

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



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Acknowledgement

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

Outline

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

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

Lipid trial

- Time to event outcome (**Y**):
 - coronary heart disease (CHD) death, or
 - or non-fatal myocardial infarction
- Exposure (**A**):
 - cholestyramine or
 - placebo
- Population:
 - people with very high levels of LDL cholesterol,
 - 35-59 years aged,
 - initially free of CHD,
 - recruited between mid-1973 and mid-1976.

Lipid trial

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

Lipid trial

Baseline prognostic factors (B)

1. baseline risk strata (ECG, LDL, smoking etc.),
2. age at randomization,
3. physical activity level at work at baseline,
4. educational status, and
5. race.

Post-randomization prognostic factors (L)

- 38 time-varying covariates

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
- alternate version excludes patients

Conditional Per-protocol (Adj. PP)

- B adjusted PP
- L adjusted PP
- B + L adjusted PP

IPW of (Adherence) Weighted Per-protocol (sIPW PP)

- model-based vs cumulative survival-based
- B and L adjusted in stab. IPWs (address artificially censoring)
- B adjusted in weighted outcome model
- 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

- 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

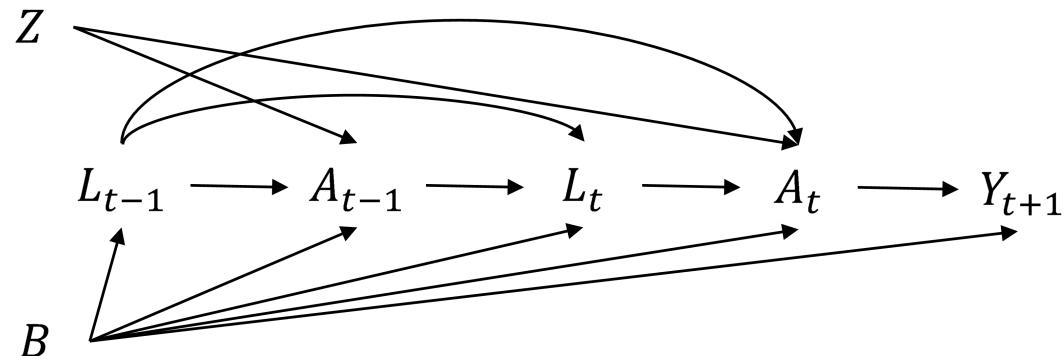
Literature search about IPW

- **Robins and Finkelstein (2000):**
 - asymptotic consistent 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,
 - differing measurement schedule, varying confounding

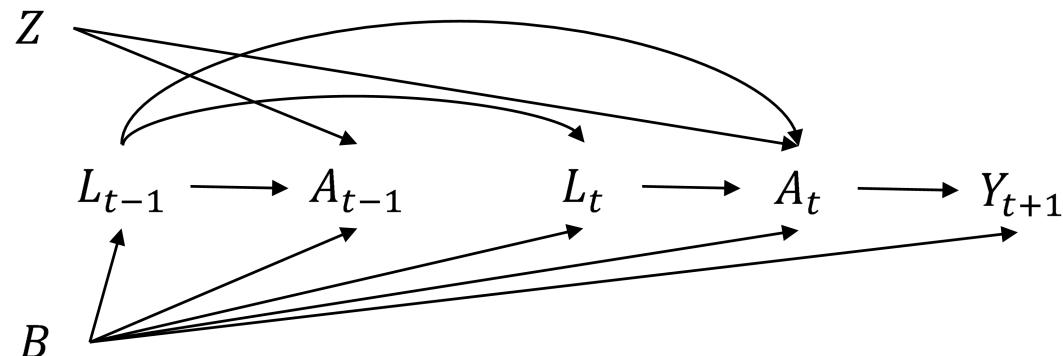
New Simulations

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

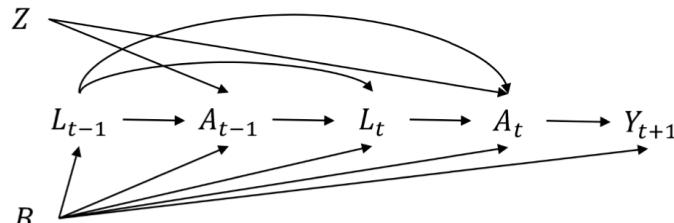


Diagram 2: B affects Y directly, but A indirectly via L

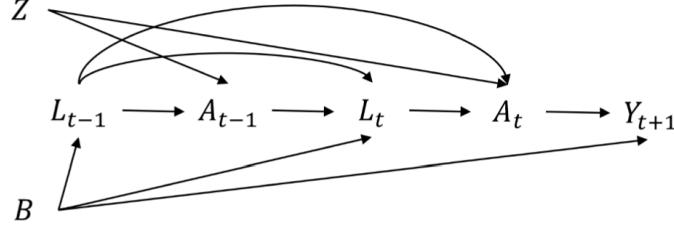


Diagram 3: B affects Y directly, but not A

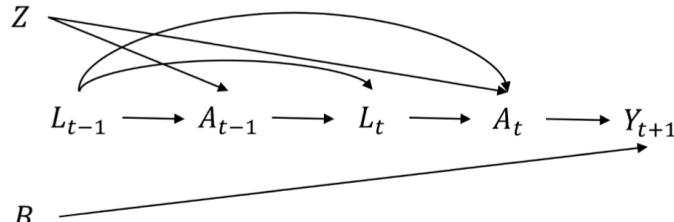
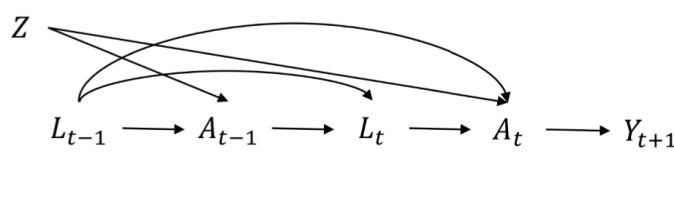
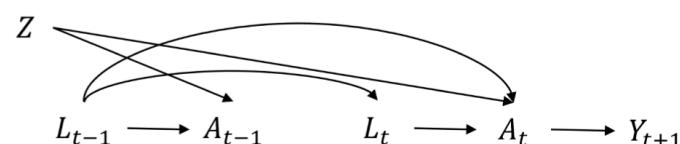
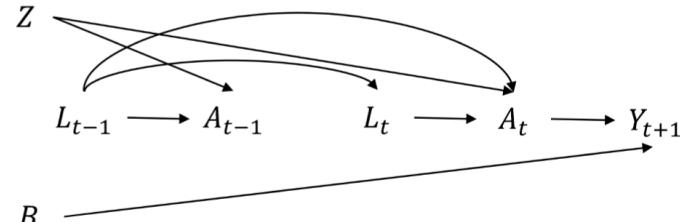
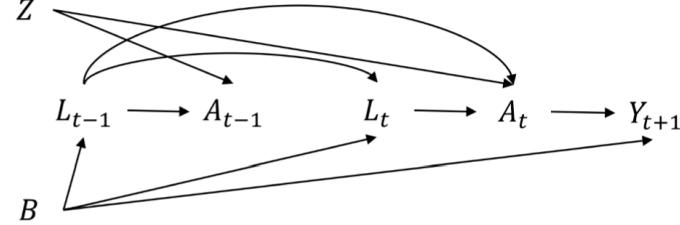
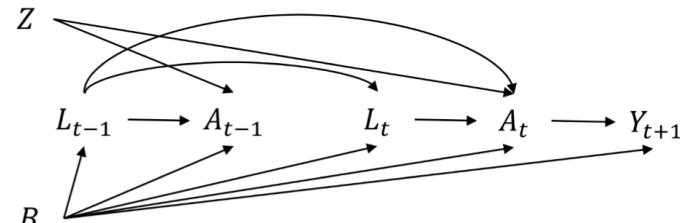


Diagram 4: B does not affect Y or A



B



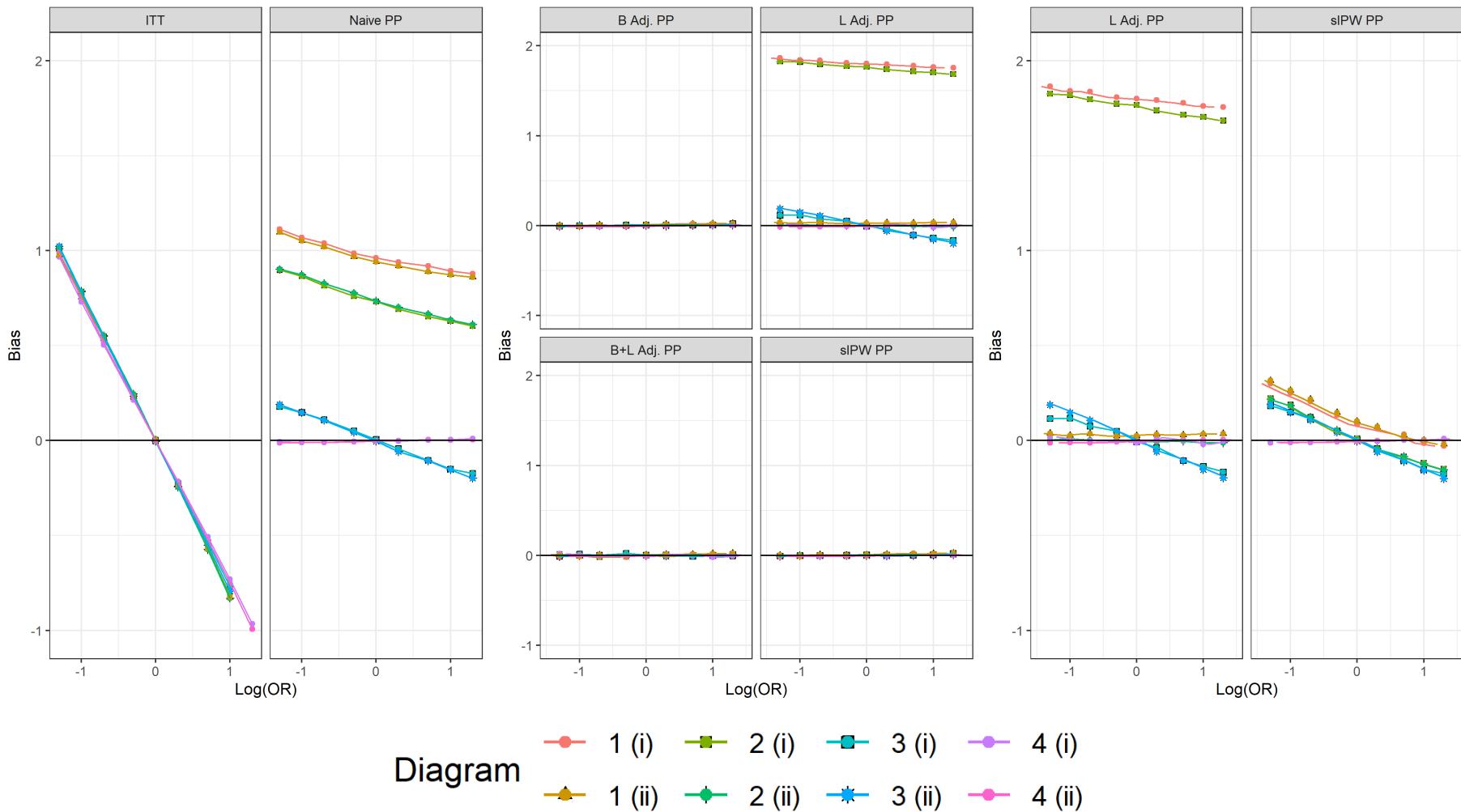
B

Bias for different DAGs

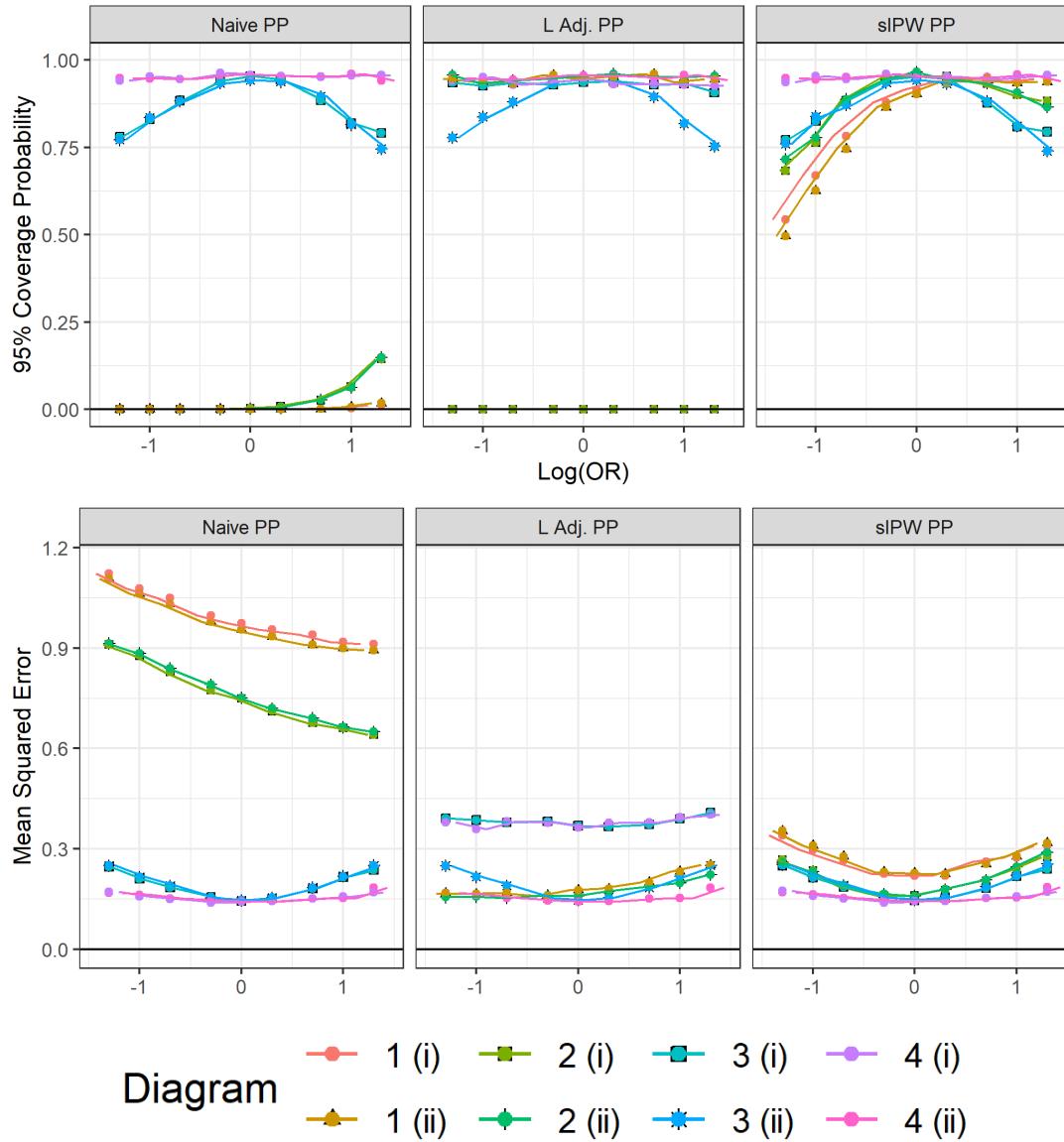
Naive estimates

B is measured

B is not measured

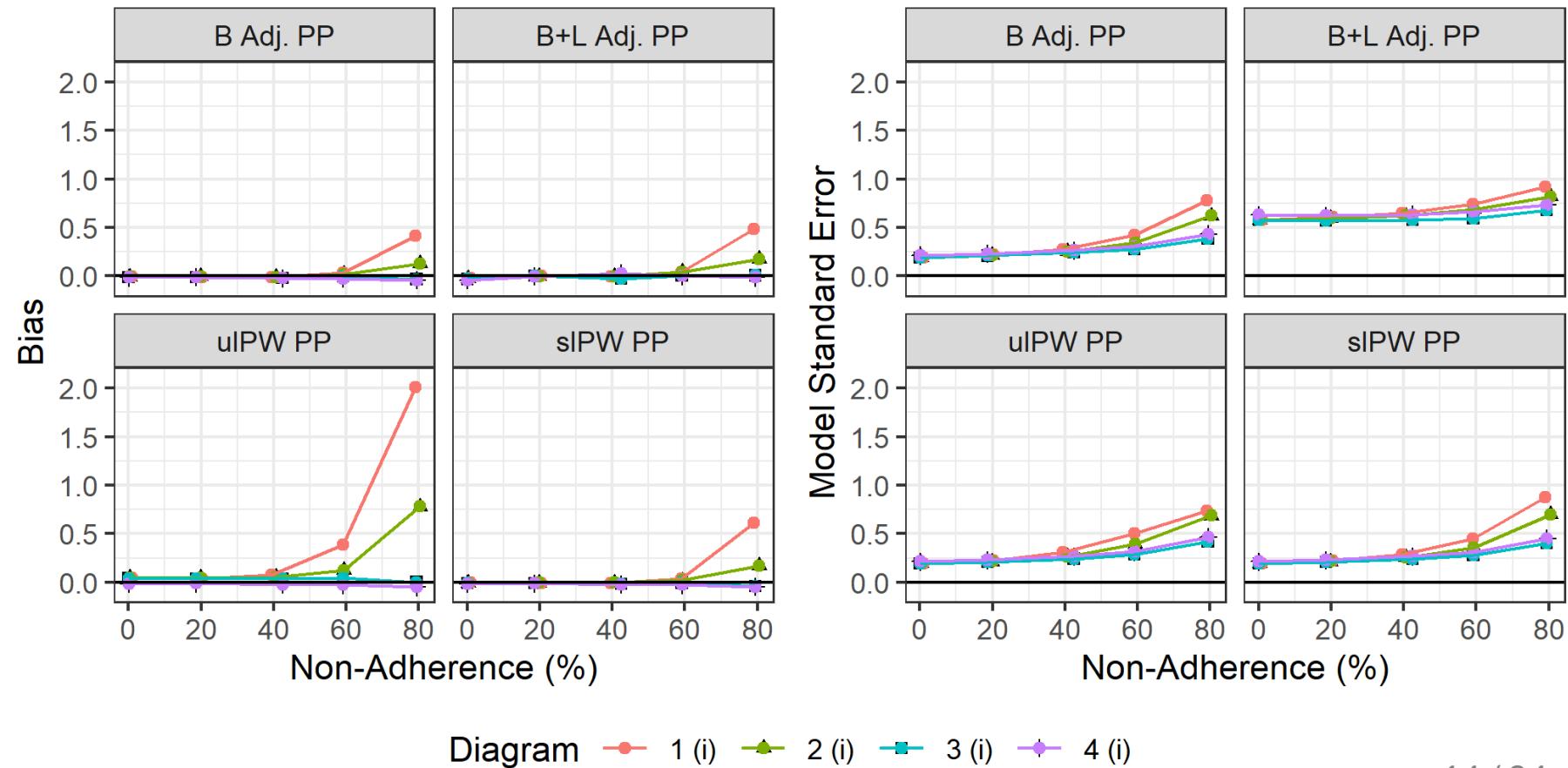


Coverage and MSE when B not measured



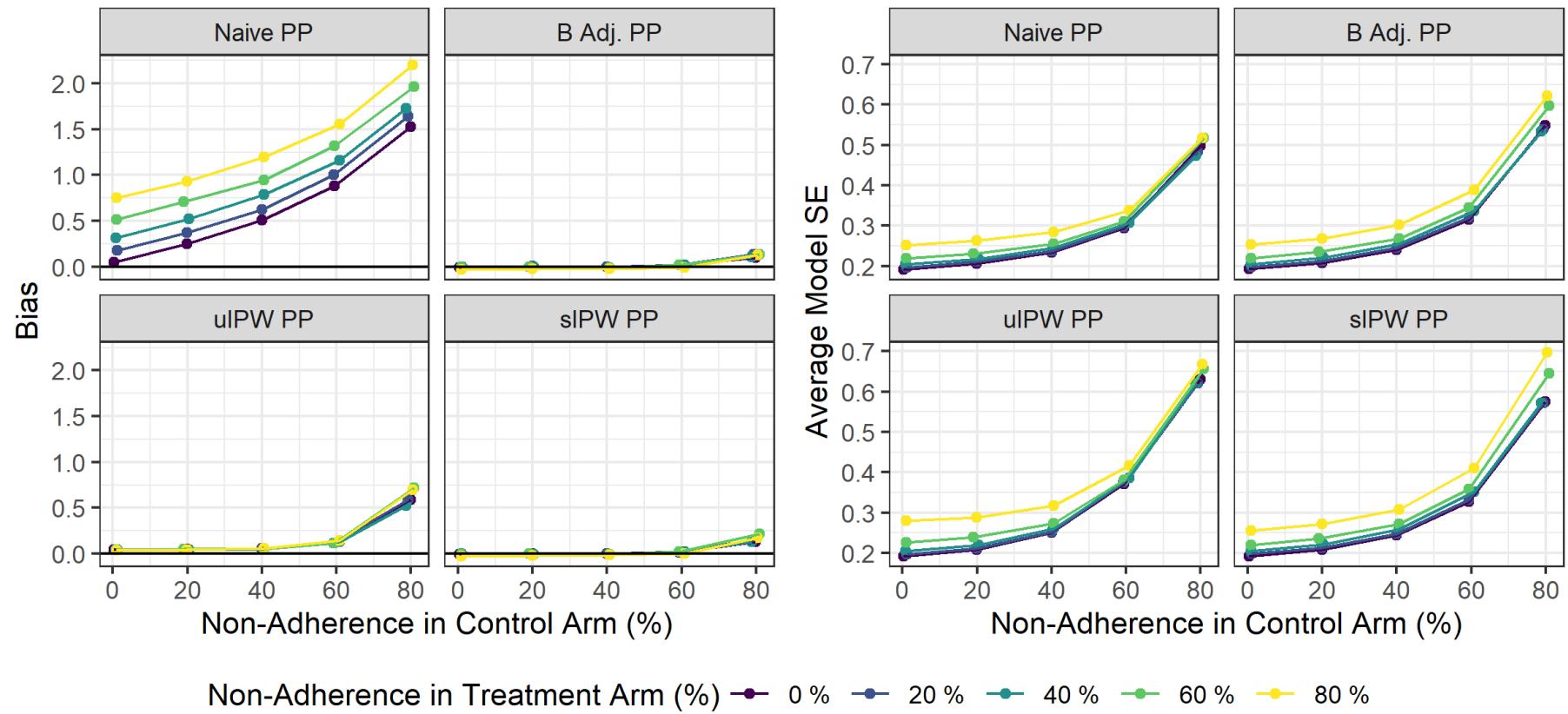
Bias and SE with increasing non-adherence

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



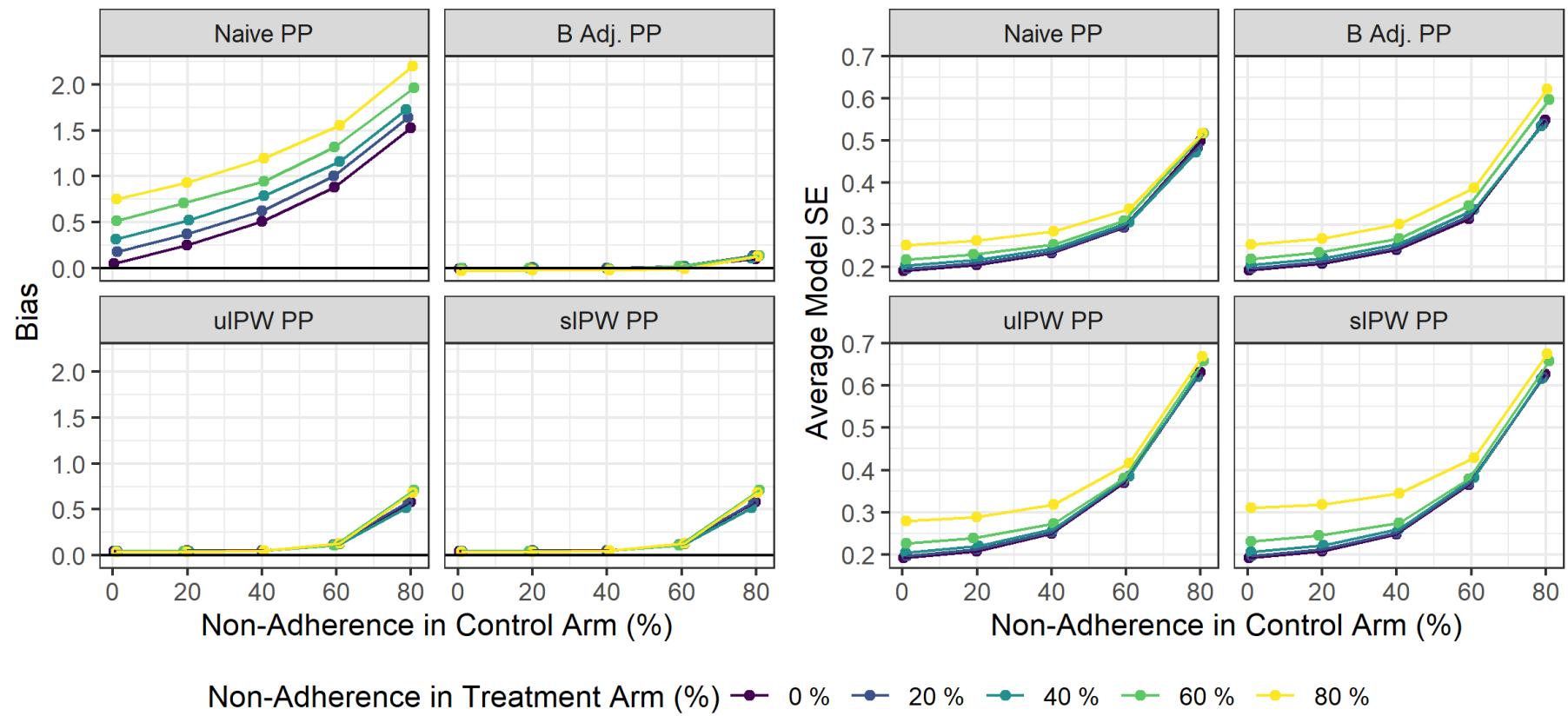
Bias and SE with increasing non-adherence

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



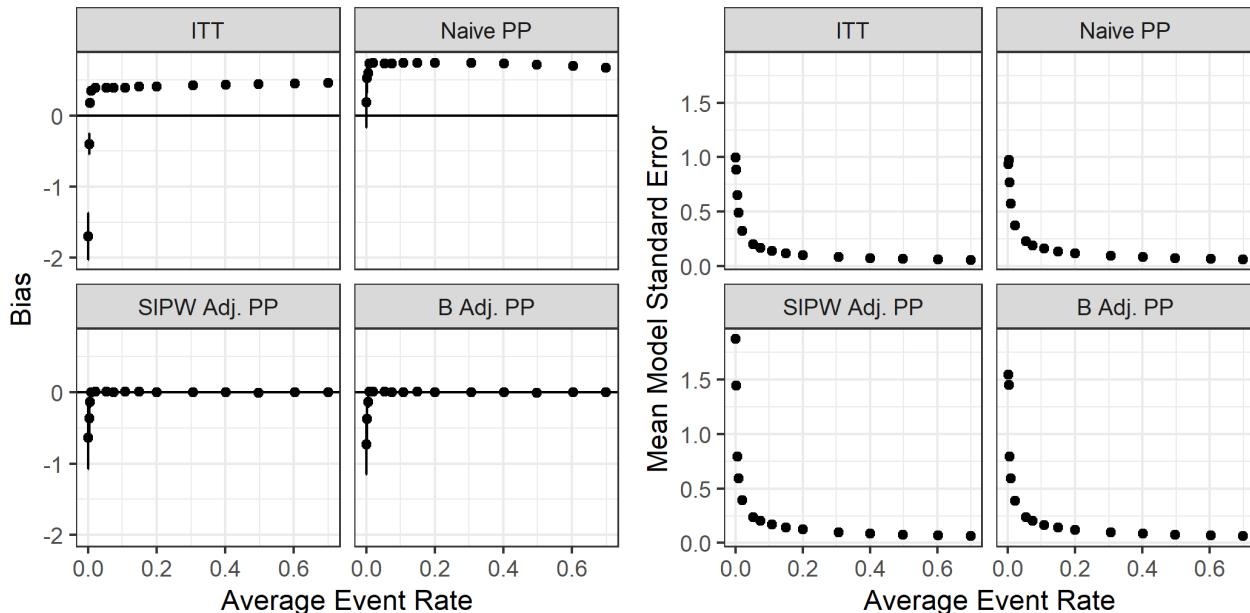
Bias and SE with increasing non-adherence

- Differential non-adherence
- B is not measured in DAG 1(i)



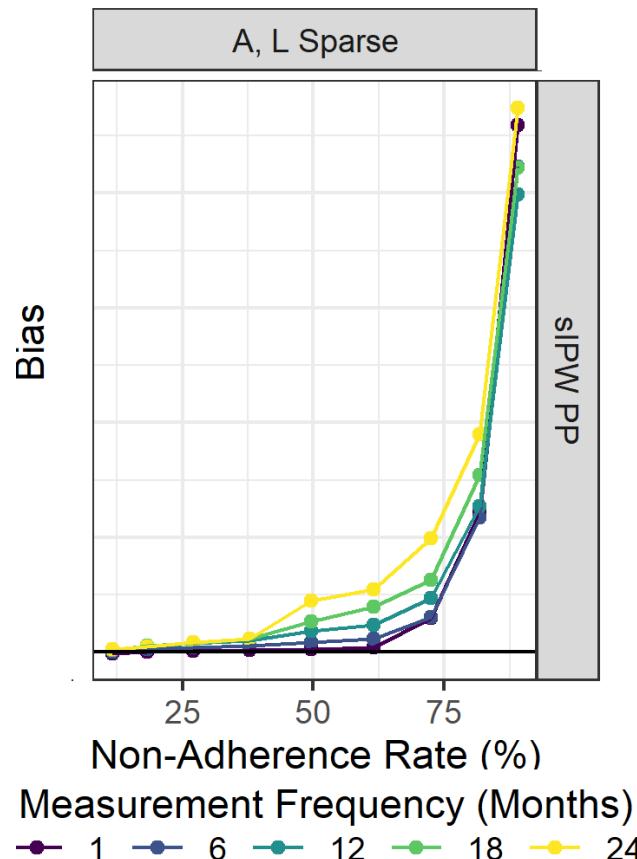
Bias and SE with increasing event rate

- 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



Treatment effect estimates

Method	Weights		Coef. (log(OR))		OR	
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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

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

Research Methods in Medicine & Health Sciences

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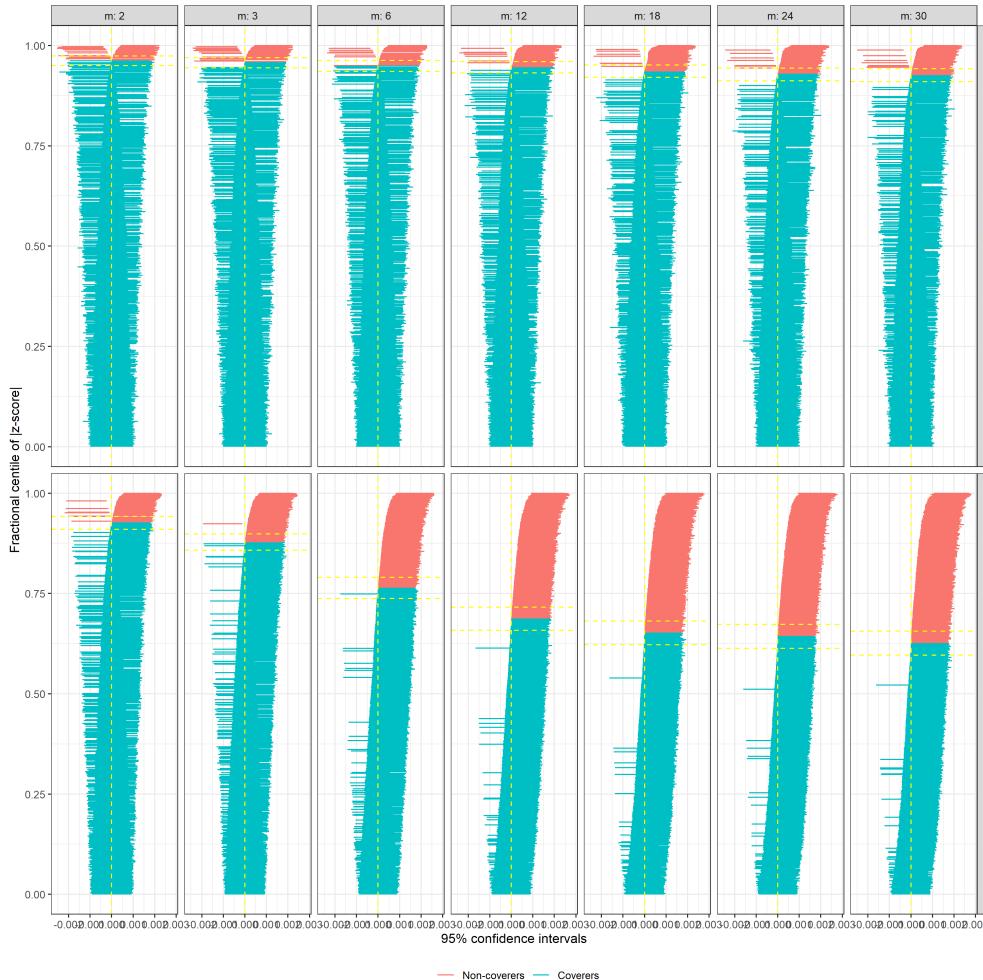
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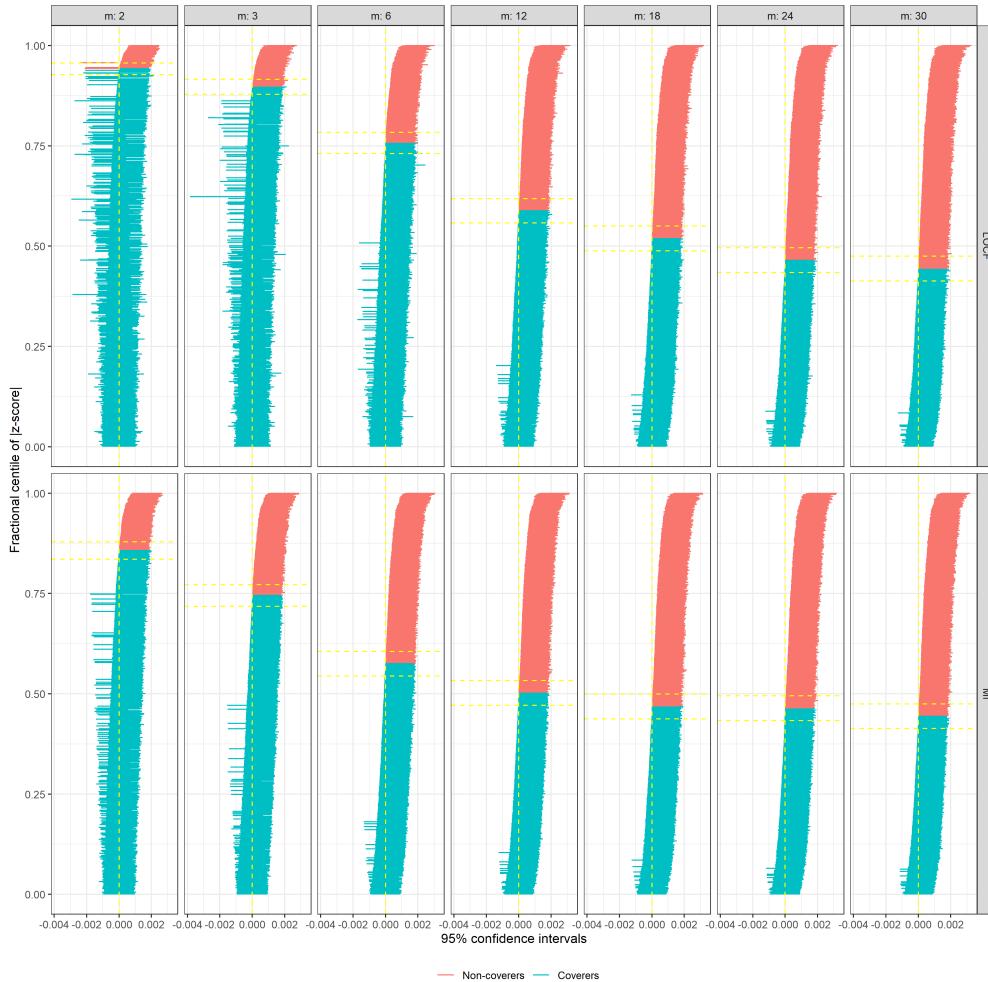
Coverage with decreasing measurement frequency

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



Coverage with decreasing measurement frequency

- B is not measured in DAG 1(i); null effect
- L imputed with LOCF and MI; MCAR



Future works

- Compare sIPW per-protocol estimates:
 - interval censored versus 80% cutpoint
- Double robust version to address model mis-specification

Thanks!

<http://ehsank.com/>