Covariate Adjustment in Randomized Experiments with Incomplete Baseline Data

Chia-Rui Chang\textsuperscript{1}, Yue Song\textsuperscript{1}, Fan Li\textsuperscript{2}, Rui Wang\textsuperscript{1,3}

\textsuperscript{1}Department of Biostatistics, Harvard T. H. Chan School of Public Health, Massachusetts, USA
\textsuperscript{2}Department of Statistical Science, Duke University, North Carolina, USA
\textsuperscript{3}Department of Population Medicine, Harvard Pilgrim Health Care Institute and Harvard Medical School, Massachusetts, USA

Abstract

When analyzing data from randomized clinical trials, covariate adjustment can be used to account for chance imbalance in baseline characteristics and to increase precision of the treatment effect estimate. A practical barrier to covariate adjustment is the presence of missing data in covariates, which raise various questions in implementation. In this paper we review several covariate adjustment methods with incomplete data, including complete data analysis and imputation-based methods, and investigate the implications of the missing data mechanism on estimating the average treatment effect in randomized clinical trials with continuous or binary outcomes. We consider both the outcome regression and propensity score weighting adjustment methods. We conduct comprehensive simulation studies to compare these methods. We find that performing adjustment with imputed covariates, regardless of adjustment method or imputation method, generally improves the precision of treatment effect estimates when the proportion of missingness is not too large and the adjusted covariate is associated with the outcome. Furthermore, we underscore the importance of including the missingness indicators as predictors in the outcome model or the propensity score model especially when covariates are missing not at random.

\textbf{Keywords}— covariate balance, imputation, missingness indicator, outcome regression, overlap weighting, propensity score

1 Introduction

Randomized controlled trials (RCT) are the gold standard for evaluating the efficacy and safety of new treatments. Randomization ensures both measured and unmeasured confounders are balanced in large samples. However, chance imbalance of patient baseline characteristics may occur due to the random
nature in allocating the treatment (Senn, 1989; Ciolino et al., 2015), especially when the sample size is small (Thompson et al., 2015). Adjusting for imbalanced covariates, particularly the ones that are predictive of the outcome, i.e. prognostic risk factors, in analysis can increase precision in estimating the treatment effects as well as improve face validity (Ciolino et al., 2015; Pocock et al., 2002; Lin, 2013). One common method for covariate adjustment in RCT is (outcome) regression adjustment (Yang and Tsiatis, 2001; Kahan et al., 2016; Leon et al., 2003; Tsiatis et al., 2008; Zhang et al., 2008) where the outcome is regressed on the treatment and covariates (Tsiatis et al., 2008; Lin, 2013), and the treatment effect is estimated by the coefficient of the treatment variable. This is also known as the analysis of covariance (ANCOVA) method. Recently, propensity score weighting has been proposed as an alternative covariate adjustment method with several conceptual and practical advantages (Williamson et al., 2014; Shen et al., 2014; Colantuoni and Rosenblum, 2015; Zeng et al., 2021). The two methods are shown to be asymptotically equivalent (Williamson et al., 2014; Zeng et al., 2021) and empirical analyses also suggest similar finite sample performances in many situations.

A practical barrier to covariate adjustment is the presence of missing data. In particular, this paper focuses on the case that outcomes are fully observed but some baseline covariates are partially observed. In this case, the analysts have several choices of estimating the treatment effect: (i) the unadjusted analysis, where one obtains a simple difference-in-mean estimator without using any covariate information; (ii) the complete-case analysis, where only fully observed units are used in the adjustment, or the complete-covariate analysis, where only fully observed covariates are used in the adjustment; (iii) the missing-indicator method (Groenwold et al., 2012), where one includes a dummy variable for missingness for the partially observed covariate in regression adjustment, and all missing values are set to the same value; (iv) the single imputation method, where one first imputes the missing covariate values and then conducts adjustment on the completed data. A series of questions naturally arise. For example, which of these methods should we choose? Does the potential efficiency gain outweigh the additional uncertainty introduced by imputation? Does the choice of imputation methods and models affect the treatment effect estimates? Does the conclusion vary between different missing data mechanisms and adjustment methods?

A number of papers have investigated these questions (Schemper and Smith, 1990; White and Thompson, 2005; Groenwold et al., 2012; Sullivan et al., 2018; Kayembe et al., 2020, 2022). A consensus is that the complete-case analysis should be avoided. White and Thompson (2005) showed that the missing-indicator method generally performs well regardless of whether missingness of baseline covariates is predictive of the outcome, whereas mean imputation is adequate when missingness is completely random (MCAR). Groenwold et al. (2012) clarified that the missing-indicator method is valid for randomized experiments and obeys the intention-to-treat principle, but it leads to bias in observational studies, a fact that was pointed out earlier (Greenland and Finkle, 1995). Sullivan et al. (2018) and Kayembe et al. (2020) investigated the use of the popular multiple imputation (MI) (Rubin, 1987) method in regression adjustment;
both concluded that MI does not improve over simpler imputation methods in most cases. An important theoretical development is due to Zhao and Ding (2021), who derived some first theoretical results on outcome regression adjustment method in RCT. Specifically, they proposed a modified missing-indicator method, where one imputes the missing covariates with zeros and then applies Lin (2013) regression estimator, which postulates an outcome model including all the imputed covariates, the missing indicators, and the covariate-treatment interactions. They show that this method is asymptotically more efficient than the unadjusted, complete-covariate and the single imputation method. They also find that, somewhat surprisingly, the choice of imputation method and the validity of the imputation model, matters little, that is, simple imputation by a constant leads to similar precision gain as imputations based on correctly specified models.

Despite the above advancements, covariate adjustment with missing covariates still has not been widely adopted in practice. And a few important questions remain. First, finite-sample performance of the modified missing-indicator method of Zhao and Ding in comparison to the alternatives has not been fully investigated. Second, propensity score weighting has been advocated as a outcome-model-free and asymptotically equivalent alternative to regression adjustment, but it is unclear how to accommodate partially missing covariates in this approach. Third, it remains to be seen whether the asymptotic equivalence between outcome regression and propensity score weighting extends to the case with missing covariates.

In this paper we aim to answer these questions. We will first briefly review covariate adjustment methods with complete data in Section 2. We then discuss these adjustment methods in the presence of missing covariates and provide intuition into the role of the missingness indicators. In particular, we present how to conduct propensity score weighting adjustment with missing covariates (Section 3). In Section 4 we conduct extensive simulation studies to compare these methods under various missing data mechanisms. In Section 5 we apply the methods to the Childhood Adenotonsillectomy Trial (CHAT) (Marcus et al., 2013) and illustrate one way to assess how the magnitude of potential efficiency gain vary according to the proportion of missingness and the covariate’s association with the outcome.

## 2 Covariate adjustment with complete data

Consider a randomized trial with two arms and \( N \) patients, where \( N_1 \) and \( N_0 \) patients are randomized into the treatment and control arm, respectively. Let \( Z_i = z \) be the binary treatment indicator, with \( z = 1 \) indicates treatment and \( z = 0 \) control. Under the potential outcome framework (Neyman, 1923) and the stable unit treatment value assumption (SUTVA), each unit has two potential outcomes \( \{Y_i(1), Y_i(0)\} \), corresponding to the treatment and control condition, respectively. For each unit, only the potential outcome under the actual assigned condition is observed, denoted by \( Y_i = Z_iY_i(1) + (1 - Z_i)Y_i(0) \).

In randomized trials, a collection of \( p \) baseline variables are recorded for each unit, denoted by \( X_i = \).
A common causal estimand is the average treatment effect (ATE):}

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

(1)

In randomized controlled trials, the treatment \(Z\) is randomly assigned with fixed probability \(r\), that is \(\Pr(Z_i = 1|X_i, Y_i(1), Y_i(0)) = \Pr(Z_i = 1) = r\). Under randomization, we have \(\tau = E(Y_i|Z_i = 1) - E(Y_i|Z_i = 0)\), and thus an unbiased estimator of the ATE is the unadjusted difference-in-means estimator: 

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

Previous research has shown that adjusting for chance imbalance in covariates that are predictive of the outcome, namely prognostic covariates, can substantially improve statistical efficiency over the unadjusted estimator.

There are two classes of covariate adjustment methods in randomized trials. The first class is outcome regression (Yang and Tsiatis, 2001; Kahan et al., 2016; Leon et al., 2003; Tsiatis et al., 2008; Zhang et al., 2008; Lin, 2013)—also known ordinary least square (OLS) regression—based on the analysis of covariance (ANCOVA) models, where the outcome is regressed on the treatment and covariates and the treatment effect is estimated by the coefficient of the treatment variable (Yang and Tsiatis, 2001; Leon et al., 2003; Tsiatis et al., 2008). Lin (2013) showed that for efficient outcome regression adjustment it is critical to include the full set of covariate-treatment interactions in the ANCOVA model. When the randomization probability is 1/2, ANCOVA returns consistent point and interval estimates even if the outcome model is misspecified (Yang and Tsiatis, 2001; Lin, 2013; Wang et al., 2019). However, misspecification of the outcome model can decrease precision in unbalanced experiments with treatment effect heterogeneity (Freedman, 2008). Despite of the asymptotic argument, including a full set of covariate-treatment interactions sometimes leads to higher variance in small samples. ANCOVA models can also lead to unstable estimates when applied to rare binary outcomes (Zeng et al., 2021). Moreover, some practitioners prefer to avoid outcome modeling in RCT analysis.

The second class of covariate adjustment methods is propensity score weighting (Williamson et al., 2014; Shen et al., 2014; Colantuoni and Rosenblum, 2015; Zeng et al., 2021). The general form of a weighted estimator for the ATE is

\[
\hat{\tau}_w = \frac{\sum_{i=1}^{n} w_1(x_i) Z_i Y_i}{\sum_{i=1}^{n} w_1(x_i) Z_i} - \frac{\sum_{i=1}^{n} w_0(x_i)(1 - Z_i) Y_i}{\sum_{i=1}^{n} w_0(x_i)(1 - Z_i)},
\]  

(2)

where \(w_1(x) = h(x)/e(x), w_0(x) = h(x)/(1 - e(x))\) are any type of balancing weights (Li et al., 2018), \(e(x) = \Pr(Z_i = 1|X_i = x)\) is the propensity score, i.e., the conditional probability of treatment given the covariates (Rosenbaum and Rubin, 1983), and \(h(x)\) is a pre-specified function of the covariates, known as the tilting function (Li and Li, 2019). In RCT, the true propensity score is known and usually fixed at \(e_i(x) = \Pr(Z_i = 1) = r\) for all units. In that case, one can show that the weighting estimator \(\hat{\tau}_w\) is unbiased for the ATE \(\tau\) regardless of the specific choice of \(h(x)\) as long as \(h(x)\) is a function of
the propensity score $e(x)$. Two examples of the balancing weights are (i) inverse probability weights (IPW): $(w_1, w_0) = (1/e(x), 1/(1 - e(x)))$, obtained by $h(x) = 1$ [Williamson et al. 2014; Shen et al. 2014; Colantuoni and Rosenblum 2015]; and (ii) overlap weights (OW): $(w_1, w_0) = (1/e(x), 1/(1 - e(x)))$, obtained by $h(x) = e(x)/(1 - e(x))$ (Li et al., 2018, 2019; Zeng et al., 2021). In the context of covariate adjustment, the propensity score $e_i$ in the weighting estimator (2) is replaced by a working propensity score $\hat{e}_i = e(X_i; \hat{\theta})$, estimated from a “working” logistic model

$$e_i = e(X_i; \theta) = \frac{\exp(\theta_0 + X_i^T \theta_1)}{1 + \exp(\theta_0 + X_i^T \theta_1)}, \quad (3)$$

with parameters $\theta = (\theta_0, \theta_1^T)^T$ and $\hat{\theta}$ being the maximum likelihood estimate of $\theta$. For example, the OW estimator for ATE is

$$\hat{\tau}_{OW} = \frac{\sum_{i=1}^n (1 - \hat{e}_i) Z_i Y_i}{\sum_{i=1}^n (1 - \hat{e}_i) Z_i} - \frac{\sum_{i=1}^n \hat{e}_i (1 - Z_i) Y_i}{\sum_{i=1}^n \hat{e}_i (1 - Z_i)} \quad (4)$$

OW has a unique exact balance property: when the propensity scores are estimated from a logistic model, the weighted average of any predictor in the model is exactly the same between the treatment and control arms [Li et al. 2018].

Zeng et al. (2021) proved that the weighting estimator $\hat{\tau}_w$ with any balancing weights is asymptotically equivalent to the efficient ANCOVA estimator for continuous outcomes. They further demonstrated via analytical derivations and simulations that the exact balance property of OW improves finite-sample efficiency in estimating ATE compared to IPW. Therefore, we will focus on OW in the next section.

Weighting methods have two practical advantages comparing to outcome regression adjustment. First, weighting obviates the need to specify an outcome model, and has the same form for all types of outcome. This is particularly desirable in handling rare binary or categorical outcomes, where outcome regression can fail to converge. Second, specification of the propensity score model is usually simpler than that of the outcome model because the former does not include covariate-treatment interactions; this can be beneficial for finite-sample performance when the sample size is small. Moreover, because weighting only involves modeling the baseline data, conceptually it might be more appealing to analysts who would avoid modeling the outcome data.

3 Covariate adjustment with incomplete baseline data

We introduce some additional notations in the presence of incomplete baseline data. For each unit $i(i = 1, \ldots, n)$ and covariate $j(j = 1, \ldots, p)$, let $R_{ij}$ be the missingness indicator, with $R_{ij} = 1$ if that value is observed and 0 if missing. Let $R_j = (R_{1j}, \ldots, R_{nj})^T$ be the missingness indicator variable for covariate $X_j$. The missingness pattern $R$ partitions the covariates $X$ into the observed and missing parts, denoted by $X_{obs}$ and $X_{mis}$, respectively. If covariate $X_j$ has missing data, let $X_j^{imp}$ denote that covariate with $X_{mis}$ being replaced by imputed values based on some imputation method.
We first classify the missingness mechanisms in our context. Using Rubin’s definition (Rubin, 1976), missing completely at random (MCAR) is when the missingness is independent of all variables, observed or unobserved: \( \Pr(R|X, Z, Y) = \Pr(R) \). In general settings, missing at random (MAR) means that the missingness can be dependent on observed data but not on unobserved data. Because outcomes are measured after the baseline covariates are measured, the missingness of baseline covariates cannot be caused by the outcome. Therefore, we consider a restricted MAR where the missingness of covariates depends on the observed baseline covariates and treatment, but not on the unobserved covariate values or the outcome, namely \( \Pr(R|X, Z, Y) = \Pr(R|X_{obs}, Y) \). If the missingness is dependent on the unobserved values even after conditional on the observed covariates and treatment, then it is missing not at random (MNAR).

When the baseline data are partially observed, the complete-case analysis should be avoided as it often leads to large bias as well as loss of sample size (White and Thompson, 2005). The complete-covariate approach is not subject to bias and may increase the precision compared to the unadjusted estimator. However, it is also restricted because a covariate, even if highly predictive of outcome, can be excluded if the values are missing for only a few units.

A more flexible approach is to first impute the missing covariates and then apply a covariate adjustment method to the imputed data. An important question is what kind of imputation method should be used and whether the results are sensitive to the imputation method. There are two common imputation methods: (i) imputation by constant: impute all missing values of a covariate by a constant, e.g. zero or the mean of the observed values of that covariate (i.e. mean imputation); (ii) model-based imputation: for a covariate \( X_j \) with missing values, fit a regression model of \( X_j \) predicted by other covariates. A popular model-based imputation method is multiple imputation by chained equations (MICE) (van Buuren et al., 2006), which iteratively imputes every incomplete covariate by all the rest covariates based on a regression model. In generic analysis setting with missing data, multiple imputation is often preferred over single imputation because it readily takes into account of uncertainty of imputed values (Rubin, 1987). The context of covariate adjustment in RCT requires considerations distinct from the generic settings. Specifically, because covariate adjustment is usually a “bonus” analysis of RCT, complex imputation methods such as MICE, which require additional modeling and computation, would likely deter practitioners; therefore, usually simple methods are preferred.

We now discuss the outcome and propensity score model for covariate adjustment once the missing covariate values are imputed. Here the missing data indicators \( R \) play an important role and we provide some intuition. When the missing data mechanism is either MACR or MAR, the missing data indicators are not predictive of the outcome. Therefore, adjusting for these indicators generally would not improve the precision of treatment effect estimates. The MNAR scenario is different. Consider a MNAR case where there is a covariate that is predictive of a unit’s outcome and also his/her propensity to missing data, and that covariate is not fully observed. As a hypothetical example, suppose that older patients...
are more likely to have a higher outcome value, and also tend to fail to report some covariates, but age is missing for some patients. In this case, the missing data indicator is a strong predictor of the outcome, and thus ensuring its balance would improve the efficiency of estimating treatment effect. A more technical explanation is given by Rosenbaum and Rubin (1984): they proposed the generalized propensity score for incomplete covariate data, \( e(X_{obs}, R) = \Pr(Z = 1 \mid X_{obs}, R) \), and showed that balancing \( e(X_{obs}, R) \) would balance both observed covariates and the missingness pattern, regardless of the missing data mechanism. This intuition is confirmed by simulations (White and Thompson, 2005) and theory (Zhao and Ding, 2021) in the context of regression adjustment, but is yet to investigated under propensity score weighting.

In practice, we do not know the missing data mechanism, so it would be safe to adjust for the missing data indicators \( R \) besides the prognostic covariates in either the outcome or the propensity score model. For simplicity, below we omit the fully observed covariates in the models but stress that prognostic covariates should always be included. For the outcome regression method with imputed missing covariates, the ANCOVA model is:

\[
Y \sim Z + X^{imp} + R + Z(X^{imp} + R),
\]

where \( X^{imp} \) is the centered covariate with imputed data. The coefficient of \( Z \) is the estimated treatment effect.

For the propensity score weighting method, we suggest to use the following model to estimate the working generalized propensity score:

\[
\logit\{e(X, R)\} = \theta_0 + \theta_1 X^{imp} + \theta_2 R + \theta_3 X^{imp} R,
\]

and then plug in the estimated propensity score to formula (4) to estimate the treatment effect. For any covariate with missing data, the interaction term \( X^{imp} R \) effectively imputes all the missing values as 0. Therefore, arbitrarily imputed values \( X^{imp} \) would result in the same interaction term. This implies that if we impute all the missing values by zero, then \( X^{imp} R = X^{imp} \) and model (6) leads to an identical fit as this model:

\[
\logit\{e(X, R)\} = \theta_0^* + \theta_1^* X^{imp} + \theta_2^* R.
\]

In fact, this equivalence also approximately holds if we impute all the missing values by any constant, but not so if we use model-based imputation because the imputed values vary between units. In practice, we prefer mean imputation (or median in categorical variables) over zero imputation because for categorical variables, the imputed zeros are indistinguishable from the actual zeros, which may cause confusion.

Below we generalize the exact balancing property of overlap weighting to the case with missing covariates. For simplicity in notation, we present the proposition with only one covariate, which is straightforward to be extended to multiple covariates.
Proposition 1 Assume the working propensity scores are estimated from the logistic regression model (6): 
\[ \hat{e}_i = \{1 + \exp[-(\hat{\theta}_0 + \hat{\theta}_1 X_{i1}^{imp} + \hat{\theta}_2 R_i + \hat{\theta}_3 X_{i2}^{imp} R_i)]\}^{-1}, \]
where \( \hat{\theta} \) is the maximum likelihood estimate of the model coefficients. Then the resulting overlap weights lead to exact balance in the means of any predictor, denoted by \( V \), in the variable set \( (X^{imp}, R, X^{imp} R) \), between the treatment and control groups. That is,
\[ \sum_i V_i Z_i (1 - \hat{e}_i) = \sum_i V_i (1 - Z_i) \hat{e}_i. \] (8)
The proof follows the same as that in Li et al. (2018) and thus is omitted. Similar to the case with complete covariates, this exact balance property is the key to improve the finite-sample efficiency over other weighting methods (Zeng et al., 2021).

4 Simulations

We conduct extensive simulations to investigate the finite-sample performance of a variety of covariate adjustment methods with different imputation methods. In particular, we examine these questions: (i) Is the choice of imputation methods important for efficiency? Does misspecified imputation models decrease efficiency? (ii) Does the asymptotic equivalence between outcome regression and propensity score weighting extend to the case with missing covariates and translate into finite-sample similarities?

4.1 Simulation Studies with Continuous Outcome

We first focus on the setting with continuous outcomes. We consider a setting with \( p = 3 \) baseline covariates, \( X_i = (X_{i1}, X_{i2}, X_{i3})^T \), among which \( X_1 \) is highly predictive of the outcome but subject to missingness, while \( X_2, X_3 \) are less predictive and completely observed. In practice, this could correspond to the scenario where \( X_1 \) is the baseline measurement of the outcome, and \( X_2, X_3 \) are some other less important covariates. Covariates \( X_{i1}, X_{i2} \) are generated from a bivariate normal distribution with mean \((0, 0)^T\), variance \((1, 1)^T\), and correlation 0.3; \( X_{i3} \) is simulated from a centered Bernoulli distribution, i.e. \( \text{Bern}(0.5) - 0.5 \). Let \( R_{i1} \) denote the missing indicator of \( X_{i1} \) and \( R_{i1} = 1 \) if \( X_{i1} \) is observed and 0 otherwise. We focus on randomized experiments of sample size \( N = 100 \) or 500 with a balanced design \((r = 1/2)\). The potential outcomes are generated from the following linear model: for \( z = 0, 1 \)
\[ Y_i(z) \sim \mathcal{N}(\beta_0 + \alpha z + X_i^T \beta_1 + z X_i^T \beta_2, \sigma_y^2) \] (9)
The observed outcome is set to be \( Y_i = Y_i(Z_i) = Z_i Y_i(1) + (1 - Z_i) Y_i(0) \). Since all covariates have mean 0, the coefficient \( \alpha \) corresponds to the true ATE on the additive scale \( \tau \), and we fix \( \alpha = \tau = 0 \). We set the intercept \( \beta_0 = 0.8 \) and the covariate main effects \( \beta_1 = (3, 0.3, 0.42) \) and the effects of treatment-covariate interactions \( \beta_2 = (0.75, 0.53, 0.38) \). The residual variance \( \sigma_y^2 \) is set to 1.

We generate three types of missing data mechanisms:
1. Missing completely at random (MCAR): $R_{i1} \sim \text{Bern}(q)$

2. Missing at random (MAR): \[
\logit\{\Pr(R_{i1} = 1)\} = \gamma_0 + \gamma_1 X_{i2} + \gamma_2 X_{i3}
\]

3. Missing not at random (MNAR): \[
\logit\{\Pr(R_{i1} = 1)\} = \zeta_0 + \zeta_1 X_{i1}
\]

We fix $\gamma_1 = \gamma_2 = \zeta_1 = -1$, and for each missing mechanism, we simulate data with approximately 10% or 30% of missingness in $X_{i1}$ through varying the values of $q, \gamma_0, \zeta_0$ respectively.

To summarize, our simulation scenarios consist of $2 \times 2 \times 3 = 12$ combinations of the total sample size (2 levels), the missing proportion (2 levels) and the missing data mechanism (3 levels), and for each scenario, we conduct covariate adjustment using both OW and ANCOVA. We compare three types of imputation methods: (1) mean imputation; (2) correct model imputation where we impute with the predicted values from the linear model $X_1 \sim X_2$ fitted to those with $X_1$ observed; (3) wrong model imputation where we impute with the predicted values from the linear model $X_1 \sim X_2 + X_3$. For each type of imputation methods, covariate adjustment is performed both with and without the missing indicators. That is, for ANCOVA, we compare the model $Y \sim Z + X_1^{imp} + X_2 + X_3 + Z(X_1^{imp} + X_2 + X_3)$ with $Y \sim Z + X_1^{imp} + X_2 + X_3 + R_1 + Z(X_1^{imp} + X_2 + X_3 + R_1)$. And for OW, the propensity score model without missing indicator is $\logit\{\Pr(Z = 1)\} \sim X_1^{imp} + X_2 + X_3$, and with missing indicator it becomes $\logit\{\Pr(Z = 1)\} \sim X_1^{imp} + X_2 + X_3 + R_1$. Additionally, we include two types of complete data analysis (complete-unit and complete-covariate), as well as an unattainable ideal case where ANCOVA/OW is applied to the full data with no missingness. The resulting estimators of $\tau$ are evaluated in terms of their empirical bias and efficiency. The relative efficiency is defined as the ratio between the Monte Carlo variance of the unadjusted estimator to that of the unadjusted estimator. The higher the relative efficiency, the more efficient that estimator is compared to the unadjusted estimator.

Table 1 summarizes the simulation results for sample size $n = 100$. All approaches produce nearly unbiased estimates of the ATE except for the complete-unit approach under the MAR and MNAR settings, where the magnitude of bias increases as the proportion of missing increases from 10% to 30%. Overall, performing covariate adjustment using either ANCOVA or OW improves efficiency over the unadjusted estimators, and adjustment with imputed $X_1$ results in further efficiency gain over adjustment with complete covariates only. On the other hand, comparisons among different imputation methods render minimal differences, which echoes the theoretical results by Zhao and Ding (2021). Inclusion of the missing indicator in the ANCOVA or the propensity score model does not appear to impact efficiency much under MCAR and MAR, as seen in Kayembe et al. (2022), but can substantially improve efficiency under the MNAR setting. Similar trends are observed for sample size $n = 500$ and the results are provided in table 2.
| Method                        | MCAR Bias | MCAR RE | MAR Bias | MAR RE | MNAR Bias | MNAR RE |
|-------------------------------|------------|---------|----------|--------|-----------|---------|
| N = 100, 30% missing          |            |         |          |        |           |         |
| Full data                     | .00        | .00     | 11.22    | 11.04  | .00       | 11.22   |
| Complete covariate            | .02        | .02     | 1.20     | 1.20   | .02       | 1.20    |
| Complete unit                 | .00        | .00     | 7.78     | 7.66   | .20       | 7.77    |
| Mean imputation w/o MI        | .01        | .01     | 2.92     | 2.92   | .01       | 2.98    |
| Mean imputation w/ MI         | .01        | .01     | 2.91     | 2.92   | .01       | 2.99    |
| Correct model imputation w/o MI | .01    | .01     | 3.05     | 3.04   | .01       | 3.08    |
| Correct model imputation w/ MI | .01    | .01     | 3.05     | 3.05   | .01       | 3.07    |
| Wrong model imputation w/o MI | .01      | .01     | 2.89     | 2.86   | .01       | 2.88    |
| Wrong model imputation w/ MI  | .01      | .01     | 2.85     | 2.86   | .01       | 2.85    |
|                             |            |         |          |        |           |         |
| N = 100, 10% missing          |            |         |          |        |           |         |
| Full data                     | .00        | .00     | 11.22    | 11.04  | .00       | 11.22   |
| Complete covariate            | .02        | .02     | 1.20     | 1.20   | .02       | 1.20    |
| Complete unit                 | .00        | .00     | 10.12    | 9.93   | .07       | 10.17   |
| Mean imputation w/o MI        | .00        | .00     | 5.70     | 5.64   | .00       | 5.61    |
| Mean imputation w/ MI         | .00        | .00     | 5.44     | 5.83   | .00       | 5.52    |
| Correct model imputation w/o MI | .00 | .00     | 5.93     | 5.87   | .00       | 5.94    |
| Correct model imputation w/ MI | .00    | .00     | 5.68     | 6.04   | .00       | 5.73    |
| Wrong model imputation w/o MI | .00      | .00     | 5.68     | 5.58   | .00       | 5.47    |
| Wrong model imputation w/ MI  | .00      | .00     | 5.38     | 5.76   | .00       | 5.32    |

Table 1: Simulation results for continuous outcomes with sample size 100. RE stands for relative efficiency compared to the unadjusted estimator; MI stands for missing indicators. The results are based on 5000 iterations.
| Method                        | Bias ANCOVA | Bias OW | RE ANCOVA | RE OW | Bias ANCOVA | Bias OW | RE ANCOVA | RE OW | Bias ANCOVA | Bias OW | RE ANCOVA | RE OW |
|------------------------------|-------------|---------|-----------|-------|-------------|---------|-----------|-------|-------------|---------|-----------|-------|
| **N = 500, 30% missing**    |             |         |           |       |             |         |           |       |             |         |           |       |
| Full data                    | .00         | .00     | 11.00     | 10.95 | .00         | .00     | 11.00     | 10.95 | .00         | .00     | 11.00     | 10.95 |
| Complete covariate           | .01         | .01     | 1.20      | 1.20  | .01         | .01     | 1.20      | 1.20  | .01         | .01     | 1.20      | 1.20  |
| Complete unit                | .00         | .00     | 7.88      | 7.85  | .21         | .21     | 7.97      | 7.92  | .23         | .23     | 7.77      | 7.74  |
| Mean imputation w/o MI       | .00         | .00     | 2.92      | 2.92  | .00         | .00     | 2.96      | 2.95  | .01         | .01     | 2.50      | 2.49  |
| Mean imputation w/ MI        | .00         | .00     | 2.91      | 2.92  | .00         | .00     | 3.00      | 3.00  | .00         | .00     | 3.41      | 3.41  |
| Correct model imputation w/o MI | .00   | .00     | 3.06      | 3.06  | .00         | .00     | 3.12      | 3.12  | .01         | .01     | 2.60      | 2.60  |
| Correct model imputation w/ MI | .00   | .00     | 3.06      | 3.06  | .00         | .00     | 3.13      | 3.13  | .00         | .00     | 3.49      | 3.49  |
| Wrong model imputation w/o MI | .00   | .00     | 2.90      | 2.90  | .00         | .00     | 2.89      | 2.86  | .00         | .01     | 2.90      | 2.48  |
| Wrong model imputation w/ MI | .00         | .00     | 2.89      | 2.90  | .00         | .00     | 2.90      | 2.90  | .00         | .00     | 3.39      | 3.39  |
| **N = 500, 10% missing**    |             |         |           |       |             |         |           |       |             |         |           |       |
| Full data                    | .00         | .00     | 11.00     | 10.95 | .00         | .00     | 11.00     | 10.95 | .00         | .00     | 11.00     | 10.95 |
| Complete covariate           | .01         | .01     | 1.20      | 1.20  | .01         | .01     | 1.20      | 1.20  | .01         | .01     | 1.20      | 1.20  |
| Complete unit                | .00         | .00     | 9.86      | 9.81  | .07         | .07     | 10.01     | 9.96  | .08         | .08     | 10.05     | 10.02 |
| Mean imputation w/o MI       | .00         | .00     | 5.73      | 5.71  | .00         | .00     | 5.65      | 5.63  | .00         | .00     | 4.50      | 4.49  |
| Mean imputation w/ MI        | .00         | .00     | 5.66      | 5.74  | .00         | .00     | 5.76      | 5.82  | .00         | .00     | 6.21      | 6.28  |
| Correct model imputation w/o MI | .00   | .00     | 5.98      | 5.96  | .00         | .00     | 6.00      | 5.98  | .00         | .00     | 4.82      | 4.81  |
| Correct model imputation w/ MI | .00   | .00     | 5.91      | 5.98  | .00         | .00     | 5.98      | 6.04  | .00         | .00     | 6.44      | 6.51  |
| Wrong model imputation w/o MI | .00   | .00     | 5.71      | 5.70  | .00         | .00     | 5.58      | 5.53  | .00         | .00     | 4.73      | 4.47  |
| Wrong model imputation w/ MI | .00         | .00     | 5.64      | 5.72  | .00         | .00     | 5.67      | 5.73  | .00         | .00     | 6.18      | 6.26  |

Table 2: Simulation results for continuous outcomes with sample size 500. RE stands for relative efficiency compared to the unadjusted estimator; MI stands for missing indicators. The results are based on 5000 iterations.
4.2 Simulation Studies with Binary Outcome

We perform another set of simulations with binary outcomes. We consider a balanced randomization design \((r = 0.5)\), and use the same covariate generating process as in the continuous outcome simulations. The potential outcomes are generated from the following logistic model: for \(z = 0, 1\),

\[
\text{logit}\{\Pr(Y_i(z) = 1)\} = \beta_0 + \alpha z + X_i^T \beta_1 + z X_i^T \beta_2
\]  

(10)

We fixed \(\beta_0 = \alpha = 0\) and \(\beta_1 = (4, 1, 1)^T, \beta_2 = (-3.5, 0.3, 0.3)^T\). Same as before, our target estimand \(\tau\) is the ATE on the additive scale, namely the marginal risk difference between the treatment and control arms. Under the current parameter setup, we have \(\tau = 0\). The simulations for binary outcomes follow the same \(2 \times 2 \times 3\) factorial design as for the continuous outcomes.

Non-collapsibility of odds ratio is a well-known issue for binary outcomes (Greenland et al., 1999). If one applies ANCOVA-type logistic regression model to estimate the marginal risk difference, one needs to first estimate the group means by standardization using the coefficients obtained from the fitted model.

To avoid such complication, we conduct ANCOVA-type covariate adjustment through the standard linear regression, which allows us to directly interpret the coefficient of the treatment indicator as the marginal risk difference. In contrast, implementation of OW is more straightforward and the ATE estimator takes the form in eq (4) for both continuous and binary outcomes. As for continuous outcomes, we compare the same three types of imputation methods, two types of complete data analysis, and the unattainable ideal case described in Section 4.1. We again consider both bias and the relative efficiency to the unadjusted estimator for each estimator.

The results for binary outcomes are presented in table 3 for \(n = 100\) and table 4 for \(n = 500\). In general, results are similar to those from the continuous outcome settings. The ANCOVA and OW estimators perform similarly for all settings with negligible differences. The complete unit analyses can be biased when data are MAR or MNAR. The complete covariate analyses are seen with reduced efficiency in these settings because of the omission of the partially-observed covariate that is predictive of the outcome. As the proportion of missingness increases, the efficiency gain by incorporating this covariate decreases. Incorporating the missing covariate in estimating the ATE in general improves efficiency, even when the imputation model is misspecified. When data are MNAR, including missingness indicator in the model can lead to further efficiency improvement.

12
| Method                      | MCAR Bias | MCAR RE | MAR Bias | MAR RE | MNAR Bias | MNAR RE |
|-----------------------------|-----------|---------|----------|--------|-----------|---------|
|                             | ANCOVA    | OW      | ANCOVA   | OW     | ANCOVA    | OW      |
| Full data                   | .00       | .00     | 1.53     | 1.52   | .00       | .00     | 1.53    | 1.52   |
| Complete covariate          | .00       | .00     | 1.22     | 1.22   | .00       | .00     | 1.22    | 1.22   |
| Complete unit               | .00       | .00     | 1.02     | 1.01   | .02       | .03     | 1.02    | 1.01   |
| Mean imputation w/o MI      | .00       | .00     | 1.40     | 1.39   | .00       | .00     | 1.41    | 1.40   |
| Mean imputation w/ MI       | .00       | .00     | 1.39     | 1.38   | .00       | .00     | 1.40    | 1.40   |
| Correct model imputation w/o MI | .00   | .00     | 1.39     | 1.38   | .00       | .00     | 1.41    | 1.40   |
| Correct model imputation w/ MI | .00 | .00     | 1.39     | 1.38   | .00       | .00     | 1.41    | 1.40   |
| Wrong model imputation w/o MI | .00   | .00     | 1.38     | 1.38   | .00       | .00     | 1.39    | 1.39   |
| Wrong model imputation w/ MI | .00   | .00     | 1.38     | 1.38   | .00       | .00     | 1.42    | 1.42   |

$N = 100, 30\%$ missing

$N = 100, 10\%$ missing

Table 3: Simulation results for binary outcomes with sample size 100. RE stands for relative efficiency compared to the unadjusted estimator; MI stands for missing indicators. The results are based on 5000 iterations.
| Method                        | Bias | RE   | Bias | RE   | Bias | RE   | Bias | RE   |
|------------------------------|------|------|------|------|------|------|------|------|
|                              | ANCOVA | OW | ANCOVA | OW | ANCOVA | OW | ANCOVA | OW | ANCOVA | OW | ANCOVA | OW |
| **N = 500, 30% missing**    |      |      |      |      |      |      |      |      |
| Full data                    | 0.00 | 0.00 | 1.51 | 1.51 | 0.00 | 0.00 | 1.51 | 1.51 | 0.00 | 0.00 | 1.51 | 1.51 |
| Complete covariate           | 0.00 | 0.00 | 1.23 | 1.23 | 0.00 | 0.00 | 1.23 | 1.23 | 0.00 | 0.00 | 1.23 | 1.23 |
| Complete unit                | 0.00 | 0.00 | 1.06 | 1.05 | 0.02 | 0.02 | 1.04 | 1.04 | 0.06 | 0.06 | 1.05 | 1.05 |
| Mean imputation w/o MI       | 0.00 | 0.00 | 1.42 | 1.42 | 0.00 | 0.00 | 1.42 | 1.42 | 0.00 | 0.00 | 1.41 | 1.41 |
| Mean imputation w/ MI        | 0.00 | 0.00 | 1.42 | 1.42 | 0.00 | 0.00 | 1.42 | 1.42 | 0.00 | 0.00 | 1.45 | 1.45 |
| Correct model imputation w/o MI | 0.00 | 0.00 | 1.42 | 1.42 | 0.00 | 0.00 | 1.42 | 1.42 | 0.00 | 0.00 | 1.41 | 1.41 |
| Correct model imputation w/ MI | 0.00 | 0.00 | 1.42 | 1.42 | 0.00 | 0.00 | 1.42 | 1.42 | 0.00 | 0.00 | 1.45 | 1.45 |
| Wrong model imputation w/o MI | 0.00 | 0.00 | 1.42 | 1.42 | 0.00 | 0.00 | 1.42 | 1.42 | 0.00 | 0.00 | 1.41 | 1.41 |
| Wrong model imputation w/ MI | 0.00 | 0.00 | 1.42 | 1.42 | 0.00 | 0.00 | 1.42 | 1.42 | 0.00 | 0.00 | 1.45 | 1.45 |
| **N = 500, 10% missing**    |      |      |      |      |      |      |      |      |
| Full data                    | 0.00 | 0.00 | 1.51 | 1.51 | 0.00 | 0.00 | 1.51 | 1.51 | 0.00 | 0.00 | 1.51 | 1.51 |
| Complete covariate           | 0.00 | 0.00 | 1.23 | 1.23 | 0.00 | 0.00 | 1.23 | 1.23 | 0.00 | 0.00 | 1.23 | 1.23 |
| Complete unit                | 0.00 | 0.00 | 1.36 | 1.36 | 0.01 | 0.01 | 1.36 | 1.35 | 0.02 | 0.02 | 1.36 | 1.35 |
| Mean imputation w/o MI       | 0.00 | 0.00 | 1.47 | 1.47 | 0.00 | 0.00 | 1.49 | 1.48 | 0.00 | 0.00 | 1.48 | 1.48 |
| Mean imputation w/ MI        | 0.00 | 0.00 | 1.47 | 1.47 | 0.00 | 0.00 | 1.49 | 1.48 | 0.00 | 0.00 | 1.48 | 1.48 |
| Correct model imputation w/o MI | 0.00 | 0.00 | 1.47 | 1.47 | 0.00 | 0.00 | 1.49 | 1.48 | 0.00 | 0.00 | 1.49 | 1.49 |
| Correct model imputation w/ MI | 0.00 | 0.00 | 1.47 | 1.47 | 0.00 | 0.00 | 1.49 | 1.48 | 0.00 | 0.00 | 1.50 | 1.50 |
| Wrong model imputation w/o MI | 0.00 | 0.00 | 1.47 | 1.47 | 0.00 | 0.00 | 1.49 | 1.48 | 0.00 | 0.00 | 1.48 | 1.48 |
| Wrong model imputation w/ MI | 0.00 | 0.00 | 1.47 | 1.47 | 0.00 | 0.00 | 1.49 | 1.48 | 0.00 | 0.00 | 1.50 | 1.50 |

Table 4: Simulation results for binary outcomes with sample size 500. RE stands for relative efficiency compared to the unadjusted estimator; MI stands for missing indicators. The results are based on 5000 iterations.
5 Application

The Childhood Adenotonsillectomy Trial (CHAT) (Marcus et al., 2013; Zhang et al., 2018) is a multi-center, single-blind, randomized, controlled trial designed to test whether children, ages 5 to 9.9 years, with mild to moderate obstructive sleep apnea randomized to early adenotonsillectomy (eAT, treatment) will show better neurocognitive functioning than children randomized to watchful waiting with supportive care (WWSC, control). Children were randomized with a 1:1 ratio to both arms. Evaluations of participants were conducted at baseline as well as at 7 month post-baseline. This paper focuses on the change of the score from the Behavior Rating Inventory of Executive Function (BRIEF). Lower BRIEF scores indicate better executive functioning. An unadjusted analysis based on data from 382 children who had valid BRIEF measurements (191 in each arm) reveals that the average decrease in BRIEF score of the eAT arm exceeds that of the WWSC arm by 3.7 points and the difference is statistically significant ($p < .001$). In this section, we investigate whether adjusting for baseline covariates can improve the efficiency of the treatment effect estimation.

Table 5 displays a summary of the baseline demographic and clinical characteristics of the participants in both arms. For each variable, we present the unadjusted absolute standardized difference (ASD) as a measure of baseline imbalance:

$$\text{ASD} = \left| \sum_{i=1}^{N} X_{ij} Z_i / \sum_{i=1}^{N} Z_i - \sum_{i=1}^{N} X_{ij}(1 - Z_i) / \sum_{i=1}^{N} (1 - Z_i) \right| / \sqrt{\frac{\hat{\text{Var}}(X_{ij}|Z_i = 1) + \hat{\text{Var}}(X_{ij}|Z_i = 0)}{2}},$$

where $\hat{\text{Var}}(\cdot)$ denote the sample variance $s^2$ for a continuous variable, and $\hat{p}(1 - \hat{p})$ for a binary variable with empirical prevalence $\hat{p}$. Two binary covariates, gender and tonsil size, have ASD larger than 10%, which has been regarded as a common threshold for imbalance (Austin and Stuart, 2015). In addition, univariate analyses reveal that the baseline BMI z-score, total score from the Pediatric Sleep Questionnaire (PSQ score) and total score from the Obstructive Sleep Apnea Quality of Life Survey (OSA score) are significantly correlated with the outcome ($p < 0.05$). The two covariates with baseline imbalance (gender and tonsil size), together with the three significant correlates of outcome (BMI z-score, PSA score and OSA score) are subsequently included in the covariate adjustment analyses. These covariates exhibit mild missingness ranging from 0.5% to 3.1%, except for gender, which is observed for all participants.
| Baseline categorical covariates (count) | All participants | eAT group | WWSC group | Unadjusted ASD (%) | Missing (p value) | Corr. with outcome (p value) |
|----------------------------------------|-----------------|-----------|------------|---------------------|-----------------|---------------------------|
| Gender (male)                          | 186             | 86        | 100        | .15                 | 0               | -.07 (.16)                |
| Race (black)                           | 205             | 102       | 103        | .01                 | 0               | .04 (.39)                 |
| Tonsil size (0-50%)                    | 94              | 42        | 52         | .12                 | .8              | .06 (.27)                 |
| Family income (<$40000)                | 150             | 73        | 77         | .01                 | 14.1            | -.03 (.62)                |
| Second-hand smoking (yes)              | 120             | 61        | 59         | .02                 | 0               | .06 (.22)                 |
| History of asthma (yes)                | 124             | 61        | 63         | .02                 | 2.4             | -.07 (.15)                |
| History of allergy (yes)               | 161             | 80        | 81         | .02                 | .3              | .00 (.96)                 |
| History of eczema (yes)                | 105             | 53        | 52         | .02                 | .8              | -.02 (.70)                |
| History of prematurity (yes)           | 58              | 27        | 31         | .07                 | 1.3             | .05 (.38)                 |
| Baseline continuous covariates (mean (sd)) |                 |           |            |                     |                 |                           |
| Age (years)                            | 6.5 (1.4)       | 6.6 (1.4) | 6.5 (1.4)  | .03                 | 0               | -.09 (.07)                |
| BMI z-score                            | 9 (1.3)         | 9.1 (1.4) | 9.1 (1.2)  | .01                 | 3.1             | -.14 (.01)                |
| Birth weight (oz)                      | 109.4 (24.1)    | 110.4 (23.5) | 108.5 (24.6) | .08               | 7.1            | -.02 (.65)                |
| PSQ score                              | .5 (.2)         | .5 (.2)   | .5 (.2)    | .01                 | .8              | -.19 (.01)                |
| OSA score                              | 53.6 (18.7)     | 53.5 (18.0) | 53.8 (19.5) | .02               | .5              | -.23 (.01)                |

Table 5: Baseline characteristics of the CHAT study by treatment groups. The unadjusted ASD and correlation with outcome are computed ignoring missing values.

We perform both mean imputation and model-based imputation of the missing covariates. For model-based imputation, we fit linear regression models with all the fully-observed covariates as predictors. We then conduct covariate adjustment using ANCOVA and OW with the 5 selected covariates. The ANCOVA models include main effects of treatment, centered covariates, and centered missing indicators of those covariates with missingness, together with treatment-covariate interactions and treatment-missing-indicator interactions. Correspondingly, the propensity score models contain the covariates and their missing indicators. We contrast both the robust sandwich variance estimate and the bootstrap variance estimates resulted from the covariate adjustment analyses to that from the unadjusted analysis. For ANCOVA, the Eicker–Huber–White robust standard error is used, and according to Lin (2013) and Zhao and Ding (2021), it is asymptotically conservative but serves as a convenient approximation to the true standard error. For OW, the robust standard errors are computed using the R package PSweight developed by Zhou et al. (2020). The complete unit analyses are included for comparison as well. The results are presented in Table 6. The relative efficiency is computed as the ratio of the bootstrap variance of the unadjusted estimate to those of the adjusted ones. Different combinations of imputation methods and adjustment methods produce similar treatment effect estimates, and on average adjusting for these three covariates leads to a 2%-11% of efficiency improvement over the unadjusted analysis.
| Covariates                                      | Method                | \( \hat{\tau} \) | \( \hat{V}_{\text{robust}} \) | Rel.Eff.robust | \( \tilde{V}_{\text{boot}} \) | Rel.Eff.boot |
|------------------------------------------------|-----------------------|-------------------|-------------------------------|----------------|-------------------------------|---------------|
| None                                           | Unadjusted            | -3.70             | .79                           | 1.00           | .80                           | 1.00          |
| Gender, Tonsil size, BMI z-score, PSQ score, OSA score w/o missing indicators | Complete unit         | ANCOVA            | -3.87                         | .77            | 1.03                           | .79           | 1.00          |
|                                                | Ow                    | -3.88             | .76                           | 1.04           | .78                           | 1.02          |
|                                                | Mean imp.             | ANCOVA            | -3.72                         | .73            | 1.08                           | .74           | 1.07          |
|                                                | Ow                    | -3.73             | .72                           | 1.09           | .73                           | 1.09          |
|                                                | Model-based imp.      | ANCOVA            | -3.72                         | .72            | 1.09                           | .74           | 1.08          |
|                                                | Ow                    | -3.72             | .72                           | 1.10           | .73                           | 1.09          |
| Gender, Tonsil size, BMI z-score, PSQ score, OSA score w/ missing indicators | Mean imp.             | ANCOVA            | -3.71                         | .71            | 1.11                           | .74           | 1.07          |
|                                                | Ow                    | -3.73             | .71                           | 1.11           | .73                           | 1.08          |
|                                                | Model-based imp.      | ANCOVA            | -3.70                         | .71            | 1.11                           | .74           | 1.07          |
|                                                | Ow                    | -3.72             | .71                           | 1.11           | .73                           | 1.08          |

Table 6: Modeling results

Through the use of a pseudo variable, we investigate how a covariate’s correlation with the outcome and its level of missingness relate to the amount of possible efficiency gain from adjusting for that covariate. Specifically, we generate \( V_i = \rho \hat{s}_i + \sqrt{(1 - \rho^2)} \hat{v}_s \epsilon_i \), where \( \epsilon_i \) \( \text{iid} \sim N(0, 1) \), \( \hat{s}_i \)'s are the residuals from fitting the unadjusted model \( Y \sim Z \) and \( \hat{v}_s \) is the sample variance of \( \hat{s}_i \). The correlation between the \( V_i \)'s generated in this way and \( Y_i \) is approximately \( \rho \). By removing the effect of \( Z_i \), \( V_i \) is uncorrelated with the randomization indicator \( Z_i \). We then consider missingness of the variable \( V \) following either a MCAR mechanism or a MNAR one where \( \logit\{Pr(Riv = 1)\} = \delta_0 + V_i \). The value of \( \delta_0 \) is varied to achieve specific levels of missingness. The empirical efficiency of the treatment effect estimates resulting from ANCOVA with missing indicators after mean imputation of missing values in \( V \) over repeated experiments is then compared to that of the unadjusted estimators. Fig. 1 shows the contour plot of relative efficiency for varying levels of \( \rho \) and proportions of missingness under MCAR and MNAR. The relative efficiencies are computed as the ratios of the average bootstrap variances of the estimators from covariate adjustment analyses to that from the unadjusted analysis. From the plot for MCAR, we observe that in order to gain a 30% increase in efficiency, the covariate needs to have a correlation of approximately 0.5 or higher with the outcome. The efficiency gain diminishes with increased percentages of missingness, which is expected. The plot for the MNAR case is largely similar.
6 Discussion

When there are missing data in covariates, performing covariate adjustment on the imputed data generally reduces the variance of treatment effect estimate. The magnitude of improvement depends on the proportion of missingness and the strength of the association between the adjusted covariate and the outcome. Because the true missing data mechanism is usually unknown in practice, it is important to add the missingness indicator in the outcome model or propensity score model (depending on the specific adjustment method), but how the missing data is imputed is not important. Also, the simulations suggest that the outcome regression and overlap weighting method lead to similar results in many settings. Therefore, we conjecture that the asymptotic equivalence between the outcome regression and propensity score weighting adjustment methods with complete covariates extends to the case of incomplete data. Nonetheless, the overlap weighting method is arguably more stable and easier to implement than outcome regression for non-continuous outcomes. As a general guideline, in the presence of incomplete covariate data in randomized trials, we recommend analysts to impute all the missing covariate values with mean (or median for categorical variables) and perform a specific covariate adjustment method (either outcome regression or propensity score weighting) on the imputed data, with the outcome or propensity score model including the missingness indicators.

The use of missing indicator method in the context of observational studies has been investigated extensively (Jones 1996; Greenland and Finkle 1995; Song et al. 2021). However, randomized experiments possess unique features that distinct them from observational studies. Heuristically, randomization balances all measured and unmeasured covariates, including the missingness patterns in the baseline covariates, between treatment and control units in large samples. Thus adding the missing indicators in
the outcome regression leads to consistent estimator of the ATE and could improve efficiency when the missingness patterns are predictive of the outcome.

In the current work, we focus on the implications of missing covariate data for estimating the ATE in randomized clinical trials with continuous and binary outcomes, and highlight the practical advantage in implementation of adjustment through propensity score weighting methods especially for binary outcomes. For the setting of missing covariate values in Cox models for a survival outcome, White and Royston compared the use of several imputation models and recommended including the event indicator and the Nelson-Aalen estimator of the cumulative baseline hazard in the imputation model (White and Royston, 2009). Yi et al. (2020) considered Cox regression with survival-time-dependent missing covariate values, proposed an inverse propensity weighting method with the propensity estimated by nonparametric kernel regression, and pointed out the need for further investigation of survival-time-dependent time-varying missingness propensity estimation. Another important direction is to investigate the implication of missing covariate values when performing covariate adjustments in cluster randomized trials, where the unit of randomization is a cluster (such as hospitals) and outcomes and covariates are measured at individual level (Turner et al., 2017). Systematic reviews suggested that the median number of clusters in a CRT is around 20 (Murray et al., 2008). Such small number of clusters renders covariate imbalance is prevalent in CRT. It is critical to differentiate imbalance caused by random chance and by post-randomization selection: the former can be addressed by covariate adjustment but the latter can not and would require additional data and assumptions (Li et al., 2021).

Data Availability Statement

The Childhood Adenotonsillectomy Trial data are available upon reasonable request at https://sleepdata.org.

Acknowledgement

Chang and Wang were partly supported by grant R01 AI136947 from the National Institute of Allergy and Infectious Disease. The Childhood Adenotonsillectomy Trial (CHAT) was supported by the National Institutes of Health (HL083075, HL083129, UL1-RR-024134, UL1 RR024989). The National Sleep Research Resource was supported by the National Heart, Lung, and Blood Institute (R24 HL114473, 75N92019R002).

References

Peter C. Austin and Elizabeth A. Stuart. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. Statistics in Medicine, 34(28):3661–3679, 2015.
Jody D. Ciolino, Renée H. Martin, Wenle Zhao, Michael D. Hill, Edward C. Jauch, and Yuko Y. Palesch. Measuring continuous baseline covariate imbalances in clinical trial data. *Statistical Methods in Medical Research*, 24(2):255–272, 2015.

Elizabeth Colantuoni and Michael Rosenblum. Leveraging prognostic baseline variables to gain precision in randomized trials. *Statistics in Medicine*, 34(18):2602–2617, 2015.

David A. Freedman. On regression adjustments in experiments with several treatments. *The Annals of Applied Statistics*, 2(1):176–196, 2008.

Sander Greenland and William D Finkle. A critical look at methods for handling missing covariates in epidemiologic regression analyses. *American journal of epidemiology*, 142(12):1255–1264, 1995.

Sander Greenland, Judea Pearl, and James M Robins. Confounding and collapsibility in causal inference. *Statistical science*, 14(1):29–46, 1999.

Rolf HH Groenwold, Ian R White, A Rogier T Donders, James R Carpenter, Douglas G Altman, and Karel GM Moons. Missing covariate data in clinical research: when and when not to use the missing-indicator method for analysis. *Canadian Medical Association Journal*, 184(11):1265–1269, 2012.

Michael P Jones. Indicator and stratification methods for missing explanatory variables in multiple linear regression. *Journal of the American statistical association*, 91(433):222–230, 1996.

Brennan C. Kahan, Helen Rushton, Tim P. Morris, and Rhian M. Daniel. A comparison of methods to adjust for continuous covariates in the analysis of randomised trials. *BMC Medical Research Methodology*, 16(1):1–10, 2016.

Mutamba T Kayembe, Shahab Jolani, Frans ES Tan, and Gerard JP van Breukelen. Imputation of missing covariate in randomized controlled trials with a continuous outcome: Scoping review and new results. *Pharmaceutical statistics*, 19(6):840–860, 2020.

Mutamba T Kayembe, Shahab Jolani, Frans ES Tan, and Gerard JP van Breukelen. Imputation of missing covariates in randomized controlled trials with continuous outcomes: Simple, unbiased and efficient methods. *Journal of Biopharmaceutical Statistics*, pages 1–23, 2022.

Selene Leon, Anastasios A Tsiatis, and Marie Davidian. Semiparametric estimation of treatment effect in a pretest-posttest study. *Biometrics*, 59(4):1046–1055, 2003.

F Li, K L Morgan, and A M Zaslavsky. Balancing covariate via propensity score weighting. *Journal of the American Statistical Association*, 113(521):390–400, 2018.

Fan Li and F Li. Propensity score weighting for causal inference with multiple treatments. *The Annals of Applied Statistics*, 13(4):2389–2415, 2019.
Fan Li, Laine E Thomas, and Fan Li. Addressing extreme propensity scores via the overlap weights. *American Journal of Epidemiology*, 188(1):250–257, 2019.

Fan Li, Zizhong Tian, Jennifer Bobb, Georgia Papadogeorgou, and Fan Li. Clarifying selection bias in cluster randomized trials. *Clinical Trials*, page in press, 2021.

Winston Lin. Agnostic notes on regression adjustments to experimental data: Reexamining freedman’s critique. *The Annals of Applied Statistics*, 7(1):295–318, 2013.

Carole L Marcus, Renée H Moore, Carol L Rosen, Bruno Giordani, Susan L Garetz, H Gerry Taylor, Ron B Mitchell, Raouf Amin, Eliot S Katz, Raanan Arens, et al. A randomized trial of adenotonsillectomy for childhood sleep apnea. *N Engl J Med*, 368:2366–2376, 2013.

David M Murray, Sherri L Pals, Jonathan L Blitstein, Catherine M Alfano, and Jennifer Lehman. Design and analysis of group-randomized trials in cancer: a review of current practices. *Journal of the National Cancer Institute*, 100(7):483–491, 2008.

J Neyman. On the application of probability theory to agricultural experiments: Essay on principles, Section 9. Masters Thesis. Portions translated into english by D. Dabrowska and T. Speed (1990) *Statistical Science*. (5):465–472, 1923.

Stuart J. Pocock, Susan E. Assmann, Laura E. Enos, and Linda E. Kasten. Subgroup analysis, covariate adjustment and baseline comparisons in clinical trial reporting: Current practice and problems. *Statistics in Medicine*, 21(19):2917–2930, 2002.

P R Rosenbaum and D B Rubin. The central role of the propensity score in observational studies for causal effects. *Biometrika*, 70(1):41–55, 1983.

Paul R Rosenbaum and Donald B Rubin. Reducing bias in observational studies using subclassification on the propensity score. *Journal of the American statistical Association*, 79(387):516–524, 1984.

D. B. Rubin. *Multiple Imputation for Nonresponse in Surveys*. New York: John Wiley & Sons, 1987.

Donald B Rubin. Inference and missing data. *Biometrika*, 63(3):581–592, 1976.

Michael Schenper and Terry L Smith. Efficient evaluation of treatment effects in the presence of missing covariate values. *Statistics in medicine*, 9(7):777–784, 1990.

S. J. Senn. Covariate imbalance and random allocation in clinical trials. *Statistics in Medicine*, 8(4):467–475, 1989.

Changyu Shen, Xiaochun Li, and Lingling Li. Inverse probability weighting for covariate adjustment in randomized studies. *Statistics in Medicine*, 33(4):555–568, 2014.
Mingyang Song, Xin Zhou, Mathew Pazaris, and Donna Spiegelman. The missing covariate indicator method is nearly valid almost always. *arXiv preprint arXiv:2111.00138*, 2021.

Thomas R Sullivan, Ian R White, Amy B Salter, Philip Ryan, and Katherine J Lee. Should multiple imputation be the method of choice for handling missing data in randomized trials? *Statistical methods in medical research*, 27(9):2610–2626, 2018.

Douglas D. Thompson, Hester F. Lingsma, William N. Whiteley, Gordon D. Murray, and Ewout W. Steyerberg. Covariate adjustment had similar benefits in small and large randomized controlled trials. *Journal of Clinical Epidemiology*, 68(9):1068–1075, 2015.

Anastasios A Tsiatis, Marie Davidian, Min Zhang, and Xiaomin Lu. Covariate adjustment for two-sample treatment comparisons in randomized clinical trials: a principled yet flexible approach. *Statistics in Medicine*, 27(23):4658–4677, 2008.

Elizabeth L. Turner, Fan Li, John A. Gallis, Melanie Prague, and David M. Murray. Review of recent methodological developments in group-randomized trials: part 1–design. *American Journal of Public Health*, 107(6):907–915, 2017.

S. van Buuren, J. P. L. Brand, C. G. M. Groothuis-Oudshoorn, and D. B. Rubin. Fully conditional specification in multivariate imputation. *Journal of Statistical Computation and Simulation*, 76(12):1049–1064, 2006.

Bingkai Wang, Elizabeth L Ogburn, and Michael Rosenblum. Analysis of covariance in randomized trials: More precision and valid confidence intervals, without model assumptions. *Biometrics*, 75(4):1391–1400, 2019.

Ian R White and Patrick Royston. Imputing missing covariate values for the cox model. *Statistics in medicine*, 28(15):1982–1998, 2009.

Ian R White and Simon G Thompson. Adjusting for partially missing baseline measurements in randomized trials. *Statistics in medicine*, 24(7):993–1007, 2005.

Elizabeth J Williamson, Andrew Forbes, and Ian R White. Variance reduction in randomised trials by inverse probability weighting using the propensity score. *Statistics in Medicine*, 33(5):721–737, 2014.

Li Yang and Anastasios A Tsiatis. Efficiency study of estimators for a treatment effect in a pretest–posttest trial. *The American Statistician*, 55(4):314–321, 2001.

Yanyao Yi, Ting Ye, Menggang Yu, and Jun Shao. Cox regression with survival-time-dependent missing covariate values. *Biometrics*, 76(2):460–471, 2020.
Shuxi Zeng, Fan Li, Rui Wang, and Fan Li. Propensity score weighting for covariate adjustment in randomized clinical trials. *Statistics in medicine*, 40(4):842–858, 2021.

Guo-Qiang Zhang, Licong Cui, Remo Mueller, Shiqiang Tao, Matthew Kim, Michael Rueschman, Sara Mariani, Daniel Mobley, and Susan Redline. The national sleep research resource: towards a sleep data commons. *Journal of the American Medical Informatics Association*, 25(10):1351–1358, 2018.

Min Zhang, Anastasios A. Tsiatis, and Marie Davidian. Improving efficiency of inferences in randomized clinical trials using auxiliary covariates. *Biometrics*, 64(3):707–715, 2008.

Anqi Zhao and Peng Ding. To adjust or not to adjust? estimating the average treatment effect in randomized experiments with missing covariates. *arXiv preprint arXiv:2108.00152*, 2021.

Tianhui Zhou, Guangyu Tong, Fan Li, Laine Thomas, and Fan Li. Psweight: Propensity score weighting for causal inference. 2020. URL [https://CRAN.R-project.org/package=PSweight](https://CRAN.R-project.org/package=PSweight). R package version 0.1.1.