Regression inference for multiple populations by integrating summary-level data using stacked imputations

Tian Gu*, Jeremy M.G. Taylor, and Bhramar Mukherjee

Department of Biostatistics, University of Michigan, Ann Arbor, U.S.A

*email: gutian@umich.edu

Summary: There is a growing need for flexible general frameworks that integrate individual-level data with external summary information for improved statistical inference. External information relevant for a risk prediction model may come in multiple forms, through regression coefficient estimates or predicted values of the outcome models. Different external models may use different sets of predictors and the algorithm they used to predict the outcome Y given these variables may or may not be known. The underlying populations corresponding to each external model may be different and they may differ from the internal study population. This paper proposes an imputation-based methodology where the goal is to fit an outcome regression model with all available variables in the internal study while utilizing summary information from external models that may have used only a subset of the predictors. The method allows for heterogeneity of covariate effects across the external populations. The proposed approach generates synthetic outcome data in each population, uses stacked multiple imputation to create a long dataset with complete covariate information, and finally analyzes the imputed data with weighted regression. This flexible and unified approach attains the following four objectives: (i) incorporating supplementary information from a broad class of externally fitted predictive models or established risk calculators which could be based on parametric regression or machine learning methods, as long as the external model can generate outcome values given covariates; (ii) improving statistical efficiency of the estimated coefficients in the internal study; (iii) improving predictions by utilizing even partial information available from models that uses a subset of the full set of covariates used in the internal study; and (iv) providing valid statistical inference for the external population with potentially different covariate effects from the internal population. Applications include prostate cancer risk prediction models using novel biomarkers that are measured only in the internal study.

Key words: Data integration; Prediction models; Synthetic data; Stacked multiple imputation.
1. Introduction

Increasingly, researchers are considering incorporating external information from large-scale studies to improve statistical inference rather than using the limited-sized data that are available to each investigator. It is often easier to have access to the summary information rather than the individual-level data due to restrictions on data privacy and sharing. Therefore, more and more emphasis has been devoted to developing general frameworks that integrate the individual-level data and the summary-level external information in a principled manner. We consider a regression model for the outcome on all available covariates measured in the internal study, while using information from multiple external data sources, which Evans et al. (2018) refer to as the regression analysis for data fusion.

Recent studies on this topic begin with incorporating external auxiliary information from large data, such as census or population-based biobank data, to improve the statistical inference of the internal study, assuming the model that relates the variables is fully/partially shared between data sources, also known as transportability (Bareinboim and Pearl, 2013). Qin (2000); Han and Lawless (2019) proposed possible solutions using empirical likelihood, Chatterjee et al. (2016) demonstrated it from the perspective of constrained maximal likelihood while Gu, Taylor, and Mukherjee (2019) utilized the idea from survey methodology to convert the external information into synthetic data. Estes, Mukherjee, and Taylor (2017) then relaxed the transportability assumption of Chatterjee et al. (2016)’s by constructing an empirical Bayes estimator that protected against the potential bias.

Later, several studies have expanded the initial problem of incorporating summary-level information from a single external data source to multiple external data sources. Kundu, Tang, and Chatterjee (2019) built upon the work of Chatterjee et al. (2016) to a meta-analysis setting while Gu, Taylor, and Mukherjee (2021) extended the work of Estes et al. (2017) by adaptively weighting multiple empirical Bayes estimators.
One challenge is to accommodate the heterogeneity among different data sources, ignoring which would lead to potential estimation bias and misleading inference during data integration. Efforts have been made to address this issue. The framework proposed by Gu et al. (2021) assigns larger weights to the more compatible external data sources to incorporate valid supplementary information into the internal study. Chen et al. (2020) used a penalty function to identify the difference of aggregate information among data sources. Yang and Ding (2020) employed a sensitivity parameter to quantify such systematic differences. Moreover, there could be other sources of information variation across the models. For example, different external studies may use different subset of covariates and the underlying prediction model may be parametric or constructed by machine learning approaches. The summary-level information may contain estimated regression coefficients or fitted predictions.

Although some of the existing approaches have considered the heterogeneity across data sources, the main focus has been on improving the statistical efficiency of the internal/main dataset with little attempts to make statistical inference on external populations or allowing heterogeneous covariate effect across data sources. Wang, Wang, and Song (2012) proposed a joint estimating procedure to merge longitudinal datasets while allowing different study-specific coefficients. The meta-analysis approach proposed by Kundu, Tang, and Chatterjee (2019) used generalized method of moments to estimate study-specific effects but only allows covariates that were measured in at least one of the external studies. Antonelli, Zigler, and Dominici (2017) proposed a unified Bayesian imputation framework built upon the work by Wang, Parmigiani, and Dominici (2012), taking into account the prior odds of including a predictor in the outcome model given that it is in the exposure model, and allowing heterogeneous treatment effects by positing different population indicators in the outcome model.

In this study, we consider the situation where moderately sized individual data is available
from the internal study, and there are $K$ populations ($K \geq 1$), each of which provides some information about the relationship between the same outcome and a slightly different set of predictors. We propose an imputation-based methodology where the goal is to fit an outcome regression model with all available variables in the internal study while utilizing summary information from external models that may have used only a subset of the predictors. The method allows for heterogeneity of covariate effects across the external populations, by first generating synthetic outcome data in each population, then using stacked multiple imputation to create a long dataset with complete covariate information, and finally analyzing the imputed data with weighted regression. This flexible and unified approach attains the following four objectives: (i) incorporating supplementary information from a broad class of externally fitted predictive models or established risk calculators based on parametric regression or machine learning methods, as long as the external model can generate outcome values given covariates; (ii) improving statistical efficiency of the estimated coefficients in the internal study; (iii) improving predictions by utilizing even partial information available from prediction models that uses a subset of the full set of covariates used in the internal study; and (iv) providing valid statistical inference for the external population with potentially different covariate effects from the internal population.

The rest of the paper is organized as follows: In Section 2, we introduce the proposed methodology. In Section 3, we evaluate the performance of our proposed approach in a simulation study. In Section 4, we apply the proposed strategy to a data example, where we build an expanded risk model to predict high-grade prostate cancer borrowing information from two existing risk prediction models. Concluding remarks are presented in Section 5.
2. Models and Methods

2.1 Notation

Let \( Y \) denote the outcome variable of interest, either continuous or binary. Consider \( X \) a set of \( P \) routinely measured variables and \( B \) a set of \( Q \) new variables, e.g., newly discovered biomarkers, where \( B \) is only available in the internal study (i.e., \( B \) are unmeasured variables in all of the external studies). Let \( S_k, k=0,...,K, \) denote the indicators of the \( K+1 \) study populations, where \( S_0 \) represents the internal population and \( S_k \)'s represents the \( K \) external populations.

We discuss the problem under the assumption that \( Y|X, B \) is linear in \( X \) and \( B \). We assume that a moderate dataset of size \( n \) with complete variables \( Y, X \) and \( B \) is available to us from the internal study. For each external population \( k \geq 1 \), a well-established reduced model for the same outcome \( Y \) is also available, each of which may use a slightly different set of predictors \( X_k \), a subset of \( X \). For example, if linear regression is used, the prediction model may look like: 

\[
E(Y|X_k) = X_k \beta_k = \beta_0 + \sum_{p=1}^{P_k} \beta_p X_p,
\]

where \( P_k \leq P \) is the dimension of \( X_k \). We do not have access to the underlying individual-level data that was used to fit the external model but only the summary information. This summary information can come in different forms that we summarize into two categories:

**Category 1:** Directly available in the form of an externally fitted parametric regression model, along with the estimated model parameters \( \hat{\beta}_k \);

**Category 2:** Any parametric or non-parametric models without knowing the exact form e.g. established risk calculators that provide the risk probability \( P(Y = 1|X_k) \), for any \( X_k \).

The target model of interest \( Y|X, B, S \) is a generalized linear model (GLM):

\[
g[E(Y|X, B, S)] = \gamma_{S_0} + \sum_{k=1}^{K} \gamma_{S_k} S_k + \sum_{p=1}^{P} \gamma_{X_p} S_0 X_p + \sum_{k=1}^{K} \sum_{p=1}^{P} \gamma_{X_p S_k} S_k X_p + \sum_{q=1}^{Q} \gamma_{B_q} S_0 B_q, \tag{1}
\]

where \( g \) is a known link function. Model 1 is the general form of the target model as it is
a saturated model allowing all intercept and X covariates to differ across populations. In practice, we would force some $\gamma_{S_k}$ and/or $\gamma_{X_p}$ to be zero based on prior knowledge. We assume that the distribution of $Y|X, B, S$ is correctly specified, which indicates that each external population can potentially differ in intercept and X covariate effect as long as those X’s were used in the external model, while for covariates that are unmeasured in the $k^{th}$ model, we assume the covariate effects are the same as the internal study. A special case of model 1 is a logistic regression model that only allows intercept differences among populations, which represents different prevalence and the same covariate effect in each population:

$$logit[\Pr(Y = 1|X, B, S)] = \gamma_{S_0} + \sum_{k=1}^{K} \gamma_{S_k} S_k + \sum_{p=1}^{P} \gamma_{X_p} X_p + \sum_{q=1}^{Q} \gamma_{B_q} B_q.$$  \hspace{1cm} (2)

We assume that the external models $Y|X_k$’s are the best-fitted models in the class of the reduced models that was considered, but this class of reduced models may not contain the true distribution of $Y|X_k$. One such example is when the full model is the logistic model shown in equation 2, but the true distribution for $Y|X_k$’s are not logistic models as collapsibility does not hold for the logit link. We consider the fitted logistic model as the best-fitted model in the class.

2.2 Proposed Data Integration and Analysis Strategy

Figure 1 illustrates the proposed five-step strategy, along with the required assumptions in each step. We will first briefly introduce the steps and then expand upon the details.

- **Step 1**: Convert each external summary-level information into a set of synthetic data according to Gu et al. (2019) and append each of the synthetic data sets to the internal data, from which we create a longer dataset as illustrated in Figure 1. The synthetic data for external study $k$ constitutes of observed $X_k$ and the simulated value of $Y$. Unmeasured variables in the external populations (all $B$ and some $X$’s) will be treated as missing data. For example, since the external study $S=1$ used $X_1$ and $X_2$ to predict $Y$, we first replicate the observed $(X_1, X_2)$ in $S=0$ a large number of times (see details of the replication number
in the following descriptive paragraph for step 1); we then utilize the summary information $Y|X_1, X_2$ from external model 1 to generate the synthetic $\hat{Y}^{S=1}$ values given $X_1$ and $X_2$; and lastly, the unmeasured variables $X_3$ and $B$ will remain missing (Figure 1). Similarly for the external study $S=2$, we replicate the observed $(X_1, X_3)$, and create synthetic $\hat{Y}^{S=2}$ values. The combined dataset is of size $N \times (P+Q+1)$.

- **Steps 2-3:** For the combined dataset created in step 1, multiply impute the missing covariates ignoring the outcome $Y$ through multiple imputation by chained equation (MICE) to create $M$ complete datasets, and then stack these $M$ datasets to create a stacked dataset. These two steps are identical to step 1-2 of the stacked imputation approach proposed by Beesley and Taylor (2020). The stacked dataset is of size $MN \times (P+Q+1)$.

- **Step 4:** Calculate weights for each row of the stacked dataset with the weights proportional to the target model distribution $f(Y|X, B, S)$. Note that all weights need to be re-scaled to 1 within individuals in the stacked dataset. Initial parameter estimates are needed for each population as discussed in subsequent paragraphs.

- **Step 5:** Estimate the parameter $\gamma$ of the target model 1 through a weighted GLM using the stacked dataset. The estimated variance of $\gamma$ can be obtained numerically through bootstrap or analytically through several existing estimators, such as the Louis information estimator or the Jackknife estimator (Beesley and Taylor, 2020, 2021).

[Figure 1 about here.]

Step 1 converts the original problem to regression modeling with missing data using a combined dataset of the internal and the synthetic data. Gu et al. (2019) provided theoretical justification in special cases to show that the synthetic data method is equivalent to a constrained semi-parametric maximum likelihood approach proposed by Chatterjee et al. (2016), and it assumed the external models were the best-fitted models in the class, but the class may not contain the true distribution (Assumption 1). In finite sample size, the
larger the number of replicates in each synthetic dataset (denoted as $r_k$ in Figure 1), the more precision gain in the estimated coefficient of $X$; when $r_k$ goes to infinity, the precision gain by incorporating external information will converge to a constant (Gu et al., 2019). In practice, it is reasonable to set the synthetic data size, i.e., $n \times r_k$, similar to the external study’s actual study size. We will assess the performance of the proposed strategy by varying the number of replicates in the simulations described in Section 3.

To implement steps 2 and 3, we require some quantities to be shared across populations, since the missing covariates are completely unobserved in one population, also known as block-wise missing structure. Assumption 2 contains two parts: (i) $X_{\text{miss}} \perp \perp S|X_{\text{obs}}$; and (ii) $B \perp \perp S|X$. These two assumptions imply that the conditional distribution of the missing covariates conditional on the observed covariates is the same across populations, and thus observed information can be shared across populations to impute missing covariate information. Therefore, the imputation models are $f(X_{\text{miss}}|X_{\text{obs}})$ and $f(B|X)$ for missing $X$ and missing $B$, respectively (e.g. $X_{\text{miss}} = [X_2, X_3]$ and $X_{\text{obs}} = X_1$ in Figure 1). The missing at random (MAR) assumption required by MICE is naturally satisfied as we have designed missingness, i.e., missing covariates are completely unobserved due to not being collected in the study, which is by design not related to the missing observations.

In step 4, initial parameter estimates, $\hat{\gamma}_0$ for the internal population and $\hat{\gamma}_k$’s for the external populations, are needed to calculate weights that are proportional to $f(Y|X, B, S)$. For the internal population $S=0$, we replace $f(Y|X, B, S = 0)$ with $f(Y|X, B, S = 0; \hat{\gamma}_0)$, where $\hat{\gamma}_0$ is the internal-data-only estimates fitted on model 1. For external populations $S=k$, $\hat{\gamma}_k$ from model $f(Y|X, B, S = k; \hat{\gamma}_k)$ is not directly available since we only have the summary information on the reduced model $Y|X_k; \hat{\beta}_k$. As described in Section 2.1, the summary information will be available in the form of either parameter estimates $\hat{\beta}_k$ (Category 1) or a risk calculator of unknown form that has the ability to estimate the probability of $Y=1$
given $X_k$ (Category 2). In the case of Category 1, we propose to derive the initial estimates
$\hat{\gamma}_k = (\hat{\gamma}_{0k}^S, \hat{\gamma}_{Xk}^k, \hat{\gamma}_{0B}^S)^T$, where $\hat{\gamma}_{0k}^S$ and $\hat{\gamma}_{Xk}^k$ are bias-corrected estimates of intercept and
$X$ coefficients from $\hat{\beta}_k$ according to Neuhaus and Jewell (1993) while $\hat{\gamma}_{0B}^S$ are estimated coefficients of $B$ using only the internal data. Assumption 2 is used again in this step, e.g.,
$E(B|X, S = 0) = E(B|X)$, so that we use the internal data to estimate the mean profile of
$B|X$ in the external populations (see Appendix for details). In the case of Category 2 where
$\hat{\beta}_k$ does not exist, we follow the same procedure as in Category 1 but use $\hat{\beta}_k^{\text{synthetic}}$ instead.
Specifically, we first create a large size of synthetic data $(\hat{Y}_{S=k}^S, X_k^{\text{synthetic}})$ as described in
Step 1, and then we fit a GLM $\hat{Y}_{S=k}^S|X_k^{\text{synthetic}}$ with main effect using only the synthetic data
and ignoring the missing data, from which we obtain $\hat{\beta}_k^{\text{synthetic}}$. Note that this main-effect
GLM is mis-specified but the best linear model in the class. Further assessment can be found
in simulation II of Section 3.

Step 4 extends Beesley and Taylor (2020) to allow multiple populations with potentially
different covariate effects in the target model. Beesley and Taylor (2020) reduces to a special
homogeneous-population case of ours when all $S$ equals to zero. In summary, we assign
weights $w_{im} = \frac{f(Y_i|X_{im}, B_{im}, S=k; \hat{\gamma}_k)}{\sum_{j=1}^{M} f(Y_i|X_{ij}, B_{ij}, S=k; \hat{\gamma}_k)}$ to each observation $i$ in the $m$th imputed dataset, where
$m \in \{1, ..., M\}$ and $k \in \{0, ..., K\}$. For internal observations, $w_{im} = \frac{f(Y_i|X_{im}, B_{im}, S=0; \hat{\gamma}_0]}{M \cdot f(Y_i|X_{im}, B_{im}, S=0; \hat{\gamma}_0]} = \frac{1}{M}$.

As mentioned in Section 2.1, step 5 assumes that the target outcome model is linear
and is correctly specified (Assumption 3). After obtaining the point estimates $\hat{\gamma}$ by fitting
the weighted GLM, several variance estimators are available to measure the variation of $\hat{\gamma}$.
Beesley and Taylor (2020, 2021) proposed three variance estimators including a bootstrap estimator by resampling the imputed datasets in step 2 and repeating steps 3-5. We propose
a new bootstrap procedure by resampling the internal data and repeating all the steps 1-5, which is more computationally intense but empirically we find it gives more accurate
estimation of the variance. We assess the performance of different variance estimators in simulations in Section 3.

3. Simulation Studies

Although our proposed approach can handle any target model that belongs to the class of GLM, we focus on a binary outcome and logistic regression to evaluate the performance of the proposed approach and comparison methods. In all scenarios, the internal data is of size 200, while we vary the synthetic data size from one times the internal data size (i.e., $r_1 = r_2 = 1$ and $N=n^*[1 + r_1 + r_2]=600$) to 10 times (i.e., $r_1 = r_2 = 10$ and $N=n^*[1 + r_1 + r_2]=4,200$) for each external population. We implement four methods, where method (1) is the benchmark, method (2) is the proposed approach, and methods (3) and (4) are two common approaches to analyze the combined dataset created in step 1 of Section 2.2:

(1) Internal data only: fit the target model on the internal data $S=0$ only, without incorporating external information;

(2) Proposed method: we implement it through MICE in R software. For example, in Figure 1 step 1, the imputation models for $X_2$, $X_3$ and B are $(X_2|X_1, X_3, B)$, $(X_3|X_1, X_2, B)$, and $(B|X_1, X_2, X_3)$, respectively. Weights are calculated after imputation;

(3) FCS: imputation through fully conditionally specification (FCS) by specifying an imputation model for each missing variable conditional on all the observed covariates and the outcome Y, and iteratively generate imputed values (Van Buuren et al., 2006). For example, in Figure 1 step 1, the imputation models for $X_2$, $X_3$ and B are $(X_2|X_1, X_3, B, Y)$, $(X_3|X_1, X_2, B, Y)$, and $(B|X_1, X_2, X_3, Y)$, respectively;

(4) IMB: “imputation by ordered monotone blocks (IMB)” strategy to handle block-wise missingness proposed by Li et al. (2014). In our case, it sequentially imputes missing covariates starting with the variable with minimum missingness conditional on the observed data,
outcome, and newly imputed data. We implement IMB through MICE by specifying a
different imputation model compared with FCS, e.g. in Figure 1 step 1, the imputation
models for $X_2$, $X_3$ and $B$ are $(X_2|X_1, Y)$, $(X_3|X_1, X_2, Y)$, and $(B|X_1, X_2, X_3, Y)$, respectively.

M=100 imputations are used for all multiple imputation. For FCS and IMB, we fit the same
target model as the proposed method but without weights, and calculate the variance via
Rubin’s combining rules (Little and Rubin, 2002).

3.1 Simulation Settings

We provide two representative examples in Simulation I and II to illustrate how to handle
the two categories of external summary-level information, respectively (Figure 2). Additional
simulation results to assess various settings and violations of assumptions can be found in
Web Supplemental Section 1.

[Figure 2 about here.]

- **Simulation I**: Idealized case where the internal data contains $(Y, X_1, X_2, B_1$[continuous],
  $B_2$[binary]), and two external models have been fitted to very large datasets that is sampled
  from the true data generating mechanism. The external models provided parameter estimates
  $\hat{\beta}_1$ and $\hat{\beta}_2$ from logistic regression models $Y|X_1$ and $Y|X_1, X_2$, respectively. In all three
  populations, $X_1, X_2$ and $B_1$ follows a standard multivariate normal distribution with zero-
  mean, standard deviation 1, and 0.3 correlation, while $B_2$ follows a Bernoulli distribution
  $B_2|X_1, X_2, B_1 \sim \text{Ber}([1 + \exp^{-1}(0.1X_1 + 0.2X_2 + 0.3B_1)])$. As shown in Figure 2, the three
  populations have similar generative outcome models with different intercepts, i.e. -1, 1 and
  3, which give prevalence of $Y=1$ of 0.3, 0.57, and 0.81, respectively. The target model is
  a logistic regression with different intercepts of the form
  \[
  \logit[\Pr(Y = 1 \mid X, B, S)] = \gamma_0 S_0 + \gamma_{S_1} S_1 + \gamma_{S_2} S_2 + \gamma_{X_1} X_1 + \gamma_{X_2} X_2 + \gamma_{B_1} B_1 + \gamma_{B_2} B_2.
  \]
**Evaluation metrics:** We assess this simulation in terms of absolute bias, the estimated variance from bootstrap and other comparisons, and the empirical variance of point estimates.

- **Simulation II:** External model 2 was derived by fitting a random forest model to a large dataset where the underlying true generative model is a logistic regression model that contained quadratic and interaction terms. Specifically, the internal study contains complete data of \((Y, X_1, X_2, X_3, X_4, B_1[\text{continuous}], B_2[\text{binary}])\), and the two external models are available in different forms of summary information, external model 1 that provides \(\hat{\beta}_1\) from a logistic regression model \(Y \mid X_1, X_2, X_3\) and external model 2 that can provide the estimated probabilities of \(Y = 1\) given \(X_1, X_2, X_3\) and \(X_4\) through a fitted random forest model. In all three populations, \(X_1, X_2\) and \(X_3\) follow a standard multivariate normal distribution with zero-mean, standard deviation 1, and 0.3 correlation, while \(X_4\) and \(B_1\) each follow a conditional normal distribution, \(X_4 \mid X_1, X_2, X_3 \sim N(0.2 \sum_{p=1}^{3} X_p, 1)\) and \(B_1 \mid X \sim N(0.2 \sum_{p=1}^{3} X_p + 0.1 X_4, 1)\), and \(B_2\) follows a Bernoulli distribution \(B_2 \mid X, B_1 \sim \text{Ber}\{(1 + \exp^{-1}[0.2 \sum_{p=1}^{3} X_p + 0.1(X_4 + B_1)]\})\), respectively. Similar to simulation I, the true generative distributions of \(Y\) in the internal and external population 1 shared the same main covariate effect but have different intercepts (-1 and 2, which corresponds to prevalence 0.3 and 0.65), while external model 2 additionally contains a quadratic term and an interaction (with intercept 3 that corresponds to prevalence 0.73). The target model is a logistic regression with the form

\[
\logit[\Pr(Y = 1 \mid X, B, S)] = \gamma_0 + \gamma_0 S_1 + \gamma_0 S_2 + \gamma_1 X_1 + \gamma_2 X_2 + \gamma_3 X_3 + \gamma_4 X_4 + \gamma_5 B_1 + \gamma_6 B_2.
\]

As described in step 4 of Section 2.2, \(\hat{\beta}_1\) can be directly used to calculate weights for \(S = 1\) while we need to estimate \(\beta_2^{\text{synthetic}}\) to calculate weights for \(S = 2\). To obtain \(\beta_2^{\text{synthetic}}\), we first generate a large synthetic data set \((\hat{Y}^{S=2}, X_1^{\text{synthetic}}, ..., X_4^{\text{synthetic}})\) by replicating the observed \((X_1, X_2, X_3, X_4)\) and generating \(\hat{Y}^{S=2}\) values through the available random forest model, and then fit a main effect logistic model \(\hat{Y}^{S=2} \mid X_1^{\text{synthetic}}, ..., X_4^{\text{synthetic}}\) using only the synthetic data and ignoring the missing \(B_1\) and \(B_2\).
Evaluation metrics: Since prediction accuracy will be the main goal in such situation in practice, we evaluate this simulation using three prediction metrics over a validation data of size $N_{\text{test}} = 2,000$: Area under the curve (AUC); Sum of squared error (SSE) = $\frac{1}{N_{\text{test}}} \sum_{i=1}^{N_{\text{test}}} (\hat{p}_i - p_{i0})^2$, where $\hat{p}_i$ and $p_{i0}$ denotes the estimated and true probability of $Y_i = 1$ given $X_i$ and $B_i$, respectively; and Scaled Brier Score (BS): $= \sum_{i=1}^{N_{\text{test}}} (Y_i - \hat{p}_i)^2 / \sum_{i=1}^{N_{\text{test}}} (Y_i - \bar{Y})^2$, where $\bar{Y} = \frac{1}{N_{\text{test}}} \sum_{i=1}^{N_{\text{test}}} Y_i$.

3.2 Simulation Results

Figure 3 shows the average results of the target model parameter estimates across 500 simulated datasets for simulation I, including point estimates in Figure 3a, variance estimators versus the empirical variance of the point estimates in Figure 3b, and the comparison of different variance estimators for the proposed strategy in Figure 3c. This figure appears in color in the electronic version of this article, and color refers to that version. Figure 3a shows that FCS (dark blue curve) and IMB (light blue curve) have similarly biased estimates, indicating these traditional imputation strategies can not distinguish heterogeneous population effects, while the proposed method (red dotted curve) always shows close results to the truth (grey dashed curve) for all covariates, especially $X_2$ and external intercepts $S=2$ where other methods show severe bias. For example, the absolute bias of $X_2$ coefficient estimates can be up to 0.2 for both FCS and IMB while it’s only 0.01 for the proposed method.

As shown in Figure 3b, each color denotes one distinct method, along with one solid curve represents the variance estimator, and one dashed curve represents the Monte Carlo empirical variance of the point estimates. If the variance is correctly estimated, the solid curve should be approximately equal to the corresponding dashed one, which is true for all methods. As expected, all methods show precision gain in estimated $X$ coefficients compared to the internal data only (the longer the distance to the black internal-data-only curve, the larger the precision gain) while no precision gain is found in $B$ covariates and the intercept.
due to no external added information and allowing population-specific effects, respectively.
The proposed method has over 50% efficiency gain in estimated X coefficients compared to the internal data. We see FCS and IMB have larger precision gain in both estimated X coefficients than the red proposed curve, which may be explained by bias-variance trade-off as they also have larger bias in the corresponding point estimates in Figure 3a. We will discuss the underlying statistical reason in Section 5.

As shown in Figure 3c, we show the result of the Louis information estimator (StackImpute-Louis), one of the three variance estimators proposed by Beesley and Taylor (2020) as they always have similar performances. Gu et al. (2019) has shown that when the synthetic data size goes to infinity, the precision gain we achieve in X covariates will converge to a constant, which is shown as the gradually stable trend of the grey curve (Monte Carlo empirical variance of the point estimates, also serves as the empirical truth here). When the synthetic data size increases from one times the internal data size to 10 times for each external study (i.e., total missing rate increases from 66.6% to 95%), the StackImpute variance estimator and Rubin’s rule variance continuously underestimate the empirical truth. On the contrary, the proposed variance estimator by bootstrapping the whole proposed procedure is always close to the empirical truth, especially in X covariates where the bias in other methods can be 10 times higher than the proposed method (i.e., 0.02 versus 0.002 in absolute bias) and could be even larger when the synthetic data size keep increasing. Moreover, in estimating the variation of the coefficient corresponding to $B_2$, the proposed method has stable bias around 0.035 while the other methods exhibit substantially larger bias. Note that the internal-data-only results (black solid curve) does not exist in external intercepts as they were not available in the internal data, whereas the bias of the internal data estimates is due to the small sample bias compared with the simulation truth.

Figure 4 shows the performance of each method in Simulation II over increasing synthetic
data size on a validation dataset that follows the true data generating mechanism, with three prediction metrics on the row and three populations on the column. In general, the results in Figure 4 are in line with Figure 3a, implying that the proposed method has better overall prediction performance compared with others. Specifically, in the first column (internal population S=0), all methods incorporating external information have consistently better prediction ability (larger AUC, smaller SSE and smaller BS) than using the internal data only (the dashed grey line). While all methods have similar performance in terms of AUC (first row) and predicting internal population (first column), the proposed approach outperforms others in terms of SSE and BS in predicting external populations, especially external study 2 where the true parameter values are quite different from the internal study values (the proposed method has up to 41% more improvement in SSE and 19% more improvement in BS compared with FCS and IMB). The proposed method shows a modest improvement in performance as the size of the synthetic data increases, e.g., for S=2, SSE decreases 12.9% from 9.3 to 8.1 in the proposed method when the synthetic data size increases from one to 10. In this particular scenario, there is little gain in performance with synthetic data more than 4 times the internal data size. Note that it is hard to distinguish FCS and IMB in the figure as they have very close results.

4. Application to Prostate Cancer Data

We apply the proposed method to predict the risk of high-grade prostate cancer (Gleason score over 6) using an internal dataset containing patients from three United States academic institutions (Tomlins et al., 2015) and two external risk calculators, one Prostate Cancer Prevention Trial risk calculator established from a United States population (Thompson
et al., 2006) and another European Randomized Study of Screening for Prostate Cancer risk calculator 3 established from a European population (Roobol et al., 2012).

The external risk calculators each used slightly different predictors to predict the same outcome through logistic regression, which we will denote as PCPTthg and ERSPC, respectively. PCPTthg and ERSPC both used prostate-specific antigen level (PSA) and digital rectal examination findings (DRE) as one of the predictors, and PCPTthg also used age, race (African American or not) and prior biopsy results while ERSPC additionally used transrectal ultrasound prostate volume (TRUS-PV):

- **PCPTthg**: \( \logit(p_i) = -3.69 + 0.89\log_2(\text{PSA}_i) + \text{DRE}_i + 0.03\text{Age}_i + 0.96\text{Race}_i - 0.36\text{Biopsy}_i \);
- **ERSPC**: \( \logit(p_i) = -3.16 + 1.18\log_2(\text{PSA}_i) + 1.81\text{DRE}_i - 1.51\log_2(\text{TRUS-PV}_i) \),

where \( p_i \) is the probability of observing high-grade prostate cancer for subject \( i \). A more detailed description of the above two equations can be found in the Supplementary Material of Gu et al. (2021).

In the internal individual-level data, in addition to all the predictors used in PCPTthg and ERSPC, we also have data on two new biomarkers, prostate cancer antigen 3 (PCA3) and TMPRSS2:ERG (T2:ERG) gene fusions, that were prognostic of prostate cancer (Tomlins et al., 2015; Truong et al., 2013). Therefore, in Table 1, we present the results of two target models using a total of eight predictors, including these two new biomarkers, one model only allows the intercept to be different across populations (“different intercept only” model corresponds to model 2), and another flexible model allows all possible covariates that used in the external populations to have population-specific effects (“different intercept and covariates” model that corresponds to model 1). The detailed model forms can be found in the table legend. A total of 678 male patients who had complete data were included in the internal data set provided by Tomlins et al. (2015), and an additional 1,174 patients’ data
were independently collected from seven community clinics throughout the United States for validation.

[Table 1 about here.]

The grey empty blocks in Table 1 imply that these predictors were not used in the certain external model, and thus in the proposed method we assume they have the same coefficient as the internal population (grey blocks with values). Results in Table 1 show (i) we will gain precision of the estimated coefficients by incorporating external model information (smaller SE highlighted in green), e.g., in the different-intercept-only model, the bootstrap SE of \( \log_2(\text{PSA}) \) reduces from 0.146 to 0.070 while it reduces for DRE from 0.299 to 0.139, compared with direct regression; (ii) when allowing population-specific effects (yellow blocks), we will not expect to see much precision gain due to variance-bias trade-off, e.g., both precision gain of \( \log_2(\text{PSA}) \) and DRE we see in the different-intercept-only model diminishes in the different-intercept-and-covariates model; and (iii) similar to the results in simulations, the analytical SE (in the round parenthesis) tends to provide a smaller estimation than the bootstrap SE (in the squared parenthesis) and potentially underestimates the true variability of the estimates.

In the prediction metrics row, we show AUC (higher value represents better discrimination) and scaled Brier score (smaller value means better calibration) calculated using the validation cohort, where the red blocks implies slightly worse overall predictive performance of PCPTgh population compared to direct regression, e.g., 0.9% reduction of AUC. This may be because that the validation cohort may represent a moderately different population than the training cohort as it has different baseline distribution as noted by Tomlins et al. (2015), which may also explain why the fitted model for the European population has better performance on the validation data.
5. Discussion

Flexibility in external models and populations: The proposed approach adds to the existing research on integrating external summary information into the internal study. It can develop improved models and provide statistical inference not only for the internal population but also for the external populations. The parameters of the external population models are allowed to differ from those of the internal population. This new strategy has the appealing feature of being able to make use of external information that comes in the form of a “black box” algorithm, i.e., an algorithm that provide a predicted probability, but the underlying model is not necessarily simple or transparent or even known. The key aspect is that the external information allows the creation of synthetic data. We further summarize some key points and concluding remarks of the proposed strategy in the subsequent paragraphs.

Using partial information through data integration: The proposed method can integrate summary information from multiple external models that each uses different covariates \( X_k \in X \) into the current study. The simulation and real data analysis showed expected results that we can only gain precision on estimated coefficient of \( X \) but not the \( B \) coefficients that are only available internally, even when \( X \) and \( B \) are correlated. This is consistent with the theoretical results in Dai et al. (2012) that the MLE estimator \( \hat{\beta} \) and \( \hat{\gamma}_B \) are always asymptotically independent under regularity conditions, where \( \hat{\beta} \) is the estimates of intercept and \( X \) coefficients in model \( Y|X; \beta \) and \( \hat{\gamma}_B \) is the estimated coefficient of \( B \) from model \( Y|X, B; \gamma \), respectively.

Principled inference post-imputation: Since the proposed strategy uses the stacked multiple imputation (StackImpute) proposed by Beesley and Taylor (2020), it also borrows strengths from StackImpute to avoid incompatibility between the imputation model and the analysis model, and can accommodate complicated outcomes such as the time-to-event outcome in survival models. In the proposed method, we introduced two types of variance
estimation, the proposed bootstrap variance and the analytical variance estimators proposed in Beesley and Taylor (2020, 2021). In general, the bootstrap variance can provide more valid variance estimation but may be more computationally intense compared with others, while analytical estimates is fast to compute but may be biased. Based on simulation results, when the predictors have small covariate effects (simulation in Section 1.2 of Web Supplemental), the bias of the analytical variance estimates is small.

**Improve not just current study but external model predictions:** To our knowledge, very few existing approaches can allow different population effects through regression analysis in data fusion, let alone improving external model predictions. It is worth noting that this same problem setting has a wide range of applications beyond regression analysis. Several approaches are proposed in the causal inference field to estimate the average causal effect, aiming to incorporate the supplementary information from the validation dataset to the main dataset and allowing heterogeneous treatment effects among different data sources. For example, Antonelli et al. (2017) proposed a unified Bayesian imputation framework built upon the work by Wang et al. (2012), introducing a dependence parameter to represent the prior odds of including a predictor in the outcome model given that it is in the exposure model, and assuming different population indicators in the outcome model. Yang and Ding (2020) posited a stochastic framework on the estimators from different data sources which flexibly leverages the supplementary information from validation datasets and they used a sensitivity parameter to quantify the systematic difference among data sources. Similarly, Huang and Qin (2020) and Chen et al. (2020) addressed this same problem in the implementation of survival data without assuming comparability among data sources.

**Allow for violation of transportability assumption:** The transportability assumption is common in data integration and causal inference when certain variables are not mutually observed across populations (Rassler, 2004; Reiter, 2012; Bareinboim and Pearl, 2013).
Compared with more strict transportability assumed in literature, e.g., Chatterjee et al. (2016) assumed transportability of the joint Y, X, B while Antonelli et al. (2017); Estes et al. (2017); Gu et al. (2021) assumed conditional transportability of $Y|X, B$, we only require conditional transportability among covariates (Assumption 2). While the simulation results (Section 1.4 of Web Supplemental) suggest that violating this assumption could have mild impact, one can consider applying additional shrinkage methods such as the empirical Bayes approaches proposed by Estes et al. (2017) and Gu et al. (2021) after obtaining estimates from the proposed approach, which can empirically strike a balance between bias and efficiency when the transportability between populations is unclear.

**Limitations:** While the results of the simulation study suggest that the proposed strategy has promising performance in providing both accurate statistical inference and prediction compared with comparison methods, some limitations are worth noticing. Particularly, the proposed method rely on good initial estimates for each external population. We propose to use a geometric approach by utilizing the observed data relationship to map the parameter estimates in the reduced model (i.e., $Y|X; \beta$) to the target model (i.e., $Y|X, B; \gamma$). While the simulation results show promising performance, caution must be exercised during implementation when the underlying true relationship is hard to verify. In a special case where the external study has the same population distribution as the internal population, the internal data estimates can directly serve as the initial estimates for the external population.

**Future directions:** An interesting extension of the proposed method is to accommodate the situation where selection bias exists and selection probability or survey weights are available for each observation in the internal population. In theory, the proposed method can be adapted to accommodate this by replacing the synthetic Y values with the inverse probability-weighted or survey weights-weighted synthetic Y values in step 1 of the proposed strategy. Alternatively, instead of copying the whole internal X’s multiple times to create
the same X distribution as the internal population, one can consider proportionally creating synthetic X through the given weights to recovery the representative distribution in the external populations. Further investigation is needed to evaluate this. Furthermore, if the exposure indicator is available as a covariate in all populations, one can also use the regression estimates from the proposed method to calculate the estimated average causal effect by averaging over the joint distribution of \((X, B)\). On the contrary, it is unclear whether we can directly use the intermediate parameter estimates from causal inference methods for regression inference. For example, the causal inference approach–guided Bayesian method adjusting for unmeasured confounding (Antonelli et al., 2017) aimed at obtaining unbiased causal effects by averaging selective regression models, can also produced the regression estimates for all covariates, which is the same as our goal. We attempted to modify their method and code to serve our purpose but the results did not seem promising, this may have been because direct comparison of the performance of two approaches is not appropriate when they have different goals.

Acknowledgements

This research was partially supported by the National Institutes of Health grant CA129102 and the National Science Foundation grant DMS1712933. The authors want to thank Dr. Lauren Beesley for many helpful suggestions that led to a significant improvement of this paper.

Data Availability Statement

Data from the illustrative example are not shared due to third-party data sharing restrictions and to protect patient privacy.
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Supporting Information

The Web Supplemental Sections referenced in Section 3 and 5 are available online. An R package SynDI implementing the proposed method can be found on GitHub at https://github.com/umich-biostatistics/SynDI.
Appendix Deriving the Initial Estimates for the External Populations

In this section, we will show how to obtain the initial parameter estimates of external population \( k \). Let \((\hat{\gamma}_0^S, \hat{\gamma}_X^S, \hat{\gamma}_B^S)^T\) be the direct regression estimates of \( Y|X, B, S = 0 \) using internal data only. For external population \( k \), we know the parameter estimates \( \hat{\beta}_k = (\hat{\beta}_0^k, \hat{\beta}_X^k)^T \) from the fitted model \( Y|X_k; \beta_k \). We assume that all predictors, \( X \) and \( B \), are centered, and the true target model parameter for the external population \( k \) is \((\gamma_0^S_k, \gamma_X^S_k, \gamma_B^S_k)^T\), assuming the coefficient of the unobserved variable \( B \) is the same as the internal population, i.e. \( \gamma_B^S_k = \gamma_B^S \).

The goal of estimating \( \gamma_0^S_k \) and \( \gamma_X^S_k \) from model \( Y|X, B, S = k; \gamma^S \) is equivalent to correcting the bias of \( \hat{\beta}_k \) in the reduced model \( Y|X_k; \beta_k \) considering covariates \( X_{(-k)} \) and \( B \) as omitted. To simplify notation, we assume \( B \) is the only omitted covariate in the derivation below. Neuhaus and Jewell (1993) provided a Taylor-series-expansion approximation to show that the ratio of coefficients remains constant in both the reduced and the full model when the omitted \( B \) is independent of the observed \( X \), i.e. \( \frac{\gamma_X^k}{\gamma_X^0} \approx \frac{\beta_X^0}{\beta_X^k} \), indicating that the relative effect size among regression coefficients remains consistent across models. In their Table 3 and equation 9, Neuhaus and Jewell (1993) provided the algebraic relationship between \( \gamma_X^S_k \) and \( \beta_X \) for exponential family when the omitted \( B \) and the observed \( X \) are correlated. In the subsequent paragraphs, we will explain in detail how to estimate \( \gamma_0^S_k \) and \( \gamma_X^S_k \) in linear regression (continuous \( Y \)) and logistic regression (binary \( Y \)), respectively.

1. Linear Regression: Suppose \( E(B|X; \theta) = \theta X \). We start by replacing \( B \) with the conditional expected value \( E(B|X; \theta) \) in the mean profile of the target model:

\[
E(Y|X, B; \gamma) = \gamma_0^S + \gamma_X^S X + \gamma_B^S B = \gamma_0^S + \gamma_X^S X + \gamma_B^S \theta X = E(Y|X; \gamma, \theta)
\]

Since \( \hat{E}(Y|X; \beta) = \hat{\beta}_0 + \hat{\beta}_X X \) is available through the externally fitted model, we can obtain the estimation of \( \gamma_0^S \) and \( \gamma_X^S \) by matching the intercept and \( X \) coefficient between \( \hat{E}(Y|X; \gamma, \theta) \) and \( \hat{E}(Y|X; \beta) \), respectively: \( \hat{\gamma}_0^S = \hat{\beta}_0 \) and \( \hat{\gamma}_X^S = \hat{\beta}_X - \theta^T \hat{\gamma}_B^S \). In a special case
where the internal and the external population only differ in intercept and S is independent of X and B, we can directly obtain the initial estimates $\gamma_k = (\hat{\beta}_0, \gamma_{X_k}^{S_kT}, \gamma_{B_k}^{S_kT})^T$.

2. Logistic Regression: In logistic regression where $g()$ is the logit link function, we connect the intercepts $\beta_0$ and $\gamma_0^{S_k}$ through the equation $\logit^{-1}(\beta_0) = E_{B|X}(\mu_0^{S_k})$, where $\mu_0^{S_k} = g^{-1}(Y|X, B; \gamma_0^{S_k} = 0) = \logit^{-1}(\gamma_0^{S_k} + B^T \gamma_{B_k}^{S_k})$. For the right hand side, we expand B, a vector of length Q, at $E(B|X)$ using the third-order Taylor series expansion as follows:

$$E_{B|X}(\mu_0^{S_k}) = E_{B|X}[\logit^{-1}(\gamma_0^{S_k} + B^T \gamma_{B_k}^{S_k})]$$

$$\approx \logit^{-1}(w)\left(1 + \frac{1}{2}(1 + e^w)^2 \sum_{i=1}^Q \sum_{j=1}^Q \gamma_{B_i}^{S_k} \gamma_{B_j}^{S_k} E_{B|X}\left[\left(B_i - E(B_i|X)\right)\left(B_j - E(B_j|X)\right)\right]\right)$$

$$\approx \logit^{-1}(w)\left[1 + \frac{1}{2}(1 + e^w)^2 \text{Var}\left(\sum_{i=1}^Q \gamma_{B_i}^{S_k} B_i|X\right)\right] \quad (A.1)$$

where $w = \gamma_0^{S_k} + E(B^T|X)\gamma_{B_k}^{S_k}$. Given $\hat{\beta}_0$, $\hat{\gamma}_{B_k}^{S_k}$, $\hat{E}(B|X)$ and $\hat{\text{Var}}(B|X)$, we can easily obtain $\hat{\gamma}_0^{S_k}$ by solving the equation $E_{B|X}(\mu_0^{S_k}) - \logit^{-1}(\hat{\beta}_0) = 0$.

After obtaining $\hat{\gamma}_0^{S_k}$, we then estimate $\gamma_X = (\hat{\gamma}_{X_1}^{S_k}, ..., \hat{\gamma}_{X_{P_k}}^{S_k})^T$ according to the following equation provided in Neuhaus and Jewell (1993):

$$\hat{\beta}_{X_p} = \left\{\gamma_{X_p}^{S_k} + \left[E(B^T|X + 1_p) - E(B^T|X)\right]\gamma_{B_k}^{S_k}\right\}\left\{1 - \frac{\text{Var}_{B|X}(\mu_0^{S_k})}{1 - E_{B|X}(\mu_0^{S_k})[1 - E_{B|X}(\mu_0^{S_k})]}\right\}$$

where $1_p$ is a zero vector with the $p^{th}$ term equals to 1 and $p \in \{1, ..., P_k\}$. Similar to equation A.1, we can also obtain the Taylor-series-expansion estimation for $E_{B|X}[\mu_0^{S_k}]^2 = E_{B|X}[\logit^{-2}(\gamma_0^{S_k} + B^T \gamma_{B_k}^{S_k})] \approx \frac{e^w}{(1 + e^w)^2} \left[1 + \frac{1}{2} \frac{2 - e^w}{(1 + e^w)^2} \sum_{i=1}^Q \sum_{j=1}^Q \gamma_{B_i}^{S_k} \gamma_{B_j}^{S_k} \text{Cov}(B_i, B_j|X)\right]$, together with $E_{B|X}(\mu_0^{S_k})$, we then obtain an approximation of $V_{B|X}(\mu_0^{S_k}) = E_{B|X}[\mu_0^{S_k}]^2 - E_{B|X}(\mu_0^{S_k})$.

Given $\hat{\beta}_X$, $\hat{\gamma}_{B_k}^{S_k}$, $\hat{E}(B|X)$, and $\hat{\gamma}_{0}^{S_k}$, we can obtain $\hat{\gamma}_X = \hat{\beta}_X(1 - \frac{\hat{\gamma}_{B_k}^{S_k}}{E_{B|X}(\mu_0^{S_k})[1 - E_{B|X}(\mu_0^{S_k})]})^{-1} \left[\hat{E}(B^T|X + 1_p) - \hat{E}(B^T|X)\right] \hat{\gamma}_{B_k}^{S_k}$.

Note that we estimate $E(B|X; \theta) = g^{-1}(\theta X)$ and $\text{Var}(B|X; \theta) = g'^{-1}(\theta X)\left[1 - g'^{-1}(\theta X)\right]$ using the internal data by regressing each B on X with appropriate link function $g'()$ based on the type of B, e.g., when B is continuous, linear regression and identity link is used; when B is binary, logistic regression and logit link is used. Given $\hat{\theta}$, $\hat{E}(B|X) = \hat{\theta}^T E(X)$ is used.
Figure 1: Diagram of the proposed strategy.
| Simulation I*: Ideal case with continuous B1 and binary B2 | Simulation II: External model 2 was derived by fitting a random forest model to a large dataset where the underlying generative model is a logistic regression model that contained quadratic and interaction terms |
|---|---|
| **Structure of the assumed model** | **Covariate distribution** |
| Internal | \( \logit P(Y=1|X_1, X_2, B_1 \text{ (cont.)}, B_2 \text{ (binary)}) \) |
| External 1 | \( \logit P(Y=1|X_1; \beta_1) \) |
| External 2 | \( \logit P(Y=1|X_1, X_2; \beta_2) \) |
| **Generative true outcome model** | \( (X_1, X_2, X_3) \sim N(0, 1), \text{ correlation 0.3} \) |
| logit \( P(Y=1|X, B) \) | \( X_3 \sim N(0.1X_1 + 0.1X_3, 1) \) |
| Internal | \( B_1 \sim \text{Ber}(1 + \exp(0.1X_1 + 0.2X_2 + 0.3B_1)) \) |
| External 1 | \( B_2 \sim \text{Ber}(1 + \exp(0.2X_1 + 0.2X_2 + 0.1X_3 + 0.1B_2)) \) |
| External 2 | \( 3X_1X_2X_3X_4 + B_1B_2 \) |
| **Available information** | **Target model** |
| Internal | Individual data \( (Y, X_1, X_2, B_1, B_2) \) |
| External 1 | \( \beta_1 = (0.32, -1.19)^T \) |
| External 2 | \( \beta_2 = (-2.11, -1.13, -1.12)^T \) |
| **Evaluation metrics** | - Area under the curve (AUC) |
| - Absolute bias | - Sum of squared errors (SSE) |
| - Variance estimation | - Scalped Brier Score (BS) |
| - Empirical variance of point estimates | |

* Additional simulation scenarios to assess the performance of the proposed approach are presented in Section 1 of Web Supplemental.
† \( \hat{\beta}_k \), \( k = 1 \) or 2, is estimated from a large dataset that follows the true data generating mechanism.
‡ The random forest model is fitted on a large dataset of \( (Y, X_1, X_2, X_3, X_4) \) that follows the true data generating mechanism.
Figure 3: Visualization of simulation I results over increasing synthetic data size (a) point estimates (b) variance estimators vs. the empirical variance (c) different variance estimators of the proposed method.
Figure 4: Visualization of prediction metrics over increasing synthetic data size for simulation II. Larger AUC (area under the curve), smaller SSE (sum of squared error) and smaller BS (Brier Score) represents better prediction.
Table 1: Results of the data example for predicting the risk of high-grade prostate cancer. Internal dataset of size n=678; validation dataset of size N^{test}=1,174; PCPThg, prostate cancer prevention trial risk calculator; ERSPC, the European Randomized Study of Screening for Prostate Cancer risk calculator 3; SE, standard error; green represents good performance with large precision gain or better model calibration, grey represents certain predictor was not used in the external calculator, yellow represents population-specific effect different from the internal population, and red represents poor performance compared with direct regression; SE in the proposed method are (StackImpute SE) [bootstrap SE from 500 replicates].

| Predicted | Original Estimated | Original Estimated | Original Estimated | Original Estimated |
|-----------|--------------------|--------------------|--------------------|--------------------|
| Intercept | -3.686 ± 0.115     | -1.409 ± 0.111     | -3.160 ± 0.455     | -1.391 ± 0.421     |
| log2(PSA) | 0.894 ± 0.124     | 0.735 ± 0.124      | 1.176 ± 0.146      | 0.891 ± 0.060      |
| DRE      | 1.145 ± 0.257     | 1.813 ± 0.269      | 1.306 ± 0.299      | 1.045 ± 0.117      |
| Age      | 0.03 ± 0.012      | 0.033 ± 0.012      | 0.032 ± 0.014      | 0.030 ± 0.008      |
| Biopsy   | -0.36 ± 0.272     | -1.444 ± 0.294     | -1.201 ± 0.294     | -0.618 ± 0.243     |
| Race     | 0.96 ± 0.288      | 0.442 ± 0.331      | 0.183 ± 0.175      | 0.434 ± 0.175      |
| log2(TRUS-PV) | -1.514 ± 0.225 | -1.697 ± 0.254 | -1.699 ± 0.254 | -1.553 ± 0.145 |
| log2(PCA3+1) | 0.495 ± 0.089 | 0.486 ± 0.083 | 0.486 ± 0.083 | 0.494 ± 0.083 |
| log2(T2:ERG+1) | 0.098 ± 0.038 | 0.092 ± 0.036 | 0.092 ± 0.036 | 0.094 ± 0.037 |

Prediction metrics on AUC 0.700 0.707 0.720 0.723 0.806 (REF) 0.804 0.804 0.804 0.805 0.797 0.802

Scaled Brier score 1.059 0.987 0.954 0.994 0.903 (REF) 0.915 0.977 0.875 0.902 0.990 0.875

The proposed method are (StackImpute SE) [bootstrap SE from 500 replicates].
1 Additional Simulation Results

In this section, we show the results of additional simulations to assess the performance of the proposed strategy for point estimates and variance estimation.

1.1 Continuous outcome Y (a supplement to Simulation I in the main manuscript)

Goal: To examine the proposed method when the outcome is continuous and the target model is linear regression.

Simulation setup: This simulation is the same as Simulation I in the main manuscript, except the generative outcome model now follows Gaussian distribution:

\[
\begin{align*}
\text{Internal: } & \quad Y|X, B \sim N(-1 - X_1 - X_2 - B_1 - B_2, 1); \\
\text{External 1: } & \quad Y|X, B \sim N(1 - X_1 - X_2 - B_1 - B_2, 1); \\
\text{External 2: } & \quad Y|X, B \sim N(3 - X_1 - X_2 - B_1 - B_2, 1). 
\end{align*}
\]

The target outcome model (model 2 in the main manuscript) is now a linear regression:

\[
E(Y|X, B, S) = \gamma_0 + \sum_{k=1}^{2} \gamma_{S_k} S_k + \sum_{p=1}^{2} \gamma_{X_p} X_p + \sum_{q=1}^{2} \gamma_{B_q} B_q,
\]

Results: Figure 1 shows similar pattern as those in Simulation I in the main manuscript, where the proposed method (red dotted curve) has the smallest bias among all for all covariates (Figure 1a), largest precision gain compared with others (Figure 1b), and the closest variance estimation to the Monte Carlo empirical variance (Figure 1c).

1.2 Smaller covariate effect (a modification to Simulation I in the main manuscript)

Goal: To assess our approach when the magnitude and the difference of covariate effects are small across different populations in the target outcome model.

Simulation setup: This simulation is the same as Simulation I in the main manuscript, except the
Figure 1: Results of Simulation 1.1 over increasing synthetic data size (a) point estimates (b) variance estimation vs. Monte Carlo empirical variance (c) different variance estimators of the proposed method.
coefficient effect is now -0.5 instead of -1, and the intercept difference is smaller among populations:

\[
\begin{align*}
\text{Internal: } & \quad \logit[\Pr(Y = 1|X, B)] = -1 - 0.5(X_1 + X_2 + B_1 + B_2), \text{ prevalence}=0.28; \\
\text{External 1: } & \quad \logit[\Pr(Y = 1|X, B)] = -0.5 - 0.5(X_1 + X_2 + B_1 + B_2), \text{ prevalence}=0.36; \\
\text{External 2: } & \quad \logit[\Pr(Y = 1|X, B)] = 0 - 0.5(X_1 + X_2 + B_1 + B_2), \text{ prevalence}=0.45.
\end{align*}
\]

**Results:** Figure 2a shows that compared with larger covariate effects in Simulation I in the main manuscript, when the X covariate effect is small, FCS and IMB have smaller bias in estimating X coefficients but still lack the ability to identify population-specific effects (i.e. intercepts of external populations). Similarly, Figure 2b shows smaller bias of variance estimation. Note that the Rubin’s rule variance estimator in Figure 2b is too large (the pink curve) so that it falls outside of the range of the figure.

![Figure 2a: Point estimates](image1)

(a) Point estimates

![Figure 2b: Different variance estimators](image2)

(b) Different variance estimators of the proposed method

Figure 2: Results of Simulation 1.2 over increasing synthetic data size (a) point estimates (b) different variance estimators of the proposed method.
1.3 Different X covariate effects in the outcome model (a more flexible outcome model compared with Simulation I in the main manuscript)

**Goal:** In the main manuscript, we only present the simulation results allowing the target model’s intercept to differ across populations. In this simulation, we additionally show the performance of the proposed method when all possible X covariates coefficients are allowed to differ across populations (similar to model 1 or “different intercept and covariates” model in the real data example in the main manuscript).

**Simulation setup:** This simulation is the same as Simulation I in the main manuscript except now that the generative outcome models are as follows:

\[
\begin{align*}
\text{Internal:} & \quad \logit[\Pr(Y = 1 | X, \mathbf{B})] = -1 - X_1 - X_2 - B_1 - B_2, \text{ prevalence} = 0.3; \\
\text{External 1:} & \quad \logit[\Pr(Y = 1 | X, \mathbf{B})] = 1 + X_1 - X_2 - B_1 - B_2, \text{ prevalence} = 0.58; \\
\text{External 2:} & \quad \logit[\Pr(Y = 1 | X, \mathbf{B})] = 3 + 3X_1 + 3X_2 - B_1 - B_2, \text{ prevalence} = 0.70.
\end{align*}
\]

**Results:** Similar to the results of Simulation I in the main manuscript, the results in Figure 3 shows outstanding performance of the proposed method in both point estimates and variance estimation compared with others. For example, the proposed method has small bias less than 0.02 when estimating $X_2$ in population $S=1$ while the bias in FCS and IMB can go up to 0.78 (i.e. almost 40 times of the proposed method).

![Figure 3](image_url)

(a) Point estimates (b) Different variance estimators of the proposed method

Figure 3: Results of Simulation 1.3 over increasing synthetic data size (a) point estimates (b) different variance estimators of the proposed method.
1.4 Violation of transportability assumption

**Goal:** To examine the proposed method when Assumption 2 (Xmiss|Xobs and B|X are transportable between the internal and the external populations) is violated. We present two examples where the violation only causes ignorable bias in case 1 while it has larger impact in case 2.

1.4.1 Case 1: different B|X distribution in external population 2

**Simulation setup:** This simulation is the same as Simulation I in the main manuscript except that now the external model 2 has different marginal B1 distribution and different conditional distribution B2|X1,X2,B1:

- B1 has mean 1.5 and standard deviation 1.5 in external population 2 while in other populations B1 has mean 0 and standard deviation 1;
- B2|X,B1 ∼ Ber{[1 + exp−1(0.2X1 + 0.3X2 + 0.4B1)]} in external population 2 while in other populations B2|X,B1 ∼ Ber{[1 + exp−1(0.1X1 + 0.2X2 + 0.3B1)]}.

Note that both B1 and B2 are only observed in the internal study and multiple imputations are needed for them, where B2|X and B2|X,B1 should be the same across populations according to Assumption 2.

**Results:** Figure 4a indicates that the violation of transportability assumption in the proposed method has limited impact of point estimation with ignorable bias while Figure 4b shows similar pattern of variance estimations as before.

![Figure 4: Results of Simulation 1.4.1 over increasing synthetic data size (a) point estimates (b) different variance estimators of the proposed method.](image-url)
1.4.2 Case 2: different marginal $X_1$ distribution in external populations

Simulation setup: This simulation is the same as Simulation I in the main manuscript except now that in the external studies, $X_1 \sim N(1,1.5)$ while in the internal study $X_1 \sim N(0,1)$. This will lead to different distribution conditional on $X_1$ and thus violates Assumption 2.

Results: Figure 5a shows that such violation leads to some bias of estimated coefficient $X_1$, i.e., 0.2 absolute bias. Besides that, the proposed method has nearly unbiased point estimates for other parameter (i.e. up to 0.014 absolute bias) while the bias in FCS and IMB can be up to 15 times the bias of the proposed method. Similarly, Figure 5b shown unbiased variance estimation of the proposed bootstrap estimator.

Figure 5: Results of Simulation 1.4.2 over increasing synthetic data size (a) point estimates (b) different variance estimators of the proposed method.