Statistical Inference of Covariate-Adjusted Randomized Experiments

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Abstract

Covariate-adjusted randomization procedure is frequently used in comparative studies to increase the covariate balance across treatment groups. However, as the randomization inevitably uses the covariate information when forming balanced treatment groups, the validity of classical statistical methods following such randomization is often unclear. In this article, we derive the theoretical properties of statistical methods based on general covariate-adjusted randomization under the linear model framework. More importantly, we explicitly unveil the relationship between covariate-adjusted and inference properties by deriving the asymptotic representations of the corresponding estimators. We apply the proposed general theory to various randomization procedures, such as complete randomization (CR), rerandomization (RR), pairwise sequential randomization (PSR), and Atkinson’s $D_A$-biased coin design ($D_A$-BCD), and compare

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their performance analytically. Based on the theoretical results, we then propose a new approach to obtain valid and more powerful tests. These results open a door to understand and analyze experiments based on covariate-adjusted randomization. Simulation studies provide further evidence of the advantages of the proposed framework and theoretical results.

**Keywords:** balancing covariates, conservative tests, covariate-adjusted randomization, Mahalanobis distance, power, rerandomization.

1 Introduction

Randomization is considered the “gold standard” to evaluate treatment effect as it mitigates selection bias and provides a foundation for statistical inference. Among all the randomization methods, covariate-adjusted randomization (CAR) procedure is frequently used because it utilizes the covariate information to form more balanced treatment groups. However, because of such a feature, the validity of classical statistical inference following such randomization is usually unclear. In this article, we establish a general theory by which properties of statistical inference can be obtained for covariate-adjusted randomization under mild conditions.

There has been extensive studies on CAR procedures. When facing categorical covariates, Pocock and Simon’s minimization method and its extensions can be used to reduce covariate imbalance of different levels (Taves 1974; Pocock and Simon 1975; Hu and Hu 2012), which can also handle continuous covariates through discretization. To avoid information loss due to discretization, many randomization methods that directly utilize continuous covariates are also proposed in the literature (Frane 1998; Lin and Su 2012; Ma and Hu 2013). Atkinson’s $D_A$-biased coin design ($D_A$-BCD) represents a large class of methods that take covariates into account in allocation rules based on certain optimality criteria (Atkinson 1982; Smith 1984a,b; Antognini and Zagoraiou 2011). When all units’ covariates are available before
the experiment starts, we can adopt rerandomization (RR) which repeats the traditional randomization process until a satisfactory configuration is achieved (Morgan and Rubin, 2012, 2015). In addition, pairwise sequential randomization (PSR) recently proposed by Qin et al. (2017) is another alternative, which achieves the optimal covariate balance and is computationally more efficient. Details of those methods will be given in Section 4. For an overview, please see Hu et al. (2014) and Rosenberger and Lachin (2015).

Since the aforementioned randomizations inevitably use the covariate information in forming more balanced treatment groups, the subsequent statistical inference is usually affected and demonstrates undesirable properties, such as reduced type I errors (Shao et al., 2010; Morgan and Rubin, 2012; Ma et al., 2015). This phenomenon of conservativeness is particularly common for a working model including only a subset of covariates used in randomization, such as two sample t test. As all the covariates are used in the randomization to generate more balanced assignments, a valid statistical procedure should incorporate all the covariates. Therefore, excluding some covariates from the working model leads to a distortion of the sampling distribution of test statistics, which consequently causes invalid statistical inference.

It is ideal that the covariates used in randomization should be included in the subsequent analysis in the context of clinical trials according to regulatory guidelines (ICH E9, 1998; EMA, 2015). However, unadjusted tests still dominate in practice (Sverdlov, 2015). For example, to avoid too many parameters, investigation sites are usually omitted in the analysis model for a multi-center clinical trial. Other reasons (not to incorporate all the covariates in practice) include simplicity of the test procedure, robustness to model misspecification and so on (Shao et al., 2010; Shao and Yu, 2013; Ma et al., 2015). Therefore, many working models may suffer from the issue of invalid statistical inference. As covariates are commonly used in comparative studies such as biomarker analysis, personalized medicine (Hu and Hu, 2012), and crowdsourced-internet experimentation (Horton et al., 2011; Chandler and Kapelner,
understanding the impact of covariate-adjusted randomization on statistical inference is an increasingly pressing problem.

The issue over the validity of statistical inference after balancing covariates is investigated mainly based on simulations in the early literature, such as Birkett (1985); Forsythe (1987). More recently, theoretical progress has been made on the inference properties for some specific covariate-adjusted randomization methods. Shao et al. (2010) prove that the two sample t test is conservative under a special stratified randomization. Ma et al. (2015) study the hypotheses testing under a linear model for discrete covariate-adaptive randomization, which assumes that the overall and marginal imbalances across covariates are bounded in probability. However, their results are limited as many covariate-adjusted procedures deal with continuous covariates directly and do not necessarily satisfy the strong balancing assumptions. In fact, inference properties of many methods, as we will show for RR, PSR, and $D_A$-BCD, are different than those studied by Shao et al. (2010) and Ma et al. (2015). In this article, we study inference properties under a general framework and demonstrate the impact of covariate-adjusted randomization on inference.

The main contributions of this article are as follows. First, we derive the statistical properties of inference following general covariate-adjusted randomization methods under the linear model framework. Most important, we explicitly display the relationship between covariate balance and inference by deriving their asymptotic representations. This result explains why inference behaves differently for various randomization methods. Second, we show that the results have broad applications, which is illustrated by applying to several randomization procedures, including CR, RR, PSR, and $D_A$-BCD. In addition, it provides a theoretical approach to formally evaluate inference properties and compare pros and cons of different randomization methods. Third, we propose a method to obtain valid and powerful tests based on our theoretical results. The study lays a foundation to understand the impact of covariate balance on post-randomization statistical inference and sheds lights on future
study in this area.

This article is organized as follows. After introducing the framework and notations in Section 2, we present our main theoretical results for statistical inference under covariate-adjusted randomization in Section 3. Using the proposed theory, we study four specific randomization methods in terms of their conservativeness in hypothesis testing in Section 4 and further propose a method to correct the conservative type I errors in Section 5. In Section 6, numerical studies are presented to illustrate the effectiveness of the proposed theory. Section 7 concludes with some remarks and future research topics. The main theoretical proofs are in Appendix.

2 General Framework

Suppose that \( n \) units are to be assigned to two treatment groups using a covariate-adjusted randomization. Let \( T_i \) be the assignment of the \( i \)-th unit, i.e., \( T_i = 1 \) for treatment 1 and \( T_i = 0 \) for treatment 2. Let \( x_i = (x_{i1}, \ldots, x_{i,p+q})^t \) represent \( p + q \) covariates observed for the \( i \)-th unit, where \( x_{ij} \) are independent and identically distributed as \( X_j \) for each unit \( i = 1, \ldots, n \). A linear regression model is assumed for the outcome \( Y_i \) of the \( i \)-th unit,

\[
Y_i = \mu_1 T_i + \mu_2 (1 - T_i) + \sum_{j=1}^{p+q} \beta_j x_{ij} + \epsilon_i, \tag{1}
\]

where \( \mu_1 \) and \( \mu_2 \) are the main effects of treatment 1 and 2, respectively, and \( \mu_1 - \mu_2 \) is the treatment effect. Furthermore, \( \beta = (\beta_1, \ldots, \beta_{p+q})^t \) represents the covariate effects, and \( \epsilon = (\epsilon_1, \ldots, \epsilon_n)^t \) is independent and identically distributed random errors with mean zero and constant variance \( \sigma^2 \), and is independent of covariates. For simplicity, all the covariates are assumed to be independent of each other and have expectations of zero, i.e., \( \mathbb{E}X_j = 0 \) for \( j = 1, \ldots, p + q \).
After allocating the units to treatment groups via covariate-adjusted randomization, a working model is used to estimate and test the treatment effect. In such a working model, it is common in practice to include a subset of covariates used in randomization, or sometimes even no covariates at all (Shao et al., 2010; Ma et al., 2015; Sverdlov, 2015). Therefore, without loss of generality, suppose that the first $p$ covariates are included in the working model,

$$
E[Y_i] = \mu_1 T_i + \mu_2 (1 - T_i) + \sum_{j=1}^{p} \beta_j x_{i,j}.
$$

(2)

Note that when $q = 0$ all the covariates are included in the working model, and when $p = 0$ no covariates are included.

Let $Y = (Y_1, ..., Y_n)^t$, $T = (T_1, ..., T_n)^t$, $X = [X_{in}; X_{ex}]$, where

$$
X_{in} = \begin{bmatrix} x_{1,1} & \cdots & x_{1,p} \\
\vdots & \ddots & \vdots \\
x_{n,1} & \cdots & x_{n,p} \end{bmatrix}, \quad X_{ex} = \begin{bmatrix} x_{1,p+1} & \cdots & x_{1,p+q} \\
\vdots & \ddots & \vdots \\
x_{n,p+1} & \cdots & x_{n,p+q} \end{bmatrix}.
$$

Further let $\beta_{in} = (\beta_1, ..., \beta_p)^t$, $\beta_{ex} = (\beta_{p+1}, ..., \beta_{p+q})^t$, so that $\beta = (\beta_{in}^t, \beta_{ex}^t)^t$. Then the working model can also be written as,

$$
E[Y] = G\theta,
$$

where $G = [T; 1_n - T; X_{in}]$ is the design matrix, $\theta = (\mu_1, \mu_2, \beta_{in}^t)^t$ is the vector of parameters of interest, and $1_n$ is the $n$-dimensional vector of ones. Therefore, the ordinary least squares (OLS) estimate of $\theta$, $\hat{\theta} = (\hat{\mu}_1, \hat{\mu}_2, \hat{\beta}_{in}^t)^t$ is,

$$
\hat{\theta} = (G^tG)^{-1}G^tY.
$$
Under the covariate-adjusted randomization, the treatment assignments $T$ depend on both $X_{in}$ and $X_{ex}$. The distribution of $\hat{\theta}$ is often difficult to obtain. However, testing the treatment effect is often the primary goal when performing a comparative study (e.g., randomized clinical trial). To detect if a treatment effect exists, we have the following hypothesis testing problem,

$$H_0 : \mu_1 - \mu_2 = 0 \text{ versus } H_1 : \mu_1 - \mu_2 \neq 0,$$

with the test statistic

$$S = \frac{L^T\hat{\theta}}{\sqrt{\hat{\sigma}_w^2 L(G^tG)^{-1}L}},$$

where $L = (1, -1, 0, ..., 0)^t$ is a vector of length $p+2$, and $\hat{\sigma}_w^2 = \|Y - G\hat{\theta}\|^2/(n-p-2)$ is the model-based estimate of the error variance $\sigma_w^2 = \sigma_e^2 + \sum_{j=1}^q \beta_{p+j}^2 \text{Var}(X_{p+j})$. The traditional testing procedure is to reject the null hypothesis at the significance level $\alpha$ if $|S| > z_{1-\alpha/2}$, where $z_{1-\alpha/2}$ is $(1 - \alpha/2)$-th quantile of a standard normal distribution.

In addition to testing the treatment effect, it is often of interest to test whether there exist covariate effects. A general form of hypothesis testing can be used for any linear combinations of the covariate effects. Let $C$ be an $m \times (p+2)$ matrix of rank $m$ ($m \leq p$) with entries in the first two columns all equal to zero (no treatment effect to test). Consider the following hypotheses,

$$H_0 : C\theta = c_0 \text{ versus } H_1 : C\theta = c_1,$$

and the test statistic is,

$$S^* = \frac{(C\hat{\theta} - c_0)^t[C(G^tG)^{-1}C]^t(C\hat{\theta} - c_0)}{m\hat{\sigma}_w^2},$$
The traditional test rejects the null hypothesis if $S^* > \chi^2_{m,(1-\alpha)}/m$, where $\chi^2_{m,(1-\alpha)}$ is $(1-\alpha)$-th percentile of a $\chi^2$ distribution with $m$ degrees of freedom. Note that we can let $C = (0, 0, 1, 0, ..., 0)$ to test the significance of a single covariate effect of $\beta_1$, and similarly for other covariate effects.

3 General Properties

Based on the framework introduced above, we study the statistical properties of estimation and hypothesis testing, i.e., (3) and (4), under covariate-adjusted randomization. Before presenting our main results, we first introduce two widely satisfied assumptions.

**Assumption 1.** *Global balance:* $n^{-1} \sum_{i=1}^{n} (2T_i - 1) \xrightarrow{P} 0$.

**Assumption 2.** *Covariate balance:* $n^{-1/2} \sum_{i=1}^{n} (2T_i - 1) x_i \xrightarrow{d} \xi$, where $\xi$ is a $(p+q)$-dimensional random vector with $E[\xi] = 0$.

Assumption 1 requires that the proportions of units in each treatment group converge to 1/2, which is usually the desired target proportion as balanced treatment assignments are more likely to provide efficient estimation and powerful tests. On the other hand, Assumption 2 specifies the asymptotic properties of the imbalance vector of covariates, i.e., $\sum (2T_i - 1)x_i$. That is, the sums of covariates in each treatment group tend to be equal as sample size increases. Together with Assumption 1, this implies the similarity of the averages for each covariate between two treatment groups. The two assumptions ensure that a covariate-adjusted randomization procedure achieves good balancing properties, both globally and across covariates. It is worth to point out that the Assumption 2 is satisfied with $\xi = 0$ under the assumptions of Ma et al. (2015) for discrete covariates.

The properties of classical statistical methods are usually well known and well studied under the full model (1) in literature. However, in practice, the final statistical inference is
often based on the working model (2). Now we present our main theoretical results based on the working model (2).

**Theorem 3.1.** Under Assumptions 1 and 2, the estimates based on the working model (2) are consistent. That is, \( \hat{\theta} \xrightarrow{p} \theta \).

Furthermore,

\[
\sqrt{n}(\hat{\theta} - \theta) = \frac{1}{\sqrt{n}} V^{-1} G^t (X_{ex} \beta_{ex} + \epsilon) + o_P(1),
\]

where \( V = \text{diag}(1/2, 1/2, \text{Var}(X_1), \ldots, \text{Var}(X_p)) \).

The representation provides a convenient way to derive the asymptotic distribution of \( \hat{\theta} \) and its linear combinations. In particular, for the estimated treatment effect \( \hat{\mu}_1 - \hat{\mu}_2 \) it holds

\[
\sqrt{n}[(\hat{\mu}_1 - \hat{\mu}_2) - (\mu_1 - \mu_2)] = \frac{2}{\sqrt{n}} \sum_{i=1}^{n} (2T_i - 1) \left( \sum_{j=1}^{q} \beta_{p+j} x_{i,p+j} + \epsilon_i \right) + o_P(1),
\]

based on which the asymptotic distribution can be obtained. We partition \( \xi = (\xi_{\text{in}}, \xi_{\text{ex}})^t \) so that \( \xi_{\text{in}} \) represents the first \( p \) dimensions of \( \xi \), and \( \xi_{\text{ex}} \) the last \( q \) dimensions. Let \( Z \) be a standard normal random variable that is independent of \( \xi_{\text{ex}} \). We have the following corollary.

**Corollary 3.2.** Under the working model (2), assume that Assumptions 1 and 2 are satisfied, we have

\[
\sqrt{n}[(\hat{\mu}_1 - \hat{\mu}_2) - (\mu_1 - \mu_2)] \overset{d}{\rightarrow} 2\sigma^2 \epsilon Z + 2\beta_{ex}^t \xi_{ex}.
\]

The corollary describes the asymptotic behavior of \( \hat{\mu}_1 - \hat{\mu}_2 \) under the working model (2). If the model parameters \( \beta \) and \( \sigma^2_{\epsilon} \) are known, statistical inference, such as Wald-type hypothesis test, can be constructed based on the asymptotic distribution. In practice, these parameters are unknown and the model-based test procedure defined in (3) is used
instead. It assumes the normal approximation for the asymptotic distribution, and the asymptotic variance is estimated by \( \hat{\sigma}_w^2 \mathbf{L}'(\mathbf{G}'\mathbf{G})^{-1}\mathbf{L} \), which is shown in Appendix to equal \( 4\sigma_w^2/n + o_P(1/n) \). Further let \( \lambda_1 = \sigma_\epsilon/\sigma_w \) and \( \lambda_2 = 1/\sigma_w \). The asymptotic properties of the test (3) under both the null and alternative hypotheses are presented in the following theorem.

**Theorem 3.3.** Under the working model (2), assume that Assumptions 1 and 2 are satisfied, we have

1. When \( H_0 : \mu_1 - \mu_2 = 0 \) is true, then

\[
S \overset{d}{\to} \lambda_1 Z + \lambda_2 \beta_{ex}^t \xi_{ex}.
\]

2. When \( H_1 : \mu_1 - \mu_2 \neq 0 \) is true, we consider a sequence of local alternatives with \( \mu_1 - \mu_2 = \delta/\sqrt{n} \) for a fixed \( \delta \neq 0 \), then

\[
S \overset{d}{\to} \lambda_1 Z + \lambda_2 \beta_{ex}^t \xi_{ex} + \frac{1}{2} \lambda_2 \delta.
\]

The asymptotic distribution of test statistic \( S \) under \( H_0 \) consists of two independent components, \( \lambda_1 Z \) and \( \lambda_2 \beta_{ex}^t \xi_{ex} \). The first component is due to the random error \( \epsilon_i \) in the underlying model (1), and remains invariant under different covariate-adjusted randomization as the randomization procedure utilizes only covariate information and does not depend on the observed responses (Hu and Rosenberger, 2006). In addition, note that \( \xi_{ex} \) in the second component is the last \( q \) dimensions of \( \xi \). By Assumption 2, \( \xi \) is the asymptotic distribution of the imbalance vector of covariates \( \sum (2T_i - 1)x_i \) and illustrates how well covariates are balanced under a specific covariate-adjusted randomization method. The better it performs in terms of covariate balance, the more concentrated \( \xi \) is distributed around 0. Therefore, the second component of \( S \) represents the impact of a covariate-adjusted randomization on the
test statistic through the level of covariate balance. Depending on to what extent covariates are balanced, the test may behave differently in terms of size and power.

When the asymptotic distribution of $S$ is no longer a standard normal distribution, the traditional test may fail to maintain the pre-specified type I error. Let $s_{1-\alpha/2}$ be $(1-\alpha/2)$-th quantile of the asymptotic distribution of $S$ under the null hypothesis. If $s_{1-\alpha/2} < z_{1-\alpha/2}$, the test is conservative in the sense that the actual type I error is smaller than the pre-specified level $\alpha$. In fact, such conservativeness is often the case for covariate-adjusted randomization and can be demonstrated by comparison of $\xi$ between complete randomization and covariate-adjusted randomization. Under complete randomization, $\xi$ follows a normal distribution that makes $S$ follow a standard normal distribution asymptotically (Section 4.1), in which case the test has valid type I error. However, covariate-adjusted randomization is used with a purpose to reduce the imbalance of covariates between treatment groups, and hence $\xi$ is more concentrated around 0 as opposed to complete randomization, leading to conservative tests. Three special cases of covariate-adjusted randomization (RR, PSR, and $D_A$-BCD) will be discussed in details in Sections 4.2, 4.3, and 4.4 respectively. The correction of conservative tests is discussed in Section 5.

Besides type I error, the explicit form of power can also be derived based on Theorem 3.3. Under the local alternatives, $\mu_1 - \mu_2 = \delta/\sqrt{n}$ for a fixed $\delta \neq 0$, the power is

$$
\mathbb{P}(|S| > z_{1-\alpha/2}) = F_S(-z_{1-\alpha/2} + \frac{1}{2}\lambda_2\delta) + F_S(-z_{1-\alpha/2} - \frac{1}{2}\lambda_2\delta) + o(1),
$$

where $F_S$ is the cumulative distribution function of the asymptotic distribution of $S$. In Section 6 power is evaluated numerically for several covariate-adjusted randomization methods.

Similarly as for the treatment effect, the inference for the covariates can also be studied following the representation given in Theorem 3.1. The next theorem illustrates the asymptotic normality of $\beta_m$ under covariate-adjusted randomization.
Corollary 3.4. Under the working model (2), assume that Assumptions 1 and 2 are satisfied, we have

\[ \sqrt{n}(\hat{\beta}_m - \beta_m) \overset{d}{\rightarrow} N(0, \sigma_w^2 \tilde{V}^{-1}). \]

where \( \tilde{V} = \text{diag}(\text{Var}(X_1), \ldots, \text{Var}(X_p)) \).

Based on the asymptotic normality of \( \hat{\beta}_m \), tests for these parameters can be constructed with the asymptotic variances replaced by their consistent estimates. The next theorem shows that the standard test under the working model defined in (4) is valid for linear combinations of \( \beta_m \).

Theorem 3.5. Under the working model (2), assume that Assumptions 1 and 2 are satisfied, we have

1. When \( H_0 : C\theta = c_0 \) is true, then

\[ S^* \overset{d}{\rightarrow} \chi^2_m / m. \]

2. When \( H_1 : C\theta = c_1 \) is true, we consider a sequence of local alternatives with \( c_1 - c_0 = \Delta / \sqrt{n} \) for a fixed \( \Delta \neq 0 \), then

\[ S^* \overset{d}{\rightarrow} \chi^2_m(\phi) / m, \phi = \Delta^t [CV^{-1}C^t]^{-1} \Delta / \sigma_w^2, \]

where \( \phi \) is the non-central parameter.

Theorem 3.5 states that the type I error is maintained when testing the covariate effects under covariate-adjusted randomization. The power, however, is reduced if not all covariate information is incorporated in the working model. Since the inference on covariate effects
is valid under covariate-adjusted randomization, we will mainly focus on testing treatment
effect in the next section.

4 Properties of Several CAR procedures

In last section, we derived the theoretical properties of general CAR procedures. Now we
apply our results to several important CAR procedures proposed in literature. These appli-
cations help us to understand the relationship between balancing and inference of a given
CAR procedure.

4.1 Complete Randomization

Complete randomization (CR) assigns units to each treatment group with the equal proba-
bility 1/2. Since the treatment assignment is independent and does depend on covariates, it
follows from the central limit theorem that

$$\sum_{i=1}^{n} (2T_i - 1)x_i \sqrt{n} \xrightarrow{d} N(0, \Sigma),$$

where $\Sigma = \text{diag}(\text{Var}(X_1), ..., \text{Var}(X_{p+q})).$

Therefore, under CR, $\xi$ defined in Assumption 2 is a normal distribution, and further-
more, $\beta_{\text{ex}}^T \xi_{\text{ex}} \sim N(0, \sum_{j=1}^{q} \beta_{p+j}^2 \text{Var}(X_{p+j}))$. By Theorem 3.3 it is easy to show that the
asymptotic distribution of the test statistic $S$ under the null hypothesis follows a standard
normal distribution, i.e., $S \xrightarrow{d} N(0, 1)$. The traditional hypothesis testing under CR is valid
with correct type I error and no adjustment is needed.
4.2 Rerandomization

To balance the covariates across treatment groups, Morgan and Rubin (2012) have proposed rerandomization (RR), for which the procedure can be summarized as follows:

(1) Collect covariate data.

(2) Specify a balance criterion to determine when a randomization is acceptable. For example, the criterion could be defined as a threshold of \( a > 0 \) on some user-defined imbalance measure, denoted as \( M \).

(3) Randomize the units into treatment groups using traditional randomization methods, such as CR.

(4) Check the balance criterion \( M < a \). If the criterion is satisfied, go to Step (5); otherwise, return to Step (3).

(5) Perform the experiment using the final randomization obtained in Step (4).

Morgan and Rubin (2012) have chosen the imbalance measure in Step (2) to be the Mahalanobis distance between the sample means across two treatment groups, which is defined by

\[
M = (\bar{x}_1 - \bar{x}_2)\text{Cov}(\bar{x}_1 - \bar{x}_2)^{-1}(\bar{x}_1 - \bar{x}_2),
\]

where \( \bar{x}_1 \) and \( \bar{x}_2 \) are the sample means of covariates in the two treatment groups. There are several advantages for adopting such an imbalance measure. Mahalanobis distance is an affinely invariant imbalance measure, which is appealing especially for multivariate data. It is an overall imbalance measure which standardizes and aggregates each covariate imbalance information. A smaller value of Mahalanobis distance indicates a better covariate balance. A low Mahalanobis distance guarantees low imbalance levels in all covariates. Other desirable
properties such as the reduction in variance of the estimated treatment effect can be found in Morgan and Rubin (2012).

Under the assumption of independent covariates, the Mahalanobis distance can be expressed as

\[ M = \sum_{j=1}^{p+q} \left( \frac{\sum_{i=1}^{n}(2T_i - 1)x_{i,j}}{\sqrt{n}\text{Var}(X_j)} \right)^2 + o_p(1). \]

By the balance criterion \( M < a \) under RR, we have

\[ \frac{\sum_{i=1}^{n}(2T_i - 1)x_i}{\sqrt{n}} \xrightarrow{d} \Sigma^{1/2}D \left| D' D < a, \right. \]

where \( \Sigma^{1/2} \) is the square root of \( \Sigma \), \( D \sim N(0, I_{p+q}) \) and \( I_{p+q} \) is the \((p+q)\)-dimensional identity matrix.

**Theorem 4.1.** Under rerandomization, we have

1. Under \( H_0 : \mu_1 - \mu_2 = 0 \), then

\[ S \xrightarrow{d} \lambda_1 Z + \lambda_2 \beta_{\text{ex}}^t \xi^\text{RR}_{\text{ex}}, \]

where \( \xi^\text{RR}_{\text{ex}} \) is the last \( q \) dimensions of \( \xi^\text{RR} = \Sigma^{1/2}D \left| D' D < a. \right. \]

2. Under \( H_1 : \mu_1 - \mu_2 \neq 0 \), where \( \mu_1 - \mu_2 = \delta/\sqrt{n} \) for a fixed \( \delta \neq 0 \),

\[ S \xrightarrow{d} \lambda_1 Z + \lambda_2 \beta_{\text{ex}}^t \xi^\text{RR}_{\text{ex}} + \frac{1}{2}\lambda_2 \delta. \]

Furthermore, the asymptotic variance of \( S \) is

\[ \lambda_1^2 + \lambda_2^2 \beta_{\text{ex}}^t \text{Var}(\xi^\text{RR}_{\text{ex}}) \beta_{\text{ex}} = \frac{\sigma^2_{\epsilon} + \nu a \sum_{j=1}^{q} \beta_{p+j}^2 \text{Var}(X_{p+j})}{\sigma^2_{\epsilon} + \sum_{j=1}^{q} \beta_{p+j}^2 \text{Var}(X_{p+j})}. \]
where $v_a$ is defined in Morgan and Rubin (2012) as

$$v_a = \frac{2}{p+q} \frac{\gamma((p+q)/2 + 1, a/2)}{\gamma((p+q)/2, a/2)} < 1,$$

and $\gamma$ is the incomplete gamma function $\gamma(b, c) = \int_0^c y^{b-1}e^{-y}dy$.

The asymptotic distribution of $S$ under RR is no longer a normal distribution, and it is more concentrated around 0 compared with the standard normal distribution, which indicates that the traditional testing procedure is more conservative. The extent of conservativeness is impacted by the value of $v_a$, which is an increasingly monotonic function of $a$. By selecting a relatively smaller value of $a$, the covariates are more balanced due to stricter balance criterion, resulting in a lower asymptotic variance of $S$. However, a smaller $a$ means that on average it takes more attempts to meet the balance criterion. More discussions on the choice of $a$ can be found in Morgan and Rubin (2012).

4.3 Pairwise Sequential Randomization

Although RR can significantly reduce the covariate balance, it is incapable to scale up for the case of large number of covariates or large number of units, which is almost ubiquitous in the era of big data. Pairwise sequential randomization (PSR) recently proposed by Qin et al. (2017) solves such a problem by sequentially and adaptively assigning units to different treatment groups and is proven to have superior performance in terms of covariate balance and variance of the estimated treatment effect. PSR involves the following steps:

1. Collect covariate data.
2. Choose the covariate imbalance measure for $n$ units, denoted as $M(n)$.
3. Randomly arrange all $n$ units in a sequence $x_1, \ldots, x_n$. 

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(4) Separately assign the first two units to treatment 1 and treatment 2.

(5) Suppose that $2i$ units have been assigned to treatment groups ($i \geq 1$), for the $(2i+1)$-th and $(2i+2)$-th units:

(5a) If the $(2i+1)$-th unit is assigned to treatment 1 and the $(2i+2)$-th unit is assigned to treatment 2 (i.e., $T_{2i+1} = 1$ and $T_{2i+2} = 0$), then we can calculate the “potential” imbalance measure, $M_{i}^{(1)}$, between the updated treatment groups with $2i+2$ units.

(5b) Similarly, if the $(2i+1)$-th unit is assigned to treatment 2 and the $(2i+2)$-th unit is assigned to treatment 1 (i.e., $T_{2i+1} = 0$ and $T_{2i+2} = 1$), then we can calculate the “potential” imbalance measure, $M_{i}^{(2)}$, between the updated treatment groups with $2i+2$ units.

(6) Assign the $(2i+1)$-th and $(2i+2)$-th units to treatment groups according to the following probabilities:

$$
\mathbb{P}(T_{2i+1} = 1|\mathbf{x}_{2i}, \ldots, \mathbf{x}_1, T_{2i}, \ldots, T_1) = \begin{cases} 
\rho & \text{if } M_{i}^{(1)} < M_{i}^{(2)} \\
1 - \rho & \text{if } M_{i}^{(1)} > M_{i}^{(2)} , \\
0.5 & \text{if } M_{i}^{(1)} = M_{i}^{(2)} 
\end{cases}
$$

where $0.5 < \rho < 1$, and assign $T_{2i+2} = 1 - T_{2i+1}$ to maintain the equal proportions.

(7) Repeat Steps (5) through (7) until all units are assigned.

Similar to RR, PSR again chooses the Mahalanobis distance as the covariate imbalance measure in Step (2) because of its affinely invariant property and other desirable properties explained in the previous section. Once the Mahalanobis distance is calculated, the value of $\rho$ is set to 0.75. For a further discussion of $\rho$, please see Hu and Hu (2012). In this algorithm,
$n$ is assumed to be even. If $n$ is odd, then the last ($n$-th) unit is randomly assigned to either treatment 1 or 2 with a probability of 0.5.

Note that the units are not necessarily observed sequentially; however, [Qin et al. (2017)] propose to allocate them sequentially (in pairs) to minimize the occurrence of covariate imbalance. The sequence in which the units are allocated is not unique. Rather, there are $n!$ different possible sequences, but their performances are similar, especially when $n$ is large.

Comparing PSR with RR, we see that both methods use covariate information. PSR uses the covariate information to decide the unit allocation in each iteration, while RR uses the covariate information to decide if a randomly generated allocation is satisfactory or not. Note that neither PSR nor RR is restricted to Mahalanobis distance. Both methods can be easily adapted to different measures of imbalance. However, Mahalanobis distance does lead to desirable properties of the subsequent analysis. For example, PSR results in the minimum asymptotic variance of the estimated treatment effect.

Under PSR, it is shown in [Qin et al. (2017)] that

$$
\sum_{i=1}^{n} (2T_i - 1)x_i = O_P(1).
$$

(5)

Then we have the following theorem.

**Theorem 4.2.** Under PSR, we have

1. Under $H_0 : \mu_1 - \mu_2 = 0$, then

   $$
   S \overset{d}{\rightarrow} N \left( 0, \frac{\sigma^2_r}{\sigma^2_r + \sum_{j=1}^{q} \beta^2_{p+j} \text{Var}(X_{p+j})} \right).
   $$

2. Under $H_1 : \mu_1 - \mu_2 \neq 0$, where $\mu_1 - \mu_2 = \delta/\sqrt{n}$ for a fixed $\delta \neq 0$,

   $$
   S \overset{d}{\rightarrow} N \left( \frac{1}{2} \lambda \delta, \frac{\sigma^2_r}{\sigma^2_r + \sum_{j=1}^{q} \beta^2_{p+j} \text{Var}(X_{p+j})} \right).
   $$
The variance from the covariates is completely eliminated out in the numerator of the asymptotic distribution of $S$, resulting in a distribution more concentrated around 0 than the standard normal distribution. In fact, the conclusion under PSR can be extended to a large class of covariate-adjusted randomization if Assumption (2) is replaced by (5). This can be considered as a natural extension of the conditions proposed in Ma et al. (2015) that lead to conservative tests for covariate-adaptive designs balancing discrete covariates. Note that the condition (5) is quite strong and is not a necessary condition to have a conservative test. For example, the condition is not satisfied under RR while the test is also conservative as shown in Section 4.2.

4.4 Atkinson’s $D_A$-Biased Coin Design

Atkinson’s $D_A$-biased coin design ($D_A$-BCD) is proposed to balance allocations across covariates in order to minimize the variance of estimated treatment effects when a classical linear model between response and covariates is assumed (Atkinson, 1982; Smith, 1984a,b). Unlike RR and PSR, it is used in the setting where covariate information are collected sequentially, such as in clinical trials. More discussions on the method and its properties can be found in Atkinson (2002), Antognini and Zagoraiou (2011) and Atkinson (2014).

$D_A$-BCD sequentially assigns units to treatment groups with an adaptive allocation probability: suppose $n$ units have been assigned to treatment groups, $D_A$-BCD assigns the $(n+1)$-th unit to treatment 1 with probability

$$\mathbb{P}(T_{n+1} = 1|x_{n+1}, ..., x_1, T_n, ..., T_1)$$

$$= \frac{[1 - (1; x'_{n+1})(F_n'F_n)^{-1}b_n]^2}{[1 - (1; x'_{n+1})(F_n'F_n)^{-1}b_n]^2 + [1 + (1; x'_{n+1})(F_n'F_n)^{-1}b_n]^2},$$

where $F_n = [1_n; X]$ and $b'_n = (2T - 1_n)'F_n$. 

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Under $D_A$-BCD, by applying result (10.5) of Smith (1984b), it holds that
\[
\sum_{i=1}^{n} \left(2T_i - 1\right)x_i \xrightarrow{d} N\left(0, \frac{1}{5}\Sigma\right),
\]

It is clear to see that under $D_A$-BCD the variance of the imbalance vector of covariates $\sum(2T_i - 1)x_i$ is reduced to $1/5$ of that under complete randomization, indicating that covariates are more balanced compared to complete randomization. The next theorem states the asymptotic distributions of $S$ under $D_A$-BCD.

**Theorem 4.3.** Under $D_A$-BCD, we have

1. Under $H_0 : \mu_1 - \mu_2 = 0$, then

   \[
   S \xrightarrow{d} N\left(0, \frac{\sigma^2 + \frac{1}{5}\sum_{j=1}^{q} \beta_{p+j}^2 \text{Var}(X_{p+j})}{\sigma^2 + \sum_{j=1}^{q} \beta_{p+j}^2 \text{Var}(X_{p+j})}\right).
   \]

2. Under $H_1 : \mu_1 - \mu_2 \neq 0$, where $\mu_1 - \mu_2 = \delta/\sqrt{n}$ for a fixed $\delta \neq 0$,

   \[
   S \xrightarrow{d} N\left(\frac{1}{2}\lambda_2 \delta, \frac{\sigma^2 + \frac{1}{5}\sum_{j=1}^{q} \beta_{p+j}^2 \text{Var}(X_{p+j})}{\sigma^2 + \sum_{j=1}^{q} \beta_{p+j}^2 \text{Var}(X_{p+j})}\right).
   \]

This theorem shows that the test statistic $S$ has the asymptotic variance smaller than 1, so the test is conservative with a reduced type I error for testing the treatment effect.

Based on above four CAR procedures, we find that: (i) Under the CR (complete randomization), the distribution of $S$ is still asymptotically standard normal, so it provides the correct type I error. This is because the CR do not use covariate information at the assignment stage. (ii) Under other three procedures (RR, $D_A$-BCD and PSR), the asymptotical distributions of $S$ are not standard normal. Therefore, their type I errors (based on $S$) are not correct anymore. Based on their distributions of $S$, we can compare their type I errors as well as their powers. In next section, we will discuss about the correction of type I error.
of CAR procedures and then we may compare their adjusted powers. We may also apply the
general theorems (in Section 3) to other CAR procedures. Numerical comparisons of these
randomization methods are given in Section 6.

5 Correction for Conservativeness

As we can see, most of the covariate-adjusted randomizations lead to conservative type I
error for testing the treatment effect, because traditional tests use standard normal distri-
bution as the null distribution. Therefore, we propose the following approach to correct the
conservative type I errors and to obtain higher powers.

Since we have derived the asymptotic distribution of $S$ in Theorem 3.3, we can obtain
the correct asymptotic critical values. However, since the asymptotic distribution depends
on unknown parameters, we need to estimate them using the observed sample to obtain the
approximated null distribution and adjust the corresponding critical values and p-values.

After adjusting the critical values and p-values, we are able to obtain more powerful
hypothesis testing results. The more conservative the traditional tests are, the more powerful
their corrected versions become. Finally, we compare the covariate-adjusted randomization
procedures mentioned above in terms of covariate balance, conservativeness of the traditional
tests, and powers of the corrected test, and summarize their advantages and disadvantages
in Table 1. The conclusions in the table are further verified through simulation in the next
section.

6 Numerical Studies

In this section, we perform simulation studies to verify the theoretical results and demon-
strate their effectiveness in obtaining high powers for hypothesis testing. We have tested
Randomization | Covariate balance | Type I error of traditional test | Power of corrected test
--- | --- | --- | ---
CR | least balanced | valid | least powerful
RR | moderately balanced | moderately conservative | moderately powerful
$D_A$-BCD | moderately balanced | moderately conservative | moderately powerful
PSR | most balanced | most conservative | most powerful

Table 1: Comparison of different covariate-adjusted randomization procedures in terms of covariate balance, traditional tests’ conservativeness, and corrected tests’ powers.

various randomization procedures, including CR, RR, PSR, and $D_A$-BCD.

### 6.1 Verification of Theoretical Results

We first verify the theoretical asymptotic distribution of $S$ under CR, RR, PSR, and $D_A$-BCD. Assume the underlying model is $Y_i = \mu_1 T_i + \mu_2 (1 - T_i) + \sum_{j=1}^{4} \beta_j x_{i,j} + \epsilon_i$ where $\mu_1 = \mu_2 = 0$, $\beta_j = 1$ for $j = 1, ..., 4$. $x_{i,j} \sim N(0,1)$ for $j = 1, ..., 4$ and is independent of each other. The random error $\epsilon_i \sim N(0,2^2)$ is independent of all $x_{i,j}$. We simulate the data according to the underlying model with sample size $n = 500$ and use the working model which includes only two covariates out of four, $\mathbb{E}[Y_i] = \mu_1 T_i + \mu_2 (1 - T_i) + \beta_1 x_{i,1} + \beta_2 x_{i,2}$, to obtain the test statistic $S$. In Figure 1, we plot the simulated distributions of $S$ along with the theoretical distributions of $S$ given by Theorem 3.3. As the figure shows, the theoretical distributions are very close to the simulated distributions for all randomization procedures, which verifies our theoretical results. For comparison, we plot the standard normal distribution in bold gray. As we move from the left panel to the right panel (i.e., from CR to PSR), we can see that the distribution of $S$ becomes narrower. Therefore, using the critical values or the p-values obtained from the standard normal distribution will result in conservative tests with reduced type I errors for RR, PSR, and $D_A$-BCD. The correction for such conservativeness will be further illustrated in the following sections.
6.2 Conservative Hypothesis Testing for Treatment Effect

From previous sections, we understand that, the traditional test for treatment effect under most covariate-adjusted randomization procedures generates conservative results. In this section, we verify such a phenomenon. Suppose the underlying model is

$$ Y_i = \mu_1 T_i + \mu_2 (1 - T_i) + \sum_{j=1}^{6} \beta_j x_{i,j} + \epsilon_i, \quad (6) $$

where $\beta_j = 1$ for $j = 1,...,6$. $x_{i,j} \sim N(0,1)$ and is independent of each other. The random error $\epsilon_i \sim N(0,2^2)$ is independent of all $x_{i,j}$. We use the following four working models to test the treatment effect, i.e., $H_0 : \mu_1 = \mu_2$ and $H_1 : \mu_1 \neq \mu_2$.

- W1: $\mathbb{E}[Y_i] = \mu_1 T_i + \mu_2 (1 - T_i)$.
- W2: $\mathbb{E}[Y_i] = \mu_1 T_i + \mu_2 (1 - T_i) + \sum_{j=1}^{2} \beta_j x_{i,j}$.
- W3: $\mathbb{E}[Y_i] = \mu_1 T_i + \mu_2 (1 - T_i) + \sum_{j=3}^{6} \beta_j x_{i,j}$.
- W4: $\mathbb{E}[Y_i] = \mu_1 T_i + \mu_2 (1 - T_i) + \sum_{j=1}^{6} \beta_j x_{i,j}$.

Note that the first model is equivalent to the two sample t test and the last working model...
Table 2: Type I error of traditional tests for treatment effect using different working models and different randomization procedures.

| Randomization | W1    | W2    | W3    | W4    |
|---------------|-------|-------|-------|-------|
| CR            | 0.0529| 0.0512| 0.0538| 0.0513|
| RR            | 0.0114| 0.0166| 0.0259| 0.0502|
| $D_A$-BCD     | 0.0071| 0.0118| 0.0249| 0.0532|
| PSR           | 0.0018| 0.0058| 0.0178| 0.0519|

is the same as the underlying model. We simulate data according to (6) with $\mu_1 = \mu_2 = 0$ and sample size $n = 500$ and obtain the type I errors of the traditional tests. The results are shown in Table 2. As we can see, under CR, all working models provide correct type I errors. However, under RR, $D_A$-BCD, and PSR, W1 W2, and W3 generate conservative type I errors below 5%, with PSR being the most conservative. This shows that the covariate-adjusted randomization leads to conservative results for traditional tests for the treatment effect. The more balanced covariates the randomization procedures provide, the more conservative the tests become. We further simulate data using $\mu_1 = 0$ and $\mu_2 = 0.3$ and obtain the power of the traditional tests and presented them in Table 3. As we can see, since the type I errors are conservative, the powers of RR, $D_A$-BCD and PSR are also affected.

Since we know the true data generating process, we could obtain the true critical values for each scenario to make sure the type I errors are at 5%. Using the true critical values, we can obtain the true power of the tests using the same setting. We present these powers in Table 4. The powers are much higher than the ones reported in Table 3. The powers from PSR are the highest among all randomization procedures because it can balance the covariate the best. These results are consistent with Table 1.

From the simulation above, we understand that PSR, $D_A$-BCD, and RR generate more balanced covariates than CR, therefore, are able to provide more powerful tests, subject to the availability of the correct critical values or p-values. Note that, in practice, we may not know the true data generating process and need to estimate the critical values and p-values.
Table 3: Power of the traditional tests for treatment effect using different working models and different randomization procedures when $\mu_1 = 0$ and $\mu_2 = 0.3$, i.e., under $H_1$.  

| Randomization | W1  | W2  | W3  | W4  |
|---------------|-----|-----|-----|-----|
| CR            | 0.1791 | 0.2149 | 0.2733 | 0.3872 |
| RR            | 0.1260 | 0.1711 | 0.2477 | 0.3841 |
| $D_A$-BCD     | 0.1116 | 0.1550 | 0.2443 | 0.3861 |
| PSR           | 0.0867 | 0.1400 | 0.2352 | 0.3864 |

Table 4: Power of the hypothesis testing for treatment effect using true critical values under different working models and different randomization procedures when $\mu_1 = 0$ and $\mu_2 = 0.3$.  

| Randomization | W1  | W2  | W3  | W4  |
|---------------|-----|-----|-----|-----|
| CR            | 0.1801 | 0.2106 | 0.2644 | 0.3825 |
| RR            | 0.2691 | 0.2971 | 0.3344 | 0.3908 |
| $D_A$-BCD     | 0.3130 | 0.3360 | 0.3695 | 0.3931 |
| PSR           | 0.3684 | 0.3770 | 0.3812 | 0.3900 |

6.3 Corrected Hypothesis Testing for Treatment Effect

In practice, to correct the type I error and obtain higher powers, we can estimate the critical values and p-values based on the estimated asymptotic distribution (Section 5). Using this approach, we repeat the same simulation as in the previous section, and present the type I errors in Table 5 and the powers in Figure 2.

As we can see in Table 5 all type I errors are successfully controlled at 5% which means the proposed approach works well. In Figure 2, we can see that as $\mu_1 - \mu_2$ increases away from 0, the powers generally increase. However, under CR, different working models provide different powers. The more covariates included in the working model, the higher the power. This is because CR cannot balance the covariate well, and the covariates not included in the working model will affect the test for the treatment effect. On the contrary, under PSR, all working models provide similar powers because PSR can balance all covariate well. Since RR, $D_A$-BCD can also balance the covariates, but not as well as PSR does, their powers are slightly better than CR but much worse than PSR.
| Randomization | W1    | W2    | W3    | W4    |
|---------------|-------|-------|-------|-------|
| CR            | 0.0477| 0.0495| 0.0459| 0.0451|
| RR            | 0.0514| 0.0498| 0.0515| 0.0510|
| $D_A$-BCD     | 0.0508| 0.0518| 0.0525| 0.0511|
| PSR           | 0.0597| 0.0584| 0.0504| 0.0477|

Table 5: Type I error of hypothesis testing for treatment effect using estimated asymptotic distribution’s critical values under different working models and different randomization procedures.

Figure 2: Power against $\mu_1 - \mu_2$ using estimated asymptotic distribution’s critical values and p-values. Sample size $n = 500$. From left panel to right panel: 1) CR, 2) RR with $a = 3$, 3) $D_A$-BCD, 4) PSR. Note that we plot the power of W4 under CR in bold gray curves in all the panels for a better comparison among different randomizations.
| Randomization | W3  | W4  |
|---------------|-----|-----|
| CR            | 0.0527 | 0.0532 |
| RR            | 0.0520 | 0.0509 |
| $D_4$-BCD     | 0.0485 | 0.0428 |
| PSR           | 0.0512 | 0.0496 |

Table 6: Type I error of hypothesis testing for covariate effect $H_0 : \beta_3 = 0$ using unadjusted critical values under different working models and different randomization procedures.

6.4 Hypothesis Testing for Covariate Effect

Lastly, we compare the performance of the traditional test for the third covariate effect, i.e., $H_0 : \beta_3 = 0$ and $H_1 : \beta_3 \neq 0$. We adopt the same setting from the previous section and choose a range of values from 0 to 1 for $\beta_3$ to calculate the power under different working models. Note that in this case, only W3 and W4 contain the third covariate. The type I errors are shown in Table 6 and powers in Figures 3. As we can see, the type I errors are all controlled at 5%, which is consistent with our theoretical results shown in Theorem 3.5. In other words, no correction is needed for testing the covariate effect. On the other hand, Figure 3 shows that, if the working model does not include all covariates, the powers are reduced. This is again consistent with the results in Theorem 3.5. It is worthwhile to note that the performance of the hypothesis testing for the covariate effect does not depend on the choice of randomization procedure as all panels of Figures 3 are almost identical.

7 Conclusion

In this article, the impact of covariate-adjusted randomization on inference properties is studied. The theoretical properties of post-randomization inference are established in Section 3 for general covariate-adjusted randomization. These results provide a theoretical foundation to analysis experiments based on covariate-adjusted randomization. Based on these results,
one can then compare different covariate-adjusted randomization procedures theoretically. We then applied the theoretical properties to several popular covariate-adjusted randomization methods in the literature. Finite sample properties are also studied via extensive simulations.

As shown in Theorem 3.3, inference properties under covariate-adjusted randomization is closely related to how well covariates are balanced, which is measured by $\xi$ asymptotically. If $\xi$ is known, the inference properties can be derived according to Theorem 3.3. However, the exact form of $\xi$ may be unknown for some randomization procedures. we can evaluate the imbalance vector of covariates numerically to estimate its asymptotic distribution, for example, using bootstrap (Shao et al., 2010). Therefore, different covariate-adjusted randomizations can be compared in terms of both balancing and inference properties.

In Section 4.3, the estimated treatment effect under PSR achieves the minimum asymptotic variance, and hence the subsequent hypothesis tests are most powerful. Since PSR is proposed in the scenario that all covariate data are available before treatment allocation, this property is also desirable in the setting of sequential allocation, such as in clinical trials (Qin et al., 2017). For categorical covariates, stratification, minimization and other procedures
that satisfy certain conditions have this property (Ma et al., 2015), but randomization with the same property for continuous covariates are still needed.

A linear model framework is assumed for the underlying model and the working model in our proposed framework. However, it is common to see other types of outcomes in practice. In Feinstein and Landis (1976) and Green and Byar (1978), the properties of unadjusted tests are studied for binary responses under which case type I error is decreased for stratified randomization compared to unstratified randomization. More recently, inference properties are studied based on generalized linear models or survival analyses for certain randomization procedures, such as stratification and minimization (Shao and Yu, 2013; Luo et al., 2016; Xu et al., 2016), but the properties for non-continuous outcomes under general covariate-adjusted methods remain unknown. It is desirable to extend the framework and results obtained in this article to the non-linear model framework.

The proposed framework and results can be generalized into several directions. First of all, the current work assumes equal allocation to each treatment, however, other target proportions may be preferred in some cases. Second, the framework in this article is based on experiments with two treatment groups, which can be extended to multiple treatments (Tymofyeyev et al., 2007). Last, other outcome types, such as time to event or categorical responses, can be studied with modifications to the proposed framework. These topics are left for future research.

8 Appendix: Proof of Main Theorems

To prove the main theorems, we first prove the following lemma.

Lemma 8.1. Under Assumption $\exists$ we have

$$
\frac{1}{n} \sum_{i=1}^{n} T_i x_{i,j} \xrightarrow{p} \frac{1}{2} \mathbb{E} X_j,
$$
and

\[ \frac{1}{n} \sum_{i=1}^{n} (1 - T_i) x_{i,j} \xrightarrow{p} \frac{1}{2} \mathbb{E} X_j, \]

for any \( j = 1, \ldots, p + q \).

**Proof of Lemma 8.1** First, it is easy to see that for any \( j = 1, \ldots, p + q \),

\[ \frac{1}{n} \sum_{i=1}^{n} T_i x_{i,j} = \frac{1}{2n} \sum_{i=1}^{n} x_{i,j} + \frac{1}{2n} \sum_{i=1}^{n} (2T_i - 1) x_{i,j}. \]

Assumption 2 implies that \( n^{-1/2} \sum_i (2T_i - 1) x_{i,j} \) converges to the \( j \)-th dimension of \( \xi \) in distribution, and thus it is bounded in probability. So we have

\[ \frac{1}{n} \sum_{i=1}^{n} (2T_i - 1) x_{i,j} \xrightarrow{p} 0. \]

Also, it follows from the weak law of large numbers that

\[ \frac{1}{2n} \sum_{i=1}^{n} x_{i,j} \xrightarrow{p} \frac{1}{2} \mathbb{E} X_j. \]

Therefore, for any \( j = 1, \ldots, p + q \),

\[ \frac{1}{n} \sum_{i=1}^{n} T_i x_{i,j} \xrightarrow{p} \frac{1}{2} \mathbb{E} X_j. \]

Similarly, it can also be shown that,

\[ \frac{1}{n} \sum_{i=1}^{n} (1 - T_i) x_{i,j} \xrightarrow{p} \frac{1}{2} \mathbb{E} X_j. \]
Proof of Theorem 3.1. The OLS estimate $\hat{\theta}$ can be written as

$$\hat{\theta} = \theta + \left( \frac{G'G}{n} \right)^{-1} \frac{G'X_{ex}\beta_{ex}}{n} + \left( \frac{G'G}{n} \right)^{-1} \frac{G'\epsilon}{n}.$$

Note it is assumed that the covariates are independent of each other and $\mathbb{E}X_j = 0$ for any $j = 1, \ldots, p + q$, then by Assumption 1 and the weak law of large numbers,

$$\frac{G'G}{n} \xrightarrow{p} \text{diag} \left( \frac{1}{2}, \frac{1}{2}, \text{Var}(X_1), \ldots, \text{Var}(X_p) \right),$$

and, together with Lemma 8.1,

$$\frac{G'X_{ex}}{n} \xrightarrow{p} 0.$$

In addition, the independence of $G$ and $\epsilon$ implies that

$$\frac{G'\epsilon}{n} \xrightarrow{p} 0.$$

Therefore, we have

$$\left( \frac{G'G}{n} \right)^{-1} \frac{G'X_{ex}\beta_{ex}}{n} + \left( \frac{G'G}{n} \right)^{-1} \frac{G'\epsilon}{n} \xrightarrow{p} 0,$$

that is, $\hat{\theta} \xrightarrow{p} \theta$.

To prove the second part of the theorem, since we have shown $n^{-1}G'G \xrightarrow{p} V$, it suffices
to show that

$$\frac{1}{\sqrt{n}} \mathbf{G}^t (\mathbf{X}_{\text{ex}} \beta_{\text{ex}} + \epsilon) = \left[ \begin{array}{c} \sum_{i=1}^{n} T_i(\sum_{j=1}^{q} \beta_{p+j} x_{i,p+j} + \epsilon_i) \\
\sum_{i=1}^{n} (1 - T_i)(\sum_{j=1}^{q} \beta_{p+j} x_{i,p+j} + \epsilon_i) \\
\sum_{i=1}^{n} x_{i,1}(\sum_{j=1}^{q} \beta_{p+j} x_{i,p+j} + \epsilon_i) \\
\vdots \\
\sum_{i=1}^{n} x_{i,p}(\sum_{j=1}^{q} \beta_{p+j} x_{i,p+j} + \epsilon_i) \end{array} \right]$$

is bounded in probability. Note that Assumption 2 implies

$$\frac{1}{\sqrt{n}} \sum_{i=1}^{n} T_i x_{i,p+j} = \frac{1}{2\sqrt{n}} \sum_{i} x_{i,p+j} + \frac{1}{2\sqrt{n}} \sum_{i} (2T_i - 1) x_{i,p+j} = O_P(1),$$

for any $j = 1, \ldots, q$. Also, using the independece of $\epsilon$ and $\mathbf{T}$, we have

$$\frac{1}{\sqrt{n}} \sum_{i=1}^{n} T_i \epsilon_i = \frac{1}{2\sqrt{n}} \sum_{i} \epsilon_i + \frac{1}{2\sqrt{n}} \sum_{i} (2T_i - 1) \epsilon_i = O_P(1).$$

Similar arguments give

$$\frac{1}{\sqrt{n}} \sum_{i=1}^{n} (1 - T_i) x_{i,p+j} = O_P(1), \quad \frac{1}{\sqrt{n}} \sum_{i=1}^{n} (1 - T_i) \epsilon_i = O_P(1),$$

which, together with the central limit theorem, yields

$$\frac{1}{\sqrt{n}} \mathbf{G}^t (\mathbf{X}_{\text{ex}} \beta_{\text{ex}} + \epsilon) = O_P(1).$$

\[\square\]

**Proof of Corollary 3.2** By the representation given in Theorem 3.1, we have

$$\sqrt{n}[(\hat{\mu}_1 - \hat{\mu}_2) - (\mu_1 - \mu_2)] = \frac{2}{\sqrt{n}} \left( \sum_{j=1}^{q} \sum_{i=1}^{n} (2T_i - 1) \beta_{p+j} x_{i,p+j} + \sum_{i=1}^{n} (2T_i - 1) \epsilon_i \right) + o_P(1),$$

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then Assumption 2 can be applied so that
\[
\frac{2}{\sqrt{n}} \left( \sum_{j=1}^{q} \sum_{i=1}^{n} (2T_i - 1)\beta_{p+j} x_{i,p+j} \right) \xrightarrow{d} 2\beta_{e\times}^t \xi_{e\times}.
\]
In addition, using the fact \((2T_i - 1)^2 = 1\) and independence of \(\epsilon\) and \(T\), we have
\[
\text{Var} \left( \frac{2}{\sqrt{n}} \sum_{i=1}^{n} (2T_i - 1)\epsilon_i \right) = \frac{4\sigma_i^2}{n},
\]
and hence,
\[
\frac{2}{\sqrt{n}} \left( \sum_{i=1}^{n} (2T_i - 1)\epsilon_i \right) \xrightarrow{d} N(0, 4\sigma_i^2).
\]
We also need to show that \(2n^{-1/2}(\sum \sum (2T_i - 1)\beta_{p+j} x_{i,p+j})\) and \(2n^{-1/2}(\sum (2T_i - 1)\epsilon_i)\) are independent. Let \(U_n = 2n^{-1/2}(\sum \sum (2T_i - 1)\beta_{p+j} x_{i,p+j})\) and \(V_n = 2n^{-1/2}(\sum (2T_i - 1)\epsilon_i)\), then given the covariate-adjusted randomization procedure, we have
\[
\mathbb{P}(U_n < u, V_n < v) = \mathbb{P}(U_n < u)\mathbb{P}(V_n < v|U_n < u)
\]
However, since \(\epsilon_i\) is independent of \(x_{i,j}\) and \(T_i\), we have
\[
\mathbb{P}(V_n < v|U_n < u)
= \mathbb{P} \left( \frac{2}{\sqrt{n}} \sum_{i=1}^{n} \tilde{\epsilon}_i < v | U_n < u \right)
= \mathbb{P} \left( \frac{2}{\sqrt{n}} \sum_{i=1}^{n} \tilde{\epsilon}_i < v \right)
= \mathbb{P}(V_n < v)
\]
where \(\tilde{\epsilon}_i\) are identically independently distributed with the same distribution as \(\epsilon_i\), and are
independent of $\epsilon_i$.

Therefore, we show that $\mathbb{P}(V_n < v|U_n < u) = \mathbb{P}(V_n < v)$, and furthermore, $\mathbb{P}(U_n < u, V_n < v) = \mathbb{P}(U_n < u)\mathbb{P}(V_n < v)$, and conclude that $U_n$ and $V_n$ are independent by definition, which completes the proof.

**Proof of Theorem 3.3.** The asymptotic distribution of the numerator of $S$ is given in Corollary 3.2, so we need to consider the denominator of $S$. Using the result $\hat{\theta} \xrightarrow{p} \theta$ by Theorem 3.1, it is easy to verify that $\hat{\sigma}_w^2 \xrightarrow{p} \sigma_w^2$. Also, notice that

$$L^t(G^tG)^{-1}L = \frac{1}{n}L^t\left(\frac{G^tG}{n}\right)^{-1}L = \frac{4}{n} + o_P\left(\frac{1}{n}\right),$$

we conclude that

$$\hat{\sigma}_w^2L^t(G^tG)^{-1}L = \frac{4\sigma_w^2}{n} + o_P\left(\frac{1}{n}\right).$$

Then it follows from Slutsky’s theorem that, under $H_0: \mu_1 - \mu_2 = 0$,

$$S \xrightarrow{d} \lambda_1 Z + \lambda_2 \beta_{ex}^t \xi_{ex},$$

and under $H_1: \mu_1 - \mu_2 \neq 0$ with a sequence of local alternatives, i.e., $\mu_1 - \mu_2 = \delta/\sqrt{n}$ for a fixed $\delta \neq 0$,

$$S \xrightarrow{d} \lambda_1 Z + \lambda_2 \beta_{ex}^t \xi_{ex} + \frac{1}{2} \lambda_2 \delta.$$

**Proof of Corollary 3.4.** By the representation given in Theorem 3.1, we have
\[ \sqrt{n}(\hat{\beta}_m - \beta_m) = \frac{1}{\sqrt{n}} \tilde{V}^{-1} \begin{bmatrix} \sum_{i=1}^{n} x_{i,1}(\sum_{j=1}^{q} \beta_{p+j} x_{i,p+j} + \epsilon_i) \\ \vdots \\ \sum_{i=1}^{n} x_{i,p}(\sum_{j=1}^{q} \beta_{p+j} x_{i,p+j} + \epsilon_i) \end{bmatrix} + o_P(1), \]

then the desired conclusion is an immediate consequence of the central limit theorem.

Proof of Theorem 3.5. The test statistic for testing covariate effects is

\[ S^* = \frac{(C\hat{\theta} - c_0)^t [C(G^t G)^{-1} C]^t}{m\tilde{\sigma}_w^2} \left( C\hat{\theta} - c_0 \right), \]

then under \( H_0 : C\theta = c_0, \)

\[ \sqrt{n}(C\hat{\theta} - c_0) = \sqrt{n} C(\hat{\theta} - \theta), \]

and under \( H_1 : C\theta = c_1, \)

\[ \sqrt{n}(C\hat{\theta} - c_0) = \sqrt{n}(C\hat{\theta} - C\theta + c_1 - c_0) = \sqrt{n} C(\hat{\theta} - \theta) + \sqrt{n}(c_1 - c_0). \]

By the definition of \( C, \) we partition \( C = [0_{m \times 2}; \tilde{C}] , \) where \( 0_{m \times 2} \) is an \( m \times 2 \) matrix of zeros, and \( \tilde{C} \) is an \( m \times p \) matrix of rank \( m. \) Then by Corollary 3.4 and the fact \( CV^{-1}C^t = \tilde{C}\tilde{V}^{-1}\tilde{C}^t, \)

\[ \sqrt{n} C(\hat{\theta} - \theta) \xrightarrow{d} N(0, \sigma_w^2 CV^{-1}C^t). \]

Also, by noticing that

\[ \frac{[C(G^t G/n)^{-1} C]^t}{\tilde{\sigma}_w^2} \xrightarrow{p} \left( \sigma^2_w CV^{-1}C^t \right)^{-1}, \]
we have, under $H_0 : C\theta = c_0$,

$$S^* \xrightarrow{d} \chi^2_{m}/m,$$

and under $H_1 : C\theta = c_1$ with a sequence of local alternatives, i.e., $c_1 - c_0 = \Delta/\sqrt{n}$ for a fixed $\Delta \neq 0$,

$$S^* \xrightarrow{d} \chi^2_{m}(\phi)/m, \quad \phi = \Delta^t[CV^{-1}C^t]^{-1}\Delta/\sigma^2_w.$$

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