|------------|------------|
| 50    | 82.45%     | 90.10%     | 95.25%     | 98.75%     |
| 75    | 17.30%     | 30.05%     | 52.90%     | 89.35%     |
| 100   | 1.50%      | 5.00%      | 14.10%     | 57.25%     |
| 150   | 0          | 0          | 0.45%      | 11.50%     |
| 200   | 0          | 0          | 0          | 1.70%      |

in the scenarios presented in Figure 2 and 3. The Williamson’s variance estimator for IPW and the sandwich variance for AIPW frequently underestimate the true variance for all three estimands, so that the associated confidence interval demonstrates under-coverage, especially when the sample size does not exceed 100. From a hypothesis testing point of view, as we are setting the average causal effect to be null, the results suggest the risk of type I error inflation using IPW or AIPW when \( N \) does not exceed 200. Both LR and OW generally improve upon IPW and AIPW by maintaining closer to nominal coverage rate, with a few exceptions. For example, we notice that the Huber-White variance for logistic regression can be unstable and biased towards zero, leading to under-coverage. On the other hand, the proposed sandwich variance for OW is always close to the true variance regardless of the target estimand. Likewise, the OW interval estimator demonstrates improved performance over IPW, LR and AIPW, and maintains close to nominal coverage even in small samples with rare outcomes, where outcome regression frequently fails to converge.

5 Application to the Best Apnea Interventions for Research Trial

The Best Apnea Interventions for Research (BestAIR) trial is an individually-randomized, parallel-group trial designed to evaluate the effect of continuous positive airway pressure (CPAP) treatment on the health outcomes of patients with high cardiovascular disease risk and obstructive sleep apnea.
but without severe sleepiness (Bakker et al., 2016). Patients were recruited from outpatient clinics at three medical centers in Boston, Massachusetts, and were randomized in a 1:1:1:1 ratio to receive conservative medical therapy (CMT), CMT plus sham CPAP, CMT plus CPAP, or CMT plus CPAP plus motivational enhancement (ME). We follow the study protocol and pool two sub-arms into the combined control group (CMT, CMT plus sham CPAP) and the rest sub-arms into the combined CPAP or active intervention group. This results in 169 participants with 83 patients in the active CPAP group and 86 patients in the combined control arm. A set of patient-level covariates were measured at baseline and outcomes were measured at baseline, 6, and 12 months.

For illustration, we consider estimating the treatment effect of CPAP on two outcomes measured at 6 month. The objective outcome is the 24-hour systolic blood pressure (SBP), measured every 20 minutes during the daytime and every 30 minutes during the sleep. The subjective outcome includes the self-reported sleepiness in daytime, measured by Epworth Sleepiness Scale (ESS) (Zhao et al., 2017). We additionally consider dichotomizing SBP (high SBP if \( \geq 130\text{mmHg} \)) to create a binary outcome, resistant hypertension. For covariate-adjusted analysis, we consider a total of 9 baseline covariates, including demographics (e.g. age, gender, ethnicity), body mass index, Apnea-Hypopnea Index (AHI), average seated radial pulse rate (SDP), site and baseline outcome measures (e.g. baseline blood pressure and ESS). In Table 3, we provide the summary statistics for the covariates and compare between the treated and the control groups at baseline. We measure the baseline imbalance of the covariates by the absolute standardized difference (ASD), which for the \( j \)th covariate is defined as,

\[
\text{ASD}^w = \left| \frac{\sum_{i=1}^{N} w_i X_{ij} Z_i}{\sum_{i=1}^{N} w_i Z_i} - \frac{\sum_{i=1}^{N} w_i X_{ij} (1 - Z_i)}{\sum_{i=1}^{N} w_i (1 - Z_i)} \right| / S_j,
\]

where \( w_i \) represents the weight for each patient and \( S_j^2 \) stands for the average variance, \( S_j^2 = \{\text{Var}(X_{ij}|Z_i = 1) + \text{Var}(X_{ij}|Z_i = 0)\}/2 \). The baseline imbalance is measured by \( \text{ASD}^\text{UNADJ} \) with \( w_i = 1 \). Although the treatment is randomized, we still notice a considerable difference for some covariates between the treated and control group, such as BMI, baseline SBP and AHI. The ASD\(^\text{UNADJ}\) for all three variables exceed 10\%, which has been considered as a common threshold for balance (Austin and Stuart, 2015). In particular, the baseline SBP exhibits the largest imbalance (ASD\(^\text{UNADJ} = 0.477\)), but is considered as the most important predictor of the 6-month SBP outcome. As we shall see later, failing to adjust for
Table 3: Baseline characteristics of the BestAIR randomized trial by treatment groups, and absolute standardized difference (ASD) between the treatment and control groups before and after weighting.

|                    | All patients | CPAP group | Control group | ASD\textsuperscript{UNADJ} | ASD\textsuperscript{PW} | ASD\textsuperscript{OW} |
|--------------------|--------------|------------|---------------|-----------------------------|-------------------------|-------------------------|
| \(N = 169\)        | \(N_1 = 83\) | \(N_0 = 86\) |               |                             |                         |                         |
| **Baseline categorical covariates, number of units and proportion (in parenthesis).** |
| Male, gender, \(N(\%)\) | 107 (65.2%) | 54 (66.7%) | 53 (63.9%) | 0.046 | 0.002 | 0 |
| Race, ethnicity, \(N(\%)\) |
| White               | 152 (90.5%) | 75 (91.5%) | 77 (89.5%) | 0.051 | 0.015 | 0 |
| Black               | 11 (6.5%)   | 5 (6.1%)   | 6 (7.0%)   | 0.060 | 0.007 | 0 |
| Other               | 5 (2.9%)    | 2 (2.4%)   | 3 (3.5%)   | 0.086 | 0.034 | 0 |
| Different hospital, \(N(\%)\) |
| Site 1              | 54 (32.1%)  | 26 (31.3%) | 28 (32.5%) | 0.046 | 0.002 | 0 |
| Site 2              | 10 (6.0%)   | 5 (6.0%)   | 5 (5.8%)   | 0.065 | 0.024 | 0 |
| Site 3              | 105 (62.5%) | 52 (62.7%) | 53 (61.6%) | 0.073 | 0.013 | 0 |
| **Baseline continuous covariates, mean and standard deviation (in parenthesis).** |
| Age (years)         | 64.4 (7.4)  | 64.4 (8.0) | 64.3 (6.8) | 0.020 | 0.017 | 0 |
| BMI (kg/m\(^2\))   | 31.7 (6.0)  | 31.0 (5.3) | 32.4 (6.5) | 0.261 | 0.042 | 0 |
| Baseline SBP (mmHg) | 124.3 (13.2) | 121.6 (11.1) | 127.0 (14.6) | 0.477 | 0.020 | 0 |
| Baseline SDP (beats/minute) | 63.1 (10.7) | 63.0 (10.4) | 63.2 (10.9) | 0.020 | 0.016 | 0 |
| Baseline AHI (events/hr) | 28.8 (15.4) | 26.5 (13.0) | 31.1 (17.2) | 0.348 | 0.039 | 0 |
| Baseline ESS        | 8.3 (4.5)   | 8.0 (4.5)  | 8.5 (4.6)  | 0.092 | 0.010 | 0 |
such a covariate leads to spurious conclusions of the treatment effect. On the other hand, if we estimate
the propensity scores with a main-effects logistic model, the resulting inverse probability weights could
reduce the baseline imbalance as ASD\textsuperscript{IPW} < 10%. Furthermore, the overlap weights completely remove
baseline imbalance such that ASD\textsuperscript{OW} = 0 for all covariates. In this regard, even before observing the
6-month outcome, the application of overlap weights (in the design stage) increases the face validity of
the trial and rescues the severe imbalance on prognostic baseline factors, which otherwise compromises
the internal validity of the comparison.

For the continuous outcomes (SBP and ESS), we estimate the ATE using \( \hat{\tau}^\text{UNADJ} \), \( \hat{\tau}^\text{IPW} \), \( \hat{\tau}^\text{AIPW} \), \( \hat{\tau}^\text{LR} \) and \( \hat{\tau}^\text{OW} \). For IPW and OW, we estimate the propensity scores using a logistic regression with main
effects of all baseline covariates. For \( \hat{\tau}^\text{LR} \), we fit the ANCOVA model with main effects of treatment and
covariates as well as their interactions. For the binary SBP, we use these five approaches to estimate
the causal risk difference, log risk ratio and log odds ratio due to the CPAP treatment. For \( \hat{\tau}^\text{LR} \) with
a binary outcome, we fit a logistic regression model for the outcome including both main effects of
the treatment and covariates, as well as their interactions, and then obtain the marginal mean of each
group via standardization (equation (22)). For each outcome, the corresponding propensity score and
outcome model specifications are used to obtain the AIPW estimator. The variances and 95% CIs of the
estimators are calculated in the same fashion as in the simulations.

Table 4 and 5 present the treatment effect estimates, standard errors (SEs), 95% confidence intervals
(CI) and p-values for these four approaches across three outcomes. For the SBP continuous outcome,
the treatment effect estimated by IPW, LR, AIPW and OW are substantially smaller than the unadjusted
estimate. Specially, the ATE changes from approximately \(-5.0\) to \(-2.7\) after covariate adjustment. This
difference is due to the fact that the control group has a higher average SBP at baseline and failing to
adjust for this discrepancy will bias the treatment effect of CPAP. In fact, one would falsely conclude
a statistically significant treatment effect if the baseline imbalance is ignored. The treatment effect be-
comes no longer statistically significant using either one of the adjusted estimator. In terms of efficiency
gain, IPW, LR, AIPW and OW provide a smaller SE compared with the unadjusted estimate and the
difference within the adjusted estimators is negligible. For the ESS outcome, the treatment effect esti-
Table 4: Treatment effect estimates of CPAP intervention on continuous outcome, blood pressure and day time sleepiness, using data from the BestAIR study. The five approaches considered are: (a) UNADJ: the unadjusted estimator; (b) IPW: inverse probability weighting; (c) LR: linear regression (for continuous outcomes, or ANCOVA) and logistic regression (for binary outcomes) for outcome; (d) AIPW: augmented IPW; (e) OW: overlap weighting.

| Method | Estimate | Standard error | 95% Confidence interval | p-value |
|--------|----------|----------------|-------------------------|---------|
|        |          |                |                         |         |
| **Continuous outcomes** |          |                |                         |         |
| **Systolic blood pressure (continuous)** |          |                |                         |         |
| UNADJ  | −5.070   | 2.345          | (−9.667, −0.473)        | 0.031   |
| IPW    | −2.638   | 1.634          | (−5.841, 0.566)         | 0.107   |
| LR     | −2.790   | 1.724          | (−6.169, 0.588)         | 0.106   |
| AIPW   | −2.839   | 1.642          | (−6.058, 0.380)         | 0.084   |
| OW     | −2.777   | 1.689          | (−6.088, 0.534)         | 0.100   |
| **Epworth Sleepiness Scale (continuous)** |          |                |                         |         |
| UNADJ  | −1.503   | 0.702          | (−2.878, −0.128)        | 0.032   |
| IPW    | −1.232   | 0.486          | (−2.184, −0.279)        | 0.011   |
| LR     | −1.260   | 0.519          | (−2.276, −0.243)        | 0.015   |
| AIPW   | −1.255   | 0.479          | (−2.193, −0.317)        | 0.009   |
| OW     | −1.251   | 0.491          | (−2.214, −0.288)        | 0.011   |
mate changes from $\hat{\tau} \approx -1.5$ to $\hat{\tau} \approx -1.25$ after the covariate adjustment while the difference among IPW, LR, AIPW and OW remains small. Despite the change in the point estimates, the 95% confidence intervals for all five estimators exclude the null, indicating a significant treatment effect on daytime sleepiness. For the binary SBP outcome, the unadjusted method gives an estimate of $-0.224$ on risk difference scale, $-0.698$ on log risk ratio scale and $-1.038$ on log odds ratio scale. Due to baseline imbalance, the unadjusted confidence intervals for all three estimands lead to statistically significant treatment effect. Similar to the analysis of the continuous SBP outcome, all four adjusted approaches move the point estimates close to the null across the three scales. This pattern further demonstrates that ignoring baseline imbalance may produce biased estimates. In terms of variance reduction, all four adjusted methods exhibit a decrease in the estimated standard error compared with the unadjusted one. Interestingly, although the 95% confidence intervals for LR, AIPW and OW all include zero, the confidence intervals for IPW excludes zero for the two ratio estimands (but not for the additive estimand) and indicate statistical significance at the 5% level. This result, however, needs to be interpreted with caution. As noticed in the simulation studies (scenario (b), (c) and (d) in Section 4.2), both the variance of IPW and AIPW tend to underestimate the actual uncertainty when the sample size is limited and the outcome is not common. In our application, the resistant hypertension has a prevalence of around 12%, which is close to the most extreme scenario in our simulation. Because IPW is likely underestimating the variability for ratio estimands, there could be a risk of type I error when interpreting its statistical significance. By contrast, the interval estimator of OW has more robust performance in small samples and the conclusions of OW remain consistent across all three estimands. Taken together, these considerations suggest the lack of significant CPAP treatment effect regarding the reduction in chance of resistant hypertension.

6 Discussion

In this article, we propose to employ the overlap weighting method for covariate adjustment in randomized clinical trials. Both OW and the previously proposed IPW belong to the general class of balancing
Table 5: Treatment effect estimates of CPAP intervention on binary outcome, resistant hypertension, using data from the BestAIR study. The five approaches considered are: (a) UNADJ: the unadjusted estimator; (b) IPW: inverse probability weighting; (c) LR: linear regression (for continuous outcomes, or ANCOVA) and logistic regression (for binary outcomes) for outcome; (d) AIPW: augmented IPW; (e) OW: overlap weighting.

| Method | Estimate | Standard error | 95% Confidence interval | p-value |
|--------|----------|----------------|-------------------------|---------|
| **Binary outcomes** | | | | |
| Resistant hypertension (SBP≥130): risk difference | | | | |
| UNADJ | −0.224 | 0.085 | (−0.391, −0.057) | 0.009 |
| IPW | −0.145 | 0.082 | (−0.306, 0.015) | 0.077 |
| LR | −0.131 | 0.074 | (−0.277, 0.014) | 0.076 |
| AIPW | −0.133 | 0.071 | (−0.272, 0.006) | 0.061 |
| OW | −0.149 | 0.083 | (−0.312, 0.013) | 0.071 |
| Resistant hypertension (SBP≥130): log risk ratio | | | | |
| UNADJ | −0.698 | 0.281 | (−1.248, −0.147) | 0.013 |
| IPW | −0.448 | 0.226 | (−0.892, −0.004) | 0.048 |
| LR | −0.401 | 0.236 | (−0.864, 0.062) | 0.090 |
| AIPW | −0.408 | 0.227 | (−0.854, 0.037) | 0.072 |
| OW | −0.454 | 0.263 | (−0.970, 0.062) | 0.084 |
| Resistant hypertension (SBP≥130): log odds ratio | | | | |
| UNADJ | −1.038 | 0.409 | (−1.838, −0.237) | 0.011 |
| IPW | −0.665 | 0.324 | (−1.300, −0.030) | 0.040 |
| LR | −0.598 | 0.346 | (−1.276, 0.080) | 0.084 |
| AIPW | −0.607 | 0.331 | (−1.256, 0.041) | 0.067 |
| OW | −0.680 | 0.387 | (−1.438, 0.079) | 0.079 |
weights. Compared with the regression adjustment approach, the propensity score methods encourage
pre-planned adjustments of baseline covariates, and promote objectivity and transparency in the design
and analysis of randomized trials. We have demonstrated that the OW and IPW estimators are asymptotically equivalent, both becoming semiparametric efficient when the true outcome surface is linear in the covariates.

Through extensive simulation studies, we find the OW estimator is consistently more efficient than
the IPW estimator in finite samples, particularly when the sample size is small (e.g. smaller than 150).
This is largely due to the exact balance property that is unique to OW, which removes all chance im-
balance in the baseline covariates adjusted for in a logistic propensity model. Our simulations also
shed light on the performance of the regression adjustment method. With a continuous outcome, linear
regression adjustment have similar efficiency to the OW and IPW estimators when the sample size is
at least \( N = 150 \). With a limited sample size, say \( N \leq 150 \), the linear regression estimator is oc-
casionally slightly more efficient than OW when correctly specified, while the OW estimator is more
efficient when the linear model is incorrectly specified. We find that when the sample size is smaller
than 100, linear regression adjustment could even be less efficient than the unadjusted estimators when
(i) the randomization probability deviates from 0.5 so that the allocation is imbalanced, and/or (ii) the
outcome model is incorrectly specified. In contrast, the OW estimator consistently leads to finite-sample
efficiency gain over the unadjusted estimator in these scenarios. The findings for binary outcomes are
somewhat different from those for the continuous outcomes, especially in small samples. In particu-
lar, while OW generally performs similarly to the logistic regression estimator, both approaches may
lead to efficiency loss over the unadjusted estimator when the sample size is limited, e.g., \( N < 100 \).
However, the efficiency loss generally does not exceed 10%. Throughout, the IPW estimator is the
least efficient and could lead to over 20% efficiency loss compared to the unadjusted estimator in small
samples. The findings for estimating the risk ratio and odds ratio are mostly concordant with those
for estimating the risk difference. On the other hand, when the binary outcome is rare, regression ad-
justment frequently run into convergence issues and fails to provide an adjusted treatment effect, while
the propensity score weighting estimators are not subject to such problems. Finally, because previous
simulations (e.g. [Moore and van der Laan, 2009; Moore et al., 2011; Colantuoni and Rosenblum, 2015]) with binary outcomes have focused on trials with at least a sample size of $N = 200$, our simulations complement those previous reports by providing recommendations and caveats when the sample size falls below 200.

We also empirically evaluated the finite-sample performance of the AIPW estimator in randomized trials. The AIPW estimator is popular in observational studies due to its double robustness and local efficiency properties. That is, the AIPW estimator is consistent when either the propensity model or the outcome model is correctly specified, and becomes asymptotically more efficient than IPW when both models are correct. In randomized trials, because the propensity score model is never misspecified, the finite-sample performance of AIPW is largely driven by the outcome model, matching the observations made in our simulation studies. In particular, we find that AIPW can be less efficient than the unadjusted estimator under outcome model misspecification (Figure 1). The sensitivity of AIPW to the outcome model specification has also been discussed in our earlier work with observational studies (e.g. [Li et al., 2013; Li and Li, 2019a]). AIPW could be slightly more efficient than OW with a correct outcome model and under substantial treatment effect heterogeneity, but it does not retain the objectivity of the simple weighting estimator and is subject to excessive variance when the outcome model is incorrect or fails to converge.

We further provide a consistent variance estimator for OW when estimating both additive and ratio estimands. Our simulation results confirmed that the resulting OW interval estimator achieved close to nominal coverage for the additive estimand (ATE), except in a few challenging scenarios where the sample size is extremely small, e.g. $N = 50$. For example, with a continuous outcome, the empirical coverage of the OW interval estimator and the IPW interval estimator ([Williamson et al., 2014]) are both around 90% when the randomization is unbalanced and the propensity score model does not account for important covariate interaction terms. In this case, the Huber-White variance for linear regression has the worst performance and barely achieved 80% coverage. This is in sharp contrast to the findings of [Raad et al., 2020], who have demonstrated superior coverage of the linear regression interval estimator over the IPW interval estimator. However, [Raad et al., 2020] only considered the model-based variance
When the outcome regression is correctly specified. Assuming a correct model specification, it is expected that the model-based variance has more stable performance than the Huber-White variance in small samples, while the former may become biased under incorrect model specification when the randomization probability deviates from 0.5 \cite{Wang2019}. For robustness and practical considerations, we therefore focused on studying the operating characteristics of the commonly recommended Huber-White variance \cite{Lin2013}. On the other hand, the OW interval estimator maintains at worst over-coverage for estimating the risk ratios and odds ratios when \(N = 50\), while the IPW interval estimator becomes liberal and exhibits under-coverage. When the outcome is rare, the logistic regression and AIPW interval estimators show severe under-coverage possibly due to constant non-convergence. Collectively, these results indicate the potential type I error inflation by using IPW, logistic regression and AIPW, and could favor the application of OW for covariate adjustment in trials with a limited sample size.

OW is easy to implement in practice. For applied researchers who are familiar with IPW, the switch to OW only involves a one-line change of the programming code: changing the weights from the reciprocal of the estimated probability of being assigned to the observed arm (IPW) to the probability of being assigned to the opposite arm (OW). Though the variance estimation is more complex, we have provided reproducible R code with implementation details in Web Appendix D and our GitHub page: https://github.com/zengshx777/OWRCT_codes_package.

There are a number of possible extensions of the proposed method. First, subgroup analysis is routinely conducted in randomized trials to examine whether the treatment effect depends on pre-specified sets of patient characteristics \cite{Wang2007}. For the same reason of transparency, it would be natural to develop propensity score weighting estimators for subgroup-specific treatment effects \cite{Dong2020}. Because the sample size of each subgroup may be limited, it is of particular interest to study whether OW is also effective in improving the efficiency in this context. Second, multi-arm randomized trials are common and the interest usually lies in determining the pairwise average treatment effect \cite{Juszczak2019}. Although the basic principle of improving efficiency via covariate adjustment still applies, there is a lack of empirical evaluation as to which adjustment approach works better in
finite samples. In particular, the performance of multi-group ANCOVA and propensity score weighting merits further study. In the context of observational studies, we have previously extended OW to multiple treatments (Li and Li, 2019b), which is potentially applicable to multi-arm randomized trials. Third, although we have examined the AIPW estimator that combines IPW and direct regression, it remains to be explored whether an alternative hybrid estimator combining OW and outcome regression can lead to further improvement (Li, 2020). Lastly, covariate adjustment is also relevant in cluster randomized controlled trials, where entire clusters of patients (such as hospitals or clinics) are randomized to intervention conditions (Turner et al., 2017). Due to a limited number of clusters available in such studies, design-based adjustment for baseline characteristics are often considered by covariate-constrained randomization (e.g. Li et al., 2016, 2017), in which case regression-based adjustment in the analysis stage is necessary not only for maintaining the type I error rate but also for efficiency improvement (e.g. Stephens et al., 2012, 2013). It remains an open question whether OW could similarly improve the performance of IPW for addressing challenges in the analysis of cluster randomized trials.

Appendix

Web appendix is available at our GitHub page: https://github.com/zengshx777/OWRCT_codes_package

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Data Availability Statement

The BestAIR trial data used in Section 5 are available upon reasonable request at https://sleepdata.org.

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