Adjusting for Selection Bias Due to Missing Eligibility Criteria in Emulated Target Trials

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Joint Statistical Meetings 2024
August 6, 2024

Challenges of Observational Studies

- Randomized control trials (RCT) are the gold standard for answering questions about comparative effectiveness.
  - Not always feasible ($$$, ethics, etc.)
- Challenges in observational studies:
  - Treatment not random (**confounding**)
  - Not always clear when to start follow-up time (**immortal time bias**)
  - Missing data, non-adherence, loss to follow-up (**selection bias**)
  - Misclassification of treatment and/or outcomes (**measurement error**)

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  - Missing data, non-adherence, loss to follow-up (**selection bias**)
  - Misclassification of treatment and/or outcomes (**measurement error**)
- To help researchers think through some of these challenges, (Hernán and Robins, 2016) introduce target trial emulation (TTE) framework
  - Specify protocol of an ideal RCT to answer the question of interest and then aligning observational emulation as closely as process.

Target Trial Emulation

Table 1 | Specification and emulation of a target trial of statin therapy and cancer risk using CALIBER observational data

Protocol component	Target trial specification	Target trial emulation
Eligibility criteria	Age ≥30, between 1 January 1998 and 29 February 2016 No history of cancer (except non-melanoma skin cancer) No statin contraindication (hepatic impairment or myopathy) No statin prescription within the past year LDL cholesterol <5 mmol L^{-1} At least 1 yr of up-to-standard data in a CPRD practice At least 1 yr of potential follow-up Baseline is defined as the first month in which all eligibility criteria are met	Same as for the target trial We defined hepatic impairment as a code for hepatic failure or ALT ≥120 IU L^{-1}, and myopathy as codes for its symptoms: muscle aches, pain or weakness We also required information on lab values measured during the past year and on lifestyle factors during the past 4 yr

Table 1. Protocol of the Target Trial to Study Adjuvant Fluorouracil-Based Chemotherapy in Stage II Colorectal Cancer and Emulation Procedure Using the SEER-Medicare Database

Protocol Component	Description of Target Trial	Description of Emulation Using SEER-Medicare Data
Eligibility criteria	• Histologic diagnosis of stage II colorectal cancer (node negative) between 2008 and 2012 • Aged into Medicare and was continuously enrolled in Parts A and B and not enrolled in an HMO for 12 mo before diagnosis • Evidence of complete resection of colon or rectal cancer • No history of cancer except nonmelanoma skin cancer • No prior chemotherapy	Same as target trial

Figure: Example "side by side" protocol components from (Dickerman et al., 2019) and (Petito et al., 2020) TTE studies, with eligibility criteria listed first.

DURABLE Electronic Health Record Database

- Database from Kaiser Permanente system designed to study long-term effects of bariatric surgery, often in comparison to **no treatment**.
- Over 45,000 bariatric surgical patients and 1.64 million non-surgical patients who in theory were plausible candidates for bariatric surgery at some time (BMI ≥ 35 kg/m^2) between 1997-2015.
  - Study eligibility not necessarily the same as treatment eligibility
  - Study eligibility criteria may include a BMI cutoff (≥ 35 kg/m^2)
  - Certain target trials may be interested in additional eligibility criteria (eg. diabetic population)
  - Study eligibility status can vary over time

Sequential Target Trial Emulation

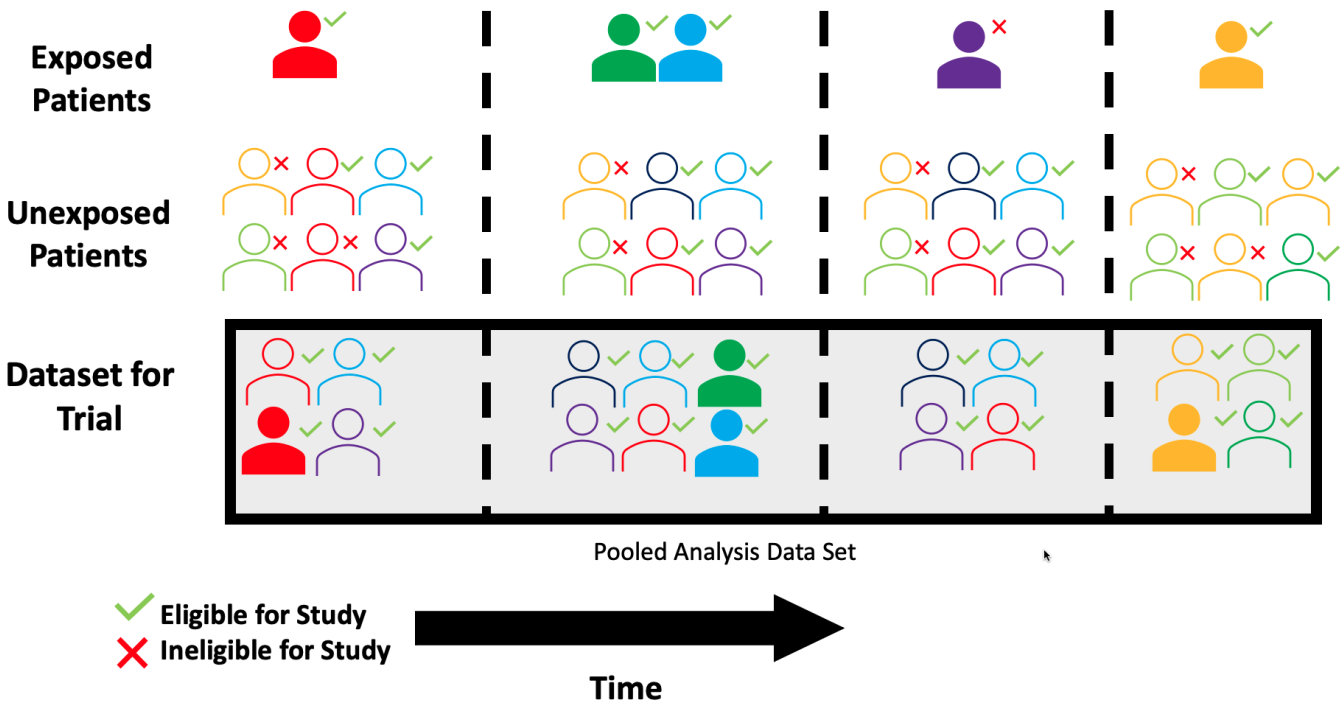

Figure: Sequential Target Trial Emulation

- When do we start follow-up time for subjects under "no treatment"?
- Could pick some fixed time as time-zero for everyone, $\rightarrow$ valid way to avoid immortal time bias
- Initiation of bariatric surgery at any fixed time is rare $\rightarrow$ low power
- Repeat this process over a sequence of fixed time (eg. one trial beginning every calendar month) and pool trials for increased power

The Problem: Missing Data in Eligibility Criteria

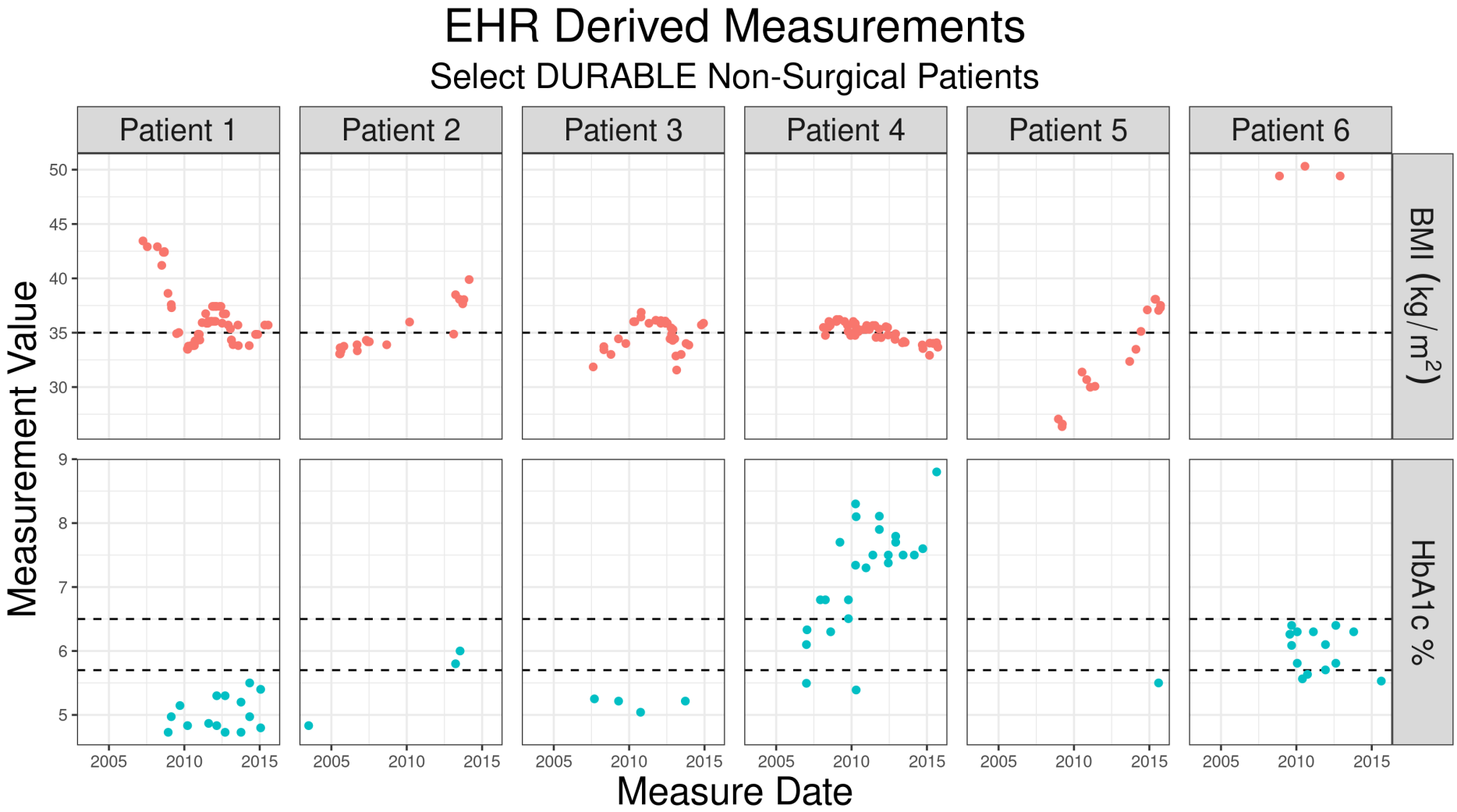

Figure: EHR Derived Information for 6 Non-Surgical Patients in DURABLE

Notational Framework

- Subject $k \in \{1, ..., K\}$
- Trials $m \in \{1, ..., M\}$
- A_{mk} binary point exposure at baseline of trial m for subject k
- E_{mk} binary eligibility indicator that subject k is eligible for trial m
- R_{mk} binary indicator for eligibility ascertainment
- $\boldsymbol{L}_{mk}$ vector of baseline covariates/confounders at baseline of trial m for subject k
  - $\boldsymbol{L}^e_{mk}$ = eligibility defining covariates
  - $\boldsymbol{L}^c_{mk}$ = additional covariates
- $T_{mk} = \min(T^*_{mk}, T^C_{mk})$ observed outcome for subject k in trial m
  - T^*_{mk} = true event time
  - T^C_{mk} = censoring time

Notational Framework

Following Hernan et al. (Hernán et al., 2008, 2000; Hernán et al., 2016), we re-express outcomes on a discrete time scale as follows:

$$\boldsymbol{Y}_{mk} = \begin{pmatrix} Y_{mk1} \\ Y_{mk2} \\ \vdots \\ Y_{mkT_{mk}} \end{pmatrix} \quad \text{where} \quad Y_{mkt} = \begin{cases} 1 & T^*_{mk} \leq t \\ 0 & T^*_{mk} > t \end{cases}$$

- Analogous binary indicators for censoring status C_{mkt} and non-adherence $N_{mkt} = \mathbb{1}(A_{mkt} = A_{mk})$

As will become clear, working in discrete time will enable the use of time-varying inverse probability weights (IPW) to control for a variety of potential biases that cannot be easily addressed in continuous time.

Estimands of Interest

Possible estimands of interest are established using pooled logistic regression, typically with the goal of estimating a common effect across all time periods.

$$\text{logit}\left[P(Y^{(\bar{a})}_{mk(t+1)} = 1 | E_{mk} = 1, \overline{Y}^{(\bar{a})}_{mkt} = 0, \overline{A}_{mk(t+1)} = a\mathbb{1}_{(t+1)})\right] = \psi^{(m)}_{0,t} + \psi a$$

- $Y^{(\bar{a})}_{mkt}$ counterfactual outcome for subject k during month t of trial m under treatment history $\overline{A}_{mkt} = \bar{a}$
- Conditioning on $E_{mk} = 1$ makes explicit that interest lies in an effect among patients eligible for the study population
- ψ log discrete time hazard ratio
- $\psi^{(m)}_{0,t}$ analogue of baseline hazard, which can vary across both time (t) and trial (m).
- Conditioning on $\overline{A}_{mk(t+1)} = a\mathbb{1}_{(t+1)} \implies$ per-protocol effect
- Conditioning instead on $A_{mk} = a \implies$ intention-to-treat effect

Selection Bias

When subjects whose eligibility can not be ascertained ($R_{mk} = 0$) **are dropped from analysis**, the estimands that standard methods will target implicitly change

$$\text{logit}\left[P(Y^{(\bar{a})}_{mk(t+1)} = 1 | E_{mk} = 1, \overline{Y}^{(\bar{a})}_{mkt} = 0, \overline{A}_{mk(t+1)} = a\mathbb{1}_{(t+1)})\right] = \psi^{(m)}_{0,t} + \psi a$$

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$$\text{logit}\left[P(Y^{(\bar{a})}_{mk(t+1)} = 1 | E_{mk} = 1, R_{mk} = 1, \overline{Y}^{(\bar{a})}_{mkt} = 0, \overline{A}_{mkt} = a\mathbb{1}_{(t+1)})\right] = \theta^{(m)}_{0,t} + \theta a$$

Selection bias occurs when $\theta \neq \psi$

- That is, when the treatment effect among eligible complete cases ($E_{mk} = 1, R_{mk} = 1$) does not equal the treatment effect among the entire eligible population ($E_{mk} = 1$).

IPW for Addressing Selection Bias

- Propose novel eligibility missing at random (MAR) assumption

$$R_{mk} \perp\!\!\!\perp E_{mk} \mid \bar{\boldsymbol{L}}^{c}_{mk}, \bar{A}_{mk}, C_{mk} = 0$$

- Whether or not one's eligibility status can be ascertained is independent of what that eligibility status is, after accounting for everything observable for all patients
- Intuition: Can correct for selection bias as long as differences between types of eligible subjects are explained by observables.

$$W^{R}_{mk} = P(R_{mk} = 1 \mid \bar{\boldsymbol{L}}^{c}_{mk}, \bar{A}_{mk}, C_{mk} = 0)^{-1}$$

IPW with the Target Trial Framework

- Don't get to observe counterfactuals, have to work with observed data
- Amounts to fitting the following pooled logistic regression model

$$\text{logit}\left[P(Y_{mk(t+1)} = 1 | E_{mk} = 1, R_{mk} = 1, \overline{Y}_{mkt} = 0, A_{mk}, \overline{N}_{mkt} = 0, \overline{C}_{mkt} = 0)\right] = \tilde{\theta}_{0,t}^{(m)} + \tilde{\theta} A_{mk}$$

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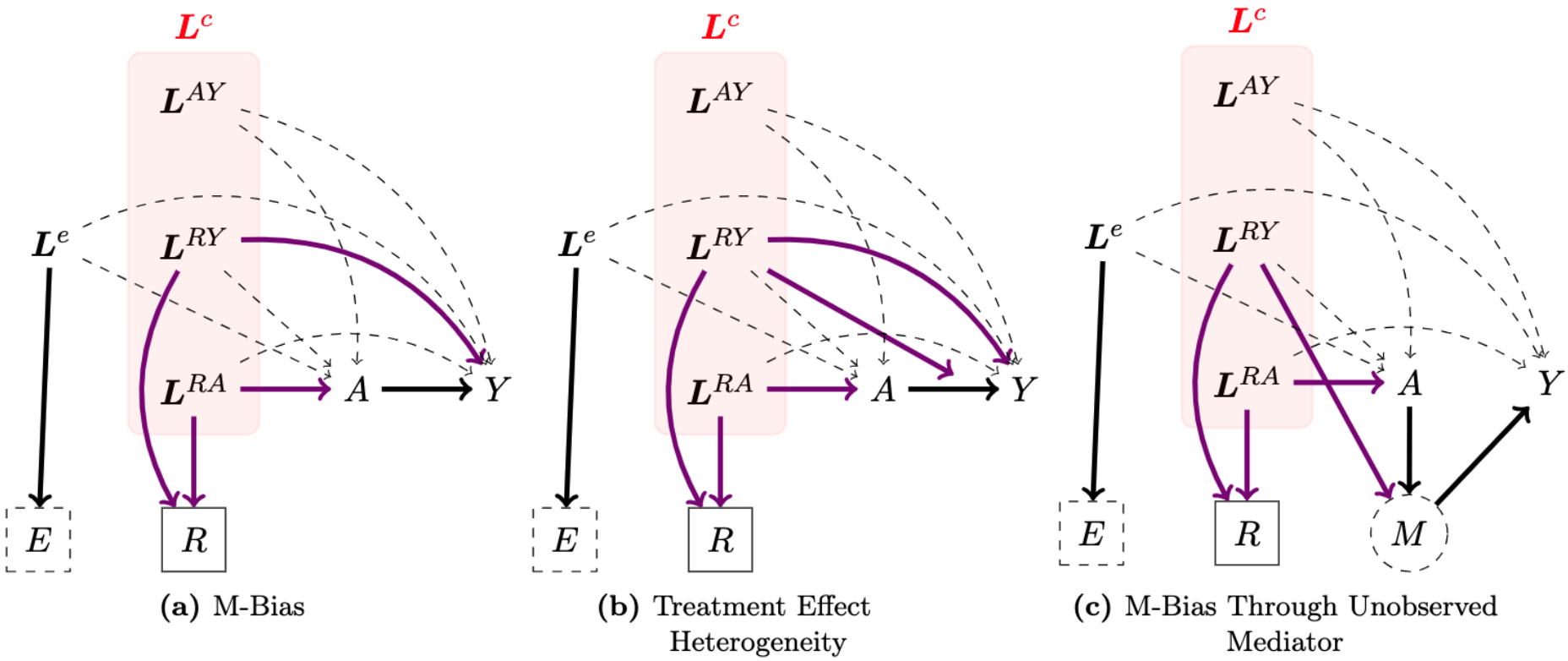
- Selection bias doesn't exist in a vacuum
- Other challenges: confounding, differential censoring/non-adherence
  - IPW has been used previously for these challenges in TTE framework

Fitting above model with weights

$$W_{mkt} = \underbrace{W_{mk}^{A} \times W_{mkt}^{C} \times W_{mkt}^{N}}_{\text{Recovers } \theta \text{ from } \tilde{\theta}} \times \underbrace{W_{mk}^{R}}_{\text{Recovers } \psi \text{ from } \theta}$$

Structures of Selection Bias



(a) M-Bias

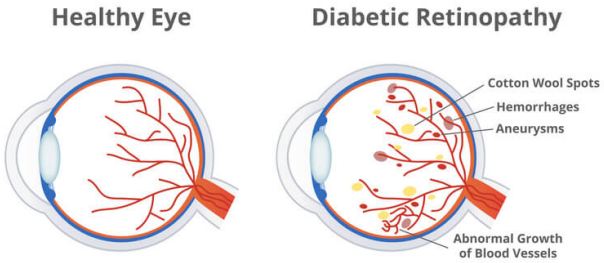
(b) Treatment Effect Heterogeneity

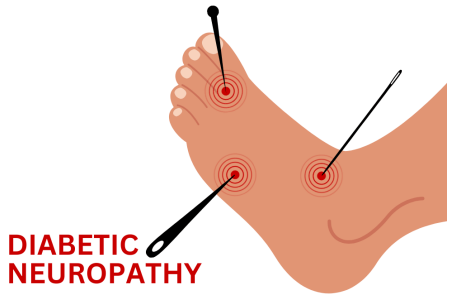
(c) M-Bias Through Unobserved Mediator

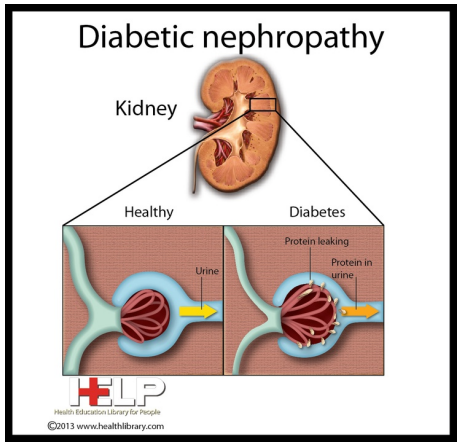
Figure: 3 example DAGs showing selection bias due to missing eligibility, even in the absence of counfounding

Data Application

- Reanalyze the question in (O'Brien et al., 2018) on the effect of bariatric surgery on incident microvascular disease among patients w/ Type II diabetes (TD2M)
  1. Retinopathy
  2. Neuropathy
  3. Nephropathy







Summary of (O'Brien et al., 2018)

- **Matched cohort**
  - 4,024 surgical patients
  - 11,059 matched non-surgical patients
  - Kaiser Permanente system
  - Underwent bariatric surgery between 2005-01-01 and 2011-12-31 and followed until 2015-09-30.
- **Eligibility criteria**
  - BMI ≥ 35 kg/m^2
  - TD2M as defined by any of the following criteria
    - Most recent A1c measure $\geq 6.5\%$ **(up to 2 years prior to index date)**
    - Most recent blood glucose ≥ 126 mg/dL **(up to 2 years prior to index date)**
    - Current prescription for diabetes medication

Target Trial Emulation

- $M = 84$ trials, each 1 month in length, from January 2005 ($m = 1$) to December 2011 ($m = 84$)
- Attempt to apply eligibility criteria to everyone in the dataset (who isn't already censored/outcome etc.) at each $m \in \{1, ..., 84\}$.
- Nearly 44 million subject trials.
- Re-run the analysis over a grid of look-back times for diabetes lab measures and BMI measures
  - BMI Lookback $\in \{1, 3, 6, 12\}$ months
  - Blood Glucose Lookback $\in \{1, 3, 6, 12, 18, 24\}$ months

Eligibility Status Distribution

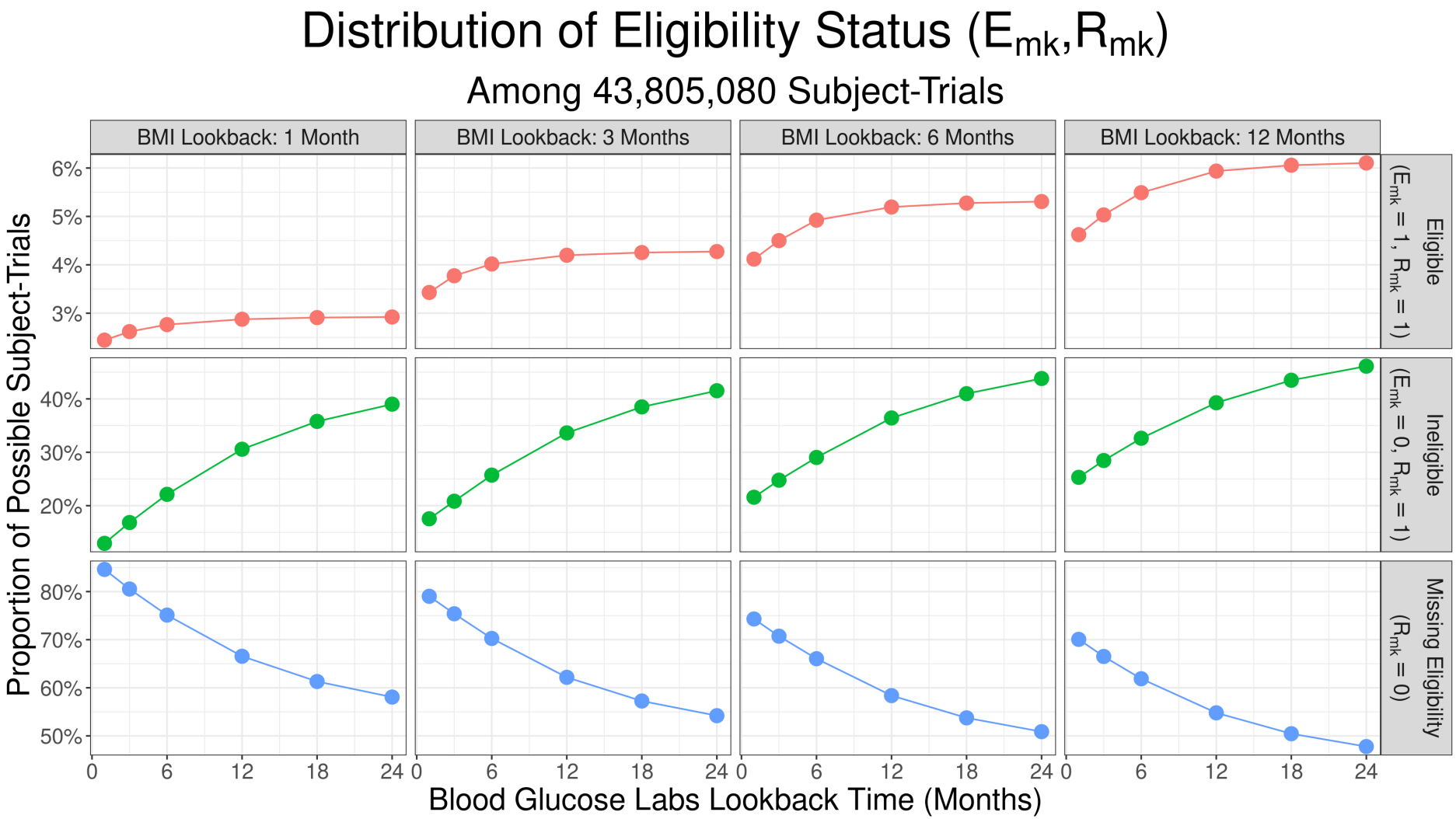
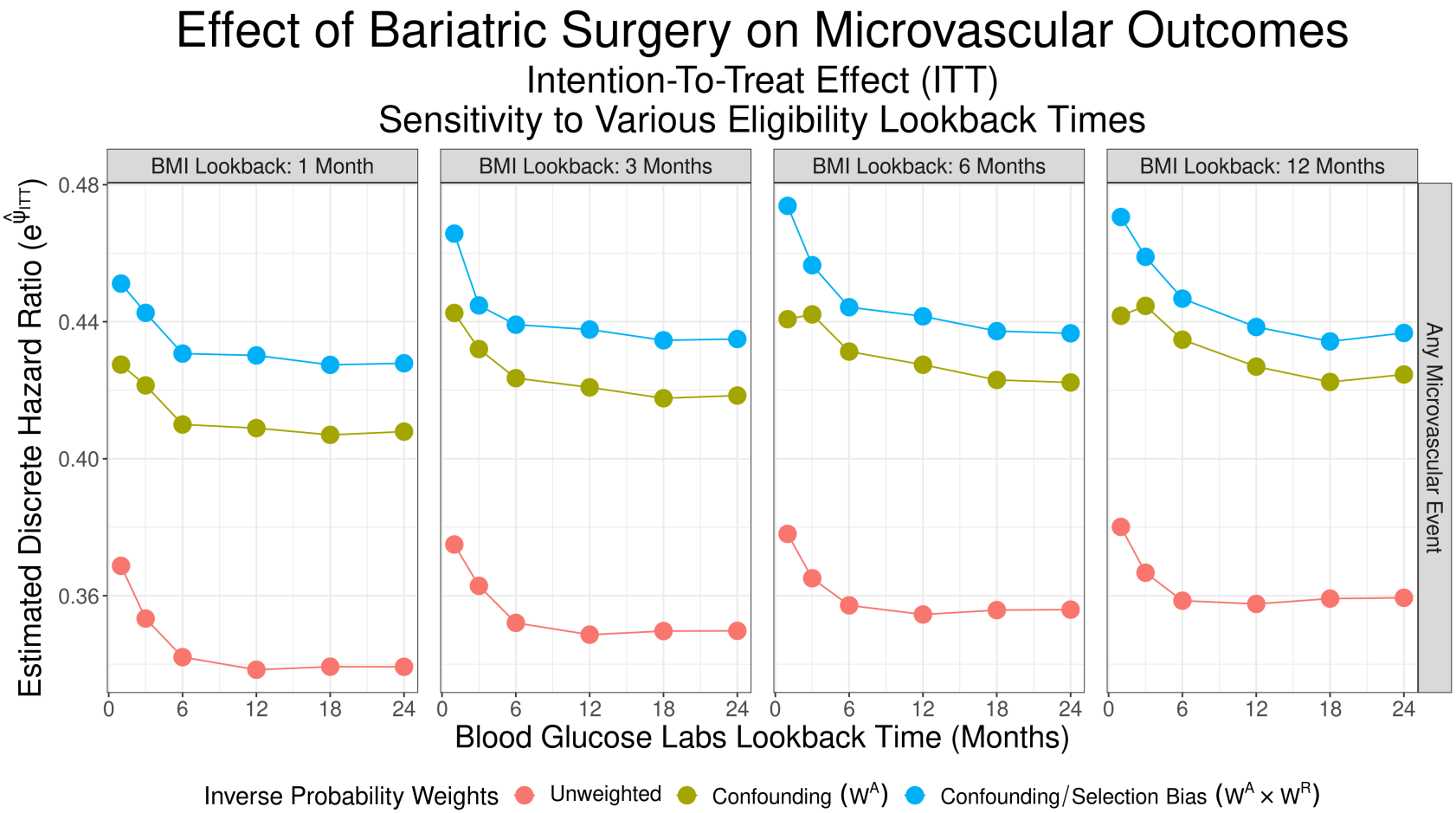


Figure: Distribution of eligibility ascertainment/status based on length of lookback windows

Sensitivity of Results to Lookback Window



- Data application confirms that bariatric surgery significantly reduces the long term risk of microvascular disease among diabetic patients with severe obesity.
- Effect estimates slightly attenuated compared to those of (O'Brien et al., 2018), which did not explicitly account for possibility selection bias.

Summary and Final Thoughts

- Target trial emulation offers a useful conceptual roadmap for thinking about and addressing numerous challenges in observational studies.
  - Missing data, especially missing data in eligibility criteria, is not a part of this roadmap. We think it should be!
- Inverse probability weights for eligibility ascertainment offer one solution.
  - Integrates well into exiting analysis pipelines
- Problem of missing eligibility data is **not restricted** to target trial emulations.
  - Similar solutions should be possible for other study designs.
  - Ongoing extensions: efficient estimators that are more robust to model mispecification.

More Information

Figure: QR Code for Pre-Print

- Code: https://github.com/lbenz730/missing_eligibility_tte

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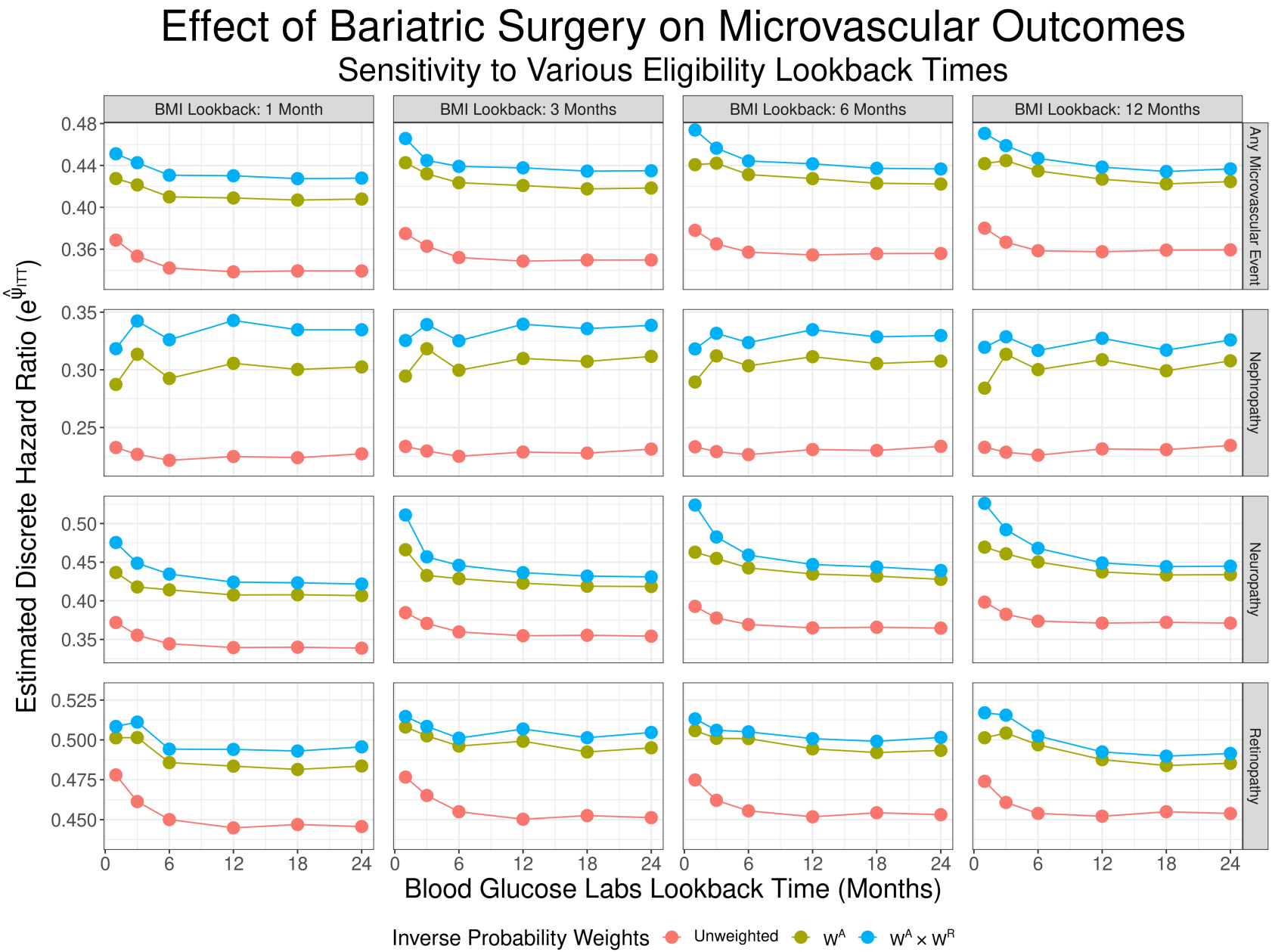
Appendix

Component Inverse Probability Weights

Weight	Purpose	Definition
W^A_{mk}	Confounding	$P(A_{mk} \mid \boldsymbol{L}_{mk}, E_{mk} = 1)^{-1}$
W^C_{mkt}	Censoring	$\prod_{i=0}^{t} P(C_{mki} = 0 \mid \overline{C}_{mk(i-1)} = 0, \overline{N}_{mk(i-1)} = 0, \boldsymbol{L}_{mki}, E_{mk} = 1, A_{mk})^{-1}$
W^N_{mkt}	Non-Adherence	$\prod_{i=0}^{t} P(N_{mki} = 0 \mid \overline{C}_{mk(i-1)} = 0, \overline{N}_{mk(i-1)} = 0, \boldsymbol{L}_{mki}, E_{mk} = 1, A_{mk})^{-1}$
W^R_{mk}	Selection Bias	$P(R_{mk} = 1 \mid \overline{A}_{mk}, \overline{\boldsymbol{L}}^c_{mk}, C_{mk} = 0)^{-1}$
SW^A_{mk}	Confounding	$\frac{P(A_{mk} \mid E_{mk}=1)}{P(A_{mk} \mid \boldsymbol{L}_{mk}, E_{mk}=1)}$
SW^C_{mkt}	Censoring	$\frac{\prod_{i=0}^{t} P(C_{mki}=0 \mid \overline{C}_{mk(i-1)}=0, \overline{N}_{mk(i-1)}=0, E_{mk}=1, A_{mk})}{\prod_{i=0}^{t} P(C_{mki}=0 \mid \overline{C}_{mk(i-1)}=0, \overline{N}_{mk(i-1)}=0, \boldsymbol{L}_{mki}, E_{mk}=1, A_{mk})}$
SW^N_{mkt}	Non-Adherence	$\frac{\prod_{i=0}^{t} P(N_{mki}=0 \mid \overline{C}_{mk(i-1)}=0, \overline{N}_{mk(i-1)}=0, E_{mk}=1, A_{mk})}{\prod_{i=0}^{t} P(N_{mki}=0 \mid \overline{C}_{mk(i-1)}=0, \overline{N}_{mk(i-1)}=0, \boldsymbol{L}_{mki}, E_{mk}=1, A_{mk})}$
SW^R_{mk}	Selection Bias	$\frac{P(R_{mk}=1 \mid \overline{A}_{mk}, C_{mk}=0)}{P(R_{mk}=1 \mid \overline{\boldsymbol{L}}^c_{mk}, \overline{A}_{mk}, C_{mk}=0)}$

Table: Summary of component inverse probability weights

Sensitivity of Results to Lookback Window



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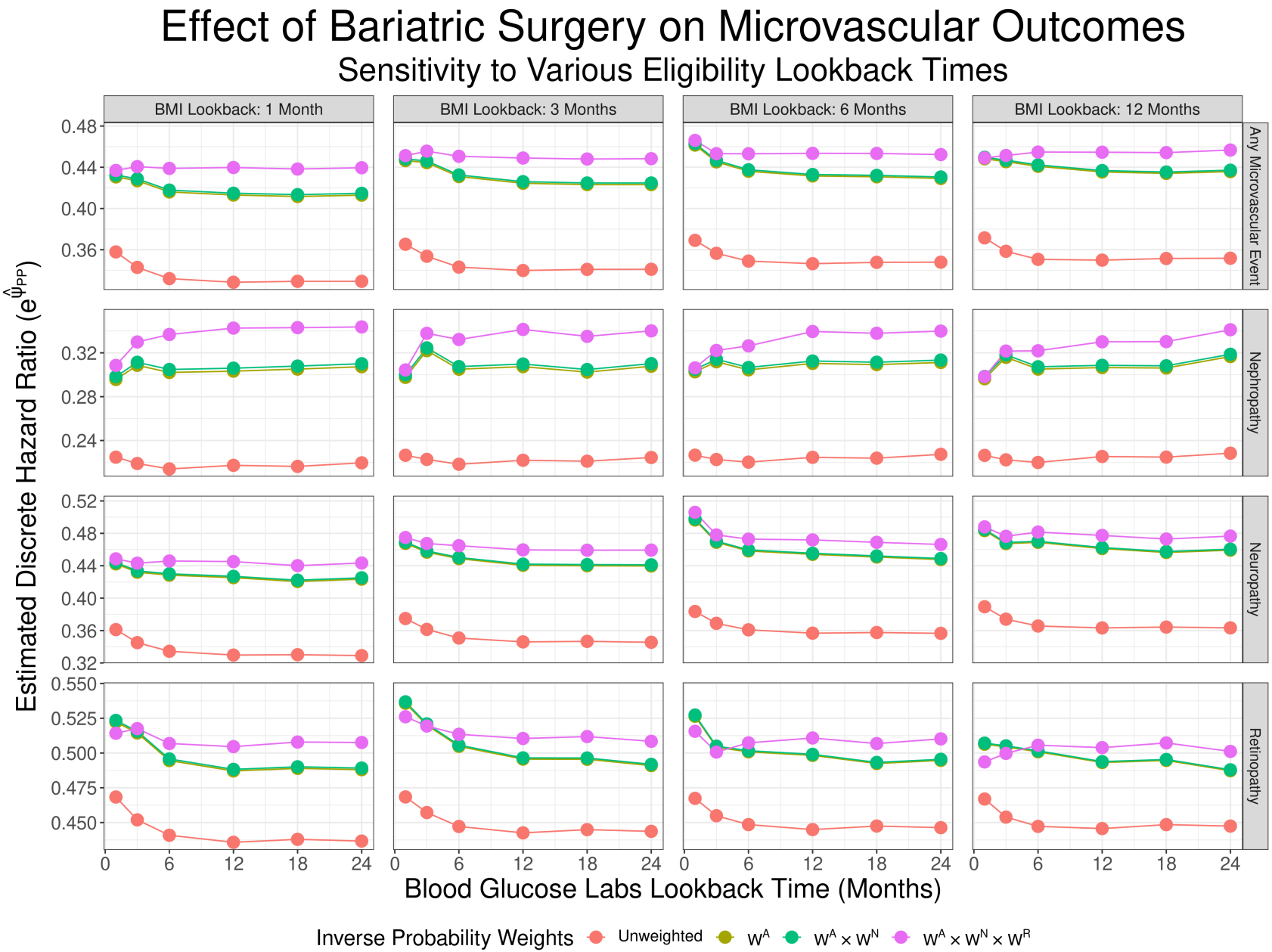

Reported Data Application Results

Outcome	**Intention-To-Treat** ($e^{\hat{\psi}_{ITT}}$)	**Per-Protocol** ($e^{\hat{\psi}_{PP}}$)
Any Microvascular Event	0.438 (0.382, 0.497)	0.429 (0.375, 0.489)
Nephropathy	0.340 (0.239, 0.458)	0.331 (0.236, 0.452)
Neuropathy	0.436 (0.367, 0.521)	0.428 (0.360, 0.512)
Retinopathy	0.507 (0.400, 0.608)	0.491 (0.394, 0.600)

Table: Discrete hazard ratio estimates and 95% confidence intervals for the effect of bariatric surgery on microvascular outcomes. Confidence intervals were computed utilizing 1,000 bootstrap replications at the subject (k) level. Eligibility (E_{mk}) was assessed utilizing a 12 month lookback window prior to the start of trial m for blood glucose measures and a 3 month lookback window for BMI measures.

Simulation Study Results

Setting		IPW Models		Mean $\hat{\psi}_{PP}$		Median $\hat{\psi}_{PP}$	
Missingness	ψ_{PP}	W^R_{mk}	W^N_{mkt}	**Bias**	**% Bias**	**Bias**	**% Bias**
M-Bias	-0.322	—	—	-0.021	6.7	-0.023	7.2
			$N \sim L^A$	-0.020	6.3	-0.022	6.7
		$R \sim L^{R,A}$	—	-0.012	3.8	-0.009	2.7
			$N \sim L^A$	-0.020	6.2	-0.018	5.7
		$R \sim L^{R,Y}$	—	-0.010	3.2	-0.016	5.1
			$N \sim L^A$	-0.009	2.9	-0.016	5.0
		$R \sim L^R$	—	0.011	-3.4	0.011	-3.3
			$N \sim L^A$	0.002	-0.7	0.002	-0.5
		$R \sim L^R + A$	—	0.011	-3.4	0.011	-3.3
			$N \sim L^A$	0.002	-0.7	0.000	0.0
Treatment Effect Heterogeneity	-0.305	—	—	0.036	-11.7	0.040	-13.3
			$N \sim L^A$	0.036	-11.7	0.039	-12.9
		$R \sim L^{R,A}$	—	0.035	-11.4	0.034	-11.1
			$N \sim L^A$	0.034	-11.2	0.035	-11.6
		$R \sim L^{R,Y}$	—	-0.005	1.7	-0.002	0.6
			$N \sim L^A$	-0.005	1.7	-0.001	0.4
		$R \sim L^R$	—	-0.004	1.3	0.003	-1.0
			$N \sim L^A$	-0.005	1.6	0.003	-1.1
		$R \sim L^R + A$	—	-0.004	1.3	0.003	-1.1
			$N \sim L^A$	-0.005	1.6	0.003	-1.1
M-Bias w/ Mediator	-0.817	—	—	0.057	-7.0	0.063	-7.7
			$N \sim L^A$	0.057	-6.9	0.062	-7.5
		$R \sim L^{R,A}$	—	0.056	-6.8	0.061	-7.4
			$N \sim L^A$	0.055	-6.7	0.061	-7.5
		$R \sim L^{R,Y}$	—	-0.001	0.1	0.006	-0.7
			$N \sim L^A$	-0.001	0.1	0.004	-0.5
		$R \sim L^R$	—	-0.004	0.5	0.005	-0.7
			$N \sim L^A$	-0.005	0.6	0.004	-0.4
		$R \sim L^R + A$	—	-0.004	0.5	0.006	-0.7
			$N \sim L^A$	-0.005	0.6	0.004	-0.5

Figure: Simulation results from hypothetical study 1

Simulation Study Results

Setting		IPW Models			Mean $\hat{\psi}_{PP}$		Median $\hat{\psi}_{PP}$	
Missingness	ψ_{PP}	**Statification**	$\boldsymbol{W}^R_{mk}$	$\boldsymbol{W}^N_{mkt}$	**Bias**	**% Bias**	**Bias**	**% Bias**
M-Bias	-0.325	Unstratified	—	—	-0.602	185.3	-0.601	185.0
				$N \sim \boldsymbol{L}^A$	-0.601	185.0	-0.600	184.4
			$R \sim \boldsymbol{L}^{R,A}$	—	-0.605	186.0	-0.604	185.8
				$N \sim \boldsymbol{L}^A$	-0.612	188.3	-0.611	188.0
			$R \sim \boldsymbol{L}^{R,Y}$	—	-0.571	175.6	-0.569	175.1
				$N \sim \boldsymbol{L}^A$	-0.570	175.3	-0.567	174.4
			$R \sim \boldsymbol{L}^R$	—	-0.568	174.8	-0.567	174.5
				$N \sim \boldsymbol{L}^A$	-0.577	177.4	-0.575	176.7
			$R \sim \boldsymbol{L}^R + A$	—	-0.568	174.8	-0.567	174.4
				$N \sim \boldsymbol{L}^A$	-0.577	177.4	-0.575	176.7
		Stratified by A	$R \sim \boldsymbol{L}^{R,A}$	—	-0.602	185.3	-0.603	185.3
				$N \sim \boldsymbol{L}^A$	-0.610	187.7	-0.609	187.4
			$R \sim \boldsymbol{L}^{R,Y}$	—	-0.006	1.8	-0.005	1.6
				$N \sim \boldsymbol{L}^A$	-0.005	1.5	-0.004	1.2
			$R \sim \boldsymbol{L}^R$	—	0.001	-0.2	0.002	-0.7
				$N \sim \boldsymbol{L}^A$	-0.008	2.4	-0.007	2.1
Treatment Effect Heterogeneity	-0.307	Unstratified	—	—	-0.108	35.3	-0.108	35.2
				$N \sim \boldsymbol{L}^A$	-0.108	35.3	-0.108	35.3
			$R \sim \boldsymbol{L}^{R,A}$	—	-0.108	35.4	-0.110	36.0
				$N \sim \boldsymbol{L}^A$	-0.109	35.4	-0.110	35.9
			$R \sim \boldsymbol{L}^{R,Y}$	—	-0.141	45.8	-0.141	46.0
				$N \sim \boldsymbol{L}^A$	-0.140	45.8	-0.143	46.5
			$R \sim \boldsymbol{L}^R$	—	-0.140	45.6	-0.139	45.4
				$N \sim \boldsymbol{L}^A$	-0.140	45.8	-0.141	45.9
			$R \sim \boldsymbol{L}^R + A$	—	-0.140	45.6	-0.139	45.4
				$N \sim \boldsymbol{L}^A$	-0.140	45.8	-0.141	46.0
		Stratified by A	$R \sim \boldsymbol{L}^{R,A}$	—	-0.108	35.4	-0.108	35.4
				$N \sim \boldsymbol{L}^A$	-0.109	35.5	-0.108	35.2
			$R \sim \boldsymbol{L}^{R,Y}$	—	0.000	0.0	-0.002	0.7
				$N \sim \boldsymbol{L}^A$	0.000	0.0	-0.001	0.4
			$R \sim \boldsymbol{L}^R$	—	0.001	-0.2	-0.001	0.2
				$N \sim \boldsymbol{L}^A$	0.000	0.0	-0.001	0.3
M-Bias w/ Mediator	-0.811	Unstratified	—	—	-0.018	2.3	-0.018	2.2
				$N \sim \boldsymbol{L}^A$	-0.016	2.0	-0.017	2.0
			$R \sim \boldsymbol{L}^{R,A}$	—	-0.020	2.5	-0.019	2.4
				$N \sim \boldsymbol{L}^A$	-0.018	2.3	-0.018	2.2
			$R \sim \boldsymbol{L}^{R,Y}$	—	-0.075	9.2	-0.074	9.1
				$N \sim \boldsymbol{L}^A$	-0.073	9.0	-0.072	8.9
			$R \sim \boldsymbol{L}^R$	—	-0.078	9.6	-0.078	9.6
				$N \sim \boldsymbol{L}^A$	-0.076	9.4	-0.076	9.4
			$R \sim \boldsymbol{L}^R + A$	—	-0.078	9.6	-0.078	9.6
				$N \sim \boldsymbol{L}^A$	-0.076	9.4	-0.076	9.4
		Stratified by A	$R \sim \boldsymbol{L}^{R,A}$	—	-0.022	2.8	-0.020	2.5
				$N \sim \boldsymbol{L}^A$	-0.020	2.5	-0.019	2.3
			$R \sim \boldsymbol{L}^{R,Y}$	—	0.001	-0.2	0.003	-0.4
				$N \sim \boldsymbol{L}^A$	0.003	-0.4	0.005	-0.6
			$R \sim \boldsymbol{L}^R$	—	-0.002	0.2	-0.001	0.1
				$N \sim \boldsymbol{L}^A$	0.000	0.0	0.002	-0.2

Figure: Simulation results from hypothetical study 2

Missing At Random Assumption

- Musings on the Missing At Random Assumption
  - Common violations of this assumption are likely to be found in cases where study eligibility criteria can be viewed as some notion of patient health, with a patient's health driving how frequently they're followed in the EHR.
  - One could additionally condition on things like eligibility history (both status E and eligibility defining covariates $\boldsymbol{L}^e$).
  - This relaxed assumption may be more likely to hold at the expense of presenting analysts with non-monotone missingness, something harder to rectify.
  - While violations of this MAR assumption are not ideal, violations where subjects with missing eligibility data were less likely to have been eligible seem somewhat less harmful than the other direction, where subjects without eligibility defining covariates were more likely to have been eligible.