Handling missing data when estimating causal effects with Targeted Maximum Likelihood Estimation

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Abstract

Causal inference from longitudinal studies is central to epidemiologic research. Targeted Maximum Likelihood Estimation (TMLE) is an established double-robust causal effect estimation method, but how missing data should be handled when using TMLE with data-adaptive approaches is unclear. Based on motivating data from the Victorian Adolescent Health Cohort Study, we conducted simulation and case studies to evaluate the performance of methods for handling missing data when using TMLE. These were complete-case analysis; an extended TMLE method incorporating a model for outcome missingness mechanism; missing indicator method for missing covariate data; and six multiple imputation (MI) approaches using parametric or machine-learning approaches to handle missing outcome, exposure, and covariate data. The simulation study considered a simple scenario (the exposure and outcome generated from main-effects regressions), and two complex scenarios (models also included interactions), alongside eleven missingness mechanisms defined using causal diagrams. No approach performed well across all scenarios and missingness mechanisms. For non-MI methods, bias depended on missingness mechanism (little when outcome did not influence missingness in any variable). For parametric MI, bias depended on missingness mechanism (smaller when outcome did not directly influence outcome missingness) and data generation scenario (larger for the complex scenarios). Including interaction terms in the imputation model improved performance. For MI using machine learning, bias depended on missingness mechanism (smaller when no variable with missing data directly influenced outcome missingness). We recommend considering missing data mechanism and, if using MI, opting for a saturated parametric or data-adaptive imputation model for handling missing data in TMLE estimation.

1 Introduction

A crucial component of epidemiologic research is causal inference from longitudinal cohort studies, where interest is commonly in estimating the average causal effect (ACE) of an exposure on an outcome. ¹⁻⁵ Targeted Maximum Likelihood Estimation (TMLE) is an established doubly robust causal effect estimation method, combining a model for the outcome and a model for the exposure, and offers several appealing properties. ⁶⁻⁸ Only one of the two models (outcome or exposure model) needs to be consistently estimated to obtain an unbiased estimate of the causal effect, and when both are consistently estimated, TMLE is an asymptotically efficient estimator under the Donsker class condition (which requires that outcome and propensity score estimators not to heavily overfit the data). ⁷⁻⁹ Under this condition, valid statistical inference can be obtained with TMLE even when data-adaptive methods are used for the exposure and outcome models. ⁷ Data-adaptive methods refer to a broad range of techniques to fit prediction models that can flexibly learn from the data and are attractive because they allow relaxation of parametric modelling assumptions, thereby reducing misspecification bias. ¹⁰ In causal inference, application of most data-adaptive methods needs to be limited to doubly robust estimators because when used with singly robust methods, such as g-computation or inverse probability weighting, they yield biased estimates and invalid confidence intervals (CIs). ¹¹

Recently, interest in the application of TMLE for ACE estimation has grown, as reflected by the increasing number of papers using the approach (**Figure 1**). Nonetheless, guidance on how missing data should be handled when using TMLE with data-adaptive approaches is currently lacking. This is problematic given that missing data are ubiquitous and can lead to biased estimates and loss of precision if handled inappropriately. 82

A review of the literature suggests that in studies using TMLE for ACE estimation, multiple imputation (MI) is one of the most commonly used approaches to handle missing data. ^{20,24,43,45,48,54,65,79,81} MI is a two-step process. First, multiple completed datasets are generated where missing data are replaced with values drawn from their posterior predictive distribution conditional on the observed data. Then each imputed dataset is analysed and results are pooled to obtain the final MI estimate and standard error (SE). ⁸³ A requirement of MI is that the imputation model must be compatible with the analysis model, which implies that the imputation model must not be less general than the analysis model and should incorporate all relationships assumed to hold in the latter. ⁸² However, how this can be achieved when data-adaptive methods are used for the exposure and/or outcome models in TMLE is unclear and poses a challenge for using MI in conjunction with this approach.

Complete-case analysis, where records with missing data for any of the variables in the exposure or outcome models are excluded, is another commonly used approach for handling missing data with TMLE. 14,15,18,32,42,45,63,73,74 Although this approach does not necessarily inflict bias, it generally leads to loss

of precision. ⁸⁴ Extending TMLE to handle missing outcome data ^{40,52,75} and a missing covariate missing indicator (MCMI) approach for handling missing confounder data ^{21,49,64} are other approaches that have been used to handle missing data in a number of studies using TMLE. For the extended TMLE approach, the TMLE implementation includes, in addition to models for the exposure and outcome, a model for the probability of having non-missing outcome conditional on the exposure and confounders. ⁸⁵ This approach is expected to perform well when the exposure and confounders are complete. However, incompleteness in exposure and confounders is common in cohort studies, in which case researchers using this approach need to delete records with incomplete data for these variables, leading to loss of precision or potential bias. Alternatively, they might use the MCMI approach to handle incomplete confounders, which relies on extending the confounder vector to include missingness indicators for these. ⁸⁶ This approach is only guaranteed to be unbiased under certain stringent assumptions about the missingness mechanism. ⁸⁶ Like extended TMLE, MCMI does not deal with incomplete exposure data. Overall, the optimal implementation of MI and its performance compared with these other available approaches are unknown.

In this paper, we seek to evaluate and compare the performance of a range of approaches for dealing with missing data when using TMLE with data-adaptive methods to estimate the ACE, including several potential implementations of MI. The article is organized as follows. First, we introduce the motivating example, which investigated the causal effect of frequent cannabis use in adolescent females on their mental health in young adulthood using data from the Victorian Adolescent Health Cohort Study (VAHCS). Then, we briefly review the ACE definition, identifiability conditions and the TMLE estimation approach in the absence of missing data. Then we describe methods for handling missing data with TMLE and the simulation study we conducted based on the VAHCS example to evaluate and compare the performance of these approaches. Finally, we illustrate the assessed approaches in the VACHS case study and conclude with a general discussion.

2 Motivating example

For our case study, the question of interest was "what is the causal effect of frequent cannabis use in adolescent females on their mental health in young adulthood?". It was based on a previous investigation using VAHCS data, which estimated an approximately two times higher odds of depression and anxiety in young adulthood for females who reported frequent cannabis use during adolescence compared with those who did not (odds ratio (OR) 1.9; 95% confidence interval (CI) 1.1, 3.3).⁸⁷

VAHCS is a longitudinal study of 1,943 participants (1,000 females), who were recruited when they were aged 14-15 years between 1992 and 1993 from 45 randomly selected schools across the state of Victoria, Australia. Bata were collected from participants every six months during their adolescence (waves one to six), using self-administered questionnaires or telephone interviews. Wave seven, conducted in 1998, was

the young adulthood survey, at which data collection was conducted using computer-assisted telephone interviews.⁸⁸

At each wave of the adolescent phase, the frequency of cannabis use in the previous six months was self-reported. Participants were classified as frequent users if they reported at least weekly use at any wave across waves two to six. The computerized revised clinical interview schedule (CIS-R) administered at all the waves was used to assess mental health. Here, instead of dichotomizing the outcome variable as in the previous investigation, we used the log-transformed and standardized CIS-R total score at wave seven as the outcome. Following the previously published paper, we considered five confounders. These were parental divorce, antisocial behaviour, depression and anxiety, alcohol use, and parental education, all measured across waves two to six, treated as binary variables, and assumed to be proxies for pre-exposure conditions. Table 1 shows descriptive statistics and proportions with missing data among the VAHCS female participants for these variables as well as age at wave two, which we made use of as an auxiliary variable (a variable that is a predictor of missing values but is not included in the analysis model on this study.

The aim of our target analysis was to estimate the ACE, as defined in the next section, of frequent cannabis use during adolescence on CIS-R score in young adulthood among VAHCS female participants.

3 Overview of ACE estimation with TMLE

For a binary exposure, the ACE is defined as the difference between the average potential outcome if everybody in the population was set to be exposed and the average potential outcome if everybody were set to be unexposed, i.e., $E[Y^{x=1}] - E[Y^{x=0}]$, where $Y^{x=1}$ and $Y^{x=0}$ are respectively the potential outcomes under exposure (x = 1) and no exposure (x = 0). In the absence of missing data, and under the assumptions of exchangeability, consistency, and positivity, it is possible to identify the ACE from observable data by the g-formula: E[E(Y|X = 1, Z) - E(Y|X = 0, Z)], where Z is a vector of confounders and the outer expectation averages over its distribution in the population. Exchangeability (no unmeasured confounding) is formally defined as $Y^x \coprod X|Z$, for all values of x. Consistency is the equality between individual's counterfactual outcome under their exposure history and their observed outcome, i.e., $Y^x = Y$ when X = x. Positivity requires a non-zero probability of receiving the exposure across all combinations of confounder strata, i.e., P[X = x|Z = z] > 0 for x = 0,1 for all values of z that occur in the population.

Several estimators are available for estimating the ACE in the absence of missing data. Here, we focus on TMLE which is a doubly robust estimator, combining a model for the outcome and a model for the exposure.⁶⁻⁸ Simply put, the implementation of TMLE in a point-exposure study involves (i) estimating a

model for the expected outcome conditional on exposure and confounders ($\widehat{\mathbb{E}}[Y|X,Z]$) and using it to predict the outcome for all records under exposure and no exposure; (ii) estimating a model for the probability of receiving the exposure conditional on confounders (i.e., the propensity score; ($\widehat{P}[X=1|Z]$)); (iii) incorporating information from the propensity score to improve the initial outcome predictions so that they solve the parameter's efficient influence curve^{8,91,92}; and (iv) plugging in the updated predictions (denoted by $\widehat{E}^*[Y|X,Z]$) in the g-formula to estimate the ACE.⁶ Influence curve is a function that describes estimator behaviour when the empirical distribution of the data is slightly perturbed. For a target parameter, an efficient influence curve is the influence curve with the smallest variance.^{91,92} The standard approach for standard error (SE) estimation with TMLE is to take the standard deviation (SD) of the influence curve, which is attractive due to its easiness.⁹² The so-called targeting step of the TMLE procedure, step (iii), ensures that the estimator is doubly robust and thereby exhibits the desirable statistical properties previously described. We refer the reader to the existing literature^{7,8} for a detailed explanation of TMLE and its theoretical underpinnings.

4 Methods for handling missing data

In the following section, we describe the methods we identified for handling missing data when estimating the ACE using TMLE. These are broadly categorised under non-MI and MI methods.

4.1 Non-MI approaches to handle missing data

4.1.1 Complete-case analysis

The simplest approach for handling missing data is a complete-case analysis. For this approach, participants with missing data for any of the variables in the target analysis are excluded and the analysis is performed using records with complete data only. In general, this approach can lead to bias, depending on the missingness mechanism, and loss of precision.⁹³

4.1.2 Extended TMLE in the sample with complete exposure and confounders (Ext TMLE):

The second approach is the extended TMLE method⁸⁵ to handle missingness in the outcome, with records with missing exposure or confounder data being excluded. In this approach, the initial model for E[Y|X,Z] is estimated among records with complete Z, X, Y data, and the predictions of the outcome are updated in the targeting step using information from both the model fitted for P[X=1|Z] as well as a model fitted for $P[M_Y=0|X,Z]$ (probability of having observed outcome conditional on the exposure and confounders, where M_Y is the missingness indicator for the outcome and coded 1 if the variable is missing and 0 if observed). Updated predictions for the outcome under exposure and no exposure are obtained for all records, regardless of their missing outcome status, and are then plugged into the g-formula to estimate the ACE. As with the exposure and outcome models, the model for M_Y can be fitted using data-adaptive approaches. In the absence of incomplete exposure and confounders, the extended TMLE method has been shown to be

unbiased under an extended exchangeability assumption (namely, $Y^x \coprod M_Y | X, Z$ and $Y^x \coprod X | Z$ for x = 0,1). This method is available in the R TMLE implementation.⁸⁵

4.1.3 Extended TMLE plus missing covariate missing indicator (MCMI) approach (Ext TMLE+MCMI): For the third approach, missing outcome data are handled as above, using the extended TMLE approach, and missing confounder data are handled using the missing covariate missing indicator (MCMI) approach, by including missingness indicators for the incomplete confounders in the confounding adjustment set. Records with missing exposure data are excluded. Blake et al. have previously shown that the MCMI approach can be expected to yield an unbiased estimate of the ACE under an extended exchangeability assumption ($Y^x \coprod X|Z$, M for x = 0,1, where M is the vector of missingness indicators for the incomplete confounders), and the assumption that the exposure or outcome only depend on the confounder when the confounder is observed. Sec. 15 It is possible to imagine scenarios where this assumption might be plausible, such as in electronic health record data, where, for example, the decision to prescribe a medication is influenced by family history of disease only when the clinician has the relevant information.

4.2. MI approaches to handle missing data

We identified various approaches to MI within the fully conditional specification (FCS) framework⁹⁶ to simultaneously handle missing exposure, confounder, and outcome data. In FCS, univariate models are specified for each incomplete variable conditional on other variables in the imputation model, and imputations are drawn sequentially until convergence, usually achieved after five cycles. The whole process is repeated multiple times to generate multiple completed datasets. Then, TMLE is performed within each complete dataset and the results are pooled to obtain the final MI estimate of the ACE and its SE using Rubin's rules.⁹⁶ In MI approaches, it is recommended that all variables in the target analysis (i.e., exposure, outcome, confounders) as well as auxiliary variables (e.g. age in the VAHCS example) be included in the imputation model, i.e., as predictors in each univariate model.

- 4.2.1 Parametric MI with no interaction linear regression to impute missing outcome (MI, no int (linear)) In this approach, the binary exposure and confounders are multiply imputed using logistic regression and the continuous outcome using linear regression. No interaction terms are included in the univariate models.
- 4.2.2 Parametric MI with no interaction predictive mean matching to impute missing outcome (MI, no int) This approach is like the previous one, but predictive mean matching (PMM) is used to multiply impute the outcome, where imputed values are drawn using the nearest observed value after fitting a linear regression. We considered this approach as, like classification and regression trees (CART) or random forest (RF) (approaches 3.2.5 and 3.2.6 described below) it can handle nonlinear associations. 97

4.2.3 Parametric MI with two-way interactions (MI,2-way int)

This approach uses logistic regression to impute the exposure and confounders, PMM to impute the outcome, and includes in the relevant univariate FCS models two-way interactions between exposure and outcome, exposure and each confounder, each confounder and outcome, and all two-way confounder-confounder interactions. Interaction terms are themselves imputed using the R mice "passive" approach, i.e., generated within each cycle of the MI algorithm from current values of relevant variables involved in the interaction term.⁹⁸

4.2.4 Parametric MI with two-, three-, and four-way interactions (MI, higher int)

The models with two-way interactions described above are further extended in this approach to additionally include three- and four-way interactions between the confounders.

4.2.5 MI using classification and regression trees (MI, CART)

In the two final MI approaches, all variables with missing data are multiply imputed using a recursive partitioning technique, using either CART or RF. Both of these methods are available in the *mice* package in R⁹⁸ and have been proposed to enable imputation that can more flexibly allow for interactions and non-linearities.⁹⁹ In CART, for a given variable with missing data, a tree is fitted, with all other variables in the imputation as predictors. Each record will belong to a donor leaf, from which a randomly selected value for the variable will be taken as the imputed value.⁹⁹

4.2.6 MI using random forest (MI, RF)

In RF, multiple bootstrap samples are drawn from the complete dataset and for each of these a separate tree is fitted. Each tree contributes a donor leaf, and a randomly selected value for the variable will be taken from all these donors.⁹⁹

5 Simulation study

To compare the performance of the above-described methods for handling missing data, we performed a simulation study, based on the VAHCS case study. We simulated 2,000 datasets, each including 2,000 records, as outlined below. We used samples of size 2,000, which was larger than the number of VACHS female participants (n=1,000), because we did not want sample size to be an issue and it is known that data-adaptive algorithms perform better with larger sample sizes. ⁹² In all scenarios, we determined the values of parameters for the data generation models by fitting similar models to the available data in VAHCS except where noted otherwise. **Supplementary Table 1** shows the parameter values used for simulating the data and **Supplementary Table 2** the distribution of the variables in the simulated data based on the specified parameter values.

5.1 Generating the complete data

We generated variables sequentially according to the DAG shown in **Figure 2**.

We used parametric regression models to generate the data and considered three scenarios (simple, complex 1, and complex 2) with increasing levels of complexity in terms of confounder-confounder interaction terms involved. Specifically, for all scenarios we generated a normally distributed auxiliary variable A and a set of binary confounders $Z = (Z_1, Z_2, Z_3, Z_4, Z_5)$ where confounders Z_2, Z_3 , and Z_4 were generated via regression on A. The models for generating these variables are detailed below (where it is assumed that all binary variables are coded 0/1 and $logit^{-1}((\cdot)) = exp(\cdot)/(1 + exp(\cdot))$:

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\begin{split} &A{\sim}N(0,1)\\ &Z_1{\sim}Binomial(1,logit^{-1}(\alpha_0))\\ &Z_2{\sim}Binomial\big(1,logit^{-1}(\beta_0+\beta_1A)\big)\\ &Z_3{\sim}Binomial(1,logit^{-1}(\gamma_0+\gamma_1A))\\ &Z_4{\sim}Binomial\big(1,logit^{-1}(\delta_0+\delta_1A)\big)\\ &Z_5{\sim}Binomial(1,logit^{-1}(\zeta_0)) \end{split}
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In generating confounders Z_3 and Z_4 , we changed the coefficient value for A from what it was in VAHCS, so that it was a stronger auxiliary variable, and modified the intercepts so that the prevalence of the variables remained the same as in the VAHCS dataset.

The scenarios differed in the exposure and outcome generation models:

Simple scenario: we generated a binary exposure X via a main-effects logistic regression on A and Z, and a continuous outcome Y via a main-effects linear regression on X and Z (**Figure 2**):

$$\begin{split} &X_{simple} \sim Binomial(1, logit^{-1}(\eta_0 + \eta_1 Z_1 + \eta_2 Z_2 + \eta_3 Z_3 + \eta_4 Z_4 + \eta_5 Z_5 + \eta_6 A)) \\ &Y_{simple} \sim N(\theta_0 + \theta_1 X + \theta_2 Z_1 + \theta_3 Z_2 + \theta_4 Z_3 + \theta_5 Z_4 + \theta_6 Z_5, sd = 1) \end{split}$$

Complex scenarios: we generated X via regression on A, Z, and two-way confounder-confounder interactions, and Y via regression on X, Z, and two-, three-, and four-way confounder-confounder interactions. The exposure and outcome models did not include interactions with Z_2 because of the low prevalence (15%) of the confounder:

$$\begin{split} X_{complex} \sim & \text{Binomial}(1, logit^{-1}(\eta_0^* + \eta_1 Z_1 + \eta_2 Z_2 + \eta_3 Z_3 + \eta_4 Z_4 + \eta_5 Z_5 + \eta_6 A + \eta_7 Z_1 Z_3 + \eta_8 Z_1 Z_4 \\ & \quad + \eta_9 Z_1 Z_5 + \eta_{10} Z_3 Z_4 + \eta_{11} Z_3 Z_5 + \eta_{12} Z_4 Z_5)) \\ Y_{complex} \sim & N(\theta_0^* + \theta_1 \ X + \theta_2 \ Z_1 + \theta_3 \ Z_2 + \theta_4 \ Z_3 + \theta_5 \ Z_4 + \theta_6 \ Z_5 + \theta_7 Z_1 Z_3 + \theta_8 Z_1 Z_4 + \theta_9 Z_1 Z_5 + \theta_{10} Z_3 Z_4 \\ & \quad + \theta_{11} Z_3 Z_5 + \theta_{12} Z_4 Z_5 + \theta_{13} Z_1 Z_3 Z_4 + \theta_{14} Z_1 Z_3 Z_5 + \theta_{15} Z_1 Z_4 Z_5 + \theta_{16} Z_3 Z_4 Z_5 \\ & \quad + \theta_{17} Z_1 Z_3 Z_4 Z_5, sd = 1) \end{split}$$

We considered two complex scenarios, setting the coefficient values for the interaction terms to values approximately two times larger (complex scenario 1) or four times larger (complex scenario 2) than what was observed in the VAHCS data. The coefficient values for the interaction terms ranged from -1.6 to 0.3

and -1.2 to 1.7 respectively in the exposure and outcome models for the complex scenario 1 and from -3.2 to 0.5 and -2.4 to 3.4 respectively in the exposure and outcome models for the complex scenario 2. In terms of the other regression coefficients, for the exposure model, we modified the coefficient value for A, so that it was a stronger auxiliary variable and the coefficient value for Z_4 , so that it was less strongly associated with X. We modified the intercept so that the prevalence of X was approximately 15% in the simulated data (12% in VAHCS) in all scenarios. For the outcome model, we modified the coefficient values for Z_2 , Z_4 , and Z_5 , so that they were stronger confounders (the coefficient values for the confounders ranged from 0.1 (for Z_1) to 0.7 (for Z_3) in the simulation study). Under all outcome generation models, we set the coefficient value for $X(\theta_1)$, which is the true value of the ACE, to 0.2. This is a moderately sized effect in that the null hypothesis of no causal effect is formally rejected (p < 0.05) in approximately 80% of the simulated datasets. We modified the intercept in the outcome model so that the mean of Y remained 0.

5.2 Imposing missing data

We considered 11 missingness scenarios, defined by m-DAGs (causal diagrams with missingness indicators for each variable with incomplete data as nodes in the DAG). These causal diagrams differ in the presence of arrows from confounders, exposure, and outcome to the missingness indicators for other variables or to their own missingness indicators, and thereby in the set of conditional independencies they imply. At These m-DAGs represent all missingness scenarios in point-exposure epidemiological studies that are distinct in terms of the implications of these conditional independencies for the identifiability of key parameters (**Figure 3**, also refer to the paper by Moreno-Betancur et al. At for details on the development of these representative m-DAGs).

To reflect the real VAHCS data, we imposed missingness on Z_2 , Z_3 , Z_4 , X and Y, through generating missingness indicators M_{Z_2} , M_{Z_3} , M_{Z_4} , M_X and M_Y , coded 1 if the variable was missing and 0 if observed. We considered variables A, Z_1 , and Z_5 , which had a small proportion of missing values within VAHCS (<10% each, **Table 1**) as fully observed in the simulation study. The models used for generating the missingness indicators were as below:

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\begin{split} & \mathsf{M}_{Z_2} \! \sim \! \mathsf{Binomial} \big( 1, \mathsf{logit}^{-1} (\iota_0 + \iota_1 Z_1 + \iota_2 Z_5 + \iota_3 Z_2 + \iota_4 X + \iota_5 Y) \big) \\ & \mathsf{M}_{Z_3} \! \sim \! \mathsf{Binomial} \big( 1, \mathsf{logit}^{-1} (\kappa_0 + \kappa_1 Z_1 + \kappa_2 Z_5 + \kappa_3 Z_3 + \kappa_4 X + \kappa_5 Y + \kappa_6 \mathsf{M}_{Z_2}) \big) \\ & \mathsf{M}_{Z_4} \! \sim \! \mathsf{Binomial} \big( 1, \mathsf{logit}^{-1} (\lambda_0 + \lambda_1 Z_1 + \lambda_2 Z_5 + \lambda_3 Z_4 + \lambda_4 X + \lambda_5 Y + \lambda_6 \mathsf{M}_{Z_2} + \lambda_7 \mathsf{M}_{Z_3}) \big) \\ & \mathsf{M}_X \! \sim \! \mathsf{Binomial} \big( 1, \mathsf{logit}^{-1} (\nu_0 + \nu_1 Z_1 + \nu_2 Z_5 + \nu_3 Z_2 + \nu_4 Z_3 + \nu_5 Z_4 + \nu_6 X + \nu_7 Y + \nu_8 \mathsf{M}_{Z_2} + \nu_9 \mathsf{M}_{Z_3} \\ & \qquad \qquad + \nu_{10} \mathsf{M}_{Z_4} \big) \big) \\ & \mathsf{M}_Y \! \sim \! \mathsf{Binomial} \big( 1, \mathsf{logit}^{-1} (\xi_0 + \xi_1 Z_1 + \xi_2 Z_5 + \xi_3 Z_2 + \xi_4 Z_3 + \xi_5 Z_4 + \xi_6 X + \xi_7 Y + \xi_8 \mathsf{M}_{Z_2} + \xi_9 \mathsf{M}_{Z_3} \\ & \qquad \qquad + \xi_{10} \mathsf{M}_{Z_4} + \xi_{11} \mathsf{M}_X \big) \big) \end{split}
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For each missingness indicator, we set the coefficient values for confounders without missing data (Z_1, Z_5) , confounders with missing data (Z_2, Z_3, Z_4) , and exposure (X) to 0 in the absence of an arrow from the variable to the missingness indicator, and to 0.9 (equivalent to an OR of 2.5) in the presence of an arrow. For

the outcome (Y), we set the coefficient value to 0 in the absence of an arrow from Y to the missingness indicator and to 0.1 (equivalent to an OR of 1.1 for one increment increase in Y on a standardised scale) in the presence of an arrow. As shown in the models above, the regression model for generating M_{Z_3} included the missingness indicator M_{Z_2} , the model for M_{Z_4} included M_{Z_2} and M_{Z_3} , the model for M_X included M_{Z_2} , M_{Z_3} , and M_{Z_4} , and the model for M_Y included all the preceding missingness indicators. We modified the coefficient values for these missingness indicators and the intercepts so that the missingness proportion for each variable and the overall proportions with missing data were the same across all missingness scenarios and approximately the same as in the real VAHCS dataset, except for the outcome, for which the proportion with missing data was increased to 20% (13% in the VACHS data). Also, we set the proportion with missing data for any of the confounders or exposure to 40% (34% in the VAHCS data) and the proportion with missing data for any variables used in the target analysis (exposure, confounders, and outcome) to 50% (40% in the VAHCS data).

5.3 Analysis of the simulated data

For each simulated dataset, we first estimated the ACE of X on Y on the complete data (prior to generating missingness), using TMLE with data-adaptive methods and Z_1 to Z_5 as confounders. We used the TMLE package in R^{85} and fitted the exposure and outcome models using Super Learner. Super Learner is an ensemble learning method that combines predictions from a library of chosen algorithms using a weighting approach, where the weights are proportional to the predictive performance of each algorithm assessed using cross-validation. We followed the current general advice for selecting the candidate algorithms for the Super Learner library, which is to include a range of parametric, semiparametric, and non-parametric methods. Compared the performance of different combinations of methods in terms of bias and computational time (Supplementary Table 3) to select the methods for the Super Learner library used in all analyses for this simulation study: mean (the average), glm (generalized linear model), glm.interaction (generalized linear model with 2-way interactions between all pairs of variables), bayesglm (Bayesian generalized linear model), gam (generalized additive model), glmnet (elastic net regression), earth (multivariate adaptive regression splines), rpart (recursive partitioning and regression trees), rpartPrune (recursive partitioning with pruning), ranger (random forest).

We then applied the nine approaches to handle missing data, described above, to the simulated incomplete datasets. For Ext TMLE and Ext TMLE+MCMI we used the same Super Library as above for the outcome missingness mechanism model. We used the mice package in R to implement all the MI approaches. Due to computational constraints, for each MI approach, we generated five completed datasets, which was fewer that we would do in practice. In the MI approaches where PMM was used to multiply impute the outcome (i.e., MI, no int; MI, 2-way int; MI, higher int), we used the default size of the donor pool in the mice package (n=5). In the MI approach with two-way interactions (MI, 2-way), we included the following

interaction terms in the relevant univariate FCS models: XY, XZ₁, XZ₃, XZ₄, XZ₅, YZ₁, YZ₃, YZ₄, YZ₅, Z₁Z₃, Z₁Z₄, Z₁Z₅, Z₃Z₄, Z₃Z₅, and Z₄Z₅. This approach included all the interaction terms that were included in the regression model for generating the exposure, but not the outcome, under the complex data generation scenarios. In addition to these two-way interactions, in the MI version with two-, three-, and four-way interactions (MI, higher int), we included the $Z_1Z_3Z_4$, $Z_1Z_3Z_5$, $Z_1Z_4Z_5$, $Z_3Z_4Z_5$, $Z_1Z_3Z_4Z_5$ interaction terms in the relevant univariate models. This approach encompassed all the interaction terms included in the regression models for generating the exposure and outcome in the complex scenarios. **Supplementary Tables 4** and **5** show the variables and interaction terms included in each imputation model for MI, 2-way int and MI, higher int approaches respectively. In MI, CART and MI, RF we used the default settings of the mice package for the hyperparameters (i.e., complexity parameter = 0.0001 and minimum leaf size = 5 for CART, number of trees to grow = 10 for RF). 98

5.4 Evaluation criteria

We compared the performance of the approaches for handling missing data by calculating bias (the difference in the estimated ACE averaged over 2000 simulated datasets and the true value of the ACE) and relative bias (bias divided by the true ACE, expressed as a percentage). We also calculated the empirical and model-based SEs, percent error in average model-based SE relative to the empirical SE, the coverage probability of the 95% CI, and the bias-eliminated coverage probability. For all measures, Monte-Carlo SEs were obtained. The formulae used for these calculations can be found in Morris et al¹⁰².

All analyses were performed in R version 3.6.1.¹⁰³

6 Simulation Study Results

6.1 TMLE performance in the complete data

Supplementary Table 6 shows the performance of TMLE in estimating the ACE in the simulated complete datasets (before generating missingness), compared with a main-effects regression approach as well as a g-computation approach that included all two-way confounder-confounder interactions, excluding interactions with Z₂. The relative bias was <1% for the three approaches in the simple scenario, it was 32% for outcome regression and <2% using the other two methods in the complex scenario 1, and 107% for outcome regression, 8% for g-computation, and 1% for TMLE in the complex scenario 2. These results confirm that a main-effects regression model would suffer from misspecification bias under the complex scenarios 1 and 2, and so would g-computation in the complex scenario 2, though to a lesser extent.

6.2 Performance of missing data methods

6.2.1 Bias

Figure 4 shows the relative bias of the assessed missing data methods in ACE estimation for the 11 m-DAGs for the simple scenario, and complex scenarios 1 and 2 (see **Supplementary Tables 7-9** for other

performance measures and Monte-Carlo SEs). Complete-case analysis and Ext TMLE yielded small biases (relative bias \leq 5%) for m-DAGs T, A, B, D, and E across all the scenarios. For the same m-DAGs, the Ext TMLE+MCMI approach was more biased (relative bias 6%-16%) compared with complete-case analysis and Ext TMLE. Of all the m-DAGs, for all the scenarios, the three non-MI approaches led to largest biases for m-DAGs H, I, J (relative bias 9%-25%).

Within each of the three scenarios, the performances of the parametric MI approaches that used either a linear regression or PMM to impute outcome data and did not include any interaction terms were similar to each other. In the simple scenario, these approaches produced small bias for m-DAGs T, A, B, C, D, E, F, I (relative bias $\leq 9\%$), and higher bias for m-DAGs G, H, J (relative bias $\leq 11\%$). Compared with the simple scenario, these approaches led to higher bias for m-DAGs T, A, D, E, F for the complex scenario 1 (relative bias $\leq 12\%$) and all m-DAGS for the complex scenario 2 (relative bias $\leq 12\%$). Across all the scenarios, the highest bias was observed for m-DAG H.

The parametric MI approaches that included the two-way interactions and two-, three-, and four-way interactions had comparable performance to each other within each of the three scenarios. Including interaction terms in the imputation model did not have a large impact on the results for the simple scenario, but it reduced the bias seen with MI without interactions for m-DAGs T, A, D, E, F for the complex scenario 1 (relative bias 0%-5%) and all m-DAGs for the complex scenario 2 (relative bias ≤19%).

Across the three scenarios, MI, CART produced estimates with similar bias. Also, MI, RF yielded estimates with similar bias for the scenarios, which was consistently higher than MI, CART (relative bias ≤27% for MI, CART and 18%-50% for MI, RF). For both approaches, of all the m-DAGs, bias was smallest for m-DAGs T, A, D, and F. Compared with the parametric MI approaches without interaction, MI, CART and MI, RF performed worse for all the m-DAGs under the simple scenario, while MI, CART performed better for m-DAGs T, A, D, F under the complex scenario 1 and all the m-DAGs under the complex scenario 2. MI, RF performed better than the parametric MI approaches without interaction for m-DAGs T, A, D, and F under the complex scenario 2. When compared with parametric MI approaches with interactions, MI, RF performed less well across the three scenarios and all the m-DAGs. Also, MI, CART performed less well than parametric MI approaches with interactions under the simple scenario and complex scenario 1, but its performance was more similar to parametric MI approaches with interactions under the complex scenario 2.

6.2.2 Empirical standard error and relative error in model-based standard error

For each missing data method, the empirical SEs (**Figure 5**) were generally similar across all the m-DAGs and scenarios. The SEs using complete-case analysis and Ext TMLE were similar (both between 0.11-0.15) and were somewhat larger compared with the Ext TMLE+MCMI (0.10-0.14) and all the MI approaches (0.06-0.14). Except for MI, RF, which had a lower empirical SE (0.6-0.8), the SEs obtained from the MI approaches were broadly similar with each other (0.09-0.14) and with the Ext TMLE+MCMI approach.

The model SEs were underestimated (**Figure 6**) using non-MI methods and overestimated using MI methods, across all scenarios and m-DAGs, with the degree of error lowest under the simple scenario and highest under the complex scenario 2. Within each scenario, the performance of non-MI approaches was similar. The performance of the MI approaches was also generally similar within each scenario, except MI, RF, which produced model SEs with considerably larger error.

6.2.3 Coverage

The coverage probabilities of the 95% CI (**Figure 7**) for the three non-MI approaches were similar within each of the scenarios, with ranges 89%-94%, 89%-92%, and 84%-90% for the simple, complex scenario 1 and 2, respectively. They were also broadly similar for the MI approaches, with ranges 94%-96%, 95%-97%, and 91%-99% for the simple scenario, and complex scenarios 1 and 2 respectively, except for MI, RF, for which it was somewhat larger, ranging from 96% to 100% across the three scenarios.

7 Application to the VAHCS case study

Similar to the analysis of the simulated data, we conducted the analysis of the VAHCS case study using the TMLE package in R,85 fitting the models using Super Learner, 100 including the following methods in the Super Learner library: mean, glm, glm.interaction, bayesglm, gam, glmnet, earth, rpart, rpartPrune, ranger. We applied the same nine missing data methods described previously. Unlike in the simulations, a small proportion of participants had missing data for parental divorce (Z_1) and parental education (Z_5) (**Table 1**), which were handled here in the same way as missing data for the other confounders. Also, the auxiliary variable age (A) had 9.3% missing data, which was multiply imputed in all the MI approaches. For the MI approaches, 100 imputations were performed. Results are shown in **Table 2**. The obtained effect sizes were small and largely similar using different methods, with the exception of MI, no int (linear) and MI, no int which yielded somewhat larger effect sizes. The standard errors for MI approaches were larger than the non-MI methods. This finding could be explained by the downward and upward biases in model SEs for non-MI and MI approaches, respectively, which we observed in our simulation study (Figure 5). For example, using the relative percent error in model SEs averaged over all m-DAGs and the three scenarios in the simulations, the corrected SEs in the case study would be 0.14 for complete-case analysis, 0.13 for MI, linear, and 0.11 for MI, RF (average relative % error in model SE for the three approaches were respectively -11.91, 12.43, and 61.88).

Of the MI approaches, MI, RF took the longest to run, followed by MI, CART. Adding interaction terms to parametric MI approaches had a small impact on the time. There were no imputation failures for any of the approaches.

8 Discussion

We compared the performance of currently available methods for handling missing data when estimating the ACE using a TMLE approach where data-adaptive methods were used for exposure and outcome models. We considered one simple and two complex scenarios for the exposure and outcome data generating models, and eleven missingness mechanisms which represented the range of plausible and distinct missingness mechanisms in epidemiological longitudinal cohort studies.⁸⁴ Overall, no approach was found to perform well across all scenarios and missingness mechanisms. For the non-MI methods, the degree of bias depended on the missingness mechanism and was generally smaller for the missingness mechanisms where outcome did not influence missingness in any of the variables. For parametric MI approaches, bias was generally smaller for the missingness mechanisms where outcome variable did not directly influence missingness in the outcome. For these approaches, bias additionally depended on the complexity of the data generation scenario, getting increasingly larger as the data generation became more complex. This bias was reduced when interaction terms were included in the imputation model. The bias of MI approaches using machine learning algorithms (MI, CART and MI, RF) was also influenced by the missingness mechanism, but not the data generation, and was smaller for missingness mechanisms where missingness in the outcome was not influenced by the outcome or any other variable with missing data. Of all the assessed approaches, MI, RF yielded estimates with the highest bias across all missingness mechanisms and scenarios. For each missing data method, the precision around the effect estimate was similar in all the missingness mechanisms and scenarios. It was slightly larger for complete-case analysis and extended TMLE, and was smallest for MI, RF. For all the non-MI methods, the model SEs had a downward bias. The model SEs were broadly similar across the three scenarios and missingness mechanisms but larger for the complex scenarios. For the MI approaches, the model SEs were upwardly biased, similar across the different missingness mechanisms for each approach, and larger for the complex scenarios. Except for MI, RF, which had a considerably higher error, the errors in model SEs were similar for the MI approaches.

In our simulation study, under m-DAGs where missingness did not depended on the outcome for any variable and the conditional distribution of the outcome was recoverable by a complete-case analysis (m-DAGs T, A, B, D, E ⁸⁴), the complete case analysis and extended TMLE in the sample with complete exposure and confounders produced estimates with small bias as expected, regardless of the complexity of the data generation procedure. The extended TMLE+MCMI approach yielded estimates with higher bias across these scenarios. A key assumption under which the MCMI approach has been shown to be unbiased is when the exposure or outcome only depend on the confounder when the confounder is observed. R6,95 This assumption is unlikely to be plausible in a prospective cohort study, such as VAHCS, where the data are not being used for medical decision-making. Therefore, we did not evaluate the methods under missingness scenarios where this assumption held.

Our results illustrate the difficulty of using MI to handle missing data when TMLE with data-adaptive approaches are used for ACE estimation. Under the simple scenario, the performance of the parametric MI model with no interactions generally led to smaller bias under missingness mechanisms where outcome variable did not directly influence missingness in the outcome (m-DAGs T, A, B, C, D, E, F, I) and higher bias under missingness mechanisms where outcome directly influenced missingness in the outcome (G, H, J). In contrast, for the complex scenarios, where the imputation model with no interactions was misspecified and likely incompatible with the analysis model (because Super Learner makes it uncertain which model has more weight), these MI approaches produced estimates with higher bias, even for m-DAGs T, A, B, C, D, E, F, I. Including interaction terms in the imputation model improved the performance of parametric MI in these scenarios. This could be explained by the fact that in this simulation study the complex scenarios were defined based on the presence and strength of confounder-confounder interaction terms in the regression models for generating exposure and outcome, meaning that the MI models with interactions would be approximately correctly specified. Unfortunately, however, in practice the data generating process underlying observational data is rarely fully understood. This limited knowledge, which itself is a motivation for using TMLE with data-adaptive approaches, makes defining parametric imputation models that are compatible with analysis models challenging.

Within the FCS framework, recursive partitioning techniques, such as CART and RF, have been suggested as alternative approaches that could automatically incorporate interactions and non-linearities in the imputation process. 99 Two previous simulation studies have shown that MI, CART performs better than parametric MI where the imputation model does not include interaction terms. 99,104 In these studies, where target analysis was an outcome regression model with interactions, interaction effects estimated following MI using CART were considerably less biased compared with the parametric MI with no interactions. The difference in bias for estimates of the main effects was less pronounced and not necessarily always smaller. The studies imposed missingness in outcome only⁹⁹ or outcome and four of the five covariates in the outcome generation model¹⁰⁴. In both, missingness only depended on fully observed variables and a correctly specified parametric analysis model was used. In the present study, compared with parametric MI approaches with no interaction, the bias in the estimated ACE was higher using MI, CART under the simple scenario, but lower under the complex scenarios. When compared with parametric MI approaches with interactions, MI, CART had higher bias for the simple scenario and complex scenario 1, but it had a similar bias with these approaches for the complex scenario 2. Bias in the ACE estimates following MI, RF was larger than MI, CART across all the scenarios. This was in line with Dove et al.'s simulation study results, where the estimates obtained following MI, RF were generally prone to higher bias than MI, CART.99 The authors of that study speculated that this poorer performance might be because the tree building process for RF could miss interactions. An interesting observation in the present study was that the biases of MI, CART and MI, RF were stable across the scenarios, i.e., they did not appear to be sensitive to the presence and

strength of interaction terms in the regression models for generating exposure and outcome. Put together with the considerations that the MI, CART implementation might be more convenient than attempting to incorporate interactions and non-linearities in an imputation model, and that the functional relation between variables is often unknown, these results suggest that MI, CART might be an attractive alternative to parametric MI, especially when working with datasets with many covariates.

In the present study, all non-MI approaches underestimated the model SE and led to below nominal 95% CIs. This was also the case for TMLE performed using the complete data and was not surprising. The TMLE variance estimation is valid if both the exposure and outcome models are consistently estimated and the Donsker class condition is satisfied.⁹ It is, however, unclear if the latter is met when data-adaptive approaches are used for exposure and outcome models.¹⁰¹ This bias has been observed in other simulation studies,^{11,101,105} and developing approaches to tackle it is an area of ongoing research. In addition, the MI Rubin variance estimator is expected to perform poorly in the presence of incompatibility,¹⁰⁶ which might explain the error we observed in model SEs for the MI approaches. This indicates that incompatibility is the key challenge of using MI together with TMLE where models are fitted using Super Learner, not only in terms of bias of point estimates, but also in terms of bias in variance estimates. A promising alternative approach for obtaining MI SE in the presence of incompatibility has been recently proposed using the bootstrap,¹⁰⁶ but we did not explore this because of the computational constraints.

Our simulation study was broadly based on VAHCS to emulate a realistic scenario. We considered 11 missingness mechanisms, which allowed us to evaluate the performance of different approaches to handle missing data using a finer-grained framework for illustrating and assessing missing data assumptions than the more commonly used missing at random (MAR)-missing not at random (MNAR) framework. For each MI approach, due to computational constraints we generated five completed datasets, which is fewer than we would do in practice. He do not expect it to have affected the comparison between MI approaches, but it could have affected comparison of non-MI with MI methods. Our simulated data had a fairly simple structure across the three assessed scenarios, with five binary confounders, a continuous outcome, and no effect modification. Even under this simple structure, our results could provide useful guidance for handling missing data when estimating the ACE using a TMLE approach. Extensions of our study could investigate the performance of these missing data methods for datasets with high-dimensional confounders, binary outcomes, and in the presence of effect modification.

9 Conclusion

We evaluated the performance of nine available approaches to handle missing data when estimating the ACE using TMLE with data-adaptive methods in a cohort study. Our results suggest that no approach performs well across all scenarios and missingness mechanisms. With missingness mechanisms where outcome does not influence missingness in any variable a complete-case analysis or an extended TMLE

approach in the sample with complete exposure and confounder data could produce estimates with small bias regardless of the data generation, but potentially with some degree of loss of precision. Parametric MI could also be expected to perform well in terms of bias, particularly for missingness mechanisms where outcome variable does not directly influence missingness in the outcome, when the imputation models are correctly specified. While, in practice, knowledge on what a correctly specified model would be is often limited, opting for saturated imputation models within the limits of the data might be a helpful strategy for improving the performance of parametric MI approaches. In settings with many covariates with likely interactions and non-linearities, it could quickly become cumbersome to model these in parametric MI, in which case MI, CART might be a useful alternative. We recommend considering missing data mechanism and, if using MI, opting for a saturated parametric or data-adaptive imputation model for handling missing data in TMLE estimation.

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Author Contributions

All authors participated in planning the simulation and case studies, the manuscript, and interpretation of the results. SGD and MMB performed the simulation and case study analyses. SGD led the writing of the manuscript. All authors read and contributed to the manuscript.

Data availability statement

Data from the Victorian Adolescent Health Cohort Study (VAHCS) are not publicly available. Those interested in replicating these findings are welcome to contact the corresponding author, or the VAHCS team (https://www.mcri.edu.au/research/projects/2000-stories/information-researchers).

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Tables

Table 1 – Description of variables used in this study, their distribution and the proportion with missing data among the VAHCS female participants (n=1,000)

	Variable	Type	Grouping/unit	Notation	N (%*)	% with
					coded 1 or	missing
					mean (SD)	data
Auxiliary variable	Age	Continuous	years, measured at wave 2	A	15.4 (0.4)	9.3
Confounder	Parental	Binary	0=Not divorced/separated by wave 6	Z1	221 (22.1)	0.1
	divorce		1= Divorced/separated by wave 6			
	Antisocial	Binary	0=No across all waves 2 to 6	Z2	106 (14.6)	27.4
	behaviour		1=Yes at any wave 2 to 6			
	Depression	Binary	0=CIS-R score <12 across all waves 2 to 6	Z3	516 (59.9)	13.8
	and anxiety		1=CIS-R score ≥12 at any wave 2 to 6			
	Alcohol	Binary	0=No across all waves 2 to 6	Z4	294 (37.2)	21.0
	use	•	1=Yes at any wave 2 to 6			
	Parental	Binary	0=Did not complete high school by wave 6	Z5	364 (37.7)	3.4
	education	-	1=Completed high school by wave 6			
Exposure	Frequent	Binary	0=Less than weekly use across all waves 2 to 6	X	86 (12.4)	30.8
_	cannabis use	-	1=At least weekly use at any wave 2 to 6			
Outcome	CIS-R total	Continuous	z-score, measured at wave 7	Y	0(1)	13.4
	score					
With any mis	sing data					40.3

Abbreviations N number; SD standard deviation; CIS-R revised clinical interview schedule *Proportions reported among those with observed data for the variable

 $Table\ 2-Estimated\ average\ causal\ effect\ (ACE)\ of\ frequent\ cannabis\ use\ during\ adolescence\ on\ CIS-R\ score\ (standardised\ z\text{-score})$

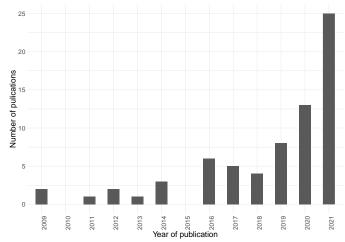
using a TMLE approach under different missing data methods within the VAHCS case study

Method	ACE	Standard	95% confidence	Time to run
	(Difference in	error	interval	
	means)*			
Complete-case	0.09	0.12	-0.14, 0.32	16.4 sec
Ext TMLE**	0.12	0.11	-0.09, 0.33	11.2 sec
Ext TMLE+MCMI***	0.13	0.13	-0.13, 0.39	21.7 sec
MI, no int (linear)	0.20	0.15	-0.09, 0.48	5.0 min
MI, no int	0.20	0.16	-0.11, 0.50	4.6 min
MI, 2-way int	0.16	0.17	-0.17, 0.49	5.8 min
MI, higher int	0.18	0.16	-0.13, 0.49	5.8 min
MI, CART	0.15	0.16	-0.16, 0.45	11.8 min
MI, RF	0.13	0.18	-0.21, 0.48	14.1 min

^{*}Average causal effect estimated as the difference in the mean potential outcome under exposure and under no exposure. **For the Ext TMLE approach records with missing exposure or confounder data were excluded. *** For the Ext TMLE+MCMI approach records with missing exposure data were excluded. Abbreviations - Ext TML: Eextended targeted maximum likelihood estimation (TMLE) approach; Ext TMLE+MCMI: extended TMLE plus missing covariate missing indicator (MCMI) approach; MI, no int (linear): parametric multiple imputation (MI) with no interaction – linear regression to impute missing outcome; MI no int: parametric MI with no interaction – predictive mean matching to impute missing outcome; MI, 2-way int: parametric MI with two-way interactions; MI higher int: parametric MI with two-, three-, and four-way interactions; MI, CART: MI using classification and regression trees; MI, RF: MI using random forest

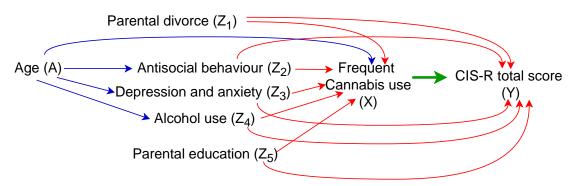
Figures

Figure 1 – Number of studies applying targeted maximum likelihood estimation approach by year of publication between 2009 and November 2021



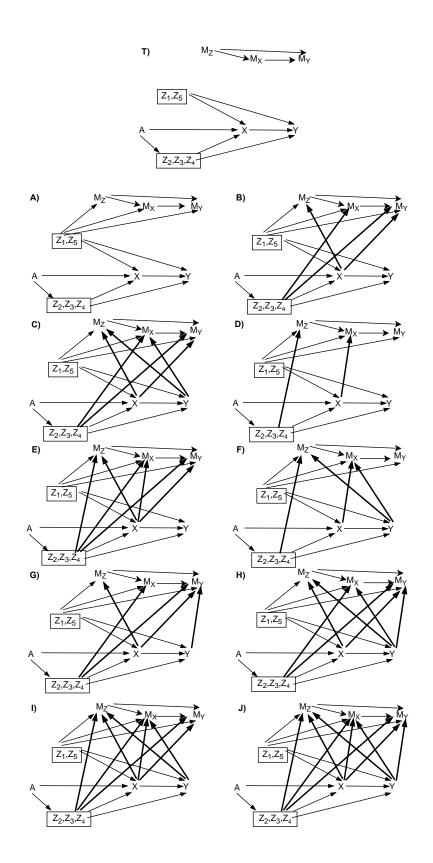
Studies¹²⁻⁸¹ were identified via a search of PubMed for papers that included "targeted maximum likelihood estimation (TMLE)" in their title or abstract. Abstracts were screened to identify studies whose focus was not on methodology and had applied TMLE to estimate causal effect of interest.

Figure 2 – Directed acyclic graph (DAG) used in data generation for the simulation study



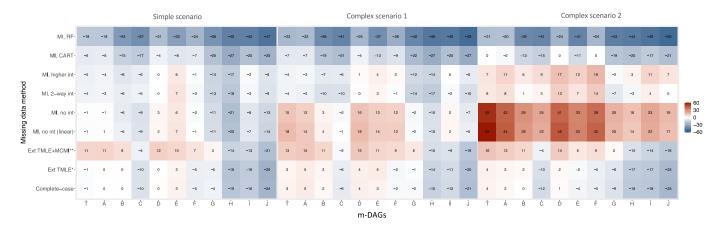
Abbreviations: CIS-R revised clinical interview schedule

Figure 3 – Missingness directed acyclic graphs (m-DAGs) illustrating the missingness scenarios considered in the simulation study. Figure has been adapted from Moreno-Betancur et al. ⁸⁴



For simplicity of exposition, confounders without missing data $(Z_1 \text{ and } Z_5)$ are presented on a single node and confounders with missing data (Z_2, Z_3, Z_4) on another single node. Also, only one missingness indicator has been included for confounders with missing data (M_Z) , coded as 1 when any of the variables Z_2 , Z_3 , Z_4 have missing data and as 0 when none has missing data. The m-DAG T (trivial m-DAG) represents the simplest missingness scenario and corresponds to a missing completely at random mechanism.

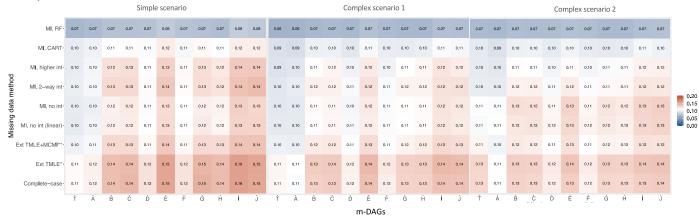
Figure 4 – Relative bias (%) in ACE estimation using different missing data methods for the 11 assessed missingness directed acyclic graphs (m-DAGs)



*For the Ext TMLE approach records with missing exposure or confounder data were excluded. ** For the Ext TMLE+MCMI approach records with missing exposure data were excluded.

The Monte Carlo standard errors for absolute bias ranged from 0.002 to 0.003 in the simple scenario, 0.001 to 0.003 in the complex scenario 1, and 0.002 to 0.003 in the complex scenario 2. Also see Supplementary Tables 7-9 for more detail. Abbreviations - Ext TML: Eextended targeted maximum likelihood estimation (TMLE) approach; Ext TMLE+MCMI: extended TMLE plus missing covariate missing indicator (MCMI) approach; MI, no int (linear): parametric multiple imputation (MI) with no interaction – linear regression to impute missing outcome; MI no int: parametric MI with no interaction – predictive mean matching to impute missing outcome; MI, 2-way int: parametric MI with two-way interactions; MI higher int: parametric MI with two-, three-, and four-way interactions; MI, CART: MI using classification and regression trees; MI, RF: MI using random forest

Figure 5 – Empirical standard error in ACE estimation using different missing data methods for the 11 assessed missingness directed acyclic graphs (m-DAGs)

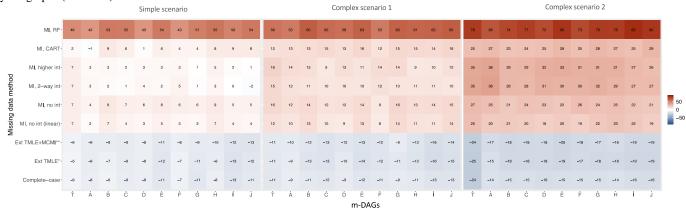


The midpoint in the graph is the average empirical standard error across all scenarios and m-DAGs (0.11).

The Monte Carlo standard errors ranged from 0.001 to 0.002 for all scenarios. Also see Supplementary Tables 7-9 for more detail. Abbreviations - Ext TML: Eextended targeted maximum likelihood estimation (TMLE) approach; Ext TMLE+MCMI: extended TMLE plus missing covariate missing indicator (MCMI) approach; MI, no int (linear): parametric multiple imputation (MI) with no interaction – linear regression to impute missing outcome; MI no int: parametric MI with no interaction – predictive mean matching to impute missing outcome; MI, 2-way int: parametric MI with two-way interactions; MI higher int: parametric MI with two-, three-, and four-way interactions; MI, CART: MI using classification and regression trees; MI, RF: MI using random forest

^{*}For the Ext TMLE approach records with missing exposure or confounder data were excluded. ** For the Ext TMLE+MCMI approach records with missing exposure data were excluded.

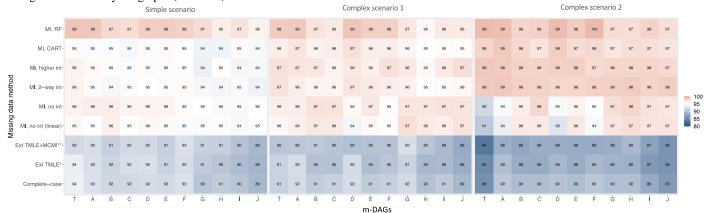
Figure 6 – Relative % error in model standard error estimation using different missing data methods for the 11 assessed missingness directed acyclic graphs (m-DAGs)



*For the Ext TMLE approach records with missing exposure or confounder data were excluded. ** For the Ext TMLE+MCMI approach records with missing exposure data were excluded.

The Monte Carlo standard errors ranged from 1.40% to 2.53% in the simple scenario, 1.36% to 2.70% in the complex scenario 1, and 1.23% to 3.01% in the complex scenario 2. Also see Supplementary Tables 7-9 for more detail. Abbreviations - Ext TML: Eextended targeted maximum likelihood estimation (TMLE) approach; Ext TMLE+MCMI: extended TMLE plus missing covariate missing indicator (MCMI) approach; MI, no int (linear): parametric multiple imputation (MI) with no interaction – linear regression to impute missing outcome; MI no int: parametric MI with no interaction – predictive mean matching to impute missing outcome; MI, 2-way int: parametric MI with two-way interactions; MI higher int: parametric MI with two-, three-, and four-way interactions; MI, CART: MI using classification and regression trees; MI, RF: MI using random forest

Figure 7 – Coverage probability of the 95% confidence interval in ACE estimation using different missing data methods for the 11 assessed missingness directed acyclic graphs (m-DAGs)



*For the Ext TMLE approach records with missing exposure or confounder data were excluded. ** For the Ext TMLE+MCMI approach records with missing exposure data were excluded.

The Monte Carlo standard errors ranged from 0.24% to 0.70% in the simple scenario, 0.24% to 0.72% the complex scenario 1, and 0.15% to 0.83% in the complex scenario 2. Also see Supplementary Tables 7-9 for more detail. Abbreviations - Ext TML: Eextended targeted maximum likelihood estimation (TMLE) approach; Ext TMLE+MCMI: extended TMLE plus missing covariate missing indicator (MCMI) approach; MI, no int (linear): parametric multiple imputation (MI) with no interaction – linear regression to impute missing outcome; MI no int: parametric MI with no interaction – predictive mean matching to impute missing outcome; MI, 2-way int: parametric MI with two-way interactions; MI higher int: parametric MI with two-, three-, and four-way interactions; MI, CART: MI using classification and regression trees; MI, RF: MI using random forest

Supplementary material

	Model for					sion coeffice								
	Widder for	Intercept	Z1	Z2	Z3	Z4	Z5	Х	Υ	Α	MZ2	MZ3	MZ4	MX
	Z1	-1.30												
	Z2	-1.90								0.40				
	Z3	0.40								0.70				
	Z4	-0.60								-0.70				
		-0.50												
omplete data							Simple sce	nario						
•	Х	-2.90	1.30	1.90	0.40	0.20	-0.30			0.70				
		-0.70	0.10	0.40	0.70	0.20	0.30	0.20		0.70				
	<u> </u>	0.70	0.10	0.40	0.70		omplex sco							
	V	-2.40	1 20	1.00	0.40			1101103						
			1.30	1.90		0.20	-0.30	0.20						
		-0.70	0.10	0.40	0.70	0.20	0.30	0.20						
		-0.85												
		-4.40									4.30			
DAG I		-4.00									3.90	1.40		
		-2.00									1.50	1.50	1.50	
		-1.60									-0.50	0.50	0.50	0.5
	MZ2	-1.45	0.90				0.90							
	MZ3	-5.60	0.90				0.90				4.80			
DAG A	MZ4	-4.70	0.90				0.90				3.90	1.50		
	MX	-2.50	0.90				0.90				1.30	1.50	1.50	
DAG T		-2.10	0.90				0.90				0.10	0.50	0.50	0.7
DAG T MZ MY DAG G MZ MY DAG G MZ MY DAG G MZ MY MY MZ DAG G MZ MX MY MY MZ DAG G MZ MX MY MZ DAG G MZ MX MY MZ DAG G MZ MX MY MZ MZ MZ MZ MZ MZ MZ MZ MZ		-1.60	0.90				0.90	0.90				2.30	2.50	
DAG T		-5.20	0.90				0.90	0.90			4.10			
DAG P												2.00		
DAG B		-4.40	0.90	0.00	0.00	0.00	0.90	0.90			3.20	2.00	1.50	
		-3.70	0.90	0.90	0.90	0.90	0.90				1.80	1.50	1.50	
		-3.25	0.90	0.90	0.90	0.90	0.90	0.90			-0.30	0.10	0.10	0.:
		-1.60	0.90				0.90	0.90	0.10					
	MZ3	-5.40	0.90				0.90	0.90	0.10		4.30			
DAG C	MZ4	-4.50	0.90				0.90	0.90	0.10		3.50	1.30		
	MX	-3.70	0.90	0.90	0.90	0.90	0.90		0.10		1.70	1.50	1.50	
	MY	-3.25	0.90	0.90	0.90	0.90	0.90	0.90			-0.40	0.10	0.10	0.:
	MZ2	-1.60	0.90	0.90			0.90							
		-6.20	0.90		0.90		0.90				4.80			
DAG D		-5.00	0.90		0.50	0.90	0.90	0.90			3.90	1.50		
57105		-2.65	0.90			0.50	0.90	0.50					1 50	
											1.30	1.50	1.50	
		-2.10	0.90	0.00			0.90	0.00			0.10	0.10	0.10	0.1
		-1.75	0.90	0.90			0.90	0.90						
		-5.70	0.90		0.90		0.90	0.90			4.10			
DAG E		-4.80	0.90			0.90	0.90	0.90			3.20	2.00		
		-3.80	0.90	0.90	0.90	0.90	0.90	0.90			1.50	1.50	1.50	
	MY	-3.20	0.90	0.90	0.90	0.90	0.90	0.90			-0.60	0.10	0.10	0.:
DAG T MZZ DAG B MZZ DAG C MZZ MX MY MY DAG C MZZ MX MY MZ	MZ2	-1.60	0.90	0.90			0.90		0.10					
	MZ3	-6.60	0.90		0.90		0.90		0.10		5.20			
DAG F	MZ4	-5.40	0.90			0.90	0.90		0.10		4.20	1.70		
		-2.55	0.90				0.90	0.90	0.10		1.20	1.30	1.30	
		-2.10	0.90				0.90				-0.30	0.10	0.10	0.4
		-1.60	0.90				0.90	0.90			0.50	0.10	0.10	
											4.10			
DAGG		-5.20	0.90				0.90	0.90				2.00		
טאטט		-4.45	0.90	0.00	0.00	0.00	0.90	0.90			3.20	2.00	1.50	
		-3.70	0.90	0.90	0.90	0.90	0.90				1.70	1.50	1.50	_
		-3.30	0.90	0.90	0.90	0.90	0.90	0.90	0.10		-0.30	0.10	0.10	0.:
	MZ2	-1.60	0.90				0.90	0.90	0.10					
	MZ3	-5.40	0.90				0.90	0.90	0.10		4.30			
DAG H	MZ4	-4.50	0.90				0.90	0.90	0.10		3.50	1.30		
	MX	-3.65	0.90	0.90	0.90	0.90	0.90		0.10		1.50	1.50	1.50	
		-3.30	0.90	0.90	0.90	0.90	0.90	0.90	0.10		-0.50	0.30	3.00	0.:
	MZ2	-1.75	0.90	0.90		-	0.90	0.90	0.10					
		-5.95	0.90		0.90		0.90	0.90	0.10		4.30			
DAGI		-4.80	0.90		5.50	0.90	0.90	0.90	0.10		3.50	1.30		
5,.51				0.90	0.00								1 50	
		-3.80	0.90		0.90	0.90	0.90	0.90	0.10		1.50	1.50	1.50	
		-3.20	0.90	0.90	0.90	0.90	0.90	0.90	0.10		-0.60	0.10	0.10	0.2
		-1.75	0.90	0.90			0.90	0.90	0.10					
	MZ3	-5.95	0.90		0.90		0.90	0.90	0.10		4.30			
DAG J	MZ4	-4.85	0.90			0.90	0.90	0.90	0.10		3.50	1.30		
		-3.80	0.90	0.90	0.90	0.90	0.90	0.90	0.10		1.50	1.50	1.50	
	MY	-3.20	0.90	0.90	0.90	0.90	0.90	0.90	0.10		0.60	0.10	0.10	0.:
r the comple	ex scenarios mode	els for X and Y a	lso include	d interactio	ns as follows	5:								
	z1z3	z1z4	z1z5	z3z4	z3z5	z4z5	z1z3z4	z1z3z5	z1z4z5	z3z4z5	z1z3z4z5			
						ex scenario 1								
	-1.60	-1.20	-0.50	-0.60	0.30	-1.50								
	-0.50	1.00	0.10	0.10	0.40	-0.10	-1.20	-1.00	-0.10	-0.40	1.70			
	-0.50	1.00	0.10	0.10				-1.00	-0.10	-0.40	1.70			
		2.22	4.00	4		ex scenario 2								
	-3.20	-2.30	-1.00	-1.20	0.50	-2.90								
	-0.90	2.00	0.10	0.20	0.70	-0.20	-2.40	-2.00	-0.30	-0.80	3.40			

 $Supplementaty \ Table \ 2 - Distribution of variables in the simulated complete data and prportion with missingness observed in the real VAHCS data and across the 11 simulated missingness mechanisms and the three scenarios considered$

% in simulated complete datasets Z1 Z2 Z3 Z4 Z5 X Y

	Z1	Z2	Z3	Z4	Z5	Х	Υ	
	21	14	59	37	38	15	15	0 (1)
			% wit	h miss	ing va	lue		
		Z2	Z3	Z4	Х	Υ	Z/X	Any
Observed		27	14	21	31	13	34	40
	DAGT	30	15	20	30	20	40	50
	DAG A	30	15	20	30	20	40	50
	DAG B	30	15	20	30	20	40	50
	DAG C	30	15	20	30	20	40	50
	DAG D	30	15	20	30	20	40	50
Simple scenario	DAG E	30	15	20	30	20	40	50
	DAG F	30	15	20	30	20	40	50
	DAG G	30	15	20	30	20	40	50
	DAG H	30	15	20	30	20	40	50
	DAGI	30	15	20	30	20	40	50
	DAG J	30	15	20	30	20	40	50
	DAGT	30	15	20	30	20	40	50
	DAG A	30	15	20	30	20	40	50
	DAG B	30	15	20	30	20	40	50
	DAG C	30	15	20	30	20	40	50
	DAG D	30	15	20	30	20	40	50
Complex scenario 1	DAG E	30	15	20	30	20	40	50
	DAG F	30	15	20	30	20	40	50
	DAG G	30	15	20	30	20	40	50
	DAG H	30	15	20	30	20	40	50
	DAGI	30	15	20	30	20	40	50
	DAG J	30	15	20	30	20	40	50
	DAGT	30	15	20	30	20	40	50
	DAG A	30	15	20	30	20	40	50
	DAG B	30	15	20	30	20	40	50
	DAG C	30	15	20	30	20	40	50
	DAG D	30	15	20	30	20	40	50
Complex scenario 2	DAG E	30	15	20	30	20	40	50
	DAG F	30	15	20	30	20	40	50
	DAG G	30	15	20	30	20	40	50
	DAG H	30	15	20	30	20	40	50
	DAGI	30	15	20	30	20	40	50
	DAG J	30	15	20	30	20	40	50

	Estimated mean	Absolute		Relative bias	Covera	-	Bias eliminate		Empiric		Model		Relative % error		
	difference	Estimate	MC SE	(%)	Estimate	MC SE	Estimate	MC SE	Estimate	MC SE	Estimate	MC SE	Estimate	MC SE	Time to ru
							Simple sc								
1	0.20	0.00	0.00	0.25	0.93	0.01	0.93	0.01	0.08	0.00	0.08	0.00	-5.39	1.50	8.9
2	0.20	0.00	0.00	0.29	0.94	0.01	0.93	0.01	0.08	0.00	0.08	0.00	-5.76	1.49	8.7
3	0.21	0.01	0.00	3.63	0.91	0.01	0.91	0.01	0.10	0.00	0.08	0.00	-17.93	1.30	10.5
4	0.20	0.00	0.00	0.27	0.93	0.01	0.93	0.01	0.08	0.00	0.08	0.00	-5.61	1.49	14.2
5	0.20	0.00	0.00	0.27	0.94	0.01	0.94	0.01	0.08	0.00	0.08	0.00	-4.33	1.51	29.9
6	0.20	0.00	0.00	0.25	0.94	0.01	0.94	0.01	0.08	0.00	0.08	0.00	-4.19	1.52	3.88
7	0.20	0.00	0.00	0.30	0.93	0.01	0.94	0.01	0.08	0.00	0.08	0.00	-5.02	1.50	4.58
8	0.20	0.00	0.00	0.30	0.94	0.01	0.94	0.01	0.08	0.00	0.08	0.00	-3.94	1.52	7.6
9	0.20	0.00	0.00	0.24	0.94	0.01	0.94	0.01	0.08	0.00	0.08	0.00	-4.10	1.52	1.7-
							Complex sc	enario 1							
1	0.21	0.01	0.00	3.11	0.92	0.01	0.92	0.01	0.08	0.00	0.08	0.00	-6.50	1.48	16.00
2	0.20	0.00	0.00	1.98	0.93	0.01	0.93	0.01	0.08	0.00	0.08	0.00	-5.71	1.49	11.05
3	0.22	0.02	0.00	7.99	0.91	0.01	0.91	0.01	0.09	0.00	0.08	0.00	-11.40	1.40	13.62
4	0.20	0.00	0.00	2.04	0.93	0.01	0.93	0.01	0.08	0.00	0.08	0.00	-5.50	1.49	27.69
5	0.20	0.00	0.00	2.16	0.93	0.01	0.93	0.01	0.08	0.00	0.08	0.00	-5.09	1.50	26.22
6	0.21	0.01	0.00	4.19	0.92	0.01	0.93	0.01	0.08	0.00	0.08	0.00	-5.81	1.49	4.9
7	0.21	0.01	0.00	2.59	0.93	0.01	0.93	0.01	0.08	0.00	0.08	0.00	-5.20	1.50	5.8
8	0.21	0.01	0.00	4.26	0.93	0.01	0.93	0.01	0.08	0.00	0.08	0.00	-4.69	1.51	25.17
9	0.21	0.01	0.00	4.00	0.92	0.01	0.93	0.01	0.08	0.00	0.08	0.00	-5.63	1.49	2.49
							Complex see	enario 2							
1	0.22	0.02	0.00	8.71	0.85	0.01	0.86	0.01	0.10	0.00	0.07	0.00	-23.45	1.21	12.98
2	0.20	0.00	0.00	0.52	0.87	0.01	0.87	0.01	0.09	0.00	0.07	0.00	-21.07	1.25	12.45
3	0.22	0.02	0.00	8.03	0.84	0.01	0.85	0.01	0.10	0.00	0.08	0.00	-25.90	1.17	15.77
4	0.20	0.00	0.00	0.13	0.87	0.01	0.87	0.01	0.10	0.00	0.08	0.00	-21.10	1.25	32.21
5	0.20	0.00	0.00	0.64	0.87	0.01	0.87	0.01	0.09	0.00	0.07	0.00	-21.30	1.24	23.52
6	0.24	0.04	0.00	17.66	0.82	0.01	0.85	0.01	0.11	0.00	0.08	0.00	-24.32	1.20	6.4
7	0.20	0.00	0.00	0.67	0.87	0.01	0.87	0.01	0.10	0.00	0.08	0.00	-20.71	1.25	7.0
8	0.23	0.03	0.00	14.42	0.84	0.01	0.85	0.01	0.10	0.00	0.08	0.00	-23.52	1.21	35.2
9	0.24	0.04	0.00	17.77	0.82	0.01	0.85	0.01	0.11	0.00	0.08	0.00	-24.45	1.19	3.50

Abbreviations MC SE Monte Carlo standard error

Libraries were:

Libraries were:
lib1 <-("SL.mean", "SL.glm", "SL.glm.interaction", "SL.bayesglm", "SL.gamm", "SL.glmnet", "SL.earth", "SL.rpart", "SL.rpart", "SL.rpartPrune", "SL.ranger")
lib2 <-("SL.mean", "SL.glm", "SL.glm.interaction", "SL.bayesglm", "SL.gam", "SL.glmnet", "SL.earth", "SL.rpart", "SL.rpartPrune", "SL.ranger")
lib3 <-("SL.mean", "SL.glm", "SL.glm.interaction", "SL.bayesglm", "SL.gam", "SL.glmnet", "SL.rpart", "SL.rpart", "SL.rpartPrune", "SL.ranger", "SL.step.interaction")
lib4 <-("SL.mean", "SL.glm", "SL.glm.interaction", "SL.bayesglm", "SL.gamm, "SL.glmnet", "SL.spart", "SL.rpart", "SL.rpartPrune", "SL.ranger", "SL.step.interaction")
lib5 <-("SL.mean", "SL.glm", "SL.glm.interaction", "SL.bayesglm", "SL.gam", "SL.glmnet", "SL.earth", "SL.rpart", "SL.rpartPrune", "SL.ranger", "SL.spart, "SL.glmnet", "SL.gamm, "SL.glmnet", "SL.earth", "SL.rpartPrune", "SL.ranger", "SL.spart, "SL.gamm, "SL.g

Supplementary Table 4 - The variables and interaction terms included in each imputation model for a multiple imputation approach that included all two-way interactions

									Var	iablesi	includ	ed in ir	nputat	ion mo	odel								
Variable imputed	Α	Z1	Z2	Z3	Z4	Z5	Х	Υ	XY	XZ1	YZ1	XZ3	YZ3	XZ4	YZ4	XZ5	YZ5	Z1Z3	Z1Z4	Z1Z5	Z3Z4	Z3Z5	Z4Z5
Z2	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Z3	1	1	1	0	1	1	1	1	1	1	1	0	0	1	1	1	1	0	1	1	0	0	1
Z4	1	1	1	1	0	1	1	1	1	1	1	1	1	0	0	1	1	1	0	1	0	1	0
X	1	1	1	1	1	1	0	1	0	0	1	0	1	0	1	0	1	1	1	1	1	1	1
Υ	1	1	1	1	1	1	1	0	0	1	0	1	0	1	0	1	0	1	1	1	1	1	1

Supplementary Table 5 - The variables and interaction terms included in each imputation model for a multiple imputation approach that included all two-, three-, and four-way interactions

									Var	iables	includ	ed in ir	nputa	tion mo	odel													
Variable imputed	Α	Z1	Z2	Z3	Z4	Z5	Х	Υ	XY	XZ1	YZ1	XZ3	YZ3	XZ4	YZ4	XZ5	YZ5	Z1Z3	Z1Z4	Z1Z5	Z3Z4	Z3Z5	Z4Z5	Z1Z3Z4	Z1Z3Z5	Z1Z4Z5	Z3Z4Z5	Z1Z3Z4Z5
Z2	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Z3	1	1	1	0	1	1	1	1	1	1	1	0	0	1	1	1	1	0	1	1	0	0	1	0	0	1	0	0
Z4	1	1	1	1	0	1	1	1	1	1	1	1	1	0	0	1	1	1	0	1	0	1	0	0	1	0	0	0
Х	1	1	1	1	1	1	0	1	0	0	1	0	1	0	1	0	1	1	1	1	1	1	1	1	1	1	1	1
V	1	1	1	1	1	1	1	Ο	Ω	1	Ο	1	Λ	1	Λ	1	Ω	1	1	1	1	1	1	1	1	1	1	1

Supplementary Table 6 - Simulation study results for complete data for simple, intermediate, and complex scenario, using outcome regression, g-computation including all two-way confounder-confounder interactions, and TMLE

	Estimated mean	Absolu	ite bias	Relative bias	Cov	erage	Bias elimina	ated coverage	Empir	ical SE	Mode	l SE	Relative % em	or in model SE
	difference	Estimate	MC SE	(%)	Estimate	MC SE	Estimate	MC SE	Estimate	MC SE	Estimate	MC SE	Estimate	MC SE
							Simple	scenario						
Outcome regression	0.20	0.00	0.00	0.03	0.95	0.00	0.95	0.00	0.07	0.00	0.07	0.00	0.06	1.58
g-computation	0.20	0.00	0.00	0.02	0.95	0.00	0.95	0.00	0.07	0.00	0.07	0.00	0.41	1.59
TMLE	0.20	0.00	0.00	0.21	0.93	0.01	0.93	0.01	0.08	0.00	0.08	0.00	-5.70	1.49
							Complex	scenario 1						
Outcome regression	0.26	0.06	0.00	31.63	0.87	0.01	0.96	0.00	0.07	0.00	0.07	0.00	4.30	1.65
g-computation	0.20	0.00	0.00	0.46	0.96	0.00	0.96	0.00	0.07	0.00	0.07	0.00	4.01	1.65
TMLE	0.20	0.00	0.00	1.99	0.93	0.01	0.93	0.01	0.08	0.00	0.08	0.00	-5.68	1.49
							Complex	scenario 2						
Outcome regression	0.41	0.21	0.00	106.63	0.22	0.01	0.96	0.00	0.08	0.00	0.08	0.00	3.38	1.64
g-computation	0.18	-0.02	0.00	-8.34	0.93	0.01	0.94	0.01	0.07	0.00	0.07	0.00	-1.66	1.56
TMLE	0.20	0.00	0.00	0.51	0.87	0.01	0.87	0.01	0.09	0.00	0.07	0.00	-21.06	1.25

Abbreviations MC SE Monte Carlo standard error

		Estimated mean	Absol	ute bias	Relative	Cover	age (%)		minated age (%)	Empir	ical SE	Mod	del SE	Relative 9	% error del SE
		difference	Estimate	MC SE	bias (%)	Estimate	MC SE	Estimate	MC SE		MC SE		MC SE	Estimate	MC SE
	Complete data	0.20	0.00	0.00	0.27	93.20	0.56	93.20	0.56	0.08	0.00	0.08	0.00	-5.61	1.5
usal Diagram	Missing data method Complete case	0.20	0.00	0.00	-0.96	93.80	0.54	93.75	0.54	0.11	0.00	0.11	0.00	-5.72	1.5
	Extended TMLE	0.20	0.00	0.00	-0.92	93.60	0.55	93.85	0.54	0.11	0.00	0.11	0.00	-5.27	1.5
	Extended TMLE+MCMI	0.22	0.02	0.00	10.67	92.00	0.61	93.00	0.57	0.10	0.00	0.10	0.00	-6.16	1.5
_	MI, no int (linear)	0.20	0.00	0.00	-0.91	95.45	0.47	95.50	0.46	0.10	0.00	0.10	0.00	6.64	1.7
Т	MI,no int	0.20	0.00	0.00	-0.75	95.75	0.45	95.80	0.45	0.10	0.00	0.11	0.00	6.71	1.7
	MI, 2-way int MI, higher int	0.19 0.19	-0.01 -0.01	0.00	-4.09 -4.66	95.80 95.85	0.45 0.45	95.85 95.80	0.45 0.45	0.10 0.10	0.00	0.11 0.11	0.00	6.64 6.95	1.7
	MI, CART	0.19	-0.01	0.00	-6.27	95.25	0.48	95.20	0.48	0.10	0.00	0.10	0.00	2.33	1.6
	MI, RF	0.16	-0.04	0.00	-17.91	98.85	0.24	99.35	0.18	0.07	0.00	0.10	0.00	45.98	2.3
	Complete case	0.20	0.00	0.00	0.06	92.60	0.59	92.60	0.59	0.12	0.00	0.11	0.00	-8.31	1.4
	Extended TMLE	0.20	0.00	0.00	0.38	92.55	0.59	92.70	0.58	0.12	0.00	0.11	0.00	-8.69	1.4
	Extended TMLE+MCMI	0.22	0.02	0.00	11.18	92.35	0.59	93.10	0.57	0.11	0.00	0.10	0.00	-8.83	1.4
Α	MI, no int (linear) MI, no int	0.20 0.20	0.00	0.00	0.58 -0.51	95.05 96.10	0.49 0.43	95.10 96.15	0.48	0.10 0.10	0.00	0.10 0.11	0.00	1.93 4.49	1.6
,,	MI, 2-way int	0.19	-0.01	0.00	-3.41	94.80	0.50	94.80	0.50	0.10	0.00	0.11	0.00	2.85	1.6
	MI, higher int	0.19	-0.01	0.00	-3.73	95.40	0.47	95.65	0.46	0.10	0.00	0.11	0.00	2.67	1.6
	MI, CART	0.19	-0.01	0.00	-5.75	94.75	0.50	95.25	0.48	0.10	0.00	0.10	0.00	-1.05	1.6
	MI, RF	0.16	-0.04	0.00	-18.03	98.70	0.25	99.50	0.16	0.07	0.00	0.10	0.00	41.57	2.2
	Complete case Extended TMLE	0.20 0.20	0.00	0.00	0.27 0.42	91.80 91.55	0.61 0.62	91.80 91.55	0.61 0.62	0.14 0.14	0.00	0.13 0.13	0.00	-5.85 -7.16	1
	Extended TMLE+MCMI	0.22	0.00	0.00	8.33	91.15	0.64	91.55	0.62	0.14	0.00	0.13	0.00	-8.67	1.
	MI, no int (linear)	0.19	-0.01	0.00	-4.64	95.95	0.44	96.05	0.44	0.12	0.00	0.13	0.00	7.22	1.
В	MI,no int	0.19	-0.01	0.00	-6.19	96.20	0.43	96.20	0.43	0.12	0.00	0.13	0.00	9.21	1.
	MI, 2-way int	0.19	-0.01	0.00	-5.89	94.35	0.52	94.45	0.51	0.13	0.00	0.13	0.00	2.00	1.
	MI, higher int	0.18	-0.02	0.00	-7.82	94.80	0.50	95.20	0.48	0.12	0.00	0.13	0.00	3.18	1.
	MI, CART	0.17 0.13	-0.03 -0.07	0.00	-14.95	94.75 97.40	0.50	95.85 99.30	0.45	0.11 0.07	0.00	0.12	0.00	8.82	1. 2.
	MI, RF Complete case	0.13	-0.07	0.00	-33.52 -9.62	91.85	0.36	99.30	0.19	0.07	0.00	0.11	0.00	52.80 -8.51	1.
	Extended TMLE	0.18	-0.02	0.00	-9.62 -9.69	92.35	0.59	92.65	0.59	0.14	0.00	0.13	0.00	-9.18	1.
	Extended TMLE+MCMI	0.19	-0.01	0.00	-4.39	92.00	0.61	92.15	0.60	0.13	0.00	0.12	0.00	-9.30	1
_	MI, no int (linear)	0.18	-0.02	0.00	-9.07	95.00	0.49	95.70	0.45	0.12	0.00	0.12	0.00	4.46	1
С	MI,no int	0.18	-0.02	0.00	-9.46	95.85	0.45	96.10	0.43	0.12	0.00	0.13	0.00	6.54	1.
	MI, 2-way int	0.19	-0.01	0.00	-4.58 5.04	94.75	0.50	95.05	0.49	0.13	0.00	0.13	0.00	1.20	1
	MI, higher int MI, CART	0.19 0.17	-0.01 -0.03	0.00	-5.94 -17.24	94.65 94.40	0.50 0.51	94.70 96.05	0.50 0.44	0.13 0.11	0.00	0.13 0.12	0.00	1.80 6.30	1.
	MI, RF	0.17	-0.03	0.00	-17.24	97.20	0.37	99.65	0.44	0.11	0.00	0.12	0.00	52.40	2.
	Complete case	0.20	0.00	0.00	0.35	92.25	0.60	92.25	0.60	0.12	0.00	0.11	0.00	-8.04	1.
	Extended TMLE	0.20	0.00	0.00	0.17	92.50	0.59	92.50	0.59	0.12	0.00	0.11	0.00	-8.04	1
	Extended TMLE+MCMI	0.22	0.02	0.00	12.31	91.95	0.61	92.75	0.58	0.11	0.00	0.10	0.00	-7.81	1.
D	MI, no int (linear)	0.20	0.00	0.00	2.44	95.50	0.46	95.40	0.47	0.11	0.00	0.11	0.00	3.48	1.
U	MI, no int MI, 2-way int	0.21 0.20	0.01	0.00	2.53 -0.22	95.80 94.90	0.45 0.49	95.95 94.85	0.44 0.49	0.11 0.11	0.00	0.11 0.12	0.00	5.89 3.56	1. 1.
	MI, higher int	0.20	0.00	0.00	0.03	95.30	0.47	95.30	0.47	0.11	0.00	0.11	0.00	2.98	1
	MI, CART	0.19	-0.01	0.00	-4.30	94.80	0.50	94.90	0.49	0.11	0.00	0.11	0.00	1.29	1.
	MI, RF	0.16	-0.04	0.00	-20.90	98.30	0.29	99.15	0.21	0.07	0.00	0.11	0.00	42.54	2.
	Complete case	0.21	0.01	0.00	3.27	91.95	0.61	91.80	0.61	0.15	0.00	0.14	0.00	-11.41	1.
	Extended TMLE	0.21	0.01	0.00	2.99	91.40	0.63	91.60	0.62	0.15	0.00	0.14	0.00	-11.82	1.
	Extended TMLE+MCMI MI, no int (linear)	0.22 0.21	0.02 0.01	0.00	10.40 6.99	91.15 95.40	0.64 0.47	91.65 95.10	0.62 0.48	0.14 0.13	0.00	0.12 0.13	0.00	-11.04 5.34	1
E	MI,no int	0.21	0.01	0.00	6.25	95.85	0.45	95.85	0.45	0.13	0.00	0.14	0.00	7.97	1.
	MI, 2-way int	0.21	0.01	0.00	7.21	94.65	0.50	94.75	0.50	0.14	0.00	0.14	0.00	2.39	1.
	MI, higher int	0.21	0.01	0.00	5.77	95.35	0.47	95.40	0.47	0.13	0.00	0.14	0.00	3.26	1.
	MI, CART	0.18	-0.02	0.00	-7.78	95.30	0.47	95.65	0.46	0.12	0.00	0.13	0.00	6.45	1
	MI, RF Complete case	0.14	-0.06 -0.01	0.00	-31.87 -5.49	98.30 92.55	0.29	99.40 92.75	0.17	0.08	0.00	0.12	0.00	53.58 -6.82	1
	Extended TMLE	0.19	-0.01	0.00	-5.21	92.35	0.59	92.60	0.58	0.12	0.00	0.12	0.00	-6.55	1
	Extended TMLE+MCMI	0.21	0.01	0.00	7.25	92.55	0.59	92.70	0.58	0.11	0.00	0.10	0.00	-7.95	1
	MI, no int (linear)	0.20	0.00	0.00	-0.73	94.70	0.50	94.70	0.50	0.11	0.00	0.11	0.00	3.47	1
F	MI,no int	0.20	0.00	0.00	-1.59	95.20	0.48	95.25	0.48	0.11	0.00	0.12	0.00	6.13	1
	MI, 2-way int	0.19	-0.01	0.00	-2.63	95.35	0.47	95.55	0.46	0.11	0.00	0.12	0.00	5.11	1
	MI, higher int MI, CART	0.20 0.19	0.00 -0.01	0.00	-1.21 -7.09	95.15 95.05	0.48 0.49	95.40 95.45	0.47 0.47	0.11 0.11	0.00	0.12 0.11	0.00	3.34 4.20	1
	MI, RF	0.15	-0.01	0.00	-7.09	98.05	0.49	99.20	0.47	0.11	0.00	0.11	0.00	43.07	2
	Complete case	0.19	-0.01	0.00	-4.25	90.30	0.66	90.30	0.66	0.15	0.00	0.13	0.00	-11.26	1
	Extended TMLE	0.19	-0.01	0.00	-5.09	90.85	0.64	90.90	0.64	0.15	0.00	0.13	0.00	-10.67	1
	Extended TMLE+MCMI	0.21	0.01	0.00	2.65	91.30	0.63	91.85	0.61	0.13	0.00	0.12	0.00	-9.46	1
G	MI, no int (linear) MI.no int	0.18	-0.02 -0.02	0.00	-10.76	94.60	0.51 0.49	95.15 95.50	0.48	0.12 0.12	0.00	0.12 0.13	0.00	3.03	1
J	MI, 2-way int	0.18 0.17	-0.02 -0.03	0.00	-11.14 -13.17	95.05 94.40	0.49	95.50 94.90	0.46 0.49	0.12	0.00	0.13	0.00	6.06 1.11	1
	MI, higher int	0.17	-0.03	0.00	-13.72	93.85	0.54	94.70	0.50	0.13	0.00	0.13	0.00	0.58	1
	MI, CART	0.16	-0.04	0.00	-19.73	93.95	0.53	96.05	0.44	0.11	0.00	0.12	0.00	4.15	1
	MI, RF	0.13	-0.07	0.00	-35.81	97.30	0.36	99.55	0.15	0.07	0.00	0.11	0.00	51.12	2
	Complete case	0.16	-0.04	0.00	-18.73	90.90	0.64	92.15	0.60	0.14	0.00	0.13	0.00	-8.00	1
	Extended TMLE Extended TMLE+MCMI	0.16 0.17	-0.04 -0.03	0.00	-19.49 -14.14	90.40 91.15	0.66 0.64	92.05 92.30	0.60 0.60	0.14 0.13	0.00	0.13 0.11	0.00	-9.13 -9.55	1
	MI, no int (linear)	0.17	-0.03	0.00	-20.03	94.75	0.50	95.60	0.46	0.13	0.00	0.11	0.00	7.33	1
Н	MI,no int	0.16	-0.04	0.00	-21.05	94.55	0.51	96.15	0.43	0.12	0.00	0.13	0.00	8.64	1
	MI, 2-way int	0.16	-0.04	0.00	-18.33	94.20	0.52	95.35	0.47	0.12	0.00	0.13	0.00	3.37	1
	MI, higher int	0.17	-0.03	0.00	-16.87	95.10	0.48	95.30	0.47	0.12	0.00	0.13	0.00	4.90	1
	MI, CART	0.15	-0.05	0.00	-27.23	93.95	0.53	96.45	0.41	0.11	0.00	0.12	0.00	8.39	1
	MI, RF Complete case	0.12 0.17	-0.08 -0.03	0.00	-42.24 -16.25	96.05 90.25	0.44	99.60 91.15	0.14	0.07	0.00	0.11	0.00	55.36 -12.64	1.
	Extended TMLE	0.17	-0.03	0.00	-16.43	89.55	0.68	90.40	0.66	0.16	0.00	0.14	0.00	-13.29	1.
	Extended TMLE+MCMI	0.17	-0.03	0.00	-12.81	90.20	0.66	91.05	0.64	0.14	0.00	0.12	0.00	-12.23	1
	MI, no int (linear)	0.19	-0.01	0.00	-7.48	94.45	0.51	94.65	0.50	0.13	0.00	0.14	0.00	4.22	1
I	MI,no int	0.18	-0.02	0.00	-7.86	94.60	0.51	95.00	0.49	0.13	0.00	0.14	0.00	4.60	1
	MI, 2-way int	0.19	-0.01	0.00	-2.72	94.55	0.51	94.45	0.51	0.14	0.00	0.14	0.00	0.15	1.
	MI, higher int	0.20	0.00	0.00	-1.76	94.20	0.52	94.25	0.52 0.44	0.14	0.00	0.14	0.00	1.73	1
	MI, CART MI, RF	0.16 0.12	-0.04 -0.08	0.00	-20.06 -42.47	95.30 96.90	0.47 0.39	96.05 99.45	0.44	0.12 0.08	0.00	0.13 0.12	0.00	8.75 50.13	1 2
	Complete case	0.12	-0.05	0.00	-24.14	89.15	0.70	91.20	0.63	0.15	0.00	0.12	0.00	-10.58	1
	Extended TMLE	0.15	-0.05	0.00	-25.12	89.00	0.70	91.00	0.64	0.15	0.00	0.14	0.00	-11.66	1
	Extended TMLE+MCMI	0.16	-0.04	0.00	-20.57	89.15	0.70	90.45	0.66	0.14	0.00	0.12	0.00	-12.80	1
,	MI, no int (linear)	0.17	-0.03	0.00	-13.84	94.75	0.50	94.85	0.49	0.13	0.00	0.14	0.00	3.63	1
J	MI,no int	0.17	-0.03	0.00	-12.76	95.10	0.48	95.75	0.45	0.13	0.00	0.14	0.00	5.42	1.
	MI, 2-way int	0.18	-0.02 -0.02	0.00	-9.00 9.26	93.95	0.53	94.25	0.52	0.14	0.00	0.14	0.00	-1.53	1.
	MI, higher int MI, CART	0.18 0.15	-0.02 -0.05	0.00	-8.26 -24.68	94.35 94.45	0.52 0.51	94.40 96.00	0.51 0.44	0.14 0.12	0.00	0.14 0.13	0.00	0.62 8.05	1
	MI, RF	0.13	-0.03	0.00	-24.66 -46.72	95.85	0.51	99.55	0.44	0.12	0.00	0.13	0.00	54.39	2

		Estimated mean	Absol	ute bias	Relative	Cove	rage (%)		minated age (%)	Empir	rical SE	Mod	lel SE		% error in del SE
		difference	Estimate	MC SE	bias (%)	Estimate	MC SE	Estimate	MC SE	Estimate	MC SE	Estimate	MC SE	Estimate	MC SE
Causal Diagram	Complete data Missing data method	0.20	0.00	0.00	2.18	0.93	0.59	0.92	0.59	0.08	0.00	0.08	0.00	-5.89	1.52
Causai Diagram	Complete case	0.21	0.01	0.00	3.36	91.30	0.63	91.45	0.63	0.11	0.00	0.10	0.00	-11.48	1.43
	Extended TMLE	0.21	0.01	0.00	2.72	91.40	0.63	91.70	0.62	0.11	0.00	0.10	0.00	-11.25	1.44
	Extended TMLE+MCMI	0.23	0.03	0.00	13.39	90.35	0.66	91.60	0.62	0.10	0.00	0.09	0.00	-10.60	1.44
Т	MI, no int (linear) MI,no int	0.24 0.23	0.04	0.00	18.02 15.29	95.60 96.05	0.46 0.44	96.45 96.65	0.41	0.10 0.10	0.00	0.11 0.11	0.00	12.20 15.51	1.84 1.90
	MI, 2-way int	0.19	-0.01	0.00	-3.74	96.90	0.39	97.00	0.38	0.10	0.00	0.11	0.00	14.92	1.90
	MI, higher int	0.19	-0.01	0.00	-3.64	96.95	0.38	97.10	0.38	0.09	0.00	0.11	0.00	17.58	1.94
	MI, CART	0.19	-0.01	0.00	-7.14	96.20	0.43	96.40	0.42	0.09	0.00	0.10	0.00	12.05	1.84
	MI, RF Complete case	0.15 0.21	-0.05 0.01	0.00	-23.09 5.15	98.40 92.10	0.28	99.65 92.45	0.13	0.06	0.00	0.10	0.00	55.88 -8.64	2.54 1.46
	Extended TMLE	0.21	0.01	0.00	5.03	92.20	0.60	91.90	0.61	0.11	0.00	0.10	0.00	-9.20	1.46
	Extended TMLE+MCMI	0.23	0.03	0.00	14.64	90.50	0.66	92.30	0.60	0.10	0.00	0.09	0.00	-10.09	1.44
Α	MI, no int (linear)	0.23	0.03	0.00	14.12	95.95	0.44	96.85	0.39	0.10	0.00	0.11	0.00	10.31	1.81
A	MI,no int MI, 2-way int	0.22 0.19	0.02 -0.01	0.00	12.43 -4.69	96.05 96.15	0.44 0.43	97.15 96.40	0.37 0.42	0.10 0.10	0.00	0.11 0.11	0.00	12.45 11.93	1.85 1.84
	MI, higher int	0.19	-0.01	0.00	-2.99	96.75	0.40	96.85	0.39	0.10	0.00	0.11	0.00	13.90	1.88
	MI, CART	0.19	-0.01	0.00	-7.13	96.75	0.40	97.20	0.37	0.09	0.00	0.10	0.00	12.71	1.85
	MI, RF Complete case	0.16	-0.04 0.00	0.00	-22.07 1.85	98.55 90.90	0.27	99.65 90.70	0.13	0.06	0.00	0.10	0.00	53.05 -10.50	2.49 1.44
	Extended TMLE	0.21	0.00	0.00	2.59	90.90	0.67	89.95	0.63	0.13	0.00	0.12	0.00	-10.50	1.44
	Extended TMLE+MCMI	0.22	0.02	0.00	10.53	90.70	0.65	91.60	0.62	0.12	0.00	0.11	0.00	-11.76	1.42
	MI, no int (linear)	0.21	0.01	0.00	3.95	96.55	0.41	96.40	0.42	0.11	0.00	0.13	0.00	13.24	1.88
В	MI,no int MI, 2-way int	0.21 0.18	0.01 -0.02	0.00	2.91 -9.75	96.90 95.70	0.39 0.45	96.95 96.05	0.38	0.11 0.12	0.00	0.13 0.13	0.00	14.37 10.86	1.90 1.85
	MI, higher int	0.19	-0.02	0.00	-6.79	96.60	0.43	96.45	0.44	0.12	0.00	0.13	0.00	13.14	1.89
	MI, CART	0.16	-0.04	0.00	-19.04	95.80	0.45	97.15	0.37	0.10	0.00	0.11	0.00	13.44	1.87
	MI, RF	0.12	-0.08	0.00	-38.11	96.85	0.39	99.85	0.09	0.07	0.00	0.11	0.00	64.71	2.69
	Complete case Extended TMLE	0.19 0.19	-0.01 -0.01	0.00	-6.39 -5.78	91.30 90.10	0.63 0.67	91.75 90.30	0.62 0.66	0.13 0.14	0.00	0.12 0.12	0.00	-11.61 -13.25	1.43 1.40
	Extended TMLE+MCMI	0.19	0.00	0.00	-5.78 -1.90	90.10	0.66	90.30	0.66	0.14	0.00	0.12	0.00	-13.25 -13.27	1.40
	MI, no int (linear)	0.20	0.00	0.00	-0.56	96.35	0.42	96.40	0.42	0.11	0.00	0.13	0.00	9.56	1.81
С	MI,no int	0.20	0.00	0.00	-1.83	96.85	0.39	96.80	0.39	0.11	0.00	0.13	0.00	11.51	1.84
	MI, 2-way int MI, higher int	0.18 0.19	-0.02 -0.01	0.00	-9.51 -6.28	95.70 95.80	0.45 0.45	96.50 96.15	0.41	0.12 0.12	0.00	0.13 0.13	0.00	9.85 9.48	1.83 1.83
	MI, CART	0.19	-0.01	0.00	-6.28 -20.91	95.80	0.43	95.15	0.43	0.12	0.00	0.13	0.00	14.51	1.83
	MI, RF	0.12	-0.08	0.00	-41.35	96.40	0.42	99.75	0.11	0.07	0.00	0.11	0.00	59.53	2.61
	Complete case	0.21	0.01	0.00	4.15	92.20	0.60	92.25	0.60	0.12	0.00	0.10	0.00	-9.42	1.45
	Extended TMLE	0.21	0.01	0.00	3.99	92.15	0.60	91.50	0.62	0.12	0.00	0.11	0.00	-10.13	1.45
	Extended TMLE+MCMI MI, no int (linear)	0.23 0.24	0.03 0.04	0.00	15.05 17.86	89.90 94.25	0.67 0.52	91.75 95.90	0.62 0.44	0.11 0.11	0.00	0.10 0.12	0.00	-11.72 8.59	1.42 1.78
D	MI,no int	0.23	0.03	0.00	15.69	95.45	0.47	96.55	0.41	0.10	0.00	0.12	0.00	12.00	1.85
	MI, 2-way int	0.20	0.00	0.00	0.46	96.60	0.41	96.40	0.42	0.11	0.00	0.12	0.00	10.48	1.83
	MI, higher int	0.20	0.00	0.00	1.38	96.50	0.41	96.50	0.41	0.10	0.00	0.12	0.00	13.15	1.87
	MI, CART MI, RF	0.19 0.15	-0.01 -0.05	0.00	-4.25 -23.61	97.05 98.80	0.38 0.24	96.90 99.90	0.39 0.07	0.10 0.07	0.00	0.11 0.11	0.00	13.14 57.59	1.86 2.56
	Complete case	0.13	0.01	0.00	3.43	90.80	0.65	90.50	0.66	0.07	0.00	0.11	0.00	-11.90	1.43
	Extended TMLE	0.21	0.01	0.00	5.04	89.75	0.68	89.70	0.68	0.14	0.00	0.12	0.00	-14.44	1.39
	Extended TMLE+MCMI	0.22	0.02	0.00	10.66	90.15	0.67	90.65	0.65	0.13	0.00	0.11	0.00	-13.25	1.40
E	MI, no int (linear) MI,no int	0.23 0.23	0.03	0.00	13.53 12.59	95.45 96.55	0.47 0.41	96.40 96.85	0.42	0.12 0.12	0.00	0.13 0.14	0.00	13.17 14.27	1.87 1.90
_	MI, 2-way int	0.21	0.01	0.00	2.71	96.35	0.42	96.55	0.41	0.12	0.00	0.14	0.00	10.13	1.84
	MI, higher int	0.21	0.01	0.00	3.95	96.00	0.44	96.10	0.43	0.12	0.00	0.13	0.00	10.78	1.85
	MI, CART	0.17	-0.03	0.00	-12.53	96.10	0.43	96.85	0.39	0.11	0.00	0.12	0.00	15.71	1.92
	MI, RF Complete case	0.13	-0.07 0.00	0.00	-37.37 -2.01	98.10 91.25	0.31	99.80 91.30	0.10	0.07	0.00	0.12	0.00	62.78 -11.01	2.65 1.43
	Extended TMLE	0.20	0.00	0.00	-2.45	90.40	0.66	90.60	0.65	0.12	0.00	0.11	0.00	-12.47	1.43
	Extended TMLE+MCMI	0.22	0.02	0.00	9.44	90.20	0.66	91.10	0.64	0.11	0.00	0.10	0.00	-12.24	1.41
-	MI, no int (linear)	0.23	0.03	0.00	13.16	95.05	0.49	95.90	0.44	0.11	0.00	0.12	0.00	8.03	1.77
F	MI,no int MI, 2-way int	0.22 0.20	0.02	0.00	11.76 -1.00	95.20 96.20	0.48 0.43	95.80 96.45	0.45 0.41	0.11 0.11	0.00	0.12 0.12	0.00	9.49 12.12	1.80 1.87
	MI, higher int	0.20	0.00	0.00	1.66	97.00	0.43	96.85	0.41	0.11	0.00	0.12	0.00	13.83	1.88
	MI, CART	0.18	-0.02	0.00	-9.03	96.20	0.43	96.55	0.41	0.10	0.00	0.11	0.00	11.56	1.83
	MI, RF	0.15	-0.05	0.00	-26.30	98.10	0.31	99.40	0.17	0.07	0.00	0.11	0.00	53.13	2.50
	Complete case	0.20	0.00	0.00	-1.85	92.10	0.60	92.10	0.60	0.13	0.00	0.12	0.00	-9.36	1.46
	Extended TMLE Extended TMLE+MCMI	0.20 0.21	0.00 0.01	0.00	-1.05 6.25	91.45 92.35	0.63 0.59	91.45 92.00	0.63 0.61	0.13 0.12	0.00	0.12 0.10	0.00	-11.12 -8.89	1.43 1.47
	MI, no int (linear)	0.20	0.00	0.00	-1.61	97.15	0.37	97.25	0.37	0.12	0.00	0.13	0.00	14.29	1.89
G	MI,no int	0.20	0.00	0.00	-2.30	96.60	0.41	96.50	0.41	0.11	0.00	0.13	0.00	15.57	1.91
	MI, 2-way int MI, higher int	0.17 0.18	-0.03 -0.02	0.00	-14.05 -11.97	95.90 96.50	0.44 0.41	96.35 97.55	0.42 0.35	0.12 0.11	0.00	0.13 0.12	0.00	10.40 14.16	1.83 1.90
	MI, CART	0.18	-0.02 -0.04	0.00	-11.97 -22.10	95.65	0.41	97.55 96.85	0.35	0.11	0.00	0.12	0.00	15.39	1.90
	MI, RF	0.12	-0.08	0.00	-40.21	96.60	0.41	99.70	0.12	0.07	0.00	0.11	0.00	63.28	2.66
	Complete case	0.17	-0.03	0.00	-14.83	90.00	0.67	90.90	0.64	0.13	0.00	0.12	0.00	-10.67	1.44
	Extended TMLE Extended TMLE+MCMI	0.17	-0.03 -0.02	0.00	-13.67	89.30 90.35	0.69	90.40 90.90	0.66	0.13 0.12	0.00	0.12	0.00	-13.09	1.40
	MI, no int (linear)	0.18 0.18	-0.02 -0.02	0.00	-10.35 -9.55	90.35	0.66 0.41	90.90 96.45	0.64 0.41	0.12	0.00	0.10 0.13	0.00	-12.54 11.48	1.41 1.84
Н	MI, no int	0.18	-0.02	0.00	-9.72	96.65	0.40	96.45	0.41	0.11	0.00	0.13	0.00	13.38	1.87
	MI, 2-way int	0.17	-0.03	0.00	-16.85	94.85	0.49	95.95	0.44	0.12	0.00	0.13	0.00	10.55	1.84
	MI, higher int	0.17	-0.03	0.00	-13.74	95.40	0.47	95.85	0.45	0.11	0.00	0.12	0.00	9.22	1.82
	MI, CART MI, RF	0.15 0.11	-0.05 -0.09	0.00	-27.16 -45.62	95.00 95.50	0.49 0.46	97.30 99.80	0.36 0.10	0.10 0.07	0.00	0.12 0.11	0.00	14.77 61.42	1.90 2.62
	Complete case	0.11	-0.02	0.00	-11.89	90.70	0.65	91.40	0.63	0.14	0.00	0.11	0.00	-13.14	1.40
	Extended TMLE	0.18	-0.02	0.00	-11.07	89.35	0.69	89.55	0.68	0.14	0.00	0.12	0.00	-16.06	1.36
	Extended TMLE+MCMI	0.18	-0.02	0.00	-9.17	89.45	0.69	89.85	0.68	0.13	0.00	0.11	0.00	-15.58	1.36
1	MI, no int (linear)	0.20 0.20	0.00	0.00	2.45 2.27	96.20 96.90	0.43 0.39	96.05 96.65	0.44	0.12 0.12	0.00	0.14 0.14	0.00	10.97 13.90	1.83 1.91
	MI no int	0.20	0.00	0.00	-1.98	95.35	0.39	95.20	0.40	0.12	0.00	0.14	0.00	10.69	1.86
	MI,no int MI, 2-way int	0.20				96.45	0.41	96.45	0.41	0.12	0.00	0.13	0.00	9.61	1.83
	·	0.20 0.20	0.00	0.00	0.20	90.45	0.11	30.43	0	0.12	0.00	0.13		5.01	
	MI, 2-way int MI, higher int MI, CART	0.20 0.16	0.00 -0.04	0.00	-20.32	95.35	0.47	97.05	0.38	0.11	0.00	0.12	0.00	14.39	1.89
	MI, 2-way int MI, higher int MI, CART MI, RF	0.20 0.16 0.11	0.00 -0.04 -0.09	0.00 0.00	-20.32 -45.07	95.35 96.35	0.47 0.42	97.05 99.75	0.38 0.11	0.11 0.07	0.00 0.00	0.12 0.12	0.00	14.39 62.56	2.66
	MI, 2-way int MI, higher int MI, CART MI, RF Complete case	0.20 0.16 0.11 0.16	0.00 -0.04 -0.09 -0.04	0.00 0.00	-20.32 -45.07 -20.90	95.35 96.35 89.15	0.47 0.42 0.70	97.05 99.75 91.35	0.38 0.11 0.63	0.11 0.07 0.14	0.00 0.00 0.00	0.12 0.12 0.12	0.00 0.00 0.00	14.39 62.56 -12.73	2.66 1.41
	MI, 2-way int MI, higher int MI, CART MI, RF	0.20 0.16 0.11	0.00 -0.04 -0.09	0.00 0.00	-20.32 -45.07	95.35 96.35	0.47 0.42	97.05 99.75	0.38 0.11	0.11 0.07	0.00 0.00	0.12 0.12	0.00	14.39 62.56	2.66
	MI, 2-way int MI, higher int MI, CART MI, RF Complete case Extended TMLE Extended TMLE+MCMI MI, no int (linear)	0.20 0.16 0.11 0.16 0.16 0.16 0.19	0.00 -0.04 -0.09 -0.04 -0.04 -0.04 -0.01	0.00 0.00 0.00 0.00 0.00 0.00	-20.32 -45.07 -20.90 -20.32 -17.99 -5.13	95.35 96.35 89.15 88.40 88.15 96.80	0.47 0.42 0.70 0.72 0.72 0.39	97.05 99.75 91.35 89.85 90.15 96.85	0.38 0.11 0.63 0.68 0.67 0.39	0.11 0.07 0.14 0.14 0.13 0.12	0.00 0.00 0.00 0.00 0.00 0.00	0.12 0.12 0.12 0.12 0.11 0.14	0.00 0.00 0.00 0.00 0.00 0.00	14.39 62.56 -12.73 -14.56 -14.11 14.27	2.66 1.41 1.38 1.38 1.90
J	MI, 2-way int MI, higher int MI, CART MI, RF Complete case Extended TMLE Extended TMLE+MCMI MI, no int (linear)	0.20 0.16 0.11 0.16 0.16 0.16 0.19	0.00 -0.04 -0.09 -0.04 -0.04 -0.01 -0.01	0.00 0.00 0.00 0.00 0.00 0.00 0.00	-20.32 -45.07 -20.90 -20.32 -17.99 -5.13 -6.78	95.35 96.35 89.15 88.40 88.15 96.80 96.70	0.47 0.42 0.70 0.72 0.72 0.39 0.40	97.05 99.75 91.35 89.85 90.15 96.85 96.80	0.38 0.11 0.63 0.68 0.67 0.39 0.39	0.11 0.07 0.14 0.14 0.13 0.12	0.00 0.00 0.00 0.00 0.00 0.00 0.00	0.12 0.12 0.12 0.12 0.11 0.14 0.14	0.00 0.00 0.00 0.00 0.00 0.00	14.39 62.56 -12.73 -14.56 -14.11 14.27 14.54	2.66 1.41 1.38 1.38 1.90 1.90
J	MI, 2-way int MI, higher int MI, CART MI, RF Complete case Extended TMLE Extended TMLE+MCMI MI, no int (linear) MI, no int MI, 2-way int	0.20 0.16 0.11 0.16 0.16 0.16 0.19 0.19	0.00 -0.04 -0.09 -0.04 -0.04 -0.01 -0.01 -0.02	0.00 0.00 0.00 0.00 0.00 0.00 0.00	-20.32 -45.07 -20.90 -20.32 -17.99 -5.13 -6.78 -10.10	95.35 96.35 89.15 88.40 88.15 96.80 96.70 95.55	0.47 0.42 0.70 0.72 0.72 0.39 0.40 0.46	97.05 99.75 91.35 89.85 90.15 96.85 96.80 96.10	0.38 0.11 0.63 0.68 0.67 0.39 0.39	0.11 0.07 0.14 0.14 0.13 0.12 0.12	0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.0	0.12 0.12 0.12 0.12 0.11 0.14 0.14	0.00 0.00 0.00 0.00 0.00 0.00 0.00	14.39 62.56 -12.73 -14.56 -14.11 14.27 14.54 9.92	2.66 1.41 1.38 1.38 1.90 1.90
J	MI, 2-way int MI, higher int MI, CART MI, RF Complete case Extended TMLE Extended TMLE+MCMI MI, no int (linear)	0.20 0.16 0.11 0.16 0.16 0.16 0.19	0.00 -0.04 -0.09 -0.04 -0.04 -0.01 -0.01	0.00 0.00 0.00 0.00 0.00 0.00 0.00	-20.32 -45.07 -20.90 -20.32 -17.99 -5.13 -6.78	95.35 96.35 89.15 88.40 88.15 96.80 96.70	0.47 0.42 0.70 0.72 0.72 0.39 0.40	97.05 99.75 91.35 89.85 90.15 96.85 96.80	0.38 0.11 0.63 0.68 0.67 0.39 0.39	0.11 0.07 0.14 0.14 0.13 0.12	0.00 0.00 0.00 0.00 0.00 0.00 0.00	0.12 0.12 0.12 0.12 0.11 0.14 0.14	0.00 0.00 0.00 0.00 0.00 0.00	14.39 62.56 -12.73 -14.56 -14.11 14.27 14.54	2.66 1.41 1.38 1.38 1.90 1.90

		Estimated mean		ute bias	Relative		age (%)	cover	minated age (%)		ical SE		el SE		del SE
	Complete data	difference 0.20	Estimate 0.00	0.00	bias (%) 0.33	Estimate 0.87	MC SE 0.76	Estimate 0.87	MC SE 0.75	Estimate 0.09	0.00	Estimate 0.07	0.00	Estimate -20.94	MC SI
al Diagram	Missing data method	0.20	0.00	0.00	0.55	0.07	0.70	0.07	0.73	0.03	0.00	0.07	0.00	20.54	1
	Complete case	0.21	0.01	0.00	3.51	85.85	0.78	86.55	0.76	0.13	0.00	0.10	0.00	-24.47	1
	Extended TMLE	0.21	0.01	0.00	3.68	85.40	0.79	85.20	0.79	0.13	0.00	0.10	0.00	-24.61	1.:
	Extended TMLE+MCMI MI, no int (linear)	0.23 0.32	0.03 0.12	0.00	15.53 59.49	83.70 90.70	0.83 0.65	85.70 97.75	0.78 0.33	0.11 0.11	0.00	0.09 0.13	0.00	-23.81 25.32	1
Т	MI, no int	0.32	0.12	0.00	55.29	91.90	0.61	97.50	0.35	0.11	0.00	0.13	0.00	27.06	2.
	MI, 2-way int	0.21	0.01	0.00	5.91	98.40	0.28	97.95	0.32	0.10	0.00	0.13	0.00	35.17	2.
	MI, higher int	0.21	0.01	0.00	6.51	98.60	0.26	98.60	0.26	0.10	0.00	0.13	0.00	34.77	2.:
	MI, CART	0.20	0.00	0.00	-0.26	97.80	0.33	97.80	0.33	0.10	0.00	0.12	0.00	25.12	2.
	MI, RF	0.16	-0.04	0.00	-20.74	99.40	0.17	99.90	0.07	0.07	0.00	0.12	0.00	78.06	2.
	Complete case Extended TMLE	0.20	0.00	0.00	2.06	90.50	0.66	90.20	0.66	0.11	0.00	0.09 0.09	0.00	-13.71	1.
	Extended TMLE+MCMI	0.21 0.23	0.01 0.03	0.00	2.59 13.19	89.85 88.50	0.68 0.71	89.60 89.60	0.68 0.68	0.11 0.10	0.00	0.09	0.00	-14.65 -16.78	1
	MI, no int (linear)	0.29	0.03	0.00	43.59	93.75	0.54	97.15	0.37	0.10	0.00	0.13	0.00	20.44	2.
Α	MI,no int	0.28	0.08	0.00	41.77	94.50	0.51	98.05	0.31	0.11	0.00	0.14	0.00	25.05	2.
	MI, 2-way int	0.22	0.02	0.00	8.12	98.60	0.26	98.65	0.26	0.10	0.00	0.14	0.00	37.56	2.
	MI, higher int	0.22	0.02	0.00	11.31	98.40	0.28	98.70	0.25	0.10	0.00	0.13	0.00	35.82	2.
	MI, CART	0.20	0.00	0.00	-2.29	98.65	0.26	98.65	0.26	0.09	0.00	0.12	0.00	26.99	2.
	MI, RF Complete case	0.16 0.20	-0.04 0.00	0.00	-20.18 -0.34	99.15 89.70	0.21	99.60 89.60	0.14	0.07	0.00	0.11	0.00	67.82 -15.37	1
	Extended TMLE	0.20	0.00	0.00	1.68	88.25	0.08	88.15	0.72	0.13	0.00	0.11	0.00	-13.37	1.
	Extended TMLE+MCMI	0.22	0.02	0.00	10.55	87.75	0.73	88.75	0.71	0.12	0.00	0.10	0.00	-18.49	1
	MI, no int (linear)	0.26	0.06	0.00	27.76	96.40	0.42	97.25	0.37	0.12	0.00	0.15	0.00	21.11	2
В	MI,no int	0.26	0.06	0.00	29.30	96.10	0.43	97.10	0.38	0.13	0.00	0.15	0.00	21.31	2
	MI, 2-way int	0.20	0.00	0.00	1.35	98.00	0.31	97.95	0.32	0.12	0.00	0.15	0.00	28.04	2
	MI, higher int	0.21	0.01	0.00	5.83	97.95	0.32	98.00	0.31	0.11	0.00	0.14	0.00	28.10	2
	MI, CART	0.17	-0.03	0.00	-12.96	97.50	0.35	98.00	0.31	0.10	0.00	0.13	0.00	23.40	2
	MI, RF	0.12	-0.08	0.00	-39.14	97.75	0.33	99.85	0.09	0.07	0.00	0.12	0.00	73.54	2
	Complete case Extended TMLE	0.18 0.18	-0.02 -0.02	0.00	-11.52 -9.96	89.65 88.15	0.68 0.72	89.75 87.80	0.68 0.73	0.13 0.13	0.00	0.11 0.11	0.00	-14.89 -18.17	1
	Extended TMLE+MCMI	0.18	-0.02	0.00	-9.96 -4.30	88.40	0.72	88.25	0.73	0.13	0.00	0.11	0.00	-18.17	1
	MI, no int (linear)	0.24	0.04	0.00	22.12	96.45	0.72	97.40	0.36	0.12	0.00	0.15	0.00	20.25	1
С	MI,no int	0.25	0.05	0.00	23.63	97.55	0.35	97.65	0.34	0.12	0.00	0.15	0.00	23.74	2
	MI, 2-way int	0.21	0.01	0.00	2.86	97.95	0.32	98.05	0.31	0.12	0.00	0.15	0.00	27.88	2
	MI, higher int	0.22	0.02	0.00	9.06	97.85	0.32	98.10	0.31	0.11	0.00	0.14	0.00	28.89	2
	MI, CART	0.17	-0.03	0.00	-15.27	96.80	0.39	97.35	0.36	0.10	0.00	0.13	0.00	24.03	2
	MI, RF	0.12	-0.08	0.00	-40.75	98.00	0.31	99.80	0.10	0.07	0.00	0.12	0.00	76.85	2
	Complete case	0.20	0.00	0.00	1.33	90.20	0.66	90.15	0.67	0.12	0.00	0.10	0.00	-16.25	1
	Extended TMLE Extended TMLE+MCMI	0.20 0.23	0.00	0.00	1.81 13.57	89.10 88.25	0.70 0.72	89.00 89.30	0.70 0.69	0.12 0.11	0.00	0.10 0.09	0.00	-17.88 -17.87	1
	MI, no int (linear)	0.29	0.03	0.00	44.82	92.90	0.72	97.40	0.36	0.11	0.00	0.14	0.00	18.38	1
D	MI,no int	0.28	0.08	0.00	41.24	94.50	0.51	97.65	0.34	0.11	0.00	0.14	0.00	23.33	2
	MI, 2-way int	0.23	0.03	0.00	13.11	97.65	0.34	98.05	0.31	0.11	0.00	0.14	0.00	31.40	2
	MI, higher int	0.23	0.03	0.00	16.60	98.10	0.31	98.20	0.30	0.10	0.00	0.14	0.00	31.61	2
	MI, CART	0.20	0.00	0.00	-0.09	98.25	0.29	98.25	0.29	0.10	0.00	0.12	0.00	25.02	2
	MI, RF	0.15	-0.05	0.00	-24.21	99.35	0.18	99.80	0.10	0.07	0.00	0.12	0.00	72.10	2
	Complete case	0.19	-0.01	0.00	-3.51	89.75	0.68	89.80	0.68	0.13	0.00	0.11	0.00	-15.11	1
	Extended TMLE Extended TMLE+MCMI	0.20 0.21	0.00 0.01	0.00	-1.92	88.25 88.15	0.72 0.72	88.05 88.25	0.73	0.14	0.00	0.11 0.10	0.00	-19.22 -19.62	1
	MI, no int (linear)	0.21	0.01	0.00	6.25 33.01	96.50	0.72	97.15	0.72 0.37	0.13 0.13	0.00	0.10	0.00	20.37	2
E	MI, no int	0.27	0.07	0.00	32.60	95.85	0.41	97.25	0.37	0.13	0.00	0.15	0.00	22.28	2
	MI, 2-way int	0.21	0.01	0.00	6.93	97.65	0.34	98.05	0.31	0.12	0.00	0.15	0.00	29.97	2
	MI, higher int	0.22	0.02	0.00	12.08	98.20	0.30	98.20	0.30	0.11	0.00	0.15	0.00	32.82	2
	MI, CART	0.18	-0.02	0.00	-11.32	97.30	0.36	97.75	0.33	0.10	0.00	0.13	0.00	27.81	2
	MI, RF	0.12	-0.08	0.00	-41.37	98.35	0.28	99.85	0.09	0.07	0.00	0.13	0.00	80.43	2
	Complete case	0.19	-0.01	0.00	-5.16	90.50	0.66	90.70	0.65	0.12	0.00	0.10	0.00	-14.86	1
	Extended TMLE	0.19 0.22	-0.01 0.02	0.00	-4.94	89.30	0.69	89.80	0.68	0.12	0.00	0.10	0.00	-17.00 -17.80	1
	Extended TMLE+MCMI MI, no int (linear)	0.22	0.02	0.00	8.67 41.97	88.05 94.45	0.73 0.51	88.35 97.15	0.72 0.37	0.11 0.12	0.00	0.09 0.14	0.00	18.59	1
F	MI,no int	0.28	0.08	0.00	39.10	94.85	0.49	97.20	0.37	0.11	0.00	0.14	0.00	25.54	2
	MI, 2-way int	0.23	0.03	0.00	13.99	98.05	0.31	98.15	0.30	0.11	0.00	0.14	0.00	30.09	2
	MI, higher int	0.24	0.04	0.00	18.81	97.35	0.36	97.95	0.32	0.10	0.00	0.14	0.00	31.23	2
	MI, CART	0.20	0.00	0.00	-0.43	97.55	0.35	97.55	0.35	0.10	0.00	0.12	0.00	24.99	2
	MI, RF	0.15	-0.05	0.00	-23.55	99.55	0.15	99.85	0.09	0.07	0.00	0.12	0.00	72.62	2
	Complete case	0.18	-0.02	0.00	-9.28	89.85	0.68	91.10	0.64	0.13	0.00	0.11	0.00	-14.62	1
	Extended TMLE Extended TMLE+MCMI	0.18 0.20	-0.02 0.00	0.00	-7.92 1.77	88.80 88.40	0.71 0.72	89.30 88.30	0.69 0.72	0.13 0.12	0.00	0.11 0.10	0.00	-18.04 -17.01	1
	MI, no int (linear)	0.20	0.00	0.00	1.//	96.70	0.72	88.30 97.70	0.72	0.12	0.00	0.10	0.00	-17.01 21.75	2
G	MI,no int	0.24	0.04	0.00	20.30	97.15	0.37	97.70	0.34	0.12	0.00	0.15	0.00	23.80	2
	MI, 2-way int	0.19	-0.01	0.00	-7.17	98.10	0.31	98.05	0.31	0.11	0.00	0.15	0.00	31.72	2
	MI, higher int	0.20	0.00	0.00	-1.70	97.70	0.34	97.65	0.34	0.11	0.00	0.14	0.00	31.20	2
	MI, CART	0.16	-0.04	0.00	-18.82	96.65	0.40	98.00	0.31	0.10	0.00	0.13	0.00	28.36	2
	MI, RF	0.11	-0.09	0.00	-42.84	97.20	0.37	99.90	0.07	0.07	0.00	0.12	0.00	78.17	2
	Complete case	0.16	-0.04	0.00	-17.51 16.62	89.80	0.68	90.20	0.66	0.13	0.00	0.11	0.00	-14.01 17.71	1
	Extended TMLE Extended TMLE+MCMI	0.17 0.18	-0.03 -0.02	0.00	-16.62 -9.88	88.55 89.35	0.71 0.69	89.10 90.00	0.70 0.67	0.13 0.12	0.00	0.11 0.10	0.00	-17.71 -16.33	1
	MI, no int (linear)	0.18	0.02	0.00	-9.88 14.25	97.10	0.38	97.10	0.87	0.12	0.00	0.10	0.00	23.34	2
Н	MI, no int	0.23	0.03	0.00	16.38	97.70	0.34	97.80	0.33	0.12	0.00	0.15	0.00	25.05	2
	MI, 2-way int	0.19	-0.01	0.00	-2.98	98.35	0.28	98.40	0.28	0.11	0.00	0.15	0.00	29.30	2
	MI, higher int	0.21	0.01	0.00	3.13	97.70	0.34	97.70	0.34	0.11	0.00	0.14	0.00	31.26	2
	A4L CART	0.16	-0.04	0.00	-20.48	97.15	0.37	98.05	0.31	0.10	0.00	0.12	0.00	26.72	2
	MI, CART		-0.09	0.00	-44.17	97.15	0.37	99.85	0.09	0.07	0.00	0.12	0.00	77.77	2
	MI, RF	0.11				88.10	0.72	89.15	0.70	0.13	0.00	0.11	0.00	-15.61	1
	MI, RF Complete case	0.16	-0.04	0.00	-18.08		~	A						40	1
	MI, RF Complete case Extended TMLE	0.16 0.17	-0.04 -0.03	0.00	-17.40	86.65	0.76	87.90	0.73	0.14	0.00	0.11	0.00	-18.99	
	MI, RF Complete case Extended TMLE Extended TMLE+MCMI	0.16 0.17 0.17	-0.04 -0.03 -0.03	0.00	-17.40 -13.79	86.65 87.40	0.74	87.85	0.73 0.73	0.14 0.12	0.00	0.10	0.00	-18.78	1
1	MI, RF Complete case Extended TMLE Extended TMLE+MCMI MI, no int (linear)	0.16 0.17 0.17 0.24	-0.04 -0.03 -0.03 0.04	0.00 0.00 0.00	-17.40 -13.79 22.28	86.65 87.40 96.70	0.74 0.40	87.85 97.40	0.73 0.73 0.36	0.14 0.12 0.13	0.00	0.10 0.16	0.00	-18.78 21.72	1 2
ı	MI, RF Complete case Extended TMLE Extended TMLE+MCMI MI, no int (linear) MI,no int	0.16 0.17 0.17 0.24 0.25	-0.04 -0.03 -0.03 0.04 0.05	0.00	-17.40 -13.79 22.28 23.23	86.65 87.40 96.70 96.85	0.74 0.40 0.39	87.85 97.40 97.70	0.73 0.73 0.36 0.34	0.14 0.12 0.13 0.13	0.00 0.00 0.00	0.10 0.16 0.16	0.00	-18.78 21.72 22.45	1 2 2
ı	MI, RF Complete case Extended TMLE Extended TMLE+MCMI MI, no int (linear)	0.16 0.17 0.17 0.24	-0.04 -0.03 -0.03 0.04	0.00 0.00 0.00 0.00	-17.40 -13.79 22.28	86.65 87.40 96.70	0.74 0.40	87.85 97.40	0.73 0.73 0.36	0.14 0.12 0.13	0.00	0.10 0.16	0.00 0.00 0.00	-18.78 21.72	1 2 2 2
ı	MI, RF Complete case Extended TMLE Extended TMLE+MCMI MI, no int (linear) MI, no int MI, 2-way int	0.16 0.17 0.17 0.24 0.25 0.21	-0.04 -0.03 -0.03 0.04 0.05 0.01	0.00 0.00 0.00 0.00 0.00	-17.40 -13.79 22.28 23.23 4.35	86.65 87.40 96.70 96.85 97.85	0.74 0.40 0.39 0.32	87.85 97.40 97.70 97.85	0.73 0.73 0.36 0.34 0.32	0.14 0.12 0.13 0.13 0.12	0.00 0.00 0.00 0.00	0.10 0.16 0.16 0.15	0.00 0.00 0.00 0.00	-18.78 21.72 22.45 26.99	1 2 2 2 2
1	MI, RF Complete case Extended TMLE Extended TMLE+MCMI MI, no int (linear) MI, no int MI, 2-way int MI, higher int	0.16 0.17 0.17 0.24 0.25 0.21	-0.04 -0.03 -0.03 0.04 0.05 0.01 0.02	0.00 0.00 0.00 0.00 0.00 0.00	-17.40 -13.79 22.28 23.23 4.35 11.32	86.65 87.40 96.70 96.85 97.85 97.80	0.74 0.40 0.39 0.32 0.33	87.85 97.40 97.70 97.85 97.80	0.73 0.73 0.36 0.34 0.32 0.33	0.14 0.12 0.13 0.13 0.12 0.12	0.00 0.00 0.00 0.00	0.10 0.16 0.16 0.15 0.15	0.00 0.00 0.00 0.00	-18.78 21.72 22.45 26.99 27.35	1 2 2 2 2 2
ı	MI, RF Complete case Extended TMLE Extended TMLE+MCMI MI, no int (linear) MI,no int MI, 2-way int MI, higher int MI, CART MI, RF Complete case	0.16 0.17 0.17 0.24 0.25 0.21 0.22 0.17 0.11	-0.04 -0.03 -0.03 0.04 0.05 0.01 0.02 -0.03 -0.09	0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.0	-17.40 -13.79 22.28 23.23 4.35 11.32 -16.78 -46.49	86.65 87.40 96.70 96.85 97.85 97.80 97.15 97.90	0.74 0.40 0.39 0.32 0.33 0.37 0.32	87.85 97.40 97.70 97.85 97.80 97.75 99.80	0.73 0.73 0.36 0.34 0.32 0.33 0.33 0.10	0.14 0.12 0.13 0.13 0.12 0.12 0.11 0.07	0.00 0.00 0.00 0.00 0.00 0.00 0.00	0.10 0.16 0.16 0.15 0.15 0.13 0.13	0.00 0.00 0.00 0.00 0.00 0.00 0.00	-18.78 21.72 22.45 26.99 27.35 24.87 83.13 -16.41	1 2 2 2 2 2 2 3
1	MI, RF Complete case Extended TMLE Extended TMLE+MCMI MI, no int (linear) MI,no int MI, 2-way int MI, higher int MI, CART MI, RF Complete case Extended TMLE	0.16 0.17 0.17 0.24 0.25 0.21 0.22 0.17 0.11	-0.04 -0.03 -0.03 0.04 0.05 0.01 0.02 -0.03 -0.09 -0.05	0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.0	-17.40 -13.79 22.28 23.23 4.35 11.32 -16.78 -46.49 -23.42 -22.61	86.65 87.40 96.70 96.85 97.85 97.80 97.15 97.90 86.70 86.15	0.74 0.40 0.39 0.32 0.33 0.37 0.32 0.76 0.77	87.85 97.40 97.70 97.85 97.80 97.75 99.80 89.00 88.15	0.73 0.73 0.36 0.34 0.32 0.33 0.33 0.10	0.14 0.12 0.13 0.13 0.12 0.12 0.11 0.07 0.14	0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.0	0.10 0.16 0.16 0.15 0.15 0.13 0.13 0.11 0.11	0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.0	-18.78 21.72 22.45 26.99 27.35 24.87 83.13 -16.41 -19.31	1 2 2 2 2 2 2 3
1	MI, RF Complete case Extended TMLE Extended TMLE+MCMI MI, no int (linear) MI,no int MI, 2-way int MI, higher int MI, CART MI, RF Complete case Extended TMLE Extended TMLE	0.16 0.17 0.17 0.24 0.25 0.21 0.22 0.17 0.11 0.15 0.15	-0.04 -0.03 -0.03 0.04 0.05 0.01 0.02 -0.03 -0.09 -0.05 -0.05	0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.0	-17.40 -13.79 22.28 23.23 4.35 11.32 -16.78 -46.49 -23.42 -22.61 -17.81	86.65 87.40 96.70 96.85 97.85 97.80 97.15 97.90 86.70 86.15 86.10	0.74 0.40 0.39 0.32 0.33 0.37 0.32 0.76 0.77	87.85 97.40 97.70 97.85 97.80 97.75 99.80 89.00 88.15 88.35	0.73 0.73 0.36 0.34 0.32 0.33 0.33 0.10 0.70 0.72	0.14 0.12 0.13 0.13 0.12 0.12 0.11 0.07 0.14 0.14	0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.0	0.10 0.16 0.16 0.15 0.15 0.13 0.13 0.11 0.11	0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.0	-18.78 21.72 22.45 26.99 27.35 24.87 83.13 -16.41 -19.31 -18.59	1 2 2 2 2 2 2 3 1 1
1	MI, RF Complete case Extended TMLE Extended TMLE+MCMI MI, no int (linear) MI,no int MI, 2-way int MI, higher int MI, CART MI, RF Complete case Extended TMLE+MCMI MI, no int (linear)	0.16 0.17 0.17 0.24 0.25 0.21 0.22 0.17 0.11 0.15 0.15 0.16	-0.04 -0.03 -0.03 0.04 0.05 0.01 0.02 -0.03 -0.09 -0.05 -0.05 -0.04 0.03	0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.0	-17.40 -13.79 22.28 23.23 4.35 11.32 -16.78 -46.49 -23.42 -22.61 -17.81 17.04	86.65 87.40 96.70 96.85 97.85 97.80 97.15 97.90 86.70 86.15 86.10 96.65	0.74 0.40 0.39 0.32 0.33 0.37 0.32 0.76 0.77 0.77 0.40	87.85 97.40 97.70 97.85 97.80 97.75 99.80 89.00 88.15 88.35 96.90	0.73 0.73 0.36 0.34 0.32 0.33 0.10 0.70 0.72 0.72 0.39	0.14 0.12 0.13 0.13 0.12 0.12 0.11 0.07 0.14 0.14 0.12 0.13	0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.0	0.10 0.16 0.16 0.15 0.15 0.13 0.13 0.11 0.10 0.16	0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.0	-18.78 21.72 22.45 26.99 27.35 24.87 83.13 -16.41 -19.31 -18.59 19.18	1 2 2 2 2 2 2 3 1 1 1
ı	MI, RF Complete case Extended TMLE Extended TMLE+MCMI MI, no int (linear) MI,no int MI, 2-way int MI, higher int MI, CART MI, RF Complete case Extended TMLE Extended TMLE+MCMI MI, no int (linear) MI, no int (linear) MI, no int (linear)	0.16 0.17 0.17 0.24 0.25 0.21 0.22 0.17 0.11 0.15 0.16 0.23 0.24	-0.04 -0.03 -0.03 -0.05 -0.05 -0.05 -0.05 -0.05 -0.05 -0.04	0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.0	-17.40 -13.79 22.28 23.23 4.35 11.32 -16.78 -46.49 -23.42 -22.61 -17.81 17.04 18.56	86.65 87.40 96.70 96.85 97.85 97.15 97.90 86.70 86.15 86.10 96.65 96.55	0.74 0.40 0.39 0.32 0.33 0.37 0.32 0.76 0.77 0.77 0.40 0.41	87.85 97.40 97.70 97.85 97.80 97.75 99.80 88.00 88.15 88.35 96.90 97.10	0.73 0.73 0.36 0.34 0.32 0.33 0.10 0.70 0.72 0.72 0.39 0.38	0.14 0.12 0.13 0.13 0.12 0.12 0.11 0.07 0.14 0.14 0.12 0.13 0.13	0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.0	0.10 0.16 0.16 0.15 0.15 0.13 0.13 0.11 0.10 0.16 0.16	0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.0	-18.78 21.72 22.45 26.99 27.35 24.87 83.13 -16.41 -19.31 -18.59 19.18 21.48	1 2 2 2 2 2 2 3 1 1 1 1 1 2
ı	MI, RF Complete case Extended TMLE Extended TMLE Extended TMLE+MCMI MI, no int (linear) MI,no int MI, 2-way int MI, higher int MI, CART MI, RF Complete case Extended TMLE Extended TMLE Extended TMLEHMCMI MI, no int (linear) MI, no int MI, 2-way int	0.16 0.17 0.17 0.24 0.25 0.21 0.22 0.17 0.11 0.15 0.16 0.23 0.24 0.20	-0.04 -0.03 -0.03 -0.04 -0.05 -0.01 -0.02 -0.03 -0.09 -0.05 -0.05 -0.04 -0.03	0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.0	-17.40 -13.79 22.28 23.23 4.35 11.32 -16.78 -46.49 -23.42 -22.61 -17.81 17.04 18.56 -0.16	86.65 87.40 96.70 96.85 97.85 97.80 97.15 97.90 86.70 86.15 86.10 96.65 96.55 98.30	0.74 0.40 0.39 0.32 0.33 0.37 0.32 0.76 0.77 0.40 0.41 0.29	87.85 97.40 97.70 97.85 97.80 97.75 99.80 89.00 88.15 88.35 96.90 97.10	0.73 0.73 0.36 0.34 0.32 0.33 0.10 0.70 0.72 0.72 0.39 0.38 0.29	0.14 0.12 0.13 0.13 0.12 0.12 0.11 0.07 0.14 0.14 0.12 0.13 0.13 0.12	0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.0	0.10 0.16 0.16 0.15 0.13 0.13 0.11 0.11 0.10 0.16 0.15	0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.0	-18.78 21.72 22.45 26.99 27.35 24.87 83.13 -16.41 -19.31 -18.59 19.18 21.48 26.74	1 2 2 2 2 2 3 1 1 1 1 2 2
ı	MI, RF Complete case Extended TMLE Extended TMLE+MCMI MI, no int (linear) MI,no int MI, 2-way int MI, higher int MI, CART MI, RF Complete case Extended TMLE Extended TMLE+MCMI MI, no int (linear) MI, no int (linear) MI, no int (linear)	0.16 0.17 0.17 0.24 0.25 0.21 0.22 0.17 0.11 0.15 0.16 0.23 0.24	-0.04 -0.03 -0.03 -0.05 -0.05 -0.05 -0.05 -0.05 -0.05 -0.05 -0.04 -0.03	0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.0	-17.40 -13.79 22.28 23.23 4.35 11.32 -16.78 -46.49 -23.42 -22.61 -17.81 17.04 18.56	86.65 87.40 96.70 96.85 97.85 97.15 97.90 86.70 86.15 86.10 96.65 96.55	0.74 0.40 0.39 0.32 0.33 0.37 0.32 0.76 0.77 0.77 0.40 0.41	87.85 97.40 97.70 97.85 97.80 97.75 99.80 88.00 88.15 88.35 96.90 97.10	0.73 0.73 0.36 0.34 0.32 0.33 0.10 0.70 0.72 0.72 0.39 0.38	0.14 0.12 0.13 0.13 0.12 0.12 0.11 0.07 0.14 0.14 0.12 0.13 0.13	0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.0	0.10 0.16 0.16 0.15 0.15 0.13 0.13 0.11 0.10 0.16 0.16	0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.0	-18.78 21.72 22.45 26.99 27.35 24.87 83.13 -16.41 -19.31 -18.59 19.18 21.48	1 2 2 2 2 2 3 1 1 1 2 2 2