

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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 - BC SUPPORT Unit
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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. Lipid trial

- Adherence adjustment methods
- Understanding Lipid trial results
- Literature

2. Simulation and results

3. Interpreting Lipid trial results

4. Follow-up work and future directions

Lipid trial

- Time to event outcome:
 - coronary heart disease (CHD) death or
 - non-fatal myocardial infarction
- Exposure:
 - 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 treatment regime
- Medication adherence
 - counts of unused medication packets
 - satisfactory adherence as \geq 80%
 - 84.0% in the treatment arm were nonadherent
 - 77.2% in the placebo arm.

Lipid trial

Baseline prognostic factors (B)

- baseline risk strata (ECG, LDL, smoking etc.),
- age at randomization,
- physical activity level at work at baseline,
- educational status, and
- 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

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

- IP Weights adjust for bias introduced by artificially censoring
- L adjusted in IP weights
- 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%
- measurement schedule varied
- LOCF was used for imputation

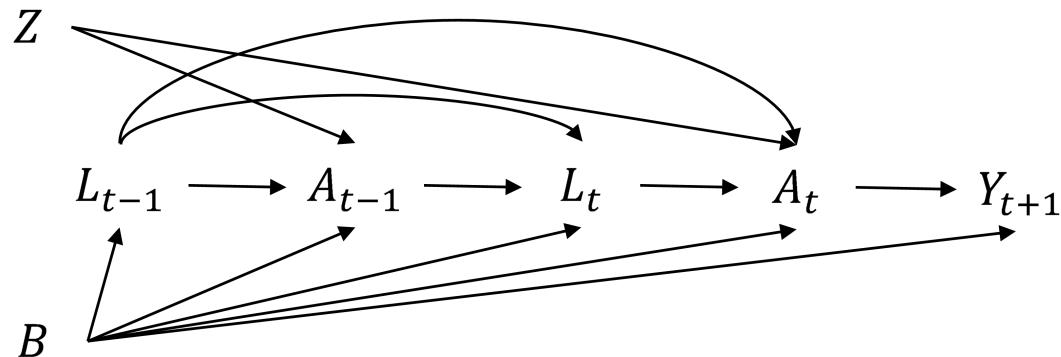
Literature search about IPW

- 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

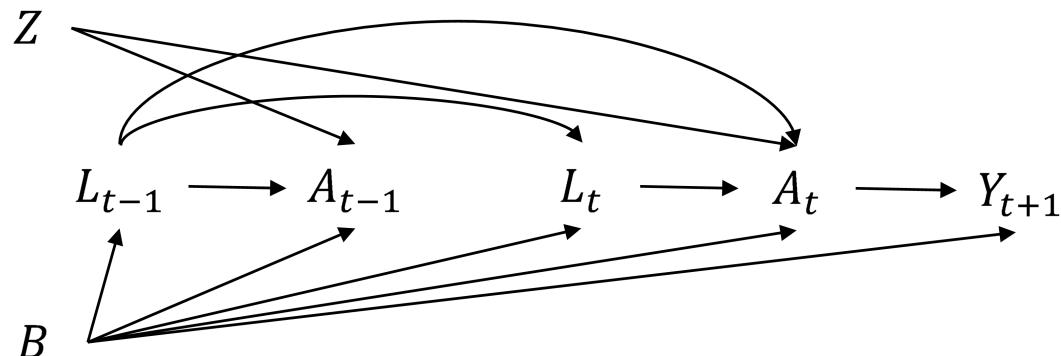
New Simulations

B affects A and Y directly:

Diag 1(i): A affects subsequent L



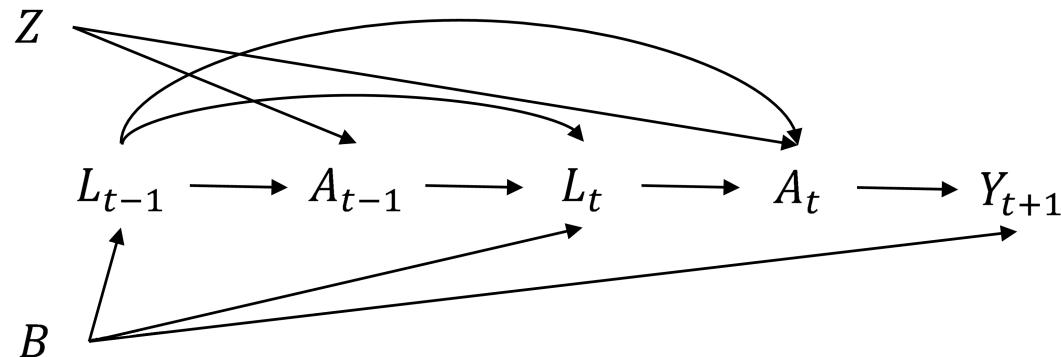
Diag 1(ii): A does not affect subsequent L



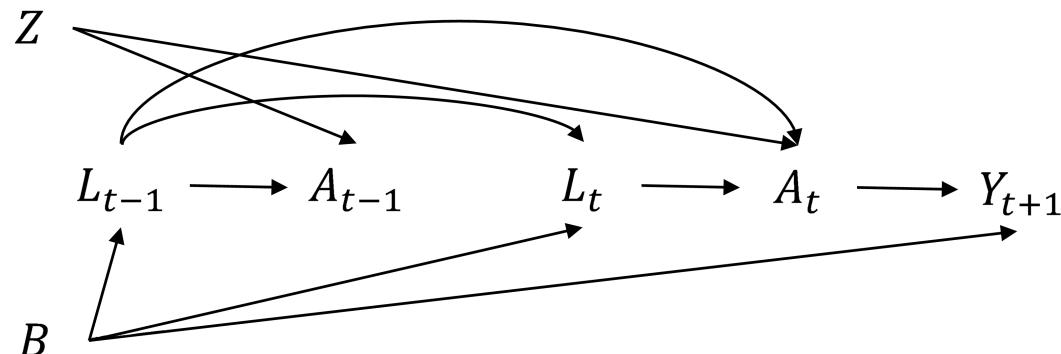
New Simulations

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

Diag 2(i): A affects subsequent L



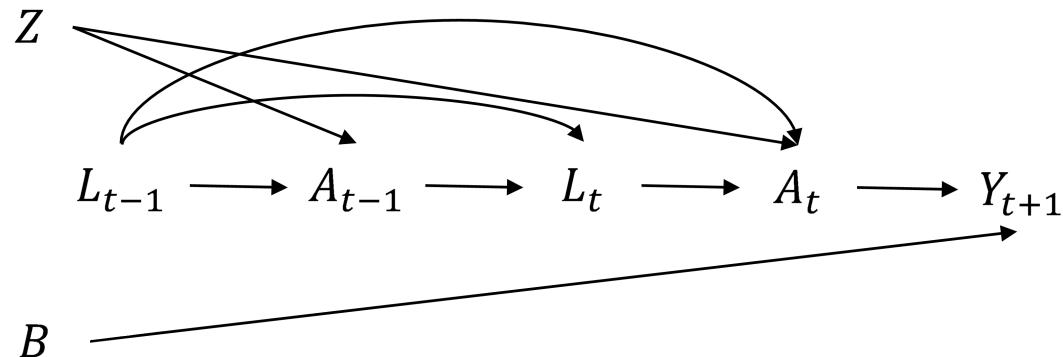
Diag 2(ii): A does not affect subsequent L



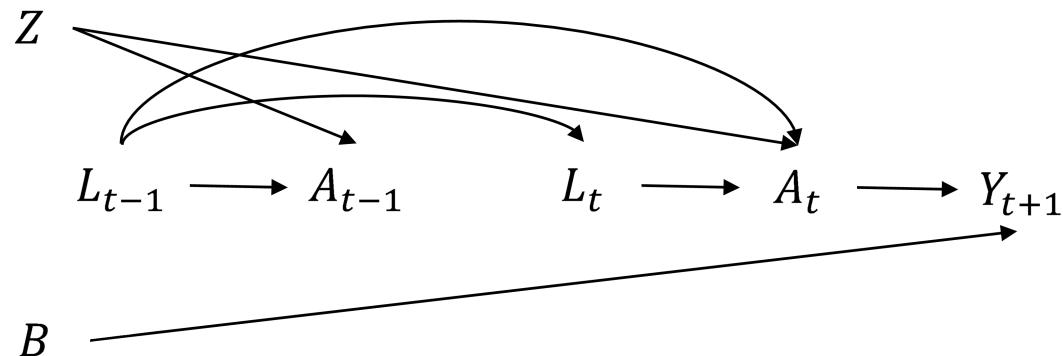
New Simulations

B affects A and Y directly, but not L:

Diag 3(i): A affects subsequent L



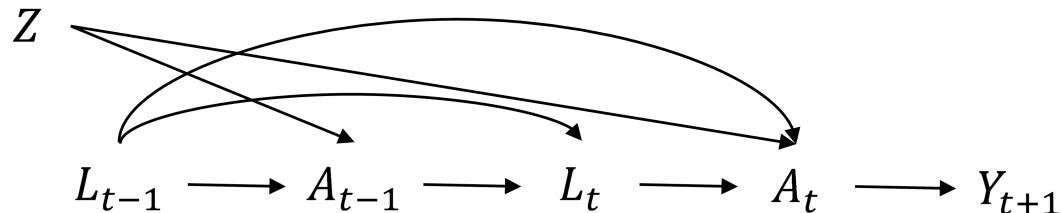
Diag 3(ii): A does not affect subsequent L



New Simulations

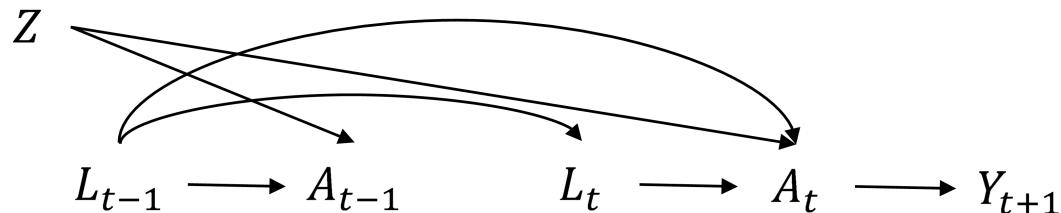
B does not affect A or Y:

Diag 4(i): A affects subsequent L



B

Diag 4(ii): A does not affect subsequent L



B

All 8 DAGs

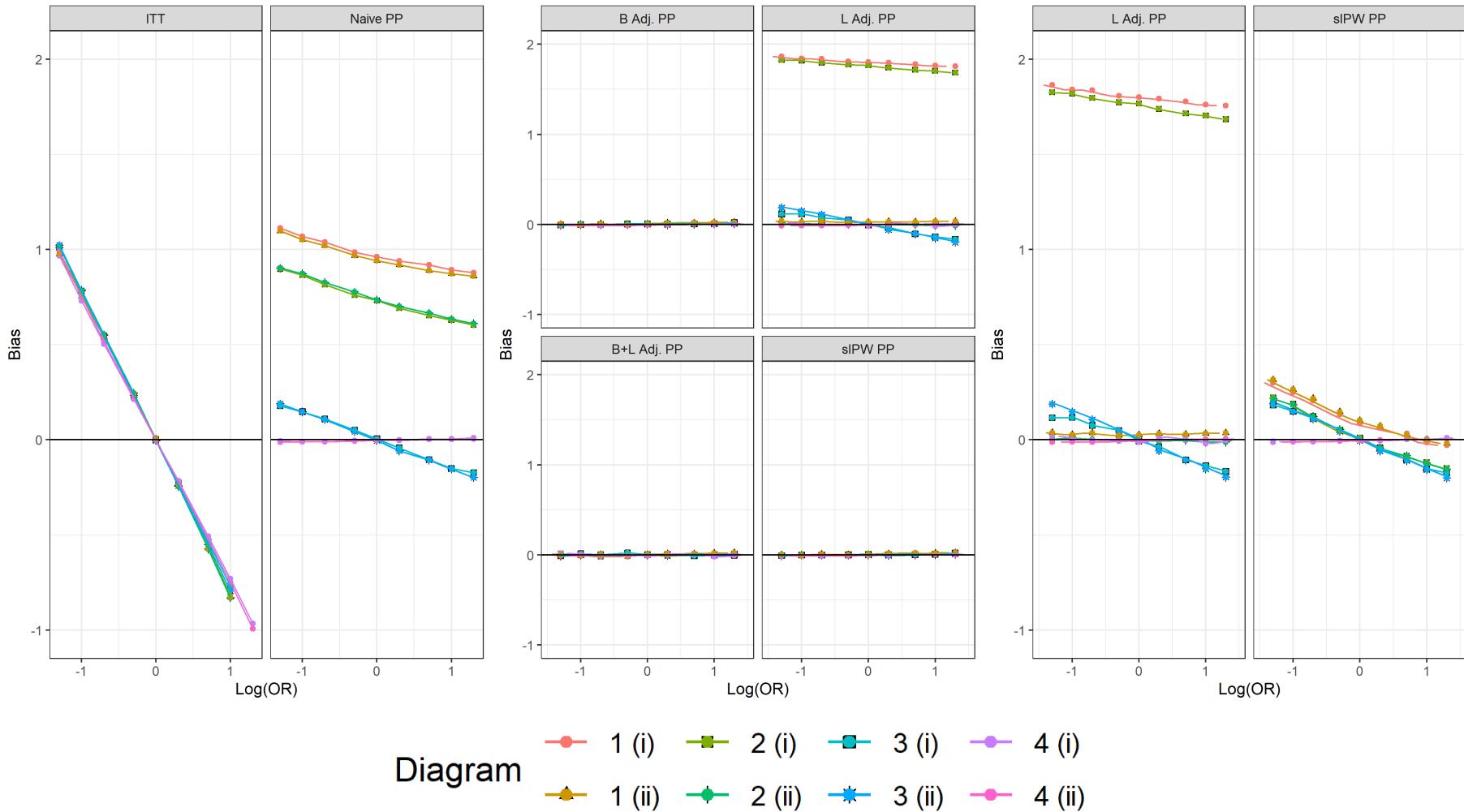
Diagram	(i) A affects subsequent L	(ii) A does not affect subsequent L
Diagram 1: B affects A and Y directly		
Diagram 2: B affects Y directly, but A indirectly via L		
Diagram 3: B affects Y directly, but not A		
Diagram 4: B does not affect Y or A		

Bias for different DAGs

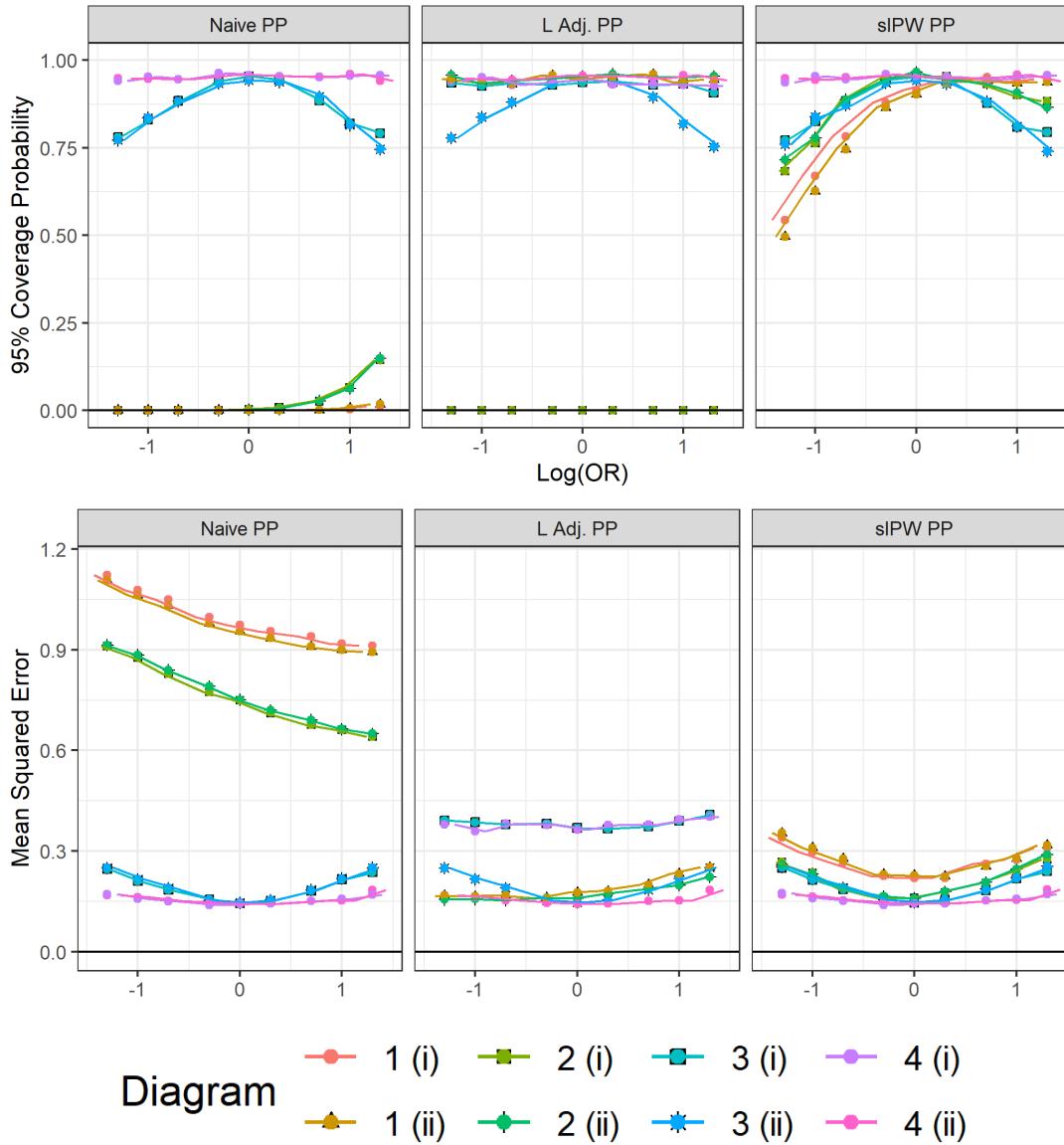
Naive estimates

B is measured

B is not measured

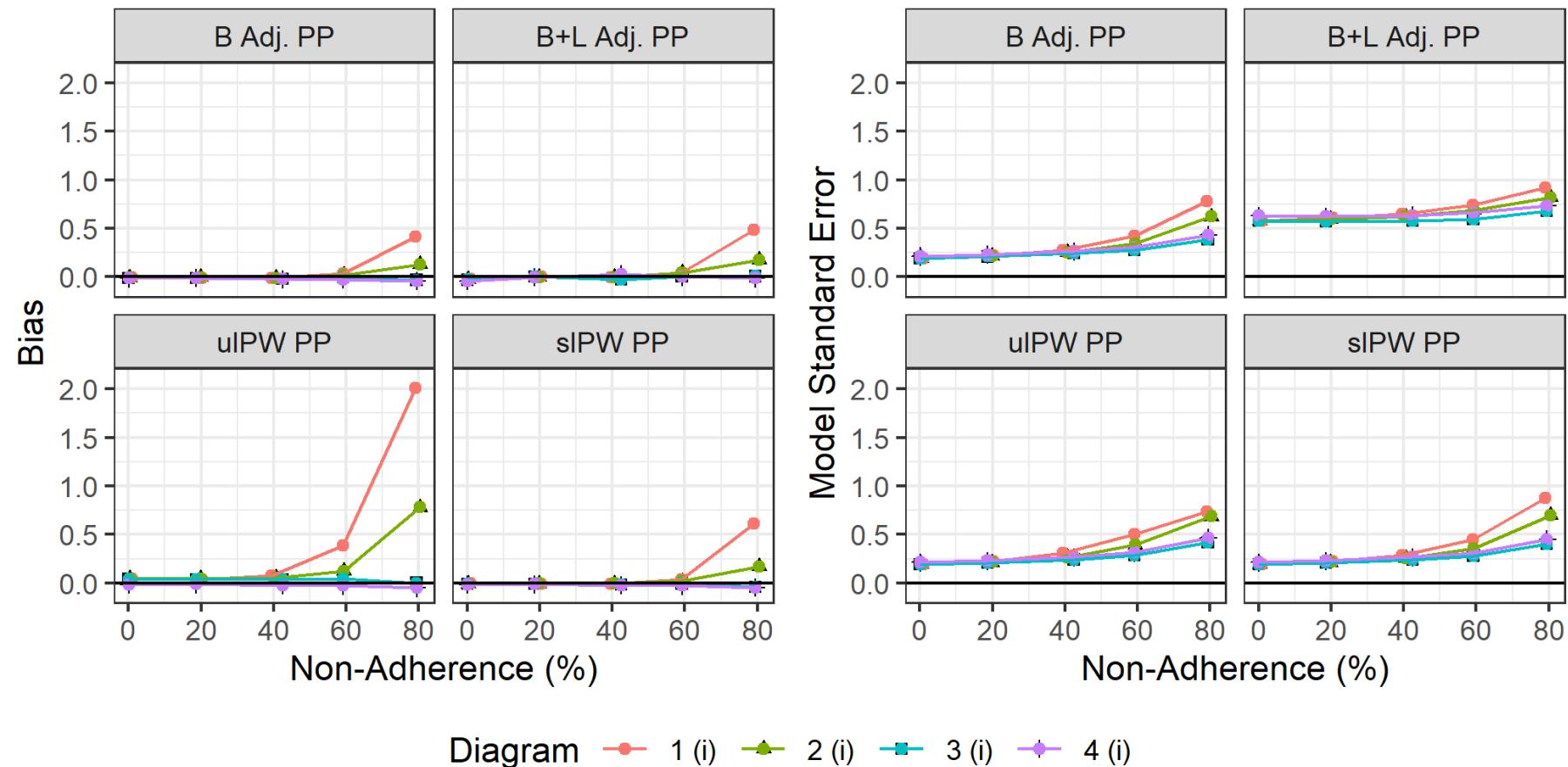


Coverage and MSE when B not measured



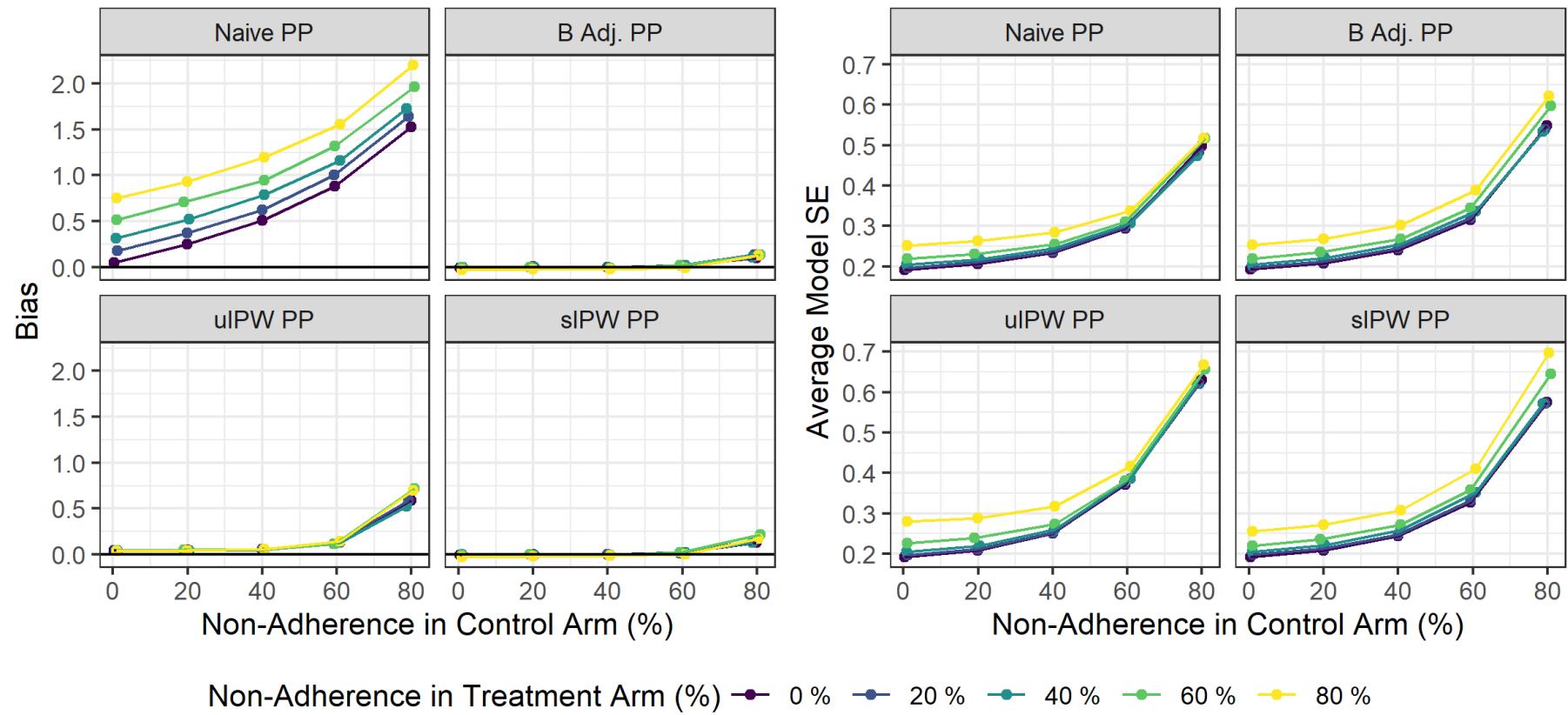
Bias and SE with increasing non-adherence

B is measured in DAG 1(i)



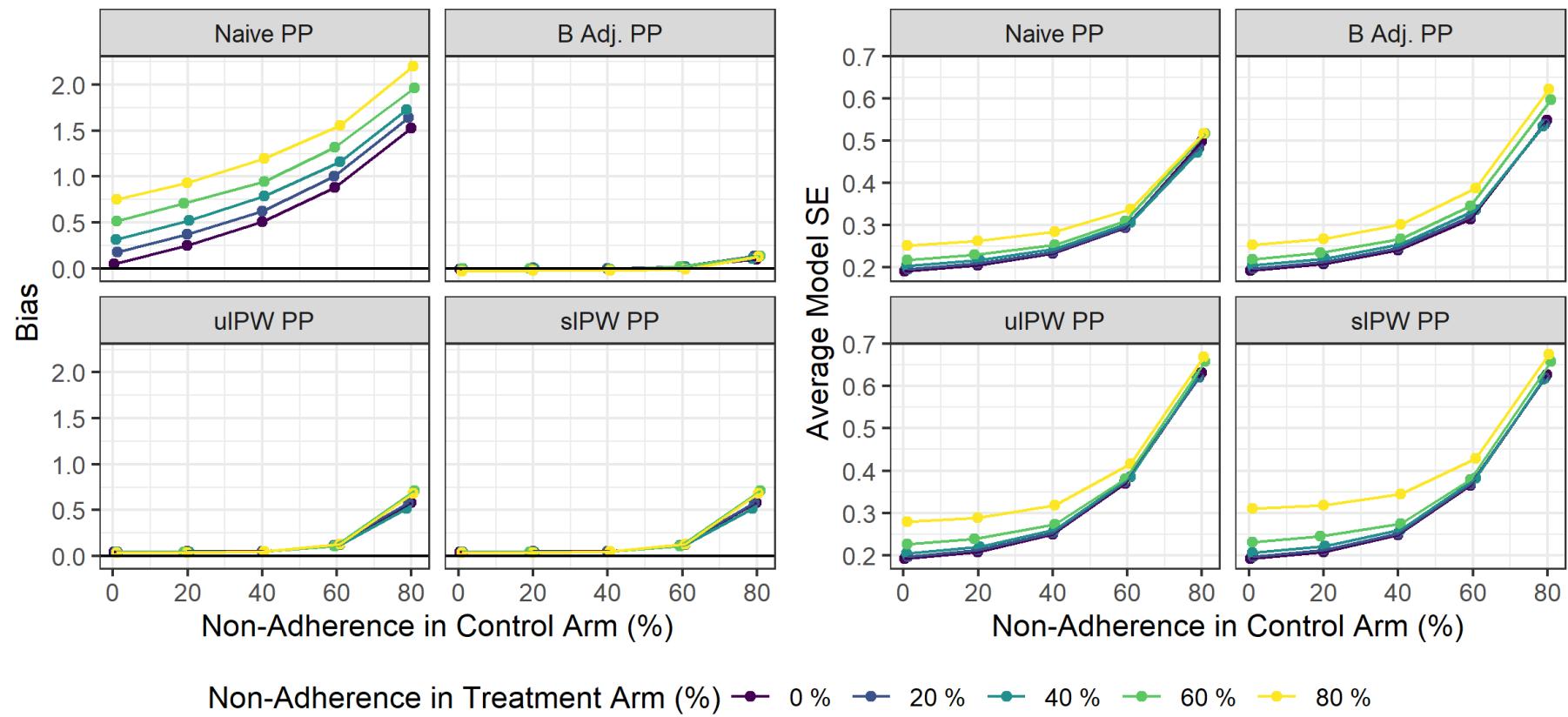
Bias and SE with increasing non-adherence

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



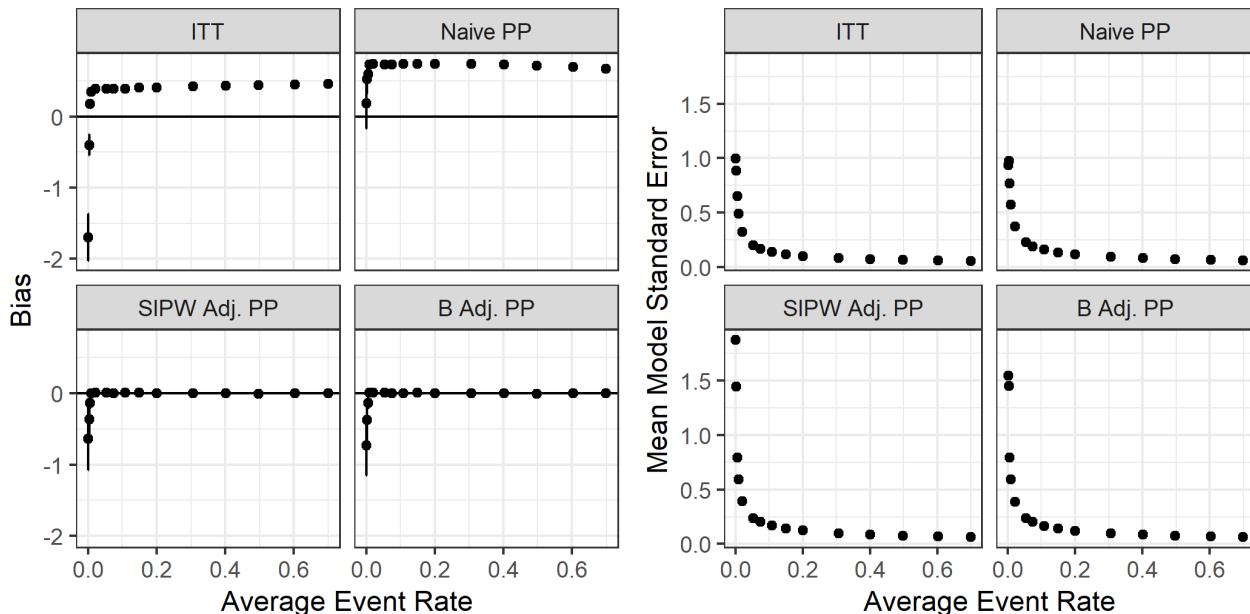
Bias and SE with increasing non-adherence

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



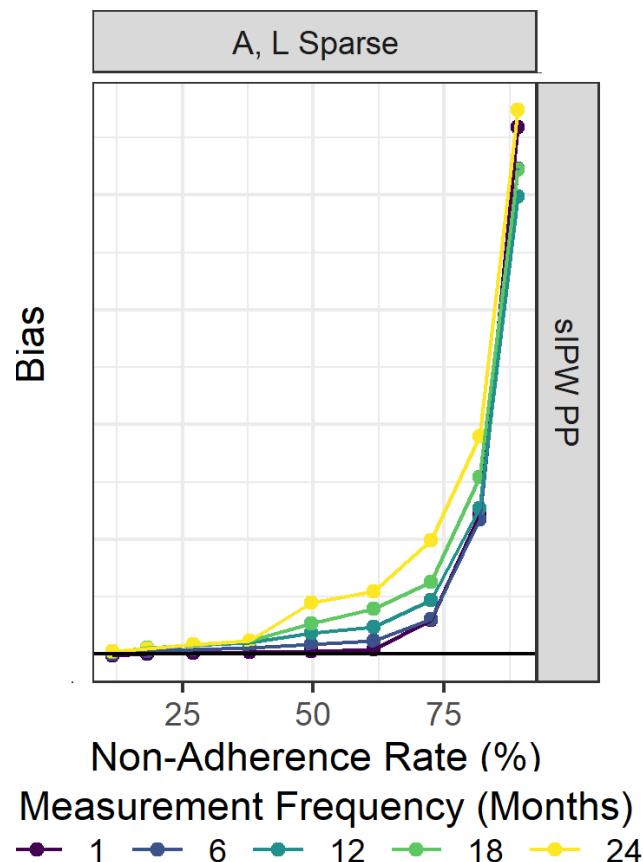
Bias and SE with increasing event rate

- 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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ITT			-0.16	0.13	0.85	0.66-1.09
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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 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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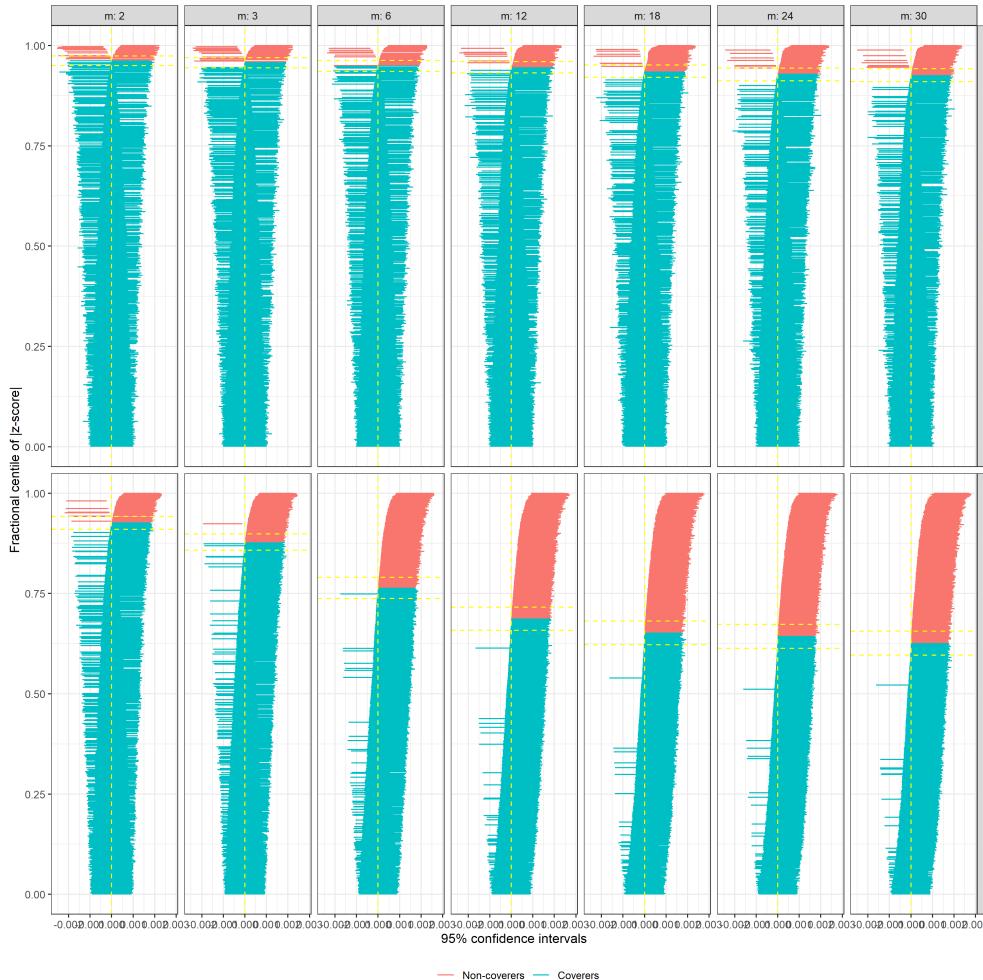
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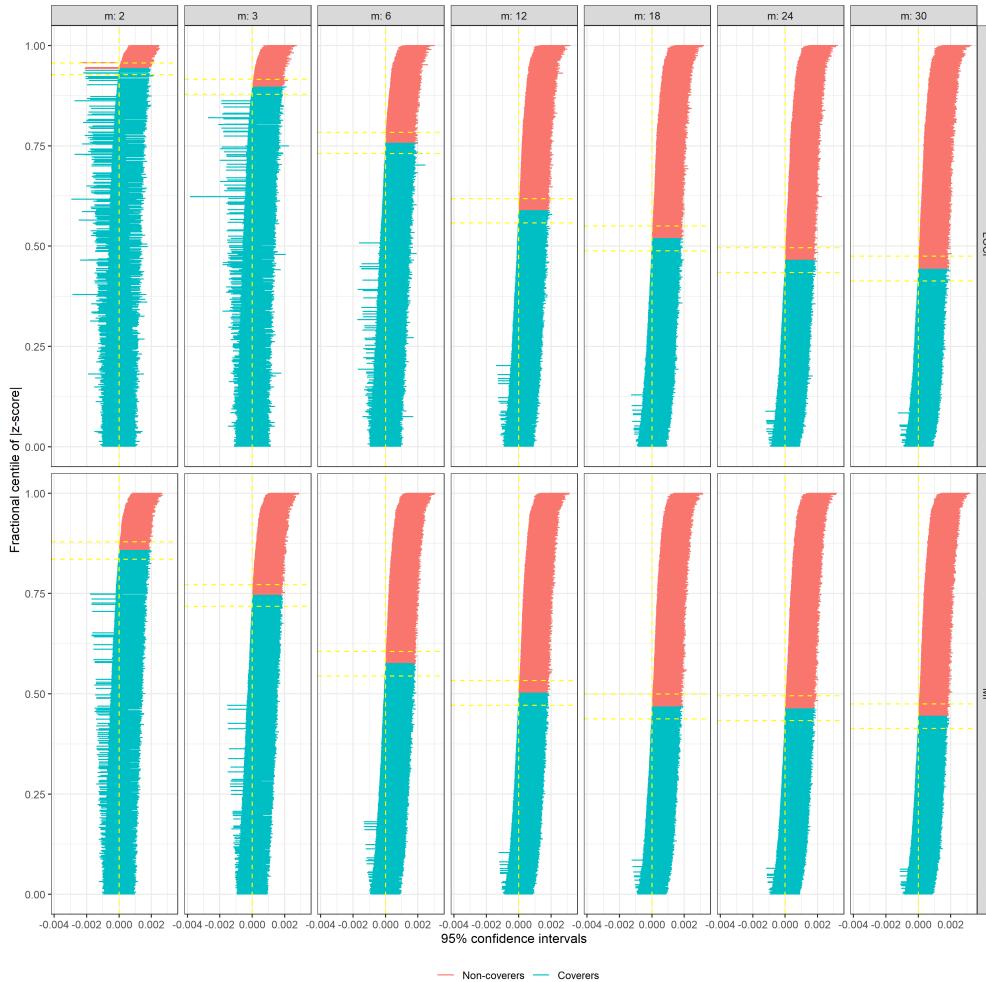
Coverage with decreasing measurement frequency

- 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/>