Randomization-based Joint Central Limit Theorem and Efficient Covariate Adjustment in Randomized Block $2^K$ Factorial Experiments

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1. Introduction

Since initially proposed by Fisher (1935) and Yates (1937), factorial experiments have been widely used to study the joint effects of several factors on a response (see, e.g., Cochran and Cox 1950; Angrist, Lang, and Oreopoulos 2009; Wu and Hamada 2009; Dasgupta, Pillai, and Rubin 2015). Consider a $2^K$ factorial experiment with $n$ units and $K$ factors ($K \geq 1$). Each factor has two levels, $-1$ and $+1$, and there are $Q = 2^K$ treatment combinations. Complete randomization of the treatment combinations can balance the covariates on average; however, as the numbers of baseline covariates and factors increase, it is likely that some covariates will exhibit imbalance in a particular treatment assignment, as observed in completely randomized experiments (Fisher 1926; Senn 1989; Morgan and Rubin 2012). Blocking, or stratification, which was initially proposed by Fisher (1926) and suggested by classical experimental design textbooks (e.g., Box, Hunter, and Hunter 2005; Wu and Hamada 2009), is the most common way to balance treatment allocations with respect to a few discrete variables that are most relevant to the response. Appropriate blocking can balance the baseline covariates and improve the treatment effect estimation efficiency (e.g., Wilk 1955; Imai 2008; Imbens and Rubin 2015). A recent survey (Lin, Zhu, and Su 2015) noted that 70% of the 224 randomized trials published in leading medical journals in 2014 had used blocking (or stratification) in the experimental design. Even when blocking (or stratification) is not used in the design stage, researchers have recommended its use at the analysis stage and have shown that this post-stratification strategy can also improve estimation efficiency (McHugh and Matts 1983; Miratrix, Sekhon, and Yu 2013).

Blocking or post-stratification balances only a few discrete variables; however, in the present era of big data, researchers often observe many other baseline covariates that are relevant to the response and that might still be imbalanced (Rosenberger and Sverdlov 2008; Liu and Yang 2020; Wang, Wang, and Liu 2021). For example, in clinical trials, demographic and disease characteristics are often collected for each patient, and it is impossible to completely balance these covariates using only blocking. Covariate adjustment or regression adjustment is a common strategy to adjust for the remaining imbalances in the additional covariates, following a similar concept in survey sampling literature (e.g., Cassel, Särndal, and Wretman 1976; Särndal, Swensson, and Wretman 2003). In practice, researchers often use analysis of covariance to analyze the results of randomized block factorial experiments (see textbooks Cochran and Cox 1950; Montgomery 2012), assuming a linear model with fixed or random block effects. However, concerns have been raised regarding the validity of the resulting inferences because the “usual” assumptions for a linear model, such as linearity,
normality, and homoscedastic errors, might not be justified by randomization in randomized block factorial experiments.

Randomization-based inference is receiving increasing attention in the field of causal inference. This inference framework allows the analysis model to be arbitrarily misspecified, and thus is more robust compared to the studies requiring work allows the analysis model to be arbitrarily misspecified, randomization in randomized block factorial experiments. In completely randomized $2^K$ factorial experiments, Dasgupta, Pillai, and Rubin (2015) defined factorial effects using potential outcomes and explored Fisher's randomization tests on sharp null hypotheses; and Lu (2016b) proposed valid randomization-based inferences for the average factorial effects. However, none of these studies considered blocking used in the design stage.

Our first contribution is to establish an asymptotic theory on the joint sampling distribution of the usual (unadjusted) factorial effect estimators in randomized block $2^K$ factorial experiments, under randomization-based inference framework, without imposing strong modeling assumptions on the true data generation process. Most relevant to our work, Liu and Yang (2020) used the results of Bickel and Freedman (1984) to establish the asymptotic normality of the blocked difference-in-means estimator in randomized block experiments, but with one-dimensional potential outcomes and two treatments. As multiple factorial effects are simultaneously of interest in randomized block factorial experiments, it is important to determine the joint asymptotic distribution to handle multiple treatments. In the literature, Li and Ding (2017) established the joint asymptotic normality of the usual average treatment effect estimator in completely randomized experiments with multiple treatments. Their result can be easily extended to randomized block $2^K$ factorial experiments in which the number of blocks is fixed with their sizes tending to infinity. However, in many applications of factorial experiments in clinical trials and industrial engineering, the number of blocks often tends to infinity with their sizes being fixed. It is unclear whether the joint asymptotic normality of Li and Ding (2017) holds in such cases. To fill in this gap, we establish the CLT of the blocked difference-in-means estimator in randomized block experiments with vector potential outcomes and multiple treatments, by making use of the techniques for obtaining the vector-form of the Wald–Wolfowitz–Hoeffding theorem for a linear (or bi-linear) rank statistic ( Hájek 1961; Šen 1995). Our new CLT is robust to model misspecification, numbers of blocks, block sizes, and propensity scores (i.e., the proportion of units under each treatment arm in each block).

Covariate adjustment or regression adjustment is widely used in randomized experiments to balance baseline covariates and improve estimation efficiency. Recently, the asymptotic properties of covariate adjustment have been investigated under randomization-based inference framework for various experimental designs, including completely randomized experiments with two treatments (Freedman 2008a, 2008b; Lin 2013; Mira-trix, Sekhon, and Yu 2013; Bloniarz et al. 2016; Lei and Ding 2021), completely randomized factorial experiments (Lu 2016a, 2016b), and randomized block experiments with two treatments (Liu and Yang 2020). Among them, Lu (2016a) proposed a covariate adjustment method and studied its efficiency gain in completely randomized factorial experiments. Again, this method can be directly extended to randomized block $2^K$ factorial experiments when the number of blocks is fixed with their sizes tending to infinity, but it is not applicable for general scenarios in which the number of blocks and their sizes both tend to infinity. Liu and Yang (2020) proposed a regression adjustment method in randomized block experiments with two treatments. This method does not require the block sizes to tend to infinity, but it works only for the cases of two treatments and equal propensity scores across blocks.

Our second contribution is to propose four covariate adjustment methods to improve the estimation efficiency of factorial effects in randomized block $2^K$ factorial experiments. The first method extends the method proposed in Liu and Yang (2020) to handle multiple treatments; the second and third methods are developed from a conditional inference perspective, which overcome the drawback of the first method regarding the requirement of equal propensity scores across blocks; and the last method is applicable in cases with only large blocks. Under appropriate conditions, we show that the resulting covariate-adjusted factorial effect estimators are all consistent and jointly asymptotically normal. Our analysis is conducted under randomization-based inference framework, so our results are robust to model misspecification. Moreover, we compare the efficiency of various factorial effect estimators, and show that the asymptotic covariance of the first covariate-adjusted factorial effect estimator is no greater than that of the unadjusted estimator when the propensity scores are the same across blocks; the second and third covariate-adjusted methods improve the efficiency even when the propensity scores differ across blocks; and the last method is generally more efficient than the first three, but it requires the number of blocks to be fixed, with their sizes tending to infinity. In addition, we propose conservative estimators for the asymptotic covariances that can be used to construct large-sample conservative confidence intervals or regions for the factorial effects.

The article proceeds as follows. Section 2 introduces the framework and notation of randomized block $2^K$ factorial experiments. Section 3 establishes the joint CLT for the unadjusted factorial effects estimator. Section 4 proposes four covariate adjustment methods to improve estimation efficiency and studies their asymptotic properties. Section 5 provides an extensive simulation study. Section 6 contains an application to a clinical trial dataset. Section 7 concludes the article with discussions. The proofs are given in the supplementary materials.

2. Framework and Notation

We follow the framework and notation introduced in Dasgupta, Pillai, and Rubin (2015) and Li, Ding, and Rubin (2020) for $2^K$ factorial experiments and generalize them to the situation in which the design stage uses blocking.

2.1. Potential Outcomes and Average Factorial Effects

In a randomized block $2^K$ factorial experiment with $n$ units and $K$ factors, each factor has two levels, $-1$ and $+1$, and there are $Q = 2^K$ treatment combinations. Before randomization,
the units are blocked into $M$ blocks according to the values of some important discrete variables, such as gender, disease stage, or location. We use the subscript \("[m]\) for block, \("k\) for factor, and \("i\) for unit. The block $m$ contains $n_{[m]}$ units, $n_{[m]} \geq Q$ and $\sum_{m=1}^{M} n_{[m]} = n$. Within block $m$ ($m = 1, \ldots, M$), $n_{[m|q]}$, ($n_{[m|q]} \geq 1$) units are randomly assigned to the treatment combination $q$ ($q = 1, \ldots, Q$). Thus, the total number of units under treatment combination $q$ is $n_q = \sum_{m=1}^{M} n_{[m|q]}$. Let $Z_{i}$ be the treatment assignment indicator for unit $i$. As the treatment assignments are independent across blocks, the probability that $Z = (Z_1, \ldots, Z_n)^T$ takes a particular value $(z_1, \ldots, z_n)^T$ is

$$P(Z = z) = \prod_{m=1}^{M} \left( \frac{\sum_{q=1}^{Q} n_{[m|q]} !}{n_{[m]} !} \right), \quad \sum_{i \in [m]} I(z_i = q) = n_{[m]}.$$ 

where $I(\cdot)$ is an indicator function, and $i \in [m]$ indexes the unit $i$ in block $m$.

We define factorial effects using the potential outcomes framework (Rubin 1974; Splawa-Neyman, Dabrowska, and Speed 1990). Let us denote $Y_i(q)$ as the potential outcome of unit $i$ under treatment combination $q$, and all $Q$ potential outcomes are denoted as a column vector $Y_i = (Y_i(1), \ldots, Y_i(Q))^T$. The unit-level factorial effects can be defined as contrasts of these potential outcomes. As each unit is assigned to only one treatment combination, we observe only one of the $Q$ potential outcomes. Therefore, the unit-level factorial effects are not identifiable without additional modeling assumptions. Fortunately, under the stable unit treatment value assumption (Rubin 1980), the average factorial effects across experimental units are estimable. For treatment combination $q$, let $t_q = (t_{q1}, \ldots, t_{qK})^T \in \{-1, +1\}^K$ be the levels of the $K$ factors, and let $\bar{Y}_{[m]}(q) = \frac{1}{n_{[m]}} \sum_{i \in [m]} Y_i(q)$ be the mean of the potential outcome $Y_i(q)$ within block $m$. The block-specific average main effect of factor $k$ within block $m$ can be defined as

$$\tau_{[m]k} = \frac{1}{n_{[m]}} \cdot \frac{2}{Q} \sum_{q=1}^{Q} \sum_{i \in [m]} I(t_{i,k} = 1) Y_i(q)$$

$$- \frac{1}{n_{[m]}} \cdot \frac{2}{Q} \sum_{q=1}^{Q} \sum_{i \in [m]} I(t_{i,k} = -1) Y_i(q)$$

$$= \frac{1}{2^{K-1}} \sum_{q=1}^{Q} t_{q,k} \bar{Y}_{[m]}(q) = \frac{1}{2^{K-1}} g_k^T \bar{Y}_{[m]},$$

where $g_k = (g_{k1}, \ldots, g_{kQ})^T = (t_{1,k}, \ldots, t_{Q,k})^T$ is called the generating vector for the main effect of factor $k$, and $\bar{Y}_{[m]} = (\bar{Y}_{[m]}(1), \ldots, \bar{Y}_{[m]}(Q))^T$. The relationship between $\tau$ and $g$ can be found in Table 1 for a $2^3$ factorial experiment.

The average main effect of factor $k$ can be defined as

$$\tau_k = \frac{1}{n} \cdot \frac{2}{Q} \sum_{q=1}^{Q} t_{q,k} \bar{Y}(q) = \frac{M}{\sum_{m=1}^{M} \pi_{[m]} \tau_{[m]k}},$$

where $\pi_{[m]} = n_{[m]}/n$ is the fraction of units in block $m$. As shown by Dasgupta, Pillai, and Rubin (2015), the interaction effect among several factors can be defined with the $g$-vector, which is an element-wise multiplication of the generating vectors for the corresponding factors’ main effects. More specifically, for $1 \leq f \leq F = 2^K - 1 = Q - 1$, let $g_f = (g_{f1}, \ldots, g_{fQ})^T \in \{-1, +1\}^Q$ be the generating vector for the $f$th factorial effect, which satisfies $\sum_{q=1}^{Q} g_{fq} = 0$. The $f$th block-specific average factorial effect in block $m$ can be defined as

$$\tau_{[m]f} = \frac{1}{2^{K-1}} g_f^T \bar{Y}_{[m]}.$$ 

Thus, each block-specific average factorial effect $\tau_{[m]f}$ is a linear contrast of the block-specific average potential outcomes $\bar{Y}_{[m]}(q)$. Let us denote the average potential outcomes as $\bar{Y}(q) = \frac{1}{n} \sum_{i=1}^{n} Y_i(q) = \sum_{m=1}^{M} \pi_{[m]} \bar{Y}_{[m]}(q)$. The vector of all average factorial effects is defined as

$$\tau = \frac{1}{2^{K-1}} \sum_{q=1}^{Q} d_q \bar{Y}(q) = \sum_{m=1}^{M} \pi_{[m]} \tau_{[m]}.$$ 

There are estimands of interest such that $g_f \notin \{-1, +1\}^Q$. For example, in conjoint experiments (a specific type of factorial experiments), researchers may want to weight treatment combinations by relative prevalence in the population (De la Cuesta, Egami, and Imai 2022) in place of the uniform weighting implied by $g_f \in \{-1, +1\}^Q$. Such estimands can be represented by linear transformations of the average factorial effects $\mathbf{C} \tau$, where $\mathbf{C} \in \mathbb{R}^{F \times F}$ ($F = \frac{1}{2} F$) is a constant matrix and has full row rank.

Before performing physical randomization, the experimenter collects an additional $p$-dimensional vector of baseline covariates $X_i = (X_{i1}, \ldots, X_{ip})^T \in \mathbb{R}^p$ for each unit $i$. In this article, we consider a finite population randomization-based inference, in which both the potential outcomes $Y_i$ and covariates $X_i$ are fixed quantities, and the only source of randomness is the treatment assignment $Z$. Under the stable unit treatment value assumption, the observed outcome $Y_{iobs}$ is a function of the treatment assignment indicator and potential outcomes: $Y_{iobs} = \sum_{q=1}^{Q} I(Z_i = q) Y_i(q)$. We aim to make robust and efficient inferences of the average factorial effects $\tau$ (and $\mathbf{C} \tau$) using the observed data $\{Y_{iobs}, X_i, Z_i\}^n_{i=1}$.

### 2.2. Notation

For potential outcomes or their transformations $R(q) = (R_1(q)^T, \ldots, R_q(q)^T)^T$, $q = 1, \ldots, Q$, where $R_q(q)$ can be a column vector, we add a bar on top and a subscript $[m]$ ($m = 1, \ldots, M$) to denote its block-specific mean, $\bar{R}_{[m]}(q) = (1/n_{[m]}) \sum_{i \in [m]} R_i(q)$. We add an additional hat to denote the corresponding block-specific sample mean, $\hat{R}_{[m]}(q) = (1/n_{[m]}) \sum_{i \in [m]} \hat{I}(Z_i = q) R_i(q)$. As covariates can be considered as potential outcomes that are not affected by

| $t_1$ | $t_2$ | $t_3$ | $t_4$ | $t_5$ | $t_6$ | $t_7$ | $t_8$ |
|---|---|---|---|---|---|---|---|
| $g_1$ | +1 | +1 | +1 | +1 | −1 | −1 | −1 |
| $g_2$ | +1 | +1 | −1 | −1 | +1 | +1 | −1 |
| $g_3$ | +1 | −1 | −1 | +1 | +1 | −1 | +1 |
treatment assignment, we denote \( X_i(q) = X_i \) and \( \tilde{X}_{[m]}(q) = \tilde{X}_{[m]} \). The overall mean is denoted as \( \bar{R}(q) = \frac{1}{n} \sum_{i=1}^{n} R_i(q) = \sum_{m=1}^{M} \pi_m \bar{R}_m(q) \), and its natural unbiased estimator is denoted as \( \hat{R}(q) = \sum_{m=1}^{M} \pi_m \hat{R}_m(q) \).

For finite population quantities \( H = (H_1, \ldots, H_q)^T \) and \( U = (U_1^T, \ldots, U_q^T)^T \), we denote the block-specific covariance of \( H \) as \( S_{[m]H} = (n_{[m]q} - 1)^{-1} \sum_{i \in [m]} (H_i - \bar{H}_m)(H_i - \bar{H}_m)^T \), and the block-specific covariance between \( H \) and \( U \) as \( S_{[m]HU} = (n_{[m]q} - 1)^{-1} \sum_{i \in [m]} (H_i - \bar{H}_m)(U_i - \bar{U}_m)^T \). Here and in what follows, both \( \bar{H}_m \) and \( \bar{U}_m \) can be column vectors, and when they are one-dimensional real numbers, we use \( S \) to replace \( S \).

The corresponding sample quantities are denoted by \( \hat{s}_{[m]H} = s_{[m]H} \) and \( \hat{s}_{[m]HU} \). All the above defined quantities depend on \( n \), but we do not index them with \( n \) for notational simplicity. For an \( L \)-dimensional vector \( u = (u_1, \ldots, u_L)^T \), let \( \|u\|_1, \|u\|_2 \) and \( \|u\|_{\infty} \) be the \( \ell_1, \ell_2 \) and \( \ell_{\infty} \) norms, respectively. For two matrices \( A \) and \( B \), we write \( A \succeq B \) if \( A - B \) is positive semidefinite, and \( A \succ B \) if \( A - B \) is positive definite. We denote \( n_m \sim b_m \) if \( n_m \) and \( b_m \) have the same order asymptotically, that is, both the superior limits of \( a_n/b_n \) and \( b_n/a_n \) are bounded by constants.

### 2.3. Blocked Difference-in-Means Estimator

The block-specific average factorial effects \( \tau_{[m]} \) can be estimated without bias using a plug-in estimator \( \hat{\tau}_{[m]} \), which replaces the block-specific mean \( \hat{Y}_{[m]} \) by the corresponding sample mean \( \hat{\bar{Y}}_{[m]} = (\hat{\bar{Y}}_{[m]}(1), \ldots, \hat{\bar{Y}}_{[m]}(q))^T \), that is, \( \hat{\tau}_{[m]} = 2^{-(K-1)} \sum_{q=1}^{Q} d_q \hat{\bar{Y}}_{[m]}(q) \). Thus, an unbiased estimator for the overall average factorial effects \( \bar{\tau} \) is

\[
\hat{\bar{\tau}}_{\text{unadj}} = \sum_{m=1}^{M} \pi_m \hat{\tau}_{[m]} = \frac{1}{2^{K-1}} \sum_{q=1}^{Q} d_q \hat{\bar{Y}}(q),
\]

where the subscript “unadj” indicates that this estimator does not adjust for covariate imbalances. We call it the blocked difference-in-means estimator.

Let \( c_{[m]q} = n_{[m]q}/n_{[m]} \) be the propensity score under treatment combination \( q \) in block \( m \). The covariance of \( \hat{\bar{\tau}}_{\text{unadj}} \) and the probability limit of its conservative estimator depend on the following \( F \times F \) covariance matrices related to \( Y \):

\[
\hat{V}_n(Y) = 2^{-2(K-1)} \sum_{m=1}^{M} \pi_m \left\{ \sum_{q=1}^{Q} \frac{1}{c_{[m]q}} S_{[m]Y(q)d_qd_q^T} \right\},
\]

\[
V_n(Y) = 2^{-2(K-1)} \sum_{m=1}^{M} \pi_m \left\{ \sum_{q=1}^{Q} \frac{1}{c_{[m]q}} S_{[m]Y(q)d_qd_q^T} \right\},
\]

where \( S_{[m]Y(q)} \) is the block-specific covariance of unit-level factorial effects \( \tau_{[m]} = 2^{-(K-1)} \sum_{q=1}^{Q} d_q Y_i(q) \), that is,

\[
S_{[m]Y(q)} = 2^{-2(K-1)} \left\{ \sum_{q=1}^{Q} S_{[m]Y(q)d_qd_q^T} + \sum_{1 \leq q, q' \leq Q} S_{[m]Y(q)Y(q')d_qd_{q'}^T} \right\}.
\]

Because \( \sum_{m=1}^{M} \pi_m S_{[m]Y(q)} \succeq 0 \), it holds that \( V_n(Y) \geq \hat{V}_n(Y) \). We have the following proposition.

**Proposition 1.** The mean and covariance of \( \hat{\bar{\tau}}_{\text{unadj}} \) are

\[
E(\hat{\bar{\tau}}_{\text{unadj}}) = \bar{\tau}, \quad \text{cov}(\hat{\bar{\tau}}_{\text{unadj}}) = \frac{1}{n} \hat{V}_n(Y).
\]

In general, \( S_{[m]Y} \) is not estimable because we cannot observe \( \tau_i \) for any unit \( i \). Fortunately, we can estimate the covariance of \( \sqrt{n} \hat{\bar{\tau}}_{\text{unadj}} \) using a Neyman-type conservative estimator when \( n_{[m]q} \geq 2 \),

\[
\hat{V}_n(Y) = 2^{-2(K-1)} \sum_{m=1}^{M} \pi_m \left\{ \sum_{q=1}^{Q} \frac{1}{c_{[m]q}} \hat{s}_{[m]Y(q)d_qd_q^T} \right\},
\]

where \( \hat{s}_{[m]Y(q)} \) is the sample covariance of \( Y_i(q) \) in block \( m \),

\[
\hat{s}_{[m]Y(q)} = \frac{1}{n_{[m]q} - 1} \sum_{i \in [m]} (Z_i(q) - \hat{\bar{Y}}_{[m]}(q))^2.
\]

Under appropriate conditions, \( \hat{V}_n(Y) \) converges in probability to the limit of \( V_n(Y) \) (see the following Theorem 3), which is consistent if the unit-level factorial effects are additive in a block-specific manner, that is, \( \tau_i = c_m \) for all \( i \in [m] \), where \( c_m \) is a constant vector.

To infer \( \bar{\tau} \) (or \( \text{C} \bar{\tau} \)) based on \( \hat{\bar{\tau}}_{\text{unadj}} \) (or \( \text{C} \hat{\bar{\tau}}_{\text{unadj}} \)), we must study its joint asymptotic sampling distribution under randomization-based inference framework. For this purpose, we need to establish a finite population vector CLT for blocked sample means in randomized block experiments with multiple treatments, \( \hat{Y} = (\hat{Y}(1), \ldots, \hat{Y}(Q)) \).

### 3. Joint Asymptotic Normality

The finite population vector CLT plays a crucial role in studying the asymptotic properties of treatment effect estimators in randomized experiments (Li and Ding 2017; Liu and Yang 2020). In this section, we first establish a general finite population vector CLT for vector potential outcomes in a randomized block experiment with multiple treatments, and then apply it to \( \hat{\tau}_{\text{unadj}} \) to infer the average factorial effects \( \bar{\tau} \).

#### 3.1. Finite Population Vector CLT

Consider a randomized block experiment with \( n \) units, \( M \) blocks, and \( Q \) treatments. Within block \( m \), \( n_{[m]q} \) \( (n_{[m]q} \geq 1) \) of \( n_{[m]} \) units are randomly selected and receive treatment \( q \) \( (q = 1, \ldots, Q) \). For unit \( i \), let \( R_i(q) \in \mathbb{R}^{L} \) be an \( L \)-dimensional \( (L \geq 1) \) vector of potential outcomes under treatment \( q \) and let \( R_i = (R_i(1)^T, \ldots, R_i(Q)^T)^T \) be the \( IQ \)-dimensional vector of all potential outcomes. For simplicity, we assume that both \( L \) and \( Q \) are fixed. In the following, \( R_i(q) \) can be \( Y_i(q), X_i \), or their transformations. Let us denote the vector of blocked sample means as \( \hat{R} = (\hat{R}(1)^T, \ldots, \hat{R}(Q)^T)^T \); we then have the following theorem regarding the mean and covariance of \( \hat{R} \).

**Theorem 1.** In a randomized block experiment with \( n \) units, \( M \) blocks, and \( Q \) treatments, the blocked sample mean \( \hat{R} \) has mean \( \bar{R} \) and covariance

\[
\text{cov}(\hat{R}) = \sum_{m=1}^{M} \pi_m^2 \left[ \text{diag} \left( \frac{1}{n_{[m]q}} S_{[m]R(q)q}, q = 1, \ldots, Q \right) - \frac{1}{n_{[m]q}} S_{[m]R} \right].
\]
where “diag” denotes a block-wise diagonal matrix with its arguments on the diagonal.

According to the finite population CLT established in Bickel and Freedman (1984) and Liu and Yang (2020), each element of \( \hat{R} \) is asymptotically normal. However, it does not imply the joint asymptotic normality of \( \hat{R} \), which is required to determine the asymptotic distribution of \( \hat{\tau}_{\text{unadj}} \). For this purpose, we need the following conditions.

**Condition 1.** For \( m = 1, \ldots, M, q = 1, \ldots, Q \), there exist constants \( e^\infty_{\{m\}} \) and \( C_1 \in (0, 0.5) \) independent of \( n \), such that \( C_1 < e^\infty_{\{m\}} < 1 - C_1 \), and as \( n \to \infty \), \( \max_{m=1,\ldots,M} \max_{q=1,\ldots,Q} |e^\infty_{\{m\}}| \to 0. \)

**Condition 2.** (a) There exists a constant \( C_2 > 0 \) independent of \( n \), such that

\[
\max_{m=1,\ldots,M} \max_{q=1,\ldots,Q} n^{-1} \sum_{i \in [m]} \| R_i(q) - \hat{R}_{\{m\}}(q) \|^2 \leq C_2.
\]

(b) As \( n \to \infty \), \( \max_{m=1,\ldots,M} \max_{q=1,\ldots,Q} \| R_i(q) - \hat{R}_{\{m\}}(q) \|^2 / n \to 0. \)

**Condition 1** ensures that the block-specific propensity scores \( e^\infty_{\{m\}} \) converge uniformly to constants between zero and one. **Condition 2**(a) assumes that the block-specific second moments of the potential outcomes are uniformly bounded. **Condition 2**(b) involves the restriction on the order of the maximum squared distance of the potential outcomes from their block-specific means, which is a typical condition for deriving the finite population CLT; see for example, Hájek (1961), Sen (1995), Li and Ding (2017), and Liu and Yang (2020).

Note that the sample size \( n \to \infty \) implies that the number of blocks \( M \to \infty \) and/or the block size \( n_{\{m\}} \to \infty \) for some \( m \). Moreover, these conditions allow for the units to change block membership as \( n \) grows.

**Theorem 2.** In a randomized block experiment with \( n \) units, \( M \) blocks, and \( Q \) treatments, under Conditions 1 and 2, if \( n \times \text{cov}(\hat{R}) \) converges to a finite limit, denoted by \( \Sigma \), then \( \sqrt{n}(\hat{R} - \overline{R}) \overset{d}{\to} \mathcal{N}(0, \Sigma) \).

**Theorem 2** establishes the joint asymptotic normality of \( \hat{R} \), which is useful for investigating the asymptotic properties of general causal estimators in randomized block experiments with multiple treatments. The conclusion holds for the cases of only large blocks, many small blocks, and some combination thereof, provided that the total number of units \( n \) tends to infinity, the propensity scores are uniformly bounded between zero and one, and \( n \times \text{cov}(\hat{R}) \) converges to a finite limit. Here and in what follows, we say a block is large if its size is much larger than the number of covariates, and a block is small if its size is smaller than or comparable to the number of covariates. When \( M = 1 \) (i.e., in completely randomized experiments with \( Q \) treatments), the conclusion of this theorem has been obtained by Li and Ding (2017) using the vector form of the Wald–Wolfowitz–Hoeffding theorem for a bi-linear rank statistic under random permutation. **Theorem 2** generalizes the result to randomized block experiments with limited requirements on the number of blocks and block sizes. **Theorem 2** also extends the results of Bickel and Freedman (1984) and Liu and Yang (2020), from the situation of one-dimensional potential outcomes and two treatments to that of \( L \)-dimensional vector potential outcomes and multiple treatments. This extension is nontrivial owing to the complex dependence structure between the elements of \( \hat{R} \) and the lack of the vector form of the Wald–Wolfowitz–Hoeffding theorem for a bi-linear rank statistic under blocked permutation.

We obtain this theorem by making use of the techniques to prove the Wald–Wolfowitz–Hoeffding theorem for a linear rank statistic (Hájek 1961; Sen 1995), that is, constructing an asymptotically equivalent random variable that is the sum of independent random variables, and then, applying the classical Linderberg–Feller CLT. The detailed proof is given in the supplementary material.

### 3.2. Joint Asymptotic Normality of \( \hat{\tau}_{\text{unadj}} \)

As \( \hat{\tau}_{\text{unadj}} \) is a linear contrast of the blocked sample means \( \hat{Y} = (\hat{Y}(1), \ldots, \hat{Y}(Q))^T \), we can obtain the joint asymptotic normality of \( \hat{\tau}_{\text{unadj}} \) by applying **Theorem 2** to \( \hat{Y} \). For this purpose, we assume the following condition which guarantees the convergence of the covariance, \( \text{cov}(\sqrt{n}\hat{\tau}_{\text{unadj}}) \).

**Condition 3.** The weighted variances and covariances, \( \sum_{m=1}^{M} \pi_{\{m\}} S_{\{m\}}^2 \text{Y}(q) / e^\infty_{\{m\}} \) and \( \sum_{m=1}^{M} \pi_{\{m\}} S_{\{m\}} \text{Y}(q) \text{Y}(q') \), \( 1 \leq q, q' \leq Q \), tend to finite limits.

**Theorem 3.** If Conditions 1, 2 for \( R_{\{m\}}(q) = Y_{\{m\}}(q) \), and 3 hold, then \( \hat{V}_{\{m\}}(\text{Y}) \) and \( V_{\{m\}}(\text{Y}) \), respectively, and \( \sqrt{n}(\hat{\tau}_{\text{unadj}} - \rho) \overset{d}{\to} \mathcal{N}(0, \hat{\Sigma}) \).

Furthermore, if \( n_{\{m\}} \geq 2 \) for \( m = 1, \ldots, M, q = 1, \ldots, Q \), then, the covariance estimator \( \hat{V}_{\{m\}}(\text{Y}) \) converges in probability to \( V(\text{Y}) \) and \( V(\text{Y}) - \hat{V}(\text{Y}) = \lim_{n \to \infty} \sum_{m=1}^{M} \pi_{\{m\}} S_{\{m\}}^2 \rho \geq 0. \)

**Theorem 3** establishes the joint asymptotic normality of \( \hat{\tau}_{\text{unadj}} \) and provides an asymptotically conservative estimator for the asymptotic covariance. The covariance estimator is consistent if \( S_{\{m\}}^2 \rho = 0 \), that is, if the unit-level factorial effects are block-specifically additive, \( \tau_i = e_{\{m\}} \) for all \( i \in [m] \), where \( e_{\{m\}} \) is a constant vector. In such a case, **Theorem 3** can be used for randomization-based inferences of factorial effects under the additive causal effects assumption, such as conducting tests or calculating p-values under Fisher’s sharp null hypothesis. In general cases, **Theorem 3** is useful for constructing large-sample conservative confidence intervals for each factorial effect or confidence regions for joint factorial effects. More specifically, if the limit of \( V(\text{Y}) \) is nonsingular, then the probability that \( V_{\{m\}}(\text{Y}) \) is nonsingular converges to one. For \( \alpha \in (0, 1) \), let \( \chi^2_{\{m\}}(1 - \alpha) \) be the \((1 - \alpha)\)th quantile of a \( \chi^2 \) distribution with degrees of freedom \( F_1 \). We can then construct a Wald-type confidence region for \( C_r \):

\[
\{ \mu : n(C_{\text{unadj}} \rho - \mu)^T C_{\text{unadj}}^{-1}(C_{\text{unadj}} \rho - \mu) \leq \chi^2_{\{m\}}(1 - \alpha) \},
\]

where \( C \in \mathbb{R}^{F_1 \times F} (F_1 \leq F) \) is a constant matrix and has full row rank and the asymptotic coverage rate is at least as large as...
1 − α. The asymptotic coverage rate equals 1 − α if and only if
\[ \lim_{n \to \infty} \sum_{m=1}^{M} \pi[m] \frac{\alpha^2}{\alpha[m]q} = 0. \]

**Remark 1.** The authors in Aronow, Green, and Lee (2014) proposed a consistent estimator for the sharp bound on the asymptotic variance of the difference-in-means estimator in completely randomized experiments with scalar outcomes and two treatments. Their proposed estimator is generally less conservative than the Neyman-type variance estimator. It will be interesting to extend their results to randomized block factorial experiments.

### 4. Covariate Adjustment

It is widely recognized that adjusting for the imbalances of baseline covariates can improve the treatment effect estimation efficiency in randomized experiments, including completely randomized experiments (Lin 2013; Lei and Ding 2021), randomized block experiments (Liu and Yang 2020), and completely randomized 2^K factorial experiments (Lu 2016a, 2016b). In this section, we propose four covariate adjustment methods in randomized block 2^K factorial experiments according to the number of blocks, block sizes, and propensity scores, and compare their efficiencies with that of the unadjusted estimator.

#### 4.1. Existence of Small Blocks, Equal Propensity Scores

Covariate adjustment is a standard statistical approach in the analysis of randomized experiments to improve estimation efficiency, following a similar spirit in the survey sampling literature (e.g., Cressel, Särndal, and Wretman 1976; Särndal, Swensson, and Wretman 2003). To increase the estimation accuracy of the mean \( \bar{Y}(q) \), \( q = 1, \ldots, Q \), an adjusted estimator of the form \( \bar{Y}(q) - (\bar{X}(q) - \bar{X})^T \hat{\beta}(q) \) is often used to replace the simple blocked sample mean \( \bar{Y}(q) \), where \( \hat{\beta}(q) \) is an (estimated) adjusted vector. In completely randomized experiments with two or more treatments, \( \hat{\beta}(q) \) can be obtained by regressing the observed outcomes on the covariates using the sample under treatment arm \( q \). More importantly, under mild conditions, the efficiency gain of estimating the individual mean \( \bar{Y}(q) \) can yield efficiency gain of estimating the average treatment effect, regardless of the correlation structure of \( \bar{Y}(q) - (\bar{X}(q) - \bar{X})^T \hat{\beta}(q) \) between treatments (Lin 2013; Lu 2016a, 2016b). However, such an efficiency gain is not guaranteed in randomized block experiments, as shown in the following **Theorem 4**. In this section, we first study how to obtain the optimal adjusted vector for estimating \( \bar{Y}(q) \) with multiple treatments, and then discuss the conditions under which the resulting covariate-adjusted factorial effects estimator is more efficient than the unadjusted estimator.

The optimal adjusted vector \( \hat{\beta}(q) \) can be obtained by minimizing the variance of \( \bar{Y}(q) - (\bar{X}(q) - \bar{X})^T \hat{\beta} \):

\[
\hat{\beta}(q) = \arg \min_{\beta} \text{var} \left[ \bar{Y}(q) - (\bar{X}(q) - \bar{X})^T \beta \right] = \arg \min_{\beta} \frac{1}{n} \sum_{m=1}^{M} \frac{\pi[m]}{\pi[m]q} \frac{\alpha^2}{\alpha[m]q} \sum_{q[m]}[Y(q) - X(q)]^T \beta, \quad (1)
\]

where the second equality is obtained by applying **Theorem 1** to the transformed outcomes \( Y(q) - X(q)^T \beta \). The optimal adjusted vector \( \beta(q) \) can be consistently estimated by replacing the block-specific variance in (1) by the corresponding sample variance:

\[
\hat{\beta}(q) = \arg \min_{\beta} \sum_{m=1}^{M} \frac{1 - \varepsilon[m]q}{\varepsilon[m]q} \frac{\pi[m]}{n[m]q - 1} \sum_{i \in [m]} I(Z_i = q) \left[ Y_i(q) - \hat{Y}_i[q(m)] - (X_i - \hat{X}[q(m)])^T \beta \right]^2.
\]

This is equivalent to performing the following linear regression with weights \( \omega_i = \{1 - \varepsilon[m]q\}n[m]q / \varepsilon[m]q(n[m]q - 1) \) for \( i \in [m] \) and \( Z_i = q \):

\[
Y_{i}^{\text{obs}} = \sum_{q=1}^{Q} \sum_{m=1}^{M} \alpha[m](q) I(Z_i = q, i \in [m]) + \sum_{q=1}^{Q} I(Z_i = q)(X_i - \bar{X})^T \beta(q) + \epsilon_i,
\]

where \( Y_{i}^{\text{obs}} = \sum_{q=1}^{Q} I(Z_i = q)Y_i(q) \) is the observed outcome. Then, \( \hat{\beta}(q) \) is equal to the weighted least squares (WLS) estimator of \( \beta(q) \). Let \( \hat{\alpha}[m](q) \) be the WLS estimator of \( \alpha[m](q) \). Replacing \( \hat{Y}(q) \) in \( \hat{\tau}_{\text{unad}} \) by \( \sum_{m=1}^{M} \pi[m] \hat{\alpha}[m](q) = \hat{Y}(q) - (\hat{X}(q) - \bar{X})^T \beta(q) \), we obtain a covariate-adjusted average factorial effects estimator of \( \tau \),

\[
\hat{\tau}_{\text{adj}} = \frac{1}{2^{K-1}} \sum_{q=1}^{Q} d_q \left[ \hat{Y}(q) - (\hat{X}(q) - \bar{X})^T \hat{\beta}(q) \right].
\]

**Remark 2.** For the case of two treatments (\( Q = 2 \)), Liu and Yang (2020) proposed to use the following adjusted vector, \( q = 1, 2 \),

\[
\tilde{\beta}(q) = \arg \min_{\beta} \sum_{m=1}^{M} \frac{\pi[m]}{n[m]q - 1} \sum_{i \in [m]} I(Z_i = q) \left[ Y_i(q) - \hat{Y}_i[q(m)] - (X_i - \hat{X}[q(m)])^T \beta \right]^2.
\]

Note that, when the propensity scores \( \varepsilon[q(m)] \) are equal across blocks, \( \hat{\beta}(q) \) has the same asymptotic limit as \( \tilde{\beta}(q) \). Thus, \( \hat{\beta}(q) \) can be considered extension of \( \tilde{\beta}(q) \) to general propensity scores and multiple treatments.

To study the asymptotic property of \( \hat{\tau}_{\text{adj}} \), we need to decompose the potential outcomes as follows: \( Y_i(q) = Y_i[q(m)] + (X_i - \hat{X}[q(m)])^T \beta(q) + \varepsilon_i(q), \) \( i \in [m], m = 1, \ldots, M \), where \( \varepsilon_i(q) \) are (fixed) decomposition errors. It is easy to see that the block-specific mean of \( \varepsilon_i(q) \) is zero, that is, \( \varepsilon_i[q(m)] = 0 \) for each block \( m \). In addition, we need the following condition:

**Condition 4.** The following weighted variances and covariances tend to finite limits:
discussion below:

• Equal propensity scores. When $\epsilon_{ij}$ is positive semidefinite, where as in general, the second term in the difference between asymptotic covariances of $\hat{\tau}_{unadj}$ and $\hat{\tau}_{adj}$ is the limit of

$$
\bar{V}_n(\hat{X}) = 2^{-2(K-1)} \sum_{m=1}^{M} \sum_{q=1}^{Q} \epsilon_{iq} S_{m}\{X_j(q)\}|X| \epsilon_{iq} | d_q d_q^T.
$$

The first term in the difference between asymptotic covariances (2) is positive semidefinite, whereas in general, the second and third terms can be either positive definite or negative definite. Thus, the difference between the asymptotic covariances of $\hat{\tau}_{adj}$ and $\hat{\tau}_{unadj}$ can be either positive or negative definite. Therefore, minimizing the covariance of $\hat{Y}(q) - \hat{X}(q) - \hat{X}^T \beta$ separately cannot guarantee the reduction of covariance for estimating the average factorial effects $\tau$. This is a significant difference between the performances of covariate adjustment in completely randomized and randomized block experiments. The last two terms are equal to zero in some special cases discussed below:

• Without blocking ($M = 1$). According to the definition of $\beta(q)$ in (1), we have $\beta(q) = \arg \min_\beta [(1 - e_{11q})/e_{11q}] S_{11}\{X_j(q) - X^T \beta\}$. Then, the decomposition errors $\epsilon_{ij}$ are orthogonal to the covariates $X_j$ in the sense that $\sum_{m=1}^{M} \hat{\pi}_m S_{m}\{X_j(q)\} = 0$, which again implies that the last two terms in (2) are equal to zero. Therefore, the covariate-adjusted factorial effect estimator $\widehat{\tau}_{adj}$ is asymptotically more efficient than, or at least as efficient as, the unadjusted estimator $\widehat{\tau}_{unadj}$. As equal propensity scores are common in practice, we discuss this special case in more detail.

We define residuals as follows: $\widehat{\epsilon}_i(q) = Y_i(q) - \widehat{\pi}_m S_{m}\{X_j(q)\} - \hat{X}_i, q = 1, \ldots, Q$. Similar to the arguments for $\widehat{\tau}_{unadj}$, the asymptotic covariance of $\widehat{\tau}_{adj}$ can be estimated by $\bar{V}_n(\hat{\epsilon})$, which is defined similarly to $\bar{V}_n(Y)$ except that $Y_i$ is replaced by $\hat{\epsilon}_i = (\widehat{\epsilon}_i(1), \ldots, \hat{\epsilon}_i(Q))^T$.

Corollary 1. Under Conditions 1, 2 for $R_i(q) = Y_i(q), X_i, 3$, and 4, if $n_{m|q} \geq 2$ for $m = 1, \ldots, M, q = 1, \ldots, Q$, then $\bar{V}_n(\hat{\epsilon})$ and $\bar{V}_n(\hat{\epsilon})$ have finite limits, denoted by $\bar{V}(\epsilon)$ and $\bar{V}(\epsilon)$, respectively, and $\sqrt{n}(\hat{\tau}_{adj} - \tau) \xrightarrow{d} N(0, \bar{V}(\epsilon))$. Furthermore, the difference between the asymptotic covariances of $\bar{V}_n(\hat{\tau}_{adj})$ and $\bar{V}_n(\hat{\tau}_{adj})$ is the limit of

$$
\bar{V}_n(\hat{X}) = 2^{-2(K-1)} \sum_{m=1}^{M} \sum_{q=1}^{Q} \epsilon_{iq} S_{m}\{X_j(q)\}|X| \epsilon_{iq} | d_q d_q^T.
$$

The last two terms are equal to zero in some special cases discussed below:

• Without blocking ($M = 1$). According to the definition of $\beta(q)$ in (1), we have $\beta(q) = \arg \min_\beta [(1 - e_{11q})/e_{11q}] S_{11}\{X_j(q) - X^T \beta\}$. Thus, the decomposition errors $\epsilon_{ij}$ are orthogonal to the covariates $X_j$ in the sense that $\sum_{m=1}^{M} \hat{\pi}_m S_{m}\{X_j(q)\} = 0$, which again implies that the last two terms in (2) are equal to zero. Therefore, the covariate-adjusted factorial effect estimator $\widehat{\tau}_{adj}$ is asymptotically more efficient than, or at least as efficient as, the unadjusted estimator $\widehat{\tau}_{unadj}$. As equal propensity scores are common in practice, we discuss this special case in more detail.

4.2 Existence of Small Blocks, Unequal Propensity Scores

It is not always possible to ensure the same propensity scores across blocks because of practical restrictions. For example,
consider an experiment with 10 men and 11 women; if blocked by gender, it is impossible to make the propensity scores equal across blocks. To improve the estimation efficiency of \( \tau \) for unequal propensity scores, we propose two covariate adjustment methods, from a conditional inference perspective. Conditional inference is an influential idea in statistics that began with the original ideas of Fisher (1959).

### 4.2.1. Conditional on a Single Factorial Effect of the Covariates

In this section, we introduce the idea of conditional inference for estimating each factorial effect \( \gamma_f \) from a conditional inference perspective. Conditional forestimating each factorialeffect

\[
\Omega_f = \sum_{i=1}^{Q} \gamma_f \theta_{i|q}\]

for \( i \in [m] \) and \( z_i = q \):

\[
y_{obs}^i = \sum_{q=1}^{M} \alpha_m(q) I(z_i = q, i \in [m]) + (X_i - \bar{X})^T \gamma + \epsilon_{i, \text{cond.}}
\]

Note that the weights are different from those used in \( \hat{\alpha}_{\text{adj}} \). Let \( \hat{\alpha}_{m, \text{cond.}}(q) \) be the WLS estimator of \( \alpha_m(q) \). Then, \( \hat{\alpha}_{\text{cond.}} \) is equal to \( \hat{\alpha}_{\text{adj.}} \) with \( \gamma \) being replaced by \( \sum_{m=1}^{M} \pi_m \hat{\alpha}_{m, \text{cond.}}(q) = \gamma(q) - [\hat{X}(\hat{q}) - \bar{X}]^T \gamma \).

**Remark 4.** By definition and simple algebra, the adjusted vector \( \gamma \) can be interpreted as a projection coefficient that minimizes the variance of \( \sum_{q=1}^{Q} \gamma_f \theta_{i|q} \). Therefore, removing the bias, \( \gamma_f \tau_f X_f - \tau_f X_f \), will result in a consistent and more accurate estimator:

\[
\hat{\gamma}_f = \hat{\gamma}_f - \hat{\gamma}_f(\hat{\tau}_f X_f - \tau_f X_f)
\]

where \( \hat{\gamma}_f \) is a consistent estimator of the adjusted vector \( \gamma_f \). The adjusted average effects estimator is \( \hat{\tau}_f = (\hat{\tau}_f, \ldots, \hat{\tau}_f) \). Let \( \hat{S}_{m|X}(q) = \text{the sample covariance of } X \text{ under treatment combination } q \text{ in block } m \).

**Proposition 2.** Under Conditions 1, 2 for \( R_i(q) = Y_i(q), X_i, 3, \) and 4, if \( n_{[m|q]} \geq 2 \) for \( m = 1, \ldots, M, q = 1, \ldots, Q \), then

\[
\Sigma_{f,n,XX} = 2^{-2(K-1)} \sum_{m=1}^{M} \pi_m \sum_{q=1}^{Q} \frac{1}{\ell_{[m|q]}} S_{m|X}(q),
\]

Furthermore, a consistent estimator of \( \gamma_f \) is

\[
\hat{\gamma}_f = \left( \sum_{m=1}^{M} \pi_m \sum_{q=1}^{Q} \frac{1}{\ell_{[m|q]}} S_{m|X}(q) \right)^{-1} \left( \sum_{m=1}^{M} \pi_m \sum_{q=1}^{Q} \frac{1}{\ell_{[m|q]}} S_{m|X}(q) \right).
\]

**Theorem 5.** Under Conditions 1, 2 for \( R_i(q) = Y_i(q), X_i, 3, \) and 4, if \( n_{[m|q]} \geq 2 \) for \( m = 1, \ldots, M, q = 1, \ldots, Q \), then \( \hat{V}_n(\hat{q}) \) have finite limits, denoted by \( \hat{V}(\hat{q}) \) and \( V(\hat{q}) \), respectively, \( \sqrt{n}_{\hat{\tau}_f - \tau_f} \xrightarrow{d} \mathcal{N}(0, \hat{V}(\hat{q})) \) and \( \hat{V}_n(\hat{q}) \xrightarrow{P} V(\hat{q}) \). Furthermore, the difference between the asymptotic covariances of \( \hat{\tau}_f \text{ and } \hat{\tau}_f \) is the limit of

\[
\hat{V}_n(\hat{q})(\hat{\tau}_f) + 2^{-2(K-1)} \sum_{m=1}^{M} \pi_m \sum_{q=1}^{Q} \frac{2}{\ell_{[m|q]}} S_{m|X}(q) \| d_q d_q^T
\]

and the asymptotic difference between the covariance estimators \( \hat{V}_n(\hat{q}) \) and \( V(\hat{q}) \) is the limit of

\[
V_n(\hat{q})(\hat{\tau}_f) + 2^{-2(K-1)} \sum_{m=1}^{M} \pi_m \sum_{q=1}^{Q} \frac{2}{\ell_{[m|q]}} S_{m|X}(q) \| d_q d_q^T.
\]

**Theorem 5** implies that \( \hat{\tau}_f \) is consistent and jointly asymptotically normal, and that its asymptotic covariance can be conservatively estimated. Similar to \( \hat{\tau}_f \) and \( \hat{\tau}_f \), an asymptotically conservative Wald-type confidence region for \( \mathbf{C} \) is

\[
\left\{ \mu : n(C\hat{\tau}_f - \mu)^T \hat{C}^{-1}(C\hat{\tau}_f - \mu) \leq \chi^2_F(1-\alpha) \right\}.
\]
To compare the efficiencies of \( \hat{\tau}_{\text{cond}} \) and \( \hat{\tau}_{\text{unadj}} \), according to Proposition 2, the adjusted vector \( \gamma = \sum_{f,n,XX}^{1} \sum_{f,n,XT} = \arg\min_{\beta} \sum_{m=1}^{M} \pi[m] \sum_{q=1}^{Q} (1/\epsilon[m,q]) S[m][Y(q) - \bar{X}\beta)^2. \) Thus, the decomposition errors \( \eta(q) \) are orthogonal to the covariates in the following sense: \( \sum_{m=1}^{M} \pi[m] \sum_{q=1}^{Q} (1/\epsilon[m,q]) S[m][X_{m}X_{q}] = 0, \) which implies \( \sum_{m=1}^{M} \pi[m] \sum_{q=1}^{Q} (1/\epsilon[m,q]) S[m][X_{m}X_{q}] = 0. \)

- When there is only one factor, that is, \( K = 1 \) and \( Q = 2, \) we have \( d_{q}^{2}d_{q}^{2} = 1 \) for \( q = 1, 2. \) Thus,

\[
2^{-2(K-1)} \sum_{m=1}^{M} \pi[m] \sum_{q=1}^{Q} 2 \epsilon[m,q] S[m][X_{m}X_{q}](q,q) d_{q}d_{q}^{T} = 0.
\]

Therefore, both the point estimator \( \hat{\tau}_{\text{cond}} \) and covariance estimator \( \hat{\Sigma}_{\text{cond}}(q) \) are no worse than \( \hat{\tau}_{\text{unadj}} \) and \( \hat{\Sigma}_{\text{unadj}}(q). \) Furthermore, for equal propensity scores, \( \hat{\tau}_{\text{cond}} \) is asymptotically equivalent to \( \hat{\tau}_{\text{adj}} \) (as implied by Theorems 4 and 5). In contrast, for unequal propensity scores, \( \hat{\tau}_{\text{adj}} \) may hurt the precision when Compared to the unadjusted estimator, whereas \( \hat{\tau}_{\text{cond}} \) does not.

- When \( K > 1, \) as the diagonal elements of \( d_{q}d_{q}^{T} \) are all equal to one, the diagonal elements of the differences between the asymptotic covariances and the limits of the covariance estimators of \( \hat{\tau}_{\text{unadj}} \) and \( \hat{\tau}_{\text{cond}} \) are greater than or equal to zero. Therefore, for each factorial effect \( \tau_{f} (f = 1, \ldots, F), \) the covariate-adjusted estimator \( \hat{\tau}_{\text{cond}} \) generally improves the estimation efficiency, and its covariance estimator \( \{\hat{\Sigma}_{\text{cond}}(q)\}_{ff} \) (the \( f \)th diagonal element of \( \hat{\Sigma}_{\text{cond}}(q) \)) is no worse than that of the unadjusted estimator, even when the propensity scores differ across blocks. However, the difference between the asymptotic covariances of \( \hat{\tau}_{\text{unadj}} \) and \( \hat{\tau}_{\text{cond}} \) is not always positive semidefinite. Hence, for some \( C, \) \( C\hat{\tau}_{\text{cond}} \) may be worse than \( C\hat{\tau}_{\text{unadj}}. \)

### 4.2.2. Conditional on all Factorial Effects of the Covariates

The joint efficiencies of \( \hat{\tau}_{\text{cond}} \) and \( \hat{\tau}_{\text{unadj}} \) are not ordered in an unambiguous manner. To address this issue and further improve the efficiency of \( \hat{\tau}_{\text{cond}}, \) we propose another estimator conditional on all of the observed factorial effects of the covariates: \( \tilde{\tau}_{X} = (\tilde{\tau}_{X,1}, \ldots, \tilde{\tau}_{X,F})^{T}. \) Applying Theorem 2 to \( (Y, X), \)

\[
\sqrt{\eta}(\tilde{\tau}_{\text{unadj}} - \tilde{\tau}_{X})^{T} \overset{d}{\rightarrow} \mathcal{N}(0, \Sigma), \quad \text{where} \quad \tau_{X} = 0 \quad \text{and} \quad \Sigma = \lim_{n \rightarrow \infty} \left( \frac{S_{n,XX}}{S_{n,XT}} \right) \left( \frac{S_{n,XT}}{S_{n,XX}} \right)^{T}.
\]

Note that \( S_{n,XT} = S_{n,XY} \), which can be consistently estimated by \( S_{n,XT} = \hat{S}_{n,XY}. \) Similar to Proposition 2, \( S_{n,XX} \) and \( S_{n,XY} \) can be consistently estimated by

\[
\hat{S}_{n,XX} = 2^{-2(K-1)} \sum_{m=1}^{M} \pi[m] \sum_{q=1}^{Q} 1 \epsilon[m,q] d_{q}d_{q}^{T} \otimes \hat{S}[m][XY(q)],
\]

where \( \otimes \) denotes the Kronecker product of two matrices. Thus, \( \hat{\Sigma} = \sum_{m=1}^{M} \sum_{q=1}^{Q} 1 \epsilon[m,q] \otimes \hat{S}[m][XY(q)]. \)

Therefore, both the point estimator \( \hat{\tau}_{\text{cond}} \) and covariance estimator \( \hat{\Sigma}_{\text{cond}}(q) \) are no worse than \( \hat{\tau}_{\text{unadj}} \) and \( \hat{\Sigma}_{\text{unadj}}(q). \) Furthermore, for equal propensity scores, \( \hat{\tau}_{\text{cond}} \) is asymptotically equivalent to \( \hat{\tau}_{\text{adj}} \) (as implied by Theorems 4 and 5). In contrast, for unequal propensity scores, \( \hat{\tau}_{\text{adj}} \) may hurt the precision when Compared to the unadjusted estimator, whereas \( \hat{\tau}_{\text{cond}} \) does not.

### 4.3. Only Large Blocks

The above three covariate adjustment methods use the block-common adjusted vectors, that is, they pool together the units of all blocks under each treatment arm. As the factorial effects \( \tau = \sum_{m=1}^{M} \pi[m] \tau[m] \) are the weighted average of block-specific factorial effects, and because randomization is conducted independently across blocks, it may be more efficient to perform block-specific covariate adjustment when there are only large blocks. More precisely, we can define block-specific optimal adjusted vectors as follows: for \( q = 1, \ldots, Q, \)

\[
\beta_{[m]}(q) = \arg \min_{\beta} \left\{ \hat{Y}_{[m]}(q) - \hat{X}_{[m]}(q) \right\}^{T} \beta = \left( \hat{S}_{[m]XX} \right)^{-1} \hat{S}_{[m]XY}(q).
\]

The optimal adjusted vector \( \beta_{[m]}(q) \) can be consistently estimated by the corresponding sample quantity (regression of \( Y_{\text{obs}} \) on \( X_{i} \) under each treatment arm and each block),

\[
\tilde{\beta}_{[m]}(q) = \left( \hat{S}_{[m]XX} \right)^{-1} \hat{S}_{[m]XY}(q).
\]

Then, the block-specific covariate-adjusted factorial effect estimator can be defined as
$$\tau_{\text{inter}} = \frac{1}{2K-1} \sum_{q=1}^{Q} d_q \sum_{m=1}^{M} \pi_{[m]} \left[ \hat{Y}_{[m]}(q) - \left[ \hat{X}_{[m]}(q) - \bar{X}_{[m]} \right] \hat{\beta}_{[m]}(q) \right].$$

Equivalently, $\tau_{\text{inter}}$ can be obtained using the following linear regression:

$$Y_{i}^{\text{obs}} = \sum_{q=1}^{Q} \sum_{m=1}^{M} \alpha_{[m]}(q) I(Z_i = q, i \in [m]) + \sum_{q=1}^{Q} \sum_{m=1}^{M} I(Z_i = q, i \in [m]) (X_i - \bar{X}_{[m]})^T \hat{\beta}_{[m]}(q) + e_{i,\text{inter}}.$$

Then, $\hat{\beta}_{[m]}(q)$ is the ordinary least squares (OLS) estimator of $\beta_{[m]}(q)$ and $\tau_{\text{inter}}$ is equal to $\tau_{\text{unadj}}$ with $\hat{Y}_{[m]}(q)$ being replaced by the OLS estimator of $\omega_{[m]}(q)$. Moreover, $\tau_{\text{inter}}$ is equivalent to projecting $\hat{\tau}_{\text{unadj}}$ on $[\hat{X}_{[m]}(q), q = 1, \ldots, Q, m = 1, \ldots, M].$

Because both $[\hat{X}(q), q = 1, \ldots, Q]$ and $\hat{\tau}$ are linear transformations of $[\hat{X}_{[m]}(q), q = 1, \ldots, Q, m = 1, \ldots, M]$, $\tau_{\text{inter}}$ has the smallest asymptotic covariance among all of the considered estimators (see Theorem 7).

To investigate the theoretical properties of $\tau_{\text{inter}}$, we need to project the potential outcomes onto the space spanned by the linear combinations of the covariates within each block,

$$Y_i(q) = \hat{Y}_{[m]}(q) + (X_i - \bar{X}_{[m]})^T \hat{\beta}_{[m]}(q) + \mu_i(q), \quad i \in [m],$$

where $\mu_i(q)$ are (fixed) projection errors. It is easy to see that $\hat{\mu}_i(q) = Y_i(q) - \hat{Y}_{[m]}(q) - [X_i - \bar{X}_{[m]}] \hat{\beta}_{[m]}(q), \quad i \in [m].$

Let $\hat{\mu}_i = (\hat{\mu}_i(1), \ldots, \hat{\mu}_i(Q))^T$ and $\hat{\mu}_i = (\hat{\mu}_i(1), \ldots, \hat{\mu}_i(Q))^T$.

Define $\hat{V}(\mu)$, $V(\mu)$, and $\hat{V}_n(\mu)$ similarly to $Y_i(q)$, $Y_i(q)$, and $\hat{V}_n(\mu)$ except that $Y_i$ is replaced by $\hat{\mu}_i$ and $\hat{\mu}_i$, respectively.

**Condition 5.** The following weighted variances and covariances of the projection errors $\mu_i(q)$ tend to finite limits:

$$\sum_{m=1}^{M} \pi_{[m]} \frac{S^2_{[m]}}{Q_{[m]}} \sum_{q=1}^{Q} \pi_{[m]} S_{[m] \mu(q)}(\mu(q)), \quad 1 \leq q, q' \leq Q.$$ 

**Condition 6.** (a) The block size $n_{[m]} \to \infty$ for $m = 1, \ldots, M$, and there exists a constant $M_{\max}$ such that $M \leq M_{\max}$; (b) the block-specific covariance matrix $S_{[m]XX}$ converges to a finite, invertible matrix, and the block-specific variance, $S^2_{[m]Y(q)}$, and covariances, $S_{[m]XY(q)}$ and $S_{[m]Y(q)Y(q')}, 1 \leq q, q' \leq Q$, converge to finite limits.

**Theorem 7.** If Conditions 1, 2 for $R_i(q) = Y_i(q), X_i, 5,$ and 6 hold, then $\hat{V}_n(\mu)$ and $V_n(\mu)$ have finite limits, denoted by $\hat{V}(\mu)$ and $V(\mu)$, respectively, $\sqrt{n}(\hat{\tau}_{\text{inter}} - \tau) \xrightarrow{d} N(0, \hat{V}(\mu))$, and $\hat{V}_n(\mu) \xrightarrow{p} V(\mu) \geq \hat{V}(\mu)$. Furthermore, $\hat{\tau}_{\text{inter}}$ has the smallest asymptotic covariance among the class of estimators of the following forms:

$$\frac{1}{2K-1} \sum_{q=1}^{Q} d_q \sum_{m=1}^{M} \pi_{[m]} \left[ \hat{Y}_{[m]}(q) - \left[ \hat{X}_{[m]}(q) - \bar{X}_{[m]} \right] \hat{\beta}_{[m]}(q) \right],$$

$$\hat{\tau}_{\text{unadj}} - \sum_{m=1}^{M} \pi_{[m]} \hat{Y}_{[m]}(q) X_{[m]},$$

where $\hat{\beta}_{[m]}(q)$ and $\hat{Y}_{[m]}(q)$ are estimated adjusted coefficients that converge in probability to finite limits. The difference between the asymptotic covariances of $\hat{\tau}_{\text{unadj}}$ and $\hat{\tau}_{\text{inter}}$ is the limit of

$$2^{-2(K-1)} \sum_{m=1}^{M} \sum_{q=1}^{Q} \frac{1}{\pi_{[m]q}} d_q \beta_{[m]}(q) S_{[m]XX} \beta_{[m]}(q) d_q - \left[ \sum_{q=1}^{Q} d_q \beta_{[m]}(q) \right] S_{[m]XX} \left[ \sum_{q=1}^{Q} d_q \beta_{[m]}(q) \right]^T,$$

and the difference between the limits of the covariance estimators, $\hat{V}_n(\mu)$ and $\hat{V}_n(\mu)$, is the limit of

$$\sum_{m=1}^{M} \sum_{q=1}^{Q} \frac{1}{\pi_{[m]q}} d_q \beta_{[m]}(q) S_{[m]XX} \beta_{[m]}(q) d_q \geq 0.$$

According to Theorem 7, $\hat{\tau}_{\text{inter}}$ is consistent and jointly asymptotically normal, and its asymptotic covariance is no greater than those of $\hat{\tau}_{\text{unadj}}, \hat{\tau}_{\text{adj}}, \hat{\tau}_{\text{cond}}$, and $\hat{\tau}_{\text{cond2}}$. Therefore, it is the most efficient method, at least asymptotically, to infer $\tau$ (or $C\tau$) when there are only large blocks. This is not surprising because previous works have shown that including interactions could improve efficiency (see, e.g., Lin 2013; Lu 2016a, 2016b; Liu and Yang 2020; Lei and Ding 2021; Su and Ding 2021). We can construct an asymptotically conservative confidence region for $C\tau$.

\[ \left\{ \mu : n(C\hat{\tau}_{\text{inter}} - \mu)^T \left[ nC\hat{V}_n(\hat{\mu})C^T \right]^{-1} (C\hat{\tau}_{\text{inter}} - \mu) \leq \chi^2_{\ell 1}(1 - \alpha) \right\}. \]

**Remark 5.** Although $\hat{\tau}_{\text{inter}}$ is optimal (asymptotically) among all of the considered estimators, evidence has suggested that this block-specific covariate adjustment method can lead to inferior performance when there exist small blocks (Liu and Yang 2020).

**4.4. Summary of Covariate-Adjusted Estimators**

From the asymptotic analysis above, $\hat{\tau}_{\text{inter}}$ is the most efficient estimator among all of the considered methods. However, $\hat{\tau}_{\text{inter}}$ may not be applicable or have inferior performance when there exist small blocks. In such cases, we can use $\hat{\tau}_{\text{unadj}}, \hat{\tau}_{\text{adj}}, \hat{\tau}_{\text{cond}}$, and $\hat{\tau}_{\text{cond2}}$. Compared to $\hat{\tau}_{\text{unadj}}, \hat{\tau}_{\text{adj}}$ increases the efficiency when the propensity scores are the same across blocks but may degrade the efficiency otherwise; $\hat{\tau}_{\text{cond}}$ increases the efficiency for estimating each factorial effect $\tau_j$ but may degrade the efficiency for estimating $C\tau$ for some $C$. $\hat{\tau}_{\text{cond2}}$ is generally more efficient than $\hat{\tau}_{\text{cond}}$ and $\hat{\tau}_{\text{unadj}}$ even when the propensity scores differ across blocks. Moreover, $\hat{\tau}_{\text{cond2}}$ is asymptotically equivalent to $\hat{\tau}_{\text{adj}}$ for the case of equal propensity scores across blocks but needs to estimate more adjusted coefficients ($pQF$ versus $pQ$). Therefore, we recommend $\hat{\tau}_{\text{adj}}$ when there exist
small blocks and the propensity scores are the same across blocks, τ_{cond} when there exist small blocks and the propensity scores differ across blocks, and τ_{inter} when there are only large blocks.

5. Simulation Study

In this section, we evaluate the finite-sample performances of the unadjusted and four covariate-adjusted estimators with a simulation study. We consider a randomized block $2^2$ factorial experiment with $Q = 4$ treatment combinations, denoted as $(-1, -1)$, $(-1, +1)$, $(+1, -1)$, and $(+1, +1)$. Besides uniform weighting, we also consider a treatment combination weighted by $(-2, -1, 2, 1)$, which is the linear transformation of the average factorial effects, $C_{\tau}$ with $C = (1, 0, -1/3)$. We call this transformation the general-weight effect. The potential outcomes and covariates are both generated according to the following equations:

$$Y_i = X_i^T \beta_{11} + \exp (X_i^T \beta_{12}) + \varepsilon_i(1), \quad i = 1, \ldots, n,$$

$$Y_i = X_i^T \beta_{21} + \exp (X_i^T \beta_{22}) + \varepsilon_i(2), \quad i = 1, \ldots, n,$$

$$Y_i = X_i^T \beta_{31} + \exp (X_i^T \beta_{32}) + \varepsilon_i(3), \quad i = 1, \ldots, n,$$

$$Y_i = X_i^T \beta_{41} + \exp (X_i^T \beta_{42}) + \varepsilon_i(4), \quad i = 1, \ldots, n,$$

where $\varepsilon_i(q), i = 1, \ldots, n, q = 1, \ldots, 4$, are iid Gaussian random variables with mean zero and variance $\sigma^2_q$. We choose $\sigma^2_q$ such that the signal-to-noise ratio equals 10. The $X_i$ is a three-dimensional vector of covariates generated from a multivariate normal distribution with mean zero and covariance matrix $\Sigma$: $\Sigma_{jj} = 1$ and $\Sigma_{ij} = 0.5^{i-j}, j \neq l, i = 1, 2, 3$. For $j = 1, 2, 3$, we generate the coefficient vectors from uniform distributions:

$$\beta_{11j} \sim U(-1, 1), \quad \beta_{12j} \sim U(-0.1, 0.1),$$

$$\beta_{21j} \sim \beta_{11j} + U(-1, 1), \quad \beta_{22j} \sim \beta_{12j} + U(-0.1, 0.1),$$

$$\beta_{31j} \sim \beta_{21j} + U(-1, 1), \quad \beta_{32j} \sim \beta_{22j} + U(-0.1, 0.1),$$

$$\beta_{41j} \sim \beta_{31j} + U(-1, 1), \quad \beta_{42j} \sim \beta_{32j} + U(-0.1, 0.1).$$

The potential outcomes and covariates are both generated once and then kept fixed. We consider three different cases of number of blocks, block sizes, and propensity scores. For each case, we conduct randomized block factorial experiments 10,000 times to compare the performances of various methods in terms of bias, standard deviation (SD), root mean square error (RMSE), empirical coverage probability (CP), and mean confidence interval length (CI length) of the 95% confidence interval (CI) for each component of factorial effects and the general-weight effect. In addition, we construct Wald-type 95% confidence regions for the joint main effects and compare their areas.

### 5.1. Many Small Blocks

The number of blocks $M$ takes values from 20 to 100, with block size $n_{[m]} = 12$. The propensity scores are set to be $c_{[m][q]} = 1/4, q = 1, \ldots, 4, m = 1, \ldots, M$. The block size is too small for the last covariate adjustment method to be applicable. Therefore, we only consider four estimators: $\hat{\tau}_{unadj}, \hat{\tau}_{adj}, \hat{\tau}_{cond}$, and $\hat{\tau}_{cond2}$.

The results are shown in Tables 2–3, Figure 1, and Figure 3 in the supplementary material (for RMSE and RMSE ratio). First, the biases of all methods are negligible, in accordance with the unbiasedness of $\hat{\tau}_{unadj}$ and the asymptotically unbiasedness of $\hat{\tau}_{adj}, \hat{\tau}_{cond}$, and $\hat{\tau}_{cond2}$. Second, $\hat{\tau}_{adj}, \hat{\tau}_{cond}$, and $\hat{\tau}_{cond2}$ decrease the RMSE and thus improve the efficiency compared with $\hat{\tau}_{unadj}$. For example, when $M = 20$ and $n_{[m]} = 12$, the RMSE ratio, CI length ratio, and area ratio of confidence regions of $\hat{\tau}_{adj}$ relative to $\hat{\tau}_{unadj}$ are approximately 28%, 28%, and 8%, respectively. Third, although $\hat{\tau}_{adj}$ and $\hat{\tau}_{cond}$ are asymptotically equivalent, $\hat{\tau}_{adj}$ has better finite-sample performance for the case of equal propensity scores across blocks (it is actually the best-performing estimator in this case). This is mainly because we need to estimate fewer adjusted coefficients for $\hat{\tau}_{adj}$ than for $\hat{\tau}_{cond}$ ($pq$ versus $pqF$). Fourth, $\hat{\tau}_{cond}$ does not perform as well as $\hat{\tau}_{cond2}$. Finally, the percentage of improvement is almost constant as the sample size increases.

#### Table 2. Simulation results for the case of many small blocks with $M = 20$ and $n_{[m]} = 12$

| Effect               | Method     | Bias  | SD    | RMSE | CP    | CI length ratio |
|----------------------|------------|-------|-------|------|-------|-----------------|
| Main effect of factor 1 | $\hat{\tau}_{unadj}$ | -0.000 | 0.171 | 1.000 | 0.960 | 0.714 |
|                      | $\hat{\tau}_{adj}$     | 0.001 | 0.048 | 0.048 | 0.964 | 0.203 |
|                      | $\hat{\tau}_{cond}$    | 0.003 | 0.084 | 0.084 | 0.981 | 0.402 |
|                      | $\hat{\tau}_{cond2}$   | 0.006 | 0.050 | 0.051 | 0.996 | 0.297 |
| Main effect of factor 2 | $\hat{\tau}_{unadj}$ | -0.000 | 0.179 | 1.000 | 0.952 | 0.714 |
|                      | $\hat{\tau}_{adj}$     | 0.000 | 0.048 | 0.048 | 0.970 | 0.203 |
|                      | $\hat{\tau}_{cond}$    | 0.000 | 0.096 | 0.096 | 0.999 | 0.402 |
|                      | $\hat{\tau}_{cond2}$   | 0.003 | 0.049 | 0.049 | 0.975 | 0.284 |
| Interaction effect   | $\hat{\tau}_{unadj}$ | -0.001 | 0.171 | 1.000 | 0.959 | 0.714 |
|                      | $\hat{\tau}_{adj}$     | -0.000 | 0.049 | 0.049 | 0.983 | 0.203 |
|                      | $\hat{\tau}_{cond}$    | -0.001 | 0.084 | 0.084 | 0.989 | 0.402 |
|                      | $\hat{\tau}_{cond2}$   | 0.003 | 0.051 | 0.051 | 0.997 | 0.299 |
| General-weight effect | $\hat{\tau}_{unadj}$ | -0.001 | 0.163 | 1.000 | 0.961 | 0.682 |
|                      | $\hat{\tau}_{adj}$     | -0.001 | 0.047 | 0.047 | 0.964 | 0.196 |
|                      | $\hat{\tau}_{cond}$    | 0.003 | 0.083 | 0.083 | 0.980 | 0.394 |
|                      | $\hat{\tau}_{cond2}$   | 0.006 | 0.049 | 0.049 | 0.991 | 0.287 |

NOTE: SD, standard deviation; RMSE, root mean squared error; RMSE ratio, ratio of RMSE relative to that of $\hat{\tau}_{unadj}$; CP, empirical coverage probability of 95% confidence interval; CI length, mean confidence interval length; Length ratio, ratio of mean confidence interval length relative to that of $\hat{\tau}_{unadj}$.

#### Table 3. Areas of the 95% confidence regions for the joint main effects and area ratios

| Method              | Many small blocks ($M = 20$) | Two large heterogeneous blocks ($n_{[m]} = 108$) |
|---------------------|-----------------------------|-----------------------------------------------|
|                     | Ellipse area | Area ratio | Ellipse area | Area ratio | Ellipse area | Area ratio |
| $\hat{\tau}_{unadj}$ | 0.063     | 1.000     | 0.210     | 1.000     |
| $\hat{\tau}_{adj}$   | 0.005     | 0.081     | 0.060     | 0.287     |
| $\hat{\tau}_{cond}$  | 0.019     | 0.305     | 0.080     | 0.381     |
| $\hat{\tau}_{cond2}$ | 0.009    | 0.136     | 0.069     | 0.329     |
| $\hat{\tau}_{inter}$ | –         | –         | 0.017     | 0.081     |
5.2. Two Large Heterogeneous Blocks

We set the number of blocks $M = 2$ and change the block size $n_{[m]}$ from 60 to 156. The propensity scores are the same across blocks, $e_{[m]q} = 1/4$, $q = 1, \ldots, 4$, $m = 1, 2$. The coefficients $\beta_{q1j}$ and $\beta_{q2j}$, for $q = 1, 2, 3, 4$, are generated separately and independently for different blocks.

The results are shown in Tables 3–4, Figure 2, and Figure 4 in the supplementary materials (for RMSE and RMSE ratio). We can see that $\hat{\tau}_{\text{inter}}$ performs the best. When $n_{[m]} = 108$, $\hat{\tau}_{\text{inter}}$ improves the RMSE, CI length, and area of the confidence region of $\hat{\tau}_{\text{adj}}$ by approximately 50%, 50%, and 70%, respectively. Because $\hat{\tau}_{\text{adj}}$, $\hat{\tau}_{\text{cond}}$, and $\hat{\tau}_{\text{cond2}}$ pool the heterogeneous blocks together, they lose efficiency when compared to $\hat{\tau}_{\text{inter}}$.

5.3. An Example with Unequal Propensity Scores

In this section, we provide an example to show that $\hat{\tau}_{\text{adj}}$ may lose efficiency when the propensity scores differ across blocks, while $\hat{\tau}_{\text{cond}}$ and $\hat{\tau}_{\text{cond2}}$ do not. We consider $K = 2$ factors and set number of blocks $M = 10$ with block size $n_{[m]} = 40$. The propensity scores are

$$
e_{[m]} = \left( \frac{m}{2M}, \frac{m}{2M}, \frac{5 - m}{2M}, \frac{5 - m}{2M} \right)^	op, \quad m = 1, \ldots, 5,$$

$$e_{[m]} = \left( \frac{5 - 5}{2M}, \frac{5 - 5}{2M}, \frac{5 - m}{2M}, \frac{5 - m}{2M} \right)^	op, \quad m = 6, \ldots, 10.$$

The potential outcomes are generated as follows:

$$Y_i((-1, -1)) = -10e_{[m]1}X_i + \varepsilon_i(1), \quad i \in [m],$$

$$Y_i((-1, +1)) = -10e_{[m]2}X_i + \varepsilon_i(2), \quad i \in [m],$$

$$Y_i((+1, -1)) = 10e_{[m]3}X_i + \varepsilon_i(3), \quad i \in [m],$$

$$Y_i((+1, +1)) = 10e_{[m]4}X_i + \varepsilon_i(4), \quad i \in [m],$$

where $\varepsilon_i(1), \varepsilon_i(2), \varepsilon_i(3), \varepsilon_i(4)$ are generated from Gaussian distribution with mean zero and variance 0.01. The $X_i$ is an one-dimensional covariate generated from a standard normal distribution.

![Figure 1. Violin plots of four factorial effect estimators for the case of many small blocks with $M = 20$ and $n_{[m]} = 12$.](image1)

| Effect Method | Bias | SD | RMSE ratio | CP | CI length ratio |
|---------------|------|----|------------|----|----------------|
| Main effect of factor 1 | $\hat{\tau}_{\text{adj}}$ | 0.001 | 0.313 | 0.313 | 1.000 | 0.960 | 1.304 | 1.000 |
| $\hat{\tau}_{\text{unadj}}$ | -0.002 | 0.187 | 0.187 | 0.597 | 0.947 | 0.731 | 0.561 |
| $\hat{\tau}_{\text{cond}}$ | 0.002 | 0.185 | 0.185 | 0.591 | 0.970 | 0.819 | 0.628 |
| $\hat{\tau}_{\text{cond2}}$ | 0.001 | 0.188 | 0.188 | 0.600 | 0.963 | 0.800 | 0.614 |
| $\hat{\tau}_{\text{inter}}$ | -0.001 | 0.093 | 0.093 | 0.296 | 0.951 | 0.371 | 0.285 |
| Main effect of factor 2 | $\hat{\tau}_{\text{adj}}$ | -0.003 | 0.331 | 0.331 | 1.000 | 0.952 | 1.304 | 1.000 |
| $\hat{\tau}_{\text{unadj}}$ | -0.003 | 0.191 | 0.191 | 0.577 | 0.942 | 0.731 | 0.561 |
| $\hat{\tau}_{\text{cond}}$ | -0.003 | 0.204 | 0.204 | 0.616 | 0.951 | 0.819 | 0.628 |
| $\hat{\tau}_{\text{cond2}}$ | -0.003 | 0.191 | 0.191 | 0.577 | 0.945 | 0.742 | 0.569 |
| $\hat{\tau}_{\text{inter}}$ | -0.001 | 0.093 | 0.093 | 0.281 | 0.950 | 0.371 | 0.285 |
| Interaction effect | $\hat{\tau}_{\text{adj}}$ | -0.003 | 0.324 | 0.324 | 1.000 | 0.955 | 1.304 | 1.000 |
| $\hat{\tau}_{\text{unadj}}$ | -0.005 | 0.184 | 0.184 | 0.569 | 0.950 | 0.731 | 0.561 |
| $\hat{\tau}_{\text{cond}}$ | -0.003 | 0.200 | 0.200 | 0.619 | 0.955 | 0.819 | 0.628 |
| $\hat{\tau}_{\text{cond2}}$ | -0.003 | 0.184 | 0.184 | 0.569 | 0.953 | 0.738 | 0.566 |
| $\hat{\tau}_{\text{inter}}$ | -0.004 | 0.093 | 0.094 | 0.289 | 0.953 | 0.371 | 0.285 |
| General-weight effect | $\hat{\tau}_{\text{adj}}$ | 0.002 | 0.331 | 0.331 | 1.000 | 0.960 | 1.373 | 1.000 |
| $\hat{\tau}_{\text{unadj}}$ | -0.000 | 0.211 | 0.211 | 0.637 | 0.944 | 0.819 | 0.597 |
| $\hat{\tau}_{\text{cond}}$ | 0.002 | 0.210 | 0.210 | 0.635 | 0.944 | 0.819 | 0.597 |
| $\hat{\tau}_{\text{cond2}}$ | 0.003 | 0.212 | 0.212 | 0.640 | 0.959 | 0.884 | 0.644 |
| $\hat{\tau}_{\text{inter}}$ | 0.000 | 0.097 | 0.097 | 0.292 | 0.949 | 0.385 | 0.280 |

NOTE: SD, standard deviation; RMSE, root mean squared error; RMSE ratio, ratio of RMSE relative to that of $\hat{\tau}_{\text{unadj}}$; CP, empirical coverage probability of 95% confidence interval; CI length, mean confidence interval length; Length ratio, ratio of mean confidence interval length relative to that of $\hat{\tau}_{\text{unadj}}$. 
distribution. In this case, $\hat{\tau}_{\text{inter}}$ is not applicable because some blocks are too small.

The results for the main effect of factor 1 are shown in Figure 3. It is easy to see that $\hat{\tau}_{\text{adj}}$ performs worse than $\hat{\tau}_{\text{unadj}}$. In fact, the RMSE of $\hat{\tau}_{\text{adj}}$ is 119.4% of that of $\hat{\tau}_{\text{unadj}}$. In contrast, $\hat{\tau}_{\text{cond}}$ and $\hat{\tau}_{\text{cond2}}$ still perform well, reducing the RMSE of $\hat{\tau}_{\text{unadj}}$ by approximately 50%.

### 6. Application

In this section, we analyze a real dataset from a clinical trial, CALGB 40603, using the proposed methods. CALGB 40603 was a randomized block $2^2$ factorial phase II trial, that sought to evaluate the impact of adding bevacizumab and/or carboplatin on pathologic complete response (pCR) rates in patients with Stage II to III triple-negative breast cancer (TNBC) (Sikov et al. 2015). For standard neoadjuvant chemotherapy, patients with TNBC received paclitaxel 80 mg/m$^2$ once per week for 12 weeks, followed by doxorubicin plus cyclophosphamide once every 2 weeks for four cycles. Factor 1 was adding bevacizumab (10 mg/kg once every 2 weeks for nine cycles), and factor 2 was adding carboplatin (once every 3 weeks for four cycles) to the standard neoadjuvant chemotherapy. The 443 patients were blocked by pretreatment clinical stage (II or III) and randomly assigned into four treatment arms with equal probabilities:

- Arm C: standard neoadjuvant chemotherapy,
- Arm A: standard neoadjuvant chemotherapy + bevacizumab,
- Arm B: standard neoadjuvant chemotherapy + carboplatin,
- Arm AB: standard neoadjuvant chemotherapy + bevacizumab + carboplatin.

The outcome of interest is the pCR breast, defined as the absence of residual invasive disease with or without ductal carcinoma in situ (ypT0/is). Removal of the patients with missing outcomes leaves 433 patients, 295 in clinical stage II and 138 in clinical stage III. We consider eight baseline covariates for adjustments, including tumor grade, clinical T stage, clinical N stage, and so on.

The point estimators and 95% CIs for each factorial effect are given in Table 5. Based on $\hat{\tau}_{\text{unadj}}$, adding bevacizumab improves the pCR rate by approximately 15%; adding carboplatin improves the pCR rate by approximately 11%; and no significant interaction effect is found for adding bevacizumab and carboplatin. These conclusions are in accordance with those obtained by Sikov et al. (2015). The covariate adjustment meth-
Figure 4. 95% confidence region for main effects of adding bevacizumab and carboplatin.

Table 5. Point estimators and 95% confidence intervals for the factorial effects of adding bevacizumab and carboplatin, and the reduction of variance relative to the unadjusted estimator.

| Method | Main effect of bev | Main effect of carbo | Interaction effect of bev and carbo | Reduction of variance |
|--------|--------------------|----------------------|-----------------------------------|----------------------|
| $\hat{\tau}_{\text{unadj}}$ | 0.140              | 0.113                | 0.029                             | 0                    |
| $\hat{\tau}_{\text{adj}}$  | [0.047, 0.233]     | [0.020, 0.207]       | [−0.064, 0.122]                   | 12.8%                |
| $\hat{\tau}_{\text{cond}}$ | 0.168              | 0.122                | [−0.070, 0.104]                   | 4.9%                 |
| $\hat{\tau}_{\text{cond2}}$ | [0.078, 0.259]     | [0.032, 0.213]       | [−0.071, 0.111]                   | 11.6%                |
| $\hat{\tau}_{\text{inter}}$ | 0.162              | 0.112                | 0.011                             | 21.2%                |

NOTE: bev, bevacizumab; carbo, carboplatin.

ods, $\hat{\tau}_{\text{adj}}$, $\hat{\tau}_{\text{cond}}$, $\hat{\tau}_{\text{cond2}}$, and $\hat{\tau}_{\text{inter}}$, give similar statistical conclusions. However, it is interesting to note that these four methods improve efficiency, as they reduce the variance by 12.8%, 4.9%, 11.6%, and 21.2%, respectively. Because the blocks are large and likely heterogeneous, $\hat{\tau}_{\text{inter}}$ performs the best. In addition, we construct Wald-type 95% confidence regions for the joint main effects, which are shown in Figure 4. Compared with $\hat{\tau}_{\text{unadj}}$, the covariate adjustment methods, $\hat{\tau}_{\text{adj}}$, $\hat{\tau}_{\text{cond}}$, $\hat{\tau}_{\text{cond2}}$, and $\hat{\tau}_{\text{inter}}$, reduce the areas of the confidence regions by 12.8%, 4.9%, 10.0%, and 21.1%, respectively.

7. Discussion

In this article, we established a general finite population vector CLT to derive the joint asymptotic distribution of blocked sample means in randomized block experiments with vector outcomes and multiple treatments. This new CLT plays a crucial role in randomization-based causal inference for the average factorial effects in randomized block $2^K$ factorial experiments. Based on the CLT, we showed that the usual (unadjusted) average factorial effects estimator is consistent and asymptotically normal, without imposing strong modeling assumptions on the potential outcomes. We proposed four covariate adjustment methods to improve the estimation and inference efficiency. We derived their asymptotic distributions, proposed conservative covariance estimators, and compared their efficiencies with that of the unadjusted estimator. Our results are robust to model misspecification and can be easily extended to more general randomized block factorial experiments with multiple-level factors, $3^K$, $4^K$, and so on.

In practice, a combination of large and small blocks may exist. In such cases, it might be more efficient to pool together small blocks into large blocks, and then use $\hat{\tau}_{\text{inter}}$. It is worth further investigating how to efficiently perform the pooling and the follow-up covariate adjustment. Moreover, in this article, we focused on using covariate adjustment in the analysis stage to improve the estimation and inference efficiency. Covariate adjustment can also be used in the design stage, such as randomization (Morgan and Rubin 2012, 2015; Li, Ding, and Rubin 2018). Branson, Dasgupta, and Rubin (2016) proposed a randomization procedure in completely randomized $2^K$ factorial experiments and Li, Ding, and Rubin (2020) established its asymptotic theory. It would be interesting to generalize the results to randomized block $2^K$ factorial experiments. Our new CLT has already established a theoretical basis for deriving the corresponding asymptotic theory. In addition, we assume that the number of covariates is fixed. In practice, however, the number of covariates can be large, even larger than the sample size. It would also be interesting to investigate robust and efficient covariate adjustment methods in randomized block factorial experiments with high-dimensional covariates.

Supplementary Materials

The supplementary material provides the proofs and additional simulation results.

Acknowledgments

The authors are grateful to the associate editor and two referees for their valuable comments. This publication is based on research using information obtained from data.projectdatasphere.org, which is maintained by Project Data Sphere. Neither Project Data Sphere nor the owner(s) of any...
information from the website have contributed to, approved, or are in any way responsible for the contents of this publication.

**Funding**

Dr. Hanzhong Liu was supported by the National Natural Science Foundation of China (grant no. 12071242) and the Guo Qiang Institute of Tsinghua University. Dr. Yuehan Yang was supported by the National Natural Science Foundation of China (grant no. 12001557), the Youth Talent Development Support Program (QYP202104), the Emerging Interdisciplinary Project, and the Disciplinary Funding of Central University of Finance and Economics.

**References**

Angrist, J., Lang, D., and Oreopoulos, P. (2009), "Incentives and Services for College Achievement: Evidence from a Randomized Trial," *American Economic Review: Applied Economics*, 1, 136–163. [136]

Aronow, P. M., Green, D. P., and Lee, D. K. K. (2014), "Sharp Bounds on the Variance in Randomized Experiments," *The Annals of Statistics*, 42, 850–871. [141]

Bickel, P. J., and Freedman, D. A. (1984), "Asymptotic Normality and the Bootstrap in Stratified Sampling," *The Annals of Statistics*, 12, 470–482. [137,140]

Bloniarz, A., Liu, H., Zhang, C. H., Sekhon, J., and Yu, B. (2016), "Lasso Adjustments of Treatment Effect Estimates in Randomized Experiments," *Proceedings of the National Academy of Sciences of the United States of America*, 113, 7383–7390. [137]

Box, G. E. P., Hunter, J. S., and Hunter, W. G. (2005), *Statistics for Experimenters: Design, Innovation and Discovery*, New York: Wiley-Interscience. [136]

Branson, Z., Dasgupta, T., and Rubin, D. B. (2016), "Improving Covariate Balance in 2k Factorial Designs via Rerandomization with an Application to a New York City Department of Education High School Study," *The Annals of Applied Statistics*, 10, 1958–1976. [149]

Cassel, C. M., Särndal, C. E., and Wretman, J. H. (1976), "Some Results on Generalized Difference Estimation and Generalized Regression Estimation for Finite Populations," *Biometrika*, 63, 615–620. [136,141]

Cochran, W. G., and Cox, G. M. (1950), *Experimental Designs*, New York: Wiley. [136]

Dasgupta, T., Pillai, N. S., and Rubin, D. B. (2015), "Causal Inference from 2k Factorial Designs by using Potential Outcomes," *Journal of the Royal Statistical Society: Series B*, 77, 727–753. [136,137,138]

De la Cuesta, B., Egami, N., and Imai, K. (2022), "Improving the External Validity of Conjoint Analysis: The Essential Role of Profile Distribution," *Political Analysis*, 30, 19–45. [138]

Fisher, R. A. (1926), "The Arrangement of Field Experiments," *Journal of Ministry of Agriculture of Great Britain*, 33, 503–513. [136]

——— (1935), *The Design of Experiments* (1st ed.), Edinburgh: Oliver and Boyd. [136]

——— (1959), *Statistical Methods and Scientific Inference* (2nd ed.), New York: Hafner Press. [143]

Freedman, D. A. (2008a), "On Regression Adjustments to Experimental Data," *Advances in Applied Mathematics*, 40, 180–193. [137]

——— (2008b), "Randomization does not Justify Logistic Regression," *Statistical Science*, 23, 237–249. [137]

Häjek, J. (1961), "Some Extensions of the Wald-Wolfowitz-Neither Theorem," *Annals of Mathematical Statistics*, 32, 506–523. [137,140]

Imai, K. (2008), "Variance Identification and Efficiency Analysis in Randomized Experiments under the Matched-Pair Design," *Statistics in Medicine*, 27, 4857–4873. [136]

Imbens, G. W., and Rubin, D. B. (2015), *Causal Inference for Statistics, Social, and Biomedical Sciences An Introduction*, Cambridge: Cambridge University Press. [136]

Lei, L., and Ding, P. (2021), "Regression Adjustment in Completely Randomized Experiments with a Diverging Number of Covariates," *Biometrika*, 108, 815–828. [137,141,145]

Li, X., and Ding, P. (2017), "General Forms of Finite Population Central Limit Theorems with Applications to Causal Inference," *Journal of the American Statistical Association*, 112, 1759–1769. [137,139,140]

Li, X., Ding, P., and Rubin, D. B. (2018), "Asymptotic Theory of Randomization in Treatment-Control Experiments," *Proceedings of the National Academy of Sciences of the United States of America*, 115, 9157–9162. [149]

Lin, W. (2013), "Agnostic Notes on Regression Adjustments to Experimental Data: Reexamining Freedman's Critique," *The Annals of Applied Statistics*, 7, 295–318. [137,141,145]

Lin, Y., Zhu, M., and Su, Z. (2015), "The Pursuit of Balance: An Overview of Covariate-Adaptive Randomization Techniques in Clinical Trials," *Contemporary Clinical Trials*, 45, 21–25. [136]

Liu, H., and Yang, Y. (2020), "Regression-Adjusted Average Treatment Effect Estimators in Stratified Randomized Experiments," *Biometrika*, 107, 953–948. [136,137,139,140,141,145]

Lu, J. (2016a), "Covariate Adjustment in Randomization-based Causal Inference for 2k Factorial Designs," *Statistics & Probability Letters*, 119, 11–20. [137,141,145]

——— (2016b), "On Randomization-based and Regression-based Inferences for 2k Factorial Designs," *Statistics & Probability Letters*, 112, 72–78. [137,141,145]

McHugh, R., and Matts, J. (1983), "Post-stratification in the Randomized Clinical Trial," *Biometrics*, 39, 217–225. [136]

Miratrix, L. W., Sekhon, J. S., and Yu, B. (2013), "Adjusting Treatment Effect Estimates by Post-stratification in Randomized Experiments," *Journal of the Royal Statistical Society*, Series B, 75, 369–396. [136,137]

Montgomery, D. C. (2012), *Design and Analysis of Experiments* (8th ed.), New York: Wiley. [136]

Morgan, K. L., and Rubin, D. B. (2012), "Rerandomization to Improve Covariate Balance in Experiments," *The Annals of Statistics*, 40, 1263–1282. [136,149]

——— (2015), "Rerandomization to Balance Tiers of Covariates," *Journal of the American Statistical Association*, 110, 1412–1421. [149]

Rosenberger, W. F., and Sverdlov, O. (2008), "Handling Covariates in the Design of Clinical Trials," *Statistical Science*, 23, 404–419. [136]

Rubin, D. B. (1974), "Estimating Causal Effects of Treatments in Randomized and Nonrandomized Studies," *Journal of Educational Psychology*, 66, 688–701. [138]

——— (1980), "Randomization Analysis of Experimental Data: The Fisher Randomization Test Comment," *Journal of the American Statistical Association*, 75, 591–593. [138]

Särndal, C.-E., Swensson, B., and Wretman, J. (2003), *Model Assisted Survey Sampling*, New York: Springer. [136,141]

Sen, P. K. (1995), "The Hájek Asymptotics for Finite Population Sampling and their Ramifications," *Kybernetika*, 31, 251–268. [137,140]

Senn, S. J. (1989), "Covariate Imbalance and Random Allocation in Clinical Trials," *Statistics in Medicine*, 8, 467–475. [136]

Sikov, W. M., Berry, D. A., Perou, C. M., Singh, B., Cirrincione, C. T., Tolanev, S. M., Kuzma, C. S., Pluard, J. T., Somlo, G., Port, E. R., Golshan, M., Bellon, J. R., Collyar, D., Hahn, O. M., Carey, L. A., Hudis, C. A., and Winer, E. P. (2015), "Impact of the Addition of Carboplatin and/or Bevacizumab to Neoadjuvant Once-per-week Paclitaxel Followed by Dose-Dense Doxorubicin and Cyclophosphamide on Pathologic Complete Response Rates in Stage II to III Triple-Negative Breast Cancer: Calgb 40603 (Alliance)," *Journal of Clinical Oncology*, 33, 13–21. [148]

Splawa-Neyman, J., Dabrowska, D. M., and Speed, T. P. (1990), "On the Application of Probability Theory to Agricultural Experiments. Essay on Principles. Section 9," *Statistical Science*, 5, 465–472. [138]

Su, F., and Ding, P. (2021), "Model-Assisted Analyses of Cluster-Randomized Experiments," *Journal of the Royal Statistical Society*, Series B, 83, 994–1015. [145]

Wang, X., Wang, T., and Liu, H. (2021), "Rerandomization in Stratified Randomized Experiments," *Journal of the American Statistical Association*, in press. [136]

Wilk, M. B. (1955), "The Randomization Analysis of a Generalized Randomized Block Design," *Biometrika*, 42, 70–79. [136]

Wu, C. F. J., and Hamada, M. S. (2009), *Experiments: Planning, Analysis, and Optimization* (2nd ed.), Hoboken, NJ: Wiley. [136]

Yates, F. (1937), *The Design and Analysis of Factorial Experiments*, Technical Communication No. 35, Imperial Bureau of Soil Sciences, Harpenden. [136]