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Propensity Score Method

Lei Li, PhD

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The opinions and information in this presentation are those of the authors and do not represent the views and/or policies of the any regulatory agencies.

Outline

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- Background and Motivation Example
- Propensity Score Method Introduction, Considerations, and Example
- Practical Issues: Missingness issue and Collinearity Issue in small sample size study
- Summary

Background

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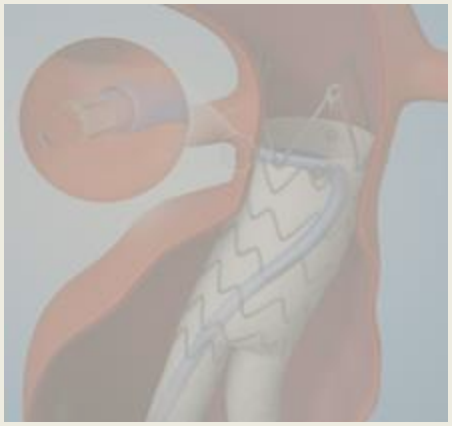
- 21st Century Cures Act
- Guidance issued to clarify how Real-World Evidence (RWE) may be used to support regulatory decisions.
- Practice in Center of Device and Radiation Health (FDA/CDRH):



- *More Examples of Real-World Evidence (RWE) Used in Medical Device Regulatory Decisions:* Examples of Real-World Evidence (RWE) Used in Medical Device Regulatory Decisions

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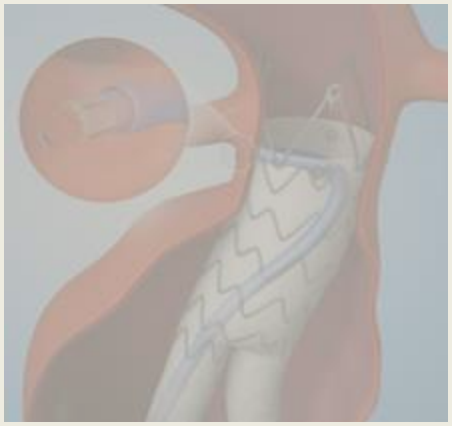

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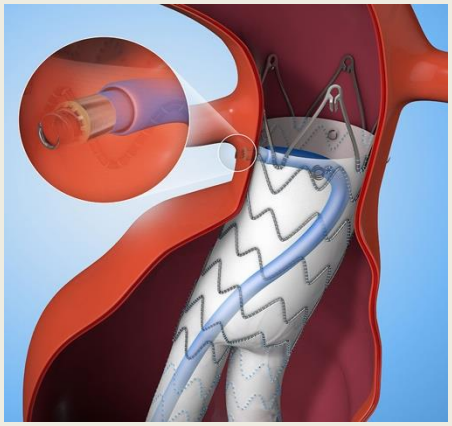

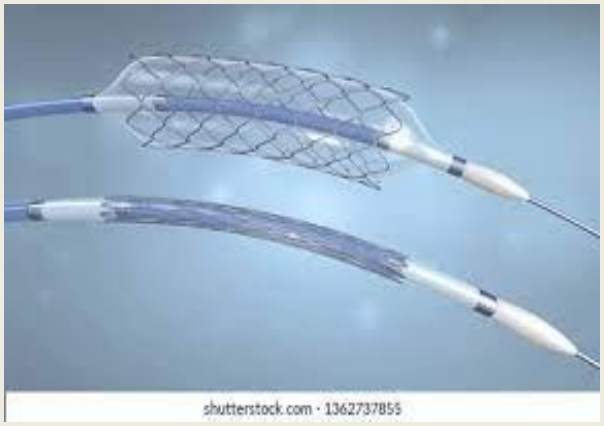

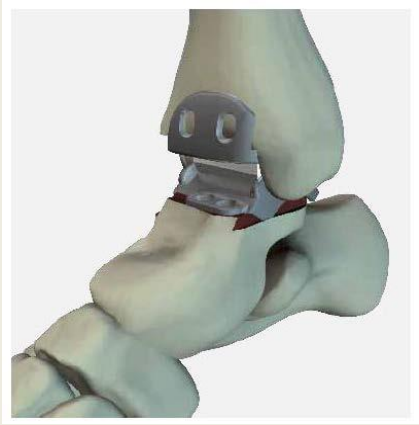

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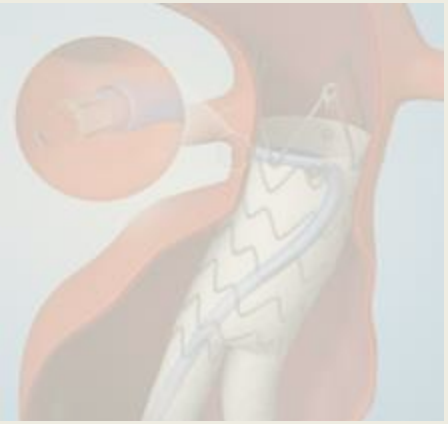

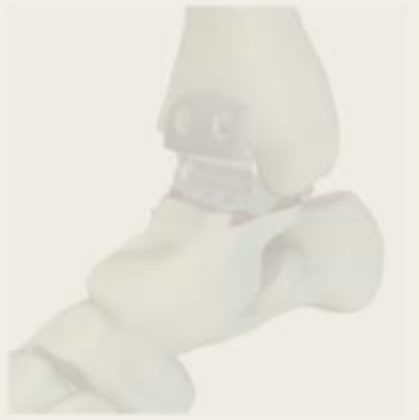

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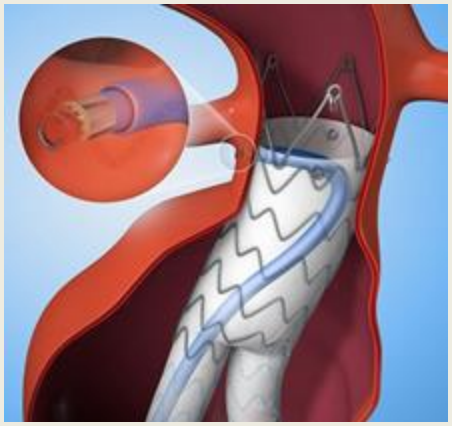

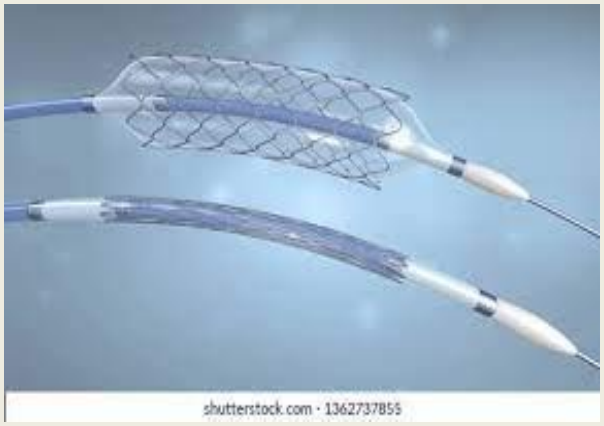

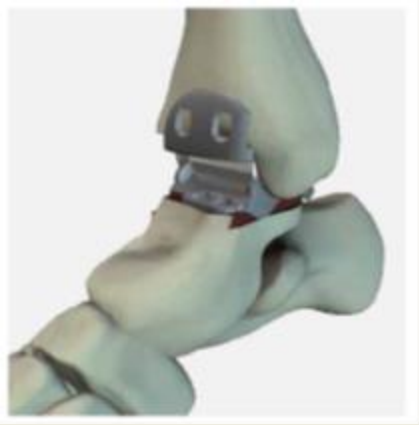

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Orthopedic and Surgical Device Area: Hypothetical Example

- Pivotal Clinical Trial:
  - Prospective, single-arm, minimum 24 months follow-up, multi-center study
  - Sample Size (typical case):
    - 100 ~ 200 subjects per treatment arm
    - 50 ~ 70 subjects for HDE (Humanitarian Device Exemption) case
  - Effectiveness Assessment: Average Treatment Effect (ATE) or Average Treatment Effect on the Treated Arm (ATT)

- External Data Sources:
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- External Data Utilization:
  - Construct and/or Augment the control group

- Common Statistical Method: Propensity Score (PS) Subclassification/Stratification, PS Matching.

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- Q: How do we know the borrowed historic data are comparable?

Propensity Score Method

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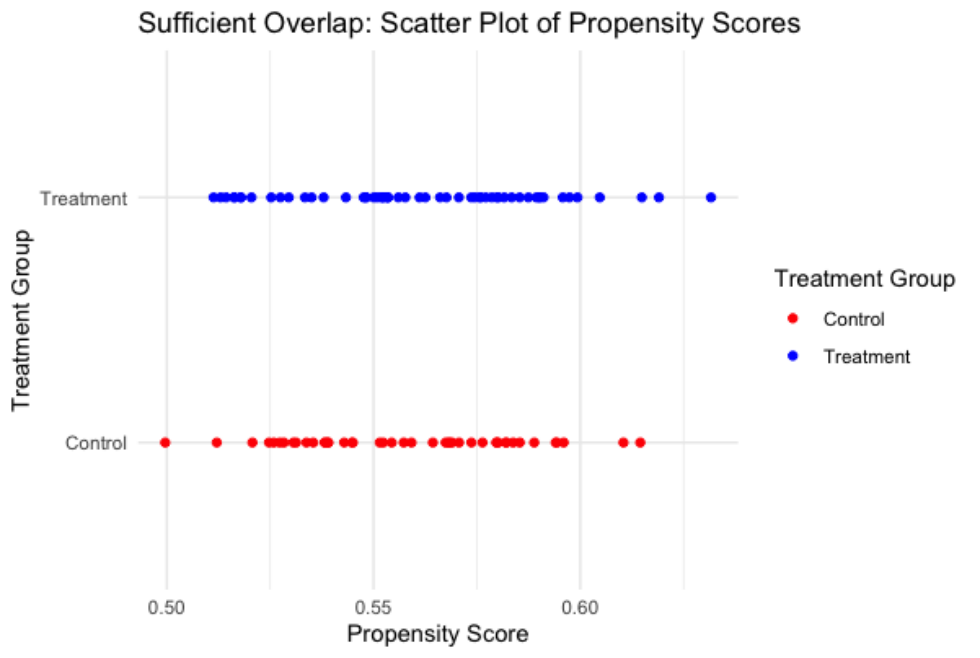

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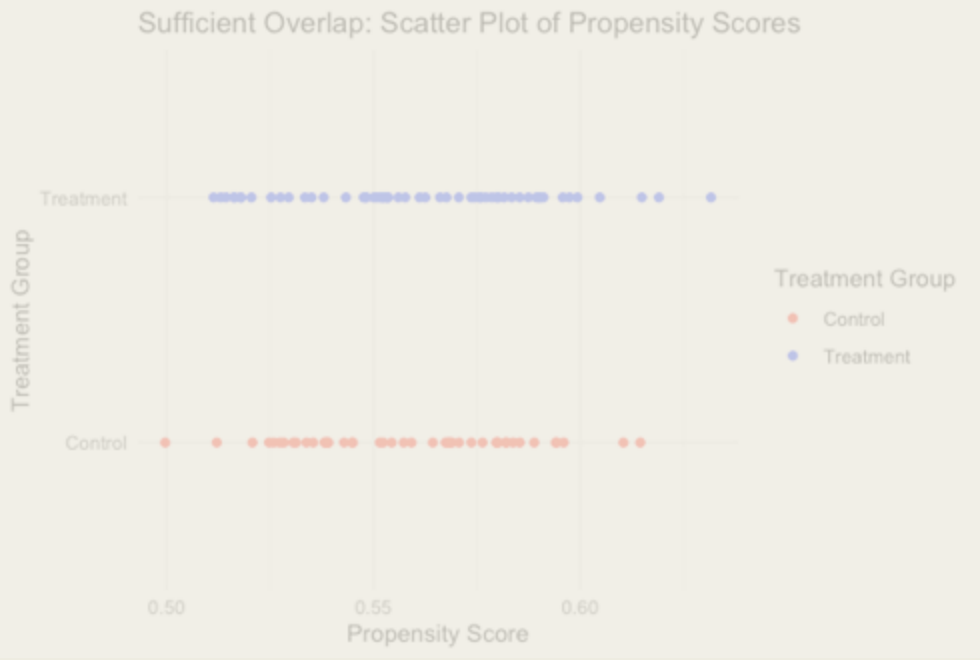

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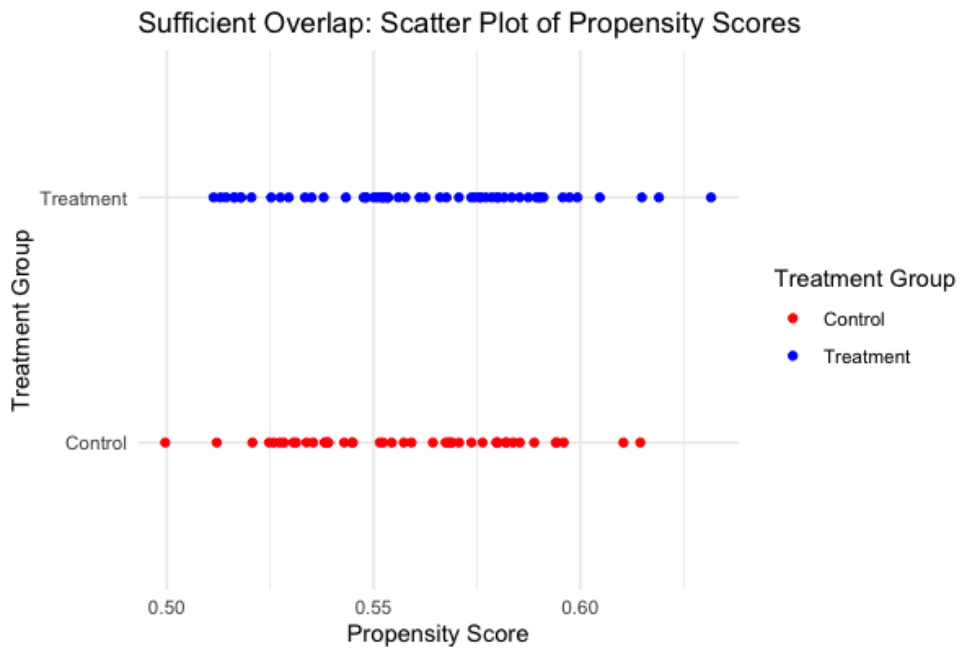

Propensity Score Method Cont.

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Subject	**Trt.**	**age**	**gender**	**BMI**	**…**
1	T	60	M	27.8	
2	T	45	F	24	
3	T	70	M	28.1	
…					
10	C	65	F	25.6	
11	C	50	F	22.3	

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Logistic Regression →

Subject	**Trt.**	**PS**
1	T	0.17
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Sufficient PS overlaps?

No

Yes

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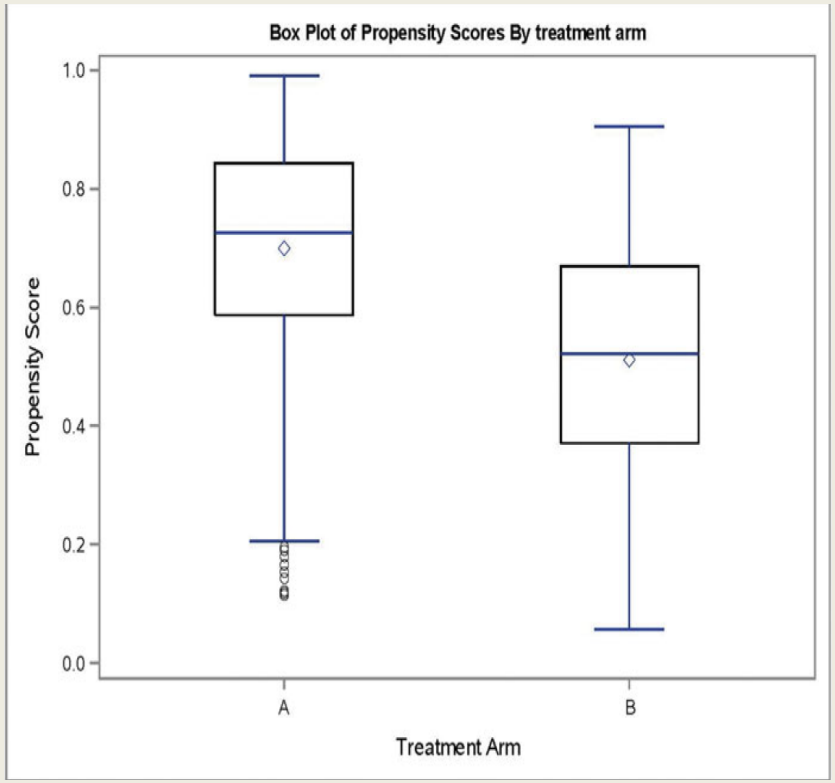

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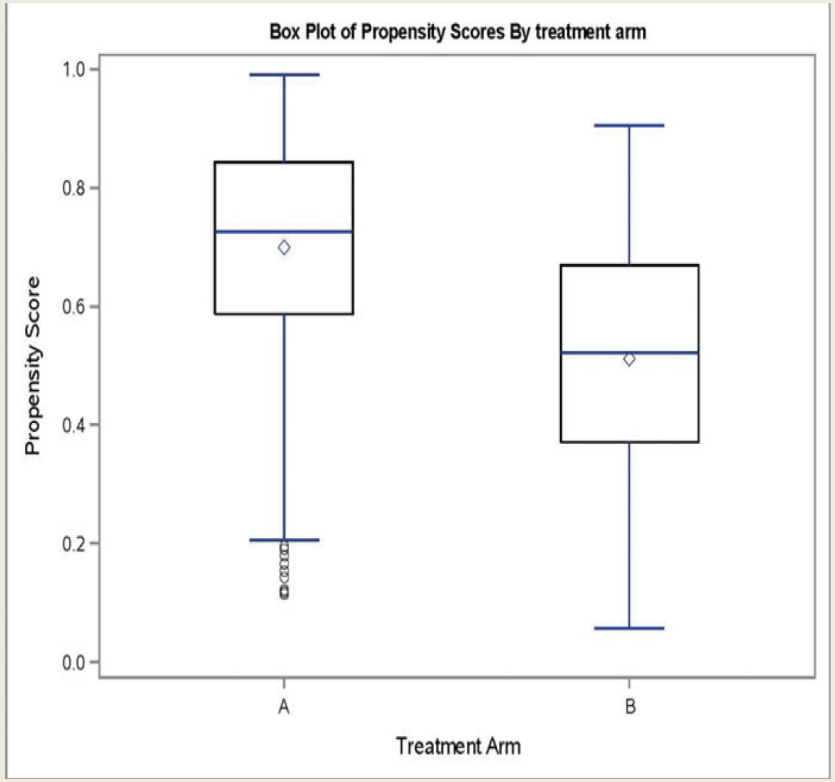

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Table: PS Stratification Illustration - Number of Subjects in each arm

	Stratum 1	Stratum 2	Stratum 3	Stratum 4	Stratum 5	Total
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Control Arm	100	80	60	40	30	310

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  ATE = E[Y(1)-Y(0)] **ATT = E[Y(1)-Y(0) | Z = 1]**

  For PS Stratification: $\boldsymbol{K}$ denotes the number of stratum, $\overline{\boldsymbol{Y_k}}(\mathbf{1}), \overline{\boldsymbol{Y_k}}(\mathbf{0})$ denote the outcome from the kth treated group and control group, respectively; $\boldsymbol{w_k}$ denotes the weight for the kth stratum.

  $\widehat{\boldsymbol{ATE}} = \sum_{k=1}^{K} \boldsymbol{w_k}[\overline{\boldsymbol{Y_k}}(\mathbf{1}) - \overline{\boldsymbol{Y_k}}(\mathbf{0})]$ $\widehat{\boldsymbol{ATT}} = \sum_{k=1}^{K} \boldsymbol{w_{kT}}[\overline{\boldsymbol{Y_{kT}}}(\mathbf{1}) - \overline{\boldsymbol{Y_{kT}}}(\mathbf{0})]$

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StatScience
Stats Power

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StatScience
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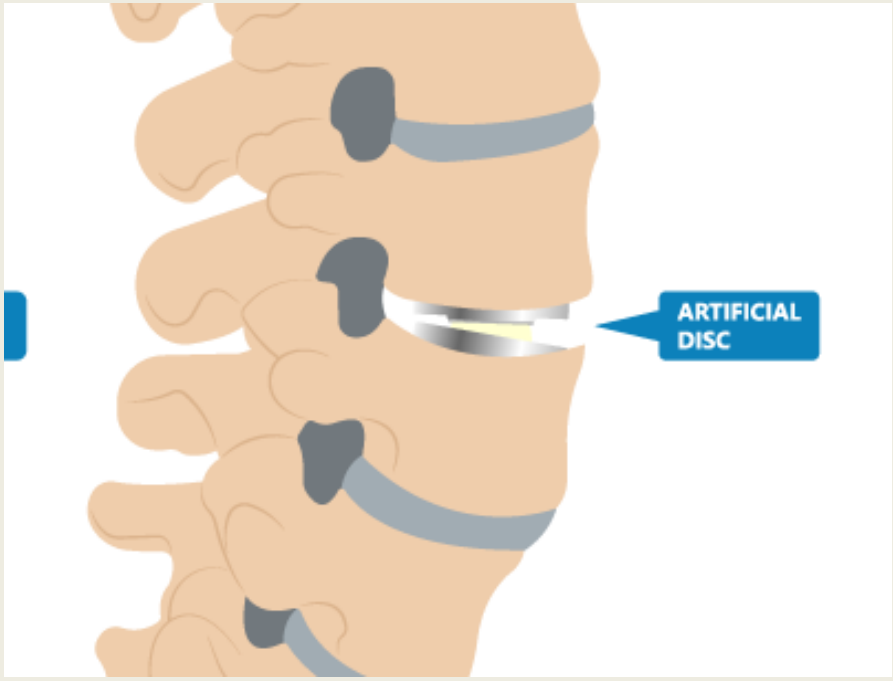

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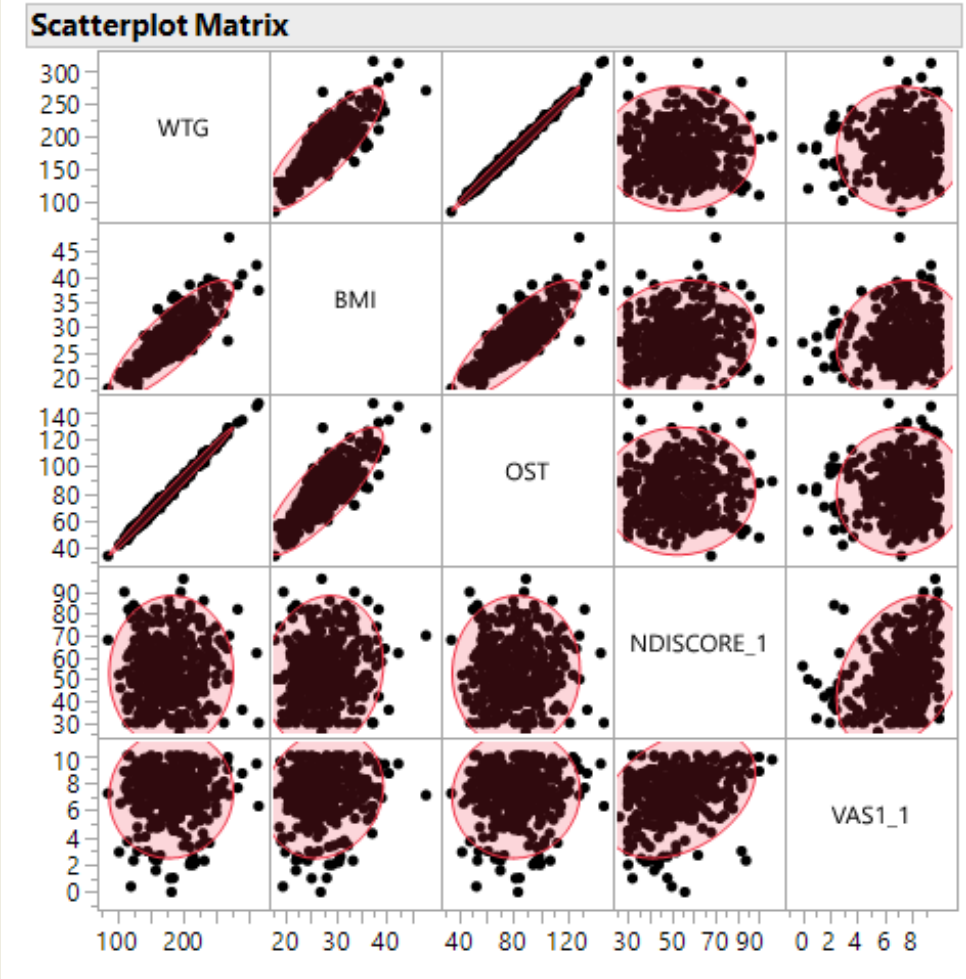

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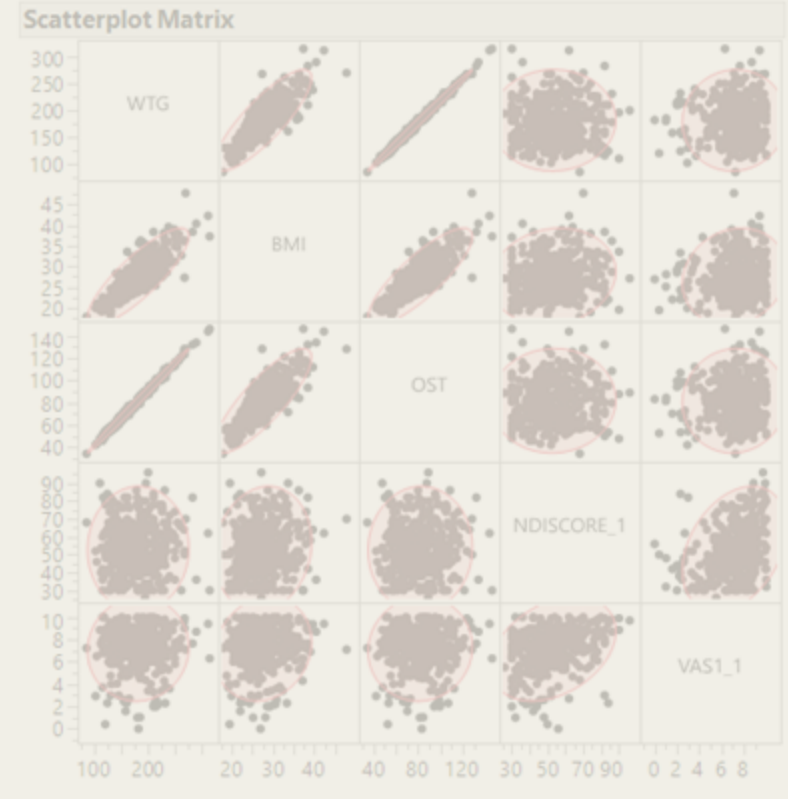

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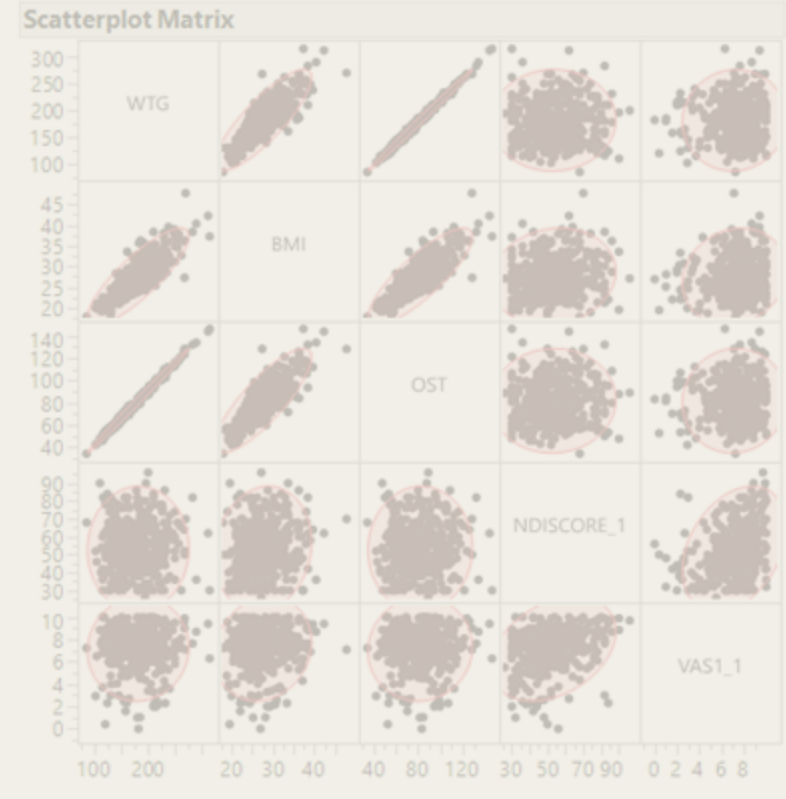

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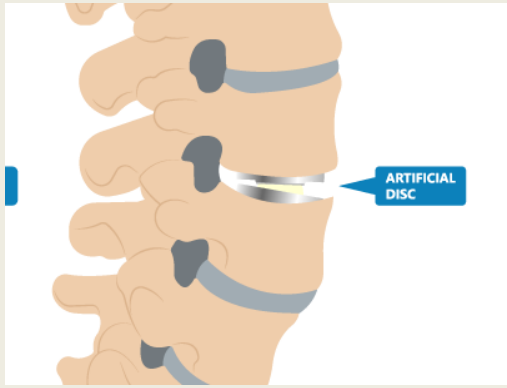

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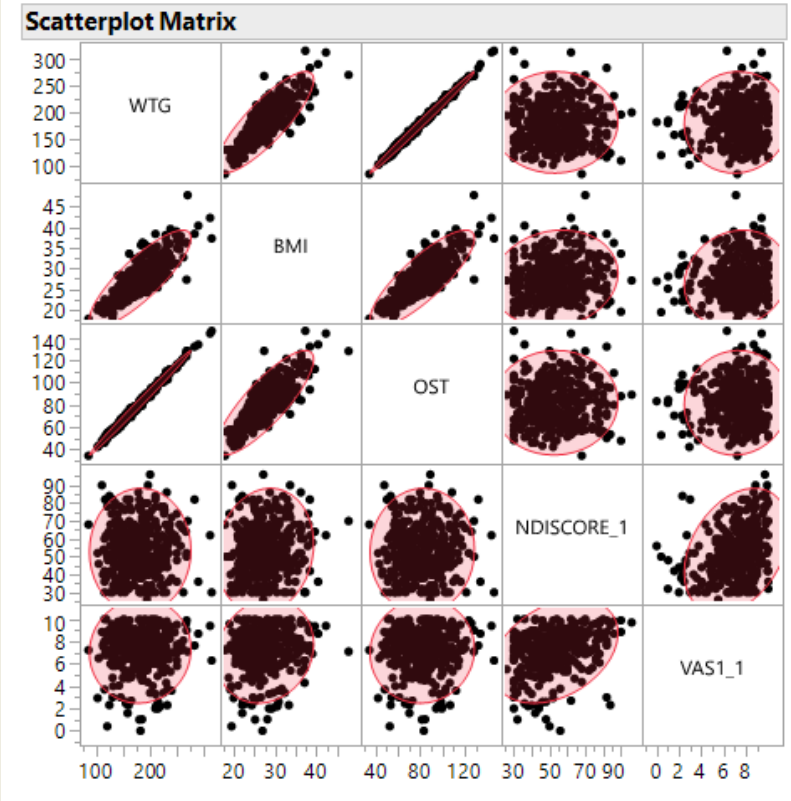

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Hypothetical Example Cont.

StatScience
Stats Power

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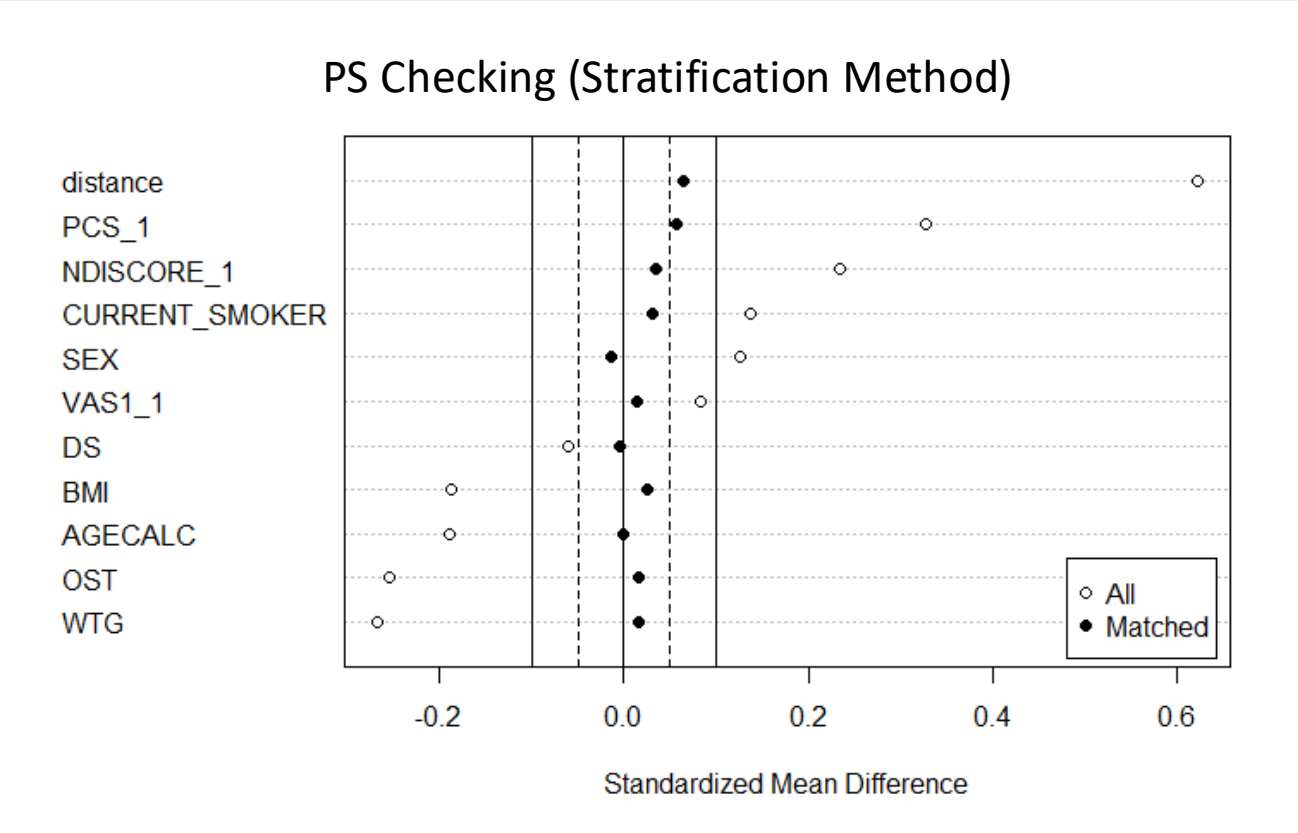

Simulation Scenarios

StatScience
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- Sample Size:

Situation	Treat	External Data
HDE	60	100
Small	**100**	**150**
Moderate	180	250

- External Data Scenarios:
  - Missing in Baseline Covariates:
    - 20% and 40% missing in partial covariates or all covariates
  - Missing in Outcomes (binary outcome & continuous outcome):
    - 20% and 40% missing
  - Missing in both Covariates and Outcomes
  - Unobserved Covariates:
    - Unobserved covariates (in control) highly correlated to observed covariates (in treatment)
- External Data Utilization Method: PS Stratification and PS Weighting
- Estimands: ATT and ATE
- **Assumption:** Missing at Random (**MAR**)

Scenario: 20% Missing

StatScience
Stats Power

- **Setting:** 100 trt, 150 ctl, 20% missing; Estimand: ATE; **Outcome**: proportion of success CCS6
- **Imputation Methods:**
  - Single Imputation: mean for continuous; module for categorical (commonly used in device application)
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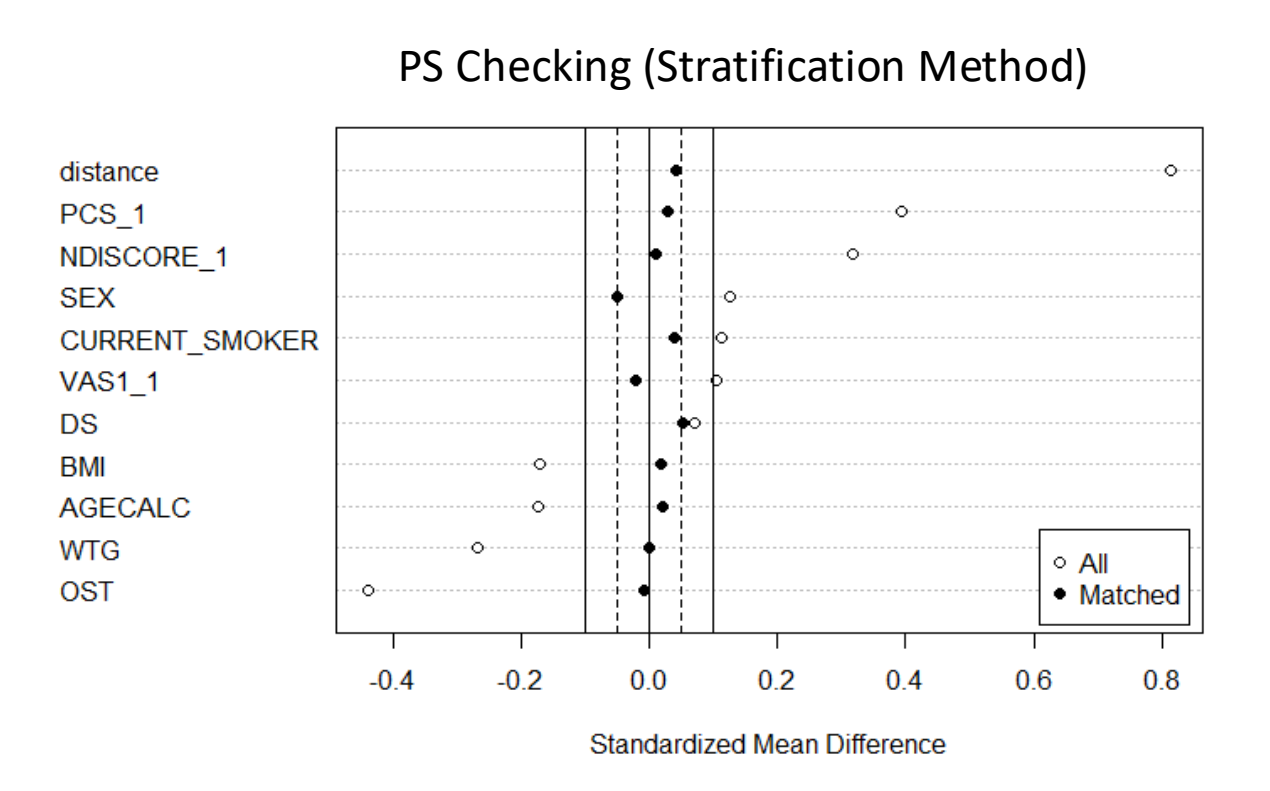

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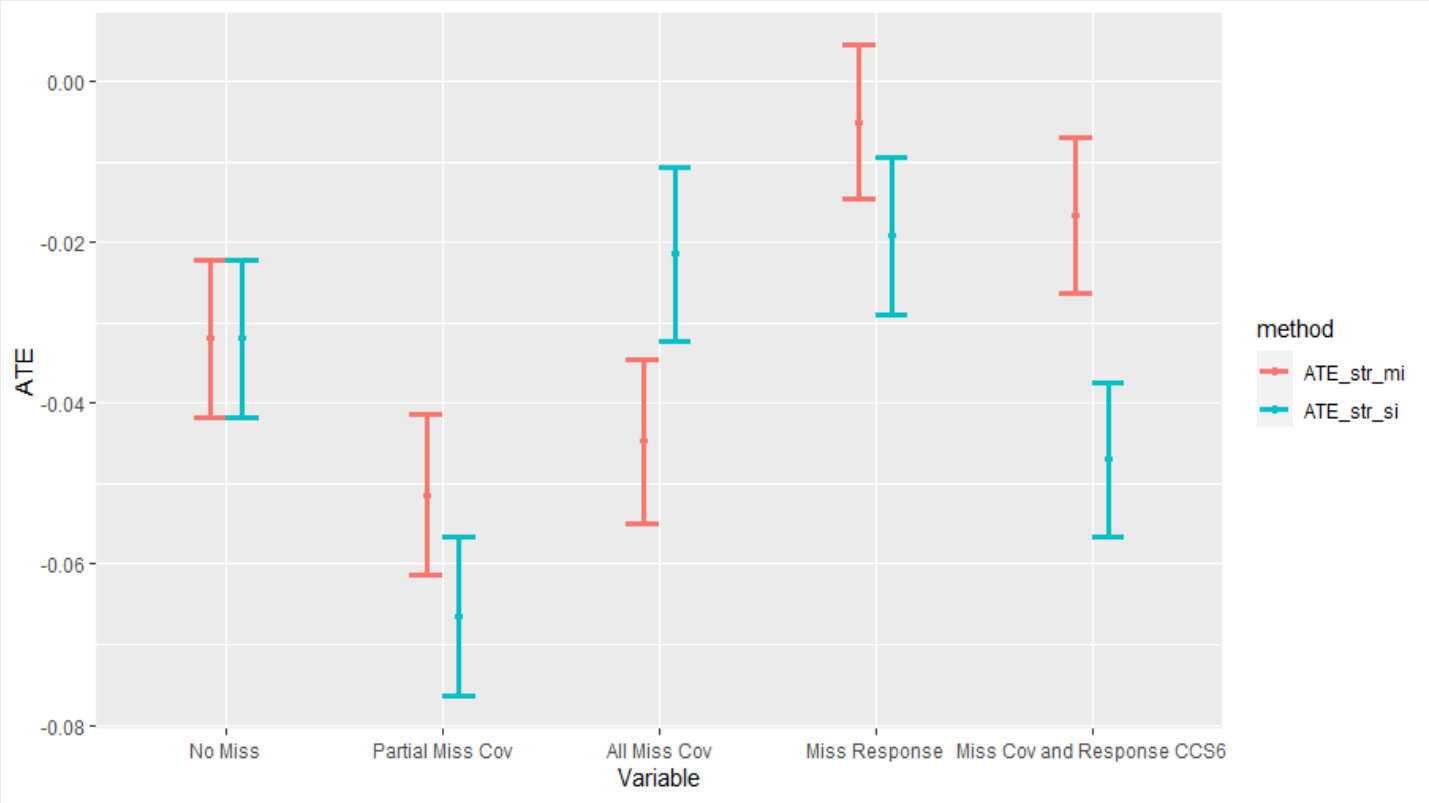


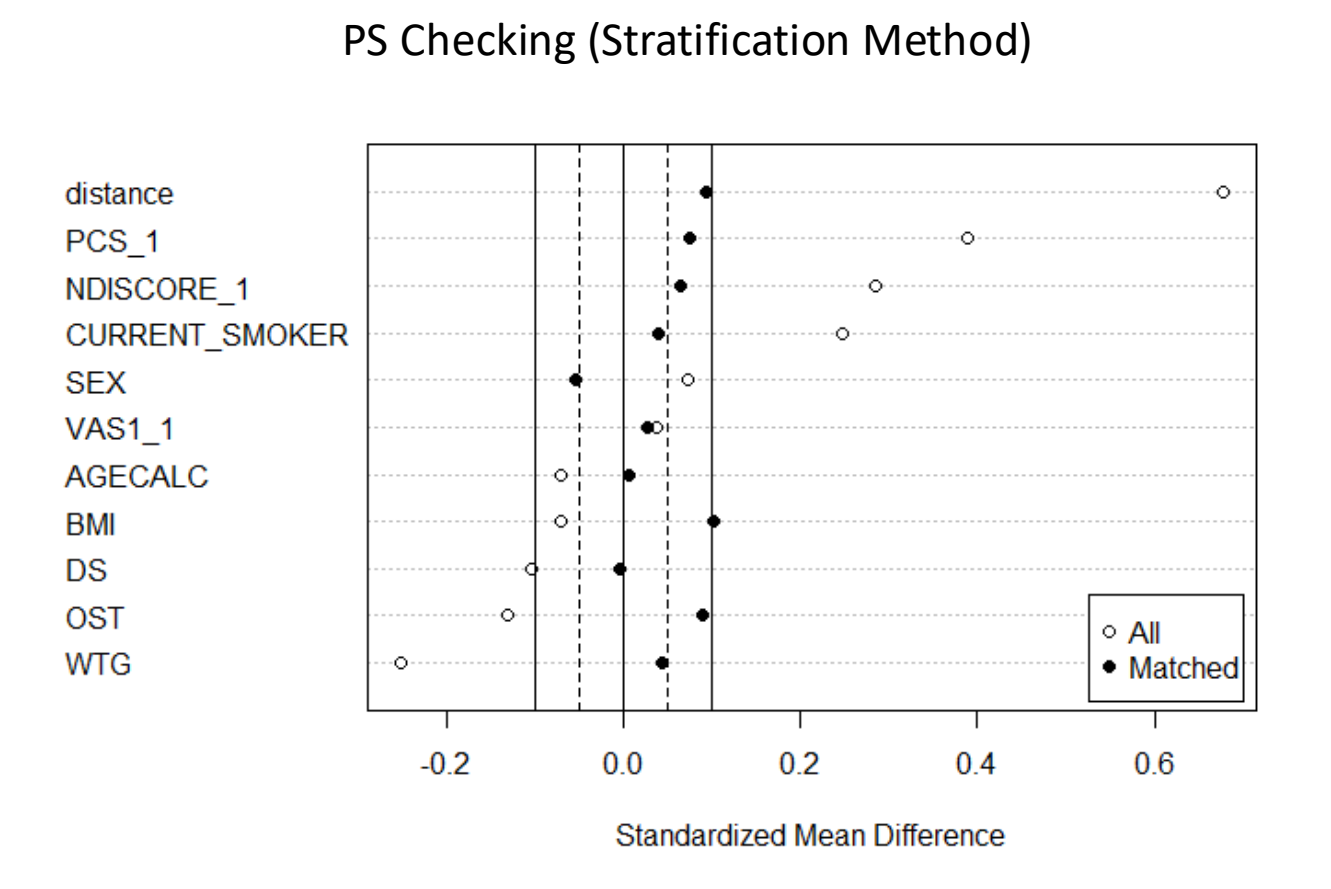
Observations: Given 20% missing,

- All produce biases but not too much
- MI slightly better than SI
- Overall, the resulted PS design is relatively reliable.

Scenario: 40% Missing

StatScience
Stats Power

Setting: 40% missing; **Estimand**: ATE; **Outcome**: proportion of success CCS6



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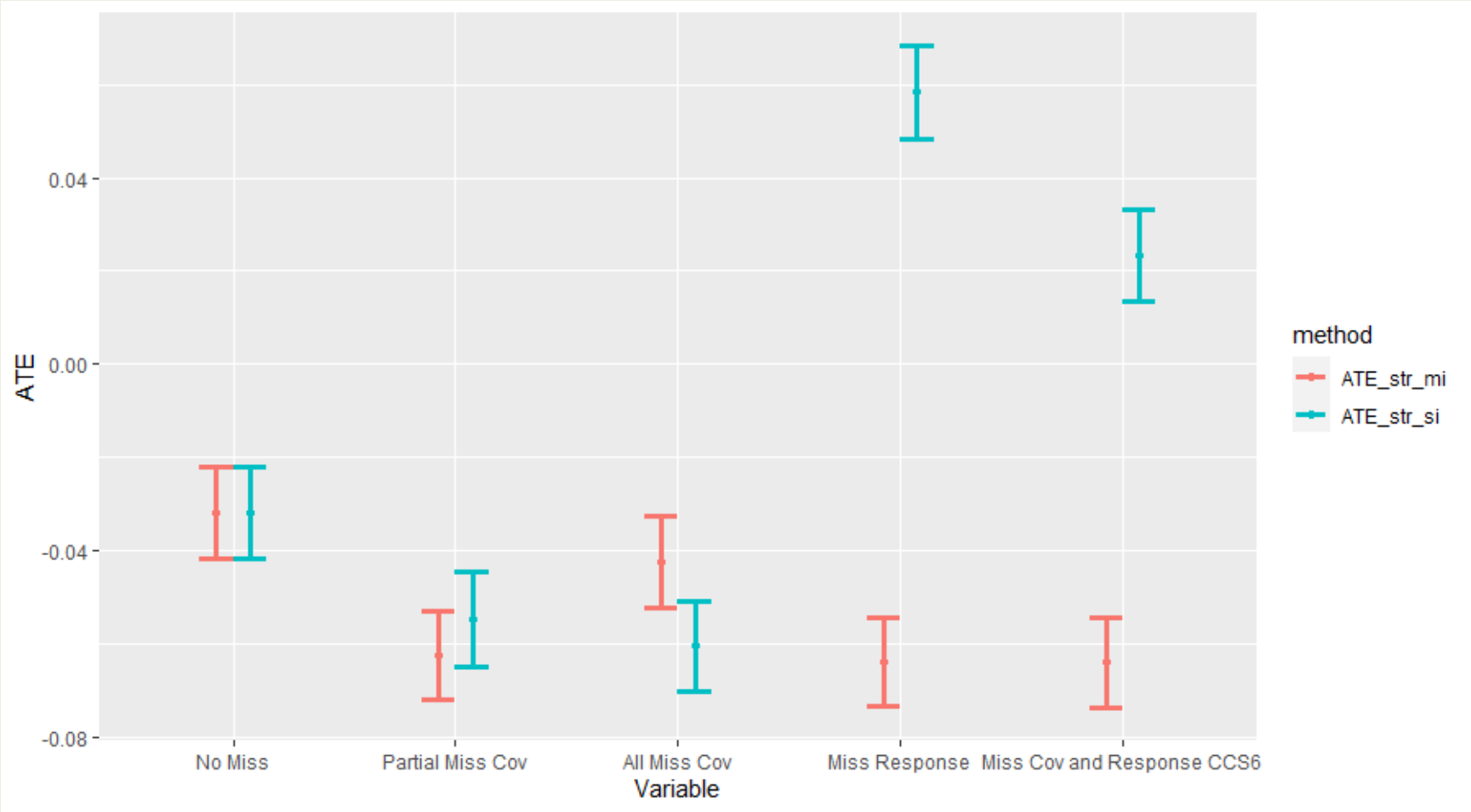

Observations:

- Biases get larger with 40% missing, especially in response missing
- MI better than SI

Scenario: Unobserved Covariates

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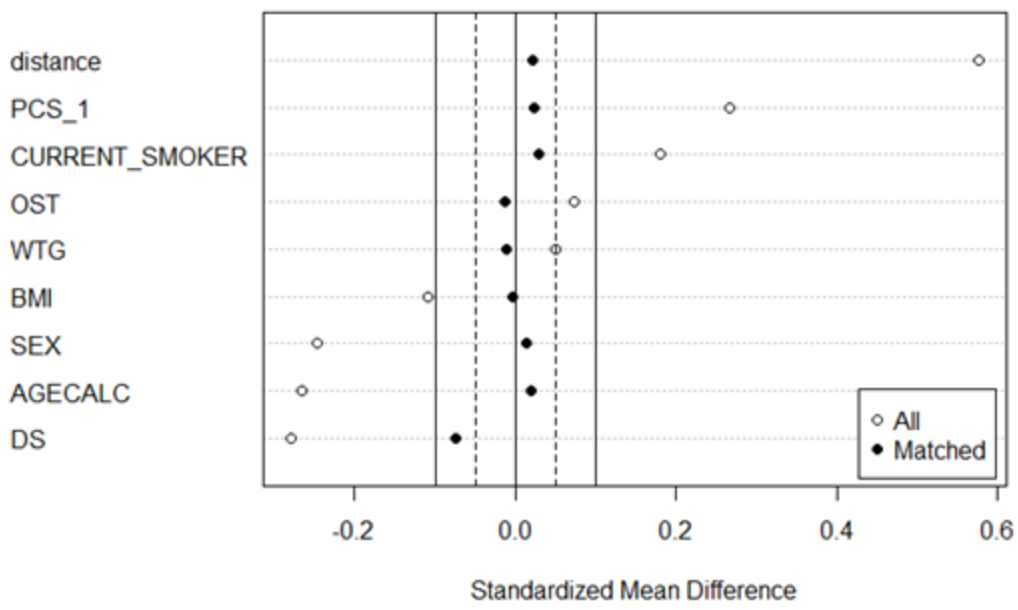
Stats Power

- **Scenario**: Covariates are often correlated to each other. For Unobserved Covariates but highly correlated with observed covariates
- In our exercise, weight and OST are highly correlated
- Simulation: one covariate unobserved, two covariates unobserved (i.e., NDISCORE and WAS)

Setting: 60 trt, 100 ctl;
Estimand: ATE;
Outcome: proportion of success CCS6

PS Checking (Stratification Method)



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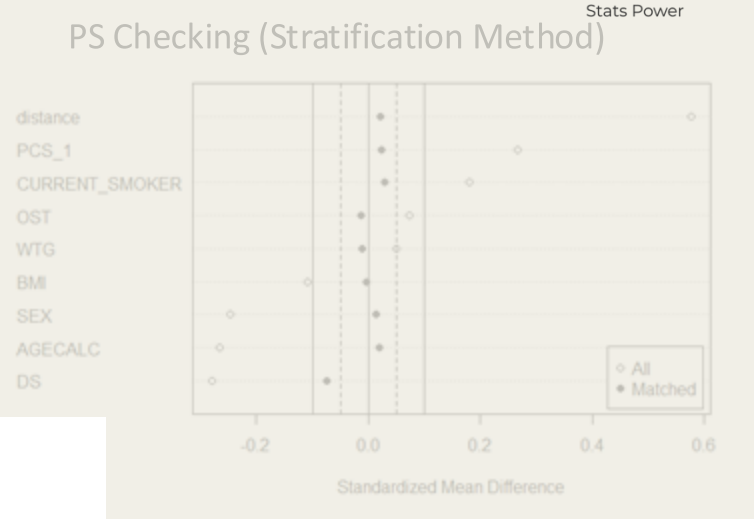

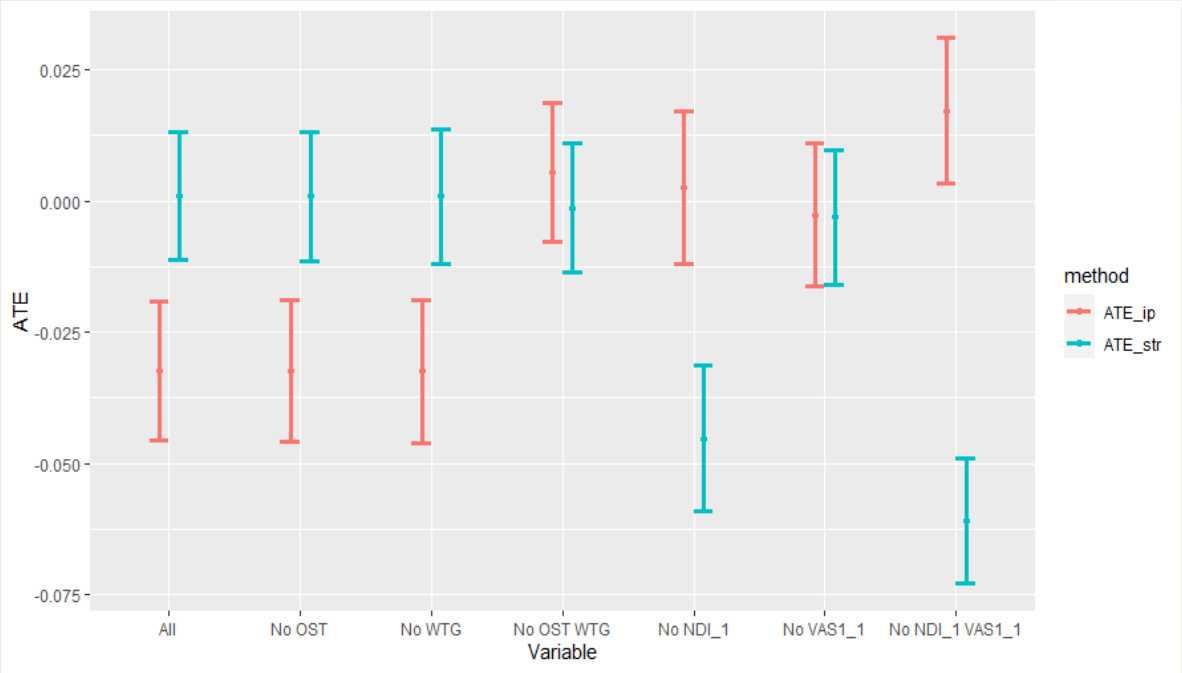

Observations:
The resulted PS design is relatively reliable when only one covariate unobserved and such covariate is highly correlated with other observed covariates.

Take Away

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- For **Missingness** Issue:
  - Categorical Missing variables (in either covariates or response) creates higher impact than Continuous Missing variables
  - Missing in response has higher impact than missing in covariates
  - Balance in PS model CANNOT yield unbiased estimate
  - Imputation could help with causal Inference:
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- Suggestion
  - Avoid Missing (especially in response)
  - Use Multiple Imputation in the existence of missing

References

StatScience
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- Austin, P. (2011a), “An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies,” Multivariate Behavioral Research, 46, 399–424.
- D’Agostino, R. B., Jr., and Rubin, D. B. (2000), “Estimating and Using Propensity Scores With Partially Missing Data,” Journal of the American Statistical Association, 95, 749–759
- Li, H., Mukhi, V., Lu, N., Xu, Y., and Yue, Q. L. (2016), “A Note on Good Practice of Objective Propensity Score Design for Premarket Nonrandomized Medical Device Studies With an Example,” Statistics in Biopharmaceutical Research, 8, 282–286
- Liu, W., Kuramoto, S. J., and Stuart, E. A. (2013). “An Introduction to Sensitivity Analysis for Unobserved Confounding in Non-experimental Prevention Research.” Prevention Science 14:570–580.
- Lu, N., Xu, Y., and Yue, Q. L. (2019), “Some Considerations on Design and Analysis Plan on a Nonrandomized Comparative Study Using Propensity Score Methodology for Medical Device Premarket Evaluation”, Statistics in Biopharmaceutical Research, 12:2, 155-163.
- Yan, X., Lee, S., and Li, N. (2009), “Missing Data Handling Methods in Medical Device Clinical Trials,” Journal of Biopharmaceutical Statistics,19, 1085–1098.
- Yue, L.Q. (2012), “Regulatory Considerations in the Design of Comparative Observational Studies Using Propensity Scores,” Journal of Biopharmaceutical Statistics, 22, 1272–1279.

StatScience

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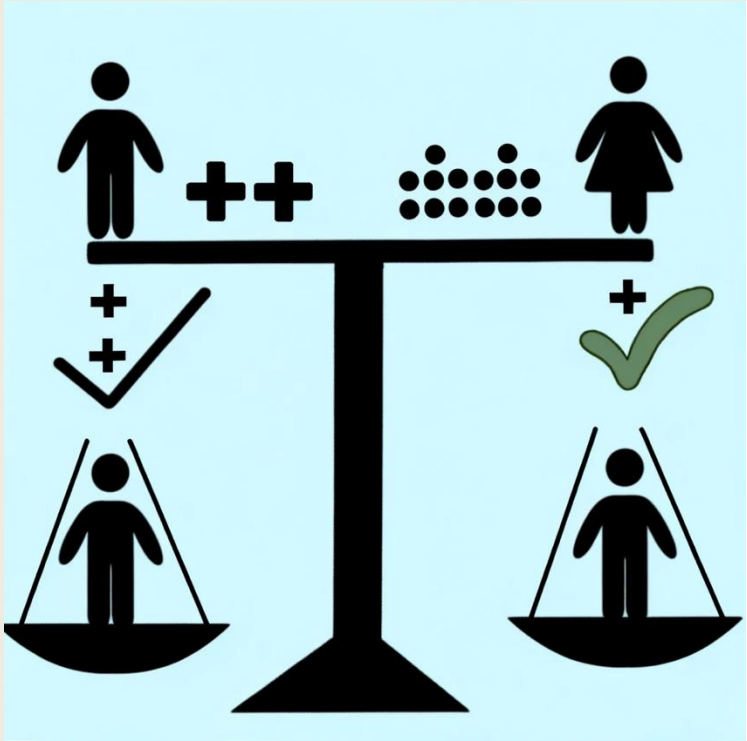
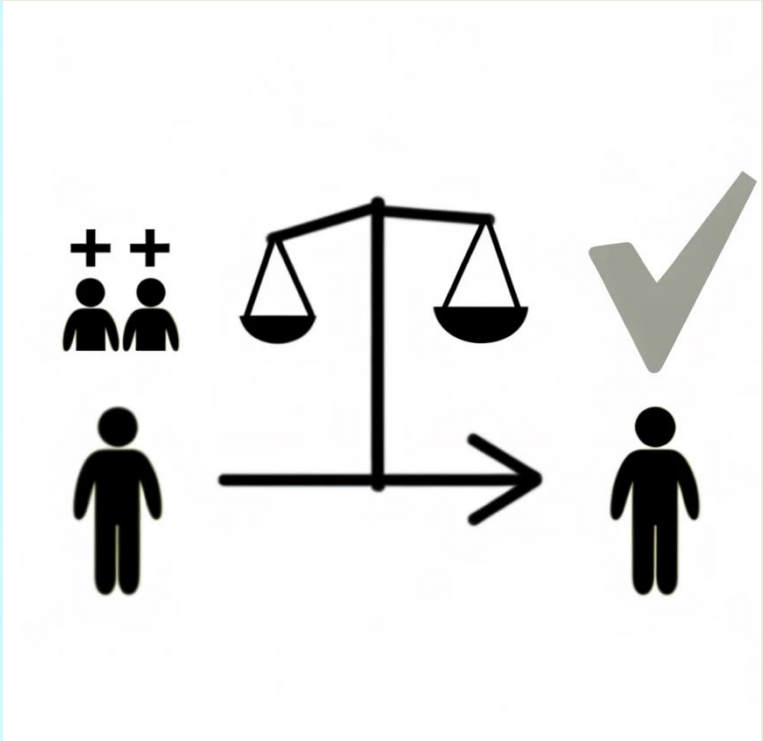
Thank you ☺

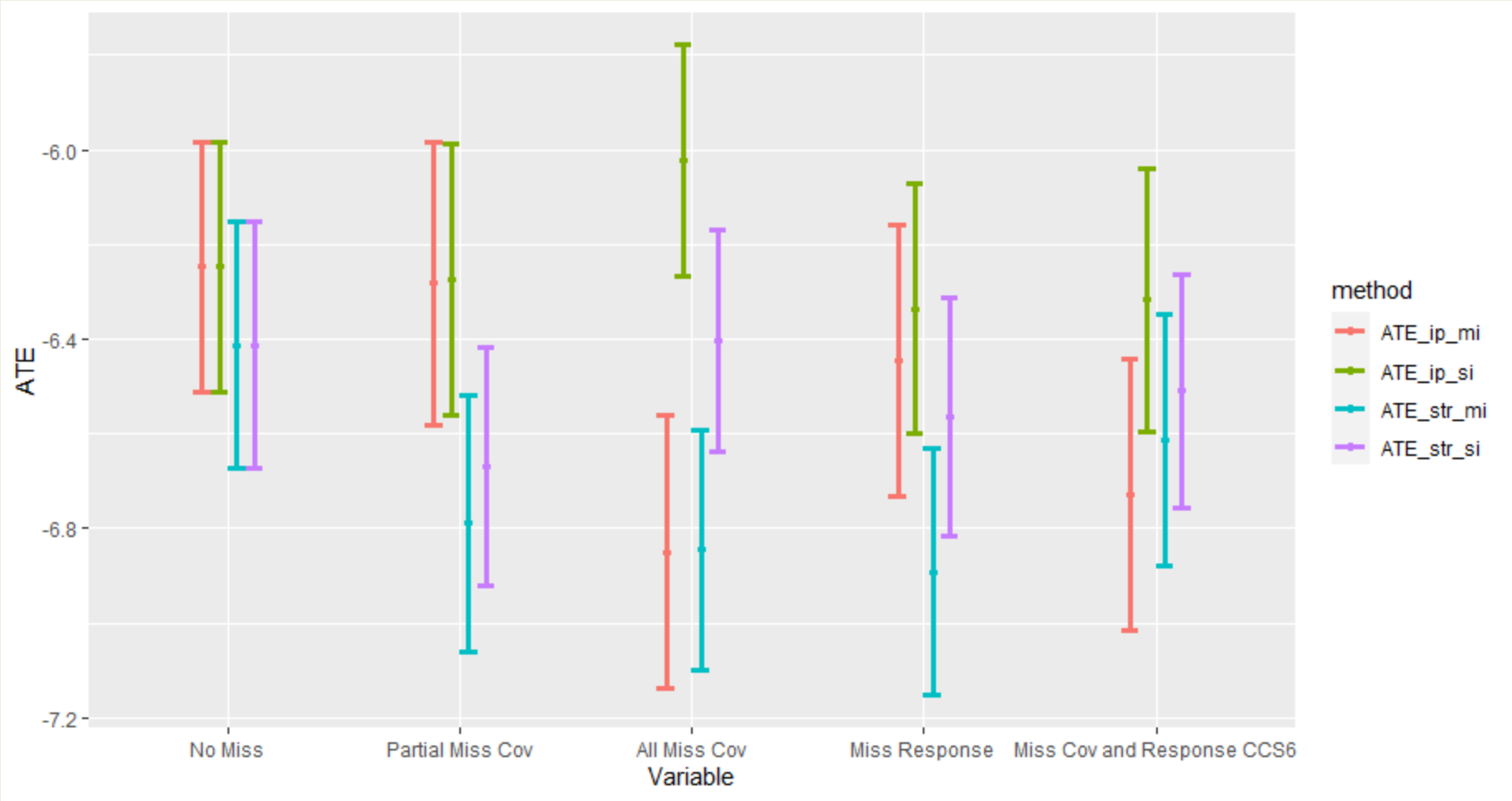
Back Up: Propensity Score Illustration





Back up: Continuous response.

Setting: Response: NDISCORE_6, 100 trt, 150 ctls, ATE, 20% miss
Indication: MI slightly better than SI



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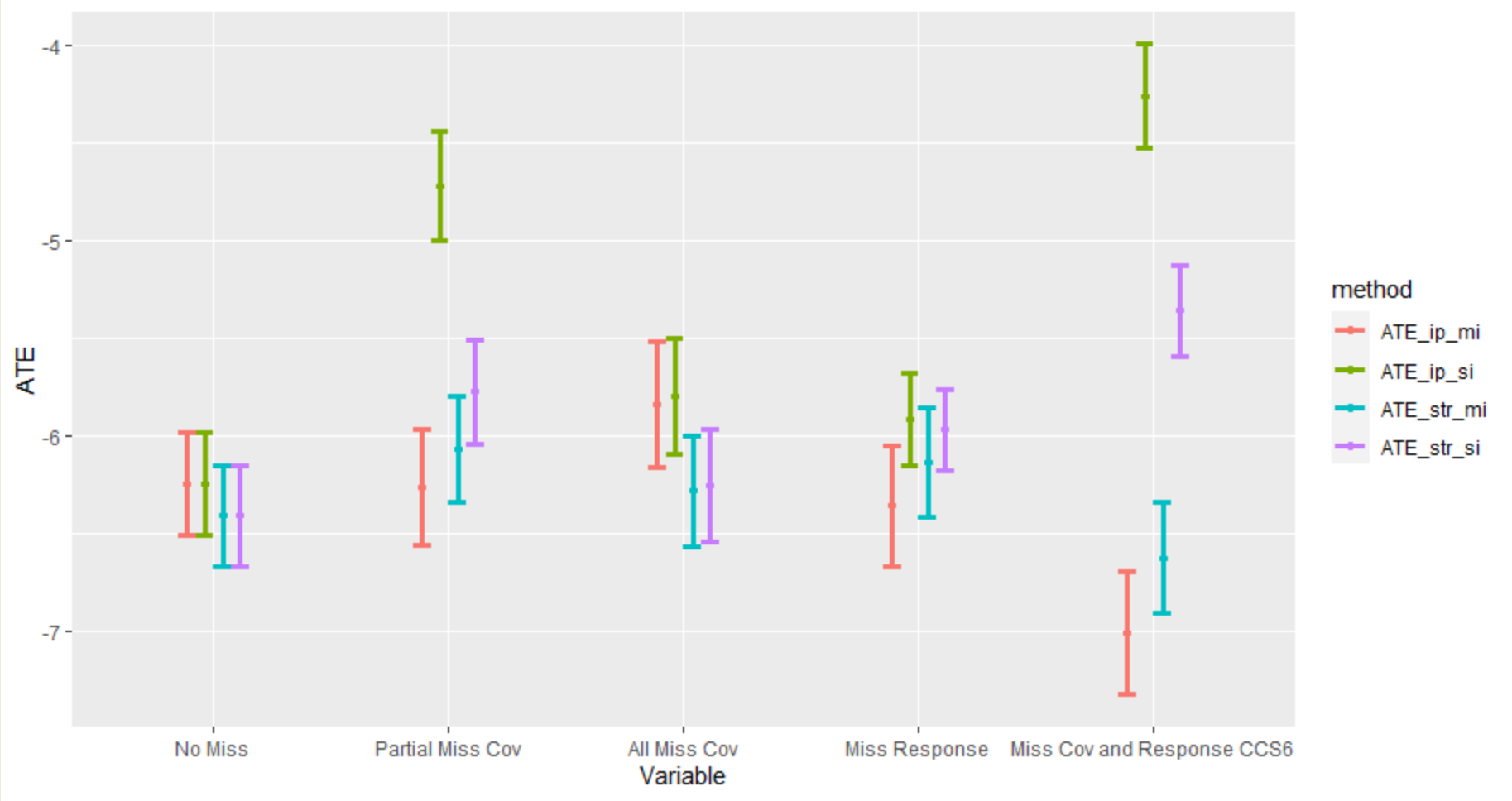

Missing Mechanism

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- **Missing Completely At Random (MCAR)**: missingness does not depend on the observed or unobserved measurements (covariates or outcomes).

- **Missing At Random (MAR)**: missingness depends only on the observed values, not on the unobserved measurements (covariates or outcomes):
  - the behavior of the post dropout observations can be predicted from the observed variables.

- **Missing Not At Random (MNAR)**: neither MCAR nor MAR, i.e., missingness depends on the unobserved measurements.

Related Literatures

StatScience
Stats Power

- Generalized Location Method with EM
  - the applied method is more statistically complicated and less commonly adopted
  - computational complicated
  - proposed under Propensity Score Matching Design

- Sensitivity Analysis methods for PS matching Design
- tipping point that negates the statistical significance of the outcome-treatment association
- derives the point estimate of the true outcome-treatment association with a 95% confidence interval