The Missing Data Problem: Using Propensity Scores to Estimate Non-Randomised Treatment Effects With Missing Covariate Data

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BACKGROUND

- In non-randomised settings, patients who receive different treatments may also differ in their underlying characteristics. Failure to adjust for such potential confounders could yield a biased interpretation of the treatment effect.
- The propensity score (PS), defined as the probability of receiving a particular treatment given the patient's underlying characteristics, summarises measured confounders into a single variable.[1]
- Although PS methods are used ubiquitously in non-randomised research, the literature is scarce regarding the impact of missing covariate data on the treatment effect calculation.[2]

OBJECTIVE

- To evaluate the performance of various PS-based methods in the presence of missing covariate data on treatment effect estimation in a simulated patient-level data set.

METHODS

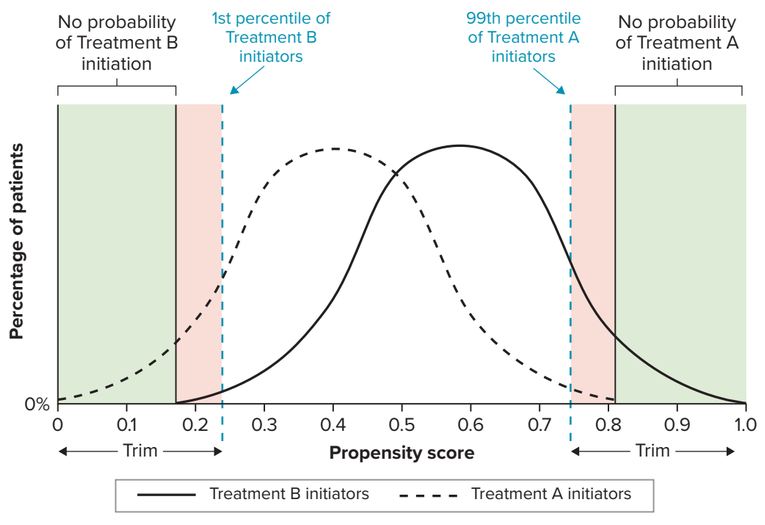
Simulated Data

- Patient-level data were simulated based on a published observational cohort study of overactive bladder disease.[3]
- Two non-randomised treatment cohorts (Treatments A and B), totalling 96,000 patients, were followed over the course of 9 years (2004 to 2012) until censoring or the occurrence of cardiovascular (CV) mortality.
- Follow-up times were simulated using the Weibull distribution, and CV mortality was simulated as a Poisson event with a log-time offset.
- Baseline covariates included demographic, clinical, and lifestyle variables.
- By design, a greater risk of CV mortality was associated with entering the study in earlier calendar years, smoking status, and history of CV conditions.
- Smoking status and CV history covariates were then set to missing at random (MAR) in 5%, 10%, and 20% of patients under the following assumptions:
  - From 2004 to 2006, these variables were optional data fields at all sites.
  - From 2007 to 2008, these variables were mandatory fields at some sites but optional at others.
  - From 2009 to 2012, these fields were mandatory data fields at all sites.

Statistical Methods

- Logistic regression was employed to compute patient-level PS values where receipt of Treatment B was modelled as a function of all covariates of interest using the non-missing data.
- PS trimming as illustrated in Figure 1 was performed to ensure comparability of treatment cohorts.

Figure 1. Schematic of PS Trimming Process



- The treatment effect was estimated in the post-trimmed population by performing a Poisson regression with a log-time offset where CV mortality was modelled as a function of the treatment cohort and PS decile category.
- This process was repeated for each MAR scenario using the following methods to estimate the treatment effect in the presence of missing data:
  - **Complete case (CC):** Generating PS values that included only patients with fully complete covariate data
  - **Separate category for missing values (SCMV):** Creating a separate category for covariates with missing values for inclusion in the PS model
  - **Multiple imputation (MI):** Employing MI using all available information in the data set to impute missing covariate values for inclusion in the PS model
  - **PS complete covariate with MI for missing covariates (PSCC + MIMC):** Generating the PS model using only covariates with complete data, then adjusting for remaining covariates in conjunction with MI in direct modelling of the outcome as a function of treatment, PS, and the multiply imputed covariates
- Relative bias in each coefficient estimate was calculated as the absolute bias (difference between the estimated and true values) divided by the true value.

RESULTS

- Patients who initiated Treatment B were more likely to be male, enter the study in earlier calendar years, be current smokers, and have histories of acute myocardial infarction and heart failure (Figure 2).
- By design, the crude and true incidence rate ratio (IRR) values were 3.00 and 1.80, respectively (Table 1).
- Results of the analytic methods in the estimation of the treatment effect under the different MAR scenarios are presented in Figure 3:
  - The CC and MI methods performed similarly, with almost identical relative biases in the 5% and 10% MAR scenarios. MI performed slightly better under the 20% MAR scenario.
  - The SCMV method produced IRR point estimates that were more shifted away from the null than estimates produced by the other methods. SCMV was the poorest-performing method across all MAR scenarios as determined by having the largest relative biases.
  - The IRR point estimates derived from the PSCC + MIMC method were the smallest in value and closest to the true IRR value of 1.80.

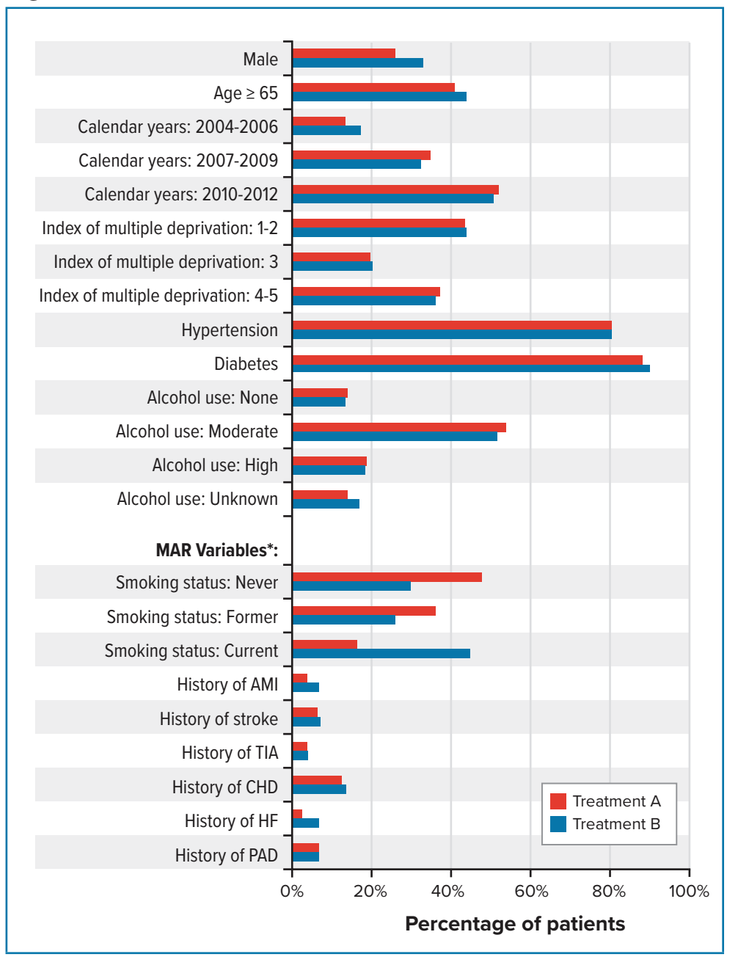
Table 1. CV Mortality and Incidence Estimates in Treatment Cohorts

	Treatment A N = 49,000	Treatment B N = 47,000
Number of CV deaths	100	293
Person-years	42,849	41,823
IR per 1,000 person-years (95% CL)	2.33 (1.90, 2.84)	7.01 (6.23, 7.86)
Crude IRR (95% CL)	Ref	3.00 (2.38, 3.81)
True IRR (by design)	Ref	1.80

CL = confidence limit; IR = incidence rate.

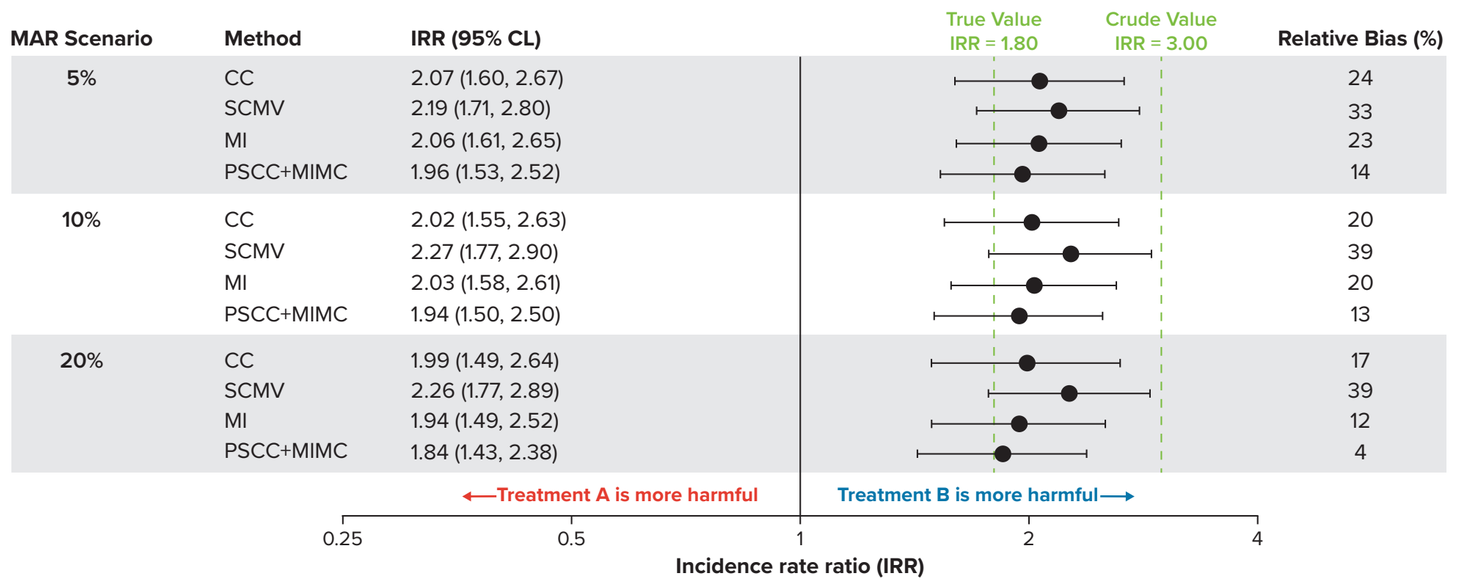
Note: 95% CLs for the IR and IRR were derived using methods described by Dobson et al.[4] and Sahai and Khurshid[5], respectively.

Figure 2. Baseline Patient Characteristics of Treatment Cohorts



AMI = acute myocardial infarction; CHD = coronary heart disease; HF = heart failure; PAD = peripheral artery disease; TIA = transient ischemic attack. *Percentages presented for variables that participated in the MAR scenarios were derived from the non-missing data; however, these values were equivalent across all MAR scenarios.

Figure 3. IRR Estimates From Different Analytic Methods and Levels of Missing Data



IRR = incidence rate ratio; CL = confidence limits

CONCLUSIONS

- In our simulation, implementing SCMV introduced a notable amount of additional bias compared with ignoring the missing data altogether in the PS analysis.
- The MI method did not yield any notable benefits, especially in scenarios of smaller amounts of missing data.
- PSCC + MIMC resulted in the least amount of bias and provided a notable benefit, especially with larger amounts of missing data.

DISCUSSION

- Relative bias was improved with increasing missingness, which may be attributable to the relationships between treatment, outcome, and covariates participating in the mechanism of missingness in this particular simulation.
- MI is often considered a default method of handling missing covariate data in PS analyses; however, our simulation results dispute its default status.
- The data in this simulation were MAR by design, but in real-world comparative effectiveness research, the mechanism of data missingness is rarely known.
- These results were based on a single simulation of a specific scenario. Repeated simulations and other simulations that vary several parameters are needed to draw more generalised conclusions.

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The power of **knowledge**.
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