Finite Sample Properties of Inverse Probability of Adherence Weighted Estimator of the per-Protocol Effect for Sustained Treatment Strategies

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  - **Lucy Mosquera** (Statistics)
  - **Md. Belal Hossain** (Population and Public Health)

Outline

1. Motivating example: Lipid trial
    - Adherence adjustment in Lipid trial data
    - Literature
2. Simulation and results
    - Interpreting Lipid trial results
    - Follow-up work and future directions

Slides at ehsanx.github.io/IPAW-slides/

Lipid trial

- Time to event outcome (Y):
  - coronary heart disease (CHD) death, or
  - or non-fatal myocardial infarction
- Exposure (A):
  - cholestyramine or
  - placebo
- Randomized to arms (Z)

Lipid trial

- 2-armed double-blind RCT
  - $3,550$ subjects eligible
  - randomized at 5th visit and
  - followed ≥ 7 years
- Static sustained treatment regime
- Medication adherence
  - counts of unused medication packets

Lipid trial

Baseline prognostic factors (**B**)

- 5 baseline covariates

Post-randomization prognostic factors (**L**)

- 38 time-varying covariates

Popular adherence adjustment methods

Intention to Treat (ITT)

- compares randomized to treatment arm vs. control arm
- no adherence adjustment

Naive Per-protocol (Naive PP)

- artificially censoring when become non-adherent
- no covariate adjustment

Conditional Per-protocol (Adj. PP)

- B (baseline only) adjusted PP
- L (time-varying only) adjusted PP
- B + L adjusted PP

IP of (Adherence) *Weighted* Per-protocol (sIPW PP)

- model-based vs cumulative survival-based
- stabilized IPWs (address artificially censoring)
- uIPW is another version with unstabilized weights

- **Treatment effect estimates**

Method	Weights		Coef. (log(OR))		OR	
	Mean	Min-Max	Estimate	SE	Estimate	95% CI
ITT			-0.16	0.13	0.85	0.66-1.09
Naïve PP			-0.22	0.29	0.80	0.45-1.41
B Adj. PP			-0.25	0.29	0.78	0.45-1.37
L Adj. PP			0.18	0.33	1.20	0.63-2.28
uIPW PP	1.34	1.00-172.49	-0.79	0.50	0.46	0.17-1.21
uIPW PP (5% truncated)	1.16	1.00-1.44	-0.27	0.29	0.76	0.43-1.34
sIPW PP	1.01	0.16-10.52	-0.31	0.29	0.74	0.42-1.29

- How reliable are these estimates?

- true DAG unknown
- unknown whether all adherence predicting factors were measured
- finite sample size: $3,550$
- high non-adherence rate
- differential non-adherence: 84% vs. 77.2%
- low event rate: 7.3% (pooled logistic model)
- measurement schedule varied: LOCF was used for imputation

Literature search about IPW

Robins and Finkelstein (2000):

IPW is asymptotic consistent for PP if model correctly specified

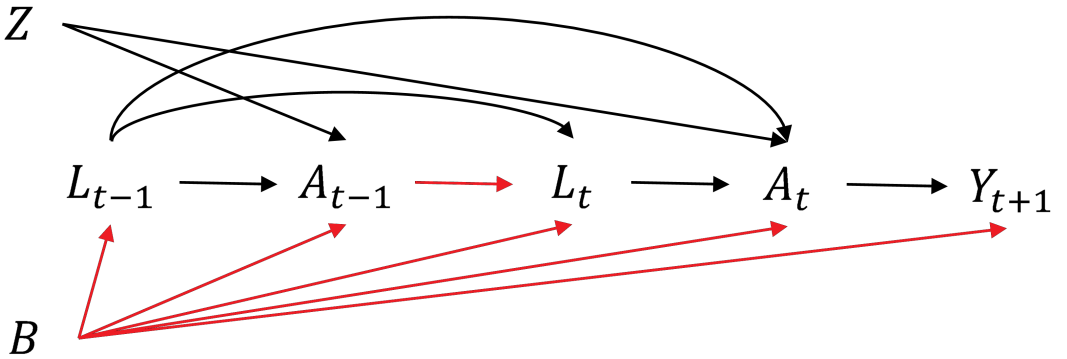
- Hernan and Robins (2017), Murray and Hernan (2016, 2018):
  - Reanalysis; addressing treatment-confounder feedback
- Morden et al. (2011), Latimer et al. (2017, 2018)
  - estimates sensitive to switching proportions

- **Young et al.** (2019):
  - interval censoring simulation framework
  - 200K, 1 DAG, null treatment effect,
  - varying measurement schedule, confounding

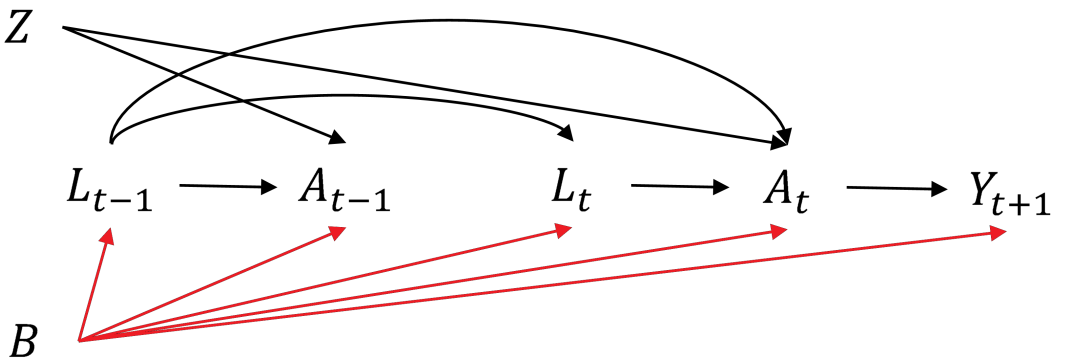
New Simulations

B affects A and Y directly: Adjusting B blocks backdoor

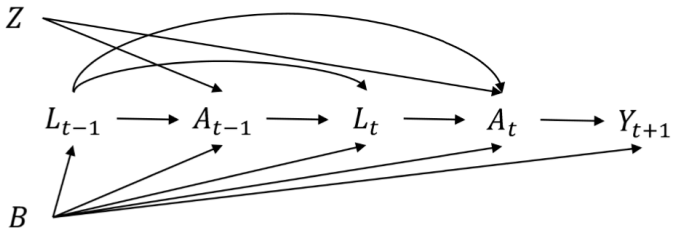
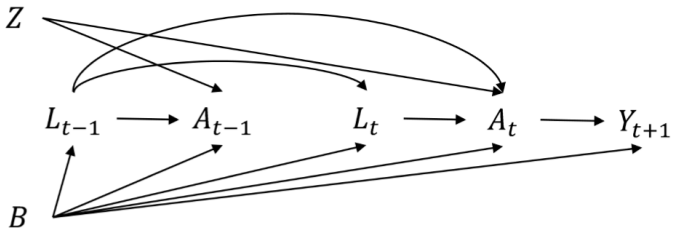
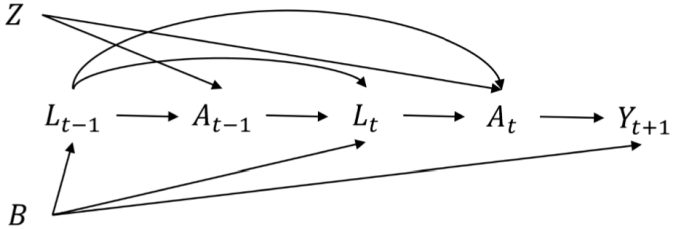
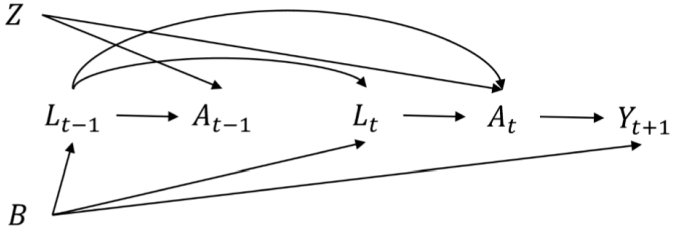
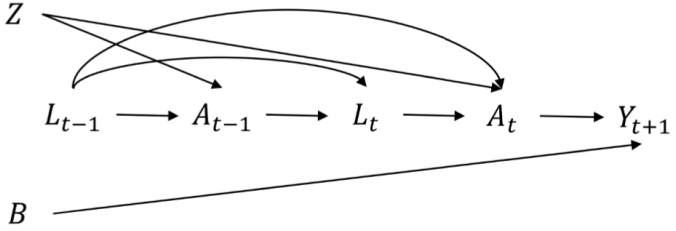
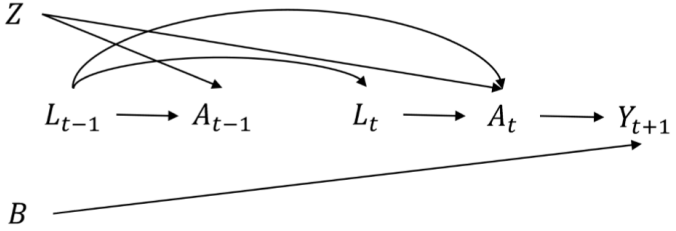
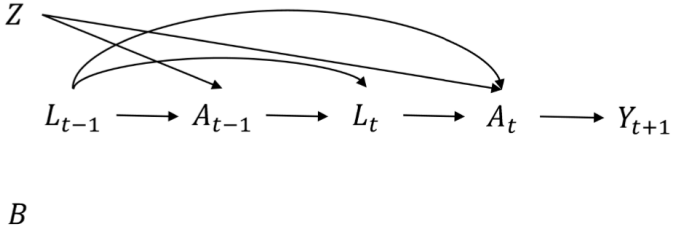
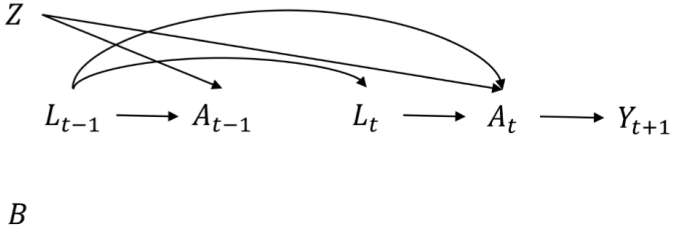
Diag 1(i): A affects subsequent L



Diag 1(ii): A does not affect subsequent L

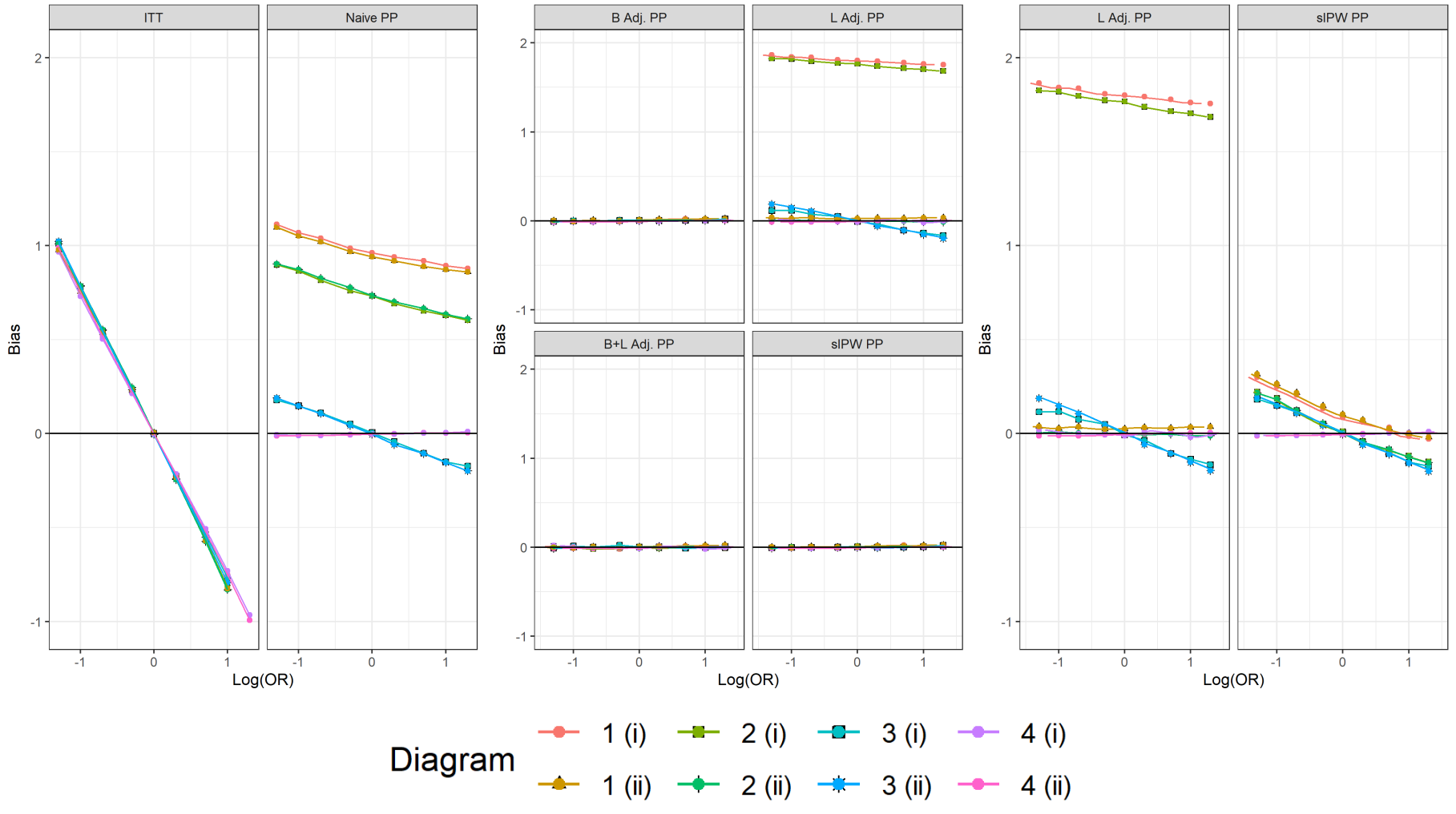


All 8 DAGs

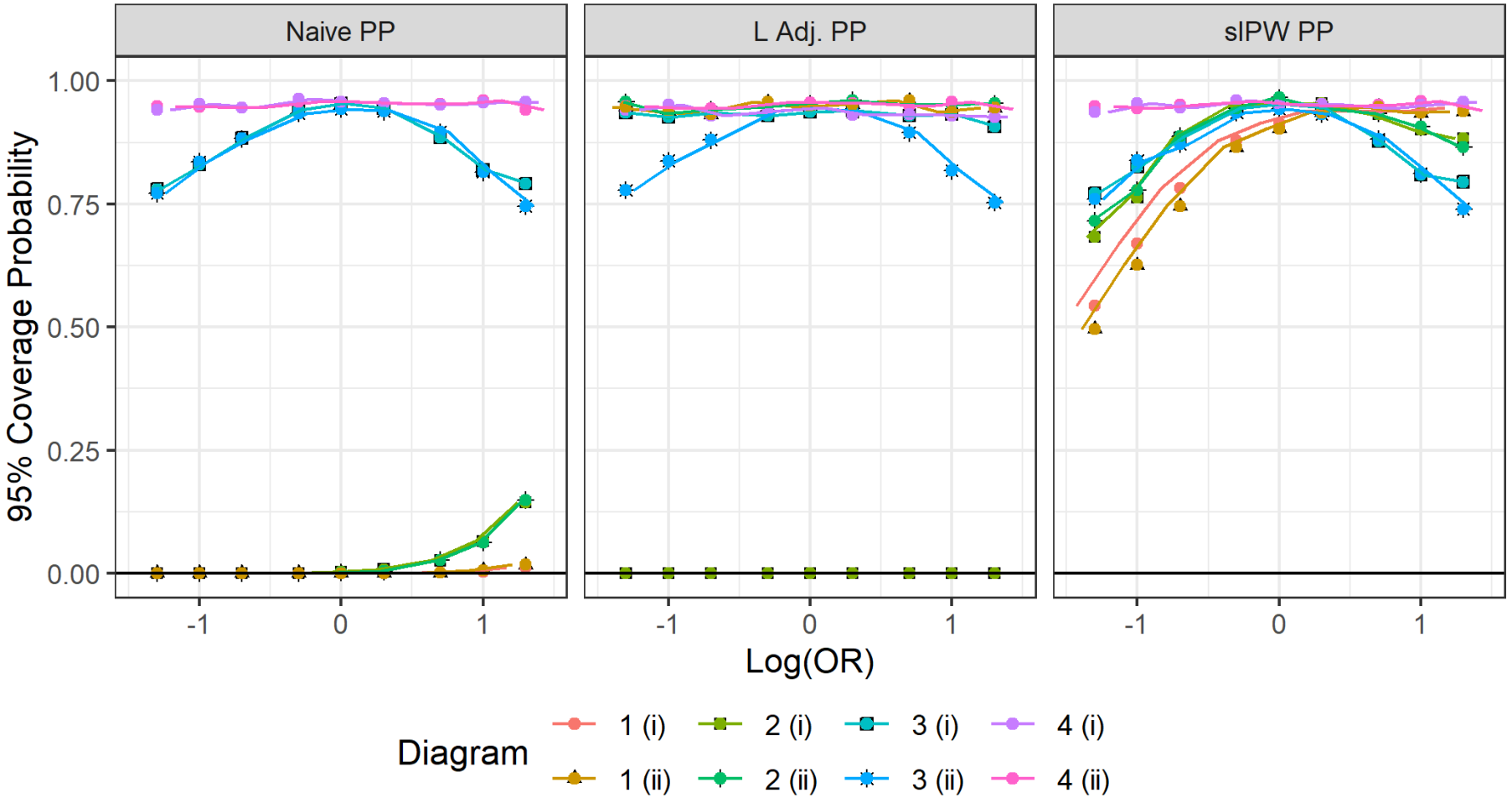
Diagram	(i) A affects subsequent L	(ii) A does not affect subsequent L
Diagram 1: B affects A and Y directly		
Diagram 2: B affects Y directly, but A indirectly via L		
Diagram 3: B affects Y directly, but not A		
Diagram 4: B does not affect Y or A		

Bias for different DAGs

Naive estimates	B is measured	B is not measured

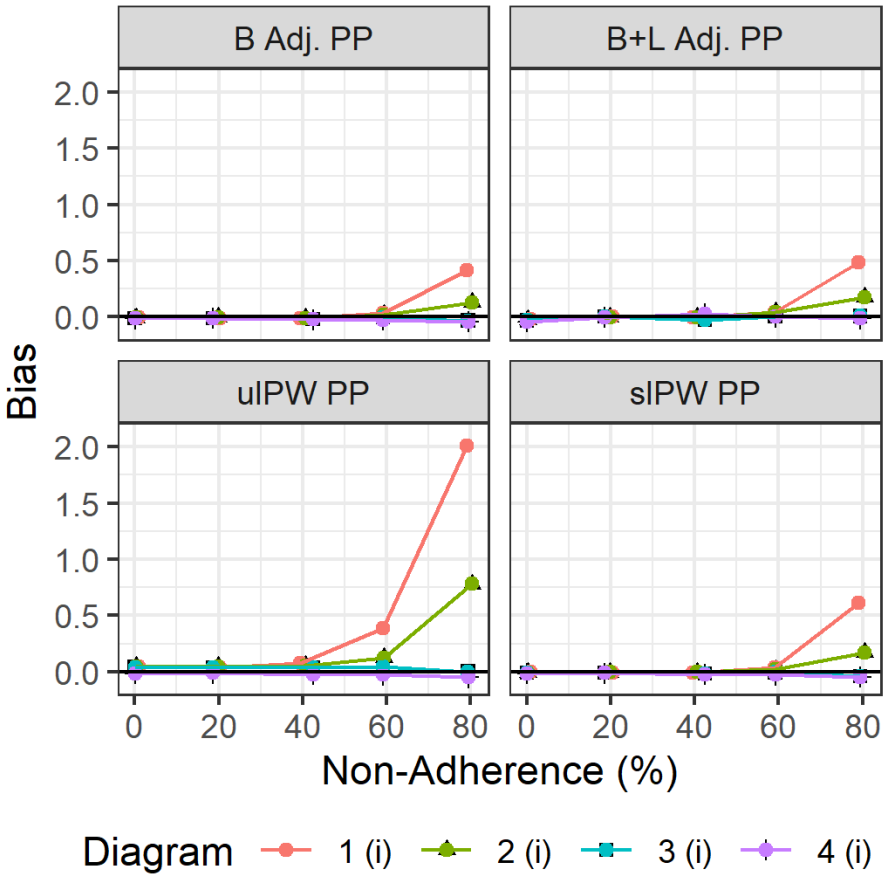


Coverage when B not measured



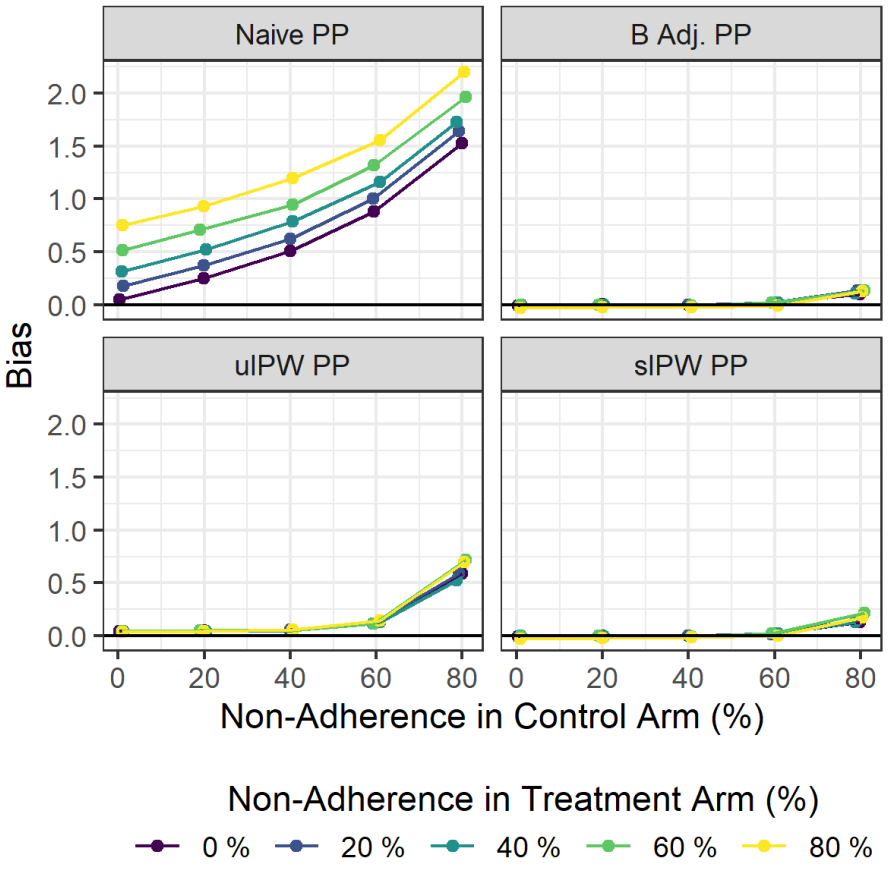
Bias with increasing non-adherence

- same rate of non-adherence in both arms
- B is measured



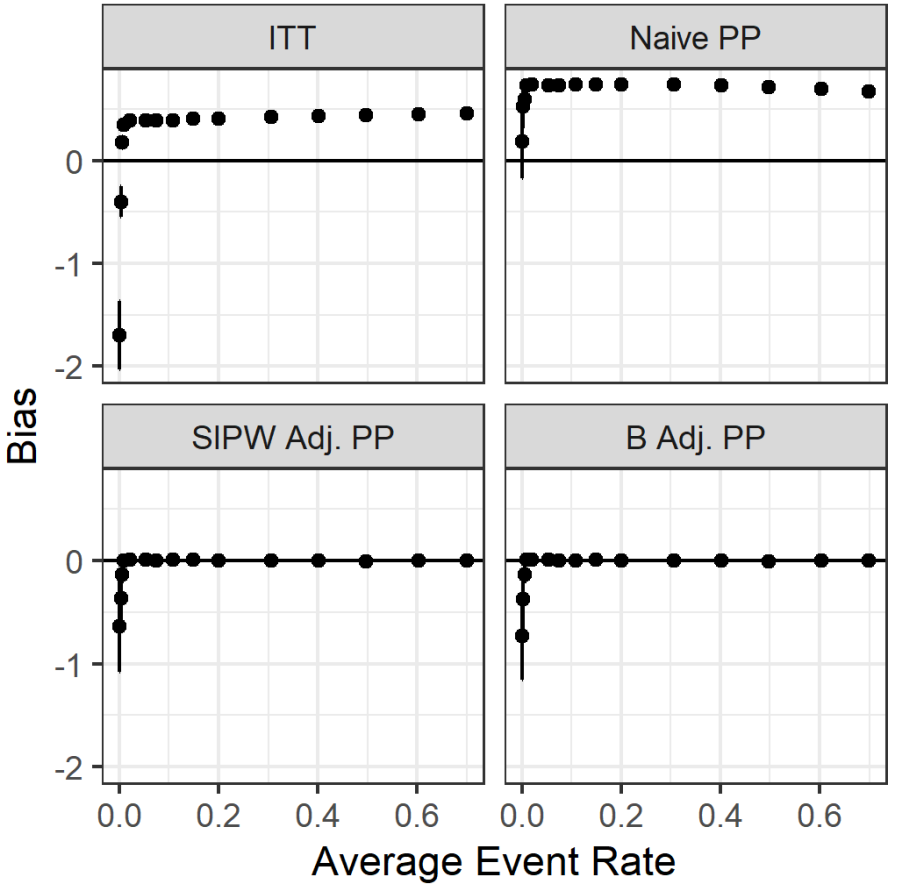
Bias with increasing non-adherence

- Differential non-adherence
- B is measured in DAG 1(i)



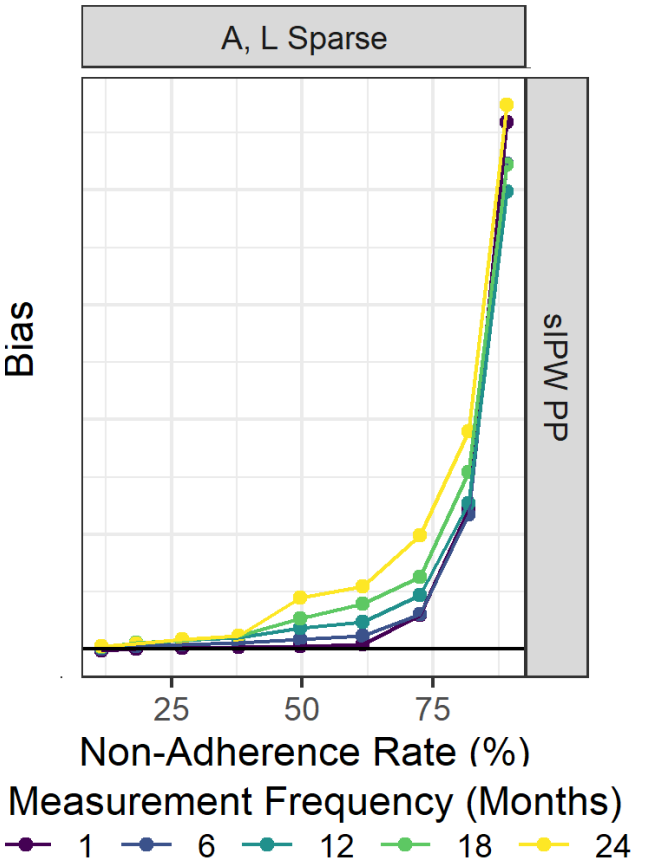
Bias with increasing event rate

- B is measured in DAG 1(i) from model-based estimates
- Cumulative survival based estimates were associated with non-convergence



Bias with decreasing measurement frequency

- B is measured in DAG 1(i)
- A and L imputed with LOCF



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sIPW PP	1.01	0.16-10.52	-0.31	0.29	0.74	0.42-1.29

- true DAG unknown (Somewhat resembles with DAG 1 or 2 (i))
- unknown whether all adherence predicting factors were measured (sIPW)
- finite sample size: 3,550 (over 1000 is OK)
- high non-adherence rate (slightly more biased above 60%)
- differential non-adherence (slightly more biased; same trend)
- low event rate: 7.3% (above 1% was OK for model-based)
- measurement schedule varied (upward bias above 40% n-ad)
- LOCF was used for imputation (variance of most SD < 2)

Recently published follow-up article

Original Research Article

RESEARCH METHODS in MEDICINE & HEALTH SCIENCES

Research Methods in Medicine & Health Sciences
2022, Vol. 0(0) 1–12

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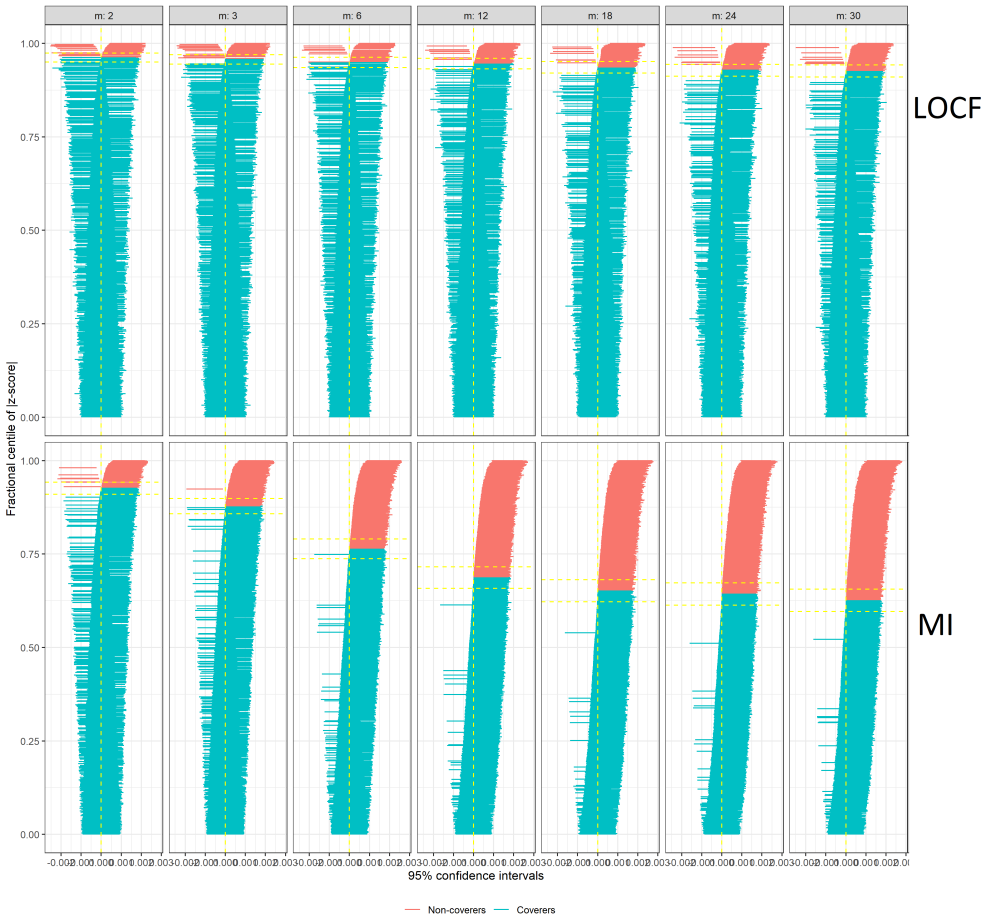
Considerations for choosing an imputation method for addressing sparse measurement issues dictated by the study design - An illustration from per-protocol analysis in pragmatic trials

Mohammad Ehsanul Karim[1,2] and Md Belal Hossain[1]

Coverage with decreasing measurement frequency

- B is measured in DAG 1(i); null effect
- L imputed with LOCF and MI; MCAR



Future works

- Compare different versions of sIPW per-protocol estimates:
  - interval censored versus 80% cutpoint
- Double robust version to address model mis-specification
  - long follow-up is a difficulty

Thanks!

http://ehsank.com/