Generalizing treatment effects with incomplete covariates: Identifying assumptions and multiple imputation algorithms

Imke Mayer¹,² | Julie Josse² | Traumabase Group³

¹Institute of Public Health, Charité – Universitätsmedizin, Berlin, Germany
²PreMeDiCaL, Inria Sophia-Antipolis, Montpellier, France
³Department of Anesthesia and Intensive Care, Beaujon Hospital, AP–HP, Clichy, France

Correspondence
Imke Mayer, Institute of Public Health, Charité – Universitätsmedizin, Charitéplatz 1, 10117 Berlin, Germany.
Email: imke.mayer@inria.fr

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Abstract
We focus on the problem of generalizing a causal effect estimated on a randomized controlled trial (RCT) to a target population described by a set of covariates from observational data. Available methods such as inverse propensity sampling weighting are not designed to handle missing values, which are however common in both data sources. In addition to coupling the assumptions for causal effect identifiability and for the missing values mechanism and to defining appropriate estimation strategies, one difficulty is to consider the specific structure of the data with two sources and treatment and outcome only available in the RCT. We propose three multiple imputation strategies to handle missing values when generalizing treatment effects, each handling the multisource structure of the problem differently (separate imputation, joint imputation with fixed effect, joint imputation ignoring source information). As an alternative to multiple imputation, we also propose a direct estimation approach that treats incomplete covariates as semidiscrete variables. The multiple imputation strategies and the latter alternative rely on different sets of assumptions concerning the impact of missing values on identifiability. We discuss these assumptions and assess the methods through an extensive simulation study. This work is motivated by the analysis of a large registry of over 20,000 major trauma patients and an RCT studying the effect of tranexamic acid administration on mortality in major trauma patients admitted to intensive care units. The analysis illustrates how the missing values handling can impact the conclusion about the effect generalized from the RCT to the target population.

Keywords
causal effect transportability, data integration, external validity, missing values, missing incorporated in attributes, multiple imputation, random forest
1 | INTRODUCTION

Observational and randomized trial data can provide different perspectives when evaluating an intervention or a medical treatment. Combining the information gathered from experimental and observational data is a promising avenue for medical research because the knowledge that can be acquired from integrative analyses would not be possible from any single-source analysis alone. Such integrative analyses can be used to estimate the effect of a treatment on a specific target population different from the original trial population, to validate observational methods by emulating a trial (Hernán & Robins, 2016), and to better estimate heterogeneous effects (which generally cannot be estimated from experimental data due to underpowered studies).

Here, we are interested in the first case, where the results obtained from an experimental study on treatment effectiveness are only valid for the population studied in this experimental study but do not reflect efficacy or effectiveness in a (slightly) different population or setting described by observational data that often better represent daily practice. The experimental data or randomized controlled trial (RCT) is thus considered a biased sample of a target population, and we wish to estimate the treatment effect on the target population represented by an observational study. Specifically, the effect is estimated using an RCT composed of covariates, treatment, and outcome, whereas the observational study is composed only of covariates. There are a multitude of methods for generalizing a treatment effect; for detailed reviews, we refer to Colnet et al. (2020) and Degtiar and Rose (2023). But all of these methods do not consider the problem of missing data, which is ubiquitous in data analysis practice (Josse & Reiter, 2018; Little & Rubin, 2014). We emphasize here that we focus on covariates with sporadic missing values in both studies, while the outcome and treatment (available in the RCT) are assumed to be fully observed.

In certain cases, naive approaches such as complete-case analysis can yield unbiased treatment effect estimates (Bartlett et al., 2015); however, in many settings, especially for observational data, the estimations are known to be biased since the complete-case observations are generally not a representative subsample of the population of interest (Little & Rubin, 2014). Moreover, this approach is sometimes not even feasible since in high-dimensional settings the probability of having complete observations decreases rapidly (Zhu et al., 2022). There are a multitude of methods to handle missing values (Little & Rubin, 2014; Mayer et al., 2022; van Buuren, 2018), such as maximum likelihood estimation or multiple imputations for parameter estimation and inference. These methods make assumptions on the mechanism that generated the missing values. More recent works also consider the question of supervised learning with missing values which is a different problem from statistical inference of model parameters (Le Morvan et al., 2020), but supervised learning methods can be useful when estimating treatment effects (Chernozhukov et al., 2018; Wager & Athey, 2018), for example, to estimate nonparametric nuisance parameters on incomplete data for doubly robust estimators (Mayer et al., 2020). Missing data approaches for causal inference require coupling identifiability assumptions for the causal parameter with assumptions regarding the missingness mechanisms (Blake et al., 2020; Kallus et al., 2018; Mattei, 2009; Mayer et al., 2020; Seaman & White, 2014; Yang et al., 2019). According to Mayer et al. (2020), identifiability of the causal effect with missing values in observational studies can be ensured by adapting the causal inference assumptions to the missingness setting with an unconfoundedness despite missing values (UDM) assumption (Mayer et al., 2020; Rosenbaum & Rubin, 1984). This assumption states that the unconfoundedness holds conditionally on the observed values and the missingness pattern. A formal definition of this assumption is provided in Section 4. However, these works only consider the case of a single dataset—or potentially multiple datasets with the same data distribution, that is, sampled from the same population of interest—and do not treat the case of transporting or generalizing a treatment effect from an RCT to a target distribution defined through an observational dataset; the RCT representing a “distorted” population due to sampling or selection bias which arises due to eligibility requirements and also the trial setting. In practice, the observed distributions between the observational data and the RCT do not only differ due to the selection bias but may also differ in terms of missing values patterns.

To address the problem described above, our main contributions in this paper consist in

1. defining several multiple imputation strategies adapted for integrating experimental and observational data (Section 3);
2. proposing alternative identifiability assumptions which can be seen as an extension of the UDM assumption from the observational data case (Mayer et al., 2020) and suggest adapted estimators (Section 4);
3. assessing the performance of the proposed estimators and naive complete case estimators in an extensive simulation study\(^1\) (Section 5), and can also be found in the following repository: https://github.com/imkemayer/combined-incomplete-data

\(^1\)The code for this simulation study as well as for the real-world data analysis is available as Supporting Information on the journal’s web page (http://onlinelibrary.wiley.com/doi/10.1002/bimj.202100294/suppinfo)
4. presenting the results of our analysis for the generalization of the effect of tranexamic acid (TXA) on major trauma patients with traumatic brain injury (TBI) from an RCT to a target population described by observational data which has motivated this work (Section 6).

Medical data analysis

Major trauma denotes injuries that endanger the life or the functional integrity of a person. The World Health Organization has recently shown that major trauma including road-traffic accidents, interpersonal violence, falls, etc. remains a worldwide public health challenge and major source of mortality and handicap (Leigh et al., 2018). We focus on trauma patients suffering from a TBI. TBI is a sudden damage to the brain caused by a blow or jolt to the head and can lead to intracranial bleeding that can be observed on a computed tomography scan. TXA is an antifibrinolytic agent that limits excessive bleeding, commonly given to surgical patients. Previous clinical trials showed that TXA decreases mortality in patients with traumatic extracranial bleeding (Shakur-Still et al., 2009). Such a result raises the possibility that it might also be effective in TBI, because intracranial hemorrhage is common in TBI patients. Therefore, the question here is to assess the potential decrease in mortality in patients with intracranial bleeding when using TXA.

While a multicenter international RCT with a majority of patients recruited in developing countries, “CRASH-2,” provides randomized data on this question, the “Traumabase,” an observational national registry, is representative of the target population on which inference is desired. The latter contains information about critical care patients admitted in mainland France. The details about these data are provided in Section 6.

2 | BACKGROUND AND NOTATIONS

We first introduce the notations, standard assumptions, and estimators in the full data case, following the lines of Colnet et al. (2020) and Nie et al. (2021).

2.1 | Notations

We consider that we have access to a trial sample (also called RCT) of \( n > 0 \) independent and identically distributed (i.i.d.) observations drawn from \( P_{\text{trial}}(X, Y(0), Y(1), A) \), where \( X \in \mathcal{X} \) is a \( p \)-dimensional vector of covariates, \( A \) denotes the binary treatment assignment, and \( Y(a) \) is the potential outcome for treatment level \( a \in \{0, 1\} \). We also have an observational sample of \( m > 0 \) i.i.d observations drawn from \( P_{\text{target}}(X, Y(0), Y(1), A) \) but where only the covariates are observed. The design considered is known as a nonnested design and is illustrated in Figure 1.

We emphasize that, in this work, the observational data are assumed to be representative of the target population. The density of \( X \) in the target population (respectively, trial population) is denoted \( p_{\text{target}}(x) \) (respectively, \( p_{\text{trial}}(x) \)). Throughout this work, we assume that there is a distributional shift between the two populations which means that \( \exists x \in \mathcal{X}, p_{\text{trial}}(x) \neq p_{\text{target}}(x) \). This makes it difficult to extrapolate average treatment effects from the trial to the target population.

We denote expectation with respect to the trial and the target distribution by \( E_{\text{trial}} \) and \( E_{\text{target}} \), respectively, and define the target population conditional average treatment effect (CATE):

\[
\forall x \in \mathcal{X}, \quad \tau(x) = E_{\text{target}}[Y(1) - Y(0) | X = x],
\]
and the target population average treatment effect (ATE) $\tau = \tau_{\text{target}} = \mathbb{E}_{\text{target}}[Y(1) - Y(0)]$, while we define the RCT (or sample) average treatment effect as $\tau_{\text{trial}} = \mathbb{E}_{\text{trial}}[Y(1) - Y(0)]$.

We denote by $\mu_{a,\text{target}}(x)$ and $\mu_{a,\text{trial}}(x)$ the conditional response surfaces under treatment $a \in \{0, 1\}$ in the general, that is, the target, and in the RCT population, respectively:

$$\mu_{a,\text{target}}(x) = \mathbb{E}_{\text{target}}[Y(a)|X = x], \quad \mu_{a,\text{trial}}(x) = \mathbb{E}_{\text{trial}}[Y(a)|X = x],$$

and by $r(x)$ the density ratio that captures the assumed distribution shift between $p_{\text{trial}}$ and $p_{\text{target}}$:

$$r(x) = \frac{p_{\text{target}}(x)}{p_{\text{trial}}(x)}, \forall x \in \mathcal{X} \text{ such that } p_{\text{trial}}(x) \neq 0.$$ 

### 2.1.1 Alternative formulation of the generalization problem

In the literature based on the potential outcomes framework, there are two equivalent formulations of the generalization problem. The distributional approach introduced above is used, for example, by Nie et al. (2021). Alternatively, it is possible to adopt a sampling or selection process point of view by introducing a binary random variable $S \in \{0, 1\}$ that indicates trial eligibility and willingness to participate.\(^2\) This approach is taken, for example, by Dahabreh and Hernán (2019) and Stuart et al. (2011). The variable $S$ is only observed for individuals in the RCT while unknown for individuals from the target population sample. Indeed, for the individuals in the RCT, we know by design that $S = 1$, but for the individuals from the target population they could have been in the RCT according to their characteristics. Hence, both values of $S$ can occur in the observational sample. It is generally assumed in this context that if an individual meets the eligibility criteria and in principle is willing to participate, then the actual trial participation is random and does not depend on other factors, observed or unobserved. Trial eligibility and willingness to participate are assumed to depend to some extent on the covariates $X$ so that there is a shift in the distributions of the trial and the target populations. The following assumptions for identifiability of the ATE on the target population can also be formulated using this alternative notation $S$ (see, e.g., Colnet et al., 2020).

### 2.2 Assumptions for identifiability of the ATE on the target population in the full data case

The main identifiability assumptions that allow for generalizing an ATE from the RCT onto a target population are as follows:

#### 2.2.1 Internal validity of the RCT

**Assumption 1** (Consistency of potential outcomes). $Y = AY(1) + (1 - A)Y(0)$.

**Assumption 2** (Treatment randomization). $\mathbb{E}_{\text{trial}}[A|Y(a), X = x] = \mathbb{E}_{\text{trial}}[A]$, for all $x \in \mathcal{X}$ and $a = 0, 1$.

Moreover, for simplicity of the following presentation, we assume a constant treatment assignment propensity in the RCT, that is, $e_{\text{trial}}(x) = Pr(A = a | X = x) = 0.5$ for all $x$.

#### 2.2.2 Generalizability of the RCT to the target population

**Assumption 3** Transportability of the CATE\(^3\). $\mathbb{E}_{\text{target}}[Y(1) - Y(0)|X = x] = \mathbb{E}_{\text{trial}}[Y(1) - Y(0)|X = x]$ for all $x \in \mathcal{X}$.

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\(^2\) It does not correspond to a deterministic variable of whether or not the eligibility criteria are met, but rather illustrates that some individuals have more or less propensity to be chosen for the trial.

\(^3\) In the literature, this assumption is sometimes also referred to as exchangeability with respect to trial eligibility and willingness (Degtiar & Rose, 2023; Stuart et al., 2011).
Assumption 4 (Support inclusion). \( \text{supp}(P_{\text{target}}(X)) \subseteq \text{supp}(P_{\text{trial}}(X)) \), where \( \text{supp}(P) \) denotes the support of distribution \( P \).

Assumption 3 states that the conditional treatment effect is stable across populations; therefore, it implies that \( X \) contains all treatment effect modifiers (in this case with respect to the absolute value of the difference in potential outcomes, i.e., on the absolute scale) that differ in distribution between the trial and target populations. With Assumption 4, we formalize an implication of the nonnested design, namely that the support of the observational sample is included within the support of the RCT. Without this support inclusion assumption, we cannot hope to generalize the effect to units from the target population which have a zero probability of being eligible and of participating in the trial. For example, if we assume that age is a treatment effect modifier and that the target population is composed mostly of older individuals than in the trial, the support inclusion assumption requires that older individuals had a nonzero chance of being eligible and included in the trial (Stuart et al., 2011).

2.3 Estimators in the full data case

The covariate distribution of the RCT population \( P_{\text{trial}} \) is generally different from that of the target population \( P_{\text{target}} \); therefore, \( \tau_{\text{trial}} \) is different from \( \tau \), and an estimator based solely on the RCT, such as the difference in means estimator

\[
\hat{\tau}_{\text{trial}} = \frac{1}{n_1} \sum_{i=1}^{n_1} A_i Y_i - \frac{1}{n_0} \sum_{i=1}^{n_0} (1 - A_i) Y_i,
\]

where \( n_a = \sum_{i=1}^{n} 1_{\{A_i = a\}} \), is biased for the ATE of interest \( \tau \). Under the previous identifiability assumptions, different estimators are available to estimate the ATE \( \tau \) (identification formula as well as their derivation are provided in Appendix A): the inverse probability of sampling weighting (IPSW) proposes to reweight, using the density ratio \( r(x) \), the RCT sample so that it “resembles” the target population with respect to the observed “shifted” covariates. The conditional outcome-based estimator proposes to model the conditional outcomes in the RCT and then to apply the model to the target population of interest. Doubly robust approaches leverage combinations of the former two, improving the robustness and efficacy.

Inverse probability of sampling weighting

This estimator is defined as the weighted difference of average outcomes between the treated and control groups in the trial (e.g., Cole & Stuart, 2010; Stuart et al., 2011). The observations are weighted by the density ratio \( r(x) \) to account for the shift of the covariate distribution from the RCT sample to the target population. The IPSW estimator can be written as follows:

\[
\hat{\tau}^{\text{IPSW}} = \frac{2}{n} \sum_{i=1}^{n} \hat{r}(X_i) Y_i (2A_i - 1),
\]

(2)

where \( \hat{r} \) is an estimate of \( r \). The IPSW estimator is consistent as long as \( r \) is consistently estimated by \( \hat{r} \). Note that the density ratio can be estimated using different strategies, for example, by moment matching (Nie et al., 2021) or, assuming that \( \hat{r}(x) = \frac{n}{m} \frac{\hat{P}(i \in S_{\text{trial}}|X_i = x)}{\hat{P}(i \in S_{\text{trial}}|X_i = x)} \) (Colnet et al., 2022), the density ratio can be estimated from the data using, for example, a logistic regression model for the indicator \( 1_{S_{\text{trial}}} \) on covariates \( X \).

Conditional outcome-based estimation

This approach fits regressions of the conditional response surfaces among trial participants. Marginalizing these regressions over the covariate distribution of the observational data gives the corresponding expected outcome (e.g., Dahabreh et al., 2019). This outcome-model-based estimator, an instantiation of the so-called g-formula estimator (Robins, 1986) or conditional outcome (CO) estimator to the case of treatment effect generalization, is then defined as

\[
\hat{\tau}^{\text{CO}} = \frac{1}{m} \sum_{i=n+1}^{n+m} (\hat{\mu}_{1,\text{trial}}(X_i) - \hat{\mu}_{0,\text{trial}}(X_i)),
\]

(3)

where \( \hat{\mu}_{a,\text{trial}}(X_i) \) is an estimator of \( \mu_{a,\text{trial}}(X_i) \). If the model is correctly specified, then the estimator is consistent.
Doubly robust estimators

The density ratio and outcome regression models used in the first two estimators can be combined to form an augmented IPSW estimator (AIPSW):

\[
\hat{\tau}_{\text{AIPSW}} = \frac{2}{n} \sum_{i=1}^{n} \hat{r}(X_i) \left[ A_i \{ Y_i - \hat{\mu}_{1,1}(X_i) \} - (1 - A_i) \{ Y_i - \hat{\mu}_{0,1}(X_i) \} \right] + \frac{1}{m} \sum_{i=n+1}^{m+n} \{ \hat{\mu}_{1,\text{trial}}(X_i) - \hat{\mu}_{0,\text{trial}}(X_i) \}. \tag{4}
\]

It is doubly robust, that is, consistent and asymptotically normal when either one of the two estimators \(\hat{r}(X)\) and \(\hat{\mu}_a,\text{trial}(X)\) \((a = 0, 1)\) is consistent (Dahabreh & Hernán, 2019).

**Calibration weighting**

IPSW is likely to be unstable if some of the estimated weights are very small (Dahabreh & Hernán, 2019). To resolve the instability of IPSW, calibration weighting (Lee et al., 2022) has been proposed. They calibrate, that is, they balance the covariates between the RCT sample and the target population: usually the balance is enforced on the first and second moments of the covariates such that the weighted mean and variance for each variable in the RCT match the ones in the observational data. More precisely, in order to calibrate, they assign an entropy-balancing weight \(\omega_i\) to each subject \(i\) in the RCT sample obtained by solving an optimization problem:

\[
\min_{\omega_1, \ldots, \omega_n} \sum_{i=1}^{n} \omega_i \log \omega_i, \tag{5}
\]

subject to \(\omega_i \geq 0\), for all \(i\), \(\sum_{i=1}^{n} \omega_i = 1\), and \(\sum_{i=1}^{n} \omega_i g(X_i) = \bar{g}\), (balancing constraint)

where \(\bar{g} = m^{-1} \sum_{i=n+1}^{m+n} g(X_i)\) is a consistent estimator of \(\mathbb{E}_{\text{target}}[g(X)]\) from the observational sample. The balancing constraint calibrates the covariate distribution of the RCT sample to the target population in terms of \(g(X)\). The objective function in (5) is the negative entropy of the calibration weights; thus, minimizing this criterion ensures that the empirical distribution of calibration weights is not too far away from the uniform, such that it minimizes the variability due to heterogeneous/extreme weights. Based on the calibration weights, the calibration weighting (CW) estimator is then defined as

\[
\hat{\tau}_{\text{CW}} = 2 \sum_{i=1}^{n} \hat{\omega}_i Y_i (2A_i - 1). \tag{6}
\]

This estimator is doubly robust in that it is a consistent estimator for \(\tau\) if either the obtained weights \(\hat{\omega}_i\) are proportional to the density ratio \(r(X)\) (Chu et al., 2022)\(^4\) or if the CATE (1) is linear in the calibration constraint.

### 2.4 Missing values mechanisms

In the taxonomy proposed by Rubin (1976), missing data mechanisms can be **missing completely at random** (MCAR) when the missingness is independent of the data, **missing at random** (MAR) when the missingness depends only on observed values, or **missing not at random** (MNAR) when missingness can depend on unobserved values. The first two mechanisms are “ignorable” in that the missing data mechanism is separable in the full data likelihood function, so missingness can be “ignored.” More formally, we denote the response pattern of the \(i\)th sample as \(R_i \in \{0, 1\}^p\) such that \(R_{ij} = 1\) if \(X_{ij}\) is observed and \(R_{ij} = 0\) otherwise. For all response patterns \(r\) and \(X = (X_{\text{obs}(r)}, X_{\text{mis}(r)})\), the partition of

\(^4\)This is the case, for example, if \(Pr(S = 1 | X)\) follows a logistic regression model, where \(S\) corresponds to the random variable from the selection process approach briefly mentioned in Section 2.1.1.
the data in realized observed and missing values given a specific realization of the pattern, we define the missing values mechanisms as follows:

(MCAR in the trial) \[ \forall r \in \{0,1\}, P(r = r | X, A, Y) = P(r = r) \] (7)

(MCAR in the target) \[ \forall r \in \{0,1\}, P(r = r | X) = P(r = r) \] (8)

(MAR in the trial) \[ \forall r \in \{0,1\}, P(r = r | X, A, Y) = P(r = r | X_{obs(r)}, A, Y). \] (9)

(MAR in the target) \[ \forall r \in \{0,1\}, P(r = r | X) = P(r = r | X_{obs(r)}). \] (10)

For more details and nuanced presentation of the missing values mechanisms and related assumptions, we refer to Mealli and Rubin (2015). In Appendix B, we give an illustration in Figure B.1 of the considered incomplete data, similar to the example of the complete data case of Figure 1.

3 | MULTIPLE IMPUTATION UNDER STANDARD IDENTIFIABILITY ASSUMPTIONS

Under the standard identifiability assumptions, namely Assumptions 1–4 and separate assumptions on the missingness mechanism as described in the previous section, multiple imputation can be an adequate strategy to address the challenge of generalizing the average treatment effect with incomplete covariates.

3.1 | General concept

Multiple imputation (MI) is one of the most powerful approaches to estimate parameters and their variance from incomplete data (Kim & Shao, 2013; Little & Rubin, 2014; Schafer, 2010). For a single dataset, it consists in generating \( M \) plausible values for each missing entry, which leads to \( M \) completed datasets. Then, an analysis is performed on each imputed dataset \( m = 1, \ldots, M \), to get an estimate for the parameter of interest, say \( \theta \) as \( \hat{\theta}^m \) and an estimate of its variance \( \hat{V}_m(\hat{\theta}^m) \) and the results are combined using Rubin (1987)'s rules to get correct inference with missing values, namely confidence intervals with the appropriate coverage.

3.2 | Adapted multiple imputation for multiple data sources with different data design

For our problem, there are multiple possibilities to derive a multiple imputation strategy to generalize a treatment effect. This is due to the multisource structure of the data and the fact that there is an additional complication due to the number of variables is not the same in the RCT and in the observational study. Indeed, we assume that the observational study does not include treatment and outcome but only covariates. We stress again that we assume missing values only occur in the covariates of both data. We suggest and describe three strategies to tackle this problem:

1. Within-study multiple imputation:
   (a) Multiple imputation of the RCT: Impute \( M \) times the covariates of the RCT using \( (X_i, A_i, Y_i)_{i \in \text{Set}_R} \).
   (b) Multiple imputation of the observational data: Impute \( M \) times the covariates of the observational data using only the covariates \( X_i_{i \in \text{Set}_o} \).
   (c) Create \( M \times M \) complete tables by concatenating all possible combinations of imputed RCT and observational data. Estimate the treatment effect on every combination using any complete case estimator as in Section 2 and aggregate these estimations using Rubin's rules.

2. Ad hoc joint covariates multiple imputation, ignoring the information on the data sources, that is, ignoring the source indicator \( 1_{\text{Set}_R} \):
   (a) Impute \( M \) times the joint datasets (the concatenation of the covariates from the RCT and the ones from the observational study) with covariates \( X \).
(b) Concatenate the outcome \(Y\) and treatment \(A\) for each imputed RCT individual.

(c) Compute the \(M\) treatment effect estimators using any complete case estimator as in Section 2 and aggregate them using Rubin’s rules.

3. Joint covariates multiple imputation, modeling the group variable as a fixed effect, that is, explicitly use the indicator \(1_{\text{Set}_R}\) for the corresponding “group”/“source” during the imputation:

(a) Impute \(M\) times the joint datasets with covariates \(X\) and model the source indicator \(1_{\text{Set}_R}\).

(b) Concatenate the outcome \(Y\) and treatment \(A\) for each imputed RCT individual.

(c) Compute the \(M\) treatment effect estimators using any complete case estimator as in Section 2 and aggregate them using Rubin’s rules.

A schematic illustration of these three strategies is given in Figure C.1 in the Appendix. The first strategy has the advantage that it takes into account the outcome \(Y\) and treatment \(A\) which are dependent variables of the covariates \(X\), when imputing the covariates of the RCT as suggested by Leyrat et al. (2019), Mattei (2009), and Seaman and White (2014) as it models the entire joint distribution. The other strategies only consider the covariates \(X\). The second strategy solely relies on the relationships between the covariates \(X\) and the assumption that these are stable across the data sources, that is, \(\text{Cov}_{\text{target}}(X) = \text{Cov}_{\text{trial}}(X)\), where \(\text{Cov}(Z)\) denotes the covariance matrix of the random vector \(Z\). Strategy 3 can be seen as a fixed effect method, where the variable \(Q\) is included as a variable in the imputation model which allows, for example, in case of multiple imputation with conditional regression models, to impute according to an analysis of covariance model (to take into account differences between the means of the variables within each data source).

All three strategies can be implemented easily using the R package mice (van Buuren, 2018), which uses conditional models such as linear and logistic regressions (by default) to perform multiple imputation.

Multiple imputation is especially suited if the missing values are ignorable as described in Section 2.4 and if the identifiability assumptions of the ATE \(\tau\) in the full data case are met, namely Assumptions 3 and 4. In the case of nonignorable missing values, multiple imputation is still possible but requires knowledge about the generating process for the missing values to explicitly model the response or missingness pattern (van Buuren, 2018). There is no clear rule about the number of multiple imputations to achieve good performances; however, an accepted rule of thumb is to choose the number of imputations to be similar to the percentage of incomplete cases (Hippel, 2009) or to the average percentage of missing data (van Buuren, 2018). In the considered settings and for the deployed imputation strategies, increasing the number of imputations from 10 to 50 does not improve the final result.

### 4 MISSING INCORPORATED IN ATTRIBUTES UNDER ALTERNATIVE IDENTIFIABILITY ASSUMPTIONS

An alternative to handle missing covariates values consists in modifying the identifiability assumptions so that they directly handle missing values but do not necessarily require assumptions on the missing values mechanism. This can be seen as an advantage as it possibly allows for MNAR data, but the new identifiability assumptions may be more difficult to satisfy than in the full data case. More precisely, to enable generalizing the RCT to the target population, we extend the work of Mayer et al. (2020) who adapt the unconfoundedness assumption to the incomplete covariates in order to identify the (average) treatment effect in the observational data case. First, we introduce an additional notation, required for the following approach: We denote the matrix of observed covariates with \(X^*_i \triangleq X_i \odot R_i + \text{NA} \odot (1 - R_i)\), with \(\odot\) the element-wise multiplication and \(1\) the matrix filled with 1, so that \(X^*_i\) takes its value in the half discrete space \(\mathcal{X}^* = \times_{1 \leq j \leq |X|} \{X^*_j \cup \{\text{NA}\}\}\). Now we can replace the previous Assumptions 3 and 4 with the following alternatives.

**Assumption 3b** (Transportability of the CATE, conditionally independent selection (CIS)). \(E_{\text{target}}[Y(1) - Y(0)|X^* = x^*] = E_{\text{trial}}[Y(1) - Y(0)|X^* = x^*]\) for all \(x^* \in \mathcal{X^*}\).

**Assumption 4b** (Support inclusion). \(\text{supp}(P_{\text{target}}(X^*)) \subseteq \text{supp}(P_{\text{trial}}(X^*))\).

The intuition behind these alternative assumptions is to assume that instead of requiring transportability of the CATE conditionally on all covariates, we only require transportability of the CATE conditionally on the observed information, meaning the observed values and the pattern of missing values. To further elucidate this assumption, we temporarily
take the alternative selection point of view introduced in Section 2.1.1: The CIS assumption, which can also be written as $S \perp \perp Y(1), Y(0) \mid X$, may be plausible in a context where trial eligibility (and willingness to participate) is defined via a set of sufficient conditions that are not all necessary conditions. In practice, one could imagine a “check list” of $L$ conditions and that it is necessary to fulfill at least $l < L$ of these to qualify for the trial. More specifically, if we consider five covariates $X_1, \ldots, X_5$ and assume that there exist different possibilities to be included in the trial, for example, a condition on $X_1, X_2,$ and $X_3$ regardless of $X_4$ and $X_5$ and another alternative condition on $X_2$ and $X_5$. In the case of such a design, the CIS assumption is potentially a suited assumption to generalize a treatment effect onto another population. Taking the example given in Figure B.1 (in Appendix B), for observation 1, only $X_1$ and $X_2$ and the fact that $X_3$ is unobserved qualify individual 1 for the trial and willingness to participate, while for observation 2 only $X_1$ and $X_3$ and the fact that $X_2$ is missing contribute to the value taken by $S$, etc.

Similar to the UDM assumption from Mayer et al. (2020), which states that $\{Y(0), Y(1)\} \perp A \mid X^*$ in the observational data case, that is, the treatment assignment is independent of the treatment effect conditionally on the observed values and the missingness pattern, Assumption 3b can be replaced by two sufficient assumptions, using the selection indicator $S$ introduced in Section 2.1.1: Assumption 3 and $S \perp \perp X \mid X^*$, thus the term conditionally independent selection.

### 4.1 Generalized estimators

Similar to D’Agostino and Rubin (2000), Mayer et al. (2020), and Rosenbaum and Rubin (1984), we define the generalized conditional response surfaces $\mu^*_{a,\text{target}}$ and $\mu^*_{a,\text{trial}}$ as follows:

$$
\mu^*_{a,\text{target}}(x^*) = E_{\text{target}}[Y(a) \mid X^* = x^*], \quad \mu^*_{a,\text{trial}}(x^*) = E_{\text{trial}}[Y(a) \mid X^* = x^*].
$$

(11)

The resulting estimators are then formed analogously to the estimators in the full data case, by substituting the corresponding nuisance parameters with their generalized counterparts. More explicitly, the outcome-model-based estimator defined by (3) becomes

$$
\hat{\tau}_{CO,*} = \frac{1}{m} \sum_{i=n+1}^{n+m} \left( \hat{\mu}^*_{1,\text{trial}}(X^*_i) - \hat{\mu}^*_{0,\text{trial}}(X^*_i) \right).
$$

(12)

Fitting the new nuisance (11) is not straightforward, since these require to fit a separate regression model for each possible pattern $r$ of missing values (Le Morvan et al., 2021). For example, if we have three incomplete covariates $X_1, X_2, X_3$, with the $2^3$ patterns of missing values, this means we need to fit a separate regression on $\{X_1, X_2, X_3\}$, on $\{X_1, X_2\}$, on $\{X_2, X_3\}$, on $\{X_1\}$, etc. We can see from this example that this is not possible in moderate and high dimensions with classical regression methods.

**Nonparametric estimation**

We propose to estimate the generalized nuisance components via random forests (Athey et al., 2019; Breiman, 2001), with missing data handled using the missing incorporated in attributes (MIA) method of Twala et al. (2008). Indeed, as noted already by Athey et al. (2019) and Mayer et al. (2020), many modern machine learning methods, including tree ensembles and neural networks, can be adapted to this context and thus readily handle missing data and enable direct fitting of the generalized regression models (11), for detailed consistency results we refer to Le Morvan et al. (2021). The resulting IPSW, CO, and AIPSW estimators will be denoted by $\hat{\tau}^{\text{PSW,*}}_{MIA}$, $\hat{\tau}^{\text{CO,*}}_{MIA}$, and $\hat{\tau}^{\text{AIPSW,*}}_{MIA}$, respectively.

In random trees, the MIA approach extends the classical splitting rules such that missing values are incorporated in the splitting criterion. More specifically, consider splitting on the $j$th attribute and assume that for some individuals, the value of $X_j$ is missing, MIA treats the missing values as a separate category or code and considers the following splits:

1. $\{i : X_{ij} \leq t \text{ or } X_{ij} \text{ is missing} \}$ vs. $\{i : X_{ij} > t \}$,
2. $\{i : X_{ij} \leq t \}$ vs. $\{i : X_{ij} > t \text{ or } X_{ij} \text{ is missing} \}$,
3. $\{X_{ij} \text{ is missing} \}$ vs. $\{X_{ij} \text{ is observed} \}$,

for some threshold $t$. The MIA approach does not seek to model why some features are unobserved; instead, it simply tries to use information about missingness to make the best possible splits for modeling the desired outcome. Thus the
MIA strategy works with arbitrary missingness mechanisms and does not require the missing data to follow a specific mechanism. This MIA approach for (generalized) random forests is implemented in the R package `grf` (Tibshirani et al., 2020), which is also used in the simulation part of this work presented in Section 5.

**Parametric alternative**

Parametric estimation is, however, possible in the case of logistic and linear regression models. This is based on work by Jiang et al. (2020) and Schafer (2010) for logistic and linear regressions with missing covariates. The regression functions \( \mu_{a,trial} \) defined in (11) that take in incomplete covariates \( x^* \) are estimated via expectation maximization (EM, Dempster et al., 1977). The resulting IPSW, CO, and AIPSW estimators will be denoted by \( \hat{\tau}_{IPSW,EM} \), \( \hat{\tau}_{CO,EM} \), and \( \hat{\tau}_{AIPSW,EM} \), respectively. The details of this approach are given in Appendix C.

However, a major limitation of this approach is that, in addition to the alternative identifiability assumptions 3b and 4b, in order to justify the use of the EM algorithm, one typically needs to make further assumptions on the missing value mechanism; in particular, this approach assumes the MAR mechanism, that is, (9) and (10). In other words, although we did not require the missing at random assumption to identify \( \tau \), this assumption is used for consistent parametric estimation of the generalized conditional regression models \( \mu_{a,trial} \).

## 5 | SIMULATIONS

We conduct a detailed simulation study to assess the performance of the previously introduced estimators to handle missing values. This controlled study allows to quantify the impact of different missing values mechanisms and identifiability assumptions on the final estimate for the ATE \( \tau \). The code for this simulation study as well as for the medical data analysis (Section 6) has been written and run using R version 4.0.2 (platform: x86_64-apple-darwin17.0, 64-bit) with packages `mice_3.14.0`, `misaem_1.0.1`, `genRCT_0.1.0`, `grf_2.0.2`, and `caret_6.0-90`.\(^5\)

### 5.1 | Data generation

#### 5.1.1 | Standard assumptions for causal identifiability and missing values mechanisms

In this setting, we consider that Assumptions 1–4 hold. If additionally, missing values are generated using a MAR mechanism ((9) and (10)), we expect the multiple imputation based methods proposed in Section 3 to perform well. The data simulation is implemented in two steps, using the selection indicator \( S \) from the selection process approach mentioned in Section 2.1.1, which provides a more transparent way to simulate adequate data: (1) a large covariates sample is drawn from the target population, then a trial sample is generated out of this sample using a model for trial eligibility and participation (selecting observations with \( S = 1 \) and discarding all other observations); (2) the target population sample is drawn from the target population independently from the first sample. This two-step simulation approach results in a covariate shift between the trial and target population as assumed throughout this work. We consider the selection model generated either as a logistic model as follows:

\[
\text{logit}\{P(S = 1|X)\} = -3.1 - 0.5X_1 - 0.3X_2 - 0.5X_3 - 0.4X_4,
\]

or according to the following nonlinear model:

\[
\text{logit}\{P(S = 1|X)\} = -2.95 - 0.5|X_1|\sin(X_1) - 0.3|X_2|X_2 - 0.75X_3 - 0.5X_4|X_1|\sin(X_1) - 0.4|X_4|X_4,
\]

where every \( X \) is drawn from a multivariate normal distribution with mean 1 and covariance matrix \( \Sigma \) such that \( \Sigma_{ij} = \begin{cases} 1 & \text{if } i = j \\ 0.6 & \text{if } i \neq j \end{cases} \) to have correlated covariates. The outcome is generated according to either the linear model below such

\[^5\] Computation of all estimators for a single replication with fixed sample size \( (n, m) = (1000, 10,000) \), fixed missingness mechanism, and proportion and fixed identifiability assumption, computing all estimators takes approximately 20 min.
that $X_1$ is a treatment effect modifier and the true ATE $\tau$ is set to 27.4,

$$Y(\alpha) = -100 + 27.4\alpha X_1 + 13.7X_2 + 13.7X_3 + 13.7X_4 + \epsilon \quad \text{with} \quad \epsilon \sim \mathcal{N}(0, 1),$$

(15)
or to the following nonlinear model with the true ATE set to 58.9.

$$Y(\alpha) = -100 + 27.4\alpha (|X_1| \sin(X_1) + 1.5) + 13.7|X_2|X_2^2
+ 20.55X_3 + 13.7X_3|X_1| \sin(X_1) + 13.7|X_4|X_4^2 + \epsilon \quad \text{with} \quad \epsilon \sim \mathcal{N}(0, 1).$$

(16)

Missing values in the covariates are generated as follows, defining different models for the response indicator $R$:

1. Missing values can occur in all four covariates.
2. Proportion of missing values in each incomplete covariate: 20%.
3. The missing values mechanism can be MCAR or MAR and is implemented in the produce_NA function\(^6\) proposed by Mayer et al. (2022). Details on the different mechanisms can be found in Appendix D.

The simulation design is summarized by Algorithm D.1 provided in Appendix D.

5.1.2 Alternative identifiability assumptions for treatment effect generalization

We also generate data according where the CIS assumption 3b is met. In such scenarios, we expect that the methods described in Section 4 will work best. The main difference with the previous setting of simulation lies in the definition of the selection model, the outcome model remaining unchanged. In this setting, we also follow a two-step simulation scheme.

In order to simulate data under the CIS assumption (3b), we need to modify the definition(s) of the selection model such that it becomes pattern-dependent.\(^7\)

$$\logit\{Pr(S = 1|X)\} = -2.5 - 0.5X_1 \odot R_1 - 0.3X_2 \odot R_2 - 0.5X_3 \odot R_3 - 0.4X_4 \odot R_4,$$

(17)

$$\logit\{Pr(S = 1|X)\} = -2.1 - 0.5(|X_1| \sin(X_1) + 1.5) \odot R_1 - 0.3|X_2|X_2 \odot R_2 - 0.75X_3 \odot R_3 - 0.4|X_4|X_4 \odot R_4,$$

(18)

In Appendix D, we summarize the simulation design and the CIS assumption in Algorithm D.2.

5.2 Estimation methods

We consider different scenarios of data-generating processes by varying the type of missing values (MCAR, MAR, MNAR), CATE transportability assumption (standard or CIS), as well as the number of observations. We compare the following methods to handle missing values (the following acronyms are identical to the method labels used in Figures 2 and 3:

1. Full data: We apply the standard full data estimators from Section 2 on the full data before introducing missing values (this would serve as a reference).
2. Complete cases (CC): We apply the standard full data estimators from Section 2 on the complete observations extracted from the incomplete data (by deleting observations with missing values).\(^8\)

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\(^6\)https://rmisstastic.netlify.app/how-to/generate/missSimul.pdf

\(^7\)As a concrete example, in the critical care context, missing values of the generally easily measurable prehospital blood pressure and heart frequency are generally indicators of severity of a trauma patient as patients with cardiac arrest or severe external hemorrhage require immediate care on the site of the accident that makes the measurements of these variables difficult or even impossible. Therefore, if prehospital assessed severity were a trial eligibility criterion, the missingness patterns of these variables would be relevant for determining $S$. But for other patients the measured values of these variables could also be of relevance to decide upon trial eligibility.

\(^8\)Note that this approach is the most common default option in many implementations.
3. Multiple imputation (MI; Section 3): We apply the standard full data estimators from Section 2 on the imputed data (5–10 imputations obtained using the R package mice; van Buuren & Groothuis-Oudshoorn, 2011) where we use either (a) within-study multiple imputation (WI-MI), (b) ad hoc multiple imputation (AH-MI), or (c) fixed effect multiple imputation (FE-MI).

4. EM (see Section 4.1): we use EM to fit logistic regression models for \( r^*(x) = \frac{Pr(i \in \text{Set}_T | X_i^* = x^*)}{Pr(i \in \text{Set}_R | X_i^* = x^*)} \) and linear regression models for \( \mu^*_{a,trial} \) on the incomplete data using the R package misaem (Jiang et al., 2020).

5. MIA (see Section 4.1): we use generalized random forests with MIA splitting criterion to estimate the generalized regression models \( r^* \) and \( \mu^*_{a,trial} \) on the incomplete data, using the R package grf (Athey et al., 2019).

Note that for the EM and MIA approach, we only compute the IPSW, CO, and AIPSW estimators (see Section 2.3) since the calibration weighting estimator in its current form is not directly applicable to incomplete data and future work is required to adapt this estimator to incomplete data.

5.3 Results

Due to the large number of different scenarios we consider in this simulation study, we first provide an overview in Table 1 of the different assumption components (e.g., missingness mechanism, causal identifiability) required by the different
FIGURE 3  Empirical bias of generalizing ATE estimators under the CIS assumption, 95% Monte Carlo confidence intervals, $n = 1000$. Different colors denote different generalization estimators; different shapes represent different strategies to handle missing values. EM failed to converge in the MNAR scenario and is therefore omitted in the corresponding panel. Full: estimation on full data; CC: estimation on complete cases; EM: estimation by expectation maximization directly handling missing values; MIA: estimation by generalized random forests with missing incorporated in attributes; WI-MI: within-study multiple imputation; FE-MI: fixed effect joint multiple imputation; AH-MI: ad hoc joint multiple imputation.

TABLE 1  Methods for handling incomplete observations in treatment effect generalization and their assumptions on the underlying data-generating process.

| Missingness | Identifiability of generalized $\tau$ | Models for $(S, Y)$ |
|-------------|--------------------------------------|---------------------|
| MCAR        | Standard ($\equiv (3)$ and (4))     | $\checkmark$       |
| MAR         | CIS ($\equiv (3b)$ and (4b))        | $\times$           |
| MNAR        | Generalized linear models            | $\checkmark$       |

$\checkmark$ indicates cases that can be handled by a method, whereas $\times$ marks cases where a method is not applicable in theory; $(X)$ indicates cases without theoretical guarantees but with good empirical performance.

Abbreviations: CC, Complete cases; CIS, conditionally independent selection; MAR, missing at random; MCAR, missing completely at random; MI, multiple imputation; MIA, missing incorporated in attributes; MNAR, missing not at random.

approaches listed above. This allows to read of the expected behavior of the different estimators in the various cases considered in this experimental study.

Some simulation results are in agreement with what is expected, but there are also some gaps between the expected and empirical behavior in the chosen simulation settings. Indeed, in Figures 2 and 3 we report the empirical bias with at 95% Monte Carlo confidence interval (based on a Monte Carlo standard error) of the estimated ATE $\hat{\tau}$ relative to the true value.
\( \tau = 27.4 \) (or \( \tau = 58.9 \) in the nonlinear setting), using \( n_{sim} = 100 \) repetitions of each scenario. We define the empirical bias and its Monte Carlo standard error, respectively, by

\[
\hat{B}_\tau = \frac{1}{n_{sim}} \sum_{i=1}^{n_{sim}} \hat{\tau}_i - \tau, \quad \hat{SE}(\hat{B}_\tau) = \sqrt{\frac{1}{n_{sim}(n_{sim} - 1)} \sum_{i=1}^{n_{sim}} \left( \hat{\tau}_i - \bar{\tau} \right)^2},
\]

where \( \bar{\tau} = \sum_{i=1}^{n_{sim}} \hat{\tau}_i \), following Morris et al. (2019).

Based on the findings reported in Figures 2 and 3 as well as the results in the nonlinear setting reported in Appendix D, we summarize the main observations below.

5.3.1 Adherence with expected results in the linear case

**Standard identifiability assumptions (Figure 2)**

As expected, we observe that the full-data estimations are unbiased in all scenarios under the standard identifiability assumptions 3 and 4 in the linear data generating process (DGP) case. The complete case estimations are, unsurprisingly, unbiased only in the MCAR case. The behavior of the MIA-based estimators is heterogeneous and tends toward biased results for all missingness mechanisms. The joint fixed effect MI estimator (FE-MI) comes closer to the expected behavior of the multiple imputation approach than the ad hoc MI (AH-MI) and the within-study MI (WI-MI) estimator as it has small or no bias under the standard causal identifiability and ignorable missingness assumptions (I+MCAR and I+MAR), but all three fail in the MNAR case (as expected). The EM- and MIA-based methods are biased in all scenarios, which is expected as these estimators rely on the alternative identifiability assumption.

Note that for the full data case, the choice of the estimator, namely parametric (in our case, glm) or nonparametric (here grf), has an impact on the bias, especially for the single-model estimators IPSW and CO. This is not surprising given the linear specification of the selection and outcome models from (13) and (15) and the rather slow convergence of the chosen nonparametric method, random forest (grf), for linear models.\(^9\)

**Alternative identifiability assumptions (Figure 3)**

Under the CIS assumption, only the full-data estimators that (partly) rely on the outcome model, namely CO, AIPSW, and CW are unbiased, whereas the parametric IPSW estimator fails under CIS. This is expected as the selection model depends on both the observed values and the missingness pattern, the latter not being available in the full-data case; on the other hand, in the simulated data, the conditional outcome model does not depend on the missingness pattern. The behavior of the EM estimations is as expected: all estimators are unbiased under CIS under MCAR and MAR. However, the AIPSW estimator performs better than the IPSW and the CO. In the MNAR case, the EM algorithm fails to converge. Under the nonlinear case, this linear approach fails to recover the true ATE in all cases of missing values mechanisms. The MIA estimations overall have either small or no bias under CIS, especially the AIPSW estimator. Furthermore, under the CIS assumption, the AIPSW estimator always performs at least as well as the simple estimators (IPSW and CO). The good performance of MIA in the MNAR case is not surprising as this method can handle the MNAR case by definition (Josse et al., 2019).

5.3.2 Deviations from expected results

**Standard identifiability assumptions (Figure 2)**

Surprisingly, the MI IPSW estimators are biased in all cases except the within-study MI estimator in the MCAR and MNAR cases. This behavior is not expected and is likely due to the low sample size and a small number of imputations compared to the multiple steps of this estimator (imputation model and nuisance parameter estimation) which cannot compensate for each other’s inaccuracies. In additional simulations, the bias decreases as the sample size and number of multiple imputations increase (not reported).

\(^9\)The random forest approach would require a lot of data to estimate linear regression functions; random forests are, however, known for their good performance in the presence of nonlinearities and high-order interaction terms (Breiman, 2001).
Alternative identifiability assumptions (Figure 3)

Surprisingly, the parametric full-data IPSW estimator recovers the true value in the MAR and MNAR case under the alternative assumptions 3b and 4b. One could attempt to explain this through the fact that missing values can be explained based on the observed values in the MAR case and based on the full data (effectively observed and missing values) in the MNAR case, thus the response pattern could be modeled and recovered from the full data, and therefore the selection model becomes identifiable from the full data.

5.3.3 Comments on the nonlinear setting

The detailed results of the simulations in the nonlinear case, that is, the simulations based on the nonlinear selection and outcome models (14) and (16), are presented and commented in Appendix D.

5.3.4 Conclusion from a simulation study

In view of the results, if one has to recommend a method, it is preferable, from the present empirical evidence, to choose the MIA-AIPSW estimator or the joint multiple imputation coupled with the CW estimator (FE-MI + CW). Both approaches are simple to use but can be computationally costly and may require large sample sizes if the true data-generating process is very nonlinear, that is, not approximately linear. Additionally, the performance of a chosen estimator might depend on the true underlying missingness mechanism, for example, the multiple imputation based estimators generally assume a MAR mechanism. In the simulation study, certain estimators performed better than expected from the theoretical considerations; a closer examination of these cases might help refining the set of sufficient identifiability assumptions.

We conclude this simulation study with a remark on inference; we have focused on bias of the proposed methods and less on inference and how well uncertainty is captured by the confidence intervals. In a preliminary simulation study, we find that a nonparametric bootstrap yields slightly lower coverage than the nominal level.10 A systematic work addressing this issue is however still required, even for task of treatment effect estimation from a single data source as works on this topic are currently still scarce (see, e.g., Imbens & Menzel, 2021; Little & Badawy, 2019).

5.4 Impact of different proportions of missing values in the RCT and observational data

It is common that the RCT presents significantly less missing values than the observational study due to a more systematic monitoring of the data collection process. This invokes the question of how the above studied methods behave in the case of unbalanced proportions of missing values or different missing values mechanisms in the different data sources. Extending the previous simulation study by such a case, we summarize in Figure 4 the performance of the different estimators under different scenarios of varying proportions of missing values in the RCT and the observational data when the data are MAR given the source indicator (or equivalently, we say it is MCAR in each dataset).

As expected, the complete case estimators are unbiased in this special case since conditionally on the source indicator, the data are MCAR. For the other estimators, results are similar across different proportions of missing values, either 10%, 50% in RCT and observational data, respectively, or 5% and 22%, respectively. These results are supporting our claim that the previous results and methods apply as well to the likely case of different proportions of missing values in the two studies. Indeed the following data analysis in Section 6 is an example of this case.

6 APPLICATION ON CRITICAL CARE DATA

In this part, we come back to the medical question introduced at the beginning of this work about the potential effect of TXA on mortality in patients with intracranial bleeding admitted in French trauma centers, which we consider as rep-

10 For a nominal level of 95%, with fixed effect MI we obtain coverage of between 84% (IPSW) and 89% (CW) in a linear setting ((13) and (15)) with missing values from a MAR mechanism.
representatives of the core entities in western European major trauma management infrastructure who admit an increasing proportion of elderly major trauma patients (Roozenbeek et al., 2013). We recall that, in order to answer this question, we have at disposal two data sources: (1) CRASH-2, a multicenter international RCT, and (2) Traumabase, an observational national registry. A detailed data analysis of the observational registry to address the above medical question has been conducted by Mayer et al. (2020). We thus refer to this previous analysis for a detailed description of the observational registry as well as their findings. These can be summarized as follows: leveraging only the observational registry does not provide evidence of a beneficial (or detrimental) effect of TXA on trauma patients with TBI in terms of head-injury-related mortality.

We will first recall a summary of the findings of the original CRASH-2 study (Shakur-Still et al., 2009) before turning to focus on how the handling of missing values in the RCT and the observational registry impacts the final estimations of the population average treatment effect.

### 6.1 Findings of the CRASH-2 RCT

The CRASH-2 (Clinical Randomisation of Antifibrinolytic in Significant Haemorrhage) trial enrolled 20,211 patients in 274 hospitals in 40 countries between May 2005 and 2009 (Shakur-Still et al., 2009). The aim of this trial was to study the effect of TXA in adult trauma patients with ongoing significant hemorrhage or at risk of significant hemorrhage, within 8 h of injury (inclusion criteria), except those for whom antifibrinolytic agents were thought to be clearly indicated or clearly counterindicated (exclusion criteria). More precisely, eligible patients were defined as trauma patients within 8 h of the injury, of age at least 16 years (i) with ongoing significant hemorrhage (systolic blood pressure [SBP] less than 90 mmHg and/or heart rate more than 110 beats per minute), or (ii) who are considered to be at risk of significant hemorrhage. The inclusion criteria and other baseline regressors are summarized in a causal diagram in Appendix E (Figure E.1).

The results of the CRASH-2 study are reported in Shakur-Still et al. (2009) and show a beneficial effect of TXA on the trial population for the primary outcome of interest (all-cause 28-day death).
6.2 Integration of the CRASH-2 trial and the Traumabase registry

In the following, we discuss common variables’ definition, outcome, treatment, and designs in order to leverage both sources of information. We recall the causal question of interest: “What is the effect of the TXA on brain-injury death on patients suffering from TBI?” This part is important for the harmonization of the study protocol.

- **Treatment exposure.** The treatment protocol of CRASH-2 frames the timing and mean of administration precisely (a first dose given by intravenous injection shortly after randomization, that is, within 8 h of the accident, and a maintenance dose given afterward (Shakur-Still et al., 2009)). In the Traumabase study, which is a retrospective analysis, this level of granularity concerning TXA is unfortunately not available. Neither the exact timing nor the type of administration is specified for patients who received the drug. However, the expert committee agreed that the assumption of treatment within 3 h of the accident is very likely since this drug is administered in the prehospital phase or within the first 30 min at the hospital (Mayer et al., 2020).

- **Outcome of interest.** The CRASH-2 trial defined primary outcome as any-cause death in the hospital within 28 days of injury. This outcome is also available in the Traumabase.

- **Covariates accounting for trial eligibility.** As noted in Section 2.1.1, the distributional shift between trial and target population can be seen from the selection perspective as well where the shifted variables are those related to the eligibility (and participation) criteria. For the CRASH-2 trial, four criteria determined inclusion: age (patients of at least 16 years old were eligible), ongoing or risk of significant hemorrhage (defined as SBP below 90 mmHg or heart rate above 110 beats per minute, or clinicians evaluation of a risk), within 8 h of injury and absence of a clear indication or contraindication of antifibrinolytic agents. The necessary variables are also available in the Traumabase, either exactly or in form of proxies, which allows the estimation of the trial inclusion model on the combined data. With these eligibility criteria, we obtain a sample size of 8248 patients in the Traumabase and of 3727 patients in the CRASH-2 trial.13

- **Additional covariates.** Note that other covariates are (partially) available in both datasets, while not responsible for trial inclusion according to CRASH-2 investigators. But as this could still be covariates moderating the outcome and treatment effect, we include them in the outcome regression models used in the CO and AIPSW estimators (3) and (4) to improve precision of the estimators. Based on expert knowledge and the available information from both data sources, we include three additional variables in the analysis: sex (binary), type of injury (categorical, 1 = blunt, 2 = penetrating, 3 = blunt and penetrating), and initial Glasgow coma scale (numeric, integers from 3 to 15). Note that these three covariates are all mentioned in the baseline of CRASH-2 results (Shakur-Still et al., 2009), arguing that they should impact the outcome. The variables central capillary refill time and respiratory rate are also mentioned but are not available in the Traumabase, we thus omit them from this joint study.

- **Missing values.** First, note that the RCT contains almost no missing values, whereas the variables for determining eligibility in the observational data contain important fractions of missing values, as shown in Figure 5. While the MCAR assumption is reasonable for the RCT (Shakur-Still et al., 2009), the missing values in the observational Traumabase are more complex and, according to the medical experts monitoring the collection process, partly nonignorable. For example, the prehospital SBP is likely to be missing for patients with severe ongoing bleeding. Since the latter is informed in the hemorrhage risk variable, we could admit the missing values in the SBP variable as being MAR. Similar reasoning can be applied to the delay between the accident and treatment administration. However, there remains uncertainty as to whether the observed variables allow to fully explain the missingness in this variable.

- **Distribution shift.** There are different ways of assessing the shift between the distributions of the two studies, for example, by univariate comparisons. When comparing group means, we note that the average patient age in the RCT is 7–9 years below the average age in the observational study; since older patients with head injuries frequently have comorbidities that increase the risk of infection, surgical risk, and mortality after the injury, this difference in age is relevant in this study given the primary endpoint of in-hospital mortality (Wutzler et al., 2009). In Appendix E, we provide a simplified comparison of the means of the covariates between the treatment groups of the two studies in Figure E.2.

- **Transportability of the CATE.** Due to the design of the CRASH-2 study, namely the eligibility criteria which all need to be observed to decide upon trial eligibility, the alternative transportability assumption CIS 3b is less plausible to hold in this case and we rather consider the standard causal identifiability assumptions 3 and 4 to be satisfied by the CRASH-2

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13 Except for underaged patients and patients with isolated TBI, all registry patients were potentially trial eligible because of the rather broad inclusion criterion of “risk of significant hemorrhage,” which is difficult to assess without medical imaging tools in the first few hours after an accident (Hamada et al., 2018).
and Traumabase studies. We consider that the assumptions for the multiple imputation strategy, namely the MCAR or MAR mechanism (7) and (9) (and (8) and (10)), can be considered plausible in this real-world example. The details of the assessment of the support inclusion assumptions 4 and 4b can be found in Appendix E. In summary, we find that the selection scores obtained using EM and MI are similar and may suggest that the support inclusion assumption is satisfied since we observe a good degree of overlap between the distributions of the scores for the two datasets. The scores estimated via MIA, however, concentrate around 0 and 1 for the observational and RCT observations, respectively, apparently contradicting the initial assumption of overlap between the RCT and observational study populations. This apparent contradiction with expert knowledge about the respective populations is rather an indicator that the MIA approach and its underlying assumption, namely the CIS assumption 3b (which implies that the distributional shift depends on the observed values and the missingness pattern) are not appropriate in this study. These results provide an additional argument in favor of the multiple imputation strategy which appears to be more adapted to the handling of missing values in this analysis; in particular, we will apply a joint fixed effect multiple imputation strategy since it outperforms the other multiple imputation strategies in the simulation study of Section 5.

6.3 Results of generalized ATE from CRASH-2 to the observational target population

We now apply the estimators presented in this work and implemented first for the simulation study of Section 5. The confidence intervals for the corresponding point estimators are computed via nonparametric stratified bootstrap (Efron & Tibshirani, 1994) using 100 bootstrap samples (using stratified sampling to preserve the study-specific sample sizes). We additionally report two consistent ATE estimators from the solely CRASH-2 data: the difference in mean estimator (Difference in mean) and the difference in conditional means where we assume logistic regression models of the outcome on covariates for the treated and controls (Difference in conditional mean). The former only involves treatment assignment \( A \) and outcome \( Y \) and thus requires no additional handling of the incomplete covariates; the latter is obtained using an EM algorithm for logistic regression with ignorable missing values in the covariates (Jiang et al., 2020). We also recall the results of the generalized random forest based AIPW estimators (Wager & Athey, 2018) for the observational study applied solely on the Traumabase data (see Mayer et al., 2020). Since AIPW combined with either missing incorporated in attributes (MIA AIPW) or multiple imputation (MI AIPW) is recommended by Mayer et al. (2020) when analyzing observational data, these are the estimators reported in this analysis.

When summarizing the results from the separate analyses on the RCT and the observational data, respectively, and the results from the joint analysis of both studies, we observe in Figure 6a discrepancy between the different results.14
FIGURE 6 Separate and joint ATE estimators and 95% confidence intervals computed on the Traumabase (observational dataset; purple), on the CRASH-2 trial (RCT; cyan), and generalized from CRASH-2 to the Traumabase target population (red). The number of variables used for adjustment in each context is given in the legend. The confidence intervals obtained on the observational dataset and on the joint datasets are obtained via nonparametric bootstrap.

However, in view of the simulation study and the domain knowledge of our clinical experts, we have more reason to believe in the results of methods based on multiple imputation. The high variability of the IPSW results is most probably due to extreme weights which are common in practice, even with stabilized weights. This is why in this case, and in general, we tend to have more confidence in estimations from AIPSW and CW. Finally, the heterogeneity in these findings aligns with the results from the simulation study: in practice, results depend on how the covariate shift and missingness mechanisms are dealt with (in identifiability assumptions and in estimation).

The large confidence intervals could be partly explained by the measurement noise in the administration delay variable in the Traumabase. Another direction to explore could be to trim the scores such as to avoid extreme weights. This could potentially reduce the size of the confidence intervals, but it is known to generally provide a biased result since trimming of the weights induces an implicit change in the definition of the target population (Li et al., 2018); contrary to the RCT, the Traumabase does not encode the exact delay of treatment administration but is defined by a noisy proxy (delay between accident and admission to the resuscitation bay). However, there exists evidence that administration delay is a treatment modifier for TXA and that only early administration has a beneficial effect (CRASH-2 Collaborators et al., 2011; Hijazi et al., 2015). This remark and the discrepancies between the findings, especially the different conclusions of the joint fixed effect multiple imputation estimators call for additional attempts to further refine the administration delay proxy variable in the Traumabase and potentially for additional analyses with supplementary data such as the CRASH-3 study (Cap, 2019), which describes another slightly different TBI patient population.

7 CONCLUSION

In this work, we have proposed several estimators that are suited for generalizing a treatment effect from an incomplete RCT to a different target population described by incomplete observational covariate data. One of the difficulties was to account for the different variables in both sources. Which of the proposed methods is preferable depends on the underlying identifiability assumptions for generalizing the treatment effect. Under the standard full data causal identifiability assumptions on the missingness mechanism, we recommend a joint

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14 With the exception of the calibration weighting estimator, all MI-based estimators are followed by GRF-based regressions for the components of the IPSW, CO, and AIPSW estimators. This choice is motivated by expert knowledge of the high complexity of the data and underlying mechanisms of the treatment and of trauma-related injuries which are believed to be better captured by nonparametric methods such as random forests.

15 Note that we use stabilized weights instead of the standard weights.
multiple imputation that models the data source as fixed effect as long as the missing values are ignorable. If the identifiability assumptions are altered to account for informative missing values implicated in the selection process, then estimators involving generalized conditional regression models are suited. These are, however, strong assumptions, and in many common examples in medicine or epidemiology these do not appear to be the most plausible ones. Nevertheless, in certain contexts such as in pragmatic trials with minimal sets of eligibility criteria, these assumptions could potentially be relevant.

On the methodological side, for all considered approaches and simulation settings, the question of varying missing values mechanisms across data sources remains to be addressed in more detail. Note as well that we have focused on missing values in both datasets, but the recommendations extend to the case where there are only missing values in the observational data and not the RCT due to different levels of systematic data collection. The problem of incomplete observations addressed here is different from the problem of inconsistent variable sets between an RCT and an observational dataset, for example, one variable is completely missing in one set, which is more related to unobserved confounding and a recent work proposes sensitivity analysis to address this issue (Colnet et al., 2022).

Finally, it should be noted that, contrary to what is often perceived by practitioners, large proportions of missing values are not an obstacle to statistical analysis per se, but the task of understanding the role of their generating process and of combining this with the original full data assumptions is challenging, as are the adjustments to subsequent estimators. It is crucial to think carefully about the plausibility of the assumptions because in our examples the considered approaches give different results. We therefore, think an important direction of future work could focus on establishing sensitivity analysis bounds to address missing values in this context.

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The authors have declared no conflict of interest.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available upon reasonable request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

OPEN RESEARCH BADGES
This article has earned an Open Data badge for making publicly available the digitally-shareable data necessary to reproduce the reported results. The data is available in the Supporting Information section.

This article has earned an open data badge “Reproducible Research” for making publicly available the code necessary to reproduce the reported results. The results reported in this article could fully be reproduced.

ORCID
Imke Mayer https://orcid.org/0000-0003-4936-5062

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**SUPPORTING INFORMATION**

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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APPENDIX A: DETAILS ON THE BACKGROUND FULL DATA IDENTIFICATION

A.1 Identification formula

Under Assumptions 1–4 the ATE can be identified based on the following formulas:

1. Reweighting formulation:

\[
\tau = \mathbb{E}_{\text{target}}[\tau_{\text{target}}(X)] \\
= \mathbb{E}_{\text{target}}[\tau_{\text{trial}}(X)] \\
= \mathbb{E}_{\text{trial}}\left[\mathbb{E}_{\text{target}}\left(\frac{A}{e_{\text{trial}}(X)} - \frac{1-A}{1-e_{\text{trial}}(X)}\right)Y|X\right] \\
= \mathbb{E}_{\text{trial}}\left[r(X)\left(\frac{A}{e_{\text{trial}}(X)} - \frac{1-A}{1-e_{\text{trial}}(X)}\right)Y\right]
\]

Law of total expectation
Assumption 3
Identifiability of \(\tau_{\text{trial}}(X)\)
Assumption 4,

where \(\tau_{\text{trial}}(x) = \mathbb{E}_{\text{trial}}[Y(1) - Y(0)|X = x]\) is identifiable under Assumptions 1 and 2 and \(e_{\text{trial}}(x) = \text{Pr}(A = 1|X = x)\) is the treatment propensity. Note that the density ratio cannot directly be estimated from the data, but it requires estimating conditional odds: the conditional odds \(\alpha(x)\) can be estimated by fitting a regression model that discriminates RCT versus observational samples, and Bayes’ rule gives

\[
\alpha(x) = \frac{\text{Pr}(i \in \text{Set}_R | X_i = x)}{1 - \text{Pr}(i \in \text{Set}_\theta | X_i = x)} \approx \frac{n}{m} \frac{P_{\text{trial}}(X)}{P_{\text{target}}(X)} = \frac{n}{m} \frac{1}{r(x)}.
\]

Finally, we have

\[
\tau = \mathbb{E}_{\text{trial}}[r(X)\tau_{\text{trial}}(X)].
\]

Note that in a fully randomized RCT, where \(e_1(x) = 0.5\) for all \(x\), this formula further simplifies to

\[
\tau = \mathbb{E}_{\text{trial}}[2r(X)(2A - 1)Y].
\]

2. Regression formulation:

\[
\tau = \mathbb{E}_{\text{target}}[\mu_{1,\text{trial}}(X) - \mu_{0,\text{trial}}(X)],
\]

which can be shown using the following derivations for \(a \in \{0, 1\}:

\[
\mathbb{E}_{\text{target}}[Y(a)] = \mathbb{E}_{\text{target}}[\mathbb{E}_{\text{target}}[Y(a)|X]] \quad \text{Law of total expectation} \\
= \mathbb{E}_{\text{target}}[\mathbb{E}_{\text{target}}[Y(a)|X]] \\
= \mathbb{E}_{\text{target}}[\mathbb{E}_{\text{trial}}[Y(a)|X]] \quad \text{Assumption 3} \\
= \mathbb{E}_{\text{target}}[\mathbb{E}_{\text{trial}}[Y(a)|X, A = a]] \quad \text{Assumption 3} \\
= \mathbb{E}_{\text{target}}[\mathbb{E}_{\text{trial}}[Y|X, A = a]] \quad \text{Assumption 1} \\
= \mathbb{E}_{\text{target}}[\mu_{a,\text{trial}}(X)]
APPENDIX B: DETAILS ON THE INCOMPLETE DATA PROBLEM

APPENDIX C: DETAILS ON THE ESTIMATION METHODS WITH MISSING VALUES

C.1  Schematic illustration of different multiple imputation strategies

C.2  Prediction on new incomplete observations with a parametric model

As mentioned in Section 4, it is possible to predict the outcome $y$ for new incomplete observations, using the regression model estimated via EM, by marginalizing over the distribution of missing data given the observed. More formally, in the logistic regression case, using a Monte Carlo approach and maximum a posteriori estimator, it is possible to predict the response $y$ for a new observation $x_i$ as follows:

1. Sample

   \[
   \left( x_{mis}^{(k)}, 1 \leq k \leq K \right) \sim p(x_{mis} \mid x_{obs})
   \]

2. Predict the response $y$ by maximum a posteriori

   \[
   \hat{y} = \arg \max_y p(y \mid x_{obs}) = \arg \max_y \int p(y \mid x)p(x_{mis} \mid x_{obs})dx_{mis}
   \]

   \[
   = \arg \max_y \mathbb{E}_{p_{mis\mid obs}} p(y \mid x)
   \]

   \[
   = \arg \max_y \sum_{k=1}^{K} p(y \mid x_{obs}, x_{mis}^{(k)})
   \]

For the linear case, the prediction proceeds in two steps:

1. Imputation of the new observation using the estimated variance-covariance matrix of the covariates $\hat{\Sigma}$.

   \[
   \hat{x}_{mis} = \left( \Sigma_{mis,mis}^{-1} \right)^{-1} \Sigma_{mis,obs} x_{obs}^{new}
   \]

2. Prediction of response $y$ using the imputed observation $[x_{obs}^{new}, \hat{x}_{mis}^{new}]$.

APPENDIX D: DETAILS ON THE SIMULATION STUDY

D.1  Missingness mechanisms

In our simulation study, we consider all three classes of missingness mechanisms as defined by Rubin’s taxonomy.
FIGURE C.1 Schematic illustrations of different multiple imputation strategies.

1. MCAR where the probability to have missing values does not depend on any variable:

\[
P(R_{i.} = r|X_i, Y_i, A_i) = P(R_{i.} = r) \quad \text{(in the trial)}
\]
\[
P(R_{i.} = r|X_i) = P(R_{i.} = r) \quad \text{(in the target)}
\]

\[(D.1)\]

2. MAR:

\[
P(R_{i.} = r|X_i, Y_i, A_i) = f_{trial}(X_{obs(r)}, A_i, Y_i) \quad \text{(in the trial)}
\]
\[
P(R_{i.} = r|X_i) = f_{target}(X_{obs(r)}) \quad \text{(in the target)}
\]

\[(D.2)\]

for some functions \(f_{trial} : \mathcal{X} \times \{0,1\} \times \mathbb{R} \rightarrow [0,1]\), and \(f_{target} : \mathcal{X} \rightarrow [0,1]\). For example, missing values in \(X_1\) are introduced for observation \(i\) using a logistic model on \(X_2, X_3, X_4\), assuming these three variables are observed for observation \(i\).
3. MNAR:

\[
\begin{align*}
\text{(in the trial)} & \quad P(R_{ij} = 0 | X_i, Y_i, A_i) = g_{\text{trial}}(X_{ij}, Y_i, A_i), \\
\text{(in the target)} & \quad P(R_{ij} = 0 | X_i) = g_{\text{target}}(X_{ij}),
\end{align*}
\]

(D.3)

for some functions \( g_{\text{trial}} : X_j \times \{0, 1\} \times \mathbb{R} \to [0, 1] \), and \( g_{\text{target}} : X_j \to [0, 1] \), for all \( j \). In this study, we use a self-masking MNAR mechanism, that is, the missingness of a variable depends on its value alone. More precisely, we use an upper quantile censorship approach. The quantile level \( q \) is chosen such that when missing values are generated on the \( q \)-quantile at random, the requested proportion of missing values is achieved. For more details about this chosen approach, we refer to the documentation of the produce_{NA} function.\(^{16}\)

### D.2 Summary of the data generation under the two alternative scenarios

**Algorithm D.1** Steps for simulation design under the standard assumption

**Result:** Joint data table \( X^* \) of RCT and observational data and additional variables \( A, Y \) for the RCT.

1. Sample \( N >> n \) observations \( X_1, \ldots, X_N \) from the target population \( P_{\text{target}}(X) \)
2. Sample \( S \) according to the selection model ((13) or (14)) on \( X \)
3. Keep only the \( \{S = 1\} \) indexed observations \( X_R \leftarrow X_{i:S_i=1} \) as the RCT
4. Sample \( A \) according to a Bernoulli distribution \( \mathcal{B}(0.5) \) (coin flip)
5. Sample \( Y \) according to the outcome model ((15) or (16)) on \( X_R \)
6. Sample \( m \) observations \( X_o \) from the target population \( P_{\text{target}}(X) \) as the observational data
7. Concatenate the datasets: \( X \leftarrow [X_R^T, X_o^T]^T \) and append the indicator \( 1_{\text{Set}_R} \) to the data (\( X \leftarrow [X, 1_{\text{Set}_R}] \))
8. Sample missing values for the \( n + m \) observations according to either (D.1), (D.2), or (D.3)

**Algorithm D.2** Steps for simulation design under the CIS assumption.

**Result:** Joint data table \( X^* \) of RCT and observational data and additional variables \( A, Y \) for the RCT.

1. Sample \( N >> n \) observations \( X_1, \ldots, X_N \) from the target population \( P_{\text{target}}(X) \)
2. Sample missing values for the \( N \) observations according to either (D.1), (D.2), or (D.3)
3. Sample \( S \) according to pattern-dependent selection model ((17) or (18)) on \( X \)
4. Keep only the \( \{S = 1\} \) indexed observations \( X_R \leftarrow X_{i:S_i=1} \) as the RCT
5. Sample \( A \) according to a Bernoulli distribution \( \mathcal{B}(0.5) \) (coin flip)
6. Sample \( Y \) according to the outcome model ((15) or (16)) on \( X_R \)
7. Sample \( m \) observations \( X_o \) from the target population \( P_{\text{target}}(X) \) as the observational data
8. Sample missing values for the \( m \) observations \( X_o \) using the same mechanism as before but possibly with different proportions
9. Concatenate \( X_R^* \) and \( X_o^* \) using the same mechanism as before and append the indicator \( 1_{\text{Set}_R} \) to the data (\( X^* \leftarrow [X^*, 1_{\text{Set}_R}] \))

### D.3 Results for the nonlinear simulation setting.

In this section, we report the detailed simulation results in the nonlinear setting in Figures D.1 and D.2.

We observe in the first row of Figures D.1 and D.2, that under both categories of identifiability assumptions, all parametric estimators (based on logistic and linear regressions) fail to recover the true ATE \( \tau \) and the bias of the estimators of the generalized effect even exceeds the “true” bias of the RCT sample ATE estimator (the difference in mean estimator for the RCT sample and therefore estimating \( \tau_{\text{trial}} \)). Surprisingly, however, this is also true for the nonparametric estimators (based on random forest regression models) shown in the second row of the same figures. While the bias of the nonparametric estimators is smaller than for the parametric estimators, as expected from random forests that are known for their good performance in the presence of nonlinearities and high-order interaction terms (Breiman, 2001), it is nonzero for all estimators, even the methods relying on the full data. An important observation is that the multiple imputation and

\(^{16}\)https://rmisstastic.netlify.app/how-to/generate/missSimul.pdf
FIGURE D.1 Empirical bias of generalizing ATE estimators in the nonlinear setting under the standard CATE transportability assumption, 95% Monte Carlo confidence intervals, $n = 2000$. Different colors denote different generalization estimators; different shapes represent different strategies to handle missing values. Full: estimation on full data; CC: estimation on complete cases; EM: estimation by expectation maximization directly handling missing values; MIA: estimation by generalized random forests with missing incorporated in attributes; WI-MI: within-study multiple imputation; FE-MI: fixed effect joint multiple imputation; AH-MI: ad hoc joint multiple imputation.

the MIA-based estimators perform almost or at least as well as the full data estimator, with the within-study multiple imputation (WI-MI) performing best throughout the different simulation scenarios. A plausible explanation for the poor performance of all estimators in the nonlinear setting is the sample size which is moderately small for the chosen regression method with a slow convergence rate. Indeed, the reported results refer to a sample size of $n = 2000$ for the RCT and $m = 20,000$ for the observational sample. When choosing a sample size five times larger, then the full data AIPS W estimator is indeed unbiased as expected (results not reported here). Furthermore, the studied estimators achieve similar bias under the adequate identifiability assumptions (Assumptions 3 and 4 for the multiple imputation based estimators and Assumptions 3b and 4b for the MIA-based estimators).

APPENDIX E: DETAILS ON THE CRITICAL CARE MANAGEMENT APPLICATION

Selection diagram of the CRASH-2 trial. In Figure E.1, we represent the selection variable $S$, the treatment assignment $TXA$ and the outcome $Y$, as well as the related covariates from the CRASH-2 trial in form of a causal diagram.

Distributional shift. The graph in Figure E.2 illustrates the fundamental difference between the two studies, namely the treatment bias in the observational study and the balanced treatment groups in the RCT but also a covariate shift between the two studies.

Selection scores. The distribution of the estimated selection scores is given in Figures E.3(a)–(c). We notice that the scores obtained using EM and MI+logistic regression are similar and suggest that the positivity assumption is satisfied since we
observe a good degree of overlap between the distributions of the scores for the two datasets. The scores estimated via MIA, however, concentrate around 0 and 1 for the observational and RCT observations, respectively, suggesting poor overlap under this model. In Appendix E, we provide further comparisons of the estimated selection scores, pointing toward the multiple imputation strategy as the suited approach in this case.

These results provide an additional argument in favor of the multiple imputation strategy, which appears to be more adapted to the handling of missing values in this analysis; in particular, we will apply a joint fixed effect multiple imputation strategy since it outperforms the other multiple imputation strategies in the simulation study of Section 5.
**FIGURE E.2** Distributional shift and difference in terms of univariate means of the trial inclusion criteria (red: group mean greater than overall mean that is taken over both datasets, blue: group mean less than overall mean, white: no significant difference with overall mean, numeric values: group mean (respectively, the proportion for categorical variables). For categorical variables a chi-squared test is used, for continuous variables a Fisher test (in a one-way analysis of variance). "Tr": treatment group, "Co": control group. Figure obtained with the cades function of the FactoMineR package (Lê et al., 2008).

![Graph 1](image1.png)

(a) EM. Obtained with the **misaem** R package.

![Graph 2](image2.png)

(b) MIA. Obtained with the **grf** R package.

![Graph 3](image3.png)

(c) Joint fixed effect MI. Obtained with the **mice** R package.

**FIGURE E.3** Estimated densities of the fitted selection scores.
We have seen in Section 6 that the scores obtained using EM and MI+logistic regression suggest that the positivity assumption is satisfied, while the scores estimated via MIA, however, concentrate around 0 and 1 for the observational and RCT observations, respectively, suggesting poor overlap under this model. This can also be observed in the scatter plots in Figure E.4, where we color the observations according to the values of the SBP (a variable with an important fraction of missing values in the observational data; see Figure 5). We notice that MIA attributes a very low selection score to all observations with a missing SBP value and thus selects the response indicator of the SBP variable to partly predict trial eligibility. This method has been studied more extensively in a regression framework and not in a classification framework, and here we find that it predicts a class according to the presence of missing values and this is not necessarily what we intend when applying this method.

**FIGURE E.4** Scatter plots of different estimated selection scores. The point color is set according to the SBP covariate values (missing SBP values are indicated by gray points).