A New Integrative Method for Multigroup Comparisons of Censored Survival Outcomes in Multiple Observational Studies

Subharup Guha
Department of Biostatistics, University of Florida
and
David C. Christiani
Departments of Environmental Health and Epidemiology, Harvard T.H. Chan School of Public Health
and
Yi Li
Department of Biostatistics, University of Michigan

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Abstract

In observational studies, covariate imbalance generates confounding, resulting in biased comparisons. Although propensity score-based weighting approaches facilitate unconfounded group comparisons for implicit target populations, existing techniques may not directly or efficiently analyze multiple studies with multiple groups, and provide generalizable results for the larger population. Moreover, few methods deliver precise inferences for various estimands with censored survival outcomes. We propose a new concordant target population approach, which constructs generalized balancing weights and realistic target populations. Our method can incorporate researcher-specified natural population attributes and synthesize information by appropriately compensating for over- or under-represented groups to achieve covariate balance. The constructed concordant weights are agnostic to specific estimators, estimands, and outcomes, and maximize the effective sample size (ESS) to deliver precise inferences. Simulation studies and descriptive comparisons of glioblastoma outcomes of racial groups in multiple TCGA studies demonstrate the strategy’s practical advantages. Unlike existing weighting techniques, the proposed concordant target population revealed a drastically different result: Blacks were more vulnerable and endured significantly worse prognoses; Asians had the best outcomes with a median overall survival of 1,024 (SE: 15.2) days, compared to 384 (SE: 1.2) and 329 (SE: 19.7) days for Whites and Blacks, respectively. In observational studies, covariate imbalance generates confounding, resulting in biased comparisons. Although propensity score-based weighting approaches facilitate unconfounded group comparisons for implicit
target populations, existing techniques may not directly or efficiently analyze multiple studies with multiple groups, and provide results generalizable to larger populations. Moreover, few methods deliver precise inferences for various estimands with censored survival outcomes. We propose a new *concordant* target population approach, which constructs generalized balancing weights and realistic target populations. Our method can incorporate researcher-specified natural population attributes and synthesize information by appropriately compensating for over- or under-represented groups to achieve covariate balance. The constructed concordant weights are agnostic to specific estimators, estimands, and outcomes, and maximize the effective sample size (ESS) for more precise inferences. Simulation studies and descriptive comparisons of glioblastoma outcomes of racial groups in multiple TCGA studies demonstrate the strategy’s practical advantages. Unlike existing weighting techniques, the proposed concordant target population revealed a drastically different result: Blacks were more vulnerable and endured significantly worse prognoses; Asians had the best outcomes with a median overall survival of 1,024 (SE: 15.2) days, compared to 384 (SE: 1.2) and 329 (SE: 19.7) days for Whites and Blacks, respectively.

*Keywords:* Concordant population; Generalized balancing weights; Meta-analysis; Propensity score; Unconfounded comparison; Weighting.

1 Introduction

A primary objective of observational studies is the unbiased comparison of two or more groups of subjects determined by race, treatment, or exposure. A ubiquitous phenomenon in these investigations is covariate imbalance, which generates confounding and results in biased group comparisons (Smith et al. 2018, Robins & Rotnitzky 1995, Rubin 2007, Li et al. 2018). This project is motivated by a multiple-site glioblastoma multiforme (GBM) study conducted at MD Anderson Cancer Center, Henry Ford Hospital, Emory University, and Case Western Reserve University. Reposited at The Cancer Genome Atlas (TCGA) portal (NCI 2022), data from each site include race (Asian, Black and White) and several clinical and demographic measurements, some of which are summarized in Table 1. Common genetic alterations in GBM include gene amplification of epidermal growth factor receptor (EGFR) and mutations in the genes TP53 and PTEN (Hill et al. 2003). These biomarker measurements were included in the \( p = 13 \) covariates for \( N = 340 \) GBM patients. These data provide an opportunity for studying racial disparities in cancer outcomes (e.g., overall
Table 1: Summary of some demographic and clinical variables of the TCGA glioblastoma multiforme dataset. Shown in parentheses are percentages.

|                      | Case Western | Emory | Henry Ford | MDACC |
|----------------------|--------------|-------|------------|-------|
| N                    | 46           | 44    | 161        | 89    |
| Mean age at diagnosis| 61.4         | 57.1  | 58.9       | 51.7  |
| Sex (Male)           |              |       |            |       |
| Asian                | 2 (4.3)      | 1 (2.3)| 4 (2.5)    | 5 (5.6)|
| Black                | 5 (10.9)     | 7 (15.9)| 17 (10.5) | 4 (4.5)|
| White                | 39 (84.8)    | 36 (81.8)| 140 (87.0)| 80 (89.9)|
| Karnofsky score      | 65.7         | 70.2  | 79.8       | 82.7  |
| Median year of diagnosis | 2009     | 2004  | 2006       | 2003  |
| Prior glioma         | 2 (4.3)      | 1 (2.3)| 2 (1.2)    | 1 (1.1)|

survival) and present a challenge with unbalanced racial groups. Due to the analytical difficulties posed by the study-specific heterogeneities of these four TCGA sites, there is an urgent need for statistical methods that can effectively integrate two or more observational studies comprising multiple unbalanced groups of subjects.

Weighting and matching (Rubin 2007, Robins & Rotnitzky 1995) are established covariate-balancing approaches facilitating unconfounded descriptive comparisons for a target population. In addition to their ease of interpretation and resulting popularity in multidisciplinary fields such as healthcare research (Austin & Stuart 2015), the superiority of weighting to matching or regression adjustment has been demonstrated by theoretical results and simulations studies (Austin 2010, Lunceford & Davidian 2004).

For single observational studies, an overwhelming majority of two-group comparisons involve the average treatment effect (ATE) or average treatment effect on the treated group (ATT) (Rosenbaum & Rubin 1983, Robins et al. 2000). Analyses are based on the propensity score (PS), defined as the probability that a subject with a given covariate vector is a member of the reference group (Rosenbaum & Rubin 1983). However, the inverse
probability weights (IPW) utilized by these weighted estimators are large when some PSs are close to 0 or 1, resulting in unstable inferences. Li et al. (2018) defined a class of balancing weights matching the covariate distribution of each subject or unit to that of a prespecified target population. From this perspective, the estimands ATE and ATT are special cases that respectively correspond to the combined and treatment target population. Several modifications of the ATE defined on truncated subpopulations of scientific interest or possessing useful statistical properties (e.g., Crump et al. 2006, Li & Greene 2013) also belong to this general class. Statistical considerations such as inferential accuracy and covariate balance have traditionally played almost as important a role as interpretability of the target population. Motivated by this, Li et al. (2018) introduced overlap weights and their corresponding estimand, the average treatment effect for the overlap population (ATO). Unlike IPWs, overlap weights are bounded. Under appropriate conditions, they minimize the asymptotic variance of the weighted average treatment effect among balancing weights in two-group, single-study settings. For single-study investigations involving two or more groups, Li & Li (2019) extended the technique of Li et al. (2018) and introduced generalized overlap weights, which are bounded and under suitable theoretical conditions minimize the total asymptotic variance of weighted estimators of pairwise group differences. Wang & Rosner (2019) extended the basic methodology in a different direction. For multiple studies involving two groups, they proposed a PS-based Bayesian nonparametric model that summarizes subject-level information from multiple studies to make inferences about the ATE.

Delivering unconfounded group comparisons by performing efficient meta-analyses of multiple observational studies comprising multiple groups is indeed a daunting challenge. The aforementioned weighting methods could be applied in multistudy-multigroup investigations by regarding each study-group combination as a “treatment,” and they would then achieve theoretical covariate balance and provide unconfounded group comparisons after
marginalizing over study. However, these approaches are plagued by several limitations. First, as some weighting methods minimize the variance of estimates of pairwise differences or contrasts of the average group responses, these techniques are guaranteed to be effective for particular types of outcomes and estimands under theoretical conditions such as across-group outcome homoscedasticity (Li et al. 2018, Li & Li 2019). Specifically, when the outcomes are censored and the study features wide-ranging estimands (e.g., 1-year survival probability and survival time percentiles), some existing weighting methods may deliver imprecise inferences, as demonstrated by our simulations and data analyses of multistudy-multigroup settings. Second, as noted in Section 2.3, implicitly or explicitly, many existing methods rely on prespecified target populations comprising no minority groups, an assumption that may not be compatible with the larger, natural cohort of interest. Moreover, as remarked in Li et al. (2018), many weighting methods in the literature imply an implausible change of group membership for some subjects that may not correspond to a meaningful, generalizable population.

To fill these important gaps, this paper develops new propensity score weighting frameworks for integrating multiple observational studies with several subject-specific characteristics to make unconfounded comparisons between two or more groups. We formulate a novel class of generalized balancing weights that adapt the target population to known attributes of the larger population of interest, while optimizing over the unknown attributes, integrating the observational studies, and adjusting for over- or under-sampled groups. The constructed target population, termed concordant target population, achieves high inferential precision by maximizing the effective sample size and balances all group features to provide meaningful statistical inferences for a wide variety of estimands. Unlike some existing weighting methods, the concordant target population involves a truly “outcome-free design” that is agnostic to not only prespecified estimators of prespecified estimands, but also to outcome types, including censored survival outcomes. Furthermore, the concordant
population is optimal under mild theoretical conditions on the outcome-free generalized balancing weights (specifically, the existence of second moments) that are unrelated to the study outcomes. Consequently, the proposed methodology may open up opportunities for effectively analyzing observational studies that feature diverse outcomes and estimands. For example, as an alternative to applications where a statistician may inadvertently influence an investigation through their preferred estimand of choice, the proposed concordant weighting method allows the scientific expert to more freely focus on estimands of interest dictated by the scientific question and construct a realistic target population unencumbered by statistical considerations.

This is an outline of the paper. Section 2 describes the elements of designing a target population using available scientific or domain knowledge, establishes the large-sample covariate balance property of the proposed class of generalized balancing weights, provides some examples of target populations, and outlines an efficient procedure for finding the concordant target population using a key analytical result. Section 3 describes the inference procedure for survival functions of group-specific censored outcomes. A simulation study in Section 4 compares the effectiveness of the concordant weighting approach with natural extensions of existing methods to multistudy-multigroup investigations. Section 5 throws light on racial differences in cancer survival by meta-analyzing the motivating glioblastoma multiforme TCGA databases using the concordant target population. Technical details are deferred to the Supplementary Material (Guha et al. 2022).

2 Designing a realistic target population

For subject $i = 1, \ldots, N$, let $Z_i \in \{1, \ldots, K\}$ denote the $K$ groups determined by race, treatment or exposure. Let $S_i \in \{1, \ldots, J\}$ be the observational study to which the $i$th subject belongs. For the motivating TCGA GBM database, $J = 4$ corresponding to the
MD Anderson Cancer Center, Henry Ford Hospital, Emory University, and Case Western Reserve University studies, and $K = 3$ racial groups if we focus primarily on Asians, Blacks, and Whites for our analysis. Suppose there are $p$ additional covariates $\mathbf{X}_i$ belonging to a space $\mathcal{X} \subset \mathbb{R}^p$. Denote by $T_i^{(z)}$ the potential outcome for subject $i$ if that individual’s group membership were $Z_i = z$, where $z = 1, \ldots, K$. The realized outcome is $T_i = T_i^{(Z_i)}$.

If $N_{sz}$ represents the number of subjects belonging to group $z$ in study $s$, then $N_s = \sum_{z=1}^{K} N_{sz}$ is the number of subjects belonging to the $s$th study, and $N_z = \sum_{s=1}^{J} N_{sz}$ is the number of subjects in the $z$th group. In general, bifactor $\Phi = (S, Z)$ represents study-group combinations and takes values, denoted by $\varphi = (s, z)$, in the set $\Omega = \{1, \ldots, J\} \times \{1, \ldots, K\}$. If the subject labels contain no meaningful information, we can regard the subject-specific measurements as i.i.d. samples from a source population with density $[\Phi, \mathbf{X}, T]$, where the symbol $[\cdot]$ generically represents a density with respect to a suitable dominating measure. Marginalizing over $T$, we obtain the “outcome-free” distribution $[\Phi, \mathbf{X}]$ which summarizes the relationships in the source population between the study and group memberships and the covariates.

For an observational study with multiple groups, Imbens (2000b) recommended using the generalized PS for statistical analyses. For multiple observational studies with two groups, Wang & Rosner (2019) created the extended PS using the reference group PS in each observational study, including the $(J - 1)$ studies to which the subject did not actually belong. We rely on an alternative definition appropriate for the multigroup-multistudy settings that motivate this paper. Our PS function is denoted by $e_\varphi(\mathbf{x})$ or $e_{sz}(\mathbf{x})$, with the notation emphasizing its dependence on the bifactor:

$$e_\varphi(\mathbf{x}) = P(\Phi = \varphi \mid \mathbf{X} = \mathbf{x}), \quad \varphi \in \Omega, \text{ and } \mathbf{x} \in \mathcal{X},$$

implying that $\sum_{\varphi \in \Omega} e_\varphi(\mathbf{x}) = 1$ for each $\mathbf{x} \in \mathcal{X}$. This construct allows the relationships
between the group memberships and covariates to be study-dependent. We may regard the observed PS of the \( N \) subjects, \( e_{\psi_1}(x_1), \ldots, e_{\psi_N}(x_N) \), as a random sample from the source distribution induced by random quantity \( [\Phi, X] \). The study-specific group PS, denoted by \( e_{z|s}(x) \) and defined as \( P(Z = z \mid X = x, S = s) \), is then available as \( e_{sz}(x)/\sum_{z' = 1}^{K} e_{sz'}(x) \).

The group-specific study PS, \( e_{s|z}(x) \), is analogously defined and evaluated. The PS is unknown in observational studies but can be estimated from the data. Viewing bifactor \( \Phi_i = (S_i, Z_i) \) as categorical responses in a multivariate regression model, available statistical or machine learning approaches can be applied to easily estimate the PS.

In the source distribution \( [\Phi, X] \), let probability \( \rho_\psi = P[\Phi = \psi] \) be strictly positive, and let \( f_\psi(x) \) denote the covariate density of group \( z \) in study \( s \). Let \( f(x) \) denote the marginal covariate density irrespective of study and group, so that \( f(x) = \sum_{\psi \in \Omega} \rho_\psi f_\psi(x) \).

Then, for all \( \psi \in \Omega \) and \( x \in X \), we have

\[
[\Phi = \psi, X = x] = \rho_\psi f_\psi(x) = e_\psi(x) f(x).
\] (2)

**Basic assumptions**

In addition to the stable unit treatment value assumption (Rubin 2007), which states that a subject’s study and group memberships do not affect the potential outcomes of any other subject given the observed covariates, we make the following assumptions about the within-study group memberships. For each study \( s = 1, \ldots, J \), group \( z = 1, \ldots, K \), and vector \( x \in X \):

- **Assumption 1 (Weak unconfoundedness):** Given covariate \( X = x \), membership in the \( z \)th group is independent of potential outcome \( T^{(z)} \).

- **Assumption 2 (Positivity):** The study-specific group PS, \( e_{sz}(x) \), is strictly positive and less than 1.

Extending Imbens (2000b), Assumption 1 states that the \( z \)th potential outcome is con-
ditionally independent of the Bernoulli indicator variable, \( I(Z = z) \):

\[
[T^{(z)} | S = s, Z = z, X = x] = [T^{(z)} | S = s, X = x].
\]  

(3)

Assumption 2 ensures that study and group memberships are stochastically (rather than deterministically) related to the covariates.

2.1 Prespecifying target population characteristics

We foster an analytical approach that constrains the target population to characteristics prespecified by the investigator, optimizes over the unknown or unspecified aspects of the target population, and appropriately adjusts for over- or under-sampled groups to meta-analyze the \( K \) groups using the \( J \) observational studies.

The first step involves fully or partially specifying target population characteristics related to individual components of bifactor \( \Phi = (S, Z) \): (a) relative amounts of information extracted from the studies, represented by \( \alpha = (\alpha_1, \ldots, \alpha_J) \); and (b) relative sizes of the \( K \) groups, \( \beta = (\beta_1, \ldots, \beta_K) \). In this manner, the specified target population characteristics can be chosen to match known aspects of the natural population of interest; all unknown characteristics are optimized by the eventual inference procedure. For example, in the TCGA studies, we could set \( \beta = (0.04, 0.10, 0.86) \) to reflect the relative proportions of Asian, Black, and White GBM patients in the United States (Ostrom et al. 2018). Similarly, stipulating \( \alpha_j = 1/4 \) extracts equal amounts of information from each TCGA study.

For bifactor \( \varphi \in \Omega \), we define the target population’s bifactor relative mass as \( \delta_\varphi = \alpha_s \beta_z \), so that \( \sum_{\varphi \in \Omega} \delta_\varphi = 1 \). Representing the unit simplex in \( \mathbb{R}^J \) by \( S_J \), possible values of \( \delta_\varphi \) belongs to \( S_J \times S_K \). If probability vectors \( \alpha \) and \( \beta \) are not fully specified, then multiple possibilities exist for vector \( \delta = \{\delta_\varphi\}_\Omega \), and the later steps optimize over options consistent with the researcher input.
Let the marginal covariate density in the target population be denoted by \( f^*(x) \) and have the same support as the source marginal covariate density, \( f(x) \). Without loss of generality, there exists a *tilting function* \( \lambda \) (Li et al., 2018) for which \( f^*(x) \propto \lambda(x)f(x) \) for all \( x \in \mathcal{X} \). As a result, \( f^*(x) = \lambda(x)f(x)/E[\lambda(X)] \), with \( x \in \mathcal{X} \) and \( X \sim f(x) \).

For interpretation, higher values of the tilting function correspond to the regions of the covariate space with higher relative weights in the target population.

For achieving balance among the studies, groups, and covariates, we formulate a new family of balanced target populations in which \( S, Z, \) and \( X \) are independent. More formally, writing \([\cdot]_*\) with subscript “*” to generically denote target population densities, the proposed target density of \((\Phi, X)\), for which \( S \perp Z \perp X \) by design, takes the form

\[
[\Phi = \varphi, X = x]_* = \alpha_s \beta_z f^*(x) = \delta_{\varphi} f^*(x) \\
= \delta_{\varphi} \lambda(x)f(x)/E[\lambda(X)], \quad \text{for } \varphi \in \Omega \text{ and } x \in \mathcal{X}.
\]

(4)

Let \( P_*[\cdot] \) denote target population probabilities; thus, \( P_*[\Phi = \varphi] = \delta_{\varphi} \). In the sequel, we compare the potential outcome of interest with respect to the new measure induced by (4). The measure uniquely identifies the target population and forms the basis of the target population densities and probabilities generically denoted by \([\cdot]_*\) and \( P_*[\cdot] \). Moreover, target population (4) is determined by tilting function \( \lambda \) and the vector of \( JK \) multifactor relative masses, \( \delta = \{\delta_{\varphi}\}_\Omega \). Each \((\delta, \lambda)\) consistent with the researcher-specified components of \( \alpha \) and \( \beta \) characterizes a distinct *admissible* target population.

Applications of the concordant target population typically set \( \beta \) equal to the known group proportions of the larger population of interest, e.g., racial decomposition of disease in the United States. By contrast, choices of the study proportions \( \alpha \) are usually related to the observational study designs rather than any tangible attributes of the larger population.

To provide realistic inferences, the study and group memberships are therefore constrained.
to be independent in expression (4). By contrast, naive applications of existing weighting methods in which the JK study-group combinations are designated as “treatments” do not satisfy this basic prerequisite.

**Generalized balancing weights** For a given target population identified by \((\delta, \lambda)\), we envision weights compensating for the differences in the source and target populations:

\[
w_\varphi(x) = \frac{[\Phi = \varphi, X = x]_\ast}{[\Phi = \varphi, X = x]} = \frac{\delta_\varphi \lambda(x)}{e_\varphi(x) E[\lambda(X)]}, \quad \varphi \in \Omega \text{ and } x \in X,
\]

applying (4), and since \([\Phi = \varphi, X = x] = e_\varphi(x)f(x)\). As \(w_\varphi(x)[\Phi = \varphi, X = x] = \frac{\delta_\varphi \lambda(x)}{e_\varphi(x)}\), these weights “rebalance” realizations from the source population so that they are distributed as the target population. We devise a set of *empirically normalized generalized balancing weights*, \(\bar{w}_1, \ldots, \bar{w}_N\), that have an empirical average of 1 and do not depend on the normalizing constant \(E[\lambda(X)]\). Specifically, writing \(\bar{w}_\varphi(x) = \delta_\varphi \lambda(x)/e_\varphi(x)\), we compute the normalized weight, \(\bar{w}_i = N\bar{w}_\varphi(x_i)/\sum_{l=1}^N \bar{w}_\varphi(x_l)\), of the \(i\)th subject, producing a weighted sample capable of providing accurate inferences about the target population, as we will discuss later.

**Large-sample covariate balance** The weights (5) are constructed to achieve theoretical balance in any target population with \(S \perp Z \perp X\). Theorem S1 of the Supplementary Material (Guha et al. 2022) establishes that, for each group, the empirically normalized weights also achieve approximate balance in the sample for large \(N\). However, the Section 4 simulation study reveals that some target populations are more successful than others at achieving balance in a finite sample.

As previously mentioned and noted later in Section 2.3 in single observational studies in which the natural population of interest consists of unequally distributed groups (e.g., minority races or race-gender combinations in cancer studies), some existing weighting
methods approaches may be imprecise and make biased comparisons. Furthermore, the
target populations of many techniques are designed to deliver precise asymptotic infer-
ences for specific types of outcomes and estimands. However, if the investigation involves
censored outcomes or a different set of post hoc endpoints, or if the underlying theoretical
assumptions are violated, then these methods are not guaranteed to be accurate, as noted
in Sections 4 and 5.

These drawbacks motivate the proposed concordant target population with its flexibility
to prespecify key aspects of the target population to resemble reality. In general, different
target populations identified by $\delta$ and $\lambda$ can be evaluated using their effective sample size
(ESS), $\mathcal{E}(\delta, \lambda) = N/[1 + \text{Var}\{w_{\Phi}(X)\}] = N/\mathbb{E}[w_{\Phi}^2(X)]$, where the moments are computed
for the source population. The ESS exists if the random generalized balancing weight,
$w_{\Phi}(X)$, has a finite second moment under the source population. The ESS represents the
number of hypothetical samples from the target population having the same information
as the $N$ samples from the source. It is asymptotically equivalent to the sample ESS,
$\hat{\mathcal{E}}(\hat{\delta}, \hat{\lambda}) = N^2/\sum_{i=1}^{n} \bar{\bar{w}}_i^2$.

Fundamentally deviating from focusing on particular weighted estimators of prespecified
estimands, we identify the concordant target population by the $(\tilde{\delta}, \tilde{\lambda})$ pair that maxi-
mizes the ESS; equivalently, minimizes the variances of the generalized balancing weights
themselves. In other words,
$$\mathcal{E}(\tilde{\delta}, \tilde{\lambda}) = \max_{\delta, \lambda} \mathcal{E}(\delta, \lambda),$$  \hspace{1cm} (6)

where the maximization is performed over all admissible (i.e., researcher-input compatible)
$\delta$ and all tilting functions $\lambda$. The simulation results and TCGA data analyses demonstrate
the practical advantages and high inferential accuracies achieved by this novel strategy,
which stabilizes the generalized balancing weights and is, therefore, agnostic to prespecified
estimands, predetermined weighted sample estimators, as well as outcome types.
2.2 Finding the concordant target population

Starting with an admissible vector of bifactor relative masses, denoted by $\delta_\psi$ in this description of the iterative procedure, the maximization consists of two steps:

- **Step I** Fixing relative masses $\delta_\psi$, maximize $\text{ESS} \ E(\delta_\psi, \lambda)$ over all tilting functions $\lambda$. The optimum solution is called the *omnibus target population*, and is identified by relative masses $\delta_\psi$ and maximizing tilting function $\psi_\delta$.

- **Step II** Fixing tilting function $\psi_\delta$, maximize $\text{ESS} \ E(\delta, \psi_\delta)$ over admissible $\delta$ to obtain the *optimized omnibus target population* identified by $\psi_\delta$ and relative masses $\delta_\psi$.

Steps I and II are iterated until convergence. Starting from several admissible $\delta$, the optimized omnibus target population with the largest ESS approximates the concordant target population, and is characterized by bifactor relative masses $\tilde{\delta}$ and tilting function $\psi_\delta$. We describe Steps I and II in detail below.

2.2.1 Step I

Under mild assumptions, the following result globally maximizes the ESS to prescribe the tilting function $\psi_\delta = \arg\max_{\lambda} \ E(\delta_\psi, \lambda)$ of the omnibus target population that corresponds to relative mass vector $\delta_\psi$. The theorem analytically identifies the nonparametric, closed-form global maximum of ESS for the conditional target density, paving the way for Step II to involve relatively straightforward parametric optimization.

**Theorem 2.1.** *Suppose the vector of JK bifactor relative masses, $\delta$, are strictly positive and held fixed. Let $\Xi_\delta$ be the set of tilting functions, $\lambda$, for which the random generalized balancing weight $w_\Phi(X)$, defined in (5), has a finite second moment under the source population. Maximizing the ESS $\mathcal{E}(\delta, \lambda)$ over all $\lambda \in \Xi$, the tilting function of the omnibus...*
target population is

$$
\psi_\delta(x) = \left( \sum_{s=1}^{J} \sum_{z=1}^{K} \delta_{z}^2 \phi_{s}(x) \right)^{-1}, \quad \text{for } x \in \mathcal{X}.
$$

The ESS of the omnibus target population equals $N \mathbb{E}[\psi_\delta(X)]$, which is strictly less than sample size $N$. Furthermore, the omnibus target population’s generalized balancing weights are uniformly bounded for $(\phi, x) \in \Omega \times \mathcal{X}$.

See the Supplementary Material (Guha et al. 2022) for a proof. For multiple studies and groups with unbalanced covariates, inverse probability weights are not necessarily bounded, and often result in significantly lower ESS and unreliable weighted inferences.

2.2.2 Step II

Finding the optimized omnibus target population corresponding to the tilting function $\psi_\delta$ involves straightforward parametric optimization constrained by the investigator input about probability vectors $\alpha$ and $\beta$. At one extreme, if the investigator exactly prespecifies the relative study weights $\alpha$ and racial group proportions $\beta$, then Step II and all further iterations are unnecessary because there is just one admissible $\delta$. On the other hand, if only the racial group proportions $\beta$ are prespecified, Step II optimizes over vector $\alpha$ belonging to the simplex $\mathcal{S}_J$. At the other extreme, if there is no investigator-supplied information about $\alpha$ or $\beta$, then unrestricted maximization occurs over $\mathcal{S}_J \times \mathcal{S}_K$. The multiparameter maximization can be performed in R using the optim function or applying the Gauss-Seidel, Jacobi, or other gradient-descent algorithms.

2.3 Practical relevance and interpretation

Our proposed new framework is general, encompassing as special cases several well-established weighting methods in single-study investigations ($J = 1$). Specifically, if the $K$ groups are equally prevalent and the source is covariate-balanced, so that $\beta_z = 1/K$ and $\phi_{s}(x) = 1/K$
Table 2: Multistudy, multigroup investigations under some special cases of the concordant target population using bifactor PS \( (1) \), specification \( (4) \), and omnibus tilting function \( (7) \); all the target populations assume equally distributed studies and groups for the bifactor relative masses, i.e., \( \alpha_s \beta_z = 1/JK \) for \( (s, z) \in \Omega \).

| Target population | Omnibus tilting function \( \psi_\delta(x) \) | Addition assumption |
|-------------------|------------------------------------------|---------------------|
| Combined          | 1                                        | \( e_\varphi(x) = 1/JK \) (balanced source) |
| Group \( z' \)    | \( e_{z'}(x) \)                           | \( e_{z'}(x) \approx 0 \) |
| Study \( s' \)    | \( e_{s'}(x) \)                           | \( e_{s'}(x) \approx 0 \) |
| Study \( s' \), Group \( z' \) | \( e_{s'z'}(x) \) | \( e_{s'z'}(x) \approx 0 \) |
| MGO               | \( (\sum_{s=1}^{J} \sum_{z=1}^{K} e^{-1}_\varphi(x))^{-1} \) | None |

for every \( z \) and \( \varphi \), then the optimal tilting function \( \psi_\delta(x) \) is constant, leading to inverse probability weights (e.g., Rosenbaum & Rubin 1983, Robins & Rotnitzky 1995) when \( K = 2 \) and generalized IPWs (Imbens 2000a) when \( K > 2 \). On the other hand, if the \( K \) groups are equally prevalent with unbalanced covariates, we obtain overlap weights (Li et al. 2018) when \( K = 2 \) and generalized overlap weights (Li & Li 2019) when \( K > 2 \). If the groups are equally prevalent and the PS of group \( z' \) is nearly 0 for all \( x \), the target population is the group \( z' \) subpopulation.

Column 2 of Table 2 presents the concordant tilting function \( \psi_\delta(x) \) for various theoretical conditions (column 3) that extend some existing weighting methods to multistudy and multigroup settings. Row 1 of Table 2 generalizes the ubiquitous (generalized) inverse probability weights to obtain the combined target population for which \( f^*(x) = f(x) \). Row 2 emphasizes the subpopulation with characteristics resembling the group \( z' \) subjects in study \( s' \). Row 5 extends overlap and generalized overlap weights to multistudy-multigroup settings, designating them as the multistudy generalized overlap (MGO) target population.

All the table entries correspond to a common bifactor relative mass of \( \delta_\varphi = 1/JK \) for each study-group combination \( \varphi \), i.e., equally weighted studies and target populations with no minority groups.
Figure 1: For two sets of propensity scores $e_{13}(x)$, $e_{21}(x)$, and $e_{23}(x)$, conditional ternary plots of the concordant tilting function in $J = 2$ studies with $\alpha_s = (0.331, 0.669)$ and $K = 3$ racial groups with $\beta_z = (0.310, 0.282, 0.408)$. See the text for further discussion.
For a vector of relative masses $\delta$, equation (7) shows that the tilting function $\psi_\delta(x)$ of concordant target population $(\delta, \psi_\delta)$ depends on $x$ only through the bifactor propensity scores $\{e_\varphi(x) : \varphi \in \Omega\}$ taking values in the simplex $S_{JK}$. Since it is difficult to display higher-dimensional simplexes, we utilize conditional ternary plots to visualize the optimal tilting function over three-dimensional compositional subspaces of $S_{JK}$. For example, consider an investigation with $J = 2$ studies with $\alpha_s = (0.331, 0.669)$, and $K = 3$ racial groups with $\beta_z = (0.310, 0.282, 0.408)$. The upper panel of Figure 1 displays a conditional ternary plot of $\psi_\delta(x)$ as a function of the propensity scores of study-group combinations $(1,1), (1,2), \text{and} (2,2)$, and conditions on the PS values, $(e_{13}(x), e_{21}(x), e_{23}(x))' = (0.050, 0.204, 0.655)'$. Vector variable $(e_{11}(x), e_{12}(x), e_{22}(x))'$ then belongs to the scaled simplex, $(1 - 0.909)S_3 = 0.091 S_3$, with each axis ranging from 0 to 0.091. The optimal tilting function apportions low importance to outlying regions of covariate space $X$ where $e_{11}(x), e_{12}(x), \text{or} e_{22}(x)$ are approximately 0, as corroborated by the blue margins around the plot edges. The optimal tilting function ranges between 0 and 0.328, with the maximum attained near $(e_{11}(x), e_{12}(x), e_{22}(x))' = (0.021, 0.042, 0.028)'$.

The lower panel of Figure 1 displays a conditional ternary plot for the same study-group combinations, but with the other propensity scores, $(e_{13}(x), e_{21}(x), e_{23}(x))'$ identical as the relative masses $(\alpha_1 \beta_3, \alpha_2 \beta_1, \alpha_2 \beta_3)' = (0.135, 0.273, 0.093)'$. Vector $(e_{11}(x), e_{12}(x), e_{22}(x))'$ then belongs to the scaled simplex $0.498 S_3$, and the optimal tilting function is found to achieve a maximum value of 1 at $(e_{11}(x), e_{12}(x), e_{22}(x))' = (0.103, 0.207, 0.189)'$.

To systematically investigate this and offer more insight, we present the following results which identify the covariate regions to which the concordant target population’s tilting function apportions the highest relative importance; the proof is in the Supplementary Material (Guha et al. 2022).

**Corollary 2.1.1.** Suppose the $JK$-vector of bifactor propensity scores, $e(x) = (e_\varphi(x) : \varphi \in \Omega)$, is a surjective (onto) function in the simplex $S_{JK}$ for $x \in X$. That is, for every $e \in S_{JK}$,
there exists an \( x' \in \mathcal{X} \) such that \( e(x') = e \). Let \( \Omega_0 \) be a (possibly empty) subset of the JK study-group indexes, so that \( \Omega_0 \subseteq \Omega \). Denote by \( \mathcal{X}_0^* \) the covariate vectors for which the PS of the study-group combinations in \( \Omega_0 \) are known and equal to \( \{ e^*_\varphi : \varphi \in \Omega_0 \} \). In other words, \( e^*_\varphi(x) = e^*_\varphi \) for all \( x \in \mathcal{X}_0^* \) and \( \varphi \in \Omega_0 \). Write \( \delta_0 = \sum_{\varphi \in \Omega_0} \delta_\varphi \) and \( e_0^* = \sum_{\varphi \in \Omega_0} e^*_\varphi \). If \( \Omega_0 \) is the empty set, define \( \mathcal{X}_0^* = \mathcal{X} \) and \( e_0^* = 0 \).

Then the supremum, over the covariate subspace \( \mathcal{X}_0^* \), of the tilting function of the concordant target population \( (\delta, \psi_\delta) \) is

\[
\sup_{x \in \mathcal{X}_0^*} \psi_\delta(x) = \left( \sum_{\varphi \in \Omega_0} \frac{\delta^2_\varphi}{e^*_\varphi} + \frac{(1 - \delta_0)^2}{(1 - e_0^*)} \right)^{-1}.
\]

The supremum is attained at an \( x' \in \mathcal{X}_0^* \) satisfying

\[
e^*_\varphi(x') = \begin{cases} 
\frac{1 - e_0^*}{1 - \delta_0} \alpha_s \beta_z & \text{if } \varphi \notin \Omega_0, \\
e^*_\varphi & \text{if } \varphi \in \Omega_0,
\end{cases}
\]

and the existence of \( x' \) is guaranteed by the surjectivity of the bifactor PS.

Figure 1 empirically illustrates these calculations for two instances of \( \Omega_0 \) consisting of three study-group combinations; however, Corollary 2.1.1 has wider applicability than ternary plots. In the lower panel of Figure 1 with \( \Omega_0 = \{(1,3), (2,1), (2,3)\} \) and \( e_0^* = \alpha_s \beta_z \) for \( \varphi \in \Omega_0 \), we have \( \delta_0 = e_0^* = \sum_{\varphi \in \Omega_0} e^*_\varphi \). Consequently, \( \sup_{x \in \mathcal{X}_0^*} \psi_\delta(x) = 1 \) is achieved at \( e^*_{\varphi}(x') = \alpha_s \beta_z \) for \( \varphi \notin \Omega_0 \), as seen in the lower ternary plot. In the upper panel, \( e_0^* = 0.909, \delta = 0.555, \) and \( \sum_{\varphi \in \Omega_0} \delta_\varphi^2/e^*_\varphi = 0.865 \). Therefore, \( \sup_{x \in \mathcal{X}_0^*} \psi_\delta(x) = 0.328 \), and the supremum occurs at \( e^*_{\varphi}(x') = \frac{1 - e_0^*}{1 - \delta_0} \alpha_s \beta_z \) for \( \varphi \notin \Omega_0 \), i.e., at \( e_{11}(x) = 0.021, e_{12}(x) = 0.042, \) and \( e_{22}(x) = 0.028 \), as observed in the figure.

Setting \( \Omega_0 = \emptyset \), Corollary 2.1.1 asserts that the global supremum of the concordant tilting function over \( \mathcal{X} \) is 1, and it is attained at \( x' \) for which the bifactor PS, \( e^*_{\varphi}(x') \),
equals the bifactor relative mass, \( \delta_\varphi = \alpha_s/\beta_z \), for all \( \varphi \in \Omega \). Informally, the optimal tilting function emphasizes covariate regions where the group propensities for the data are compatible ("concordant") with the group proportions in the larger natural population.

If the prevalences of the \( K \) groups are identical in the larger population, the tilting function should promote covariate subspaces where the group propensities are approximately equal. However, in investigations involving minority groups, this strategy may be suboptimal if it disregards key population aspects. This may explain why some generalized weighting methods listed in Table 2 are less precise in the simulation studies and TCGA meta-analysis compared to the concordant target population that assumes more realistic group proportions.

3 Survival Functions of Group-specific Outcomes

As commented below expression (4), we may define the survival function of \( T(z) \) in the target population as

\[
S^{(z)}_s(t) = P_s[T^{(z)} > t] \quad \text{for } t > 0 \text{ and } z = 1, \ldots, K, \tag{8}
\]

which informs the unconfounded comparisons across the \( K \) groups. We estimate these group-specific survival functions with right-censored responses. First, as previously noted, the realized outcome is related to the potential outcome as \( T = T^{(Z)} \). Analogously to the assumption of study-specific weak unconfoundedness (Assumption 1) for the source population in Section 2, we then make an identical assumption in the target population. That is, all full conditionals of the realized outcome \( T \) are identical in the source and target; for every \((s, z) \in \Omega \) and \( x \in X \), we have \([T \mid S = s, Z = z, X = x]_s = [T \mid S = s, Z = z, X = x]_* \). As before, \([\cdot]_*\) with subscript "∗" denotes target population densities.
Consequently, like the source population, simplifications such as \( [T|\Phi = \varphi, X = x]_* = [T|S = s, X = x]_* \), which is independent of group membership, are available for the target population. However, unlike the source population, the balanced target population guarantees that \( [T|Z = z]_* = [T(z)]_* \) as shown in the Supplementary Material (Guha et al. 2022).

For \( i = 1, \ldots, N \), denote the censoring time by \( C_i \), observed survival time by \( Y_i = \min\{T_i(Z_i), C_i\} \), and event indicator by \( \vartheta_i = \mathcal{I}(T_i(Z_i) \leq C_i) \). For the target population, using the empirically normalized generalized balancing weights, and extending the approaches of Kaplan & Meier (1958) and Xie & Liu (2005), we maximize pseudo-likelihood \( \mathcal{L}_z = \prod_{i:Z_i=z} \left\{ \left[ f_\ast^{(z)}(Y_i) \right]^{\vartheta_i} \left[ S_\ast^{(z)}(Y_i) \right]^{1-\vartheta_i} \right\}^{N\bar{w}_i} \), based only on subjects belonging to the \( z \)th group, and with \( f_\ast^{(z)}(t) \) representing the target population density corresponding to \( S_\ast^{(z)}(t) \). We refer to the nonparametric maximizer of \( \mathcal{L}_z \) as the balance-weighted Kaplan-Meier estimator (BKME) of target survival function \( S_\ast^{(z)}(t) \). From this perspective, since all \( N \) subjects have a weight of \( 1/N \) in the source (rather than target) population, we obtain the usual likelihood and product-limit estimator of Kaplan & Meier (1958) for the source survival function.

Suppose the observed failures of the \( N \) subjects, with possible ties, occur at the distinct times \( 0 < t_1 < \ldots < t_D \). For the \( z \)th group, using the empirically normalized generalized balancing weights, the weighted number of deaths and the weighted number of subjects at risk at time \( t_j \) are, respectively, \( d_j^{(z)} = N \sum_{i:Y_i=t_j,\vartheta_i=1} \bar{w}_i \mathcal{I}(Z_i = z) \) and \( R_j^{(z)} = N \sum_{i:Y_i \geq t_j} \bar{w}_i \mathcal{I}(Z_i = z) \), for \( j = 1, \ldots, D \). Assuming that the normalized balancing weights \( \bar{w}_1, \ldots, \bar{w}_N \) are known or equal to their estimated values, and maximizing pseudo-likelihood \( \mathcal{L}_z \), we obtain the BKME of the \( z \)th survival function (8) in the target population:

\[
\hat{S}_\ast^{(z)}(t) = \prod_{j:t_j \leq t} \left( 1 - \frac{d_j^{(z)}}{R_j^{(z)}} \right) \tag{9}
\]

Variance estimate \( \hat{\text{Var}}(\hat{S}_\ast^{(z)}(t)) = \left( \hat{S}_\ast^{(z)}(t) \right)^2 \prod_{j:t_j \leq t} \frac{d_j^{(z)}}{R_j^{(z)}(R_j^{(z)}-d_j^{(z)})} \) can then be applied to
compute pointwise confidence intervals.

Pseudo-likelihood function $L_z$ is isomorphic to the classical likelihood function of right-censored outcomes. So the maximizer $[9]$ and its variance estimate have similar forms as the corresponding quantities of the product-limit estimator, for which detailed arguments are given in Kaplan & Meier (1958). Intuitively, the $N$ subjects are assigned equal weights in the source population, but the weights are redistributed as $\bar{w}_1, \ldots, \bar{w}_N$ in the target population, resulting in adjusted numbers of deaths and subjects at risk. The BKME is the product-limit estimator using the weight-adjusted counts of the target population. Consequently, the BKME is consistent and asymptotic normal as an estimator of $S^*(t)$, and its variance estimate is also consistent (Fleming & Harrington 2011).

If some groups, such as White-minority races in cancer cohorts, are undersampled, large-sample inferences may not be valid for those groups. We could then apply nonparametric bootstrap methods (Efron & Tibshirani 1994) for estimating the standard error of estimator $[9]$ based on $B$ bootstrap samples of size $N$ each. Let $\hat{S}^{(z,b)}_x(t)$ be the BKME for the $b$th bootstrap sample, and let $\bar{S}^{(B)}_x(t) = \frac{1}{B} \sum_{b=1}^{B} \hat{S}^{(z,b)}_x(t)$. A bootstrap estimate of the BKME standard error is $s^{(B)}_x(t) = \left\{ \frac{1}{B-1} \sum_{b=1}^{B} (\hat{S}^{(z,b)}_x(t) - \bar{S}^{(B)}_x(t))^2 \right\}^{1/2}$. For fixed $N$, we have $s^{(B)}_x(t) \overset{p}{\to} \sqrt{\text{Var}(\hat{S}^*_x(t))}$ as $B \to \infty$. If $B$ is large, $S^{(B)}_x(t)$ and $s^{(B)}_x(t)$ can be used to construct 95% confidence intervals for $S^*_x(t)$. Alternatively, the 2.5th and 97.5th percentiles of $\hat{S}^{(z,1)}_x(t), \ldots, \hat{S}^{(z,B)}_x(t)$ give distribution-free 95% confidence intervals. Similarly, we could compute 95% confidence bands for the group-specific target survival functions.

4 Simulation Study

To examine the effectiveness of the proposed weighting strategy, we randomly generated and analyzed 1,000 multistudy datasets. Each dataset consisted of $J = 3$ observational studies, $p = 10$ covariates, and $N = 450$ subjects belonging to $K = 3$ groups. For each
study, the covariates were allowed to either opt out or be associated with the study-specific group memberships in a linear or non-linear manner. The studies, groups, covariates, and outcomes of the $N$ subjects were generated as follows:

1. **Study memberships**  Generate the study allocation probability vector, $\rho = (\rho_1, \ldots, \rho_J)$ from a symmetric Dirichlet distribution. For $i = 1, \ldots, N$, randomly allocate the $i$th subject to a study by independently sampling $S_i$ from the multinomial distribution with $J$ categories and probability vector $\rho$. That is, $P[S_i = s] = \rho_s$ for $s = 1, \ldots, J$.

2. **Covariates**  For the subjects belonging to the $s$th study and a study-specific mean $\mu_s \sim N_p(0, I_p)$, generate covariate vectors $x_i = (x_{i1}, \ldots, x_{ip})' \overset{i.i.d.}{\sim} N_p(\mu_s, I_p)$. Steps 1 and 2 induce unique study-specific PSs, $e_1(x_i), \ldots, e_J(x_i)$, and source covariate marginal density, $f(x_i)$.

3. **Group memberships**  For study $s = 1, \ldots, J$, we allow each covariate to be a predictor or non-predictor, and further, allow each predictor to have a linear or quadratic, positive or negative relationship with group membership. Specifically:

   (a) **Non-predictor, linear or non-linear covariate predictor:**  For the covariates indexed by $t = 1, \ldots, p$, independently generate an indicator variable, $\chi_{st}$, with values 0, 1, and 2, respectively signifying that the $t$th covariate is a non-predictor, linear predictor, and quadratic predictor, with $P[\chi_{st} = 0] = 0.5$, $P[\chi_{st} = 1] = 0.25$, and $P[\chi_{st} = 2] = 0.25$.

   (b) **Positive or negative association association:**  Designate the first group as the reference group. For the covariates indexed by $t = 1, \ldots, p$, independently generate a sign variable $\zeta_{stz} \in \{-1, +1\}$ with probability 0.5 for group $z = 2, \ldots, K$. The values $-1$ and $+1$ respectively indicate whether the conditional association with group membership is negative or positive for the $t$th covariate-predictor.
(c) **Simulation scenarios** Given similarity parameter $\omega$, compute the regression coefficient $\theta_{szt} = \omega(z - 1)\zeta_{stz}$ for non-reference groups $z = 2, \ldots, K$. We consider two scenarios: (i) *High similarity*: Setting $\omega = 0.005$ results in relatively similar covariate distributions for the $K$ groups, and (ii) *Low similarity*: Setting $\omega = 0.025$ results in dissimilar covariate distributions, with low propensities associated with one or more groups for some covariates.

(d) For the intercepts $\theta_{sz0}$ of the $K - 1 = 2$ non-reference groups, randomly sample without replacement from the set $\{0.5, 1\}$.

(e) For subjects $i$ belonging to study $s$ and group $z$, evaluate their linear predictor, $\eta_{isz} = \theta_{sz0} + \sum_{t=1}^{p} \theta_{szt} x_{it} \mathbb{I}(\chi_{st} = 1) + \sum_{t=1}^{p} \theta_{szt} x_{it}^2 \mathbb{I}(\chi_{st} = 2)$. Non-predictor covariates do not appear in this expression, whereas linear (non-linear) predictors appear exclusively in the second (third) additive term. Set $\eta_{is1} = 0$ for reference group $z = 1$.

(f) For the $N_s$ subjects belonging to study $s = 1, \ldots, J$, independently generate their groups $Z_i$ using the study-specific group PS: $e_{z|s}(x_i) = \exp(\eta_{isz})/\sum_{z'=1}^{K} \exp(\eta_{isz'})$, for $z = 1, \ldots, K$. For any study-group combination, using the study-specific PS $e_s(x_i)$ obtained in Step 2 we can evaluate the bifactor PS as $e_s(x_i) e_{z|s}(x_i)$.

4. **Observed survival times and event indicators**

(a) Let $X_s$ denote the covariate matrix of the $N_s$ subjects belonging to the $s$th study. For study $s = 1, \ldots, J$ and group $z = 1, \ldots, K$, generate regression vectors $v_{sz} = (v_{sz1}, \ldots, v_{szp}) \overset{\text{indep}}{\sim} N_p(0, \Sigma_s)$, where $\Sigma_s = 5N_s(X'_sX_s)^{-1}$.

(b) For subject $i = 1, \ldots, N$, generate the realized outcomes: $\log T_i^{(z_i)} \overset{\text{indep}}{\sim} (35 + v'_{iz_i} x_i, \tau_{iz_i}^2)$, with the study-specific error variances chosen so that the overall $R^2$ is approximately 0.9. Also, independently generate the censoring times,
\[ \log C_i \overset{\text{indep}}{\sim} N(37.5 + \mathbf{u}'_{s_i z_i} \mathbf{x}_i, \tau^2_{s_i}) , \] which results a censoring rate of 20\% to 30\% in each multistudy dataset.

For each dataset, the bifactor PS of the subjects were estimated by random forests (Breiman 2001). The estimated PS, \( \hat{\varphi}(\mathbf{x}_i) \), \( i = 1, \ldots, N \), was used for further computation.

As described in Section 2.2, we maximized the ESS to obtain the empirically normalized concordant weights \( \bar{w}_1, \ldots, \bar{w}_N \) for each dataset. Specifically, due to the absence of a larger natural population of interest in this example, the admissible values of bifactor \( \delta_{\varphi} \) belong to the unrestricted set \( S_J \times S_K \). The computational costs were insignificant because Theorem 2.1 gives the analytical form of the optimal weights in Step I of Section 2.2. The maximization in Step II was performed in R using the fast-converging \texttt{optim} function.

To examine whether the balance-weighted samples achieve approximate covariate balance, we computed the following sample averages for each target population: \( \bar{x}_{tsz} = \sum_{i=1}^{N} \bar{w}_i x_{it} \mathcal{I}(s_i = s, z_i = z) / \sum_{i=1}^{N} \bar{w}_i \mathcal{I}(s_i = s, z_i = z) \) for study \( s = 1, \ldots, J \), group \( z = 1, \ldots, K \), and covariate \( t = 1, \ldots, p \). With \( S^2_{tsz} \) denoting the \textit{unweighted} sample variance of the \( t \text{th} \) covariate and study-group combination \((s, z)\), the absolute standardized difference (ASD) was computed as
\[
\text{ASD} = \max \left\{ \frac{|\bar{x}_{tsz} - \bar{x}_{t's'z'}|}{\sqrt{S^2_{tsz} / N_{tsz} + S^2_{t's'z'} / N_{t's'}}} : 1 \leq t \leq p, 1 \leq s, s' \leq J, 1 \leq z, z' \leq K \right\} .
\]
A small ASD is evidence that a weighting method achieves a high level of covariate balance.

For comparison, we computed the ASDs for the crude (unweighted) sample and the combined and MGO target populations introduced earlier in Table 2. The upper panel of Figure 2 displays the boxplot of ASD for the 1,000 datasets in the more challenging “low similarity” scenario. The results for the “high similarity” scenario were better, as expected, but qualitatively similar. Irrespective of the simulation scenario, the concordant and MGO target populations achieved comparable and systematically smaller ASD values than the combined population. Overall, the weighting methods displayed significantly better covari-
Figure 2: For the 1,000 artificial datasets in the “low overlap” simulation scenario, side-by-side boxplots of the absolute standardized differences (upper panel) and percent ESS (lower panel) for the crude (i.e., unadjusted), combined, MGO, and concordant target populations. The concordant population’s median ESS was the highest with an interquartile range of only 0.5%. The results for the “high overlap” scenario were qualitatively similar and are not shown.
ate balance than crude analyses, with the percent relative reductions in median ASD of the concordant, MGO, and combined weights equal to 20%, 17%, and 10%, respectively.

We compared the weighting procedures based on their percent ESS, defined as the effective sample size for 100 subjects. The lower panel of Figure 2 presents side-by-side boxplots for the combined, MGO, and concordant target populations in the low similarity scenario. Unsurprisingly, all the methods had larger ESS in the high similarity scenario, which is not shown in the figures. The MGO and combined target populations had a median ESS of 20.5% and 23.7% respectively. The concordant target population outperformed the other methods, as anticipated by Theorem 2.1, with a significantly higher median ESS of 46.3% corresponding to 208.5 subjects. Additionally, the concordant ESS was remarkably stable over the 1,000 artificial datasets with an interquartile range of just 0.5 percentage points, compared to 7.9 and 10.8 percentage points for the ESS of MGO and combined target populations. The MGO and combined weights corresponded to 92.2 and 106.5 median effective number of subjects, respectively, suggesting relatively imprecise downstream inferences for several estimands, as we observe below.

For the $K = 3$ groups, we estimated the survival curves $S^*_z$ for each target population, defined as in (8), using the BKME $\hat{S}_z$ defined in (9). We made inferences about various features of the survival times for the three sets of generalized balancing weights. Since the target population features vary with the weighting scheme, we evaluated the accuracy of each estimator with respective to its own target estimand computed by Monte Carlo methods. For the 1,000 simulated datasets of the low similarity scenario, Table 3 displays the RMSEs and absolute biases of unconfounded estimates of various percentiles of the failure times, as well as 2-year and 3-year survival probability percentages of the three groups of subjects. For every estimand, represented by a table row, the target population with the lowest RMSE and lowest absolute bias is marked in bold. We find that the concordant target population typically delivers the best performance with respect to both metrics, often
Table 3: For the **low similarity** simulation scenario, estimated RMSEs and absolute biases of various survival time features in different target populations. For each group-specific estimand (row), the best weighting scheme (column) is marked in bold.

| Group (z) | Combined | MGO | Concordant | Combined | MGO | Concordant |
|-----------|----------|-----|------------|----------|-----|------------|
|           | **RMSE** |     | **Absolute bias** |          |     |            |
|           | Median Survival Time |     |            |          |     |            |
| 1         | 1.536    | 1.729 | **1.495** | 0.159    | 0.241 | 0.206      |
| 2         | 1.459    | 1.590 | **0.941** | 0.010    | 0.057 | 0.032      |
| 3         | 1.583    | 1.621 | **0.890** | 0.044    | 0.029 | 0.078      |
|           | **Lower Quartile Survival Time** |     |            |          |     |            |
| 1         | **1.302**| 1.542 | 1.340      | 0.103    | **0.009** | 0.123      |
| 2         | 1.975    | 1.849 | **1.046** | 0.082    | 0.140 | **0.003**  |
| 3         | 2.067    | 1.994 | **1.025** | 0.131    | 0.307 | **0.074**  |
|           | **Upper Quartile Survival Time** |     |            |          |     |            |
| 1         | **2.047**| 2.309 | 2.295      | **0.201**| 0.190 | 0.192      |
| 2         | 1.452    | 1.547 | **1.246** | 0.143    | 0.165 | **0.058**  |
| 3         | 1.860    | 2.038 | **0.962** | 0.277    | 0.391 | **0.010**  |
|           | **2-year survival probability %** |     |            |          |     |            |
| 1         | 0.396    | 0.346 | **0.034**  | 0.002    | 0.018 | **0.001**  |
| 2         | 5.116    | 4.501 | **2.001**  | **0.034**| 0.057 | 0.063      |
| 3         | 6.277    | 5.919 | **3.293**  | 0.400    | 0.406 | **0.133**  |
|           | **3-year survival probability %** |     |            |          |     |            |
| 1         | 8.927    | 10.482| **7.927**  | **0.511**| 0.684 | 0.577      |
| 2         | 9.603    | 10.312| **7.357**  | 0.287    | 0.090 | **0.024**  |
| 3         | 8.271    | 8.616 | **5.941**  | 0.725    | 0.888 | **0.155**  |
outperforming the MGO and combined target populations. The results for the “high similarity” scenario, which are omitted in the interest of space, revealed even greater benefits for the concordant target population due to the greater between-group resemblances of the covariates. The simulation results demonstrate the practical advantages of the concordant weighting strategy, which stabilizes the generalized balancing weights themselves instead of optimizing specific types of weighted estimators of predetermined estimands.

5 Analysis of the glioblastoma multiforme multistudy data

We made descriptive comparisons of overall survival (OS) of three racial groups by meta-analyzing the four glioblastoma multiforme (GBM) TCGA datasets, discussed in Section 1. The relative proportions of Asian, Black, and White GBM patients in the United States are 4%, 10%, and 86% respectively (Ostrom et al. 2018). Compared to the US population, Black and Asian patients were underrepresented in most of the TCGA datasets. An effective method for unconfounded descriptive comparisons must account for this deficiency while adjusting for confounders such as clinical, demographic, and biomarker variables. However, the combined population, an extension of the ubiquitous inverse probability weights, assumes a hypothetical target population with equally weighted studies and racial groups, i.e., 33.3% Asian, Black, and White patients, and so does not resemble important aspects of the US population relevant to detecting racial disparities. The same is true of the extensions of other existing weighting methods in rows 1-5 of Table 2. By contrast, the concordant target population utilized in this analysis guarantees relative weights of 4%, 10%, and 86% in conformity with the racial prevalence of GBM cases in the United States. The percent ESS of the combined population was 18.0% or about 61 patients. The relatively small ESS, and the implausible assumption of a target population with no racial minorities, call into
question the validity of inferences about racial disparities using the combined population.

Starting with arbitrary study weights $\alpha$ for the four TCGA studies, and fixing the vector of racial proportions $\beta$ equal to the US population values of 4%, 10%, and 86% for GBM patients, we estimated the concordant target population as described in Section 2.2. Compared to the combined population, the concordant population had a higher ESS of 45.5% or about 155 patients, suggesting that its inferences may be more reliable for a wide variety of target population features. The optimal amounts of aggregated information, $\hat{\alpha}$, from the MD Anderson Cancer Center, Henry Ford Hospital, Emory University, and Case Western Reserve University datasets were estimated to be 12%, 79%, 5%, and 4%, respectively; these values were not proportional to the study sizes. By contrast, the study weights are fixed at 25% by the combined target population.

Finally, the survival functions of the failure times of the $K = 3$ races (Whites, Blacks, and Asians) were estimated for the concordant target population as follows. The patient deaths occurred, with occasional ties, at $5 = t_1 < \ldots < t_D = 3,667$ days for $D = 241$ distinct time points. For the $z$th racial group, $z = 1, 2, 3$, and using the empirically normalized concordant weights, the weighted number of deaths, $d_j^{(z)}$, and the weighted number of subjects at risk, $R_j^{(z)}$, were evaluated for $j = 1, \ldots, D$. The balance-weighted Kaplan-Meier estimator (BKME) of equation (9) was evaluated using these quantities. Due to the relatively small number of Black and Asian patients in the four TCGA studies, uncertainty estimation was performed using $B = 1,000$ bootstrap samples. A similar analysis was conducted for the combined target population.

Figures 3A–3C respectively present comparisons of cancer survival between White, Black and Asian GBM patients for the crude (naive) analysis, combined target population, and concordant target population. The crude and combined target populations reached qualitatively similar conclusions that Whites experience the worst outcomes, Blacks have the best prognoses for high overall survival (OS), and Asians have a median OS of 705
Figure 3: For the TCGA glioblastoma multiforme patients, estimated overall survival (OS) curves and median OS (vertical dashed lines) for Whites (blue dotted lines), Blacks (green dashed lines), and Asians (red solid lines) in the crude, combined, and proposed concordant target populations.

days. However, the proposed concordant target population revealed a drastically different situation: Blacks are more vulnerable and endure significantly worse prognoses for low to middle OS; Asians almost uniformly (except for high OS) have the best outcomes with median OS of 1,024 days, compared to 384 and 329 days for Whites and Blacks, respectively. The respective standard errors for Asians, Whites, and Blacks were 15.2 days, 1.2 days, and 19.7 days for the concordant target population.

Table 4 displays the race-specific lower quartile and median OS by the three methods. The numbers demonstrate that the concordant target population detected significantly poorer prognoses for low to middle OS in Black patients compared to Whites and Asians. On the other hand, the crude analysis did not find any significant differences in the lower quartile or median OS of Blacks versus Whites, whereas the combined population found significantly better outcomes for Blacks relative to Whites. Furthermore, comparing the concordant and combined populations, the median OS was significantly smaller for Blacks, significantly larger for Asians, and not significantly different for Whites. Comparing the concordant and combined populations, the lower quartile OS was significantly smaller for Blacks, not significantly different for Asians, and significantly larger for Whites.

Despite being considerably different from the competing methods in important aspects,
Table 4: Lower quartile and median OS of Whites, Blacks, and Asians for the crude analysis, combined target population, and concordant target population in the glioblastoma multiforme TCGA datasets. Shown in parentheses are the estimated standard errors.

| Method     | Blacks   | Whites   | Asians   |
|------------|----------|----------|----------|
| **Crude**  |          |          |          |
| Lower Quartile OS (days) |          |          |          |
| Blacks     | 121 (2.6)| 178 (0.7)| 476 (7.8)|
| Whites     | 202 (4.3)| 167 (1.6)| 476 (9.2)|
| Asians     | 82 (5.0) | 199 (1.5)| 506 (14.2)|
| Median OS (days) |          |          |          |
| Blacks     | 384 (12.1)| 377 (0.6)| 705 (12.1)|
| Whites     | 460 (20.2)| 383 (1.5)| 705 (13.2)|
| Asians     | 329 (19.7)| 384 (1.2)| 1,024 (15.2)|

the findings of the concordant target population are indeed more plausible. For example, the detected disparities in Figure 3C can be partially explained by race-related disadvantages in health utilization due to socioeconomic status (SES) (Cook et al. 2009, Nguyen et al. 2020). Although the TCGA data provide limited information about SES, the U.S. Census Bureau found the median household income of Asians in 2021 to be the highest, followed by Whites (Census 2021). This crucial SES measure is consistent with the order of the outcomes in the concordant, but not the crude or combined target population, and Figure 3C is the most credible scenario from this perspective. Additionally, the implicit premise of the combined target population that there are no racial minorities challenges the real world validity of its conclusions about health disparities. These analyses reveal the importance of incorporating realistic study population attributes and appropriately adjusting for confounders to gain clearer insight into racial differences. In turn, this facilitates the proper allocation of resources to achieve more equitable cancer outcomes. An R package for implementing the proposed method is available on GitHub.
6 Discussion

Inherent differences in subject characteristics over multiple groups and observational studies make it challenging to meta-analyze databases while compensating for any over- or under-sampled groups. This paper optimizes a general class of balancing weights to obtain a new weighting strategy for theoretical and asymptotic covariate balance, termed the concordant target population. Distinguished from some existing weighting methods that focus on the properties of weighted estimators of specific estimands, the concordant target population directly optimizes the stability of the generalized balancing weights by way of the ESS, thereby achieving a “response-free design” that disregards specific types of estimands, estimators, outcomes types, and censoring mechanisms. The strategy achieves high inferential accuracy for right-censored outcomes and various estimands of the survival times while flexibly accommodating known characteristics of the natural cohort of interest. This feature makes our method an appealing alternative to existing weighting methods by allowing investigators to efficiently analyze observational studies that accommodate wide-ranging outcomes and even unplanned estimands for group comparisons.

The proposed method globally maximizes the ESS conditional on a few parameters of the target population density; consequently, the remaining step of the iterative procedure performs fast-converging optimization of those parameters with negligible computational costs to identify the concordant population. Simulation results and analyses of TCGA cancer databases demonstrate the success of the technique compared to established weighting approaches for unconfounded group comparisons.

Routinely collected information, especially in retrospective studies, increasingly features high dimensional subject-specific attributes such as demographic, socioeconomic, dietary, clinicopathological, and biomarker measurements. Similarly to existing weighting approaches, the proposed methodology is challenged by the problem of effectively incorpo-
rating large numbers of covariates and of highlighting the complex interplay between the
different studies, multiple groups of subjects, individual attributes, and various outcomes.
These important issues will motivate future extensions of the proposed methodology.

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