Impact of covariate misclassification on the power and type I error in clinical trials using covariate-adaptive randomization

LIQIONG FAN
SHARON D. YEATTS
WENLE ZHAO

MEDICAL UNIVERSITY OF SOUTH CAROLINA
DEPARTMENT OF PUBLIC HEALTH SCIENCE
DATA COORDINATION UNIT

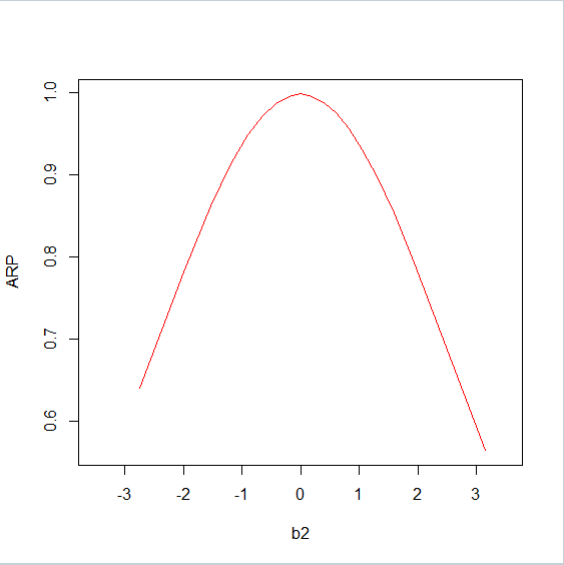
Background

- Properties of covariate-adaptive randomization
  - Well balance important prognostic covariate
  - More generalizable and convincing result
  - Increase power for subgroup analysis
  - Require correct specification of analysis model for hypothesis testing

Shao J, Yu X. Validity of tests under covariate-adaptive biased coin randomization and generalized linear models. Biometrics. 2013;69:960-9.

Background

- Covariate adjustment during analysis
  - Type of analysis: model based
  - Type of outcome: Dichotomized
  - Covariate adjustment in logistic regression
    - Precision
    - Efficiency



Robinson LD, Jewell NP. Some Surprising Results About Covariate Adjustment In Logistic Regression Models. International Statistical Review. 1991;58:227-40.

Background

- Motivation
  - Interventional Management of Stroke III (IMS III)
    - Stratified biased-coin randomization: Stroke severity
    - Misclassification Rate: 2%, non-differential
    - Primary analysis: True severity VS. Randomized severity
  - High-Dose Deferoxamine in Intracerebral Hemorrhage (Hi-DEF)
    - Stratified biased-coin randomization: time from symptom onset to treatment
    - Misclassification Rate: 27.3% and 6.3%, differential
    - Primary analysis: Anticipated time window VS. Actual time window

Issues?

- Impact of adjusting with misclassified covariates under covariate adaptive randomization.

— IMS III

NIHSS STRATUM (RANDOMIZED)	NIHSS STRATUM (ACTUAL)			
	NIHSS 19 OR LOWER		NIHSS 20 OR HIGHER	
	N	% Randomized	N	% Randomized
NIHSS 19 OR LOWER	448	98.03%	9	1.97%
NIHSS 20 OR HIGHER	4	2.01%	195	97.99%

— Hi-DEF

TIME WINDOW (RANDOMIZED)	TIME WINDOW (ACTUAL)			
	Actual <= 12 hours		Actual > 12 hours	
	N	% Anticipated	N	% Anticipated
Anticipated <= 12 hour	8	72.7%	3	27.3%
Anticipated > 12 hours	1	6.3%	15	93.8%

Method

- Simulation
  - Regression based analysis: Logistic regression
    - 1 prognostic covariate: subject to misclassification
    - 1 perfect measured variable: treatment assignment
    - No interaction
    - Dichotomized outcome
  - Randomization schemes
    - Simple randomization
    - Covariate adaptive randomization:
      - Stratified Block Randomization
      - Stratified Biased-coin Randomization

Method

- Simulation
  - Scenarios
    - Fixed control group rate (40%) and treatment group rate (50%)
    - Varied covariate effect: -3 to +3 (OR: 0.064-23.2)
    - Varied misclassification rate: 0% to 40%
    - Type of misclassification: non-differential

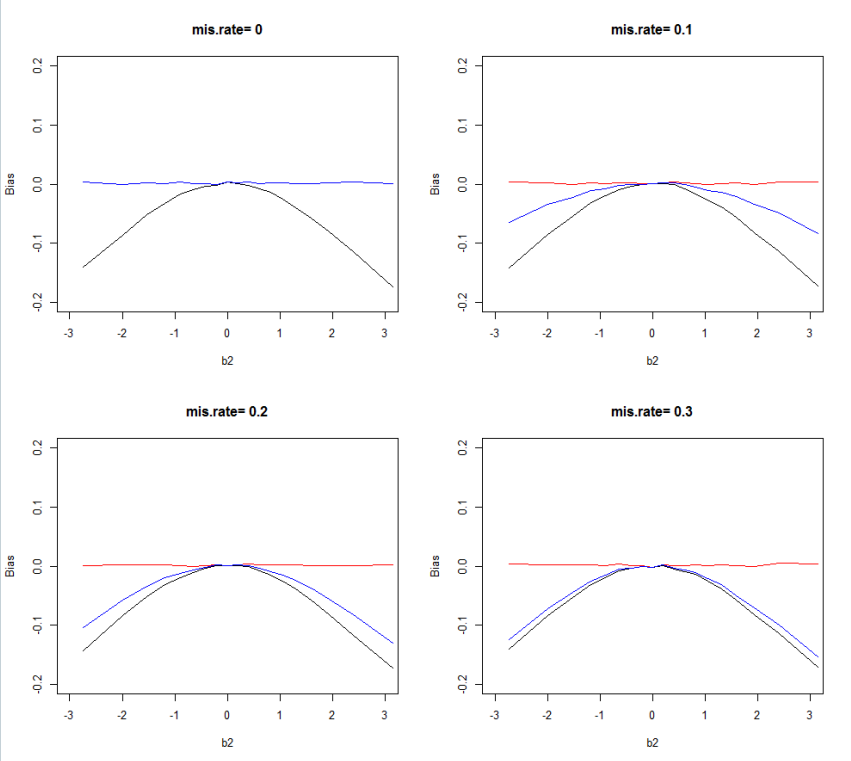
Method

- Simulation
  - Models compared
    - Unadjusted model
    - Model adjusted with misclassified covariate
    - Model adjusted with corrected covariate
  - Operating characteristics evaluated
    - Bias
    - Power
    - Type I error rate

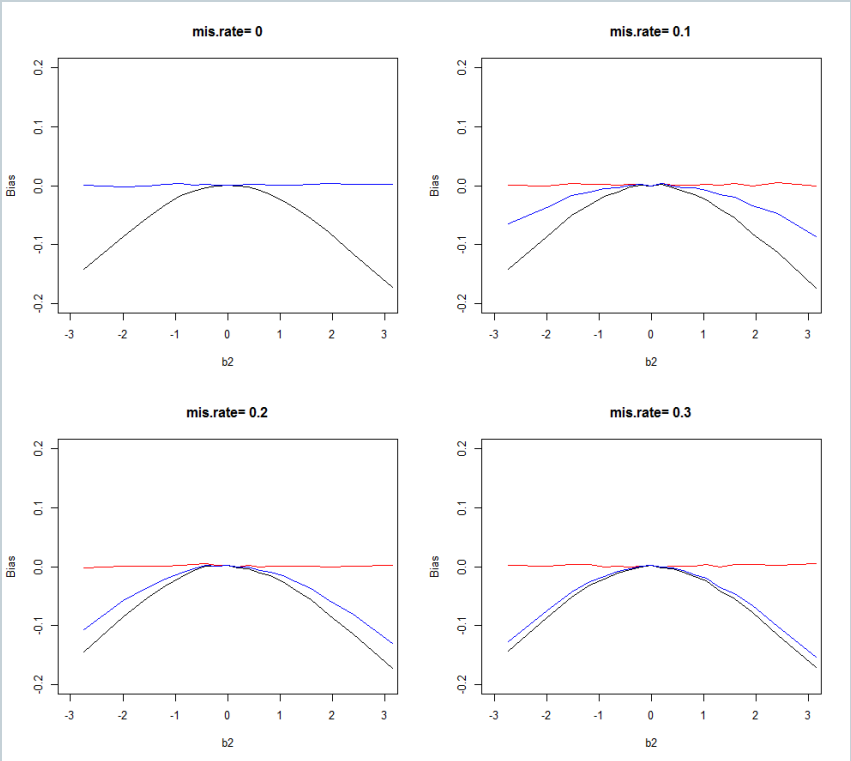
Result-Bias

True model
Naive model
Unadjusted model

Simple Randomization



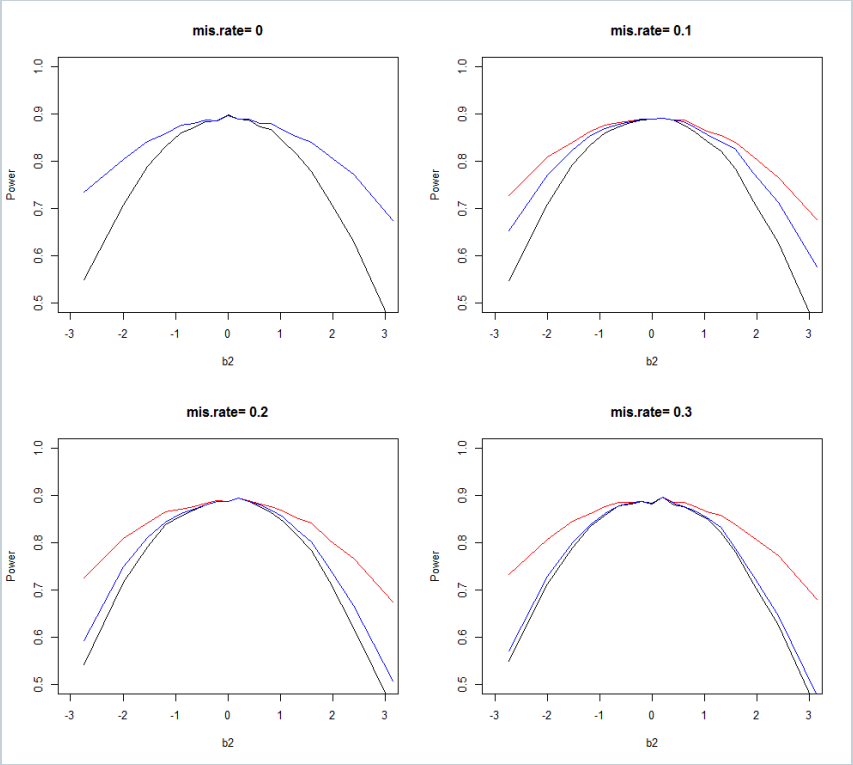
Covariate adaptive Randomization



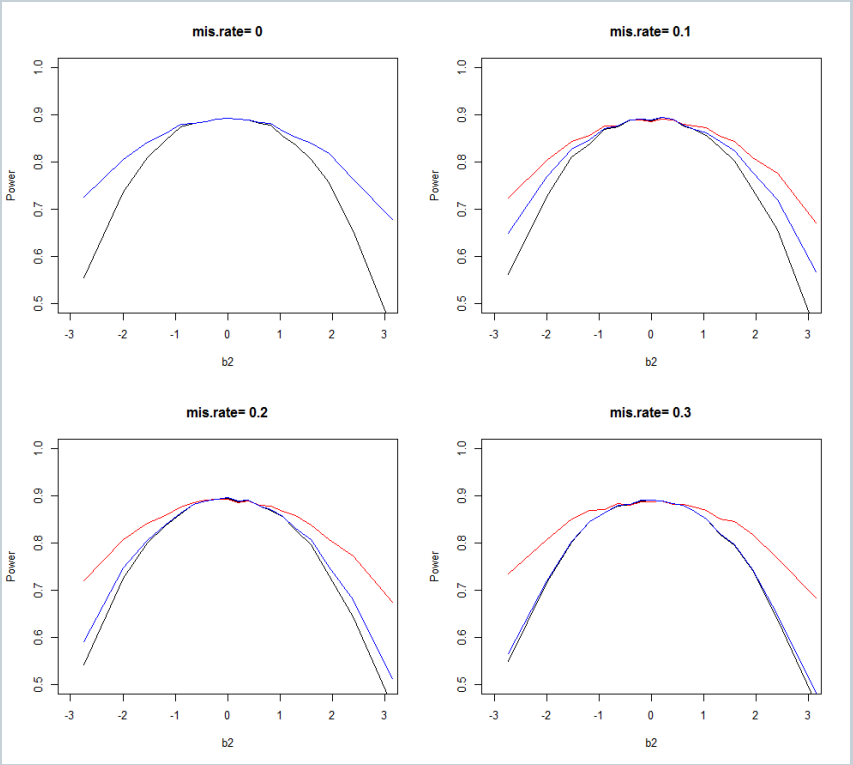
Result-Power

True model
Naive model
Unadjusted model

Simple Randomization



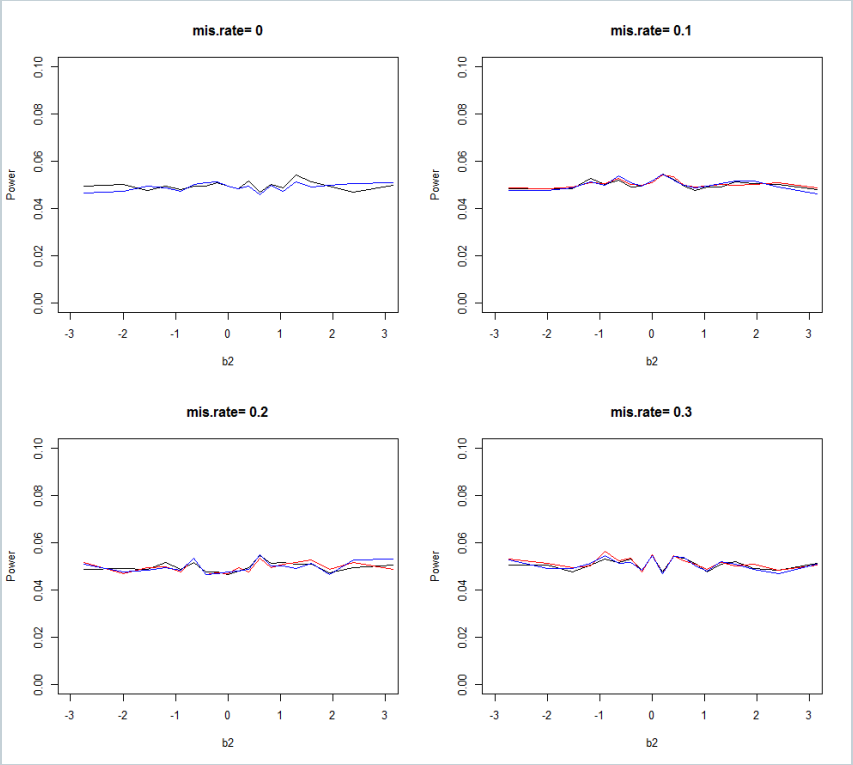
Covariate adaptive Randomization



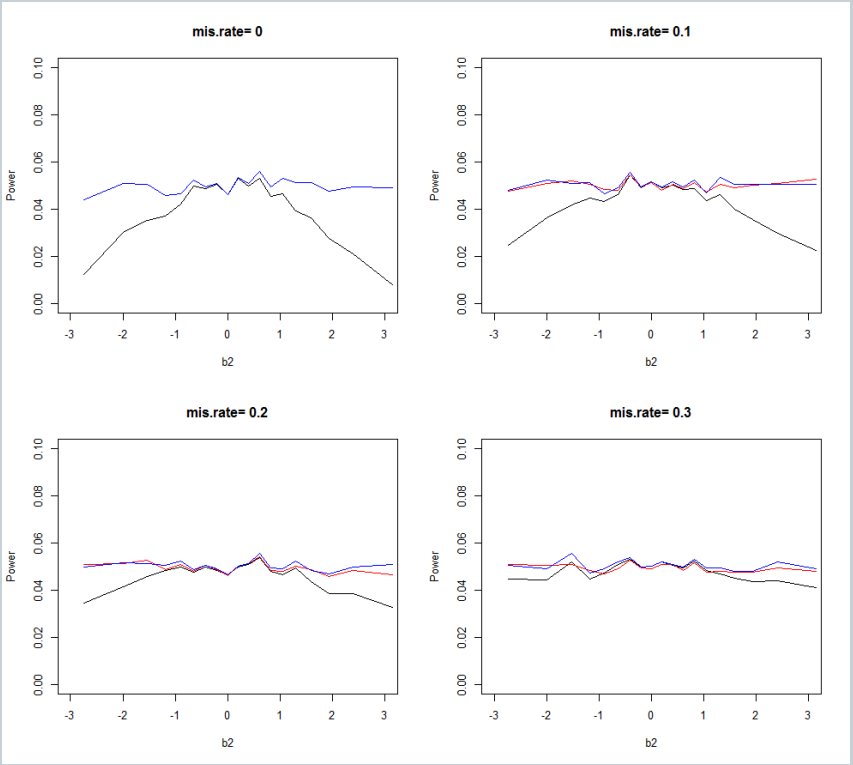
Result-Type I error Rate

True model
Naive model
Unadjusted model

Simple Randomization



Covariate adaptive Randomization



Conclusion

- Impact on the estimate of treatment effect
  - Direction: Bias towards Null
    - Same direction of "bias" caused by unadjusting covariate
    - Adjusted estimate VS. unadjusted estimate
  - Magnitude
    - Misclassification rate: about 30% misclassification is almost the same as not adjusting the covariate.
    - The covariate effect on the outcome given the treatment effect

Greenland S. The effect of misclassification in the presence of covariates. American journal of epidemiology. 1980;112:564-9.

John MNN, P. Jewell. A geometric approach to assess bias due to omitted covariates in generalized linear models. Biometrika. 1993;80:807-15.

Conclusion

- Impact on power for detecting treatment effect
  - Randomization schemes do not have effect on power
  - Adjusting with corrected covariate minimize the power loss due to study design
  - The amount of power loss
    - Misclassification rate
    - Covariate effect on the outcome given the treatment

Conclusion

- Impact on type I error rate
  - Simple randomization: maintained
  - Covariate-adaptive randomization
    - Adjusting with corrected covariate: maintained
    - Adjusting with misclassified covariate: maintained
    - Without adjusting covariate: conservative

Discussion

- Under covariate adaptive randomization, adjusting randomized covariate is always recommended for final analysis
- Randomization scheme does not have an "add-on" effect on bias and power loss caused by covariate misclassification
- Attention should be drawn to correct the bias in estimating the effect of treatment and sample size reassessment with the presence of covariate misclassification

Questions?