





Improving trial generalizability using observational studies

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Abstract

Complementary features of randomized controlled trials (RCTs) and observational studies (OSs) can be used jointly to estimate the average treatment effect of a target population. We propose a calibration weighting estimator that enforces the covariate balance between the RCT and OS, therefore improving the trial-based estimator's generalizability. Exploiting semiparametric efficiency theory, we propose a doubly robust augmented calibration weighting estimator that achieves the efficiency bound derived under the identification assumptions. A nonparametric sieve method is provided as an alternative to the parametric approach, which enables the robust approximation of the nuisance functions and data-adaptive selection of outcome predictors for calibration. We establish asymptotic results and confirm the finite sample performances of the proposed estimators by simulation experiments and an application on the estimation of the treatment effect of adjuvant chemotherapy for early-stage non-small-cell lung patients after surgery.

KEYWORDS

causal inference, double robustness, generalizability, semiparametric efficiency, transportability

1 | INTRODUCTION

Randomized controlled trials (RCTs) are the gold standard to evaluate treatment effects. However, due to restrictive inclusion and exclusion criteria, the trial sample is narrowly defined and can be systematically different from the real-world patient population to which the new treatment is supposed to be given. Therefore, the findings from RCTs often lack external validity (Rothwell, 2005). On the other hand, observational studies (OSs) often include large samples that are representative of real-world patient populations; however, there are concerns about whether or not confounding has been addressed adequately in the analyses of OSs. In cancer research, there is an in-depth discussion on the strengths and limitations of utilizing data from

RCT and OSs for comparative effectiveness analyses (Korn and Freidlin, 2012).

The problems of extending findings from RCT to a target population has been termed as *generalizability* (e.g., Cole and Stuart, 2010; Tipton, 2013; Dahabreh *et al.*, 2019) and *transportability* (e.g., Pearl and Bareinboim, 2011; Rudolph and van der Laan, 2017; Westreich *et al.*, 2017). Most existing methods rely on direct modeling of the sampling score, the sampling analog of the propensity score. The subsequent sampling score adjustments include inverse probability of sampling weighting (IPSW; Cole and Stuart, 2010; Buchanan *et al.*, 2018), stratification (Tipton, 2013), and augmented IPSW (AIPSW; Dahabreh *et al.*, 2019). Most sampling score adjustment approaches require the sampling score model to be correctly specified. Moreover,

weighting estimators are unstable if the sampling score is too extreme.

We consider combining an RCT sample and an OS sample to estimate the average treatment effect (ATE) of a target population, where the RCT sample is subject to selection bias and the OS sample is representative of the target population with a known sampling mechanism. In contrast to the dominant approaches that focus on predicting sample selection probabilities, we estimate the sampling score weights directly by calibrating covariates balance between the RCT sample and the design-weighted OS sample to address the selection bias of the RCT sample. Calibration weighting (CW) is widely used to integrate auxiliary information in survey sampling (Wu and Sitter, 2001) and causal inference (Qin and Zhang, 2007; Hainmueller, 2012). Hartman *et al.* (2015) implemented CW to estimate the population ATEs by combining RCTs with OSs.

The efficiency of the CW estimator can be further improved. We derive the semiparametric efficiency bound for the ATE under the identification assumptions, which provides the benchmark for estimation efficiency. We propose the augmented CW (ACW) estimator that is doubly robust and also achieves the semiparametric efficiency bound when both nuisance models are correctly specified. However, the parametric approach is prone to model misspecification, especially when there is complex confounding. To cope with model misspecification, we adopt a method of sieves (Chen, 2007), which allows flexible data-adaptive estimation of the nuisance functions while the ACW estimator retains the usual root- n consistency under regularity conditions. In comparison with other nonparametric and machine learning methods, the proposed ACW estimator with the sieve approximation is attractive: (1) unlike black-box machine learning methods, calibration weighting is straightforward and transparent; and (2) our framework allows for selecting important sieve basis terms that are related to the outcome to calibrate and enforcing the balance on these covariates for efficient estimation.

In the presence of many covariates, variable or sieve basis selection for calibration becomes necessary. We classify covariates into three types: the covariates that are associated with both trial participation and outcome as confounders, that affect outcome only through trial participation as instrumental variables (IVs), and that are predictive of the outcome as precision variables or outcome predictors. In other causal inference contexts, studies have shown that in addition to the confounding variables, including outcome predictors in the propensity score may improve efficiency, whereas including IVs may decrease efficiency (e.g., Tang *et al.*, 2020). Despite the importance of proper basis selection for the efficient causal estimator, the current literature lacks a principled approach to

guide basis selection for covariate balancing. Capitalizing on an explicit connection between calibration weighting and estimating equations under parametric models, we propose a penalized estimating equation approach for variable selection with an emphasis on outcome predictors.

2 | BASIC SETUP

2.1 | Notation: Causal effect and two data sources

Let X be the p -dimensional vector of covariates, A be the binary treatment $\{0, 1\}$, and Y be the outcome of interest. We use the potential outcomes framework to formulate the causal problem. We assume that each subject has a potential outcome $Y(a)$, $a \in \{0, 1\}$, representing the outcome had the subject been given the treatment a . The conditional average treatment effect (CATE) is $\tau(X) = E\{Y(1) - Y(0) | X\}$. We are interested in estimating the population ATE $\tau_0 = E\{\tau(X)\}$, where the expectation is taken with respect to the distribution of the target population. Let $\delta = 1$ denote RCT participation, and let $\tilde{\delta} = 1$ denote the OS participation. Also, define the sampling score as $\pi_\delta(X) = P(\delta = 1 | X)$, the design weight for the OS sample as $d = 1/P(\tilde{\delta} = 1 | X)$, and the conditional outcome mean function as $\mu_{a,\delta}(X) = E(Y | X, A = a, \delta)$ for $a, \delta \in \{0, 1\}$.

To generalize findings to the future patient population, we consider a superpopulation framework that describes the distribution of all patients with a certain disease to whom the new treatment is intended to be given. The data structure is demonstrated in Figure 1. The RCT is a sample from the target population with an unknown sampling mechanism, and the OS sample is a random sample from the target population with a known sampling mechanism. Therefore, our problem is in line with that of generalizability, extending the ATE result from the trial to its larger population (Dahabreh *et al.*, 2019). A closely related problem is transportability which tries to extend the trial results to an external population (Westreich *et al.*, 2019); for example, when one wants to transport an RCT conducted in one country to a population in another country (Pearl, 2015). Subtle differences exist in the two problems in terms of estimands and identification assumptions; see Web Appendix A for details. In general, there are nested and nonnested study designs in the problem of generalization (Dahabreh *et al.*, 2019). For nested designs, the RCT sample is a subsample from the OS sample. Examples include pragmatic trial studies embedded in health care systems or comprehensive cohort studies, where all trial-eligible participants constitute the OS sample, and participants who agree to be randomized constitute the RCT sample. For nonnested designs, the RCT sample and the OS sample are

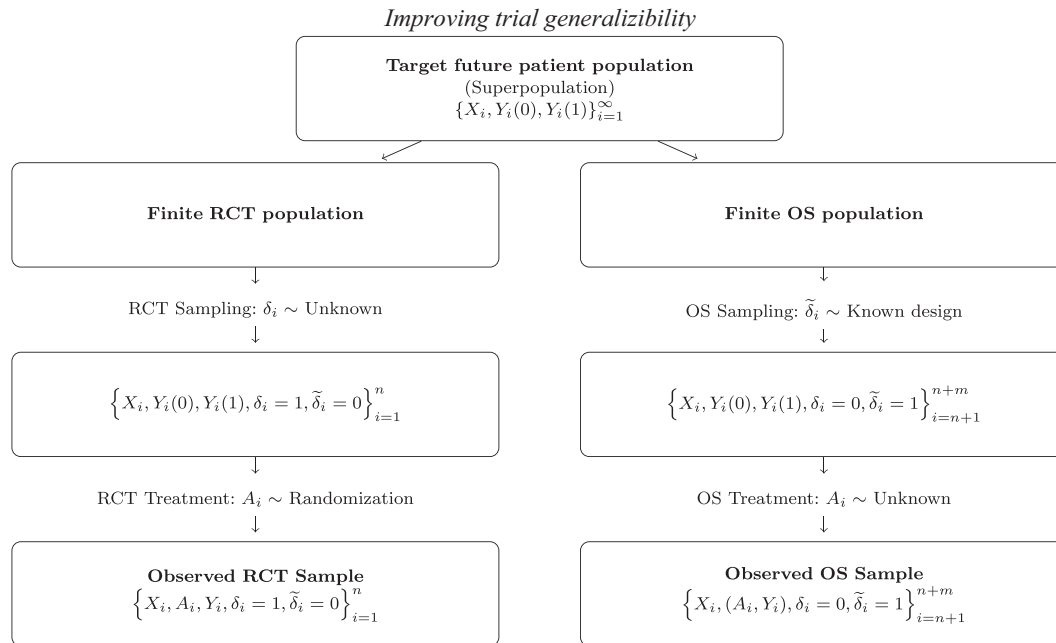


FIGURE 1 Demonstration of the sampling and treatment assignment regimes for the RCT and OS samples within the target population.

separate. Our motivating application falls in the latter category, where we link an existing RCT to a large cancer register database. We also assume that the RCT and OSs are independent. This assumption holds naturally if the two separate studies are conducted independently by different researchers; it is also plausible in our motivating example where the patients for the two studies were accrued in two separate time periods (see Section 6).

2.2 | Identification assumptions

To identify the ATE, we make the following assumptions:

Assumption 1 (Consistency). $Y = AY(1) + (1 - A)Y(0)$.

Assumption 2 (Ignorability and positivity of treatment assignment). (i) $\{Y(0), Y(1)\} \perp\!\!\!\perp A \mid (X, \delta = 1)$; and (ii) $0 < P(A = 1 \mid X, \delta = 1) < 1$ with probability 1.

Assumption 3 (Generalizability of the CATE and positivity of trial participation). (i) $E\{Y(1) - Y(0) \mid X, \delta = 1\} = \tau(X)$; and (ii) $\pi_{\delta}(X) > 0$ with probability 1.

Assumption 1 implies that trial encouragement effects are absent (Dahabreh and Hernán, 2019). Assumption 2 holds for the RCT by default. Assumption 3 (i) is similar to the generalizability in effect measure condition (Dahabreh *et al.*, 2019, Supporting Information). Even though this assumption is formally weaker than the mean exchangeability over trial participation (Dahabreh *et al.*, 2019), that

is, $E\{Y(a) \mid X, \delta = 1\} = E\{Y(a) \mid X\}$ for $a = 0, 1$, and the ignorability assumption on trial participation (Stuart *et al.*, 2011), that is, $\{Y(0), Y(1)\} \perp\!\!\!\perp \delta \mid X$, it suffices to identify the ATE. Under Assumptions 1–3, the ATE is identified by $\tau_0 = E[\tilde{\delta}d\{\mu_{1,1}(X) - \mu_{0,1}(X)\}]$.

Although being essential, Assumption 3 (i) is not verifiable based on the observed data but relies on subject matter experts to assess its plausibility. It is plausible if X captures all variables that are related to the trial participation and outcome (Buchanan *et al.*, 2018). Assumption 3 (ii) requires the absence of patient characteristics that prohibit participation. When Assumption 3 (ii) is violated, generalization can only be made to a restricted population without extrapolation (Yang and Ding, 2018).

2.3 | Existing estimation methods

Because the RCT assigns treatments randomly to the participants, $\tau(X)$ is identifiable and can be estimated by standard estimators solely from the RCT. However, $f(X \mid \delta = 1)$ is different from $f(X)$ in general; therefore, $E\{\tau(X) \mid \delta = 1\}$ is different from τ_0 , and the ATE estimator using trial data only is biased of τ_0 generally. A widely used approach is the IPSW estimator that predicts the sampling score $\pi_{\delta}(X)$ and uses the inverse of the estimated sampling score to account for the shift of the covariate distribution from the RCT sample to the target population. Specifically, most of the empirical literature assumes that $\pi_{\delta}(X)$ follows a logistic regression model $\pi_{\delta}(X; \eta)$ and can be estimated by $\pi_{\delta}(X; \hat{\eta})$. The AIPSW estimator has also been proposed to

improve it by employing both the sampling score and outcome regression. The forms of the (A)IPSW estimators are provided in Web Appendix B, along with another identification formula based on the IPSW estimator.

3 | CALIBRATION WEIGHTING ESTIMATOR

We propose to use calibration originated in survey sampling to eliminate the selection bias in the trial-based ATE estimator. The calibration weighting approach is similar to the idea of entropy balancing weights introduced by Hainmueller (2012). We calibrate subjects in the RCT sample so that after calibration, the covariate distribution of the RCT sample empirically matches the target population. Our insight is that for any vector-valued function $\mathbf{g}(X)$, the following equations hold:

$$E \left[\frac{\{\pi_\delta(X)\}^{-1} \delta}{E[\{\pi_\delta(X)\}^{-1} \delta]} \mathbf{g}(X) \right] = E\{\tilde{\delta} d \mathbf{g}(X)\} = E\{\mathbf{g}(X)\}. \quad (1)$$

Here, $\mathbf{g}(X)$ contains the covariate functions to be calibrated, which could be moment functions of the original covariate X or any sensible transformations of X . To this end, we assign a weight q_i to each subject i in the RCT sample so that

$$\sum_{i=1}^N \delta_i q_i \mathbf{g}(X_i) = \tilde{\mathbf{g}}, \quad (2)$$

where $\tilde{\mathbf{g}} = \sum_{i=1}^N \tilde{\delta}_i d_i \mathbf{g}(X_i) / \sum_{i=1}^N \tilde{\delta}_i d_i$ is a design-weighted estimate of $E\{\mathbf{g}(X)\}$ from the OS sample, and N is the target population size, not necessarily known. Constraint (2) is referred to as the balancing constraint, and weights $Q = \{q_i : \delta_i = 1\}$ are the calibration weights. The balancing constraint calibrates the RCT covariate distribution to the target population in terms of $\mathbf{g}(X)$. The choice of $\mathbf{g}(X)$ is critical for both bias and variance considerations, which we discuss in Section 4.2.

We estimate Q by solving the optimization problem:

$$\min_Q \sum_{i=1}^n q_i \log q_i, \quad (3)$$

subject to $q_i \geq 0 \forall i$; $\sum_{i=1}^n q_i = 1$, and the constraint (2), where n is the RCT sample size. The objective function in (3) is the negative entropy of the calibration weights; thus, minimizing these criteria ensures that the empirical distribution of calibration weights is not too far away from the uniform, such that it minimizes the variability due to heterogeneous weights (Owen, 2001).

The optimization problem can be solved using convex optimization with the Lagrange multiplier. By introducing the Lagrange multiplier λ , the objective function becomes

$$L(\lambda, Q) = \sum_{i=1}^n q_i \log q_i - \lambda^\top \left\{ \sum_{i=1}^n q_i \mathbf{g}(X_i) - \tilde{\mathbf{g}} \right\}. \quad (4)$$

Minimizing (4) leads to $\hat{q}_i = q(X_i; \hat{\lambda}) = \exp\{\hat{\lambda}^\top \mathbf{g}(X_i)\} / \sum_{i=1}^n \exp\{\hat{\lambda}^\top \mathbf{g}(X_i)\}$ and $\hat{\lambda}$ solves

$$U(\lambda) = \sum_{i=1}^n \exp\{\lambda^\top \mathbf{g}(X_i)\} \{\mathbf{g}(X_i) - \tilde{\mathbf{g}}\} = 0, \quad (5)$$

which is the dual problem to the optimization problem (3).

Let $\pi_{A_i} = P(A_i = 1 | X_i, \delta_i = 1)$ be the treatment propensity score for subject i . For RCTs, it is common that the propensity score π_{A_i} is known. The CW estimator becomes

$$\hat{\tau}^{\text{CW}} = \sum_{i=1}^n \hat{q}_i \left\{ \frac{A_i Y_i}{\pi_{A_i}} - \frac{(1 - A_i) Y_i}{1 - \pi_{A_i}} \right\}. \quad (6)$$

To investigate the properties of the CW estimator, we impose the regularity conditions on the sampling designs for the RCT the OS samples.

Assumption 4. Let $\mu_{g_0} = E\{\mathbf{g}(X)\}$. The design weighted estimator $\hat{\mu}_g = N^{-1} \sum_{i=1}^N \tilde{\delta}_i d_i \mathbf{g}(X_i)$ satisfies $V(\hat{\mu}_g) = O(m^{-1})$, and $\{V(\hat{\mu}_g)\}^{-1/2} (\hat{\mu}_g - \mu_{g_0}) \rightarrow \mathcal{N}(0, 1)$ in distribution, as $m \rightarrow \infty$, where m is the OS sample size.

Assumption 5 (Linearity of the CATE). $\tau(X) = \gamma_0^\top \mathbf{g}(X)$.

Assumption 6 (Loglinear sampling score). The sampling score of RCT participation follows a loglinear model, that is, $\pi_\delta(X) = \exp\{\eta_0^\top \mathbf{g}(X)\}$ for some η_0 .

Based on the above assumptions, we establish the double robustness property of the CW estimator in the following theorem and relegate all proofs to Web Appendix C. The proof is similar to the one in Zhao and Percival (2017).

Theorem 1 (Double robustness of the CW estimators). *Under Assumptions 1–4, if either Assumption 5 or 6 holds, $\hat{\tau}^{\text{CW}}$ in (6) is consistent for τ_0 .*

In the estimation of calibration weights, we only require specifying $\mathbf{g}(X)$. Thus, calibration weighting evades explicitly modeling either the sampling score model or the outcome mean models. Under Assumption 6, we show

that there is a direct correspondence between calibration weight $q(X_i; \hat{\lambda})$ and the estimated sampling score $\pi_\delta(X_i; \hat{\eta})$, that is, $q(X_i; \hat{\lambda}) = \{N\pi_\delta(X_i; \hat{\eta})\}^{-1} + o_p(N^{-1})$. That is, calibration weights from the objective function (3) have the same functional form as inverse probability of sampling score weights under Assumption 6 asymptotically. Other objective functions, such as $\sum_{i=1}^n (q_i - 1) \log(q_i - 1)$, $\sum_{i=1}^n \{q_i \log q_i + (1 - q_i) \log(1 - q_i)\}$ (Zhao, 2019; Josey *et al.*, 2020) or $\sum_{i=1}^n (q_i - n^{-1})^2$ (Chattopadhyay *et al.*, 2020), can also be used. When the sampling score follows a logistic regression model, the objective function $\sum_{i=1}^n (q_i - 1) \log(q_i - 1)$ results in weights that resemble the inverse of logistic sampling scores (Zhao, 2019; Josey *et al.*, 2020). However, if the fraction n/N of the RCT sample in the target population is small, the loglinear model in Assumption 6 is close to the logistic regression model; our simulation studies show that the proposed CW estimator is not sensitive to the choice of the objective function for the optimization.

The entropy balancing has been studied in the indirect comparison literature (Signorovitch *et al.*, 2010; Phillippo *et al.*, 2018; Petto *et al.*, 2019). The goal is to adjust for the imbalance between two separate randomized trials with common comparative arms, similar to the transportability problem. On the other hand, the proposed CW estimator is motivated by generalizing findings from RCT. Importantly, building on the CW estimator, we propose an improved estimator capitalizing semiparametric efficiency theory in the next section and a data-adaptive selection of outcome predictors for calibration, which is absent in the literature. The proposed framework can incorporate nonparametric sieve approximation of the outcome mean function and sampling score while providing valid inferences.

4 | SEMIPARAMETRIC EFFICIENT ESTIMATOR

4.1 | Augmented calibration weighting estimator

The following theorem gives the semiparametric efficiency bound for τ_0 in our data integration setting. Let $\Delta_a = Y - \mu_{a,1}(X; \beta_a)$.

Theorem 2 (Semiparametric efficiency bound). *Under Assumptions 1–4, the semiparametric efficiency score for τ_0 is*

$$\phi(X, A, Y, \delta, \tilde{\delta}) = \frac{\delta}{\pi_\delta(X)} \left[\frac{A\Delta_1}{\pi_A} - \frac{(1-A)\Delta_0}{1-\pi_A} \right] + \tilde{\delta} d\{\tau(X) - \tau_0\}. \quad (7)$$

The semiparametric efficiency bound for τ_0 is

$$V_{\text{eff}} = E \left[\frac{\delta}{\pi_\delta(X)^2} \left\{ \frac{V\{Y(1)|X, \delta\}}{\pi_A} + \frac{V\{Y(0)|X, \delta\}}{1-\pi_A} \right\} + \tilde{\delta} d^2\{\tau(X) - \tau_0\}^2 \right]. \quad (8)$$

The result in Theorem 2 serves as a foundation to derive efficient estimators combining two data sources. Under Assumption 2, $\tau(X) = \mu_{1,1}(X) - \mu_{0,1}(X)$. The score $\phi(X, A, Y, \delta, \tilde{\delta})$ has unknown nuisance functions $\pi_\delta(X)$ and $\mu_{a,1}(X)$, $a = 0, 1$. Therefore, to estimate τ_0 , we posit models for the nuisance functions, denoted by $\pi_\delta(X; \eta)$ and $\mu_{a,1}(X; \beta_a)$. For example, we assume $\pi_\delta(X)$ is a loglinear model as in Assumption 6. By the correspondence between the loglinear model and the calibration weighting algorithm, we can estimate η_0 following the optimization algorithm in (3). We also posit models $\mu_{a,1}(X; \beta_a)$, $a = 0, 1$. By Assumption 2, we are able to obtain a consistent estimator $\hat{\beta}_a$ based on the trial sample. Based on the semiparametric efficiency score, we propose a new estimator for the ATE. As the outcome mean models in the semiparametric efficiency score can be viewed as an augmentation to the CW estimator, we refer to the proposed estimator as the augmented calibration weighting (ACW) estimator. Let $\hat{\Delta}_{a,i} = Y_i - \mu_{a,1}(X_i; \hat{\beta}_a)$. The ACW estimator is

$$\hat{\tau}^{\text{ACW}} = \sum_{i=1}^N \delta_i \hat{q}_i \left\{ \frac{A_i \hat{\Delta}_{1,i}}{\pi_{A_i}} - \frac{(1-A_i) \hat{\Delta}_{0,i}}{1-\pi_{A_i}} \right\} + \left(\sum_{i=1}^N \tilde{\delta}_i d_i \right)^{-1} \times \sum_{i=1}^N \tilde{\delta}_i d_i \left\{ \mu_{1,1}(X_i; \hat{\beta}_1) - \mu_{0,1}(X_i; \hat{\beta}_0) \right\}. \quad (9)$$

We now show that $\hat{\tau}^{\text{ACW}}$ achieves double robustness and local efficiency. For a vector v , we use $\|v\|_2 = (v^\top v)^{1/2}$ to denote its Euclidean norm. For a function $f(V)$, where V is a generic random variable, we define its L_2 -norm as $\|f(V)\| = \{\int f(v)^2 dP(v)\}^{1/2}$.

Theorem 3 (Double robustness and local efficiency). *Under Assumptions 1–4, if either Assumptions 5 or 6 holds, $\hat{\tau}^{\text{ACW}}$ is consistent for τ_0 . When both assumptions hold, $N^{1/2}(\hat{\tau}^{\text{ACW}} - \tau_0) \rightarrow \mathcal{N}(0, V_{\text{eff}})$ in distribution, as $n \rightarrow \infty$, where V_{eff} is defined in Theorem 2, that is, $\hat{\tau}^{\text{ACW}}$ is locally efficient.*

By the empirical processes theory, the effect of nuisance parameter estimation in $\hat{\tau}^{\text{ACW}} - \tau_0$ is bounded by $\|\pi_\delta(X; \hat{\eta}) - \pi_\delta(X)\| \sum_{a=0}^1 \|\mu_{a,1}(X; \hat{\beta}_a) - \mu_{a,1}(X)\|$; see Web Appendix C.4 for details. If this bound is of rate $o_p(n^{-1/2})$, it is asymptotically negligible. Thus, $\hat{\tau}^{\text{ACW}}$ is semiparametric efficient. In general, there exist

different combinations of convergence rates of $\pi_\delta(X; \hat{\eta})$ and $\mu_{a,1}(X; \hat{\beta}_a)$ ($a = 0, 1$) that result in a negligible error bound accommodating different smoothness conditions of the underlying nuisance functions. The following theorem formalizes the above statement.

Theorem 4. *Suppose Assumptions 1–4 hold. Let $\pi_\delta(X; \hat{\eta})$ and $\mu_{a,1}(X; \hat{\beta}_a)$ ($a = 0, 1$) be general semiparametric models for $\pi_\delta(X)$ and $\mu_{a,1}(X)$ ($a = 0, 1$), respectively. Assume the following regularity conditions hold: (C1) $\|\pi_\delta(X; \hat{\eta}) - \pi_\delta(X)\| = o_p(1)$ and $\|\mu_{a,1}(X; \hat{\beta}_a) - \mu_{a,1}(X)\| = o_p(1)$, for $a = 0, 1$; (C2) $\|\pi_\delta(X; \hat{\eta}) - \pi_\delta(X)\| \sum_{a=0}^1 \|\mu_{a,1}(X; \hat{\beta}_a) - \mu_{a,1}(X)\| = o_p(n^{-1/2})$. Then $\hat{\tau}^{\text{ACW}}$ is consistent for τ_0 and achieves the semiparametric efficiency bound.*

The semiparametric efficiency bound is attained as long as either $\hat{\eta}$ or $(\hat{\beta}_0, \hat{\beta}_1)$ approximate the underlying sampling score model or the outcome models well. (C1) states that we require that the posited models be consistent. (C2) states that the combined rate of convergence of the posited models is of $o_p(n^{-1/2})$. In Section 4.2, we construct such estimators using the method of sieves, which satisfies (C1) and (C2) in Theorem 4 under regularity conditions.

For the locally efficient estimator $\hat{\tau}^{\text{ACW}}$, the variance estimator can be calculated as

$$\begin{aligned} \hat{V}(\hat{\tau}^{\text{ACW}}) &= \sum_{i=1}^N \delta_i \hat{q}_i \left[\frac{\hat{V}\{Y(1)|X_i, \delta_i\}}{\pi_{Ai}} + \frac{\hat{V}\{Y(0)|X_i, \delta_i\}}{1 - \pi_{Ai}} \right] \\ &+ \left\{ \sum_{i=1}^N \tilde{\delta}_i d_i \right\}^{-2} \\ &\sum_{i=1}^N \tilde{\delta}_i d_i^2 \left\{ \mu_{1,1}(X_i; \hat{\beta}_1) - \mu_{0,1}(X_i; \hat{\beta}_0) - \hat{\tau}^{\text{ACW}} \right\}^2, \end{aligned} \quad (10)$$

where $\hat{V}\{Y(a)|X_i, \delta_i\}$ is a consistent estimator of $V\{Y(a)|X_i, \delta_i\}$ for $a = 0, 1$. However, the plug-in variance estimator requires an additional consistent estimator of $V\{Y(a)|X_i, \delta_i\}$, which can be difficult to obtain. The bootstrap variance estimator is more straightforward, and it can accommodate situations where either one of the nuisance models is misspecified.

4.2 | Semiparametric models by the method of sieves

To overcome the model misspecification issue inherent to parametric models, we consider the method of sieves, which allows flexible models for $\pi_\delta(X)$ and $\mu_{a,1}(X)$, ($a =$

$0, 1$). Although general sieves such as Fourier series, splines, wavelets, and artificial neural networks (Chen, 2007) are applicable, the power series is most common. For a p -vector of nonnegative integers $\kappa = (\kappa_1, \dots, \kappa_p)$, let $|\kappa| = \sum_{l=1}^p \kappa_l$ and $X^\kappa = \prod_{l=1}^p X_l^{\kappa_l}$. Define a series $\{\kappa(k) : k = 1, 2, \dots\}$ for all distinct vectors of κ such that $|\kappa(k)| \leq |\kappa(k+1)|$. Based on this series, we consider a K -vector $\mathbf{g}(X) = \{g_1(X), \dots, g_K(X)\}^\top = \{X^{\kappa(1)}, \dots, X^{\kappa(K)}\}^\top$.

In the presence of many sieve basis terms, variable selection is needed to include necessary terms and to exclude terms that could result in efficiency loss. To guide selection, we attempt to compare the semiparametric efficiency bound V_{eff} in Theorem 2 with different types of covariates, which, however, does not lead to a definitive conclusion. Fortunately, given that the OS sample is much larger than the trial sample, the first term of V_{eff} often dominates the second term. Thus, we focus on the comparison of the first term.

Lemma 1. *Let X^C be confounders, X^O be outcome predictors, and X^I be IVs, where X^C, X^O, X^I are subsets of $\mathbf{g}(X)$. Also, let $X^{C+I} = X^C \cup X^I$. Define the first term of V_{eff} that depends on X^* as*

$$V_1^* = E \left[\frac{\delta}{\pi_\delta(X^*)^2} \left\{ \frac{V\{Y(1)|X^*, \delta\}}{\pi_A} + \frac{V\{Y(0)|X^*, \delta\}}{1 - \pi_A} \right\} \right], \quad (11)$$

where $*$ can be $C, O, C+I$. Then, we have $V_1^O \leq V_1^C \leq V_1^{C+I}$.

The proof of Lemma 1 is in Web Appendix C.5. Lemma 1 suggests that including outcome predictors and excluding IVs reduces V_1 . Thus, we propose a new basis selection procedure for sieves estimation and calibration adjusting for outcome predictors. First, we approximate $\mu_a(X)$ by the generalized sieve functions $\mu_a(X; \beta_a^*) = m_a\{\beta_a^{*\top} \mathbf{g}(X)\}$ with $\beta_a^{*\top} = \arg \min_{\beta} E[\mu_a(X) - m_a\{\beta^\top \mathbf{g}(X)\}]^2$ for $a = 0, 1$. Since the number of basis functions controls the smoothness of sieves estimators, we can specify a sufficiently large K as an initial number and apply the penalization to regularize the variability of the estimators. Specifically, let $\hat{\beta}_a = \arg \min_{\beta \in \mathbb{R}^K} \sum_{i=1}^N (\delta_i I(A_i = a) [Y_i - m_a\{\beta^\top \mathbf{g}(X_i)\}]^2 + \sum_{j=1}^K p_{\xi_a}(|\beta_j|))$, where $p_{\xi_a}(\cdot)$ is the smoothly clipped absolute deviation (SCAD) penalty function (Fan and Li, 2001), for $a = 0, 1$. We choose the tuning parameters ξ_a via cross-validation. Under certain regularity conditions, $\hat{\beta}_a$ satisfies the selection consistency and oracle properties (see Fan and Li, 2001).

Second, we calibrate the sieve basis terms that are predictive of the outcome. Instead of calibrating the selected basis terms of the outcome predictors directly, we can construct the sieve basis for $\log\{\pi_\delta(X)\}$ by power series

of the selected variables to capture the possible nonlinear relationship between $\log\{\pi_\delta(X)\}$ and X . Then, we conduct penalized sieve estimation of $\pi_\delta(X)$ by solving the system of estimating equations (5) with the SCAD penalty. By emphasizing the outcome predictors, our strategy provides guidance for variable selection for covariate balancing and efficient estimation. Following Shortreed and Ertefaie (2017), an alternative strategy of prioritizing outcome predictors is to use the outcome-adaptive Lasso for the sampling score model with the sieve basis of all covariates. This approach incorporates the outcome-covariate association to impose heavier penalties on the covariates that are not or weakly associated with outcome.

Coupling sieve approximation and variable selection, $\hat{\tau}^{\text{ACW}}$ with flexible approximations of the two nuisance functions achieves the root- n consistency and the semi-parametric efficiency bound under mild regularity conditions; see Web Appendix D.

4.3 | Related works

There are several recent articles that focus on regularized balancing methods. Athey *et al.* (2018) proposed an approximate residual balancing method that first fits a regularized linear outcome model and then reweights the residuals to minimize covariate imbalance. Unlike our method, Athey *et al.* (2018) relied on the linear outcome model. Ning *et al.* (2020) considered a doubly robust estimator that uses penalized maximum likelihood estimation of the nuisance functions and calibrates the estimated propensity score by balancing the selected outcome predictors. Similarly, Tan (2020a, 2020b) proposed a doubly robust estimator through regularized calibrated estimation using the expected calibrated loss function when fitting the propensity score model. Unlike these approaches that estimate the propensity score that satisfies covariate balancing conditions, our method directly achieves the balance in the covariates through calibration weights, similar to Chan *et al.* (2016). Moreover, our approach uses the non-parametric sieve method which provides more robust estimation of the nuisance functions. The difference between our approach and Chan *et al.* (2016) is that their approach enforces a three-way balance between the treated, the controls, and the combined data, whereas our method only requires a two-way balance between the RCT and the OS sample. Even though the three-way balancing approach is not necessary for generalizing trial results, it could be useful when generalizing observational results to a larger population. For example, in order to achieve double robustness in the observational setting, the CW estimator requires the three-way balance. It is analogous to the Covariate Balancing Propensity Score (CBPS; Imai and Ratkovic, 2014)

method, which is doubly robust under the constant CATE whereas it requires the three-way balance to achieve double robustness under the heterogeneous CATE (Fan *et al.*, 2021). Moreover, Chan *et al.* (2016) did not solve the problem about which terms to calibrate, whereas we propose a principled approach for selecting calibration terms.

Wang and Zubizarreta (2020) studied a class of weights that have minimum dispersion and showed that achieving approximate covariate balance corresponds to regularizing inverse probability weights, without explicitly involving the propensity score model. A special case is the stable balancing weights method (SBW; Zubizarreta, 2015; Chattopadhyay *et al.*, 2020) which finds weights with the minimum variance that achieves covariate balance approximately. The approximately balancing methods could be useful when the costs of balancing are too high, since they have the flexibility to trade bias for variance. Our strategy of handling large-dimensional calibration terms is different. We first reduce the number of calibration terms by selecting the outcome predictors and further use penalized estimating equations (Yang *et al.*, 2020) to obtain calibration weights. Both steps involve convex optimization with regularization, whose numerical and theoretical properties are well studied in the literature (Fan and Li, 2001; Johnson *et al.*, 2008). Our solution for handling the large-dimension calibration terms is thus attractive in terms of feasibility and efficiency.

4.4 | ACW estimator when Y and A are available in OS

We consider another setting where we have access to additional information on (A, Y) from the OS sample (e.g., Dahabreh *et al.*, 2020). Most causal inference methods invoke the “no unmeasured confounding” assumption that A is independent of the potential outcomes given X in the OS sample (e.g., Lu *et al.*, 2019). To leverage the predictive power of the OS sample, we assume generalizability of the outcome mean functions from the RCT to the OS sample.

Assumption 7. For $a = 0, 1$, $E(Y | X, A = a, \tilde{\delta} = 1) = \mu_{a,1}(X)$.

Collectively, combining Assumptions 1–4 and 7 leads to generalizability of the CATE function: $E(Y | X, A = 1, \tilde{\delta} = 1) - E(Y | X, A = 0, \tilde{\delta} = 1) = \tau(X)$. The nuisance functions $\mu_{a,1}(X)$ ($a = 0, 1$) in the ACW estimator $\hat{\tau}^{\text{ACW}}$ in (9) can be estimated by the OS sample to further boost efficiency. The indication is that the OS has no unmeasured confounding on the mean difference measure conditional on X (VanderWeele, 2012). Assumption 7 is testable

TABLE 1 Simulation settings: description of four scenarios and estimators

Scenarios	Details
1. O:C/S:C	Both outcome and sampling score models are correctly specified
2. O:C/S:W	The outcome model is correctly specified; the sampling score model is incorrectly specified by using X^* in the generative model
3. O:W/S:C	The outcome model is incorrectly specified by using X^* in the generative model; the sampling score model is correctly specified
4. O:W/S:W	Both outcome and sampling score models are incorrectly specified by using X^* in the generative model
Estimators	Details
Naive	The difference in sample means of the two treatment groups in the RCT sample
IPSW	The IPSW estimator with a logistic sampling score model
AIPSW	The AIPSW estimator with a logistic sampling score model
AIPSW(S)	The AIPSW estimator using methods of sieve with $\mathbf{g}(X) = \mathbf{g}_2(X)$ for sampling score and outcome models based on the trial sample
SBW	The IPSW estimator with SBW-1 weights (Chattopadhyay <i>et al.</i> , 2020) of the ATT, with the OS being the treatment group and the RCT sample being the control group
CW	The CW estimator defined by (6) with $\mathbf{g}(X) = \mathbf{g}_1(X)$
ACW-t	The ACW estimator defined by (9) with $\mathbf{g}(X) = \mathbf{g}_1(X)$ and the nuisance functions $\mu_a(X, 1)$, and $\mu_0(X, 1)$ are estimated based on the trial sample
ACW-t(S)	The penalized ACW-t estimator using the method of sieves with $\mathbf{g}(X) = \mathbf{g}_2(X)$ for sampling score and outcome models, respectively
ACW-t(S ^O)	The penalized ACW estimator using the method of sieves with $\mathbf{g}(X) = \mathbf{g}_2(X)$ for outcome models and construct the sieve basis for $\pi_\delta(X)$ by power series of the selected outcome predictors
ACW-b	The ACW estimator defined by (9) with $\mathbf{g}(X) = \mathbf{g}_1(X)$ and the nuisance functions $\mu_1(X)$ and $\mu_0(X)$ are estimated based on both RCT and OS samples
ACW-b(S)	The penalized ACW-b estimator using the method of sieves with $\mathbf{g}(X) = \mathbf{g}_2(X)$ for sampling score and outcome models, respectively
ACW-b(S ^O)	The penalized ACW-b estimator using the method of sieves with $\mathbf{g}(X) = \mathbf{g}_2(X)$ for outcome models and construct the sieve basis for $\pi_\delta(X)$ by power series of the selected outcome predictors

because it is based only on the observed data. For example, one can use a likelihood ratio test for testing a reduced model with the same outcome mean model specification versus a full model with different model specifications in the RCT and OS samples. Note that failure to reject this assumption does not ensure the whole set of Assumptions 1–4 and 7 holds; subject matter knowledge should be consulted, for example, Dahabreh *et al.* (2020).

5 | SIMULATION STUDY

We conduct simulation studies to evaluate the finite sample performances of the proposed estimators. Table 1 describes four simulation scenarios and 12 estimators to be compared, and Figure 2 displays the results with boxplots of the estimators. Details of the data-generating process and numerical results are provided in Web Appendix E.1. It can be seen that the naive and IPSW estimators fail to adjust for the selection bias associated with the RCT sample. The SBW and CW estimators can correct the

selection bias and are doubly robust, but they have larger variances than other doubly robust estimators. In Scenario 3 when the outcome model is misspecified, the AIPSW estimator has a larger bias than other doubly robust estimators. This is because the AIPSW estimator is inflicted by the inverse probability of sampling weights, which, as shown in Scenario 1, results in the large finite-sample bias of the IPSW estimator. The ACW estimators do not involve weighting by the inverse probability of sampling and are more stable, thus we recommend the ACW estimators in practice. The ACW-t(S^O) and ACW-b(S^O) are shown to be doubly robust and more efficient than other doubly robust estimators. The ACW-t, ACW-t(S), ACW-b, and ACW-b(S) are unbiased but show high variability, which could be due to the inclusion of IVs. In Scenario 4 where both outcome and sampling score models are misspecified, the ACW estimators focusing on outcome predictors, that is, ACW-t(S^O) and ACW-b(S^O) are still unbiased and efficient. Moreover, ACW-b(S^O) has smaller variance than ACW-t(S^O) by exploiting the predictive power from the OS sample.

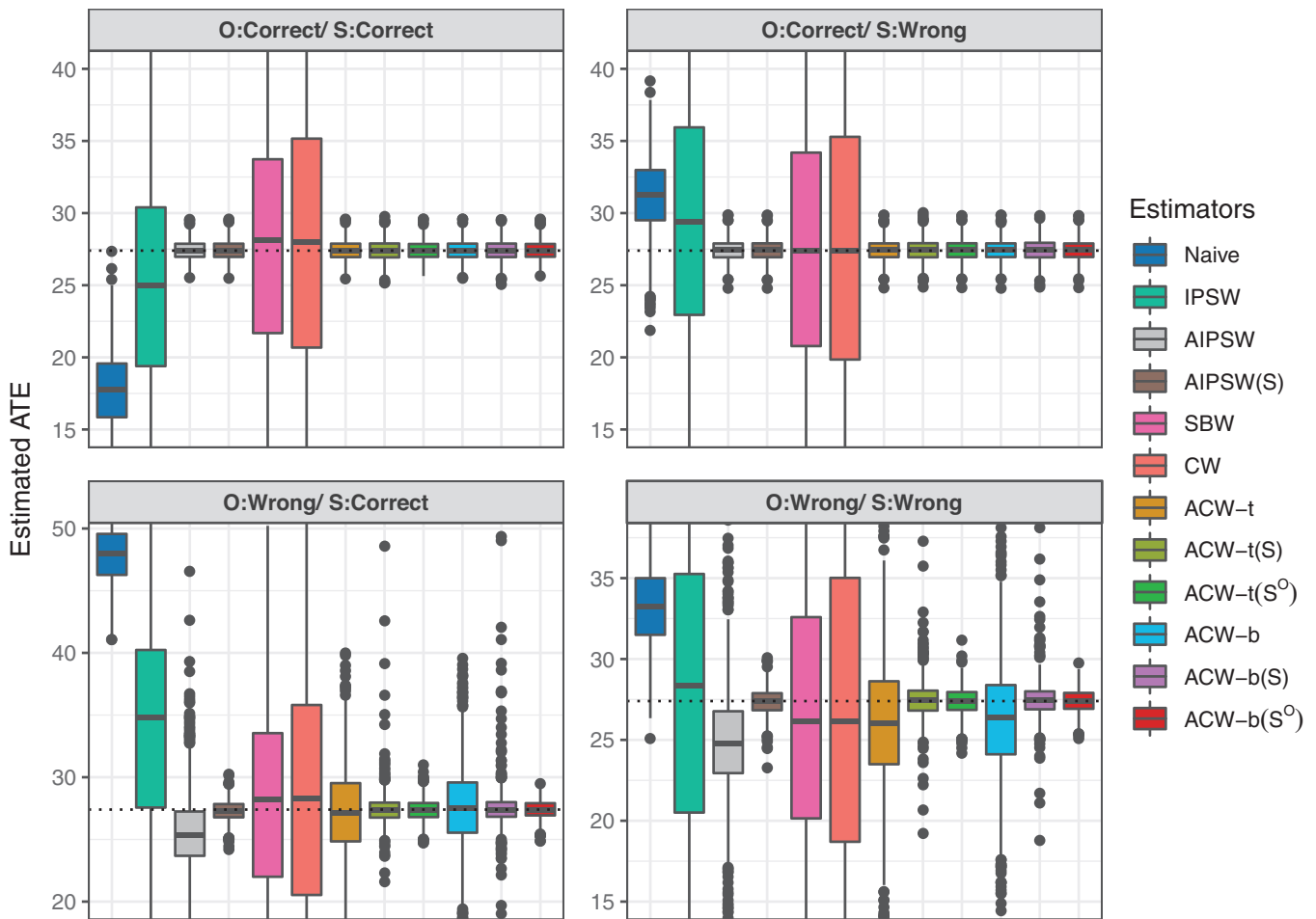


FIGURE 2 Boxplot of estimators under four model specification scenarios, where a few outliers are removed for visualization. This figure appears in color in the electronic version of this article, and color refers to that version.

6 | REAL DATA APPLICATION

We apply the proposed estimators to evaluate the effect of adjuvant chemotherapy for early-stage resected non-small-cell lung cancer (NSCLC). Adjuvant chemotherapy for resected NSCLC is shown to be effective in stages II and IIIA disease based on RCTs (Massarelli *et al.*, 2003); however, its utility in the early-stage disease remains unclear. Cancer and Leukemia Group B (CALGB) 9633 is the only trial designed specifically to evaluate the benefit of adjuvant chemotherapy over observation for stage IB NSCLC patients after surgery (Strauss *et al.*, 2008). Additional OS data for stage IB NSCLC patients were extracted from National Cancer Database (NCDB) with the same eligibility criteria as CALGB 9633. NCDB is a large joint project of the American Cancer Society and the American College of Surgeons, and it captures 70% of all cancers diagnosed in the United States. It is designed to be a registry, and there is no design weights associated with this database (Jairam and Park, 2019). As the extracted OS samples from NCDB were diagnosed between the years 2004 and 2016,

and CALGB 9633 enrolled patients between the years 1996 and 2003, the patients of the two sources can be considered independent.

Table 2 discusses the plausibility of the identification assumptions, and Table 3 (panel a) summarizes the baseline characteristics of the CALGB 9633 trial sample and the NCDB sample. The treatment indicator A is coded as 1 for adjuvant chemotherapy and 0 for on observation. The outcome is the indicator of cancer recurrence within 3 years after the surgery. The four covariates have been considered strong prognostic factors for disease recurrence after surgical resection for early NSCLC. As seen in Table 3 (panel a), there are significant differences in the distribution of these covariates between the two data sources. Specifically, CALGB 9633 has a significantly higher percentage of male and younger (<70 years old) patients with smaller tumor size. While adjuvant chemotherapy is now recommended to stage IB NSCLC patients with a tumor size > 4 cm (National Comprehensive Cancer Network, 2021), it remains an important question whether adjuvant chemotherapy benefits the general NSCLC patient

TABLE 2 Justification of the identification assumptions in the context of the CALGB 9633 trial and the NCDB sample

Assumptions	Justifications
1 Consistency	The extracted OS samples are stage IB NSCLC patients who had surgery and then received either adjuvant chemotherapy or on observation (i.e., no chemotherapy) and with age greater than 20. Like CALGB 9633 patients, they did not receive any of the neoadjuvant chemotherapy, radiation therapy, induction therapy, immunotherapy, hormone therapy, transplant/endocrine procedures, or systemic treatment before their surgery. Thus, the same treatment or comparison conditions were given in the same setting in both studies.
2 Treatment ignorability and positivity	The CALGB 9633 trial implemented treatment randomization and had good patient compliance (Strauss <i>et al.</i> , 2008).
3 Sampling ignorability and positivity	The four covariates, gender, age, histology, and tumor size, have been considered strong prognostic factors or disease recurrence after surgical resection for early NSCLC. The positivity condition holds because the OS data for NSCLC stage IB patients were extracted from NCDB with the same eligibility criteria as CALGB 9633.
7 Generalizability of the outcome mean functions from the RCT sample to the OS sample	The likelihood ratio test of a reduced model (i.e., a single logistic regression with the sieve basis for the combined sample) against a full model (that is, two separate logistic regressions with the sieve basis for the two samples) has a p -value of 0.09. If a conservative investigator uses 0.1 to determine the critical value, the investigator can choose estimators using only trial data, for example, ACW-t(S) and ACW-t(S ^O). On the other hand, if the investigator uses 0.05 to determine the critical value, one can choose estimators using both data sources, that is, ACW-b(S) and ACW-b(S ^O).

population represented by NCDB, with a higher percentage of female and older age and larger tumor size. As these covariates are strong prognostic factors of disease recurrence and they may even be modifiers for the treatment effect of adjuvant chemotherapy, naive estimators based only on CALGB 9633 data will lead to biased quantification of the true treatment effect defined on the entire population of early-stage NSCLC patients.

We compare the proposed estimators with other ATE estimators, same as in the simulation studies. For sieves estimators, the basis functions are the first- and second-order moments of the four covariates. We select a subsample using 1:10 matching based on the observed covariate and combine the RCT and matched OS samples for fitting outcome regression in the ACW-b(S) and ACW-b(S^O) methods. Bootstrap variance estimation is applied to estimate the standard errors. Table 3 (panel b) reports the results. The results indicate that in the RCT sample there is an 8.3% decrease in the risk of recurrence for adjuvant chemotherapy over observation. The IPSW, AIPSW, AIPSW(S), SBW, ACW-t(S), and ACW-t(S^O) estimators, which utilized OS covariate information, show a 9–14% decrease in the risk of recurrence. However, the causal effect is not significant according to the 95% confidence interval. By leveraging the predictive power of the OS sample, the ACW-b(S) and ACW-b(S^O) estimators give an estimate of 17% risk decrease, which is significant at 0.05 level. Moreover, the ACW-t(S^O) and ACW-b(S^O) estimators gain efficiency by focusing on outcome predictors, compared to ACW-t(S) and ACW-b(S). All of the sampling score corrected estimators have steeper declines in recurrence risk

compared to the naive estimator, which suggests that the causal risk difference in the target population is larger than the one of the RCT sample, that is, the effect of adjuvant chemotherapy is more profound in the real patient population.

7 | DISCUSSION

In this paper, we have developed a new semiparametric framework to evaluate the ATEs integrating the complementary features of the RCTs and OSs under assumptions of RCT randomization of treatment, generalizability of the CATE, or the outcome mean functions and positivity of trial participation. The proposed framework can be extended to the indirect comparison problem (e.g., Phillippo *et al.*, 2018) under the transportability of CATEs, which we will pursue in the future.

In real data application, we assume that the RCT sample and the OS sample are independent based on the study designs for the CALGB trial and the NCDB study. In general, this assumption would be violated if there is a significant overlapping of the two data sources, that is, they involve the same subset of patients. We note that the violation of this assumption would not affect the unbiasedness of the estimators but variance estimation. Recently, Saegusa (2019) developed a new weighted empirical process theory for merged data from potential overlapping sources. This inference framework does not require identifying duplicated individuals and therefore is attractive. In the future, we will extend this inference framework to our general setting of combining RCTs and OSs.

TABLE 3 (a) Summary of baseline characteristics of the CALGB 9633 trial sample and the NCDB sample. (b) Point estimate, standard error, and 95% percentile confidence interval of the causal risk difference between adjuvant chemotherapy and observation based on the CALGB 9633 trial sample and the NCDB sample

(a)	RCT: CALGB 9633	OS: NCDB	
	n = 319	n = 15,379	
Recurrence (Y), $n(\%)$	79 (25)	5060 (33)	
Treatment (A), $n(\%)$			
Adjuvant chemotherapy	156 (49)	4324 (28)	
Observation	163 (51)	11055 (72)	
Gender (X_1), $n(\%)$			
Male	204 (64)	8458 (55)	
Female	115 (36)	6921 (45)	
Age (X_2), $mean \pm SD$	60.83 \pm 9.62	67.87 \pm 10.18	
Histology (X_3), $n(\%)$			
Squamous	128 (40)	5998 (39)	
Non-squamous	191 (60)	9381 (61)	
Tumor size (X_4), $mean \pm SD$	4.6 \pm 2.08	4.94 \pm 3.04	
(b)	$\hat{\tau}$	$\widehat{SE}(\hat{\tau})$	95% CI
Naive	-0.083	0.044	(-0.163, -0.018)
IPSW	-0.088	0.060	(-0.211, 0.019)
AIPSW	-0.088	0.060	(-0.187, 0.041)
AIPSW(S)	-0.106	0.068	(-0.233, 0.020)
SBW	-0.090	0.057	(-0.187, 0.017)
CW	-0.105	0.058	(-0.221, 0.000)
ACW-t(S)	-0.139	0.106	(-0.309, 0.041)
ACW-t(S ^o)	-0.122	0.080	(-0.237, 0.054)
ACW-b(S)	-0.174	0.098	(-0.360, -0.044)
ACW-b(S ^o)	-0.172	0.088	(-0.357, -0.050)

We have focused on the setting when all relevant covariates in X are captured in both RCTs and OSs. However, because OSs were not initially collected for research purposes, some important covariates may not be available from the OS. Yang and Ding (2019) developed integrative causal analyses of the ATEs combining big main data with unmeasured confounders and smaller validation data with a full set of confounders; however, they assumed that the validation sample (i.e., the RCT sample in our context) is representative of the target population. In the presence of unmeasured covariates in the OSs, there may be lingering selection biases after calibration on the measured covariates. The future work will investigate the sensitivity to the unmeasured covariates (Nguyen *et al.*, 2017; Yang and Lok, 2017).

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DATA AVAILABILITY STATEMENT

The data that support the findings of the paper were assembled through agreements with third parties for licensed use. Without the permission of these third parties and to avoid unintended leakage of patient privacy, we elect to not share the data.

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SUPPORTING INFORMATION

Web Appendices referenced in Sections 2–5, and R codes for implementing the proposed methods are available with this paper at the Biometrics website on Wiley Online Library.

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Supporting Information for “Improving trial generalizability using observational studies” by

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Supporting information is organized as the following. In Web Appendix A, we discuss the subtle differences between generalizability and transportability. In Web Appendix B, we specify the IPSW and AIPSW estimators and provide an identification formula based on inverse sampling score weighting. In Web Appendix C, we provide the proofs of Theorems 1–4 and Lemma 1. Web Appendix D provides regularity conditions for the sieves estimator. Web Appendix E provides simulation study details and additional simulation results.

Web Appendix A: Generalizability and Transportability

The problems of generalizability (Cole and Stuart, 2010; Stuart et al., 2011; Hernan and VanderWeele, 2011; Tipton, 2013; O’Muircheartaigh and Hedges, 2014; Stuart et al., 2015; Keiding and Louis, 2016; Dahabreh and Hernán, 2019; Dahabreh et al., 2019) and transportability (Pearl and Bareinboim, 2011; Rudolph and van der Laan, 2017; Westreich et al., 2017; Josey et al., 2021) aim at extending findings from a randomized controlled trial (RCT) to a target population (Dahabreh et al., 2020). However, there are subtle differences between the problems of generalizability and transportability in terms of estimands and identification assumptions. The differences in generalizability and transportability are summarized in Table S1 and also illustrated using causal diagrams in Figure S1.

The goal of generalizability is to generalize results from a trial to its larger population, whereas the goal of transportability is to extend results from a trial to a different external population. In generalizability, one assumes that the triplet $\{X, Y(0), Y(1)\}$ in the target population follows $P\{X, Y(0), Y(1)\}$, and the observational sample ($\tilde{\delta} = 1$) is representative of the target population. The trial sample ($\delta = 1$) is selected from the population according to $P(\delta = 1 | X)$. The generalizability problem tries to use the trial sample to draw conclusions for the population, leveraging the observational sample. Thus, the estimand of interest is the functional form of $P\{X, Y(0), Y(1)\}$, e.g., the average treatment effect (ATE),

$E\{Y(1) - Y(0)\}$. On the other hand, in transportability, we have two study samples following $P\{X, Y(0), Y(1) \mid \delta = 1\}$ and $P\{X, Y(0), Y(1) \mid \tilde{\delta} = 1\}$ respectively, where we try to transport some features of $P\{X, Y(0), Y(1) \mid \delta = 1\}$ to $P\{X, Y(0), Y(1) \mid \tilde{\delta} = 1\}$. Thus, the estimand of interest is the functional form of $P\{X, Y(0), Y(1) \mid \tilde{\delta} = 1\}$, e.g., the target population average treatment effect (TATE; Josey et al., 2021), $E\{Y(1) - Y(0) \mid \tilde{\delta} = 1\}$. In transportability, we do not necessarily have to define $P\{X, Y(0), Y(1)\}$, and we can use the conditional odds, $P\{\tilde{\delta} = 1 \mid X, (\delta = 1 \text{ or } \tilde{\delta} = 1)\} / P\{\delta = 1 \mid X, (\delta = 1 \text{ or } \tilde{\delta} = 1)\}$, without defining $P(\delta = 1 \mid X)$ to estimate the TATE. Under generalizability, $P\{X, Y(0), Y(1) \mid \tilde{\delta} = 1\} = P\{X, Y(0), Y(1)\}$, i.e., both trial and observational samples are drawn from the broader trial population, whereas under transportability, $P\{X, Y(0), Y(1) \mid \tilde{\delta} = 1\} \neq P\{X, Y(0), Y(1)\}$, i.e., the observational sample is drawn from the external population. We call the population which we want to make inferences about as the target population.

Identification assumptions (i) - (ii) are common for both generalizability and transportability and hold for well-defined RCTs in general. The key differences between generalizability and transportability are identification assumptions (iii) - (iv), which are often needed to extend RCT findings to the target population. Unlike transportability where these assumptions are often needed for the target population with $\tilde{\delta} = 1$, for generalizability, these assumptions are needed for all x such that $P(X = x) > 0$, assuming that the trial sample is drawn from the target population. Moreover, the positivity assumption of the trial participation (iv) requires the probability of sampling to be bounded away from 0 for generalizability, whereas bounded away from 0 and 1 for transportability (Degtiar and Rose, 2021). These suggest that in transportability analysis, variables separating the trial sample from the target population should be excluded from the measure exchangeability/mean exchangeability/ignorability assumption over δ (Tipton, 2013; Dahabreh et al., 2020).



Figure S1: Illustrations of causal diagrams in the problems of generalizability and transportability. In (a), the RCT sample is subject to selection bias (indicated by X pointing to δ). In (b), the two populations differ by covariate distributions (indicated by δ and $\tilde{\delta}$ pointing to X) and the two populations differ in their treatment assignment mechanism (δ and $\tilde{\delta}$ pointing to A). (b) is modified from Pearl and Bareinboim (2011).

Table S1: Differences of the problems of Generalizability (G) and Transportability (T)

G	Goal	Generalize results from a trial to <i>its larger population</i>		
	Samples, populations	A trial sample and an observational sample from a target population		
	Study design	Nested design, non-nested design		
	Estimand	ATE	$E\{Y(1) - Y(0)\}$	
	Identification assumptions	(i) Mean exchangeability over A	$E\{Y(a) X, \delta = 1, A = a\} = E\{Y(a) X, \delta = 1\}$ for $a = 0, 1$	
		(i*) Ignorability on A	$Y(a) \perp\!\!\!\perp A (X, \delta = 1)$ for $a = 0, 1$	
		(ii) Positivity of A	$0 < P(A = a X = x, \delta = 1) < 1 \forall x$ s.t. $P(X = x \delta = 1) > 0$	
(iii) Measure exchangeability over δ		$E\{Y(1) - Y(0) X, \delta = 1\} = E\{Y(1) - Y(0) X\}$		
(iii*) Mean exchangeability over δ		$E\{Y(a) X, \delta = 1\} = E\{Y(a) X\}$ for $a = 0, 1$		
(iii**) Ignorability on δ		$Y(a) \perp\!\!\!\perp \delta X$ for $a = 0, 1$		
(iv) Positivity of δ	$P(\delta = 1 X = x) > 0$ with probability 1			
T	Goal	Extend results from a trial to a <i>different external population</i>		
	Samples, populations	A trial sample from a trial population and an observational sample from a target population where the trial and the target population are not identical		
	Study design	Non-nested design		
	Estimand	TATE	$E\{Y(1) - Y(0) \tilde{\delta} = 1\}$	
	Identification assumptions	(i) Mean exchangeability over A	same as in G(i)	
		(i*) Ignorability on A	same as in G(i*)	
		(ii) Positivity of A	same as in G(ii)	
(iii) Measure exchangeability over δ		$E\{Y(1) - Y(0) X = x, \delta = 1\} = E\{Y(1) - Y(0) X = x, \tilde{\delta} = 1\}$ $\forall x$ s.t. $P(X = x \tilde{\delta} = 1) > 0$		
(iii*) Mean exchangeability over δ		$E\{Y(a) X = x, \delta = 1\} = E\{Y(a) X = x, \tilde{\delta} = 1\}$ $\forall x$ s.t. $P(X = x \tilde{\delta} = 1) > 0$ and $a = 0, 1$		
(iii**) Ignorability on δ		$Y(a) \perp\!\!\!\perp \delta X = x \forall x$ s.t. $P(X = x \tilde{\delta} = 1) > 0$ and $a = 0, 1$		
(iv) Positivity of δ	$0 < P(\delta = 1 X = x) < 1 \forall x$ s.t. $P(X = x \tilde{\delta} = 1) > 0$			

Web Appendix B: IPSW and AIPSW

The IPSW estimator of the ATE is

$$\hat{\tau}^{\text{IPSW}} = \frac{\sum_{i=1}^n \pi_{\delta}(X_i; \hat{\boldsymbol{\eta}})^{-1} A_i Y_i}{\sum_{i=1}^n \pi_{\delta}(X_i; \hat{\boldsymbol{\eta}})^{-1} A_i} - \frac{\sum_{i=1}^n \pi_{\delta}(X_i; \hat{\boldsymbol{\eta}})^{-1} (1 - A_i) Y_i}{\sum_{i=1}^n \pi_{\delta}(X_i; \hat{\boldsymbol{\eta}})^{-1} (1 - A_i)}. \quad (\text{A1})$$

The augmented inverse probability weighting estimator (AIPSW) has been proposed to improve it by employing both the sampling score and outcome regression

$$\begin{aligned} \hat{\tau} = & \frac{\sum_{i=1}^n \pi_{\delta}(X_i; \hat{\boldsymbol{\eta}})^{-1} A_i \{Y_i - \hat{\mu}_{1,1}(X)\}}{\sum_{i=1}^n \pi_{\delta}(X_i; \hat{\boldsymbol{\eta}})^{-1} A_i} - \\ & \frac{\sum_{i=1}^n \pi_{\delta}(X_i; \hat{\boldsymbol{\eta}})^{-1} (1 - A_i) \{Y_i - \hat{\mu}_{0,1}(X_i)\}}{\sum_{i=1}^n \pi_{\delta}(X_i; \hat{\boldsymbol{\eta}})^{-1} (1 - A_i)} + \\ & \frac{1}{m} \sum_{i=n+1}^{n+m} \{\hat{\mu}_{1,1}(X_i) - \hat{\mu}_{1,1}(X_i)\}. \end{aligned} \quad (\text{A2})$$

B.1 Identification of IPSW estimator

We provide another identification formula based on IPSW. We first show that $\pi_{\delta}(X)$ is identifiable up to a constant $P(\delta = 1)$ based on

$$\pi_{\delta}(X) = P(\tilde{\delta} = 1 | X) \frac{f(X | \delta = 1) P(\delta = 1)}{f(X | \tilde{\delta} = 1) P(\tilde{\delta} = 1)} := \tilde{\pi}_{\delta}^c(X) \frac{P(\delta = 1)}{P(\tilde{\delta} = 1)},$$

where we assume that $P(\tilde{\delta} = 1 | X)$ is known by design, $f(X | \delta = 1)$ and $f(X | \tilde{\delta} = 1)$ are observed data distributions, but $P(\delta = 1)/P(\tilde{\delta} = 1)$ is identifiable without the knowledge of the sizes of the underlying populations. Nonetheless, the ATE can be identified based on

$$\tau_0 = E \left[\frac{\delta \tilde{\pi}_{\delta}^c(X)^{-1} A Y / \pi_A(X)}{\delta \tilde{\pi}_{\delta}^c(X)^{-1} A / \pi_A(X)} - \frac{\delta \tilde{\pi}_{\delta}^c(X)^{-1} (1 - A) Y / \{1 - \pi_A(X)\}}{\delta \tilde{\pi}_{\delta}^c(X)^{-1} (1 - A) / \{1 - \pi_A(X)\}} \right].$$

Web Appendix C: Proofs

C.1 Proof of Theorem 1

Proof of the double robustness of the calibration weighting estimator

Let $\boldsymbol{\mu}_{g_0} = E\{\mathbf{g}(X)\}$, $\bar{\mathbf{g}}_0 = \mathbf{g}(X) - \boldsymbol{\mu}_{g_0}$. To use the M-estimator theory (Boos and Stefanski, 2013), we write (4) as the following estimating equations

$$\frac{1}{N} \sum_{i=1}^N C(X_i, \tilde{\delta}_i; \boldsymbol{\mu}_{\mathbf{g}}) = \frac{1}{N} \sum_{i=1}^N \tilde{\delta}_i d_i \{\mathbf{g}(X_i) - \boldsymbol{\mu}_{\mathbf{g}}\} = 0, \quad (\text{A3})$$

$$\frac{1}{N} \sum_{i=1}^N \zeta(X_i, \delta_i; \boldsymbol{\lambda}, \boldsymbol{\mu}_g) = \frac{1}{N} \sum_{i=1}^N \delta_i \exp\{\boldsymbol{\lambda}^\top \mathbf{g}(X_i)\} \{\mathbf{g}(X_i) - \boldsymbol{\mu}_g\} = 0. \quad (\text{A4})$$

First consider the case where Assumption 6 holds, we have $\pi_\delta(X) = \exp\{\boldsymbol{\eta}_0^\top \mathbf{g}(X)\}$. Notice that $\boldsymbol{\mu}_{g0}$ is the solution to $E\{C(X; \boldsymbol{\mu}_g)\} = 0$. Taking expectation on the left hand side of (A4) with $\boldsymbol{\mu}_g = \boldsymbol{\mu}_{g0}$ leads to

$$E\{\zeta(X, \delta; \boldsymbol{\lambda}, \boldsymbol{\mu}_{g0})\} = E\{E(\zeta(X, \delta; \boldsymbol{\lambda}, \boldsymbol{\mu}_{g0})|X)\} = E\left(\pi_\delta(X) \exp\{\boldsymbol{\lambda}^\top \mathbf{g}(X)\} [\mathbf{g}(X) - E\{\mathbf{g}(X)\}]\right).$$

For the above conditional expectation to be zero, one needs $\pi_\delta(X) \exp\{\boldsymbol{\lambda}^\top \mathbf{g}(X)\}$ to be a constant. As $\pi_\delta(X) = \exp\{\boldsymbol{\eta}_0^\top \mathbf{g}(X)\}$, we have $\pi_\delta(X) \exp\{\boldsymbol{\lambda}^\top \mathbf{g}(X)\} = \exp\{(\boldsymbol{\eta}_0 + \boldsymbol{\lambda})^\top \mathbf{g}(X)\}$. Thus $\boldsymbol{\lambda} = -\boldsymbol{\eta}_0$ makes (A4) a system of unbiased estimating equations. We point out that denominator in \hat{q}_i is an estimator of the population size N , i.e.,

$$\begin{aligned} \frac{1}{N} \sum_{i=1}^n \exp\{\boldsymbol{\lambda}^\top \mathbf{g}(X_i)\} &= \frac{1}{N} \sum_{i=1}^N \delta_i \exp\{\boldsymbol{\lambda}^\top \mathbf{g}(X_i)\} \\ &= \frac{1}{N} \sum_{i=1}^N \delta_i \exp\{-\boldsymbol{\eta}_0^\top \mathbf{g}(X_i)\} + O_p(n^{-1/2}N^{-1}) \\ &= 1 + O_p(N^{-1/2}) + O_p(n^{-1/2}N^{-1}) \\ &= 1 + o_p(1). \end{aligned}$$

Therefore,

$$\hat{q}_i = q(X_i; \hat{\boldsymbol{\lambda}}) = \frac{\exp\{\hat{\boldsymbol{\lambda}}^\top \mathbf{g}(X_i)\}}{\sum_{i=1}^n \exp\{\hat{\boldsymbol{\lambda}}^\top \mathbf{g}(X_i)\}} = \frac{1}{N} \frac{1}{\pi_\delta(X_i; \boldsymbol{\eta}_0)} + O_p(n^{-1/2}N^{-1}); \quad (\text{A5})$$

i.e., $\hat{q}_i \{N\pi_\delta(X_i; \boldsymbol{\eta}_0)\} \rightarrow 1$ as $n \rightarrow \infty$. Based on (A5), we have

$$\begin{aligned} \hat{\tau}^{\text{CW}} &= \sum_{i=1}^N \hat{q}_i \delta_i \left\{ \frac{A_i Y_i}{\pi_{Ai}} - \frac{(1 - A_i) Y_i}{1 - \pi_{Ai}} \right\} \\ &= \frac{1}{N} \sum_{i=1}^N \frac{\delta_i}{\pi_\delta(X_i; \boldsymbol{\eta}_0)} \left\{ \frac{A_i Y_i}{\pi_{Ai}} - \frac{(1 - A_i) Y_i}{1 - \pi_{Ai}} \right\} = \tau_0 + O_p(N^{-1/2}) + O_p(n^{-1/2}) \\ &= \tau_0 + o_p(1). \end{aligned} \quad (\text{A6})$$

Therefore, $\hat{\tau}^{\text{CW}}$ is consistent for τ_0 .

Now consider the case where Assumption 5 holds. Then we have

$$\begin{aligned}
E \left(\sum_{i=1}^n \hat{q}_i \left\{ \frac{A_i Y_i}{\pi_{A_i}} - \frac{(1 - A_i) Y_i}{1 - \pi_{A_i}} \right\} \right) &= E \left[\sum_{i=1}^n \hat{q}_i E \left\{ \frac{A_i Y_i}{\pi_{A_i}} - \frac{(1 - A_i) Y_i}{1 - \pi_{A_i}} \mid X_i, \delta_i = 1 \right\} \right] \\
&= E \left[\sum_{i=1}^n \hat{q}_i E \{ Y(1) - Y(0) \mid X_i, \delta_i = 1 \} \right] \\
&= \gamma_0^\top E \left\{ \sum_{i=1}^n \hat{q}_i \mathbf{g}(X_i) \right\} = \gamma_0^\top E \left\{ \frac{1}{N} \sum_{i=1}^N \tilde{\delta}_i d_i \mathbf{g}(X_i) \right\} \\
&= E \left\{ \gamma_0^\top \mathbf{g}(X) \right\} = \tau_0,
\end{aligned}$$

where the equation on the third line is obtained by the balancing constraint (1). Under regularity conditions for unbiased M-estimators, $\hat{\tau}^{\text{CW}}$ is consistent for τ_0 .

We thus conclude the double robustness of $\hat{\tau}^{\text{CW}}$.

Proof of the asymptotic variance for the calibration weighting estimator

We derive the asymptotic variance of $\hat{\tau}^{\text{CW}}$ under Assumption 5 and 6 to facilitate the efficiency comparison of $\hat{\tau}^{\text{CW}}$ and $\hat{\tau}^{\text{ACW}}$.

Let $\boldsymbol{\theta} = (\boldsymbol{\mu}_g^\top, \boldsymbol{\lambda}^\top, \pi_A, \tau)^\top$ to denote the vector of all parameters. The estimating function for $\boldsymbol{\theta}$ is

$$\boldsymbol{\psi}(X, A, Y, \delta, \tilde{\delta}; \boldsymbol{\theta}) = \begin{pmatrix} C(X, \tilde{\delta}; \boldsymbol{\mu}_g) \\ \zeta(X, \delta; \boldsymbol{\lambda}, \boldsymbol{\mu}_g) \\ h(X, A, \delta; \boldsymbol{\lambda}, \pi_A) \\ t(X, A, Y, \delta; \boldsymbol{\lambda}, \pi_A, \tau) \end{pmatrix},$$

where $C(X, \tilde{\delta}; \boldsymbol{\mu}_g)$ and $\zeta(X, \delta; \boldsymbol{\lambda}, \boldsymbol{\mu}_g)$ are given in (A3), (A4), respectively, and

$$\begin{aligned}
h(X, A, \delta; \boldsymbol{\lambda}, \pi_A) &= \delta \exp\{\boldsymbol{\lambda}^\top \mathbf{g}(X)\} (A - \pi_A), \\
t(A, X, Y, \delta; \boldsymbol{\lambda}, \pi_A, \tau) &= \delta \exp\{\boldsymbol{\lambda}^\top \mathbf{g}(X)\} \left\{ \frac{AY}{\pi_A} - \frac{(1 - A)Y}{1 - \pi_A} - \tau \right\}.
\end{aligned}$$

Then $\hat{\boldsymbol{\theta}} = (\hat{\boldsymbol{\mu}}_g^\top, \hat{\boldsymbol{\lambda}}^\top, \hat{\pi}_A, \hat{\tau}^{\text{CW1}})^\top$ solves the joint estimating equation

$$\frac{1}{N} \sum_{i=1}^N \boldsymbol{\psi}(X_i, A_i, Y_i, \delta_i; \boldsymbol{\theta}) = \mathbf{0}.$$

Under standard regularity conditions in the M-estimator theory, we have

$$\widehat{\boldsymbol{\theta}} - \boldsymbol{\theta}_0 = \frac{1}{N} \sum_{i=1}^N \boldsymbol{\psi}(X_i, A_i, Y_i, \delta_i; \boldsymbol{\theta}_0) + o_p(N^{-1/2}),$$

where $A(\boldsymbol{\theta}_0) = E\{-\nabla_{\boldsymbol{\theta}_0} \boldsymbol{\psi}(\boldsymbol{\theta}_0)\}$, and $\boldsymbol{\theta}_0 = (\boldsymbol{\mu}_{g_0}^\top, -\boldsymbol{\eta}_0^\top, \pi_A, \tau_0)^\top$. The asymptotic variance of $N^{-1/2}(\widehat{\boldsymbol{\theta}} - \boldsymbol{\theta}_0)$ is $A^{-1}(\boldsymbol{\theta}_0)B(\boldsymbol{\theta}_0)A^{-1}(\boldsymbol{\theta}_0)^\top$, where $B(\boldsymbol{\theta}_0) = E\{\boldsymbol{\psi}(\boldsymbol{\theta}_0)\boldsymbol{\psi}(\boldsymbol{\theta}_0)^\top\}$.

To further express the asymptotic variance, we denote $q_0 = q_0(X) = \exp\{-\boldsymbol{\eta}_0^\top \mathbf{g}(X)\}$ and $\bar{\tau}(Y, A) = \{AY/\pi_A - (1-A)Y/(1-\pi_A) - \tau_0\}$. Note that $E\{\bar{\tau}(Y, A)|X, \delta = 1\} = \tau(X) - \tau_0$ and $E(\bar{\tau}d) = 1$. Under Assumption 6 and 5, $\pi_\delta(X)q_0(X) = 1$ and $\tau(X) - \tau_0 = \boldsymbol{\gamma}_0^\top \bar{\mathbf{g}}_0$. In the following derivation we use \Rightarrow to indicate equality when both Assumption 5 and 6 hold.

Using iterated expectation, we have

$$\begin{aligned} A(\boldsymbol{\theta}_0) &= E\{-\nabla_{\boldsymbol{\theta}_0} \boldsymbol{\psi}(\boldsymbol{\theta}_0)\} \\ &= E \begin{pmatrix} \tilde{\delta}dI_K & \mathbf{0}_{K \times K} & \mathbf{0}_{K \times 1} & \mathbf{0}_{K \times 1} \\ \delta q_0 I_K & -\delta q_0 \bar{\mathbf{g}}_0 \mathbf{g}^\top & \mathbf{0}_{K \times 1} & \mathbf{0}_{K \times 1} \\ \mathbf{0}_{1 \times K} & -\delta q_0 (A - \pi_A) \mathbf{g}^\top & \delta q_0 & 0 \\ \mathbf{0}_{1 \times K} & -\delta q_0 \bar{\tau}(Y, A) \mathbf{g}^\top & \delta q_0 \left\{ \frac{AY}{\pi_A^2} + \frac{(1-A)Y}{(1-\pi_A)^2} \right\} & \delta q_0 \end{pmatrix} \\ &= \begin{pmatrix} I_K & \mathbf{0}_{K \times K} & \mathbf{0}_{K \times 1} & \mathbf{0}_{K \times 1} \\ E(\delta q_0) I_K & -E\{\delta q_0 (\mathbf{g} - \boldsymbol{\mu}_{g_0}) \mathbf{g}^\top\} & \mathbf{0}_{K \times 1} & \mathbf{0}_{K \times 1} \\ \mathbf{0}_{1 \times K} & \mathbf{0}_{1 \times K} & E(\delta q_0) & 0 \\ \mathbf{0}_{1 \times K} & -E[\pi_\delta(X)q_0 \{\tau(X) - \tau_0\} \mathbf{g}^\top] & E\left[\delta q_0 \left\{ \frac{AY}{\pi_A^2} + \frac{(1-A)Y}{(1-\pi_A)^2} \right\}\right] & E(\delta q_0) \end{pmatrix}. \end{aligned}$$

By block matrix inversion,

$$A(\boldsymbol{\theta}_0)^{-1} = \begin{pmatrix} I_K & \mathbf{0}_{K \times K} & \mathbf{0}_{K \times 1} & \mathbf{0}_{K \times 1} \\ E(\delta q_0 \bar{\mathbf{g}}_0 \mathbf{g}^\top)^{-1} E(\delta q_0) & -E(\delta q_0 \bar{\mathbf{g}}_0 \mathbf{g}^\top)^{-1} & \mathbf{0}_{K \times 1} & \mathbf{0}_{K \times 1} \\ \mathbf{0}_{1 \times K} & \mathbf{0}_{1 \times K} & E(\delta q_0)^{-1} & 0 \\ A_{41} & A_{42} & A_{43} & A_{44} \end{pmatrix},$$

where

$$\begin{aligned} A_{41} &= E\left[\delta q_0(X) \{\tau(X) - \tau_0\} \mathbf{g}^\top\right] E\left\{\delta q_0(X) \bar{\mathbf{g}}_0 \mathbf{g}^\top\right\}^{-1} \Rightarrow \boldsymbol{\gamma}_0^\top I_K, \\ A_{42} &= -E\{\delta q_0(X)\}^{-1} E\left[\pi_\delta(X)q_0(X) \{\tau(X) - \tau_0\} \mathbf{g}^\top\right] E\left\{\delta q_0(X) \bar{\mathbf{g}}_0 \mathbf{g}^\top\right\}^{-1} \Rightarrow -\boldsymbol{\gamma}_0^\top I_K, \\ A_{43} &= -E\{\delta q_0(X)\}^{-2} E\left[\delta q_0(X) \left\{ \frac{AY}{\pi_A^2} + \frac{(1-A)Y}{(1-\pi_A)^2} \right\}\right] \Rightarrow -E\left[\delta q_0(X) \left\{ \frac{Y(1)}{\pi_A} + \frac{Y(0)}{1-\pi_A} \right\}\right], \\ A_{44} &= E\{\delta q_0(X)\}^{-1} \Rightarrow 1. \end{aligned}$$

Taking iterated expectation again, we have

$$\begin{aligned}
B(\boldsymbol{\theta}_0) &= E \left\{ \boldsymbol{\psi}(\boldsymbol{\theta}_0) \boldsymbol{\psi}(\boldsymbol{\theta}_0)^\top \right\} \\
&= E \left(\begin{array}{cccc}
\widetilde{\delta d^2} \bar{\boldsymbol{g}}_0 \bar{\boldsymbol{g}}_0^\top & \mathbf{0}_{K \times K} & \mathbf{0}_{K \times 1} & \mathbf{0}_{K \times 1} \\
\mathbf{0}_{K \times K} & \delta q_0(X)^2 \bar{\boldsymbol{g}}_0 \bar{\boldsymbol{g}}_0^\top & \delta q_0(X)^2 (A - \pi_A) \bar{\boldsymbol{g}}_0 & \delta q_0(X)^2 \bar{\tau}(Y, A) \bar{\boldsymbol{g}}_0 \\
\mathbf{0}_{1 \times K} & \delta q_0(X)^2 (A - \pi_A) \bar{\boldsymbol{g}}_0^\top & \delta q_0(X)^2 (A - \pi_A)^2 & \delta q_0(X)^2 \bar{\tau}(Y, A) (A - \pi_A) \\
\mathbf{0}_{1 \times K} & \delta q_0(X)^2 \bar{\tau}(Y, A) \bar{\boldsymbol{g}}_0^\top & \delta q_0(X)^2 \bar{\tau}(Y, A) (A - \pi_A) & \delta q_0(X)^2 \bar{\tau}(Y, A)^2
\end{array} \right) \\
&= \begin{pmatrix} B_{11} & \mathbf{0}_{K \times K} & \mathbf{0}_{K \times 1} & \mathbf{0}_{K \times 1} \\ \mathbf{0}_{K \times K} & B_{22} & \mathbf{0}_{K \times 1} & B_{24} \\ \mathbf{0}_{1 \times K} & \mathbf{0}_{1 \times K} & B_{33} & B_{34} \\ \mathbf{0}_{1 \times K} & B_{24}^\top & B_{34} & B_{44} \end{pmatrix},
\end{aligned}$$

where

$$\begin{aligned}
B_{11} &= E \left(\widetilde{\delta d^2} \bar{\boldsymbol{g}}_0 \bar{\boldsymbol{g}}_0^\top \right), \\
B_{22} &= E \{ \delta q_0(X)^2 \bar{\boldsymbol{g}}_0 \bar{\boldsymbol{g}}_0^\top \} \Rightarrow E \{ q_0(X) \bar{\boldsymbol{g}}_0 \bar{\boldsymbol{g}}_0^\top \}, \\
B_{24} &= E \left[\delta q_0(X)^2 \{ \tau(X) - \tau_0 \} \bar{\boldsymbol{g}}_0 \right] \Rightarrow E \left\{ q_0(X) \gamma_0^\top \bar{\boldsymbol{g}}_0 \bar{\boldsymbol{g}}_0 \right\}, \\
B_{33} &= E \{ \delta q_0(X)^2 V(A|X) \} \Rightarrow \pi_A (1 - \pi_A) E \{ q_0(X) \}, \\
B_{34} &= E \{ \delta q_0^2(X) \bar{\tau}(Y, A) (A - \pi_A) \} = E \left[\delta q_0^2(X) \{ (1 - \pi_A) Y(1) + \pi_A Y(0) \} \right], \\
B_{44} &= E \{ \delta q_0^2(X) \bar{\tau}(Y, A)^2 \} = E \left[\delta q_0^2(X) \left\{ \frac{Y(1)^2}{\pi_A} + \frac{Y(0)^2}{1 - \pi_A} - 2\tau(X)\tau_0 + \tau_0^2 \right\} \right].
\end{aligned}$$

We can express the asymptotic variance of $N^{-1/2}(\hat{\tau}^{\text{CW}} - \tau_0)$ as $V^{\text{CW}} = A_{41} B_{11} A_{41}^\top + A_{44}^2 B_{44}$.

Under Assumption 5 and 6, we have $A_{41} B_{11} A_{41}^\top = E \left[\widetilde{\delta d^2} \{ \tau(X) - \tau_0 \}^2 \right]$. Therefore, V^{CW} can be simplified as

$$V^{\text{CW}} = E \left[\widetilde{\delta d^2} \{ \tau(X) - \tau_0 \}^2 \right] + E \left[\delta q_0^2(X) \left\{ \frac{Y(1)^2}{\pi_A} + \frac{Y(0)^2}{1 - \pi_A} - 2\tau(X)\tau_0 + \tau_0^2 \right\} \right].$$

C.2 Proof of Theorem 2

Let $Z = (X, A, Y, \delta, \widetilde{\delta})$ be a vector of random variables. Assumptions 1 - 3 constitute the semiparametric model. The semiparametric likelihood based on a single Z is

$$f(Z) = \{ f(X) f(A, Y|X, \delta = 1) \pi_\delta(X) \}^\delta \{ f(X) \}^{\widetilde{\delta}},$$

where $f(\cdot)$ is a density function for a continuous random variable and is a probability mass function for a discrete random variable.

Assuming that $\delta \widetilde{\delta} = 0$, the score function (Hahn, 1998) satisfies

$$S(X, A, Y, \delta, \tilde{\delta}) = S(X, A, Y, \delta) + \tilde{\delta}S(X).$$

We first list four identities that are used in the following derivation of the efficiency bound:

- I1. For any function $h(X, A, \delta)$, we have $E\{h(X, A, \delta)S(Y|X, A, \delta)\} = 0$;
- I2. any function $h(X, A, \delta)$, we have $E[h(X, A, \delta)\{Y - E(Y|X, A, \delta)\}] = 0$;
- I3. any $h(X, A, Y)$, if $E\{\tilde{\delta}h(X, A, Y)\} = 0$, we have $E\{\tilde{\delta}h(X, A, Y)S(X, A, Y, \delta)\} = 0$
- I4. any $h(X, A, Y)$, if $E\{\delta h(X, A, Y)\} = 0$, we have $E\{\delta h(X, A, Y)\tilde{\delta}S(X)\} = 0$.

To derive the semiparametric efficiency score, we use the method of parametric submodel (Bickel et al., 1993). Let $\{f_t(Z) : t \in \mathbb{R}\}$ be a regular parametric submodel which contains the truth at $t = 0$, i.e., $f_t(Z)|_{t=0} = f(Z)$.

Note that $\tau(X) = E(Y|X, A = 1, \delta = 1) - E(Y|X, A = 0, \delta = 1)$ and $\tau_0 = E\{\tilde{\delta}d\tau(X)\}$. Let $\tau_t = E_t\{\tilde{\delta}d\tau_t(X)\}$ denote the parameter τ evaluated with respect to the regular parametric submodel $f_t(Z)$. Following Bickel et al. (1993), the semiparametric efficiency score $\phi = \phi(Z)$ is the pathwise derivative of the target parameter in the sense that

$$\left. \frac{\partial}{\partial t} \tau_t \right|_{t=0} = E\{\phi S(Z)\},$$

where $S(Z) = \partial \log f_t(Z) / \partial t|_{t=0}$. Toward this end, we express

$$\left. \frac{\partial}{\partial t} \tau_t \right|_{t=0} = E\{\tilde{\delta}d\tau(X)S(X)\} + E\left\{\left. \frac{\partial \tau_t(X)}{\partial t} \right|_{t=0}\right\}. \quad (\text{A7})$$

For the first term in the right hand side of (A7), we have

$$\begin{aligned} E\{\tilde{\delta}d\tau(X)S(X)\} &= E\left[\tilde{\delta}d\{\tau(X) - \tau_0\}S(X)\right] \\ &= E\left[\tilde{\delta}d\{\tau(X) - \tau_0\}\{S(X, A, Y, \delta) + \tilde{\delta}S(X)\}\right] \\ &= E\left[\tilde{\delta}d\{\tau(X) - \tau_0\}S(X, A, Y, \delta, \tilde{\delta})\right], \end{aligned} \quad (\text{A8})$$

where (A8) holds because of identity I3. To express further the second term in the right hand side of (A7), we have

$$\begin{aligned} \left. \frac{\partial \tau_t(X)}{\partial t} \right|_{t=0} &= \left\{ \int y \frac{\partial}{\partial t} f_t(y|X, \delta = 1, A = 1) dy - \int y \frac{\partial}{\partial t} f_t(y|X, \delta = 1, A = 0) dy \right\} \Big|_{t=0} \\ &= \left\{ \int y S(y|X, A = 1, \delta = 1) f_t(y|X, A = 1, \delta = 1) dy \right\} \Big|_{t=0} \end{aligned}$$

$$\begin{aligned}
& - \left\{ \int y S(y|X, A=0, \delta=1) f_t(y|X, A=0, \delta=1) dy \right\} \Big|_{t=0} \\
& = E \left\{ \frac{\delta AY}{\pi_\delta(X) \pi_A} S(Y|A, X, \delta) | X \right\} - E \left\{ \frac{\delta(1-A)Y}{\pi_\delta(X)(1-\pi_A)} S(Y|A, X, \delta) | X \right\} \\
& = E \left[\frac{\delta}{\pi_\delta(X)} \left\{ \frac{AY}{\pi_A} - \frac{(1-A)Y}{(1-\pi_A)} \right\} S(Y|A, X, \delta) | X \right].
\end{aligned}$$

Therefore,

$$\begin{aligned}
E \left\{ \frac{\partial \tau_t(X)}{\partial t} \Big|_{t=0} \right\} & = E \left[\frac{\delta}{\pi_\delta(X)} \left\{ \frac{AY}{\pi_A} - \frac{(1-A)Y}{(1-\pi_A)} \right\} S(Y|A, X, \delta) \right] \\
& = E \left(\frac{\delta}{\pi_\delta(X)} \left[\frac{A\{Y - \mu_{1,\delta}(X)\}}{\pi_A} - \frac{(1-A)\{Y - \mu_{0,\delta}(X)\}}{1-\pi_A} \right] S(Y|A, X, \delta) \right)
\end{aligned} \tag{A9}$$

$$= E \left(\frac{\delta}{\pi_\delta(X)} \left[\frac{A\{Y - \mu_{1,\delta}(X)\}}{\pi_A} - \frac{(1-A)\{Y - \mu_{0,\delta}(X)\}}{1-\pi_A} \right] S(X, A, Y, \delta) \right) \tag{A10}$$

$$= E \left(\frac{\delta}{\pi_\delta(X)} \left[\frac{A\{Y - \mu_{1,\delta}(X)\}}{\pi_A} - \frac{(1-A)\{Y - \mu_{0,\delta}(X)\}}{1-\pi_A} \right] S(X, A, Y, \delta, \tilde{\delta}) \right). \tag{A11}$$

In the above derivation, (A9) follows by identity I1, (A10) follows by identity I2, and (A11) follows by identities I3 and I4.

Substituting back to (A7), we have

$$\frac{\partial}{\partial t} \tau_t \Big|_{t=0} = E \left\{ \left(\tilde{d} \{ \tau(X) - \tau_0 \} + \frac{\delta}{\pi_\delta(X)} \left[\frac{A\{Y - \mu_{1,\delta}(X)\}}{\pi_A} - \frac{(1-A)\{Y - \mu_{0,\delta}(x)\}}{1-\pi_A} \right] \right) S(X, A, Y, \delta, \tilde{\delta}) \right\}$$

Thus, the semiparametric efficiency score is

$$\phi = \tilde{d} \{ \tau(X) - \tau_0 \} + \frac{\delta}{\pi_\delta(X)} \left[\frac{A\{Y - \mu_{1,\delta}(X)\}}{\pi_A} - \frac{(1-A)\{Y - \mu_{0,\delta}(X)\}}{(1-\pi_A)} \right].$$

It follows that the semiparametric efficiency bound is

$$E(\phi^2) = E \left[\tilde{d}^2 \{ \tau(X) - \tau_0 \}^2 + \frac{\delta}{\pi_\delta^2(X)} \left\{ \frac{V\{Y(1)|X, \delta\}}{\pi_A} + \frac{V\{Y(0)|X, \delta\}}{1-\pi_A} \right\} \right].$$

C.3 Proof of Theorem 3

Proof of the double robustness of the ACW estimator

Let $\boldsymbol{\theta} = (\boldsymbol{\eta}, \boldsymbol{\beta}_0, \boldsymbol{\beta}_1)$ denote the vector of nuisance parameters. Note that $\hat{\tau}^{\text{ACW}}$ is the solution to the estimating equation $N^{-1} \sum_{i=1}^N \phi(X_i, A_i, Y_i, \delta_i, \tilde{\delta}_i; \tau, \hat{\boldsymbol{\theta}}) = 0$, where

$$\begin{aligned} \phi(X, A, Y, \delta, \tilde{\delta}; \tau, \boldsymbol{\theta}) = & \frac{\delta}{\pi_\delta(X; \boldsymbol{\eta})} \left[\frac{A \{Y - \mu_{1,\delta}(X; \boldsymbol{\beta}_1)\}}{\pi_A} - \frac{(1-A) \{Y - \mu_{0,\delta}(X; \boldsymbol{\beta}_0)\}}{1 - \pi_A} \right] \\ & + \tilde{\delta}d \{\mu_{1,1}(X; \boldsymbol{\beta}_1) - \mu_{0,1}(X; \boldsymbol{\beta}_0)\} - \tau. \end{aligned}$$

Let $\boldsymbol{\theta}^*$ be the probability limits of $\hat{\boldsymbol{\theta}}$. It suffices to show that $E \left\{ \phi(X, A, Y, \delta, \tilde{\delta}; \tau_0, \boldsymbol{\theta}^*) \right\} = 0$ if either $\pi(X; \boldsymbol{\eta})$ or $\mu_{a,1}(X; \boldsymbol{\beta}_a)$ ($a = 0, 1$) is correctly specified. Under standard regularity conditions for M-estimators, $\hat{\tau}^{\text{ACW}}$ is consistent for τ . Use iterated expectation, we can write

$$\begin{aligned} E \left\{ \phi(X, A, Y, \delta, \tilde{\delta}; \tau_0, \boldsymbol{\theta}^*) \right\} = & E \left[\frac{\delta}{\pi_\delta(X; \boldsymbol{\eta}^*)} \left\{ \frac{AY}{\pi_A} - \frac{(1-A)Y}{1 - \pi_A} \right\} - \tau_0 \right] + \\ & E \left[\left\{ \tilde{\delta}d - \frac{\delta}{\pi_\delta(X; \boldsymbol{\eta}^*)} \right\} \{\mu_{1,1}(X; \boldsymbol{\beta}_1^*) - \mu_{0,1}(X; \boldsymbol{\beta}_0^*)\} \right]. \quad (\text{A12}) \end{aligned}$$

The first term on the left-hand side of (A12) is 0 either one of the $\pi(X; \boldsymbol{\eta})$ or $\mu_{a,1}(X; \boldsymbol{\beta}_a)$ ($a = 0, 1$) is correctly specified, as shown in the proof of consistency in the CW estimators. Now consider the second term on the left-hand side of (A12).

Firstly, if $\pi_\delta(X; \boldsymbol{\eta})$ is correctly specified, we have $\pi_\delta(X; \boldsymbol{\eta}^*) = \pi_\delta(X)$. Take iterated expectation conditional on X , we have the second term on the left-hand side of (A12)

$$\begin{aligned} E \left[\left\{ \tilde{\delta}d - \frac{\delta}{\pi_\delta(X)} \right\} \{\mu_{1,1}(X; \boldsymbol{\beta}_1^*) - \mu_{0,1}(X; \boldsymbol{\beta}_0^*)\} \right] \\ = E \left[\{\mu_{1,1}(X; \boldsymbol{\beta}_1^*) - \mu_{0,1}(X; \boldsymbol{\beta}_0^*)\} E \left\{ \tilde{\delta}d - \frac{\delta}{\pi_\delta(X)} \middle| X \right\} \right] = 0, \end{aligned}$$

as $E \left\{ \tilde{\delta}d - \delta/\pi_\delta(X) \middle| X \right\} = 0$. Thus, (A12) equals to zero.

Secondly, if outcome model $\mu_{a,1}(X; \boldsymbol{\beta}_a)$ ($a = 0, 1$) is correctly specified, we have $\mu_{1,1}(X; \boldsymbol{\beta}_1^*) - \mu_{0,1}(X; \boldsymbol{\beta}_0^*) = \boldsymbol{\gamma}_0^\top \mathbf{g}(X)$. Then the second term on the left-hand side of (A12) satisfies

$$E \left[\left\{ \tilde{\delta}d - \frac{\delta}{\pi_\delta(X)} \right\} \{\mu_{1,1}(X; \boldsymbol{\beta}_1^*) - \mu_{0,1}(X; \boldsymbol{\beta}_0^*)\} \right] = E \left[\boldsymbol{\gamma}_0^\top \left\{ \tilde{\delta}d - \delta/\pi_\delta(X; \boldsymbol{\eta}^*) \right\} \mathbf{g}(X) \right] = 0$$

by the balancing constraint (1). Thus, (A12) equals to zero under this scenario as well. This completes the proof of the double robustness of $\hat{\tau}^{\text{ACW}}$.

C.4 Proof of Theorem 3 and Theorem 4

Proof of local efficiency

Following the empirical process literature, let \mathbb{P}_N denote the empirical measure. For a random variable V , $\mathbb{P}\{f(V)\} = \int f(v)d\mathbb{P}$ is the expectation of $f(V)$ under the true data-generating process. Recall that $Z = (X, A, Y, \delta, \tilde{\delta})$, $\boldsymbol{\theta} = (\boldsymbol{\eta}, \boldsymbol{\beta}_0, \boldsymbol{\beta}_1)$, $\boldsymbol{\theta}^*$ is the probability limits of $\hat{\boldsymbol{\theta}}$ and $\boldsymbol{\theta}_0$ is the corresponding true parameter value. Let

$$\begin{aligned}
\psi(Z; \boldsymbol{\theta}) &= \frac{\delta}{\pi_\delta(X; \boldsymbol{\eta})} \left[\frac{A \{Y - \mu_{1,1}(X; \boldsymbol{\beta}_1)\}}{\pi_A} - \frac{(1-A) \{Y - \mu_{0,1}(X; \boldsymbol{\beta}_0)\}}{1 - \pi_A} \right] \\
&\quad + \tilde{\delta} d \{ \mu_{1,1}(X; \boldsymbol{\beta}_1) - \mu_{0,1}(X; \boldsymbol{\beta}_0) \} \\
&= \frac{\delta}{\pi_\delta(X; \boldsymbol{\eta})} \frac{A \{Y - \mu_{1,1}(X; \boldsymbol{\beta}_1)\}}{\pi_A} + \tilde{\delta} d \mu_{1,1}(X; \boldsymbol{\beta}_1) \\
&\quad - \frac{\delta}{\pi_\delta(X; \boldsymbol{\eta})} \frac{(1-A) \{Y - \mu_{0,1}(X; \boldsymbol{\beta}_0)\}}{1 - \pi_A} - \tilde{\delta} d \mu_{0,1}(X; \boldsymbol{\beta}_0) \\
&=: \psi_1(Z; \boldsymbol{\theta}) - \psi_0(Z; \boldsymbol{\theta}).
\end{aligned}$$

Under the conditions specified in Theorem 3 or the conditions specified in Theorem 4, and assume that $\psi(Z; \boldsymbol{\theta})$ belongs to Donsker classes (van der Vaart and Wellner, 1996; Kennedy, 2016), $\mathbb{P}\psi_1(Z; \boldsymbol{\theta}^*) = \mu_1$, $\mathbb{P}\psi_0(Z; \boldsymbol{\theta}^*) = \mu_0$ and $\mathbb{P}\psi(Z; \boldsymbol{\theta}^*) = \mu_1 - \mu_0 = \tau_0$. Thus,

$$\begin{aligned}
\hat{\tau}^{\text{ACW}} - \tau_0 &= \mathbb{P}_N \psi(Z; \hat{\boldsymbol{\theta}}) - \mathbb{P} \psi(Z; \boldsymbol{\theta}^*) \\
&= (\mathbb{P}_N - \mathbb{P}) \psi(Z; \hat{\boldsymbol{\theta}}) + \mathbb{P} \{ \psi(Z; \hat{\boldsymbol{\theta}}) - \psi(Z; \boldsymbol{\theta}^*) \} \\
&= (\mathbb{P}_N - \mathbb{P}) \psi(Z; \boldsymbol{\theta}^*) + \mathbb{P} \{ \psi(Z; \hat{\boldsymbol{\theta}}) - \psi(Z; \boldsymbol{\theta}^*) \} + o_p(N^{-1/2}). \tag{A13}
\end{aligned}$$

We now show that

$$\mathbb{P} \{ \psi(Z; \hat{\boldsymbol{\theta}}) - \psi(Z; \boldsymbol{\theta}^*) \} = \mathbb{P} \{ \psi_1(Z; \hat{\boldsymbol{\theta}}) - \psi_1(Z; \boldsymbol{\theta}^*) \} - \mathbb{P} \{ \psi_0(Z; \hat{\boldsymbol{\theta}}) - \psi_0(Z; \boldsymbol{\theta}^*) \}$$

is a small order term under conditions in Theorem 3 or Theorem 4. We write

$$\begin{aligned}
\mathbb{P} \{ \psi_1(Z; \hat{\boldsymbol{\theta}}) - \psi_1(Z; \boldsymbol{\theta}^*) \} &= \mathbb{P} \left[\frac{\delta}{\pi_\delta(X; \hat{\boldsymbol{\eta}})} \frac{A \{Y - \mu_{1,1}(X; \hat{\boldsymbol{\beta}}_1)\}}{\pi_A} + \tilde{\delta} d \mu_{1,1}(X; \hat{\boldsymbol{\beta}}_1) - \mu_1 \right] \\
&= \mathbb{P} \left[\left\{ \frac{\delta}{\pi_\delta(X; \hat{\boldsymbol{\eta}})} - 1 \right\} \{ \mu_{1,1}(X) - \mu_{1,1}(X; \hat{\boldsymbol{\beta}}_1) \} + (\tilde{\delta} d - 1) \mu_{1,1}(X; \hat{\boldsymbol{\beta}}_1) \right] \\
&= \mathbb{P} \left[\left\{ \frac{\pi_\delta(X) - \pi_\delta(X; \hat{\boldsymbol{\eta}})}{\pi_\delta(X; \hat{\boldsymbol{\eta}})} \right\} \{ \mu_{1,1}(X) - \mu_{1,1}(X; \hat{\boldsymbol{\beta}}_1) \} \right].
\end{aligned}$$

Similarly, we have

$$\mathbb{P}\{\psi_0(Z; \hat{\boldsymbol{\theta}}) - \psi_0(Z; \boldsymbol{\theta}^*)\} = \mathbb{P}\left[\left\{\frac{\pi_\delta(X) - \pi_\delta(X; \hat{\boldsymbol{\eta}})}{\pi_\delta(X; \hat{\boldsymbol{\eta}})}\right\}\left\{\mu_{0,1}(X) - \mu_{0,1}(X; \hat{\boldsymbol{\beta}}_0)\right\}\right].$$

Therefore, by Cauchy-Schwarz inequality and the positivity of $\pi_\delta(X; \hat{\boldsymbol{\eta}})$, $|\mathbb{P}\{\psi(Z; \hat{\boldsymbol{\theta}}) - \psi(Z; \boldsymbol{\theta}^*)\}|$ is bounded above by

$$\|\pi_\delta(X) - \pi_\delta(X; \hat{\boldsymbol{\eta}})\| \sum_{a \in \{0,1\}} \|\mu_{a,1}(X) - \mu_{a,1}(X; \hat{\boldsymbol{\beta}}_a)\|. \quad (\text{A14})$$

Under the conditions in Theorem 3, if $\pi_\delta(X; \boldsymbol{\eta})$ is a correctly specified parametric model for $\pi_\delta(X)$, then $\|\pi_\delta(X) - \pi_\delta(X; \hat{\boldsymbol{\eta}})\| = O_p(n^{-1/2})$; and if $\mu_{a,1}(X; \boldsymbol{\beta}_a)$ is a correctly specified parametric model for $\mu_{a,1}(X)$, then $\|\mu_{a,1}(X) - \mu_{a,1}(X; \hat{\boldsymbol{\beta}}_a)\| = O_p(n^{-1/2})$. Therefore, the product (A14) is $O_p(n^{-1})$, which makes $\mathbb{P}\{\psi(Z; \hat{\boldsymbol{\theta}}) - \psi(Z; \boldsymbol{\theta}^*)\}$ in (A13) asymptotically negligible. Under the conditions in Theorem 4, the product (A14) is $o_p(n^{-1/2})$ and therefore the term $\mathbb{P}\{\psi(Z; \hat{\boldsymbol{\theta}}) - \psi(Z; \boldsymbol{\theta}^*)\}$ in (A13) is asymptotically negligible. The result follows.

C.5 Proof of Lemma 1

Since $\pi_\delta(X^O) = \pi_\delta(X^C)$ and $V\{Y(a) | X^O\} \leq V\{Y(a) | X^C\}$ for $a = 0, 1$,

$$\begin{aligned} V_1^O &= E \left[\frac{1}{\pi_\delta(X^O)} \left\{ \frac{V\{Y(1) | X^O\}}{\pi_A} + \frac{V\{Y(0) | X^O\}}{1 - \pi_A} \right\} \right] \\ &= E \left[\frac{1}{\pi_\delta(X^C)} \left\{ \frac{V\{Y(1) | X^O\}}{\pi_A} + \frac{V\{Y(0) | X^O\}}{1 - \pi_A} \right\} \right] \\ &\leq E \left[\frac{1}{\pi_\delta(X^C)} \left\{ \frac{V\{Y(1) | X^C\}}{\pi_A} + \frac{V\{Y(0) | X^C\}}{1 - \pi_A} \right\} \right] = V_1^C, \end{aligned}$$

which proves the first part of inequalities.

For the second part, since $V\{Y(a) | X^C, X^I\} = V\{Y(a) | X^C\}$ for $a = 0, 1$,

$$\begin{aligned} V_1^{C+I} &= E \left[\frac{1}{\pi_\delta(X^C, X^I)} \left\{ \frac{V\{Y(1) | X^C, X^I\}}{\pi_A} + \frac{V\{Y(0) | X^C, X^I\}}{1 - \pi_A} \right\} \right] \\ &= E \left[E \left\{ \frac{1}{\pi_\delta(X^C, X^I)} \mid X^C \right\} \left\{ \frac{V\{Y(1) | X^C\}}{\pi_A} + \frac{V\{Y(0) | X^C\}}{1 - \pi_A} \right\} \right] \\ &\geq E \left[\frac{1}{E\{\pi_\delta(X^C, X^I) | X^C\}} \left\{ \frac{V\{Y(1) | X^C\}}{\pi_A} + \frac{V\{Y(0) | X^C\}}{1 - \pi_A} \right\} \right] \\ &= E \left[\frac{1}{\pi_\delta(X^C)} \left\{ \frac{V\{Y(1) | X^C\}}{\pi_A} + \frac{V\{Y(0) | X^C\}}{1 - \pi_A} \right\} \right] = V_1^C, \end{aligned}$$

where the second and third lines are from the double expectation and Jensen's inequality, respectively.

Web Appendix D: Conditions for the Sieves Estimator

Following Hirano et al. (2003), we assume the following regularity conditions on the data generating process and the nuisance functions.

Condition D1 (Distribution of X) Let $\mathcal{X} \subseteq \mathbb{R}^p$ be the support of X . Assume that \mathcal{X} is a Cartesian product of compact intervals, i.e., $\mathcal{X} = \prod_{j=1}^p [l_j, u_j]$, $l_j, u_j \in \mathbb{R}$. The density of X , $f(X)$, is bounded above and below away from 0 on \mathcal{X} .

Condition D2 (Basis functions) There exist constant l and u such that

$$l \leq \rho_{\min}\{\mathbf{g}(X)^\top \mathbf{g}(X)\} \leq \rho_{\max}\{\mathbf{g}(X)^\top \mathbf{g}(X)\} \leq u,$$

almost surely where ρ_{\min} and ρ_{\max} denote the minimum and maximum eigenvalues of a matrix.

Condition D3 (Potential outcomes) The second moment of the potential outcomes are finite. i.e., $E\{Y(a)^2\} < \infty$, for $a = 0, 1$.

Condition D4 (Smoothness) The log sampling score function $\log \pi_\delta(x)$ is s_δ -times continuously differentiable and the outcome mean function $\mu_a(x)$ is s_{μ_a} -times continuously differentiable, $\forall x \in \mathcal{X}$, $a = 0, 1$; The sieves estimators of $\log \pi_\delta(x)$ and $\mu_a(x)$ use a power series; the smoothness condition is $s > 4p$, for $s = s_\delta$ and $s = s_{\mu_a}$ ($a = 0, 1$), respectively.

The constraint $s > 4p$ is required such that ν exists in the following condition for the number of basis functions.

Condition D5 (Number of basis function) The number of basis functions K satisfies $K = O(n^\nu)$, where $p/(2s - 4p) < \nu < 1/4$.

Under the above conditions, the bias of the sieves approximations are $O_p(K^{1-s/(2p)}) = o_p(n^{-1/4})$. Moreover, because $K^4 = o(n)$, the variances of the sieves approximations are $O_p(K/n) = o_p(n^{-1/2})$.

To present regularity conditions for the penalization approach to choosing K , we introduce more notation. Let the support of model parameters be

$$\mathcal{M}_\delta = \{1 \leq j \leq \tilde{K} : \boldsymbol{\eta}_j^* \neq 0\}, \quad \mathcal{M}_a = \{1 \leq j \leq \tilde{K} : \boldsymbol{\beta}_{a,j}^* \neq 0\}, \quad (a = 0, 1).$$

Define $K_\boldsymbol{\eta} = \|\boldsymbol{\eta}^*\|_0$, $K_a = \|\boldsymbol{\beta}_a^*\|_0$ ($a = 0, 1$), $K = \max(K_\boldsymbol{\eta}, K_0, K_1)$, and $\xi_{\min} = \min(\xi, \xi_0, \xi_1)$. Let C , C_1 and C_2 be generic constants. For any $\mathcal{J} \subseteq \{1, \dots, \tilde{K}\}$ and any vector $\boldsymbol{\eta} \in \mathbb{R}^{\tilde{K}}$, let $\boldsymbol{\eta}_{\mathcal{J}}$ be the sub-vector of $\boldsymbol{\eta}$ formed by elements of $\boldsymbol{\eta}$ whose indexes are in \mathcal{J} . Let \mathcal{J}^c be the complement of \mathcal{J} .

Assumption D1 The following regularity conditions hold.

- (A1) The parameter $(\boldsymbol{\eta}^\top, \boldsymbol{\beta}_0^\top, \boldsymbol{\beta}_1^\top)^\top$ belongs to a compact subset in $\mathbb{R}^{3\tilde{K}}$, and $(\boldsymbol{\eta}^{*\top}, \boldsymbol{\beta}_0^{*\top}, \boldsymbol{\beta}_1^{*\top})^\top$ lies in the interior of the compact subset.
- (A2) Let $\epsilon_{\delta,i}(\boldsymbol{\eta}) = \delta_i - \exp\{\boldsymbol{\eta}^\top \mathbf{g}(X_i)\}$. There exists a constant C such that $E\{|\epsilon_{\delta,i}(\boldsymbol{\eta}^*)|^{2+\delta}\} \leq C$ for all i and some $\delta > 0$. There exist constants C_1 and C_2 such that $E[\exp\{C_1|\epsilon_{\delta,i}(\boldsymbol{\eta}^*)|\} | X_i] \leq C_2$ for all i .
- (A3) $\exp^{(1)}\{\boldsymbol{\eta}^\top \mathbf{g}(X_i)\}$, $\exp^{(2)}\{\boldsymbol{\eta}^\top \mathbf{g}(X_i)\}$, and $\exp^{(3)}\{\boldsymbol{\eta}^\top \mathbf{g}(X_i)\}$ (which denote the first, second and third derivative of $\exp\{\boldsymbol{\eta}^\top \mathbf{g}(X_i)\}$, respectively) are uniformly bounded away from ∞ on $\mathcal{N}_{\delta,\tau} = \{\boldsymbol{\eta} \in \mathbb{R}^{\tilde{K}} : \|\boldsymbol{\eta}_{\mathcal{M}_\delta} - \boldsymbol{\eta}_{\mathcal{M}_\delta}^*\| \leq \tau\sqrt{K/n}, \boldsymbol{\eta}_{\mathcal{M}_\delta^c} = 0\}$ for some $\tau > 0$.
- (A4) For $a = 0, 1$, let $\epsilon_{a,i}(\boldsymbol{\beta}_a) = Y_i(a) - m_a\{\boldsymbol{\beta}_a^\top \mathbf{g}(X_i)\}$. There exists a constant C such that $E\{|\epsilon_{a,i}(\boldsymbol{\beta}_a^*)|^{2+\delta}\} \leq C$ for all i and some $\delta > 0$. There exist constants C_1 and C_2 such that $E[\exp\{C_1|\epsilon_{a,i}(\boldsymbol{\beta}_a^*)|\} | X_i] \leq C_2$ for all i .
- (A5) For $a = 0, 1$, $m_a^{(1)}\{\boldsymbol{\beta}_a^\top \mathbf{g}(X)\}$, $m_a^{(2)}\{\boldsymbol{\beta}_a^\top \mathbf{g}(X)\}$, and $m_a^{(3)}\{\boldsymbol{\beta}_a^\top \mathbf{g}(X)\}$ (which denote the first, second and third derivative of $m_a\{\boldsymbol{\beta}_a^\top \mathbf{g}(X)\}$, respectively) are uniformly bounded away from ∞ on $\mathcal{N}_{a,\tau} = \{\boldsymbol{\beta}_a \in \mathbb{R}^{\tilde{K}} : \|\boldsymbol{\beta}_{a,\mathcal{M}_a} - \boldsymbol{\beta}_{a,\mathcal{M}_a}^*\| \leq \tau\sqrt{K/n}, \boldsymbol{\beta}_{a,\mathcal{M}_a^c} = 0\}$ for some $\tau > 0$.
- (A6) $\min_{j \in \mathcal{M}_\delta} |\eta_j^*|/\xi \rightarrow \infty$ and $\min_{j \in \mathcal{M}_a} |\beta_{a,j}^*|/\xi_a \rightarrow \infty$, ($a = 0, 1$) as $n \rightarrow \infty$.
- (A7) $K = o(n^{1/3})$, $\xi_{\min} \rightarrow 0$, $(\log n)^2 = o(n\xi_{\min}^2)$, $\log(\tilde{K}) = o\{n\xi_{\min}^2/(\log n)^2\}$, $\tilde{K}K^4(\log n)^6 = o(n^3\xi_{\min}^2)$, $\tilde{K}K^4(\log n)^8 = o(n^4\xi_{\min}^4)$, as $n \rightarrow \infty$.

These assumptions are typical in the penalization literature. Assumptions (A2) and (A4) hold for Gaussian distribution, sub-Gaussian distribution, and so on. Assumptions (A3) and (A5) hold for common models. Assumption (A7) specifies the restrictions on the initial number of sieves functions \tilde{K} and the maximum dimension of the true nonzero coefficients K . To gain insight, when the true model size $K = O(n^\nu)$, where ν satisfies Condition D5, then $\tilde{K} = O(n^{\tilde{\nu}})$ with $\tilde{\nu} < 2 - 4\nu$ meets the (A7) requirement.

Web Appendix E: Simulation Study

E.1 Simulation Details

In this section, we evaluate the finite sample performances of the proposed estimators via a set of simulation experiments. Covariate $X \in \mathbb{R}^5$ is generated from $X_j \sim \mathcal{N}(1, 1)$ for each $j = 1, \dots, 5$. We generate potential outcome according to

$$Y(a)|X = -100 + 27.4aX_3 + 13.7X_4 + 10aX_4 + 13.7X_5 - 10aX_5 + \epsilon,$$

where $\log \epsilon \sim \mathcal{N}(0, 0.25)$ for $a = 0, 1$. Under this setting, the true ATE is $\tau_0 = 27.4$. From the hypothetical RCT eligible population, we generate the indicator of trial participation

according to $\delta \mid X \sim \text{Bernoulli}\{\pi_\delta(X)\}$, where $\log\{\pi_\delta(X)\} = -7.7 + 2X_1 + 0.3X_2 - 0.4X_3$. Note that X_3, X_4, X_5 are outcome predictors, and X_1 is an IV that is highly predictive of trial participation.

By this design, there are approximately $n = 440$ subjects in the RCT sample. The treatment assignment in the RCT sample is $A \sim \text{Bernoulli}(0.5)$. From the observational study population, we select a random sample of size $m = 2000$ to form an observational sample. For subjects in the observational sample, the treatment assignment is generated by $A \mid X \sim \text{Bernoulli}\{e_A(X)\}$, where $\text{logit}\{e_A(X)\} = -X_1 + 0.4X_2 - 0.25X_3 - 0.1X_4 + 0.1X_5$. The actual observed outcome Y is $Y = AY(1) + (1 - A)Y(0)$.

To study the impact of model misspecification, adapting from Kang and Schafer (2007), we define a nonlinear transformation of X to be

$$X^* = [\exp(X_1/10), (X_3 + X_5 + 20)^2, X_2/\{2 + 0.5\exp(X_4)\}, (X_1 + X_4 + 20)^2, 0.5X_2X_3 + X_5]^\top,$$

and further scale and center X^* such that $E(X_j^*) = 1$ and $V(X_j^*) = 1$, for $j = 1, \dots, 5$. Throughout, we use X for fitting models. We assume X^* to be unobserved, but it can be used in the true generative models, in which cases the fitted models are misspecified.

To demonstrate the double robustness of the ACW estimator against parametric model misspecification, we consider $\mathbf{g}_1(X) = (X_1, X_2, X_3, X_4, X_5)^\top$ as the calibration variables in all four scenarios. Moreover, we consider the ACW estimator using sieves estimation, extending $\mathbf{g}_1(X)$ to include further all two-way interaction terms and quadratic terms, i.e. $\mathbf{g}_2(X) = (X_1, \dots, X_5, X_1X_2, \dots, X_4X_5, X_1^2, \dots, X_5^2)^\top$. We compare the proposed outcome-prioritized sieve method, denoted (S^O), with the less efficient method that constructs the sieve basis for $\pi_\delta(X)$ by power series of X and solves penalized estimating equation, denoted (S).

Note that for ACW estimators, the outcome mean functions can be estimated by using either trial sample (A, Y) only or both RCT and observational sample. We denote the former by ACW-t to indicate that only trial data is used and the latter by ACW-b to emphasize the use of both data sources.

We compare the proposed CW and ACW estimators with other ATE estimators in Table 1 in the main paper. We use bootstrap variance estimation for all estimators with $B = 50$. All simulations are based on 1000 Monte Carlo replications; Table S2 summarizes the results.

Table S2: Simulation results under four scenarios. Bias is the empirical bias of point estimates; ESE is the empirical standard error of estimates; MSE is the mean squared error of estimates; RSE is the relative bias (%) of bootstrap standard error estimates; CP is the empirical coverage probability of the 95% confidence intervals.

	Scenario 1: O:C/S:C					Scenario 2: O:C/S:W				
	BIAS	ESE	MSE	RSE(%)	CP(%)	BIAS	ESE	MSE	RSE(%)	CP(%)
Naive	-9.62	2.77	100.23	-0.3	6.7	3.77	2.54	20.69	-0.3	65.1
IPSW	-2.05	9.66	97.44	-24.5	85.9	1.91	11.50	135.81	-30.3	85.2
AIPSW	0.03	0.67	0.45	3.0	95.5	0.03	0.70	0.49	-1.1	94.8
AIPSW(S)	0.03	0.67	0.45	2.9	95.6	0.03	0.70	0.49	-1.2	94.8
SBW	0.51	9.54	91.26	4.9	94.9	0.21	10.56	111.49	-1.8	93.9
CW	0.56	11.25	126.70	-10.1	90.3	0.21	12.48	155.69	-15.3	88.4
ACW-t	0.03	0.68	0.46	2.1	95.2	0.03	0.70	0.49	-1.0	94.6
ACW-t(S)	0.02	0.71	0.50	2.6	95.8	0.03	0.72	0.52	0.4	95.0
ACW-t(S ^O)	0.03	0.67	0.45	3.2	95.7	0.03	0.70	0.48	-1.0	94.3
ACW-b	0.03	0.68	0.46	2.4	95.8	0.03	0.70	0.49	-0.6	94.5
ACW-b(S)	0.03	0.70	0.49	3.8	96.0	0.03	0.72	0.52	0.1	95.9
ACW-b(S ^O)	0.03	0.66	0.44	3.0	95.2	0.03	0.69	0.48	-1.5	95.2

	Scenario 3: O:W/S:C					Scenario 4: O:W/S:W				
	BIAS	ESE	MSE	RSE(%)	CP(%)	BIAS	ESE	MSE	RSE(%)	CP(%)
Naive	20.53	2.52	427.79	-0.8	0.0	5.88	2.51	40.92	-1.7	35.8
IPSW	6.08	11.44	167.69	-30.6	70.6	-0.07	12.96	167.77	-33.3	86.0
AIPSW	-1.84	3.23	13.82	-27.2	75.0	-2.45	3.98	21.87	-35.1	69.1
AIPSW(S)	-0.10	0.84	0.71	-12.1	90.5	-0.07	0.82	0.68	-15.0	90.8
SBW	0.45	8.74	76.48	0.7	93.8	-1.21	9.97	100.69	-1.8	92.5
CW	0.87	11.22	126.58	-16.4	87.4	-1.05	12.48	156.75	-17.9	85.4
ACW-t	-0.15	3.59	12.86	-14.9	90.2	-1.40	3.98	17.77	-17.2	86.6
ACW-t(S)	0.05	1.44	2.07	21.1	96.5	0.05	1.35	1.84	2.7	95.1
ACW-t(S ^O)	-0.04	0.88	0.77	-0.8	94.1	-0.02	0.85	0.72	-5.0	93.4
ACW-b	0.14	3.41	11.62	-15.6	91.4	-1.18	3.65	14.68	-19.5	87.5
ACW-b(S)	0.15	2.37	5.64	3.6	96.6	0.18	2.17	4.74	-1.8	97.0
ACW-b(S ^O)	0.01	0.74	0.54	1.9	95.9	0.01	0.73	0.53	0.6	94.5

E.2 Additional Simulation: Three-way Calibration

In this subsection, we present simulation results of the CW and ACW estimators that achieve the three-way balance between the treated RCT, the control RCT, and the observational sample, similar to Chan et al. (2016). We use the same simulation setting that is described in Web Appendix E.1. Table S3 and Figure S2 summarise the simulation results based on 1000 Monte Carlo replications. It can be seen that three-way calibration is comparable under Scenario 1 and Scenario 2 but more unstable under Scenario 3 and Scenario 4 than the two-way calibration in general.

Table S3: Simulation results of the three-way calibration. Bias is the empirical bias of point estimates; ESE is the empirical standard error of estimates; MSE is the mean squared error of estimates; RSE is the relative bias (%) of bootstrap standard error estimates; CP is the empirical coverage probability of the 95% confidence intervals.

	Scenario 1: O:C/S:C					Scenario 2: O:C/S:W				
	BIAS	ESE	MSE	RSE(%)	CP(%)	BIAS	ESE	MSE	RSE(%)	CP(%)
CW	0.018	0.703	0.493	-3.6	92.4	0.020	0.693	0.480	-1.3	93.7
ACW-t	0.017	0.743	0.552	-6.7	91.9	0.020	0.723	0.522	-3.2	92.7
ACW-t(S)	0.024	0.796	0.634	-2.3	94.1	0.021	0.760	0.578	2.7	95.9
ACW-t(S^O)	0.015	0.695	0.483	-1.2	94.1	0.020	0.689	0.474	0.6	95.1
ACW-b	0.016	0.743	0.552	-6.0	91.8	0.020	0.722	0.522	-3.9	91.8
ACW-b(S)	0.018	0.785	0.615	-0.1	94.4	0.023	0.770	0.593	2.2	96.0
ACW-b(S^O)	0.019	0.687	0.472	-0.1	94.7	0.019	0.683	0.466	1.0	95.4

	Scenario 3: O:W/S:C					Scenario 4: O:W/S:W				
	BIAS	ESE	MSE	RSE(%)	CP(%)	BIAS	ESE	MSE	RSE(%)	CP(%)
CW	0.042	3.293	10.837	-31.4	81.1	-1.333	3.664	15.188	-37.5	75.8
ACW-t	7.105	6.466	92.252	-31.5	54.5	3.282	7.284	63.771	-38.2	69.4
ACW-t(S)	0.221	2.658	7.108	-6.5	96.6	0.292	2.273	5.247	-8.4	95.8
ACW-t(S^O)	0.225	1.277	1.679	-11.3	93.6	0.193	1.109	1.267	-9.4	93.3
ACW-b	2.886	6.631	52.251	-32.5	73.7	0.165	7.314	53.469	-37.3	77.5
ACW-b(S)	0.128	2.883	8.320	33.8	97.4	0.232	2.819	7.994	22.0	96.9
ACW-b(S^O)	0.010	1.154	1.331	-3.4	94.5	0.010	1.223	1.494	-6.5	94.2

E.3 Additional Simulation: Increased Observational Sample Size

We consider increasing the observational sample size to $m = 15,000$ while keeping the RCT sample size and other simulation settings the same as those in Web Appendix E.1. This resembles the data structure of CALGB 9633 and NCDB described in Section 6. Table S4 and Figure S3 summarize the results based on 500 Monte Carlo replications. It can be seen that when the sample sizes are larger, the advantages of our proposed estimators become more obvious. Especially in Scenario 3 and Scenario 4 where outcome models are not correct, the proposed ACW-t(S^O) and ACW-b(S^O) estimators outperform other doubly robust estimators in terms of robustness and efficiency.

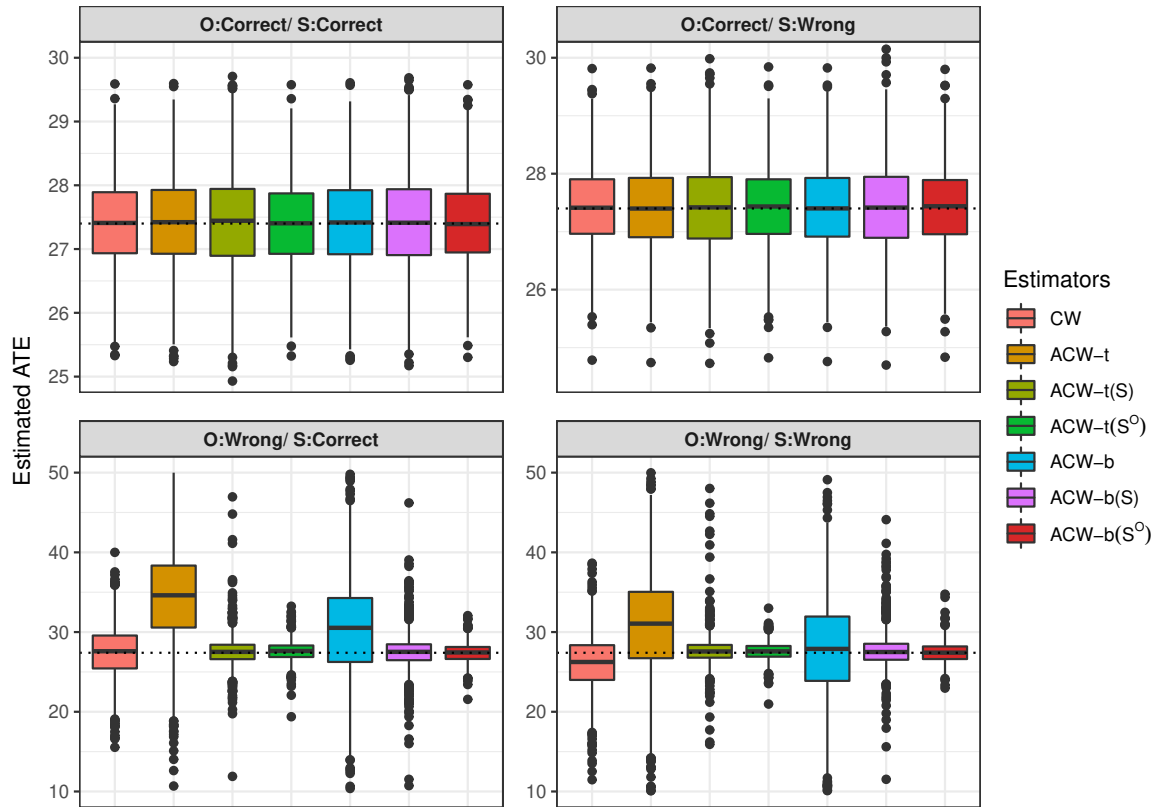


Figure S2: Boxplot of the CW and ACW estimators with three-way calibration between the treated RCT, the control RCT, and the observational sample. We removed a few outliers for visualization.

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Table S4: Simulation results when the observational sample size is 15,000. Bias is the empirical bias of point estimates; ESE is the empirical standard error of estimates; MSE is the mean squared error of estimates; RSE is the relative bias (%) of bootstrap standard error estimates; CP is the empirical coverage probability of the 95% confidence intervals.

	Scenario 1: O:C/S:C					Scenario 2: O:C/S:W				
	BIAS	ESE	MSE	RSE(%)	CP(%)	BIAS	ESE	MSE	RSE(%)	CP(%)
Naive	-9.717	2.876	102.683	-3.5	8.0	3.709	2.534	20.161	0.1	68.6
IPSW	-0.931	10.406	108.927	-22.2	89.2	1.035	13.110	172.598	-30.8	84.2
AIPSW	-0.006	0.263	0.069	-0.6	95.2	0.011	0.256	0.065	3.3	93.8
AIPSW(S)	-0.006	0.267	0.071	-1.6	94.6	0.012	0.265	0.070	2.1	94.8
SBW	0.368	8.615	74.210	14.2	95.6	0.222	10.318	106.305	-2.6	94.0
CW	0.776	10.460	109.792	-5.6	90.2	-0.054	12.271	150.281	-14.8	88.4
ACW-t	-0.005	0.272	0.074	0.3	95.0	0.011	0.263	0.069	4.4	95.8
ACW-t(S)	0.004	0.311	0.096	9.0	95.6	0.009	0.327	0.107	3.3	95.2
ACW-t(S^O)	-0.006	0.246	0.061	4.8	95.8	0.005	0.236	0.056	7.4	96.4
ACW-b	-0.005	0.273	0.075	0.0	94.8	0.010	0.263	0.069	4.3	95.0
ACW-b(S)	0.000	0.316	0.100	9.1	96.4	0.019	0.316	0.100	9.1	96.4
ACW-b(S^O)	0.001	0.245	0.060	3.4	94.8	0.004	0.236	0.056	6.5	96.6

	Scenario 3: O:W/S:C					Scenario 4: O:W/S:W				
	BIAS	ESE	MSE	RSE(%)	CP(%)	BIAS	ESE	MSE	RSE(%)	CP(%)
Naive	20.481	2.613	426.273	-3.9	0.0	5.924	2.553	41.594	-4.1	35.2
IPSW	3.504	12.013	156.306	-33.7	77.2	-1.697	12.673	163.171	-29.3	87.0
AIPSW	-1.240	3.369	12.866	-27.8	81.8	-2.060	4.721	26.490	-37.8	77.2
AIPSW(S)	-0.084	0.676	0.463	-22.7	87.6	-0.023	0.742	0.550	-31.9	85.6
SBW	0.693	8.244	68.304	4.3	93.6	-1.361	9.863	98.928	-3.1	92.6
CW	0.894	11.174	125.400	-18.2	84.2	-1.375	12.375	154.728	-17.2	85.6
ACW-t	-0.146	3.505	12.283	-14.6	91.2	-1.298	4.190	19.205	-20.5	87.2
ACW-t(S)	-0.049	2.343	5.479	-33.9	95.0	0.042	1.119	1.252	9.9	94.8
ACW-t(S^O)	-0.055	0.694	0.483	-1.6	95.0	0.001	0.675	0.455	-10.7	93.4
ACW-b	0.160	3.318	11.010	-15.1	92.2	-1.261	3.792	15.939	-22.0	87.2
ACW-b(S)	0.133	2.169	4.715	0.2	97.2	0.091	1.141	1.307	63.8	97.2
ACW-b(S^O)	-0.032	0.574	0.329	-5.3	94.6	0.034	0.565	0.320	-3.5	95.2

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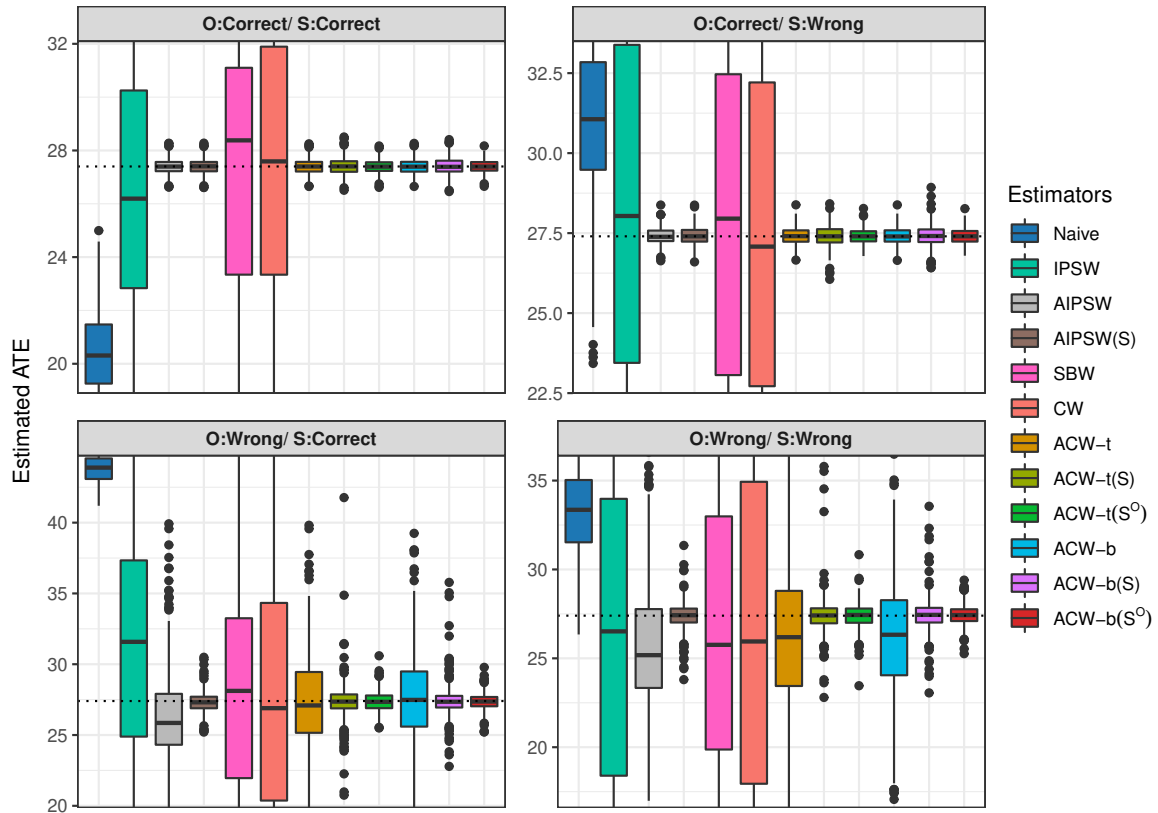


Figure S3: Boxplot of estimators with increased observational study sample size. We removed a few outliers for visualization.

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