Model-robust and efficient inference for
cluster-randomized experiments

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Abstract

Cluster-randomized experiments are increasingly used to evaluate interventions in routine practice conditions, and researchers often adopt model-based methods with covariate adjustment in the statistical analyses. However, the validity of model-based covariate adjustment is unclear when the working models are misspecified, leading to ambiguity of estimands and risk of bias. In this article, we first adapt two conventional model-based methods, generalized estimating equations and linear mixed models, with weighted g-computation to achieve robust inference for cluster- and individual-average treatment effects. Furthermore, we propose an efficient estimator for each estimand that allows for flexible covariate adjustment and additionally addresses cluster size variation dependent on treatment assignment and other cluster characteristics. Such cluster size variations often occur post-randomization and can lead to bias of model-based methods if ignored. For our proposed method, we show that when the nuisance functions are consistently estimated by machine learning algorithms, the estimator is consistent, asymptotically normal, and efficient. When the nuisance functions are estimated via parametric working models, it remains triply-robust. Simulation studies and the analysis of a recent cluster-randomized experiment demonstrate that the proposed methods are superior to existing alternatives.

Keywords: Estimand; Group-randomized trial; Covariate adjustment; Unequal cluster size.

1 Introduction

Cluster-randomized experiments refer to study designs that randomize treatment at the cluster level; clusters can be villages, hospitals, or worksites (Murray et al., 1998). Cluster randomization is often used to study group-level interventions or to prevent treatment
contamination, and is increasingly adopted in pragmatic clinical trials evaluating interventions in routine practice conditions. In analyses of cluster-randomized experiments, covariate adjustment is essential to address chance imbalances and improve precision. However, challenges in covariate adjustment persist due to the inherent multilevel data structure under cluster randomization. First, although model-based methods, including generalized estimating equations and generalized linear mixed models, are commonly used to perform covariate adjustment, it remains unclear whether the treatment effect coefficient corresponds to a clearly-defined estimand of interest, especially when the working model is misspecified. Even in the absence of covariates, Wang et al. (2022) has demonstrated that the treatment coefficient from exchangeable generalized estimating equations can correspond to an ambiguous estimand. Second, participants are frequently sampled after cluster randomization such that the observed cluster size may depend on treatment assignment and other cluster attributes. Failure to address such cluster-dependent sampling schemes can lead to bias. For example, when the observed cluster size depends on cluster-level covariates, the standard difference-in-means estimator is biased (Bugni et al., 2022). To date, methods that can simultaneously maximize the precision gain from covariate adjustment and address cluster-dependent sampling are unavailable in cluster-randomized experiments.

In this article, we address the aforementioned challenges in estimating two classes of estimands: the cluster-average treatment effect and individual-average treatment effect. The two estimands represent treatment effects at different levels and differ when there is treatment effect heterogeneity by cluster size (Kahan et al., 2022). We first adapt generalized estimating equations and linear mixed models through weighted g-computation for these two estimands, and provide a set of sufficient conditions to achieve model-robustness, i.e., consistency and asymptotic normality under arbitrary model misspecification. However, the weighted g-computation estimators can be inefficient in covariate adjustment and biased when the sufficient conditions fail, or when the observed cluster size depends on additional cluster attributes. To address such limitations, we characterize the efficient influence function for each estimand and propose efficient estimators that allow for the use of a wide
class of working nuisance models for performing covariate adjustment and address cluster-dependent sampling. When the nuisance functions are estimated by parametric models, the proposed estimators are triply-robust, that is, they are consistent if two out of the three nuisance functions are consistently estimated. When the nuisance working models are all consistently estimated, for example, by machine learning algorithms with cross-fitting, the proposed estimators achieve the efficiency lower bound given our causal models.

Our results build on but differ from the existing literature on causal inference for cluster-randomized experiments. Imai et al. (2009) and Middleton and Aronow (2015) proposed cluster-level methods for estimating the average treatment effect but did not consider covariate adjustment to improve efficiency. Schochet et al. (2021) established the finite-population central limit theorem for linearly-adjusted estimators, and Su and Ding (2021) extended their results by providing a unified theory for a class of estimands under covariate adjustment. These prior works considered a finite-population framework with linear working models and an independence working correlation structure. In contrast, we contribute a super-population framework and address efficient estimation that can allow for specifications of a wider class of working models. Balzer et al. (2021) and Benitez et al. (2021) applied targeted maximum likelihood estimation under hierarchical structural models for cluster-randomized experiments. However, they did not consider cluster size variation arising from cluster-dependent sampling. Bugni et al. (2022) developed moment-based estimators addressing cluster-dependent sampling but did not consider covariate adjustment. We improve these existing methods by proposing efficient estimators to achieve flexible covariate adjustment and accommodate cluster-dependent sampling.

2 Notation and assumptions

We consider a cluster-randomized experiment with $m$ clusters. For each cluster $i$, we let $N_i$ denote the total number of individuals in the underlying source population, $M_i$ be the observed number of individuals sampled into the study, $A_i \in \{0, 1\}$ be the cluster-level
treatment indicator, and $C_i$ be a $q$-dimensional vector of cluster-level covariates. For each individual $j$ in cluster $i$, we define $Y_{ij}$ as the outcome, $X_{ij}$ as a $p$-dimensional vector of baseline covariates, and $S_{ij} \in \{0, 1\}$ as the sampling indicator, i.e., recruited into the experiment. By definition, the observed cluster size $M_i = \sum_{j=1}^{N_i} S_{ij} \leq N_i$.

We proceed under the potential outcome framework and define $Y_{ij}(a)$ as the potential outcome and $S_{ij}(a)$ as the potential sampling indicator if cluster $i$ were assigned to treatment group $a \in \{0, 1\}$. We assume consistency such that $Y_{ij} = A_i Y_{ij}(1) + (1 - A_i) Y_{ij}(0)$ and $S_{ij} = A_i S_{ij}(1) + (1 - A_i) S_{ij}(0)$. As a result, the potential observed cluster size in a treated cluster, denoted as $M_i(1) = \sum_{j=1}^{N_i} S_{ij}(1)$, can be different from its counterpart in a control cluster, denoted as $M_i(0) = \sum_{j=1}^{N_i} S_{ij}(0)$. Defining $Y_i(a) = \{Y_{i1}(a), \ldots, Y_{IN_i}(a)\} \in \mathbb{R}^{N_i}$ as the collection of potential outcomes, $S_i(a) = \{S_{i1}(a), \ldots, S_{IN_i}(a)\} \in \mathbb{R}^{N_i}$ as the collection of potential sampling indicators, and $X_i = (X_{i1}, \ldots, X_{IN_i})^\top \in \mathbb{R}^{N_i \times p}$, we write the collection of all random variables in a cluster as $W_i = \{Y_i(1), Y_i(0), S_i(1), S_i(0), N_i, C, X_i\}$.

We introduce the following assumptions on the complete, while not fully observed, data $\{(W_1, A_1), \ldots, (W_m, A_m)\}$.

**Assumption 1** (Super-population). (a) Random variables $W_1, \ldots, W_m$ are mutually independent. (b) The source population size $N_i$ follows an unknown distribution $\mathcal{P}^N$ over a finite support on $\mathbb{N}^+$. (c) Given $N_i$, $W_i$ follows an unknown distribution $\mathcal{P}^{W|N}$ with finite second moments.

**Assumption 2** (Cluster randomization). The treatment indicator $A_i$ for each cluster is an independent realization from a Bernoulli distribution $\mathcal{P}^A$ with $\text{pr}(A = 1) = \pi \in (0, 1)$. Furthermore, $(A_1, \ldots, A_m)$ is independent of $(W_1, \ldots, W_m)$.

**Assumption 3** (Cluster-dependent sampling). For $a \in \{0, 1\}$, the potential observed cluster size $M(a) = h_a(N, C, \epsilon_a)$ for some unknown function $h_a$ and exogenous random noise $\epsilon_a$ that is independent of $\{N, C, X, Y(a)\}$. Further, for each possible $N$-dimensional binary vector $s$ with $M(a)$ ones, $\text{pr}\{S(a) = s \mid Y(a), M(a), X, N, C\} = (N!)^{-1} \{M(a)\}! \{N - M(a)\}!$.

Assumption 1(a) implies that the data vectors from different clusters are independent,
while the outcomes and covariates in the same cluster can be arbitrarily correlated. Assumption 1(b)-(c) formalize the condition that $W_1, \ldots, W_m$ are marginally identically distributed according to a mixture distribution, $\mathcal{P}^{W|N} \times \mathcal{P}^N$. This technical condition is useful for handling the varying dimension of $W_i$ across clusters. Assumption 2 holds under cluster randomization. Given Assumptions 1-2, the expectation on $(W_i, A_i)$ is taken with respect to $\mathcal{P}^{W|N} \times \mathcal{P}^N \times \mathcal{P}^A$. Assumption 3 implies that the number of sampled individuals can depend on the assignment $A$ and cluster characteristics (source population size $N$ and cluster covariates $C$), but the sampling process is random given the number of sampled individuals and the source population size. This assumption relaxes the setting of Bugni et al. (2022) to allow for arm-specific sampling. Important special cases of Assumptions 3 include full enrollment such that $M(a) = N$; random sampling with an arm-specific fixed size such that $M(a) = m_a$ for some integer $m_a \leq N$; and independent cluster-specific sampling such that each $S_{ij}(a)$ is independently determined by flipping a cluster-specific coin. Assumption 3 can be violated when individual participation in the study additionally depends on individual-level covariates, which are generally unobserved for nonparticipants. This sampling mechanism leads to post-randomization selection bias (Li et al., 2022), and we leave this form of selection bias for separate work.

We define the class of cluster-average treatment effect ($\Delta_C$) and individual-average treatment effect ($\Delta_I$) estimands as

$$\Delta_C = f\{\mu_C(1), \mu_C(0)\}, \quad \Delta_I = f\{\mu_I(1), \mu_I(0)\},$$

where $f$ is a pre-specified smooth function determining the scale of effect measure and, for $a = 0, 1$,

$$\mu_C(a) = E\left\{\frac{\sum_{j=1}^{N_i} Y_{ij}(a)}{N_i}\right\}, \quad \mu_I(a) = \frac{E\left\{\sum_{j=1}^{N_i} Y_{ij}(a)\right\}}{E(N_i)}.$$

For example, $f(x, y) = x - y$ leads to the difference estimands, $f(x, y) = x/y$ leads to the relative risk estimands, and $f(x, y) = x(1 - y)/\{y(1 - x)\}$ leads to the odds ratio estimands. The two classes of estimands $\Delta_C$ and $\Delta_I$ differ based on the corresponding
treatment-specific mean potential outcomes, $\mu_C(a)$ versus $\mu_I(a)$. The former represents the average potential outcome associated with treatment $a$ for a typical cluster along with its natural source population, while the latter represents the average potential outcome associated with treatment $a$ for a typical individual. These two estimands can be considered as the super-population analogs to those considered in Su and Ding (2021) and Kahan et al. (2022) under the finite-population framework and a generalization of the difference estimands in Bugni et al. (2022). We refer to Kahan et al. (2022) for an in-depth discussion of the two estimands and their relevance to cluster-randomized experiments.

Finally, we write the observed data for cluster $i$ as $O_i = (Y_i^o, M_i, A_i, N_i, C_i, X_i^o)$, where $Y_i^o = \{Y_{ij} : S_{ij} = 1, j = 1, \ldots, N_i\} \in \mathbb{R}^{M_i}$ and $X_i^o = \{X_{ij} : S_{ij} = 1, j = 1, \ldots, N_i\} \in \mathbb{R}^{M_i \times p}$. The relationships among these random variables are summarized in Supplementary Material Figure 1. The central task is to estimate $\Delta_C$ and $\Delta_I$ with $O_1, \ldots, O_m$. Of note, we assume that the source population size $N_i$ is available or can be elicited from stakeholders; this is practically feasible for cluster-randomized experiments conducted within healthcare delivery systems, schools, or worksites. When the source population size in each cluster is unknown, we will discuss how to estimate $\Delta_C$ in Section 4, but $\Delta_I$ is generally not identifiable unless we impose $N = M$.

3 Sufficient conditions for robust inference via model-based methods

3.1 Generalized estimating equations

One popular approach to analyze cluster-randomized experiments is through generalized estimating equations, often specified through the marginal mean model, $g\{E(Y_{ij} | U_{ij})\} = U_{ij}^\top \beta$, where $g$ is the link function, $U_{ij} = (1, A_i, L_{ij})^\top$ for arbitrary user-specified covariates $L_{ij}$ as a function of $(N_i, C_i, X_{ij})$, and $\beta = (\beta_0, \beta_A, \beta_L^\top)^\top$. We assume that $g$ is the canonical link, e.g., $g(x) = x$ for continuous outcomes and $g(x) = \log\{x/(1 - x)\}$ for binary outcomes.
The parameters $\beta$ are estimated by solving the following estimating equations:

$$
\sum_{i=1}^{m} D_i^T V_i^{-1} (Y_i^o - \mu_i^o) = 0,
$$

where $\mu_i^o = \{E(Y_{ij} \mid U_{ij}) : S_{ij} = 1\} \in \mathbb{R}^{M_i}$, $D_i = \partial \mu_i^o / \partial \beta^T$, $V_i = Z_i^{1/2} R_i(\rho) Z_i^{1/2}$ with $R_i(\rho) \in \mathbb{R}^{M_i \times M_i}$ being a working correlation matrix and $Z_i = \text{diag} \{v(Y_{ij}) : S_{ij} = 1\} \in \mathbb{R}^{M_i \times M_i}$ for some known variance function $v$. We consider two working correlation structures that are commonly used for analyzing cluster-randomized experiments: the independence correlation, $R_i(\rho) = I_{M_i}$, and the exchangeable correlation, $R_i(\rho) = (1 - \rho) I_{M_i} + \rho 1_{M_i} 1_{M_i}^T$, where $I_{M_i} \in \mathbb{R}^{M_i \times M_i}$ is the identity matrix and $1_{M_i} \in \mathbb{R}^{M_i}$ is a vector of ones. The estimator for $\beta$ is denoted by $\hat{\beta}$, and the correlation parameter $\rho$ is estimated by a moment estimator $\hat{\rho}$ described in Example 4 of Liang and Zeger (1986). For analyzing cluster-randomized experiments, a conventional practice is to directly use the coefficient $\hat{\beta}_A$ along with robust sandwich variance for inference. However, this practice can lead to an ambiguous treatment effect estimand even in the absence of covariate adjustment (Wang et al., 2022).

To estimate our target estimands $\Delta_C$ and $\Delta_I$, we propose a simple weighted g-computation approach, defined as $\hat{\Delta}_{C \text{ GEE-g}} = f \{ \hat{\mu}_{C \text{ GEE-g}}(1), \hat{\mu}_{C \text{ GEE-g}}(0) \}$ and $\hat{\Delta}_{I \text{ GEE-g}} = f \{ \hat{\mu}_{I \text{ GEE-g}}(1), \hat{\mu}_{I \text{ GEE-g}}(0) \}$, where, for $a = 0, 1$,

$$
\hat{\mu}_{C \text{ GEE-g}}(a) = \frac{1}{m} \sum_{i=1}^{m} \frac{1}{M_i} \sum_{j:S_{ij} = 1} g^{-1} \left( \hat{\beta}_0 + \hat{\beta}_A a + \hat{\beta}_L^T L_{ij} \right),
$$

$$
\hat{\mu}_{I \text{ GEE-g}}(a) = \frac{1}{\sum_{i=1}^{m} N_i} \sum_{i=1}^{m} \frac{N_i}{M_i} \sum_{j:S_{ij} = 1} g^{-1} \left( \hat{\beta}_0 + \hat{\beta}_A a + \hat{\beta}_L^T L_{ij} \right).
$$

To proceed, we additionally make the following assumption, which implies that the observed cluster size within each arm has only exogenous randomness.

**Assumption 4 (Arm-specific random observed cluster sizes).** For $a \in \{0, 1\}$, $M(a)$ is independent of $\{N, C, X, Y(a)\}$.

Theorem 1 below articulates several model specifications of generalized estimating equations such that $\hat{\Delta}_{I \text{ GEE-g}}$ and $\hat{\Delta}_{C \text{ GEE-g}}$ are consistent and asymptotically normal, leading to valid
statistical inference for well-defined estimands. The regularity conditions required are moment and continuity assumptions similar to those invoked in Theorem 5.31 of van der Vaart (1998) for M-estimators. Particularly, model specifications S2-S4 in Theorem 1 make no assumption on the underlying distribution for the potential outcomes, and hence allow for model-robust estimation of both estimands.

**Theorem 1.** (a) Under Assumptions 1-4 and regularity conditions in the Supplementary Material, \( m^{1/2} (\Delta_C^{GEE-g} - \Delta_C) \overset{d}{\to} \mathcal{N}(0, V_C^{GEE-g}) \) if any of the following conditions holds: (S1) the mean model \( g\{E(Y_{ij} | U_{ij})\} = U_{ij}^T \beta \) is correctly specified; (S2) an independence working correlation structure is used; (S3) \( g \) is the identity link function and the working variance is constant with \( \nu(Y_{ij} | U_{ij}) = \sigma^2 \); (S4) the mean model does not involve individual-level covariates \( X_{ij} \) (instead, cluster-level covariates \( C_i \) can be used). (b) If the estimating equations (1) are additionally weighted by the source population size \( N_i \) for each cluster \( i \), then \( m^{1/2} (\Delta_I^{GEE-g} - \Delta_I) \overset{d}{\to} \mathcal{N}(0, V_I^{GEE-g}) \) if any of the above conditions (S1-S4) holds. The explicit forms of \( V_C^{GEE-g} \) and \( V_I^{GEE-g} \) and their consistent estimators are provided in the Supplementary Material.

**Remark 1.** Assumption 4 can be relaxed under model specification (S1) or (S2) if each cluster is further weighted by \( 1/M_i \) in Equations (1) before applying the weighted g-computation formulas. In other cases, Assumption 4 is generally required for valid inference of the g-computation estimators.

### 3.2 (Generalized) linear mixed models

Generalized linear mixed models are another popular method for analyzing cluster-randomized experiments. If we write \( b_i \) as the random effect for cluster \( i \), a typical generalized linear mixed model applied to cluster-randomized experiment often includes the following assumptions: (i) \( b_1, \ldots, b_m \) are independent, identically distributed from \( \mathcal{N}(0, \tau^2) \), where \( \tau^2 \) is an unknown variance component; (ii) \( Y_{i1}, \ldots, Y_{iN_i} \) are conditionally independent given \( (U_{i1}, \ldots, U_{iN_i}, b_i) \); and (iii) the distribution \( Y_{ij} \mid (U_{i1}, \ldots, U_{iN_i}, b_i) \) is a member of the exponential family with \( E(Y_{ij} \mid U_{i1}, \ldots, U_{iN_i}, b_i) = E(Y_{ij} \mid U_{ij}, b_i) = g^{-1}(U_{ij}^T \alpha + b_i) \), where \( g \) is
the canonical link and $\alpha = (\alpha_0, \alpha_A, \alpha_L^\top)^\top$. Given the above assumptions, the marginal likelihood of observed data can be written as $\prod_{i=1}^m \int \prod_{j:S_{ij}=1} p(Y_{ij} \mid U_{ij}, b_i; \alpha) \phi(b_i; \tau^2) db_i$, where $p(Y_{ij} \mid U_{ij}, b_i; \alpha)$ is the conditional density of $Y_{ij}$ and $\phi(b_i; \tau^2)$ is the normal density of $b_i$. In general, the estimation of model parameters proceeds by maximizing this likelihood function, and a common practice is to consider $\alpha_A$ as the treatment effect parameter. However, the interpretation of $\alpha$ is conditional on random effects, and if the mixed model is misspecified, $\alpha$ lacks direct connection to our marginal estimands, with an important exception that we detail below.

An interesting special case where the mixed model provides model-robust inference in cluster-randomized experiments is when a linear mixed model is considered as the working model. In this case, the conditional density becomes $p(Y_{ij} \mid U_{ij}, b_i; \alpha, \sigma^2) = (2\pi\sigma^2)^{-1/2} \exp\{-(Y_{ij} - U_{ij}^\top \alpha - b_i)^2/(2\sigma^2)\}$, and the closed-form maximizer of $\alpha$ in the marginal likelihood function is available. We define the weighted g-computation estimators as $\hat{\Delta}_{LMM-g}^C = f\left\{\widehat{\mu}_{LMM-g}^C(1), \widehat{\mu}_{LMM-g}^C(0)\right\}$ and $\hat{\Delta}_{LMM-g}^I = f\left\{\widehat{\mu}_{LMM-g}^I(1), \widehat{\mu}_{LMM-g}^I(0)\right\}$, where

$$\widehat{\mu}_{LMM-g}^C(a) = \widehat{\beta}_0 + \widehat{\beta}_A a + \widehat{\beta}_L \frac{\sum_{i=1}^m T_i'}{m}, \quad \widehat{\mu}_{LMM-g}^I(a) = \widehat{\beta}_0 + \widehat{\beta}_A a + \widehat{\beta}_L \frac{\sum_{i=1}^m N_i T_i'}{\sum_{i=1}^m N_i}$$

with $T_i' = M_i^{-1} \sum_{j=1}^{N_i} S_{ij} L_{ij}$ being the average covariate value for cluster $i$. When the interest lies in the difference estimands with $f(x, y) = x - y$, we have $\hat{\Delta}_{LMM-g}^C = \widehat{\beta}_A$ and $\hat{\Delta}_{LMM-g}^I = \widehat{\beta}_A$, but these two coefficients are estimated via different weights applied to the log-likelihood as we explain in Theorem 2. Theorem 2 shows that $\hat{\Delta}_{LMM-g}^C$ and $\hat{\Delta}_{LMM-g}^I$ are asymptotically valid if the observed cluster size is only subject to exogenous variation within each arm, even when the linear mixed model is arbitrarily misspecified.

**Theorem 2.** Under Assumptions 1-4 and regularity conditions provided in the Supplementary Material, $m^{1/2}(\hat{\Delta}_{LMM-g}^C - \Delta_C) \overset{d}{\rightarrow} \mathcal{N}(0, V_{LMM-g}^C)$. If each cluster is weighted by $N_i$ in the log-likelihood function of the working linear mixed model, then $m^{1/2}(\hat{\Delta}_{LMM-g}^I - \Delta_I) \overset{d}{\rightarrow} \mathcal{N}(0, V_{LMM-g}^I)$. The explicit forms of $V_{LMM-g}^C$ and $V_{LMM-g}^I$ and their consistent estimators are provided in the Supplementary Material.

Theorem 2 can be considered as the counterpart of Theorem 1 for linear mixed models.
in cluster-randomized experiments. Compared to generalized estimating equations with an identity link function and working exchangeable covariance structure, linear mixed models yield similar estimating equations, but the estimators for nuisance parameters are different, i.e., moment estimation for $\rho$ in generalized estimating equations versus maximum likelihood estimation for $\sigma^2$, $\tau^2$ in linear mixed models, leading to slightly different asymptotic variances. In the special case that $M_i(1) = M_i(0)$, $N_i$ is constant, $f(x, y) = x - y$, and $Y_{ij}$ are marginally identically distributed, Theorem 2 reduces to Theorem 1 of Wang et al. (2021).

Finally, while generalized estimating equations and generalized linear mixed models are the most widely used approach for analyzing cluster-randomized experiments, there are two alternative estimators, the augmented generalized estimating equations (Stephens et al., 2012) and targeted maximum likelihood estimation (Balzer et al., 2021; Benitez et al., 2021) that can also provide robust estimation under Assumptions 1-4 when certain aspects of working models are misspecified. We provide a brief review of those approaches in the Supplementary Material.

4 Efficient estimation

4.1 Efficient influence functions

For model-based methods to provide model-robust inference, Theorems 1 and 2 require the observed cluster size to be independent of cluster characteristics ($N, C$). To address this limitation, we develop more principled estimators to simultaneously optimize covariate adjustment and address variable observed cluster sizes arising from cluster-dependent sampling schemes. The proposed estimators are motivated by the efficient influence function, which is a non-parametric functional of observed data that characterizes the target estimand (Hines et al., 2022). With the efficient influence function, one can derive the efficiency bound for an estimand, i.e., the asymptotic variance of all regular and asymptotically linear estimators over the underlying causal model is lower bounded by the variance of the efficient influence function. More importantly, recent advances in causal inference (e.g.
van der Laan et al., 2011; Chernozhukov et al., 2018) showed how to use the efficient influence functions to construct an efficient estimator, i.e., achieving the efficiency bound, by incorporating machine learning algorithms for estimating nuisance parameters. Theorem 3 provides the efficient influence functions for $\mu_C(a)$ and $\mu_I(a)$, from which the efficient influence functions for $\Delta_C$ and $\Delta_I$ can be obtained by the chain rule.

**Theorem 3.** (a) Given Assumptions 1-3, the efficient influence function for $\mu_C(a)$ is

$$EIF_C(a) = \frac{I\{A = a\}}{\pi^a(1 - \pi)^{1-a}} \{\bar{Y}^o - E(\bar{Y}^o | A = a, X^o, M, N, C)\}$$

$$+ \frac{pr(A = a | M, N, C)}{\pi^a(1 - \pi)^{1-a}} \{E(\bar{Y}^o | A = a, X^o, M, N, C) - E(\bar{Y}^o | A = a, N, C)\}$$

$$+ E(\bar{Y}^o | A = a, N, C) - \mu_C(a), \quad a \in \{0, 1\},$$

where $I\{A = a\}$ is an indicator function of $A = a$ and $\bar{Y}^o = M^{-1} \sum_{j=1}^{N} S_j Y_j$ refers to the average outcome among the observed participants in each cluster. (b) Given Assumptions 1-3, the efficient influence function for $\mu_I(a)$ is

$$EIF_I(a) = \frac{N}{E(N)} \{EIF_C(a) + \mu_C(a) - \mu_I(a)\}, \quad a \in \{0, 1\}. $$

The efficient influence functions in Theorem 3 involve three nuisance functions, which we denote by $\eta^*_a = E(\bar{Y}^o | A = a, X^o, M, N, C)$, $\zeta^*_a = E(\bar{Y}^o | A = a, N, C)$, and $\kappa^*_a = pr(A = a | M, N, C)$. Compared to $EIF_C(a)$, $EIF_I(a)$ additionally includes a weight, $N/E(N)$, to target the individual-average treatment effect. When $M$ is identical to the source population size $N$, the number of sampled individuals can be treated as a pre-randomization variable, and the efficient influence function for $\mu_C(a)$ reduces to that in Balzer et al. (2019), where the only nuisance function is $\eta^*_a$. In more general settings as we consider here, two additional nuisance functions, $\zeta^*_a$ and $\kappa^*_a$, are needed to leverage the post-randomization information $X^o$ for improving efficiency. Next, we construct new estimators for $\Delta_C$ and $\Delta_I$ based on the efficient influence functions.
4.2 Efficient estimation based on the efficient influence functions

Based on Theorem 3, we propose the following estimator for $\mu_C(a)$ and $\mu_I(a)$:

$$
\hat{\mu}_C^{\text{Eff}}(a) = \frac{1}{m} \sum_{i=1}^{m} \left[ \frac{I\{A_i = a\}}{\pi^a(1 - \pi)^{1-a}} \left\{ \tilde{Y}_i - \tilde{\eta}_a(X_{i}^0, M_i, N_i, C_i) \right\} \right] + \frac{\tilde{\kappa}_a(M_i, N_i, C_i)}{\pi^a(1 - \pi)^{1-a}} \left\{ \tilde{\eta}_a(X_{i}^0, M_i, N_i, C_i) - \tilde{\zeta}_a(N_i, C_i) \right\} + \tilde{\zeta}_a(N_i, C_i),
$$

$$
\hat{\mu}_I^{\text{Eff}}(a) = \frac{1}{\sum_{i=1}^{m} N_i} \sum_{i=1}^{m} N_i \left[ \frac{I\{A_i = a\}}{\pi^a(1 - \pi)^{1-a}} \left\{ \tilde{Y}_i - \tilde{\eta}_a(X_{i}^0, M_i, N_i, C_i) \right\} \right] + \frac{\tilde{\kappa}_a(M_i, N_i, C_i)}{\pi^a(1 - \pi)^{1-a}} \left\{ \tilde{\eta}_a(X_{i}^0, M_i, N_i, C_i) - \tilde{\zeta}_a(N_i, C_i) \right\} + \tilde{\zeta}_a(N_i, C_i),
$$

where $\tilde{\eta}_a, \tilde{\zeta}_a, \tilde{\kappa}_a$ are user-specified estimators for nuisance functions $\eta_a^*, \zeta_a^*, \kappa_a^*$, respectively. Then the target estimands defined in Section 2 are estimated by $\hat{\Delta}_C^{\text{Eff}} = f \{ \hat{\mu}_C^{\text{Eff}}(1), \hat{\mu}_C^{\text{Eff}}(0) \}$ and $\hat{\Delta}_I^{\text{Eff}} = f \{ \hat{\mu}_I^{\text{Eff}}(1), \hat{\mu}_I^{\text{Eff}}(0) \}$. Among the many possibilities for estimating these nuisance functions, we primarily consider the following two approaches.

The first approach considers parametric working models, that is, $\tilde{\eta}_a = \eta_a(\hat{\theta}_{\eta,a}), \tilde{\zeta}_a = \zeta_a(\hat{\theta}_{\zeta,a}), \tilde{\kappa}_a = \kappa_a(\hat{\theta}_{\kappa,a})$ for pre-specified functions $\eta_a, \zeta_a, \kappa_a$ with finite-dimensional parameters $\theta_{\eta,a}, \theta_{\zeta,a}, \theta_{\kappa,a}$. Example working models include generalized estimating equations, generalized linear mixed models, penalized regression for variable selection, among others; in all cases, the associated parameters are estimated by solving estimating equations, and we assume that the estimating equations satisfy regularity conditions provided in the Supplementary Material such that the nuisance parameter estimators are asymptotically linear. For the subsequent technical discussions, we denote the probability limit of $(\hat{\theta}_{\eta,a}, \hat{\theta}_{\zeta,a}, \hat{\theta}_{\kappa,a})$ as $(\theta_{\eta,a}, \theta_{\zeta,a}, \theta_{\kappa,a})$.

The second approach uses machine learning algorithms with cross-fitting to estimate all nuisance functions. We assume that each nuisance function estimator is consistent to the truth at an $m^{1/4}$ rate such that $m^{1/4} \| \tilde{\eta}_a - \eta_a^* \|_2 = o(1)$, $m^{1/4} \| \tilde{\zeta}_a - \zeta_a^* \|_2 = o(1)$, and $m^{1/4} \| \tilde{\kappa}_a - \kappa_a^* \|_2 = o(1)$, where $\| \cdot \|_2$ denote the $L_2(\mathcal{P})$-norm. This rate can be achieved by many methods such as random forests (Wager and Walther, 2015), neural networks (Farrell et al., 2021), and boosting (Luo and Spindler, 2016). In addition, we assume a regularity condition
that \( \hat{\kappa}_a \) and \( E\{ (\eta_a^*)^2 \mid M, N, C \} \) are uniformly bounded, a similar condition invoked in Chernozhukov et al. (2018) for controlling the remainder term and consistently estimating the variance. Cross-fitting is used for achieving asymptotic normality for machine-learning algorithms. To implement cross-fitting, we randomly partition \( m \) clusters into \( K \) parts with roughly equal sizes, and the nuisance function prediction for each part is obtained by the model trained on the other \( K - 1 \) parts. In practice, we recommend choosing \( K \) such that \( m/K \geq 10 \). Theorem 4 summarizes the asymptotic behaviors of our proposed estimators under both strategies for estimating the nuisance functions.

**Theorem 4.** Given Assumptions 1-3 and above regularity conditions, (a) when the nuisance functions are estimated by parametric working models, if \( \kappa_a(\theta_{\kappa,a}) = \kappa_a^* \) or \( E\{ \eta_a(\theta_{\eta,a}) \mid M, N, C \} = \zeta_a(\theta_{\zeta,a}) \), then \( m^{1/2}(\hat{\Delta}_{\text{Eff}}^C - \Delta_C) \overset{d}{\to} \mathcal{N}(0, V_{\text{Eff-PM}}^C) \) and \( m^{1/2}(\hat{\Delta}_{\text{Eff}}^I - \Delta_I) \overset{d}{\to} \mathcal{N}(0, V_{\text{Eff-PM}}^I) \). (b) When the nuisance functions are consistently estimated using machine learning algorithms with cross-fitting at an \( m^{1/4} \)-rate, then \( m^{1/2}(\hat{\Delta}_{\text{Eff}}^C - \Delta_C) \overset{d}{\to} \mathcal{N}(0, V_{\text{Eff-ML}}^C) \) and \( m^{1/2}(\hat{\Delta}_{\text{Eff}}^I - \Delta_I) \overset{d}{\to} \mathcal{N}(0, V_{\text{Eff-ML}}^I) \), where \( V_{\text{Eff-ML}}^C \) and \( V_{\text{Eff-ML}}^I \) achieve the efficiency bound for estimating \( \Delta_C \) and \( \Delta_I \). In both cases, the asymptotic variance expressions and their consistent estimators are provided in the Supplementary Material.

For the proposed estimators with parametric working models, Theorem 4 implies that the estimator is consistent if \( \kappa_a \) is correctly specified, or the working models \( \eta_a \) and \( \zeta_a \) are equivalent conditioning on \( M, N, C \). In the special case that all cluster-level covariates are discrete, the latter condition can be satisfied by setting \( \eta_a(\theta_{\eta,a}) = \zeta_a + \beta^\top (\bar{X}_n - \sum_{n,c} I\{ N = n, C = c \} \theta_{n,c}) \), where \( \beta \) is an arbitrary \( p \)-dimensional vector and \( \theta_{n,c} = E\{ X_{\cdot,n,c} \mid N = n, C = c \} \); in this special case, the resulting estimators are in fact robust to arbitrary working model misspecification. In more general cases with non-discrete cluster-level covariates, the proposed estimators are at least triply-robust. That is, they are consistent to their respective target estimands as long as two out of the three nuisance functions are correctly modeled, since \( E(\eta_a^* \mid M, N, C) = \zeta_a^* \) as proved in the Supplementary Material.

For the proposed estimators using machine learning algorithms, efficiency can be achieved when all nuisance parameters are consistently estimated, leading to higher asymptotic pre-
cision than potentially misspecified parametric working models. For modeling $\eta^*_a$, since $X^o$ is a matrix and its dimension may change across clusters, a feasible practical strategy is to fit $Y_{ij}$ on $(X_{ij}, M_i, N_i, C_i)$ and pre-specified summary statistics of $X^o_i$ with fixed dimensions, e.g., $\bar{X}^o_i$, and then compute the cluster-average of predictions as the model fit. Alternatively, one can directly model $\bar{Y}^o_i$ on $(M_i, N_i, C_i)$ and functions of $X^o_i$, which can be potentially high-dimensional in order to capture its higher-order association with $\bar{Y}^o_i$.

**Remark 2.** In practice, each of the two approaches for nuisance function estimation has its pros and cons. The machine learning methods are asymptotically more precise, but the efficiency gain typically requires a fairly decent number of clusters. In addition, although the cross-fitting procedure yields the desired convergence property, it may be prone to finite-sample bias especially when the sample size is limited (Hines et al., 2022). This finite-sample bias can be potentially alleviated by using parsimonious parametric working models, thereby trading precision for better finite-sample performance characteristics.

**Remark 3.** If the observed cluster size $M < N$, our proposed estimators require an accurate estimate of the source population size for efficient estimation. If $N$ is not fully available for all clusters, one can still use the observed data $(\bar{Y}^o_i, A_i, C_i)$ to infer $\Delta_C$, and the efficient influence function for $\mu_C(a)$ becomes $I\{A = a\}(\bar{Y}^o - \zeta^*_a)/\{\pi^a(1 - \pi)^{1-a}\} + \zeta^*_a - \mu_C(a)$, based on which an estimator for $\Delta_C$ can be constructed. For example, we can apply our proposed estimator with $\hat{\eta}_a$ set to be equal to $\hat{\zeta}_a$ and get a consistent estimator for $\Delta_C$ even when $\hat{\zeta}_a$ is incorrectly specified. The individual-average treatment effect $\Delta_I$, however, is generally not identifiable without observing $N$.

## 5 Simulation experiments

### 5.1 Simulation design

We conducted two simulation experiments to compare different methods for analyzing cluster-randomized experiments. The first simulation study focused on estimating the difference
estimands of the cluster- and individual-average treatment effect for continuous outcomes, while the second study focused on the relative risk estimands for binary outcomes. In each experiment, we considered a small, $m = 30$, or large, $m = 100$, number of clusters, and random observed cluster sizes, i.e., $M_i$ is independent of other variables as a special case of Assumption 4, or cluster-dependent observed cluster sizes, i.e., $M_i$ depends on treatment and cluster-level covariates. Combinations of these specifications are labeled as scenarios 1-4 in Table 1 and Table 2.

In the first simulation experiment, we let $(N_i, C_{i1}, C_{i2})$, $i = 1, \ldots, m$ be independent draws from distribution $\mathcal{P}^N \times \mathcal{P}^{C_1|N} \times \mathcal{P}^{C_2|N,C_1}$, where $\mathcal{P}^N$ is uniform over support $\{10, 50\}$, $\mathcal{P}^{C_1|N} = \mathcal{N}(N/10, 4)$, and $\mathcal{P}^{C_2|N,C_1} = \mathcal{B} [\expit \{\log(N/10)C_1\}]$ is a Bernoulli distribution with $\expit(x) = (1 + e^{-x})^{-1}$. Next, for each individual in the source population, we generated the individual-level covariates from $X_{ij1} \sim \mathcal{B} (N_i/50)$, $X_{ij2} \sim \mathcal{N} \left\{ \sum_{j=1}^{N_i} X_{ij1}(2C_{i2} - 1)/N_i, 9 \right\}$, and potential outcomes from $Y_{ij}(1) \sim \mathcal{N} \left\{ N_i/5 + N_i \sin(C_{i1})(2C_{i2} - 1)/30 + 5e^{X_{ij1}} | X_{ij2} |, 1 \right\}$ and $Y_{ij}(0) \sim \mathcal{N} \left\{ \gamma_i + N_i \sin(C_{i1})(2C_{i2} - 1)/30 + 5e^{X_{ij1}} | X_{ij2} |, 1 \right\}$ where $\gamma_i \sim \mathcal{N}(0, 1)$ is a cluster-level random intercept to allow for residual intracluster correlations. Furthermore, we set $M_i(1) = M_i(0) = 9 + \mathcal{B}(0.5)$ for the random observed cluster size scenario, and $M_i(1) = N_i/5 + 5C_{i2}$, $M_i(0) = 3I \{ N_i = 50 \} + 3$ for the cluster-dependent observed cluster size scenario. Then, we independently sampled $A_i \sim \mathcal{B}(0.5)$ and defined $Y_{ij} = A_i Y_{ij}(1) + (1 - A_i) Y_{ij}(0)$ and $M_i = A_i M_i(1) + (1 - A_i) M_i(0)$. Finally, for each cluster, we uniformly sampled without replacement $M_i$ individuals, for whom $S_{ij} = 1$, and the observed data in each simulation replicate are $\{ Y_{ij}, A_i, M_i, C_{i1}, C_{i2}, X_{ij1}, X_{ij2} : S_{ij} = 1, i = 1, \ldots, m, j = 1, \ldots, N_i \}$.

For the second simulation study, the data were generated following the first simulation study, except that the potential outcomes were drawn from the following Bernoulli distributions: $Y_{ij}(1) \sim \mathcal{B} \left[ \expit \left\{ -N_i/20 + N_i \sin(C_{i1})(2C_{i2} - 1)/30 + 1.5e^{X_{ij1}} | X_{ij2} |^{1/2} \right\} \right]$ and $Y_{ij}(0) \sim \mathcal{B} \left[ \expit \left\{ \gamma_i + N_i \sin(C_{i1})(2C_{i2} - 1)/30 + 1.5(2X_{ij1} - 1) | X_{ij2} |^{1/2} \right\} \right]$. We compared the following methods. The unadjusted method (Bugni et al., 2022) is equivalent to our proposed method setting $\hat{\eta}_a = \hat{\zeta}_a$ to be a constant. Generalized estimating equations with weighted g-computation were implemented as described in Section 3.1 with
an exchangeable working correlation for continuous outcomes and an independence working correlation for binary outcomes. Linear mixed models with weighted g-computation were implied as described in Section 3.2 for both continuous and binary outcomes. For our proposed methods, we considered both parametric working models and machine learning algorithms, where the former used generalized linear models for all nuisance functions, and the latter exploited SuperLearner (van der Laan et al., 2007) for model-fitting with generalized linear models, regression trees, and neural networks. Across the comparators, individual-level regression working models adjusted for covariates \((N_i, C_{i1}, C_{i2}, X_{ij1}, X_{ij2})\), and cluster-level working models adjusted for covariates \((N_i, C_{i1}, C_{i2})\). We used the consistent variance estimator described in Supplementary Material with the degree-of-freedom adjustment to improve the small-sample performance. For each scenario of both simulation experiments, we randomly generated 10,000 data sets and tested the above methods on each data set.

5.2 Simulation Results

Table 1 summarizes the simulation results for continuous outcomes. Since the outcome distribution varies by the source population size, the cluster-average treatment effect \(\Delta_C = 6\), which differs from the individual-average treatment effect \(\Delta_I = 8.67\). Across all scenarios, the proposed methods with no covariate adjustment, parametric working models, or machine learning algorithms have negligible bias and nominal coverage, while the model-based methods, i.e., generalized estimating equations and linear mixed models, show bias and under-coverage if the observed cluster sizes are cluster-dependent.

For scenarios 1 and 3, since the observed cluster size is completely random, the model-based estimators perform well, which confirms the theoretical results in Section 3. Among all methods, our method with machine learning algorithms has the highest precision: its variance is \(35 \sim 93\%\) and \(49 \sim 89\%\) smaller than the other methods for estimating the \(\Delta_C\) and \(\Delta_I\), respectively, demonstrating its potential to flexibly leverage baseline covariates for improving study power. Our estimator that uses parametric models for covariate adjustment
Table 1: Results in the first simulation experiment with continuous outcomes.

| Setting | Method       | Cluster-average treatment effect $\Delta_C = 6$ | Individual-average treatment effect $\Delta_I = 8.67$ |
|---------|--------------|-----------------------------------------------|---------------------------------------------------|
|         |              | Bias  | ESE  | ASE  | CP   | Bias  | ESE  | ASE  | CP   |
| Scenario 1: Small $m$ with random observed cluster sizes | Unadjusted | -0.08 | 4.85 | 4.88 | 0.95 | -0.15 | 4.60 | 4.28 | 0.93 |
|         | GEE-g        | 0.13  | 2.77 | 2.45 | 0.92 | -0.13 | 3.64 | 3.10 | 0.89 |
|         | LMM-g        | 0.12  | 2.77 | 2.78 | 0.96 | -0.13 | 3.63 | 2.94 | 0.90 |
|         | Eff-PM       | -0.03 | 3.23 | 2.66 | 0.92 | -0.10 | 3.89 | 3.38 | 0.91 |
|         | Eff-ML       | 0.03  | 2.24 | 2.05 | 0.95 | 0.03  | 2.59 | 2.49 | 0.95 |
| Scenario 2: Small $m$ with cluster-dependent observed cluster sizes | Unadjusted | 0.17  | 5.33 | 5.31 | 0.95 | -0.18 | 4.82 | 4.48 | 0.93 |
|         | GEE-g        | 1.98  | 3.75 | 3.25 | 0.86 | 0.87  | 4.53 | 3.66 | 0.88 |
|         | LMM-g        | 1.74  | 3.63 | 3.69 | 0.94 | 0.79  | 4.26 | 3.83 | 0.93 |
|         | Eff-PM       | 0.08  | 3.87 | 3.47 | 0.93 | 0.09  | 4.32 | 3.97 | 0.93 |
|         | Eff-ML       | -0.21 | 3.42 | 3.47 | 0.95 | -0.06 | 4.20 | 3.84 | 0.93 |
| Scenario 3: Large $m$ with random observed cluster sizes | Unadjusted | 0.01  | 2.62 | 2.65 | 0.96 | 0.06  | 2.68 | 2.63 | 0.95 |
|         | GEE-g        | 0.04  | 1.40 | 1.38 | 0.95 | -0.01 | 1.89 | 1.83 | 0.94 |
|         | LMM-g        | 0.04  | 1.40 | 1.42 | 0.96 | -0.01 | 1.89 | 1.55 | 0.90 |
|         | Eff-PM       | 0.00  | 1.40 | 1.38 | 0.95 | -0.01 | 1.93 | 1.92 | 0.95 |
|         | Eff-ML       | 0.04  | 0.70 | 0.71 | 0.95 | 0.00  | 0.77 | 0.81 | 0.97 |
| Scenario 4: Large $m$ with cluster-dependent observed cluster sizes | Unadjusted | -0.04 | 2.94 | 2.89 | 0.95 | -0.06 | 2.57 | 2.48 | 0.94 |
|         | GEE-g        | 1.80  | 1.89 | 1.82 | 0.82 | 0.74  | 2.21 | 2.12 | 0.91 |
|         | LMM-g        | 1.72  | 1.87 | 1.89 | 0.85 | 0.72  | 2.20 | 2.00 | 0.91 |
|         | Eff-PM       | 0.03  | 1.89 | 1.83 | 0.94 | 0.01  | 2.21 | 2.16 | 0.94 |
|         | Eff-ML       | 0.01  | 1.91 | 1.83 | 0.94 | 0.00  | 2.23 | 2.13 | 0.94 |

Unadjusted: the unadjusted estimator. GEE-g: generalized estimating equations with weighted g-computation. LMM-g: linear mixed models with weighted g-computation. Eff-PM: our proposed method with parametric working models. Eff-ML: our proposed method with machine learning algorithms. ESE: empirical standard error. ASE: average of estimated standard error. CP: coverage probability based on $t$-distribution.
has comparable precision to model-based methods and is more efficient than the unadjusted estimator.

For scenarios 2 and 4, more individuals are enrolled in treated clusters with a larger source population, leading to bias for methods that utilized individual-level data without adjusting for this cluster-dependent sampling scheme. Specifically, model-based methods have bias ranging from 0.72 to 1.98, and 1% to 13% under coverage. In contrast to the issues caused by adapting model-based methods, our proposed methods show both validity and precision. The validity is reflected by the negligible bias and nominal coverage, and the precision is borne out by their smaller empirical variance than the unadjusted estimator.

Table 2 summarizes the simulation results for binary outcomes, and the patterns are generally similar to those for continuous outcomes. In particular, the proposed methods remain valid across scenarios, but the advantage of machine-learning algorithms over parametric modeling is less obvious. Finally, comparing a small versus large number of clusters, all methods perform less stably with a smaller number of clusters, as expected. When \( m = 30 \), methods with covariate adjustment tend to underestimate the true standard error, causing 0 \( \sim \) 5% under coverage. When \( m \) increases to 100, the estimated standard errors match the empirical standard error, thereby implying the validity of our variance estimator.

In the Supplementary Material, we provide additional simulation results for augmented generalized estimating equations and targeted maximum likelihood estimation under the same settings. Augmented generalized estimating equations were adapted with weighted g-computation to target our estimands and showed similar performance to generalized estimating equations with weighted g-computation. The target maximum likelihood estimator was unbiased when it only adjusted for cluster-level covariates, while it had bias for \( \Delta_I \) if the sampling was cluster-dependent. In most scenarios, both methods were less precise than our proposed method coupled with machine learning estimators for the nuisance functions.
### Table 2: Results in the second simulation experiment with binary outcomes.

| Setting | Method | Cluster-average treatment effect $\Delta_C = 1.54$ | Individual-average treatment effect $\Delta_I = 1.18$ |
|---------|--------|---------------------------------------------------|---------------------------------------------------|
|         |        | Bias     ESE  ASE  CP                          | Bias     ESE  ASE  CP                          |
| Scenario 1: Small $m$ with random observed cluster sizes | Unadjusted | 0.04 0.25 0.24 0.94 | 0.03 0.15 0.13 0.93 |
|         | GEE-g  | 0.01 0.23 0.19 0.92 | 0.03 0.22 0.13 0.93 |
|         | LMM-g  | 0.01 0.22 0.19 0.92 | 0.03 0.16 0.13 0.93 |
|         | Eff-PM | 0.01 0.21 0.20 0.93 | 0.02 0.16 0.15 0.95 |
|         | Eff-ML | 0.03 0.22 0.20 0.94 | 0.03 0.15 0.14 0.95 |
| Scenario 2: Small $m$ with cluster-dependent observed cluster sizes | Unadjusted | 0.05 0.30 0.29 0.94 | 0.03 0.17 0.14 0.93 |
|         | GEE-g  | −0.18 0.30 0.20 0.69 | −0.05 0.16 0.17 0.89 |
|         | LMM-g  | −0.12 0.24 0.20 0.78 | −0.04 0.15 0.16 0.90 |
|         | Eff-PM | 0.04 0.28 0.26 0.92 | 0.03 0.17 0.17 0.95 |
|         | Eff-ML | 0.06 0.30 0.30 0.93 | 0.05 0.19 0.17 0.95 |
| Scenario 3: Large $m$ with random observed cluster sizes | Unadjusted | 0.01 0.13 0.13 0.95 | 0.01 0.07 0.07 0.95 |
|         | GEE-g  | 0.00 0.11 0.10 0.95 | 0.00 0.07 0.07 0.95 |
|         | LMM-g  | 0.00 0.11 0.10 0.94 | 0.01 0.07 0.07 0.95 |
|         | Eff-PM | 0.01 0.10 0.10 0.95 | 0.00 0.07 0.08 0.97 |
|         | Eff-ML | 0.01 0.10 0.10 0.95 | 0.01 0.06 0.07 0.97 |
| Scenario 4: Large $m$ with cluster-dependent observed cluster sizes | Unadjusted | 0.01 0.15 0.15 0.95 | 0.01 0.08 0.08 0.94 |
|         | GEE-g  | −0.20 0.10 0.10 0.44 | −0.06 0.07 0.09 0.88 |
|         | LMM-g  | −0.14 0.11 0.10 0.67 | −0.05 0.07 0.08 0.89 |
|         | Eff-PM | 0.01 0.13 0.13 0.94 | 0.00 0.07 0.08 0.97 |
|         | Eff-ML | 0.01 0.14 0.13 0.94 | 0.01 0.08 0.08 0.97 |

Unadjusted: the unadjusted estimator. GEE-g: generalized estimating equations with weighted g-computation. LMM-g: linear mixed models with weighted g-computation. Eff-PM: our proposed method with parametric working models. Eff-ML: our proposed method with machine learning algorithms. ESE: empirical standard error. ASE: average of estimated standard error. CP: coverage probability based on $t$-distribution.
6 Numeric example based on the Stop Colorectal Cancer study

The Stop Colorectal Cancer study is a recently-completed, pragmatic cluster-randomized experiment evaluating the effectiveness of a mailed outreach program in improving the completion rate for fecal immunochemical test (Coronado et al., 2018). Twenty-six qualified health clinics were randomly assigned in a 1:1 ratio to implement intervention, i.e., mailing fecal immunochemical test kits to patients due for colorectal cancer screening, or the usual care, i.e., opportunistic colorectal cancer screening. Within each cluster, all eligible patients were enrolled by an automated system embedded in the electronic health record system. The cluster size varied from 461 to 3,299, with 41,193 patients enrolled in total. The primary outcome was a binary indicator of completing a fecal immunochemical test during the 12-month follow-up. We considered adjusting for the following covariates: the baseline national quality forum score, which measures the proportion of patients already compliant with colorectal cancer screening, and cluster sizes at the cluster level, and age, gender, and racial group at the individual level.

To illustrate the proposed methods, we performed two analyses: a full data analysis and a hypothetical cluster-dependent sampling analysis, aiming to compare statistical methods from multiple viewpoints based on the real data. For both analyses, we estimated $\Delta_C$ and $\Delta_I$ on the risk difference scale. The full data analysis was implemented on the original data, assuming $M = N$ and therefore full enrollment of the source population in each cluster. The cluster-dependent sampling analysis simulated the inclusion of participants by setting $M_i = 5 + 5A_i(1 + 2\lceil 9 - 10W_i \rceil)$, where $W_i$ is the proportion of white individuals in cluster $i$ and $\lceil \cdot \rceil$ is the ceiling function. We compared the same methods as in the simulation study.

The results of full data analysis are summarized in Table 3. For each estimand, all methods provide similar point estimates up to the second digit, while their variance estimates differ. Compared to the unadjusted estimator, covariate adjustment provides little precision gain since covariates are only weakly prognostic. Among the comparison methods, general-
ized estimating equations and linear mixed models may be biased due to the varying cluster sizes as discussed in Section 3.

Table 3: Results from the full data analysis for the STOP CRC cluster-randomized experiment.

| Method  | Cluster-average treatment effect (ΔC) | 95% C.I. | RE | Individual-average treatment effect (ΔI) | 95% C.I. | RE |
|---------|-------------------------------------|---------|----|----------------------------------------|---------|----|
| Unadjusted | 0.04     | (−0.01, 0.08) | 1.00 | 0.03                                   | (−0.02, 0.09) | 1.00 |
| GEE-g    | 0.03     | (−0.02, 0.08) | 1.24 | 0.03                                   | (−0.05, 0.11) | 1.81 |
| LMM-g    | 0.03     | (−0.01, 0.08) | 0.98 | 0.03                                   | (−0.04, 0.10) | 1.40 |
| Eff-PM   | 0.03     | (−0.01, 0.08) | 0.94 | 0.03                                   | (−0.03, 0.09) | 0.94 |
| Eff-ML   | 0.04     | (−0.01, 0.09) | 1.03 | 0.03                                   | (−0.03, 0.09) | 1.05 |

Unadjusted: the unadjusted estimator. GEE-g: generalized estimating equations with weighted g-computation. LMM-g: linear mixed models with weighted g-computation. Eff-PM: our proposed method with parametric working models. Eff-ML: our proposed method with machine learning algorithms. 95% C.I.: 95% confidence interval based on t-distribution. RE: relative efficiency relative to the unadjusted estimator.

Table 4 gives the results for the cluster-dependent sampling analysis. By the data generating process, the unadjusted estimators from the full data analysis are considered as the gold standards, based on which we evaluate the bias and coverage probability of methods in the simulated data. In addition, the cluster-dependent sampling analysis reflects the real-world setting, i.e., the distribution of outcome and covariates is based on real data and is unspecified. Consistent with our simulation results in Section 5, the cluster-dependent sampling leads to bias of model-based methods for both estimands, while our proposed methods have negligible bias and nominal coverage.

7 Concluding remarks

Our contributions to the emerging causal inference literature on cluster-randomized experiments are two-fold. First, we clarified sufficient conditions under which two mainstream model-based regression estimators are robust for identifying the cluster-average treatment effect and individual-average treatment effect. Second, we proposed efficient estimators for
Table 4: Results from the cluster-dependent sampling analyses based on 1,000 simulation draws using the STOP CRC study.

| Method    | Cluster-average treatment effect | Individual-average treatment effect |
|-----------|---------------------------------|------------------------------------|
|           | $\Delta_C = 0.0357$ from the full data analysis | $\Delta_I = 0.0342$ from the full data analysis |
|           | Relative bias | ESE  | ASE  | CP    | Relative bias | ESE  | ASE  | CP    |
| Unadjusted| 0.08         | 0.05 | 0.05 | 0.95  | 0.02         | 0.05 | 0.05 | 0.94  |
| GEE-g     | -0.36        | 0.07 | 0.05 | 0.83  | -0.59        | 0.08 | 0.05 | 0.80  |
| LMM-g     | 0.43         | 0.05 | 0.05 | 0.92  | 0.61         | 0.05 | 0.05 | 0.91  |
| Eff-PM    | 0.04         | 0.05 | 0.05 | 0.94  | 0.00         | 0.06 | 0.05 | 0.92  |
| Eff-ML    | 0.05         | 0.05 | 0.05 | 0.95  | 0.06         | 0.06 | 0.06 | 0.94  |

Unadjusted: the unadjusted estimator. GEE-g: generalized estimating equations with weighted g-computation. LMM-g: linear mixed models with weighted g-computation. Eff-PM: our proposed method with parametric working models. Eff-ML: our proposed method with machine learning algorithms. Relative bias: bias divided by the truth. ESE: empirical standard error. ASE: average of estimated standard error. CP: coverage probability based on $t$-distribution.

the two classes of estimands that allow for principled covariate adjustment and additionally address the cluster-dependent sampling. The new estimators open the door for flexibly leveraging parametric working models or machine learning algorithms to model the potentially complex data generation mechanism without compromising the validity of inference in cluster-randomized experiments.

A common objective for covariate adjustment in cluster-randomized experiments is to address chance imbalance and improve precision (Su and Ding, 2021). However, how to best select the optimal set and functional forms of covariates is an open problem that remains to be addressed in future research. For cluster-randomized experiments, this problem may be more challenging due to the unknown intracluster correlations of the outcomes and covariates within each cluster. In many cases where the investigators can only include a limited number of clusters, there will be a trade-off between the loss of degrees of freedom by adjusting for weakly prognostic covariates and the potential asymptotic power gain by including more baseline variables. While the proposed estimators may be a useful vehicle to incorporate variable selection techniques in the working models, we maintain the recommendation of pre-specifying prognostic covariates for adjustment in the design stage based on subject-matter knowledge for practical applications.
For developing the asymptotic properties of the model-robust estimators, we have focused on simple randomization, whereas stratified randomization and cluster rerandomization are useful alternative strategies to address baseline imbalance and further improve the study power. For example, Wang et al. (2021) proved that stratified randomization leads to more efficient average treatment effect estimators under a working linear mixed model in cluster-randomized experiments. Lu et al. (2022) recently developed the asymptotic theory for cluster rerandomization under a finite-population framework. It would be useful to further extend our results to accommodate stratified cluster randomization and cluster rerandomization.

Acknowledgement

Research in this article was partially supported by a Patient-Centered Outcomes Research Institute Award® (PCORI® Award ME-2020C3-21072). The statements presented in this article are solely the responsibility of the authors and do not necessarily represent the official views of PCORI®, or its Board of Governors or Methodology Committee. The authors thank Drs. Gloria Coronado and William Vollmer from the Center for Health Research, Kaiser Permanente, for sharing the de-identified data from the STOP CRC study.

Supplementary material

Supplementary material includes the causal graph mentioned in Section 2, regularity conditions, proofs, consistent variance estimators, and review of other methods for cluster-randomized experiments.

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Supplementary Material for “Model-robust and efficient inference for cluster-randomized experiments”

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In Section A, we provide a causal graph describing the relationship of considered random variables. In Section B, we provide the regularity conditions needed for our theorems. In Section C, we provide the proofs for our theorems. In Section D, we provide the consistent variance estimators. In Section E, we review other methods for cluster-randomized experiments mentioned in the main paper and provide additional simulation results for these methods.

A A causal graph for observed and unobserved random variables

![Causal Graph]

Figure 1: A graph representation of causal relationship among variables. Observed and unobserved nodes have solid and dashed boundaries, respectively.
Let \( \psi(O, \theta) \) be a vector of (generic) estimating functions of observed data \( O \) and parameters \( \theta \). The parameters are estimated by solving \( \sum_{i=1}^{m} \psi(O_i, \hat{\theta}) = 0 \). The estimating functions we specified are defined in (1) and (2) for GEE-g and (3) and (4) for LMM-g. For our proposed efficient estimator with user-specified parametric working models, we denote \( \psi(O, \theta) \) as the estimating equations for parameters \( \theta = (\theta_{\eta,1}, \theta_{\zeta,1}, \theta_{\kappa,0}, \theta_{\eta,0}, \theta_{\zeta,0}, \theta_{\kappa,0}) \). We make the following regularity assumptions on \( \psi(O, \theta) \):

1. \( \theta \in \Theta \), a compact subset of the Euclidean space.

2. The function \( \theta \mapsto \psi(o, \theta) \) is dominated by a square-integrable function and twice continuously differentiable for every \( o \) in the support of \( O \) with nonsingular derivative matrix \( B_{\theta} \) that is continuous on \( \theta \). Furthermore, the first and second order derivatives of \( \theta \mapsto \psi(o, \theta) \) are also dominated by a square-integrable function in a small neighborhood of \( \theta \).

3. There exists a unique solution in the interior of \( \Theta \), denoted as \( \theta_{\hat{\theta}} \), to the equations \( E[\psi(O, \theta)] = 0 \).

4. \( \{\psi(o, \theta) : ||\theta - \theta_{\hat{\theta}}|| < \delta\} \) is P-Donsker (Chapter 19 of \textit{van der Vaart}, 1998) for some \( \delta > 0 \). One sufficient condition is that \( ||\psi(o, \theta) - \psi(o, \tilde{\theta})||_2 \leq m(o)||\theta - \tilde{\theta}||_2 \) for some square-integrable function \( m(o) \) and every \( \theta, \tilde{\theta} \in \Theta \).

Of note, regularity condition 3 does not imply a correctly specified model. Instead, it solely requires the uniqueness of maxima in quasi-likelihood estimation. This can be achieved by carefully designing the estimating equations and restricting parameter space \( \Theta \) to rule out degenerative solutions. For example, if \( \psi \) is the estimating equations for a linear regression, then it is equivalent to the invertibility of the covariance matrix of covariates.

For the proposed estimator, we additionally assume:

5. For parametric working models, the class of functions \( \{\eta_a(\theta_{\eta,a}), \zeta_a(\theta_{\zeta,a}), \kappa_a(\theta_{\kappa,a}) : \theta_a \in \Theta, a \in \{0, 1\}\} \) is dominated by a square-integrable function, twice continuously differ-
entialable in $\theta_a$ with dominated first and second order derivatives, and P-Donsker when $||\theta_a - \theta_a||_2 < \delta$ for some $\delta > 0$, where $\theta_a = (\theta_{\eta,a}, \theta_{\zeta,a}, \theta_{\kappa,a})$ and $\theta_a = (\theta_{\eta,a}, \theta_{\zeta,a}, \theta_{\kappa,a})$.

6. For data-adaptive estimation with crossing fitting, we assume that $\hat{\kappa}_a$ and

$$E[\{\eta'_a(X^0, M, N, C)\}^2|M, N, C]$$

are uniformly bounded.

\section*{C Proofs}

\subsection*{C.1 Lemmas}

\textbf{Lemma 1.} Given Assumptions 1-3, we have (i) $X \perp (A, M)|(N, C)$, (ii) $(A, X, Y, C) \perp S|(M, N)$, and (iii) $X \perp S \perp A|(M, N, C)$.

\textit{Proof.} (i) Assumption 3 implies that $M(a) \perp X|(N, C)$, which further implies $M \perp X|(A, N, C)$ since $A \perp (M(a), X, N, C)$ and $M = AM(1) + (1 - A)M(0)$. Hence

$$pr(X|A, M, N, C) = \frac{pr(X, A, M, N, C)}{pr(A, M, N, C)} = \frac{pr(M|X, A, N, C)pr(X, N, C)pr(A)}{pr(M|A, N, C)pr(A)pr(N, C)} = pr(X|N, C).$$

(ii) Assumptions 2-3 imply that $pr\{S(a) = s|A, Y(a), X, M(a), N, C\} = \binom{N}{M(a)}^{-1}$ and, hence, $pr\{S = s|A, Y, X, M, N, C\} = \sum_a I\{A = a\}pr\{S(a) = s|A = a, Y(a), X, M(a), N, C\} = \binom{N}{M}^{-1}$, thereby indicating $(A, X, Y, C) \perp S|(M, N)$.

(iii) We have

$$pr(X, S, A|M, N, C) = \frac{pr(X, S, A, M, N, C)}{pr(M, N, C)}$$

$$= \frac{pr(S|M, N, X, A, C)pr(X|A, M, N, C)pr(A, M, N, C)}{pr(M, N, C)}$$

$$= pr(S|M, N, C)pr(X|M, N, C)pr(A|M, N, C),$$

where the last equation results from (i) and (ii). \hfill \Box

\textbf{Lemma 2.} Recall the notation $\overline{Y}(a) = \frac{1}{N} \sum_{j=1}^{N} Y_j(a)$, $\overline{Y} = \overline{Y}(A)$, $\overline{Y}'(a) = \frac{1}{M(a)} \sum_{j=1}^{N} S_j(a)Y_j(a)$, and $\overline{Y}' = \overline{Y}'(A)$. Given Assumptions 1-3, we have

$$E[\overline{Y}(a)|N, C] = E[\overline{Y}'(a)|N, C] = E[\overline{Y}'|A = a, N, C] = E[\overline{Y}'|A = a, M, N, C].$$
Proof. We first prove \(E\left[\bar{Y}(a)|N,C\right] = E\left[\bar{Y}'(a)|N,C\right]\). Assumption 3 implies that, for each \(j = 1, \ldots, N\),

\[
pr\{S_j(a) = 1|Y(a), X, M(a), N, C\} = \frac{\binom{N-1}{M(a)-1}}{\binom{N}{M(a)}} = \frac{M(a)}{N}.
\]

Hence, for \(a = 0, 1\),

\[
E\left[\bar{Y}'(a)\right| N, C\right] = E\left[\frac{\sum_{j=1}^{N} S_j(a)Y_j(a)}{M(a)}\right| Y(a), X, M(a), N, C\right| N, C\right]
\]

\[
= E\left[\frac{\sum_{j=1}^{N} E[S_j(a)|Y(a), X, M(a), N, C] \times Y_j(a)}{M(a)}\right| N, C\right]
\]

\[
= E\left[\frac{\sum_{j=1}^{N} Y_j(a)}{N}\right| N, C\right]
\]

\[
= E\left[\bar{Y}(a)|N, C\right]
\]

Next, since \(A \perp W\) and \(\bar{Y}(a)\) is a function of \(W\), then \(E\left[\bar{Y}'|A = a, N, C\right] = E[a\bar{Y}'(1) + (1-a)\bar{Y}'(0)|A = a, N, C\right] = E[Y(a)|N, C\] as desired.

Finally, we prove \(E\left[\bar{Y}(a)|N, C\right] = E\left[\bar{Y}'|A = a, M, N, C\right]\). Assumption 3 implies that \(E\left[\bar{Y}(a)|N, C\right] = E\left[\bar{Y}(a)|M(a), N, C\right]\). Using again the conditional distribution of \(S(a)\), we have \(E\left[\bar{Y}(a)|M(a), N, C\right] = E\left[\bar{Y}'(a)|M(a), N, C\right]\). Since \(A \perp W\), we get

\(E\left[\bar{Y}'(a)|M(a), N, C\right] = E\left[\bar{Y}'|A = a, M, N, C\right]\), which completes the proof. \(\square\)

Lemma 3. Let \(O_1, \ldots, O_m\) be i.i.d. samples from a common distribution on \(O\). Given the regularity conditions 1-4 for \(\psi(O, \theta)\), we have \(\hat{\theta} \xrightarrow{P} \theta\) and \(m^{1/2}(\hat{\theta} - \theta) \xrightarrow{d} N(0, V)\), where \(V = E[IF(O, \theta)IF(O, \theta)^\top]\) and \(IF(O, \theta) = -E\left[\frac{\partial \psi(O, \theta)}{\partial \theta}|_{\theta = \hat{\theta}}\right]^{-1} \psi(O, \hat{\theta})\) is the influence function for \(\hat{\theta}\). Furthermore, the sandwich variance estimator \(m^{-1} \sum_{i=1}^{m} \hat{IF}(O_i, \hat{\theta}) \hat{IF}(O_i, \hat{\theta})^\top\) converges in probability to \(V\), where \(\hat{IF}(O_i, \hat{\theta}) = \left\{m^{-1} \sum_{i=1}^{m} \frac{\partial \psi(O_i, \hat{\theta})}{\partial \theta}|_{\theta = \hat{\theta}}\right\}^{-1} \psi(O_i, \hat{\theta})\).

Proof. By regularity conditions 1 and 2, Example 19.8 of van der Vaart (1998) implies that \(\{\psi(O, \theta) : \theta \in \Theta\}\) is P-Glivenko-Cantelli. Then, with the regularity condition 3, Theorem 5.9 of van der Vaart (1998) shows that \(\hat{\theta} \xrightarrow{P} \theta\). We then apply Theorem 5.31 of van der Vaart
(1998) to obtain the asymptotic normality. Regularity conditions 1-4 implies that the assumptions for Theorem 5.31 of van der Vaart (1998) are satisfied with \( \hat{\eta} = \eta = \eta \) set to be a constant. Then we have

\[
m^{1/2}(\hat{\theta} - \theta) = -m^{-1/2}E \left[ \frac{\partial \psi(O, \theta)}{\partial \theta} \right]^{-1} \left\{ E[\psi(O, \theta)] + \frac{1}{m} \sum_{i=1}^{m} \psi(O_i, \hat{\theta}) \right\} + o_p(1)
\]

\[
= m^{-1/2} \sum_{i=1}^{m} IF(O_i, \hat{\theta}) + o_p(1),
\]

which implies the desired asymptotic normality by the Central Limit Theorem.

We next prove the consistency of the sandwich variance estimator. First, we prove that

\[
m^{-1} \sum_{i=1}^{m} \frac{\partial \psi(O, \theta)}{\partial \theta} \bigg|_{\theta = \hat{\theta}} = \frac{P}{E} \left[ \frac{\partial \psi(O, \theta)}{\partial \theta} \right] \bigg|_{\theta = \hat{\theta}}.
\]

Denoting \( \dot{\psi}_{ij}(\hat{\theta}) \) as the transpose of the \( j \)th row of \( \frac{\partial \psi(O, \theta)}{\partial \theta} \bigg|_{\theta = \hat{\theta}} \), we apply the multivariate Taylor expansion to get

\[
m^{-1} \sum_{i=1}^{m} \dot{\psi}_{ij}(\hat{\theta}) - m^{-1} \sum_{i=1}^{m} \dot{\psi}_{ij}(\theta) = m^{-1} \sum_{i=1}^{m} \ddot{\psi}_{ij}(\hat{\theta})(\hat{\theta} - \theta)
\]

for some \( \tilde{\theta} \) on the line segment between \( \hat{\theta} \) and \( \theta \) and \( \ddot{\psi}_{ij} \) being the derivative of \( \dot{\psi}_{ij} \). By the regularity condition 2 and \( \hat{\theta} \overset{P}{\rightarrow} \theta \), we have \( m^{-1} \sum_{i=1}^{m} \dot{\psi}_{ij}(\hat{\theta}) = O_p(1) \). As a result, \( \hat{\theta} - \theta = o_p(1) \) implies that \( m^{-1} \sum_{i=1}^{m} \dot{\psi}_{ij}(\hat{\theta}) - m^{-1} \sum_{i=1}^{m} \dot{\psi}_{ij}(\theta) = o_p(1) \). Then the first step is completed by the fact that \( m^{-1} \sum_{i=1}^{m} \dot{\psi}_{ij}(\theta) = E[\dot{\psi}_{ij}(\theta)] + o_p(1) \), which results from law of large numbers on \( \hat{\theta} \) and the regularity condition 2. Next, we prove \( m^{-1} \sum_{i=1}^{m} \psi(O_i, \theta)\psi(O_i, \hat{\theta})^\top \overset{P}{\rightarrow} E[\psi(O, \theta)\psi(O, \hat{\theta})^\top] \) following a similar procedure to the first step. Letting \( \psi_{ij}(\theta) \) be the \( j \)th entry of \( \psi(O_i, \theta) \), we apply the multivariate Taylor expansion and get

\[
m^{-1} \sum_{i=1}^{m} \psi_{ij}(\hat{\theta})\psi(O_i, \hat{\theta}) - m^{-1} \sum_{i=1}^{m} \psi_{ij}(\theta)\psi(O_i, \theta)
\]

\[
= m^{-1} \sum_{i=1}^{m} \left\{ \psi(O_i, \hat{\theta})\dot{\psi}_{ij}(\hat{\theta})^\top + \psi_{ij}(\hat{\theta})\frac{\partial \psi(O_i, \theta)}{\partial \theta} \bigg|_{\theta = \hat{\theta}} \right\} (\hat{\theta} - \theta)
\]

\[
= O_p(1)o_p(1),
\]

which, combined with law of large numbers on \( m^{-1} \sum_{i=1}^{m} \psi_{ij}(\theta)\psi(O_i, \theta) \), implies the desired
result in this step. Finally, by the Continuous Mapping Theorem, we have

\[ m^{-1} \sum_{i=1}^{m} \tilde{I}F(O_i, \hat{\theta}) \tilde{I}F(O_i, \hat{\theta})^\top \]

\[ = \left\{ m^{-1} \sum_{i=1}^{m} \frac{\partial \psi(O_i, \theta)}{\partial \theta} \bigg|_{\theta=\hat{\theta}} \right\}^{-1} m^{-1} \sum_{i=1}^{m} \psi(O_i, \hat{\theta}) \psi(O_i, \hat{\theta}) \left\{ m^{-1} \sum_{i=1}^{m} \frac{\partial \psi(O_i, \theta)}{\partial \theta} \bigg|_{\theta=\hat{\theta}} \right\}^{-1} \]

\[ = \left\{ E \left[ \frac{\partial \psi(O, \theta)}{\partial \theta} \bigg|_{\theta=\hat{\theta}} \right] + o_p(1) \right\}^{-1} \left\{ E [\psi(O, \theta) \psi(O, \theta)^\top] + o_p(1) \right\} \left\{ E \left[ \frac{\partial \psi(O, \theta)}{\partial \theta} \bigg|_{\theta=\hat{\theta}} \right] + o_p(1) \right\}^{-1} \]

\[ = V + o_p(1). \]

\[ \square \]

C.2 Proof of Theorem 1

Proof of Theorem 1. We first introduce a few notations. For each cluster \( i \), let \( j_{i,1} < \cdots < j_{i,M_i} \) be the ordered list of indices such that the observed outcomes are \( Y_i = (Y_{i,j_{i,1}}, \ldots, Y_{i,j_{i,M_i}}) \in \mathbb{R}^{M_i} \) and the observed individual-level covariates are \( X_i = (X_{i,j_{i,1}}, \ldots, X_{i,j_{i,M_i}})^\top \in \mathbb{R}^{M_i \times p} \). We define \( H_i = [e_{j_{i,1}}^N, e_{j_{i,2}}^N, \ldots, e_{j_{i,M_i}}^N] \in \mathbb{R}^{N_i \times M_i} \), where \( e_j^N \in \mathbb{R}^N \) is the standard orthonormal basis with the \( j \)-th entry 1 and the remaining entries 0. This allows us to write \( Y_i = H_i^\top Y_i \), \( X_i = H_i^\top X_i \), \( H_i = H_i^\top H_i = I_{M_i} \) and \( H_i H_i^\top = \text{diag} \{ S_i \} \), where \( Y_i = (Y_{i,1}, \ldots, Y_{i,N_i})^\top \) and \( X_i = (X_{i,1}, \ldots, X_{i,N_i})^\top \). We further define \( \tilde{\mu}_i = (E[Y_{i,1}|U_{i,1}], \ldots, E[Y_{i,N_i}|U_{i,N_i}])^\top \), \( \tilde{D}_i = \frac{\partial \tilde{\mu}_i}{\partial \beta} \) and \( \tilde{Z}_i = \text{diag} \{ v(Y_{i,j}) : j = 1, \ldots, N_i \} \), which imply \( D_i = H_i^\top \tilde{D}_i \) and \( Z_i^{-1/2} = H_i^\top \tilde{Z}_i^{-1/2} H_i \). Then the estimating equation (1) becomes

\[ \sum_{i=1}^{m} \tilde{D}_i^\top H_i \left( H_i^\top \tilde{Z}_i^{-1/2} H_i \right) R_i^{-1}(\rho) \left( H_i^\top \tilde{Z}_i^{-1/2} H_i \right) H_i^\top (Y_i - \mu_i) = 0. \]

To simplify the above equation, we observe that (i) the canonical link function \( g \) implies that \( \tilde{D}_i = \tilde{Z}_i U_i \), where \( U_i = (U_{i,1}, \ldots, U_{i,N_i})^\top \); (ii) \( (H_i H_i^\top) \tilde{Z}_i^{-1/2} = \tilde{Z}_i^{-1/2} (H_i H_i^\top) \) since \( H_i H_i^\top \) and \( \tilde{Z}_i^{-1/2} \) are both diagonal matrices; and (iii) \( R_i^{-1}(\rho) = \frac{1}{1-\rho} I_{M_i} - \frac{\rho}{(1-\rho)(1+M_i \rho - \rho)} I_{M_i} 1_{M_i}^\top \), altogether
yields
\[
\sum_{i=1}^{m} U_i^T \tilde{Z}_i^{1/2} H_i \left\{ \frac{1}{1-\rho} I_{M_i} - \frac{\rho}{(1-\rho)(1+M\rho-\rho)} I_{M_i} \right\} H_i^T \tilde{Z}_i^{-1/2} (Y_i - \mu_i) = 0
\]
\[
\Leftrightarrow \sum_{i=1}^{m} U_i^T \left\{ \frac{1}{1-\rho} \text{diag}(S_i) - \frac{\rho}{(1-\rho)(1+M\rho-\rho)} \tilde{Z}_i^{1/2} S_i \tilde{Z}_i^{-1/2} \right\} (Y_i - \mu_i) = 0
\]
\[
\Leftrightarrow \sum_{i=1}^{m} U_i^T B_i (Y_i - \mu_i) = 0,
\]
where \( B_i = \frac{1}{1-\rho} \text{diag}(S_i) - \frac{\rho}{(1-\rho)(1+M\rho-\rho)} \tilde{Z}_i^{1/2} S_i \tilde{Z}_i^{-1/2} \).

Denoting \( \theta_C = (\mu_C(1), \mu_C(0), \beta, \rho) \) and \( \theta_I = (\mu_I(1), \mu_I(0), \beta, \rho) \), we define the following estimating equations
\[
\psi_C(O, \theta_C) = \begin{pmatrix}
\mu_C(1) - \frac{1}{M} S^\top \mu(1, \beta) \\
\mu_C(0) - \frac{1}{M} S^\top \mu(0, \beta) \\
U^\top B\{Y - \mu(A, \beta)\} \\
k(N)\rho - h(Y, U, M, \beta)
\end{pmatrix},
\]
(1)
\[
\psi_I(O, \theta_I) = \begin{pmatrix}
N\mu_I(1) - \frac{N}{M} S^\top \mu(1, \beta) \\
N\mu_I(0) - \frac{N}{M} S^\top \mu(0, \beta) \\
NU^\top B\{Y - \mu(A, \beta)\} \\
k(N)\rho - h(Y, U, M, \beta)
\end{pmatrix},
\]
(2)
where \( \mu(a, \beta) \) is the assumed mean function setting \( A = a \) and \( k(N)\rho - h(Y, U, M, \beta) \) is a prespecified estimating function for constructing the moment estimator for \( \rho \), i.e., \( k(N) = N(N - 1)/2 - p - q - 3 \) and \( h(Y, U, M, \beta) = \sum_{j<j'} S_{i,j} S_{i,j'} Y_{i,j} Y_{i,j'} - \nu(Y_{i,j}) \). Of note, if an independence working correlation structure is used, then the last estimating function simplifies to \( \rho \). Then the GEE-g method described in the main paper equivalently solves \( \sum_{i=1}^{m} \psi_C(O_i, \theta_C) = 0 \) and \( \sum_{i=1}^{m} \psi_I(O_i, \theta_I) = 0 \).

We next show that \( \hat{\mu}_{C}^{\text{GEE-g}}(a) \) converges in probability to \( \mu_C(a) \) for \( a = 0, 1 \) given any condition among (S1-S4) described in the theorem statement. Given the regularity conditions, Lemma 3 implies \( \hat{\theta}_C \xrightarrow{P} \theta_C \), where \( \theta_C = (\hat{\mu}_C^{\text{GEE-g}}(1), \hat{\mu}_C^{\text{GEE-g}}(0), \beta_C, \hat{\rho}_C) \) solves \( E[\psi_C(O, \theta_C)] = 0 \). Since Lemma 1 implies \( E[\frac{1}{M} S^\top \mu(a, \beta)] = E[\frac{1}{M} E[S|M, N]^\top \mu(a, \beta)] = E[\frac{1}{N} 1_N^\top \mu(a, \beta)] \), then
\[ E[\psi_C(O, \theta_C)] = 0 \] yields \( \mu_C^{GEE-g}(a) = E\left[\frac{1_N \mu(a, \beta_C)}{N}\right] \). To connect \( \mu_C^{GEE-g}(a) \) to \( \mu_C(a) \), we focus on the equation \( E[U^T B\{Y - \mu(A, \beta_C)\}] = 0 \), which is implied by \( E[\psi_C(O, \theta_C)] = 0 \). First consider condition (S1) that the mean model is correctly specified, i.e., \( E[Y|U] = \mu(A, \beta^*) \) for some \( \beta^* \). Then we get \( E[U^T E[B|U]\{\mu(A, \beta^*) - \mu(A, \beta_C)\}] = 0 \) by taking the conditional expectation on \( U \) and the fact that \( S \perp Y|U \), thereby indicating that \( \beta_C = \beta^* \) is a solution. By the regularity condition that \( \beta_C \) is unique, we get \( \beta_C = \beta^* \), and hence \( \mu_C^{GEE-g}(a) = E\left[\frac{1_N \mu(a, \beta_C)}{N}\right] \) by Assumptions 3 and 4.

Next consider condition (S2) that an independence working correlation structure is used, which implies that \( B = \text{diag}\{S\} \). Since \( U = (1_N, A1_N, L) \), then the first two equations of \( E[U^T B\{Y - \mu(A, \beta_C)\}] = 0 \) are

\[
E[S^T \{Y - \mu(A, \beta_C)\}] = 0,
\]

\[
E[AS^T \{Y - \mu(A, \beta_C)\}] = 0.
\]

By Lemma 1, \( S \perp (A, Y, X, C)|(M, N) \) and \( E[S|M, N] = \frac{M}{N}1_N \). Hence, the above two equations imply that \( E[M(a)\bar{Y}(a)] = E[\frac{M(a)}{N}1_N \mu(a, \beta_C)] \) for \( a = 0, 1 \). By Assumption 4, we get \( E[\bar{Y}(a)] = E[\frac{1}{N}1_N \mu(a, \beta_C)] \) and hence \( \mu_C(a) = \mu_C^{GEE-g}(a) \). Next consider condition (c) that \( g \) is the identity link function, i.e., \( Y \) is the continuous outcome. Since we use the canonical link function, then \( \tilde{Z}_i = \sigma^2 I_{N_i} \), indicating \( 1_N^\top B_i = \frac{1}{1 - \rho} S_i^\top - \frac{M_i \rho}{(1 - \rho)(1 + M_i \rho - \rho)} S_i^\top = \frac{1}{1 + (M_i - 1)\rho} S_i^\top \). Then the first two equations of \( E[U^T B\{Y - \mu(A, \beta_C)\}] = 0 \) are

\[
E \left[ \frac{1}{1 + (M - 1)\rho} S_i^\top \{Y - \mu(A, \beta_C)\} \right] = 0,
\]

\[
E \left[ \frac{1}{1 + (M - 1)\rho} AS_i^\top \{Y - \mu(A, \beta_C)\} \right] = 0.
\]

Following a similar procedure as for condition (S2), we get \( \mu_C(a) = \mu_C^{GEE-g}(a) \) since \( \frac{M}{1 + (M-1)\rho} \perp (Y, U) \) by Assumptions 3 and 4. Finally, for condition (S4) that GEE excludes X, we get \( \mu(a, \beta) = 1_N \mu_0(a, \beta) \) for a scalar \( \mu_0(a, \beta) \) and \( \tilde{Z} = q(\mu(A, \beta))I_N \) for some function \( q \) since \( v(Y_{ij}) \) is a function of \( \mu_{ij} \) in the assumed model. Then it is straightforward that
implies \( C \) conditions (S1-S4) will yield Continuous Mapping Theorem and regularity conditions for \( f \).

We next show that \( \hat{\mu}_C^{\text{GEE-g}}(a) \) converges in probability to \( \mu_I(a) \) for \( a = 0, 1 \). Likewise, \( \hat{\theta}_I \xrightarrow{P} \theta_I \), where \( \theta_I = (\mu_I^{\text{GEE-g}}(1), \mu_I^{\text{GEE-g}}(0), \beta_I, \mu_0) \) solves \( E[\psi_I(O, \theta_I)] = 0 \), and \( \hat{\mu}_I^{\text{GEE-g}}(a) = \frac{E[\hat{\mu}(a, \beta_I)]}{E[N]} \). The proof is similar to the proof for showing the consistency of \( \hat{\mu}_C(a) \) except that the estimating equation \( E[NU^\top B\{Y - \mu(A, \beta_C)\}] = 0 \) involves a factor \( N \). Consequently, conditions (S1-4) will yield \( E[1_N^\top Y(a)] = E[1_N^\top \mu(a, \beta_I)] \), implying the desired consistency result.

We next prove the asymptotic normality. By the regularity conditions, Lemma 3 implies that
\[
m^{1/2}(\hat{\theta}_C - \theta_C) = m^{-1/2} \sum_{i=1}^m G_C^{-1} \psi_C(O_i, \theta_C) + o_p(1),
\]
\[
m^{1/2}(\hat{\theta}_I - \theta_I) = m^{-1/2} \sum_{i=1}^m G_I^{-1} \psi_I(O_i, \theta_I) + o_p(1),
\]
where \( G_C = E \left[ \frac{\partial}{\partial \theta} \psi_C(O, \theta_C) \big| \theta_C = \theta_C \right] \) and \( G_I = E \left[ \frac{\partial}{\partial \theta} \psi_I(O, \theta_I) \big| \theta_I = \theta_I \right] \). Thus, the asymptotic normality is obtained by Central Limit Theorem.

To get the asymptotic variance for \( \hat{\Delta}_C^{\text{GEE-g}} \) and \( \hat{\Delta}_I^{\text{GEE-g}} \), we compute the influence function for \( (\hat{\mu}_C^{\text{GEE-g}}(1), \hat{\mu}_C^{\text{GEE-g}}(0)) \) and \( (\hat{\mu}_I^{\text{GEE-g}}(1), \hat{\mu}_I^{\text{GEE-g}}(0)) \) by computing \( G_C^{-1} \) and \( G_I^{-1} \). Under condition (S1-4), tedious algebra shows that the first two rows of \( G_C^{-1} \) are
\[
\begin{bmatrix}
1 & 0 & 0 & \cdots & 0 \\
0 & 1 & -\frac{\pi E \left[ \frac{M(1)}{1+(M(0)-1)\beta_C} \right]}{1+(M(0)-1)\beta_C} & \cdots & 0 \\
\end{bmatrix},
\]
and the influence function for \( (\hat{\mu}_C^{\text{GEE-g}}(1), \hat{\mu}_C^{\text{GEE-g}}(0)) \) is
\[
IF_C^{\text{GEE-g}} = \begin{bmatrix} \frac{\pi}{1+\beta_C} \left[ \frac{M(1)}{1+(M(1)-1)\beta_C} \right]^{-1} S^\top \{ Y - \mu(A, \beta_C) \} + \frac{1}{M} S^\top \mu(1, \beta_C) - \mu_C(1) \\
\frac{\pi}{1+\beta_C} \left[ \frac{M(0)}{1+(M(0)-1)\beta_C} \right]^{-1} S^\top \{ Y - \mu(A, \beta_C) \} + \frac{1}{M} S^\top \mu(0, \beta_C) - \mu_C(0) \end{bmatrix},
\]
leading to the asymptotic covariance matrix as \( E[IF_C^{\text{GEE-g}} IF_C^{\text{GEE-g}\top}] \). Then \( V_C^{\text{GEE-g}} \), the asymptotic variance of \( \hat{\Delta}_C^{\text{GEE-g}} \), is \( \nabla f^\top E[IF_C^{\text{GEE-g}} IF_C^{\text{GEE-g}\top}] \nabla f \) by the Delta method, where
\( \nabla f \) is the gradient of \( f \) evaluated at \((\mu_C(1), \mu_C(0))\). For \( \theta_I \), a similar procedure gives the influence function \((\hat{\mu}_I^{\text{GEE-}}(1), \hat{\mu}_I^{\text{GEE-}}(0))\) as

\[
IF_I^{\text{GEE-}} = \frac{N}{E[N]} \left( \frac{\Delta E \left[ \frac{M(1)}{1+(M(1)-1)\varrho} \right]^{-1}}{1-A} \frac{1}{1-\pi} E \left[ \frac{M(0)}{1+(M(0)-1)\varrho} \right]^{-1} \right) \begin{pmatrix} S^T \{Y - \mu(A, \beta_I)\} + \frac{1}{M} S^T \mu(1, \beta_I) - \mu_I(1) \\ \frac{1}{M} S^T \mu(0, \beta_I) - \mu_I(0) \end{pmatrix},
\]

and the asymptotic variance \( V_I^{\text{GEE-}} \) is then \( \nabla f^T E[IF_I^{\text{GEE-}}IF_I^{\text{GEE-}T}]\nabla f \).

The sandwich variance estimators for \( V_C^{\text{GEE-}} \) and \( V_I^{\text{GEE-}} \) are provided in Section D, whose consistency are implied by Lemma 3 and the Continuous Mapping Theorem.

### C.3 Proof of Theorem 2

**Proof of Theorem 2.** For continuous outcomes where \( g \) is the identity link, the likelihood function becomes

\[
\prod_{i=1}^m \int \prod_{j:S_{ij}=1} (2\pi\sigma^2)^{-1/2} \exp \left\{ -\frac{1}{2\sigma^2} (Y_{ij} - U_{ij}^T \alpha - b_i)^2 \right\} (2\pi\tau^2)^{-1/2} \exp \left\{ -\frac{b_i^2}{2\tau^2} \right\} \, db = \prod_{i=1}^m \left( 2\pi \Sigma_i \right)^{-1/2} \exp \left\{ -(Y_i^o - U_i^o \alpha)^T \Sigma_i^{-1} (Y_i^o - U_i^o \alpha) / 2 \right\},
\]

where \( \Sigma_i = \sigma^2 I_{M_i} + \tau^2 I_{M_i}^T I_{M_i} \), \( Y_i^o = \{Y_{ij} : S_{ij} = 1\} \) is the observed outcome vector, and \( U_i^o = \{U_{ij} : S_{ij} = 1\} \in \mathbb{R}^{M_i \times (p+q+3)} \) is the observed design matrix. We further define \( H_i \) as the in the proof of Theorem 1, \( \tilde{\Sigma}_i = \sigma^2 I_{N_i} + \tau^2 I_{N_i}^T I_{N_i} \), \( U_i = (U_{i1}, \ldots, U_{iN_i})^T \), and the log-likelihood function is

\[
- \frac{1}{2} \sum_{i=1}^m \left\{ 2\pi M_i + \log(|H_i^T \tilde{\Sigma}_i H_i|) + (Y_i - U_i \alpha)^T H_i (H_i^T \tilde{\Sigma}_i H_i)^{-1} H_i^T (Y_i - U_i \alpha) \right\},
\]

whose derivative over \((\alpha, \sigma^2, \tau^2)\) is

\[
- \frac{1}{2} \sum_{i=1}^m \begin{pmatrix} U_i^T V_i (Y_i - U_i \alpha) \\ -\text{tr}(V_i) + (Y_i - U_i \alpha)^T V_i^2 (Y_i - U_i \alpha) \\ -1_{N_i}^T V_i 1_{N_i} + (Y_i - U_i \alpha)^T V_i^1 1_{N_i}^T V_i (Y_i - U_i \alpha) \end{pmatrix},
\]

where \( V_i = \nabla \mu(I_i^o, \tilde{\Sigma}_i) \).
where \( V_i = H_i \left( H_i^T \Sigma_i H_i \right)^{-1} H_i^T \) and \( \text{tr}(V_i) \) is the trace of \( V_i \). We then define the estimating equations as

\[
\psi_C(O, \eta_C) = \begin{pmatrix}
\mu_C(1) - \frac{1}{M} S^T U(1) \alpha \\
\mu_C(0) - \frac{1}{M} S^T U(0) \alpha \\
U^T V(Y - U \alpha) \\
- \text{tr}(V) + (Y - U \alpha)^T V^2 (Y - U \alpha) \\
- 1_N^1 V_1 + (Y - U \alpha)^T V_1 N_1^1 V(Y - U \alpha)
\end{pmatrix},
\]

where \( \eta_C = (\mu_C(1), \mu_C(0), \alpha, \sigma^2, \tau^2)^T \) and \( U(a) = U \) with \( A \) substituted by \( a \). The MLE \( \hat{\eta}_C \) for \( \eta_C \) is then a solution to \( \sum_{i=1}^n \psi_C(O_i, \eta_C) = 0 \).

We next prove consistency of \( \hat{\Delta}_C^{LMM-g} \) following a similar proof to the consistency of \( \hat{\Delta}_C^{GEE-g} \). Lemma 3 implies that \( \hat{\eta}_C \xrightarrow{P} \eta_C \), where \( \eta = (\mu_C^{LMM-g}(1), \mu_C^{LMM-g}(0), \eta_C, \sigma_C^2, \tau_C^2) \) solves \( E[\psi_C(O, \eta_C)] = 0 \). Then we have \( E[U^T V(Y - U \alpha)] = 0 \), whose first two equations are

\[
E[1_N^1 V(Y - U \alpha)] = 0, \\
E[A1_N^1 V(Y - U \alpha)] = 0.
\]

Since \( \Sigma_i^{-1} = \frac{1}{\sigma^2} I_M - \frac{\tau^2}{\sigma^2(M + \tau^2)} I_M I_M^T \), we get \( 1_N^1 V = \frac{1}{\sigma_C^2 + M_1 \tau_C^2} S^T \), which implies

\[
E \left[ \frac{1}{\sigma_C^2 + M_1 \tau_C^2} S^T (Y - U \alpha) \right] = 0, \\
E \left[ A \frac{1}{\sigma_C^2 + M_1 \tau_C^2} S^T (Y - U \alpha) \right] = 0.
\]

By Assumption 3 and Lemma 1, we get \( S \perp (A, Y, U)|(M, N) \) and \( E[S|M, N] = \frac{M}{N} I_N \), which implies \( E[A \frac{M(a)}{\sigma^2 + (M(a)) \tau^2}(\bar{Y}(a) - \bar{U}(a) \alpha)] = 0 \) for \( a = 0, 1 \), where \( \bar{U}(a) = 1_N^1 U(a) / N \). Given Assumption 4, we got \( \mu_C(a) = E[\bar{Y}(a)] = E[\bar{U}(a) \alpha] = \mu_C(a) \). Then \( \hat{\Delta}_C \xrightarrow{P} \Delta_C \) can be obtained by the Continuous Mapping Theorem.

We next prove the asymptotic normality, which is also similar to the corresponding part in the proof of Theorem 1. By the regularity conditions, Lemma 3 implies that

\[
m^{1/2}(\hat{\eta}_C - \eta_C) = m^{-1/2} \sum_{i=1}^m G_C^{-1} \psi_C(O_i, \eta_C) + o_p(1),
\]
where $G_C = E\left[\frac{\partial}{\partial \eta} \psi_C(O, \eta_C) \bigg| \eta_C = \eta_c\right]$. Thus, the asymptotic normality is obtained by Central Limit Theorem. The influence function for $(\hat{\mu}_C^{LMM-g}(1), \hat{\mu}_C^{LMM-g}(0))$ is

$$IF_C^{LMM-g} = \left(\frac{A}{\pi} E \left[\frac{M(1)}{\sigma^2 + M(1)\sigma^2} \right]^{-1} \left[\frac{1}{\sigma^2 + M\sigma^2} \right] \frac{1}{\sigma^2 + M\sigma^2} S^T \{Y - U\} + \frac{1}{M} S^T U(1) \alpha - \mu_C(1) \right),$$

and $V_C^{LMM-g} = \nabla f^T E[IF_C^{LMM-g} IF_C^{LMM-g\top}] \nabla f$, where $\nabla f$ is the gradient of $f$ evaluated at $(\mu_C(1), \mu_C(0))$.

For estimating $\Delta_I$, we can follow the same procedure to get the desired result and hence omit the detailed proof here. The corresponding estimating equations are

$$\psi_I(O, \eta_I) = \left(\begin{array}{c} N \mu_I(1) - \frac{N}{M} S^T U(1) \alpha \\ N \mu_C(0) - \frac{N}{M} S^T U(0) \alpha \\ NU^T V(Y - U\alpha) \\ -\text{tr}(V) + N(Y - U\alpha)^T V^2 (Y - U\alpha) \\ -1^T N V_1 N + N(Y - U\alpha)^T V_1 N 1_N^T V(Y - U\alpha) \end{array}\right),$$

where $\eta_I = (\mu_I(1), \mu_I(0), \alpha, \sigma^2, \tau^2)^\top$, and the influence function for $(\hat{\mu}_I^{LMM-g}(1), \hat{\mu}_I^{LMM-g}(0))$ is

$$IF_I^{LMM-g} = \frac{N}{E[N]} \left(\frac{A}{\pi} E \left[\frac{M(1)}{\sigma^2 + M(1)\sigma^2} \right]^{-1} \left[\frac{1}{\sigma^2 + M\sigma^2} \right] \frac{1}{\sigma^2 + M\sigma^2} S^T \{Y - U\} + \frac{1}{M} S^T U(1) \alpha - \mu_I(1) \right),$$

Then $V_I^{LMM-g} = \nabla f^T E[IF_I^{LMM-g} IF_I^{LMM-g\top}] \nabla f$.

The sandwich variance estimators for $V_C^{LMM-g}$ and $V_I^{LMM-g}$ are provided in Section D, whose consistency are implied by Lemma 3 and the Continuous Mapping Theorem.

**C.4 Proof of Theorem 3**

*Proof of Theorem 3.* By Lemma 2 and the iteration of conditional expectation, we have

$$E \left[\bar{Y}(a)\right] = E \left[ E \left[ E \left[\bar{Y}^\circ A = a, N, C \right] | N \right] \right] = E \left[ E \left[ E \left[\bar{Y}^\circ A = a, X^\circ, M, N, C \right] | A = a, M, N, C \right] A = a, N, C \right] | N \right].$$
For $E \left[ Y \mid A = a, X^o, M, N, C \right]$, since $(X^o, M)$ is a deterministic function of $X, S$, we could denote $f(X, S, N, C) = E \left[ Y \mid A = a, X^o, M, N, C \right]$ for some function $f$. By Lemma 1 (iii), we have $f(X, S, N, C) \perp A \mid (M, N, C)$, which implies

$$E \left[ E \left[ Y \mid A = a, X^o, M, N, C \right] \mid A = a, M, N, C \right] = E \left[ f(X, S, N, C) \mid A = a, M, N, C \right] = E \left[ E \left[ Y \mid A = a, X^o, M, N, C \right] \mid M, N, C \right].$$

Therefore, the estimand can be written as

$$E \left[ \sum_{j=1}^{N} \frac{Y_j(a)}{N} \right] = E \left[ E \left[ E \left[ E \left[ Y \mid A = a, X^o, M, N, C \right] \mid M, N, C \right] \mid A = a, N, C \right] \mid N \right].$$

Next, we follow the steps provided by Hines et al. (2022) to compute the EIF of the target estimand. Denote the observed data for each cluster as $O_i = (Y_i^o, X_i^o, M_i, A_i, N_i, C_i)$, the observed data distribution as $P = P_{Y^o|X^o,M,A,N,C} P_{X^o|M,N,C} P_{M|A,N,C} P_{A|N,C} P_{N} P_{A}$, $E \left[ \sum_{j=1}^{N} \frac{Y_j(a)}{N} \right] = \Psi(P)$, and a parametric submodel $P_t = t \hat{P} + (1 - t)P$ for $t \in [0, 1]$, where $\hat{P}$ is a point-mass at $o_i$ in the support of $P$. Furthermore, let $f$ denote the density of $P$, $1_{\delta}(o)$ denote the Dirac
implies that (iii) and Assumptions 2-3, we get

\[
\frac{d\Psi(\mathcal{P}_t)}{dt} \bigg|_{t=0} = \frac{d}{dt} \int \Psi f_t(y^o|a, x^o, m, c, n) f_t(x^o|m, c, n) f_t(m|a, c, n) f(c|n) f_1(n) dy^o dx^o dm dc dn \bigg|_{t=0} = \int \Psi f(y^o|a, x^o, m, c, n) f(x^o|m, c, n) f(m|a, c, n) f(c|n) f(n)
\]

\[
\left\{ \frac{1_o(o)}{f(y^o, a, x^o, m, c, n)} - \frac{1_o, \bar{m}, \bar{c}, \bar{n}(a, x^o, m, c, n)}{f(a, x^o, m, c, n)} + \frac{1_{\bar{m}, \bar{c}, \bar{n}}(x^o, m, c, n)}{f(x^o, m, c, n)} - \frac{1_{\bar{m}, \bar{c}, \bar{n}}(m, c, n)}{f(m, c, n)} \right\} dy^o dx^o dm dc dn
\]

\[
= \frac{1_o(a) \{ \Psi - E[\Psi] A = a, X^o = \bar{x}^o, M = \bar{m}, C = \bar{c}, N = \bar{n} \} pr(A = a|M = \bar{m}, C = \bar{c}, N = \bar{n})}{pr(A = a|X^o = \bar{x}^o, M = \bar{m}, C = \bar{c}, N = \bar{n})} pr(A = a|C = \bar{c}, N = \bar{n})
\]

\[
+ \left\{ E[\Psi] A = a, X^o = \bar{x}^o, M = \bar{m}, C = \bar{c}, N = \bar{n} \right\} - E[\Psi] A = a, M = \bar{m}, C = \bar{c}, N = \bar{n} \}
\]

\[
\times \frac{pr(M = \bar{m}|A = a, C = \bar{c}, N = \bar{n})}{pr(M = \bar{m}|C = \bar{c}, N = \bar{n})}
\]

\[
+ \frac{1_o(a)}{pr(A = a|C = \bar{c}, N = \bar{n})} \left\{ E[\Psi] A = a, M = \bar{m}, C = \bar{c}, N = \bar{n} \right\} - E[\Psi] A = a, C = \bar{c}, N = \bar{n} \}
\]

\[
+ E[\Psi] A = a, C = \bar{c}, N = \bar{n} \] - $\Psi(\mathcal{P})$.

By Lemma 1 (iii) and Assumptions 2-3, we get $pr(A = a|X^o = \bar{x}^o, M = \bar{m}, C = \bar{c}, N = \bar{n}) = pr(A = a|M = \bar{m}, C = \bar{c}, N = \bar{n})$ and $pr(A = a|C = \bar{c}, N = \bar{n}) = pr(A = a)$. Therefore,

\[
EFI_a = \frac{I\{A = a\}}{pr(A = a)} \{ \Psi - E[\Psi] A = a, X^o, M, N, C \}
\]

\[
+ \frac{pr(M|A = a, N, C)}{pr(M|N, C)} \left\{ E[\Psi] A = a, X^o, M, N, C \right\} - E[\Psi] A = a, M, N, C \}
\]

\[
+ \frac{I\{A = a\}}{pr(A = a)} \left\{ E[\Psi] A = a, M, N, C \right\} - E[\Psi] A = a, N, C \}
\]

\[
+ E[\Psi] A = a, N, C \] - $E[\Psi] A = a$.

Lemma 2 implies that $E[\Psi] A = a, M, N, C] = E[\Psi] A = a, N, C]$. Additionally, from Assumption 2, we find $pr(A = a, N, C) = pr(A = a)pr(N, C)$, which leads to

\[
\frac{pr(M|A = a, N, C)}{pr(M|N, C)} = \frac{pr(A = a, M, N, C)}{pr(M, N, C)} \frac{pr(N, C)}{pr(A = a, N, C)} = \frac{pr(A = a|M, N, C)}{\pi^a(1 - \pi)^{1-a}}.
\]
Combining the established results, we get the desired formula of $EIF_a$.

For estimand $\frac{E[\sum_{j=1}^{N} Y_j(a)]}{E[N]}$, Lemma 2 implies

$$
\frac{E[\sum_{j=1}^{N} Y_j(a)]}{E[N]} = \frac{1}{E[N]} E[E[NY^o(a)|N] | C | N]
$$

$$
= \frac{1}{E[N]} E [E [E [NY^o|A = a, X^o, M, N, C] | M, N, C | A = a, N, C] | N]] .
$$

Define $\Psi(P) = \frac{\Psi_1(P)}{\Psi_2(P)}$, where $\Psi_1(P) = E[\sum_{j=1}^{N} Y_j(a)]$ and $\Psi_2(P) = E[N]$, we have

$$
d\Psi(P_t) \bigg|_{t=0} = \frac{1}{\Psi_2(P_t)} \frac{d\Psi_1(P_t)}{dt} \bigg| _{t=0} - \frac{\Psi_1(P) \frac{d\Psi_2(P_t)}{dt}}{\Psi_2(P)^2} \bigg| _{t=0} ,
$$

where $\frac{d\Psi_1(P_t)}{dt} \bigg| _{t=0}$ is the same as $EIF_a$ in Equation (1) except that $Y^o$ is substituted by $NY^o$, and $\frac{d\Psi_2(P_t)}{dt} \bigg| _{t=0} = N - E[N]$ by straightforward calculation. Hence, the influence function for $\frac{E[\sum_{j=1}^{N} Y_j(a)]}{E[N]}$ is

$$
\frac{1}{E[N]} \left\{ N EIF_a + NE[Y^o|A = a] - E[NY^o|A = a] \right\} - \frac{E[NY^o|A = a]}{E[N]^2} (N - E[N])
$$

$$
= \frac{N}{E[N]} \left\{ EIF_a + E[Y^o|A = a] - \frac{E[NY^o|A = a]}{E[N]} \right\} .
$$

\[\square\]

C.5 Proof of Theorem 4

Proof. Denote $P_m X = m^{-1} \sum_{i=1}^{m} X_i$ and $G_m X = m^{1/2} (P_m X - E[X])$ for any i.i.d. samples $X_1, \ldots, X_m$ from a distribution on $X$. Below we give the proof for estimating $\Delta_C$; the results for $\Delta_I$ can be obtained in a similar way.

We first prove the desired results for $\hat{\Delta}^{\text{Eff}}_C$ based on parametric working models. Define

$$
U_a \{ O; \theta_a, \mu_C(a) \} = \frac{I\{A = a\}}{\pi^a(1 - \pi)^{1-a}} \left\{ Y^o - \eta_a(X^o, M, N, C; \theta_{\eta,a}) \right\}
$$

$$
+ \frac{\kappa_a(M, N, C; \theta_{\kappa,a})}{\pi^a(1 - \pi)^{1-a}} \left\{ \eta_a(X^o, M, N, C; \theta_{\eta,a}) - \zeta_a(N, C; \theta_{\eta,a}) \right\}
$$

$$
+ \zeta_a(N, C; \theta_{\eta,a}) - \mu_C(a).
$$
Then we have $P_m U_1 \{ O; \hat{\theta}_a, \hat{\mu}_C^{\text{Eff}}(a) \} = 0$ for $a = 0, 1$. By definition, $\hat{\theta} = (\hat{\theta}_1, \hat{\theta}_0)$ is computed by solving estimating equations, $P_m \psi(O; \hat{\theta}) = 0$ for a known function $\psi$. By Lemma 3, $m^{1/2} (\hat{\theta} - \theta) \xrightarrow{d} N(0, V)$ for some matrix $V$. Define the estimating equations as

$$
\tilde{\psi}(\theta, \mu) = \begin{pmatrix}
U_1 \{ O; \hat{\theta}_1, \mu_C(1) \} \\
U_0 \{ O; \hat{\theta}_0, \mu_C(0) \}
\end{pmatrix},
$$

where $\mu_C = (\mu_C(1), \mu_C(0))$. By regularity condition 5, $U_1$ and $U_0$ are continuous in parameters and dominated by an integrable function, and hence P-Glivenko Cantelli by Example 19.8 of van der Vaart (1998). Then, Theorem 5.9 of van der Vaart (1998) implies that $(\hat{\theta}, \hat{\mu}_C^{\text{Eff}}) \xrightarrow{p} (\theta, \mu_C^{\text{Eff}})$, where $\hat{\mu}_C^{\text{Eff}}(a)$ satisfies $E[U_a \{ O; \hat{\theta}_a, \mu_C^{\text{Eff}}(a) \}] = 0$. To see when $\hat{\mu}_C^{\text{Eff}}(a) = \mu_C(a)$, we have, using Lemma 2 and $A \perp (N, C)$,

$$
E[U_a \{ O; \hat{\theta}_a, \mu_C(a) \}] = \mu_C(a) - E \left[ \frac{I\{A = a\} - \kappa_a(\hat{\theta}_a)}{\pi^a(1 - \pi)^{1-a}} \eta_a(\hat{\theta}_a) \right] - E \left[ \frac{\kappa_a(\hat{\theta}_a)}{\pi^a(1 - \pi)^{1-a}} - \frac{\kappa_a^*(\hat{\theta}_a)}{\pi^a(1 - \pi)^{1-a}} \right] \mu_C^{\text{Eff}}(a).
$$

Given the condition that (i) $\kappa_a(\hat{\theta}_a) = \kappa_a^*$ or (ii) $E[\eta_a(\hat{\theta}_a)|M, N, C] = \zeta_a(\hat{\theta}_a)$, we obtain $\hat{\mu}_C^{\text{Eff}}(a) = \mu_C(a)$. Then, given regularity conditions 1-5, we apply Theorem 5.31 of van der Vaart (1998) and get

$$
m^{1/2}(\hat{\mu}_C^{\text{Eff}} - \mu_C) = m^{1/2} E \left[ \tilde{\psi}(\hat{\theta}, \hat{\mu}_C^{\text{Eff}}) \right] + \mathbb{G}_m \tilde{\psi} \left( \hat{\theta}, \hat{\mu}_C^{\text{Eff}}, \mu_C^{\text{Eff}} \right) + o_p \left( 1 + m^{1/2} ||E[\tilde{\psi}(\hat{\theta}, \mu_C^{\text{Eff}})]||_2 \right).
$$

To briefly check the triple-robustness property of $\hat{\mu}_C^{\text{Eff}}$, if suffices to discuss the case when $\hat{\eta}_a$ and $\hat{\zeta}_a$ are consistent whereas $\hat{\kappa}_a$ may be inconsistent. In fact, this case satisfies the second condition (ii) because $E[\eta_a(\hat{\theta}_a)|M, N, C] = E[\eta_a|M, N, C] = \zeta^* = \zeta_a(\hat{\theta}_a)$. Therefore, if at least two nuisance functions are consistently estimated, $\hat{\mu}_C^{\text{Eff}}$ achieves the semiparametric efficiency bound.

By the continuity of $\tilde{\psi}$ on $\theta$ and the asymptotic normality of $\hat{\theta}$, the delta method implies $m^{1/2} E[\tilde{\psi}(\hat{\theta}, \mu_C^{\text{Eff}})] = \mathbb{G}_m u(\hat{\theta}, \mu_C^{\text{Eff}})$ for some function $u$ and $m^{1/2} ||E[\tilde{\psi}(\hat{\theta}, \mu_C^{\text{Eff}})]||_2 = O_p(1), 
leading to the asymptotic normality of $\hat{\mu}_C^{\text{Eff}}$. Then we get the desired result for $\hat{\Delta}_C^{\text{Eff}}$ by delta method. The asymptotic variance of $\hat{\Delta}_C^{\text{Eff}}$ is

$$\nabla f^{\top} E \left[ \left\{ u(\theta, \mu_C^{\text{Eff}}) + \tilde{\psi}(\theta, \mu_C^{\text{Eff}}) \right\} \left\{ u(\theta, \mu_C^{\text{Eff}}) + \tilde{\psi}(\theta, \mu_C^{\text{Eff}}) \right\}^{\top} \right] \nabla f^{\top},$$

whose variance estimators are provided in Section D. The consistence of the variance estimators are implied by Lemma 3 and regularity conditions 2 and 5.

We next prove the desired results for $\hat{\Delta}_C^{\text{Eff}}$ based on data-adaptive estimation with cross-fitting. Let $O_k$, $k = 1, \ldots, K$ be the split observed data and $O_{-k} = \bigcup_{k' \in \{1, \ldots, K\} \setminus \{k\}} O_{k'}$ be the training data for $O_k$. Without loss of generalization, we assume that each $O_k$ has the same sample size. Let $h_a = (\eta_a, \kappa_a, \zeta_a)$ denote the nuisance functions, $\tilde{h}_{a,k} = (\tilde{\eta}_{a,k}, \tilde{\kappa}_{a,k}, \tilde{\zeta}_{a,k})$ denote data-adaptive estimation trained on $O_{-k}$, and $h^* = (\eta^*_a, \kappa^*_a, \zeta^*_a)$ denote the true nuisance functions.

Denote $\mathbb{P}_k X = |O_k|^{-1} \sum_{i \in O_k} X_i$ and $\mathbb{G}_k = |O_k|^{1/2}(\mathbb{P}_k X - E[X_i])$. Finally, we define

$$D_a(h_a) = \frac{I\{A = a\}}{\pi^a(1 - \pi)^{1-a}} \left\{ \overline{Y}^o - \eta_a(X^o, M, N, C) \right\} + \frac{\kappa_a(M, N, C)}{\pi^a(1 - \pi)^{1-a}} \left\{ \eta_a(X^o, M, N, C) - \zeta_a(N, C) \right\} + \zeta_a(N, C),$$

and $D(h) = (D_1(h_1), D_0(h_0))$. Given the above definitions, we have $\hat{\mu}_C^{\text{Eff}} = K^{-1} \sum_{k=1}^K \mathbb{P}_k D(\tilde{h}_k)$ and $\mu_C = E[D(h^*)]$ with $\tilde{h}_k = (\tilde{h}_{1,k}, \tilde{h}_{0,k})$ and $h^* = (h^*_1, h^*_0)$. Then,

$$m^{1/2}(\hat{\mu}_C^{\text{Eff}} - \mu_C)$$

$$= K^{-1/2} \sum_{k=1}^K \left[ \mathbb{G}_k D(h^*) + \mathbb{G}_k \{D(\tilde{h}_k) - D(h^*)\} + \left( \frac{m}{K} \right)^{1/2} E[D(\tilde{h}_k) - D(h^*)|O_{-k}] \right]. \quad (6)$$

The first term $K^{-1/2} \sum_{k=1}^K \mathbb{G}_k D(h^*)$ provides the asymptotic normality, so it suffices to show that the latter two terms are $o_P(1)$. Specifically, we denote $R_1 = \mathbb{G}_k \{D(\tilde{h}_k) - D(h^*)\}$ and $R_2 = \left( \frac{m}{K} \right)^{1/2} E[D(\tilde{h}_k) - D(h^*)|O_{-k}]$, and we show that $R_1 = o_p(1)$ and $R_2 = o_p(1)$ in the rest of the proof.

For $R_1$, by Theorem 2.14.2 of van der Vaart and Wellner (1996), we get

$$E \left[ \left| \mathbb{G}_k \{D(\tilde{h}_k) - D(h^*)\} \right| \left| O_{-k} \right. \right] \leq c E \left[ \left| D(\tilde{h}_k) - D(h^*) \right|^2 \left| O_{-k} \right. \right]^{1/2}$$

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for some constant \(c\), where \(\|\cdot\|\) is the \(L_2\) vector norm. By the assumption that \(||\hat{h}_k - h^*||_2 \to 0\) and Markov’s inequality, we have
\[
E \left[ ||\hat{h}_k - h^*||^2 \bigg| \mathcal{O}_{-k} \right] \to 0.
\]
Since \(\hat{h}_k\) is fixed conditioning on \(\mathcal{O}_{-k}\), we have, for \(a = 0, 1\)
\[
E \left[ D_a(\hat{h}_k) - D_a(h^*) \right]^2 \bigg| \mathcal{O}_{-k} \right] \tag{7}
\]
\[
= \frac{1}{\pi_a} E[\kappa_a^*(1 - \kappa_a^*)(\eta_a^* - \hat{\eta}_{a,k})^2 | \mathcal{O}_{-k}] + E \left[ \frac{1}{\pi_a} (\hat{\kappa}_{a,k} - \kappa_a^*)(\hat{\eta}_{a,k} - \hat{\zeta}_{a,k}) + \frac{\kappa_a^*}{\pi_a} (\hat{\zeta}_{a,k} - \zeta_a^*) \right]^2 \bigg| \mathcal{O}_{-k} \right]
\]
\[
\leq \frac{1}{\pi_a} E[(\kappa_a^*(1 - \kappa_a^*)(\eta_a^* - \hat{\eta}_{a,k})^2 | \mathcal{O}_{-k}] + \frac{2}{\pi_a^2} E[(\hat{\kappa}_{a,k} - \kappa_a^*)^2(\hat{\eta}_{a,k} - \hat{\zeta}_{a,k})^2 | \mathcal{O}_{-k}]
\]
\[
+ \frac{2}{\pi_a^2} E[(\kappa_a^* - \pi_a)^2(\hat{\zeta}_{a,k} - \zeta_a^*)^2 | \mathcal{O}_{-k}]
\]
\[
\leq \frac{1}{\pi_a} E[(\eta_a^* - \hat{\eta}_{a,k})^2 | \mathcal{O}_{-k}] + \frac{2}{\pi_a^2} E[(\hat{\kappa}_{a,k} - \kappa_a^*)^2(\hat{\eta}_{a,k} - \hat{\zeta}_{a,k})^2 | \mathcal{O}_{-k}]
\]
\[
+ \frac{2}{\pi_a^2} E[(\kappa_a^* - \pi_a)^2(\hat{\zeta}_{a,k} - \zeta_a^*)^2 | \mathcal{O}_{-k}]
\]
\[
= o_p(1) + O_p(1) o_p(1) + O_p(1) o_p(1) + o_p(1) + o_p(1)
\]
\[
= o_p(1),
\]
where \(\pi_a = \pi^a(1 - \pi)^{(1-a)}\). In the above derivation, the first line results from algebra and \(pr(A = a | M, N, C) = \kappa_a^*\), the second line uses the Cauchy-Schwarz inequality, the third line is implied by \(\kappa_a^* \in [0, 1]\), the fourth line again comes from the Cauchy-Schwarz inequality, and the fifth line results from the assumption that \(E \left[ ||\hat{h}_k - h^*||^2 \bigg| \mathcal{O}_{-k} \right] = o_p(1)\) and regularity condition 6. In particular, \(E[(\hat{\kappa}_{a,k} - \kappa_a^*)^2(\eta_a^* - \zeta_a^*)^2 | \mathcal{O}_{-k}] = o_p(1)\) is obtained as follows:
\[
E[(\hat{\kappa}_{a,k} - \kappa_a^*)^2(\eta_a^* - \zeta_a^*)^2 | \mathcal{O}_{-k}] = E[(\hat{\kappa}_{a,k} - \kappa_a^*)^2 E\{ (\eta_a^* - \zeta_a^*)^2 \big| M, N, C \} | \mathcal{O}_{-k}]
\]
\[
= E[(\hat{\kappa}_{a,k} - \kappa_a^*)^2 E\{ (\eta_a^* - E(\eta_a^* | M, N, C))^2 \big| M, N, C \} | \mathcal{O}_{-k}]
\]
\[
= E[(\hat{\kappa}_{a,k} - \kappa_a^*)^2 \text{var}(\eta_a^* | M, N, C) | \mathcal{O}_{-k}]
\]
\[
\leq E[(\hat{\kappa}_{a,k} - \kappa_a^*)^2 E\{ (\eta_a^*)^2 \big| M, N, C \} | \mathcal{O}_{-k}]
\]
\[
= O_p(1) E[(\hat{\kappa}_{a,k} - \kappa_a^*)^2 | \mathcal{O}_{-k}]
\]
\[
= o_p(1).
\]
The second equality is from $E[\eta_a^*|M, N, C] = E[Y^*|M, N, C] = \zeta_a^*$. The third equality is from
the definition of the conditional variance, and the first inequality is based on $\text{var}(X|Y) \leq E(X^2|Y)$. The upper bound in the last line is from regularity condition 6, and the asymptotic rate is from the assumption. Therefore, $G_k\{D(\hat{h}_k) - D(h^*)\} = o_p(1)$ given $O_{-k}$, which implies
$R_1 = o_p(1)$.

For $R_2$, we can compute that, for each $k$,
\[
\left(\frac{m}{K}\right)^{1/2} E[D(\hat{h}_k) - D(h^*)]|O_{-k}]
= \frac{1}{\pi_a}\left(\frac{m}{K}\right)^{1/2} E[(\hat{\kappa}_{a,k} - \kappa_a^*)(\hat{\eta}_{a,k} - \zeta_{a,k})]|O_{-k}]
= \frac{1}{\pi_a}\left(\frac{m}{K}\right)^{1/2} E[(\hat{\kappa}_{a,k} - \kappa_a^*)(\hat{\eta}_{a,k} - \eta_a^*)]|O_{-k}]
= \frac{1}{\pi_a}\left(\frac{m}{K}\right)^{1/2} E[(\hat{\kappa}_{a,k} - \kappa_a^*)^2]|O_{-k}]^{1/2}
\leq \frac{1}{\pi_a}\left(\frac{m}{K}\right)^{1/2} E[(\hat{\kappa}_{a,k} - \kappa_a^*)^2]|O_{-k}]^{1/2} + \frac{1}{\pi_a}\left(\frac{m}{K}\right)^{1/2} E[(\hat{\eta}_{a,k} - \eta_a^*)^2]|O_{-k}]^{1/2}
= o_p(1),
\]
where the first line comes from algebra and Lemma 2, the second line is implied by $E[\eta_a^*|M, N, C] = E[Y^*|M, N, C] = \zeta_a^*$, yielding that $E[(\hat{\kappa}_{a,k} - \kappa_a^*)(\eta_a^* - \zeta_a^*)]|O_{-k}] = E[\hat{\kappa}_{a,k} - \kappa_a^*|O_{-k}]E[\eta_a^* - \zeta_a^*|M, N, C] = 0$, the third line results from the Cauchy-Schwarz inequality, and the last line uses the assumption that nuisance functions are estimated at $m^{1/4}$-rate.

Finally, the Equation (6) becomes $m^{1/2}(\hat{\mu}_C^\text{Eff} - \mu_C) = K^{-1/2}\sum_{k=1}^K G_k D(h^*) = \zeta_m D(h^*) + o_p(1)$. Since $D_a(h_a^*) = EIF_{C,a} + \mu_C(a)$, we get $m^{1/2}(\hat{\mu}_C^\text{Eff} - \mu_C) = \zeta_m EIF_C + o_p(1)$, which indicates the asymptotic linearity. Then the asymptotic normality is implied by the Central Limit Theorem if we can show $EIF_C$ has finite second moments. This is implied by Assumption 1 and regularity condition 6.

For completeness, we show the consistency of the variance estimate of cross-fitting estimator. Let us denote $\hat{S}_k = |O_k|^{-1}\sum_{i \in O_k}\{D(\hat{h}_k) - \hat{\mu}_{k,C}^\text{Eff}\\{D(\hat{h}_k) - \hat{\mu}_{k,C}^\text{Eff}\}^\top$ where $\hat{\mu}_{k,C}^\text{Eff} = \mathbb{P}_k\{D(\hat{h}_k)\}$. The proposed variance estimate for $\hat{\mu}_C^\text{Eff}$ is $\hat{\Sigma} = K^{-1}\sum_{k=1}^K \hat{S}_k$. Therefore, it suffices to show that $\hat{\Sigma}$ is consistent for $\Sigma = \text{var}\{D(h^*)\}$. Let us consider the following
decomposition of $\widehat{\Sigma}_k - \Sigma$:

$$\widehat{\Sigma}_k - \Sigma = \underbrace{\widehat{\Sigma}_k - \Sigma}_{(A)} + \underbrace{\Sigma_k - \Sigma}_{(B)},$$

$$\Sigma_k = \frac{1}{|O_k|} \sum_{i \in O_k} \{ D_i(h^*) - \mu_C \} \{ D_i(h^*) - \mu_C \}^\top.$$

The second term $(B)$ is then $o_p(1)$ from the law of large numbers. Denoting $\Delta_i = D_i(\widehat{h}_k) - \mu_{\text{Eff}}^k - D_i(h^*) + \mu_C$, the first term $(A)$ is represented as

$$(A) = \frac{1}{|O_k|} \sum_{i \in O_k} \left[ \Delta_i \Delta_i^\top + \Delta_i \{ D_i(h^*) - \mu_C \}^\top + \{ D_i(h^*) - \mu_C \} \Delta_i^\top \right].$$

From the Hölder’s inequality and the matrix norm, we find

$$|| (A) ||^2 \leq \left[ \frac{1}{|O_k|} \sum_{i \in O_k} \Delta_i \Delta_i \right]^2$$

$$+ 2 \left[ \frac{1}{|O_k|} \sum_{i \in O_k} \Delta_i \Delta_i \right] \left[ \frac{1}{|O_k|} \sum_{i \in O_k} \{ D_i(h^*) - \mu_C \}^\top \{ D_i(h^*) - \mu_C \} \right]$$

$$= \left[ \frac{1}{|O_k|} \sum_{i \in O_k} \Delta_i \Delta_i \right]^2 + 2 \left[ \frac{1}{|O_k|} \sum_{i \in O_k} \Delta_i \Delta_i \right] \left( \Sigma_k(1,1) + \Sigma_k(2,2) \right).$$

Since $\Sigma_k = \Sigma + o_p(1)$ and $\Sigma$ is finite, we have $\Sigma_k(1,1) + \Sigma_k(2,2) = O_p(1)$. Therefore, if $|O_k|^{-1} \sum_{i \in O_k} \Delta_i \Delta_i$ is $o_p(1)$, we establish $(A) = o_p(1)$. We expand $|O_k|^{-1} \sum_{i \in O_k} \Delta_i \Delta_i$ as follows:

$$\frac{1}{|O_k|} \sum_{i \in O_k} \Delta_i \Delta_i = \frac{1}{|O_k|} \sum_{i \in O_k} \left[ \{ D_i(\widehat{h}_k) - D_i(h^*) \} - \{ \mu_{\text{Eff}}^k - \mu_C(a) \} \right]^2$$

$$\leq \frac{2}{|O_k|} \sum_{i \in O_k} \left[ \{ D_i(\widehat{h}_k) - D_i(h^*) \} \right]^2 + 2 \left| \mu_{\text{Eff}}^k - \mu_C(a) \right|^2$$

$$= 2E \left[ \left| \{ D_i(\widehat{h}_k) - D_i(h^*) \} \right|^2 \bigg| \mathcal{O}_{-k} \right] + o_p(1) + 2 \left| \mu_{\text{Eff}}^k - \mu_C(a) \right|^2$$

$$= o_p(1).$$

The inequality is from $(a - b)^2 \leq 2a^2 + 2b^2$. The third line is from applying the law of large numbers on $\left| \{ D_i(\widehat{h}_k) - D_i(h^*) \} \right|^2$. The last line is from (7) and the consistency result of $\mu_{\text{Eff}}^k$, i.e., $\mu_{\text{Eff}}^k - \mu_C(a) = o_p(1)$. This concludes the proof.
D Sandwich variance estimators

Denote $\mathbb{P}_m X = \frac{1}{m} \sum_{i=1}^{m} X_i$ for quantities $X_1, \ldots, X_m$.

For GEE-g, we use the derived influence function for variance computation. Let

$$\widehat{IF}^\text{GEE-g}_C = \left[ \left\{ \mathbb{P}_m \frac{AM}{1+(M-1)\rho_C} \right\}^{-1} \frac{A}{1+(M-1)\rho_C} S^T \{ Y - \mu(A, \hat{\beta}_C) \} + \frac{1}{M} S^T \mu(1, \hat{\beta}_C) - \hat{\mu}_C^\text{GEE-g}(1) \right],$$

where $\hat{\theta}_C = (\hat{\mu}_C^\text{GEE-g}(1), \hat{\mu}_C^\text{GEE-g}(0), \hat{\beta}, \hat{\rho})$ is estimated by solving the empirical estimating equations (1). Then the variance of $\widehat{\Delta}_C^\text{GEE-g}$ is estimated by

$$\nabla f\{\hat{\mu}_C^\text{GEE-g}(1), \hat{\mu}_C^\text{GEE-g}(0)\}^\top \left( \mathbb{P}_m \widehat{IF}^\text{GEE-g}_C \widehat{IF}^\text{GEE-g}_C^\top \right) \nabla f\{\hat{\mu}_C^\text{GEE-g}(1), \hat{\mu}_C^\text{GEE-g}(0)\},$$

where $\nabla f\{\hat{\mu}_C^\text{GEE-g}(1), \hat{\mu}_C^\text{GEE-g}(0)\}$ is the gradient of $f$ evaluated at $\hat{\mu}_C^\text{GEE-g}(1), \hat{\mu}_C^\text{GEE-g}(0)$. Similarly, the variance of $\widehat{\Delta}_I^\text{GEE-g}$ is estimated by

$$\nabla f\{\hat{\mu}_I^\text{GEE-g}(1), \hat{\mu}_I^\text{GEE-g}(0)\}^\top \left( \mathbb{P}_m \widehat{IF}^\text{GEE-g}_I \widehat{IF}^\text{GEE-g}_I^\top \right) \nabla f\{\hat{\mu}_I^\text{GEE-g}(1), \hat{\mu}_I^\text{GEE-g}(0)\},$$

where

$$\widehat{IF}^\text{GEE-g}_I = \frac{N}{\mathbb{P}_m N} \left[ \left\{ \mathbb{P}_m \frac{AM}{1+(M-1)\rho_I} \right\}^{-1} \frac{A}{1+(M-1)\rho_I} S^T \{ Y - \mu(A, \hat{\beta}_I) \} + \frac{1}{M} S^T \mu(1, \hat{\beta}_I) - \hat{\mu}_I^\text{GEE-g}(1) \right].$$

For LMM-g, the variance estimation is the same as GEE-g, except that $\hat{\theta}_C$ is substituted by $\{\hat{\mu}_C^\text{LMM-g}(1), \hat{\mu}_C^\text{LMM-g}(0), \hat{\alpha}, \hat{\tau}^2(\hat{\tau}^2+\hat{\sigma}^2)^{-1}\}$ and $\hat{\theta}_I$ is substituted by $\{\hat{\mu}_I^\text{LMM-g}(1), \hat{\mu}_I^\text{LMM-g}(0), \hat{\alpha}, \hat{\tau}^2(\hat{\tau}^2+\hat{\sigma}^2)^{-1}\}$.

For the proposed estimator with parametric working models, the estimating equations for all parameters are

$$\phi(\hat{\theta}) = \left\{ \begin{array}{c} \tilde{\psi}(\hat{\theta}, \mu_C) \\ \hat{\psi}(\hat{\theta}) \end{array} \right\},$$

where $\hat{\theta} = (\mu_C, \theta)$. We define the estimated influence function for $\mu_C(1), \mu_C(0)$ as the $\widehat{IF}^\text{Eff-PM}_C$, which is the first two entries of

$$-\left\{ \mathbb{P}_m \frac{\partial}{\partial \theta} \phi_i(\hat{\theta}_m) \right\}^{-1} \phi(\hat{\theta}_m),$$
where \( \tilde{\theta}_m \) denotes the estimated parameters. We estimate the variance of \( \hat{\Delta}_C^{\text{Eff-PM}} \) by
\[
\nabla f\{\hat{\mu}_C^{\text{Eff-PM}}(1), \hat{\mu}_C^{\text{Eff-PM}}(0)\}^\top \left( \mathbb{P}_m \hat{I}_C^{\text{Eff-PM}} \hat{I}_C^{\text{Eff-PM} \top} \right) \nabla f\{\hat{\mu}_C^{\text{Eff-PM}}(1), \hat{\mu}_C^{\text{Eff-PM}}(0)\},
\]
and the variance of \( \hat{\Delta}_I^{\text{Eff-PM}} \) is estimated following a similar procedure.

For the proposed estimator with machine learning algorithms, the variance for
\[
\nabla f\{\hat{\mu}_C^{\text{Eff-ML}}(1), \hat{\mu}_C^{\text{Eff-ML}}(0)\}^\top \left( K^{-1} \sum_{k=1}^{K} \hat{\Sigma}_k \right) \nabla f\{\hat{\mu}_C^{\text{Eff-ML}}(1), \hat{\mu}_C^{\text{Eff-ML}}(0)\},
\]
where \( \hat{\Sigma}_k = |\mathcal{O}_k|^{-1} \sum_{i \in \mathcal{O}_k} \{ D(\hat{h}_k) - \hat{\mu}_k^{\text{Eff}} \} \{ D(\hat{h}_k) - \hat{\mu}_k^{\text{Eff}} \}^\top \) with \( D(h) = \{ D_1(h_1), D_0(h_0) \} \)
and
\[
D_a(h_a) = I\{ A = a \} \left\{ \frac{\pi^a}{\pi^a(1 - \pi)^{1-a}} \{ \hat{Y} - \eta_a(X, M, N, C) \} \right. \\
+ \frac{\kappa_a(M, N, C)}{\pi^a(1 - \pi)^{1-a}} \left\{ \eta_a(X, M, N, C) - \zeta_a(N, C) \right\} + \zeta_a(N, C),
\]
and \( \hat{h}_k \) is the prediction of nuisance function trained on \( \mathcal{O}_{-k} \). The variance for \( \hat{\Delta}_I^{\text{Eff-ML}} \) are estimated similarly.

## E Review of other methods

### E.1 Other methods

The augmented generalized estimating equations (Aug-GEE, Stephens et al., 2012) is an approach that incorporates the augmentation technique in semiparametric theory to improve the robustness and precision of GEE. Instead of modeling the conditional expectation of \( Y_{ij} \) on \( A_i \) and \( X_{ij} \), Aug-GEE solves the following estimating equations to estimate \( (\beta_0, \beta_A) \):
\[
\sum_{i=1}^{m} D_i^\top V_i^{-1} \{ Y_i^o - \mu_i^0(A) \} - (A_i - \pi) \gamma(N_i, C_i, X_i^o) = 0,
\]
where the first part \( D_i^\top V_i^{-1} \{ Y_i^o - \mu_i^0(A) \} \) is the same as GEE except that covariates \( (N, C, X^o) \) are omitted, and the remaining part \( -(A_i - \pi) \gamma(N_i, C_i, X_i^o) \) is the augmentation term with
\( \gamma(N_i, C_i, X_i^o) \) being an arbitrary \( M_i \)-dimensional function. Popular choices of the augmentation term involves parametric working models for \( Y_i^o \) on \( A_i, N_i, C_i, X_i^o \) and can be found in Stephens et al. (2012). Given \( (\hat{\beta}_0, \hat{\beta}_A) \) from Aug-GEE, we can follow the steps in Section 3 for GEE-g to construct Aug-GEE-g targeting \( (\Delta_C, \Delta_I) \). Given similar conditions (Assumptions 1-4 and S1-S4) in Theorem 1, we can get the consistency and asymptotically normality of Aug-GEE-g. Compared to GEE, the asymptotic results for Aug-GEE requires less assumptions: a correctly-specified model for \( E[Y_{ij}|U_{ij}] \) is not needed as long as the estimates for the augmentation term converge. In terms of precision, Aug-GEE has the potential to improve precision over GEE, while simulation studies showed that this efficiency gain is at most moderate, especially for studies with few clusters (Stephens et al., 2012; Benitez et al., 2021).

Targeted maximum likelihood estimation (TMLE, van der Laan and Rubin, 2006) as a general framework for causal inference also has applications for clustered data. Among them, two most relevant methods are cluster-level TMLE and hierarchical TMLE proposed by Balzer et al. (2019). In our setting, both methods assume \( M_i = N_i \). The cluster-level TMLE targets \( \Delta_C \) and works on cluster averages of outcomes and covariates, i.e., \((\overline{Y}_i, A_i, N_i, C_i, \overline{X}_i)\). Although individual-level information is not utilized, cluster-level TMLE avoids the complexity of accounting for intracluster correlations. Thus, the cluster-level TMLE enjoys the precision gain from covariate adjustment without the need of a correctly specified mean model. However, under the potentially informative within-cluster sampling schemes as we consider in this paper, \( \overline{X}_i \) is no longer independent of \( A_i \), and directly adjusting for them may cause bias. Hierarchical TMLE, also known as individual-level TMLE, performs TMLE on \( E[Y_{ij}|U_{ij}] \) and aggregates model predictions to estimate \( \Delta_I \). Unlike cluster-level TMLE, the asymptotic validity of hierarchical TMLE needs additional assumptions for convergence of TMLE given dependent data. With the additional assumptions, hierarchical TMLE can also target \( \Delta_C \) by modifying the cluster weights, and cluster-level TMLE can utilize the model predictions from the hierarchical TMLE to further improve power. Both TMLE-based methods have been demonstrated to be more precise than GEE and Aug-GEE in
simulation studies (Benitez et al., 2021), while less is known about their validity and efficiency when \( M_i \neq N_i \) or the treatment effect is related to \( N_i \) as we consider here. In the simulation study, we showed that the hierarchical TMLE has bias and under coverage when \( M_i \leq N_i \).

In addition to the above discussed methods, Schochet et al. (2021); Su and Ding (2021) established the asymptotic theory for a class of linearly-adjusted estimators under the randomization inference framework, and Bugni et al. (2022) proposed unadjusted estimators that accounts for treatment effects that vary by \( N_i \). Under the super-population framework, their estimators can be viewed as special cases of GEE-g with identity link and independence working correlation structure (with \( 1/M_i \) weighting for the unadjusted estimator), whose property has been discussed and hence omitted.

### E.2 Addition simulation studies

For our two simulation experiments described in Section 5, we additional implemented Aug-GEE-g and TMLE as two comparison methods, and describe our findings below. For Aug-GEE-g, we used the R package CRTgeeDR (Prague et al., 2016) with weighted g-computation (defined in Section 3 of the main manuscript). For TMLE, we implemented the cluster-level TMLE with cluster-level data for \( \Delta_C \) and hierarchical TMLE with individual-level data for \( \Delta_I \), following the description in Benitez et al. (2021) to compute point estimates and variances. The nuisance functions in TMLE were estimated by an ensemble method of generalized linear models, regression trees, and neural networks using the \texttt{tmle} R package (Gruber and van der Laan, 2012). Both methods adjusted for the same set of covariates as our proposed estimators.

The full simulation results are summarized in Tables 1 and 2 below for completeness. Across experiments and scenarios, Aug-GEE-g has comparable performance to GEE-g in terms of bias and precision. TMLE for cluster-average treatment effect is valid across scenarios as expected, since it only uses cluster-level information. However, TMLE for individual-average treatment effects has large bias because it targets the average treatment effect among
the enrolled population, rather than among the entire source population of interest. In terms of variance, TMLE can improve precision by covariate adjustment, while this precision gain lacks consistency across simulation scenarios and is generally smaller compared to our proposed methods with machine learning algorithms.
Table 1: Results in the first simulation experiment with continuous outcomes.

| Setting | Method       | Bias   | ESE  | ASE  | CP   | Bias   | ESE  | ASE  | CP   |
|---------|--------------|--------|------|------|------|--------|------|------|------|
|         | Cluster-average treatment effect $\Delta_C = 6$ |        |      |      |      |        |      |      |      |
|         | Unadjusted   | −0.08  | 4.85 | 4.88 | 0.95 | −0.19  | 4.51 | 4.25 | 0.93 |
|         | GEE-g        | 0.13   | 2.77 | 2.45 | 0.92 | −0.13  | 3.64 | 3.10 | 0.89 |
|         | LMM-g        | 0.12   | 2.77 | 2.78 | 0.96 | −0.13  | 3.63 | 2.94 | 0.90 |
| Scenario 1: | Aug-GEE-g    | −0.03  | 2.77 | 2.31 | 0.90 | −0.11  | 3.76 | 2.66 | 0.84 |
| Small m with | TMLE         | −0.01  | 3.13 | 2.87 | 0.93 | −2.27  | 1.96 | 1.55 | 0.66 |
| random observed cluster sizes | Eff-PM | −0.03 | 3.23 | 2.66 | 0.92 | −0.10  | 3.89 | 3.38 | 0.91 |
|         | Eff-ML       | 0.03   | 2.24 | 2.05 | 0.95 | 0.03   | 2.59 | 2.49 | 0.95 |
|         | Scenario 2: | Unadjusted | 0.17 | 5.33 | 5.31 | 0.95 | 1.63   | 4.66 | 4.19 | 0.90 |
| Small m with | GEE-g        | 1.98   | 3.75 | 3.25 | 0.86 | 0.87   | 4.53 | 3.66 | 0.88 |
| cluster-dependent observed cluster sizes | LMM-g | 1.74 | 3.63 | 3.69 | 0.94 | 0.79   | 4.26 | 3.83 | 0.93 |
|         | Aug-GEE-g    | 1.14   | 3.70 | 2.82 | 0.85 | 1.40   | 4.57 | 3.52 | 0.86 |
|         | TMLE         | 0.10   | 3.84 | 3.61 | 0.94 | 0.99   | 3.00 | 2.21 | 0.84 |
|         | Eff-PM       | 0.08   | 3.87 | 3.47 | 0.93 | 0.09   | 4.32 | 3.97 | 0.93 |
|         | Eff-ML       | −0.21  | 3.42 | 3.47 | 0.95 | −0.06  | 4.20 | 3.84 | 0.93 |
|         | Scenario 3: | Unadjusted | 0.01 | 2.62 | 2.65 | 0.96 | −0.03  | 2.35 | 2.36 | 0.95 |
| Large m with | GEE-g        | 0.04   | 1.40 | 1.38 | 0.95 | −0.01  | 1.89 | 1.83 | 0.94 |
| random observed cluster sizes | LMM-g | 0.04 | 1.40 | 1.42 | 0.96 | −0.01  | 1.89 | 1.55 | 0.90 |
|         | Aug-GEE-g    | 0.00   | 1.39 | 1.35 | 0.95 | −0.01  | 1.91 | 1.58 | 0.90 |
|         | TMLE         | 0.07   | 1.81 | 1.52 | 0.92 | −2.13  | 0.91 | 0.67 | 0.19 |
|         | Eff-PM       | 0.00   | 1.40 | 1.38 | 0.95 | −0.01  | 1.93 | 1.92 | 0.95 |
|         | Eff-ML       | 0.04   | 0.70 | 0.71 | 0.95 | 0.00   | 0.77 | 0.81 | 0.97 |
|         | Scenario 4: | Unadjusted | −0.04 | 2.94 | 2.89 | 0.95 | 1.49   | 2.45 | 2.38 | 0.88 |
| Large m with | GEE-g        | 1.80   | 1.89 | 1.82 | 0.82 | 0.74   | 2.21 | 2.12 | 0.91 |
| cluster-dependent observed cluster sizes | LMM-g | 1.72 | 1.87 | 1.89 | 0.85 | 0.72   | 2.20 | 2.00 | 0.91 |
|         | Aug-GEE-g    | 1.02   | 1.86 | 1.63 | 0.86 | 0.92   | 2.28 | 2.26 | 0.90 |
|         | TMLE         | 0.08   | 2.12 | 1.92 | 0.92 | 0.08   | 1.20 | 0.82 | 0.82 |
|         | Eff-PM       | 0.03   | 1.89 | 1.83 | 0.94 | 0.01   | 2.21 | 2.16 | 0.94 |
|         | Eff-ML       | 0.01   | 1.91 | 1.83 | 0.94 | 0.00   | 2.23 | 2.13 | 0.94 |
Table 2: Results in the second simulation experiment with binary outcomes.

| Setting                          | Method  | Effect $\Delta_C = 1.54$ |         |         |         | Effect $\Delta_I = 1.18$ |         |         |         |
|---------------------------------|---------|--------------------------|---------|---------|---------|--------------------------|---------|---------|---------|
|                                 |         | Bias         | ESE     | ASE     | CP      | Bias         | ESE     | ASE     | CP      |
| Scenario 1: Small $m$ with      | Unadjusted | 0.04         | 0.25    | 0.24    | 0.94    | 0.03         | 0.16    | 0.13    | 0.94    |
| random observed cluster sizes   | GEE-g   | 0.01         | 0.23    | 0.19    | 0.92    | 0.03         | 0.22    | 0.13    | 0.93    |
|                                 | LMM-g   | 0.01         | 0.22    | 0.19    | 0.92    | 0.03         | 0.16    | 0.13    | 0.93    |
|                                 | Aug-GEE-g | 0.02         | 0.20    | 0.18    | 0.93    | 0.03         | 0.16    | 0.11    | 0.89    |
|                                 | TMLE    | -0.02        | 0.30    | 0.24    | 0.89    | 0.35         | 0.20    | 0.15    | 0.41    |
|                                 | Eff-PM  | 0.01         | 0.21    | 0.20    | 0.93    | 0.02         | 0.16    | 0.15    | 0.95    |
|                                 | Eff-ML  | 0.03         | 0.22    | 0.20    | 0.94    | 0.03         | 0.15    | 0.14    | 0.95    |
| Scenario 2: Small $m$ with      | Unadjusted | 0.05         | 0.30    | 0.29    | 0.94    | -0.03        | 0.15    | 0.16    | 0.92    |
| cluster-dependent observed      | GEE-g   | -0.18        | 0.30    | 0.20    | 0.69    | -0.05        | 0.16    | 0.17    | 0.89    |
| cluster sizes                   | LMM-g   | -0.12        | 0.24    | 0.20    | 0.78    | -0.04        | 0.15    | 0.16    | 0.90    |
|                                 | Aug-GEE-g | -0.15        | 0.23    | 0.16    | 0.66    | -0.02        | 0.24    | 0.13    | 0.81    |
|                                 | TMLE    | 0.01         | 0.33    | 0.30    | 0.92    | 0.12         | 0.17    | 0.11    | 0.80    |
|                                 | Eff-PM  | 0.04         | 0.28    | 0.26    | 0.92    | 0.03         | 0.17    | 0.17    | 0.95    |
|                                 | Eff-ML  | 0.06         | 0.30    | 0.30    | 0.93    | 0.05         | 0.19    | 0.17    | 0.95    |
| Scenario 3: Large $m$ with      | Unadjusted | 0.01         | 0.13    | 0.13    | 0.95    | 0.01         | 0.07    | 0.07    | 0.95    |
| random observed cluster sizes   | GEE-g   | 0.00         | 0.11    | 0.10    | 0.94    | 0.00         | 0.07    | 0.07    | 0.95    |
|                                 | LMM-g   | 0.00         | 0.11    | 0.10    | 0.94    | 0.01         | 0.07    | 0.07    | 0.95    |
|                                 | Aug-GEE-g | 0.01         | 0.10    | 0.10    | 0.95    | 0.00         | 0.07    | 0.06    | 0.92    |
|                                 | TMLE    | 0.00         | 0.14    | 0.11    | 0.89    | 0.35         | 0.10    | 0.09    | 0.01    |
|                                 | Eff-PM  | 0.01         | 0.10    | 0.10    | 0.95    | 0.00         | 0.07    | 0.08    | 0.97    |
|                                 | Eff-ML  | 0.01         | 0.10    | 0.10    | 0.95    | 0.01         | 0.06    | 0.07    | 0.97    |
| Scenario 4: Large $m$ with      | Unadjusted | 0.01         | 0.15    | 0.15    | 0.95    | -0.05        | 0.07    | 0.09    | 0.91    |
| cluster-dependent observed      | GEE-g   | -0.20        | 0.10    | 0.10    | 0.44    | -0.06        | 0.07    | 0.09    | 0.88    |
| cluster sizes                   | LMM-g   | -0.14        | 0.11    | 0.10    | 0.67    | -0.05        | 0.07    | 0.08    | 0.89    |
|                                 | Aug-GEE-g | -0.19        | 0.10    | 0.08    | 0.37    | -0.07        | 0.07    | 0.06    | 0.74    |
|                                 | TMLE    | 0.02         | 0.19    | 0.14    | 0.90    | 0.10         | 0.08    | 0.06    | 0.69    |
|                                 | Eff-PM  | 0.01         | 0.13    | 0.13    | 0.94    | 0.00         | 0.07    | 0.08    | 0.97    |
|                                 | Eff-ML  | 0.01         | 0.13    | 0.13    | 0.94    | 0.01         | 0.08    | 0.08    | 0.97    |
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