A Comparison of Missing Data Methods for Clinical Trials

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Background

- Missing data emerges in various ways in randomized controlled trials (RCTs), such as patient withdrawal.
- Improper handling of missing data may lead to bias and reduced precision in estimating treatment effect.
- There has not been a comprehensive evaluation of the relative performance of missing data methods for RCTs.

Objectives

- Evaluate the performance of common missing data handling approaches under different missing data mechanisms via statistical simulations.
- Provide practical suggestions and recommendations on dealing with missingness in RCTs.

Methods

Simulation Settings

- We used R statistical software to simulate a trial with continuous outcomes under a linear regression model:

$$y = \beta_0 + \beta_1 x_{i1} + \beta_2 x_{i2} + \beta_3 x_{i3} + \beta_4 z_i + \epsilon_i$$

  - The random error: $\epsilon_i \sim N(0,10)$
  - The intercept: $\beta_0 = 0$
  - The coefficients: $\beta_1 = \beta_2 = \beta_3 = 1$
  - All x variables correlates with each other with a correlation = 0.5
  - The treatment effect: β_4 is independent of all x variables
- Sample size: n = 200, 500
- We ran 1000 simulations for each trial

Missing Data Methods & Analysis

We applied common missing data approaches to each simulated trial, including:

- **complete-case analysis (CC)**
- **Regression Imputation (RI):** We imputed missing values with the predicted values from a regression model.
- **Multiple Imputations (MI):** We imputed multiple completed datasets using multiple imputation by chained equations and then pools the treatment effect estimates from each imputed dataset using the Rubin's rule.
- **Inverse Probability Weighting (IPW):** We used logistic regression and BART to estimate the probability of being observed and then estimate the treatment effect using a weighted linear regression.
- We studied both **unadjusted** (no adjustment of x) & **adjusted treatment effect** under each simulated trial.

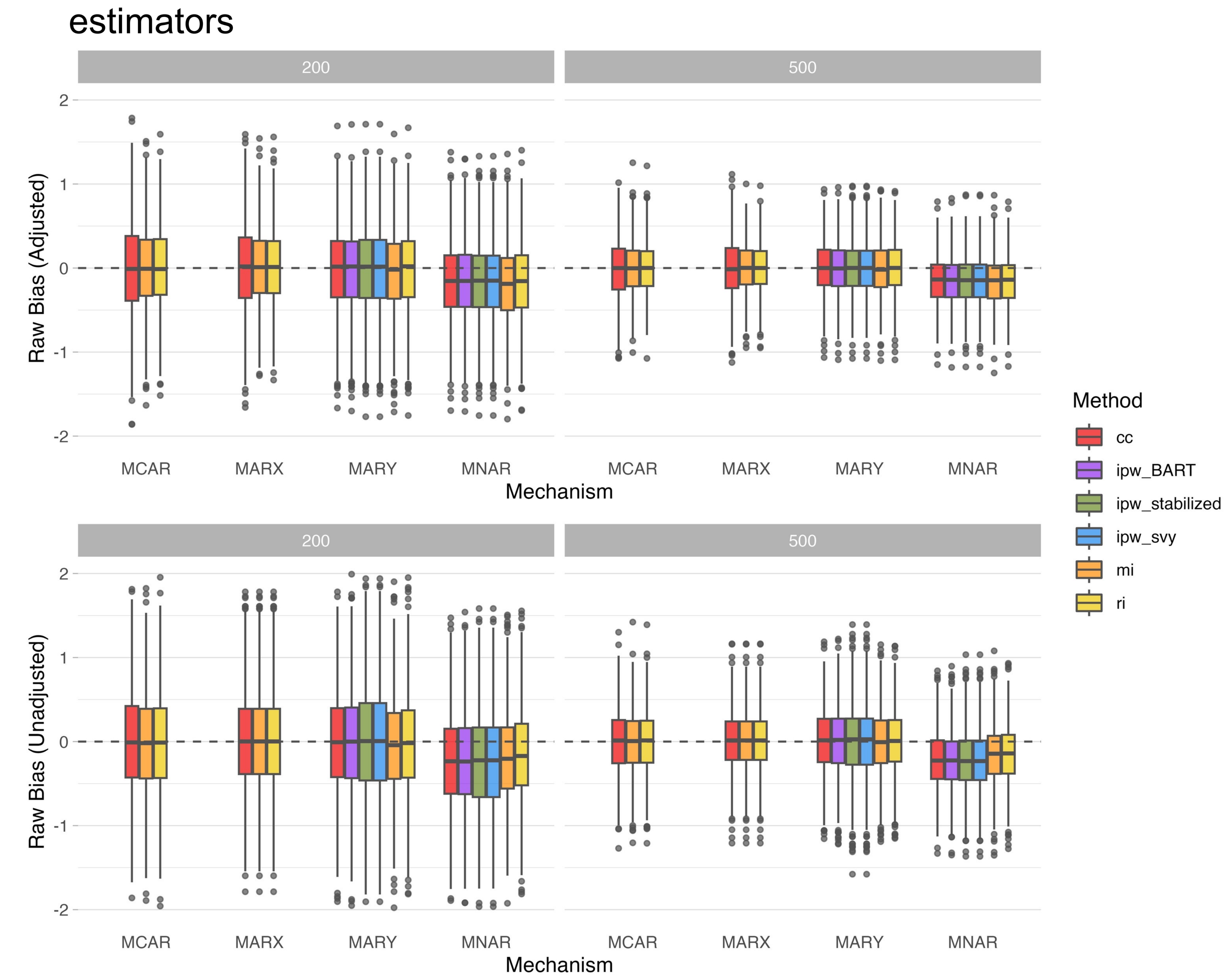
Missing Mechanisms

We simulated trials contain missing data under various missing mechanisms:

- **Missing Completely at Random (MCAR)**: 10% prob. of missing for x variables and 15% for y variable.
- **Missing at Random (MAR)**
  - **MARX:** x variables contains missingness, prob. of missing is predicted by other covariates.
  - **MARY:** y variable contains missingness, prob. of missing is predicted by all 3 covariates.
- **Missing Not at Random (MNAR):** the higher probability of missing for y values that are further away from it's mean.

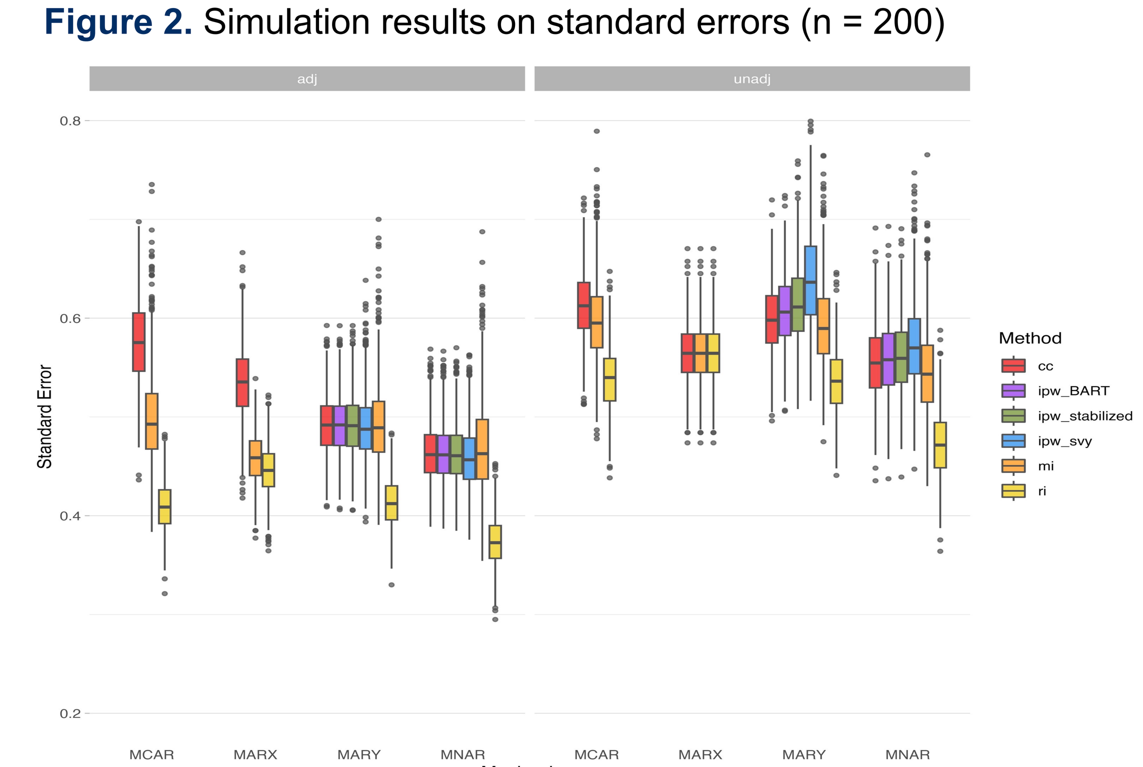
Results

Figure 1. Simulation results on the bias distribution of treatment effect estimators



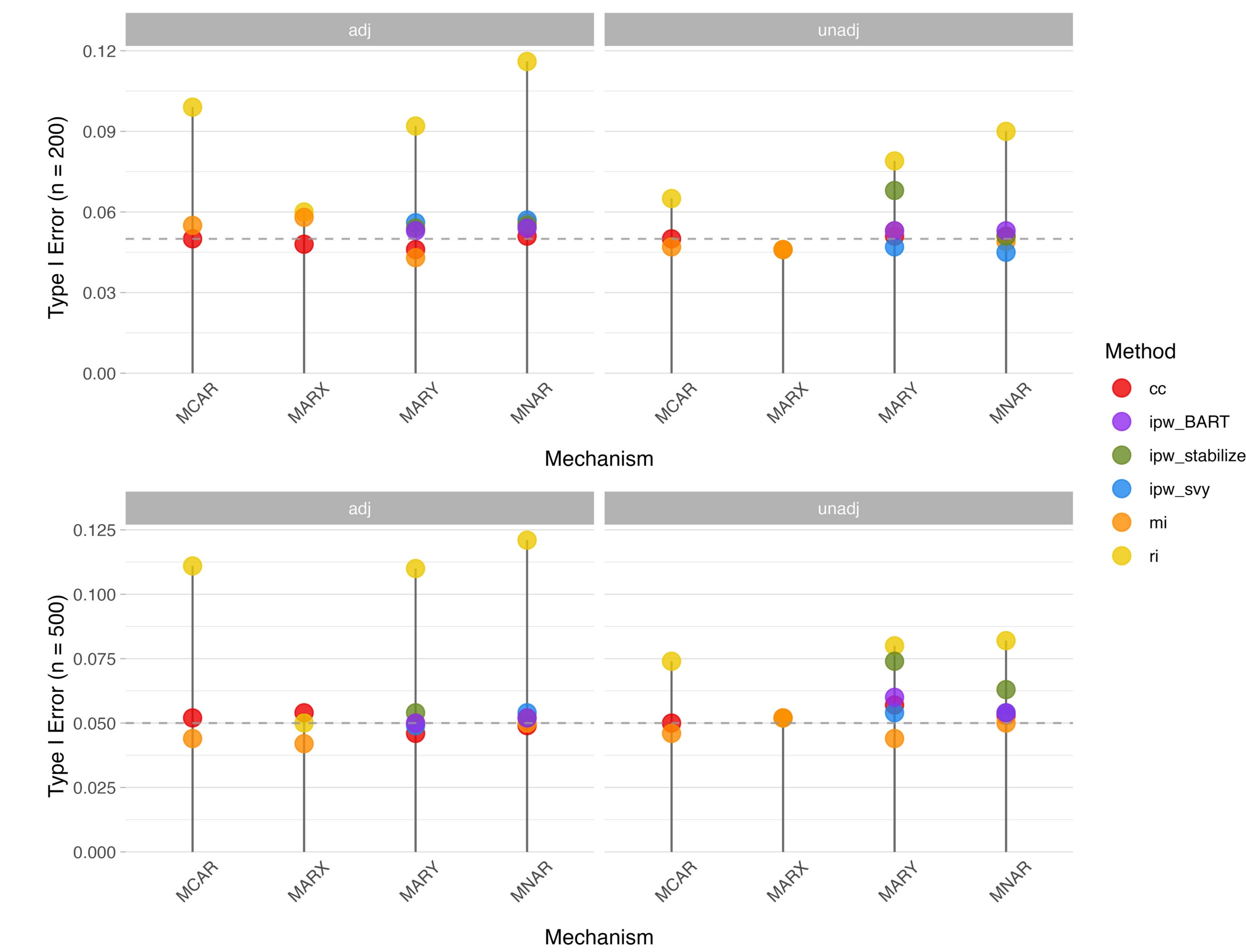
- The bias of all methods are comparable.
- The adjusted analysis yielded less biased result than the unadjusted analysis.
- MNAR: no methods used in this study corrected the bias.

Figure 2. Simulation results on standard errors (n = 200)



- Unadjusted analysis yielded higher standard error than adjusted analysis.
- RI returned the lowest standard errors under all missing mechanisms.
- MI yielded the largest standard errors under MARY and MNAR than other methods.

Figure 3. Type I Error lollipop plots



- RI method returned the highest type I Error.
- Other approaches achieved close to nominal type I error rate of 0.05.

Conclusion & Outlook

- under MCAR: Imputation methods are not needed to correct bias.
- under MARX: Imputation methods and complete case analysis yielded comparable bias.
- under MARY: Multiple imputations is not preferred due to large standard error. In contrast, weighting methods work well.
- under MNAR: none of the methods worked well without knowing the correct missing model!
- Address the complexity of the MNAR scenario!
- RCTs with binary outcomes & survival outcomes!

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