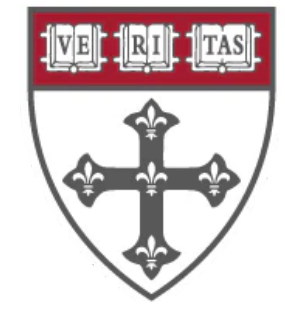


Adjusting for Selection Bias Due to Missing Eligibility Criteria in Emulated Target Trials



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Introduction

Missingness in variables that define eligibility criteria presents a major challenge towards determining the eligible population when emulating a target trial with an observational study. In practice, patients with incomplete data are almost always excluded from analysis despite the possibility of selection bias.

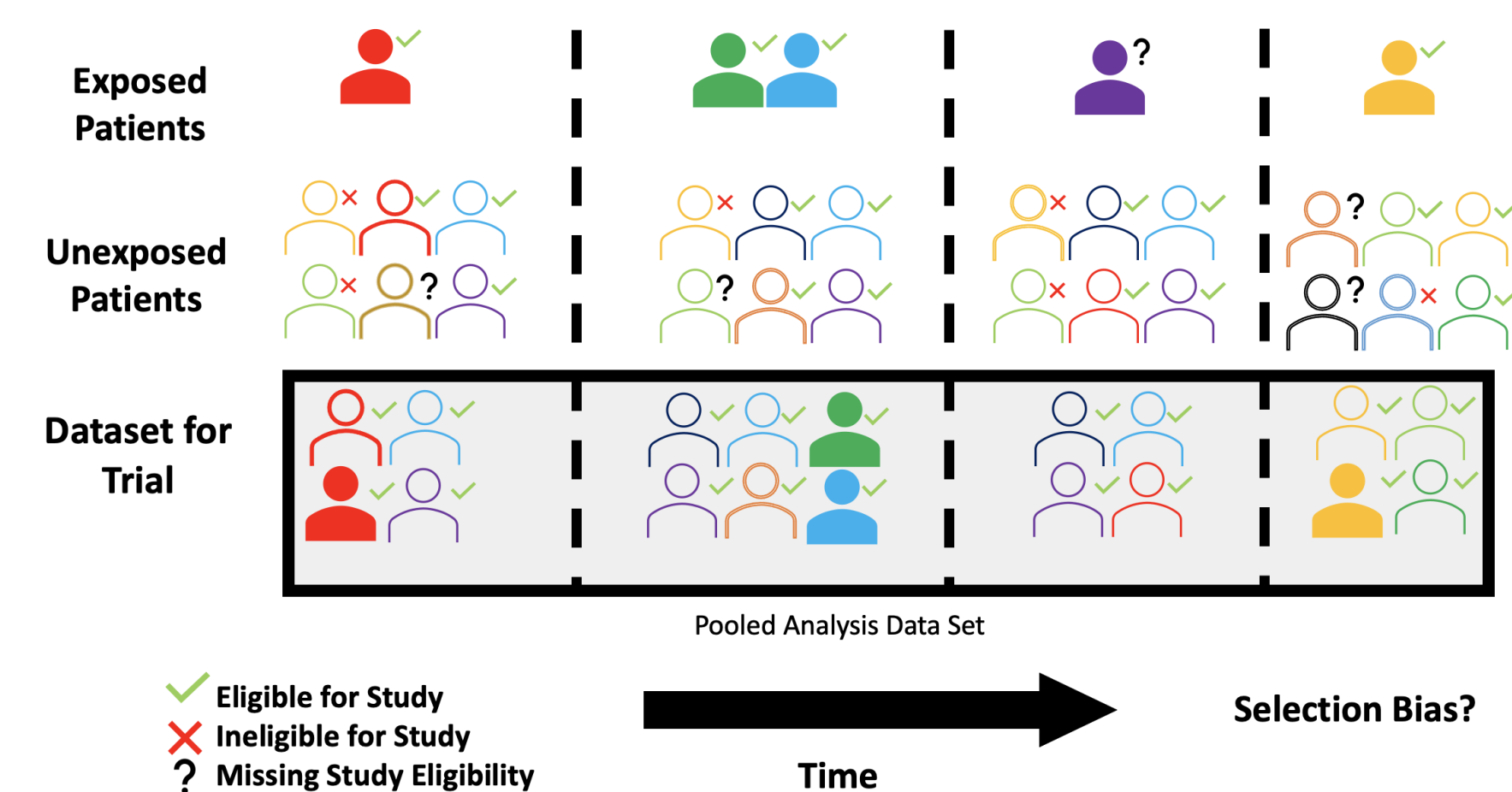


Figure 1: Overview of sequential target trial emulation

Inverse Probability of Ascertainment Weights

Selection bias occurs when the treatment effect (eg. from a pooled logistic regression) among eligible complete cases ($E_{mk} = 1, R_{mk} = 1$), θ , does not equal the treatment effect among the entire eligible population ($E_{mk} = 1$), ψ .

$$\logit[P(Y_{mk(t+1)} = 1 | E_{mk} = 1, \bar{Y}_{mkt}^{(a)} = 0, A_{mk} = a)] = \psi_{0,t}^{(m)} + \psi a$$

$$\logit[P(Y_{mk(t+1)} = 1 | E_{mk} = 1, R_{mk} = 1, \bar{Y}_{mkt}^{(a)} = 0, A_{mk} = a)] = \theta_{0,t}^{(m)} + \theta a$$

Propose eligibility missing at random (MAR) assumption that eligibility ascertainment (R_{mk}) is independent of eligibility status (E_{mk}) given histories of treatment (A_{mk}) and covariates that **do not define study eligibility** L_{mk}^c

$$R_{mk} \perp\!\!\!\perp E_{mk} \mid L_{mk}^c, A_{mk}, C_{mk} = 0$$

- Whether eligibility status can be ascertained is independent of what that eligibility status is, after accounting for everything observable for all patients.
- Can correct for selection bias via inverse probability weighting (IPW) as long as differences between types of eligible subjects are explained by observables.

$$W_{mk}^R = P(R_{mk} = 1 \mid L_{mk}^c, A_{mk}, C_{mk} = 0)^{-1}$$

- Can be used along with IPW for confounding, non-adherence, etc.

Target Trial for Bariatric Surgery

We emulate a target trial examining the effect of bariatric surgery on time to incident microvascular disease among patients with type II diabetes (T2DM), using an EHR database (DURABLE) from 3 large Kaiser Permanente sites (Washington, North/South California). This operationalizes as a sequence of 84 trials between 2005-2011.

Eligibility criteria:

- BMI ≥ 35 kg/m²
- T2DM as defined by any of the following
 - Most recent A1c measure $\geq 6.5\%$
 - Most recent blood glucose ≥ 126 mg/dL
 - Current prescription for diabetes medication
- No history of microvascular disease
- No pregnancy w/in last 12 months

Sensitivity Analysis over Ascertainment Lookback Windows:

- BMI assessed using the most recent value within {1, 3, 6, 12} months prior to baseline
- T2DM status was assessed using the most recent blood glucose lab measurements available with {1, 3, 6, 12, 18, 24} months prior to baseline

EHR Derived Measurements

Select DURABLE Non-Surgical Patients

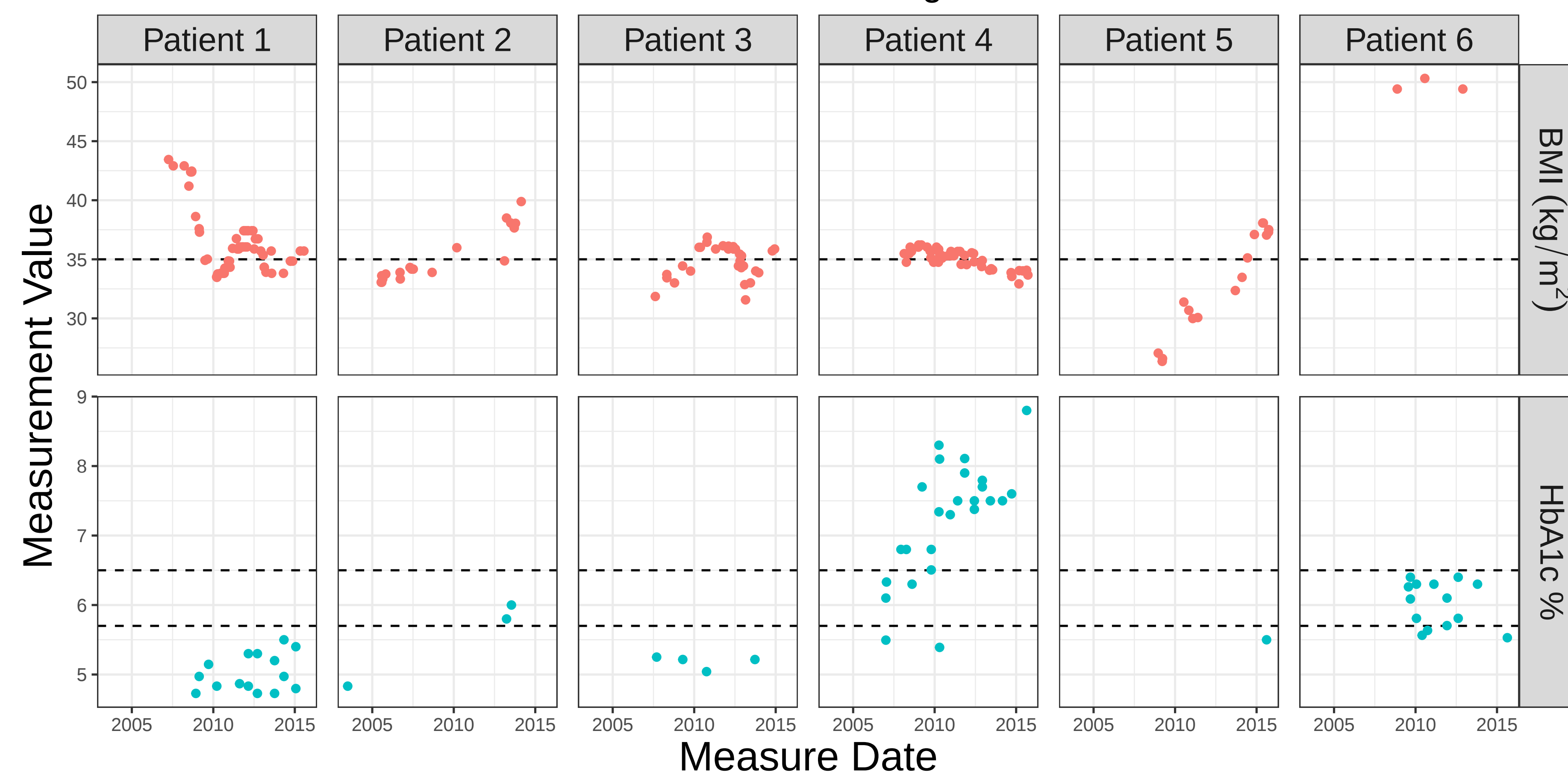


Figure 2: Substantial heterogeneity in the patterns and frequency of observed information in the EHR making ascertainment study eligibility easy for some patients and difficult/impossible for others.

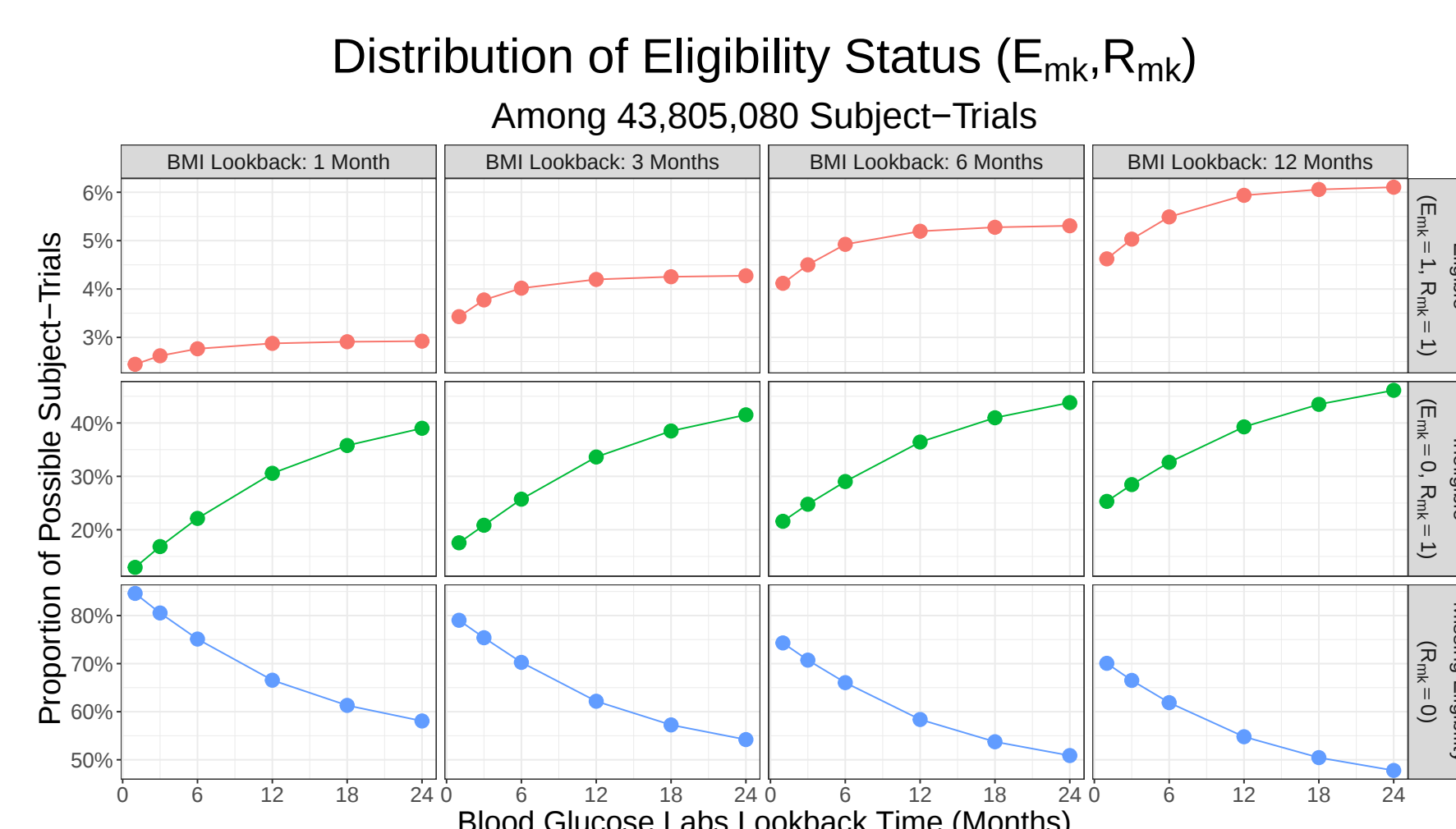


Figure 3: Allowing longer lookback times increases the number of subject-trials for whom eligibility can be ascertained. However, measurement values from longer lookbacks may less accurately reflect a subjects' eligibility defining covariates.

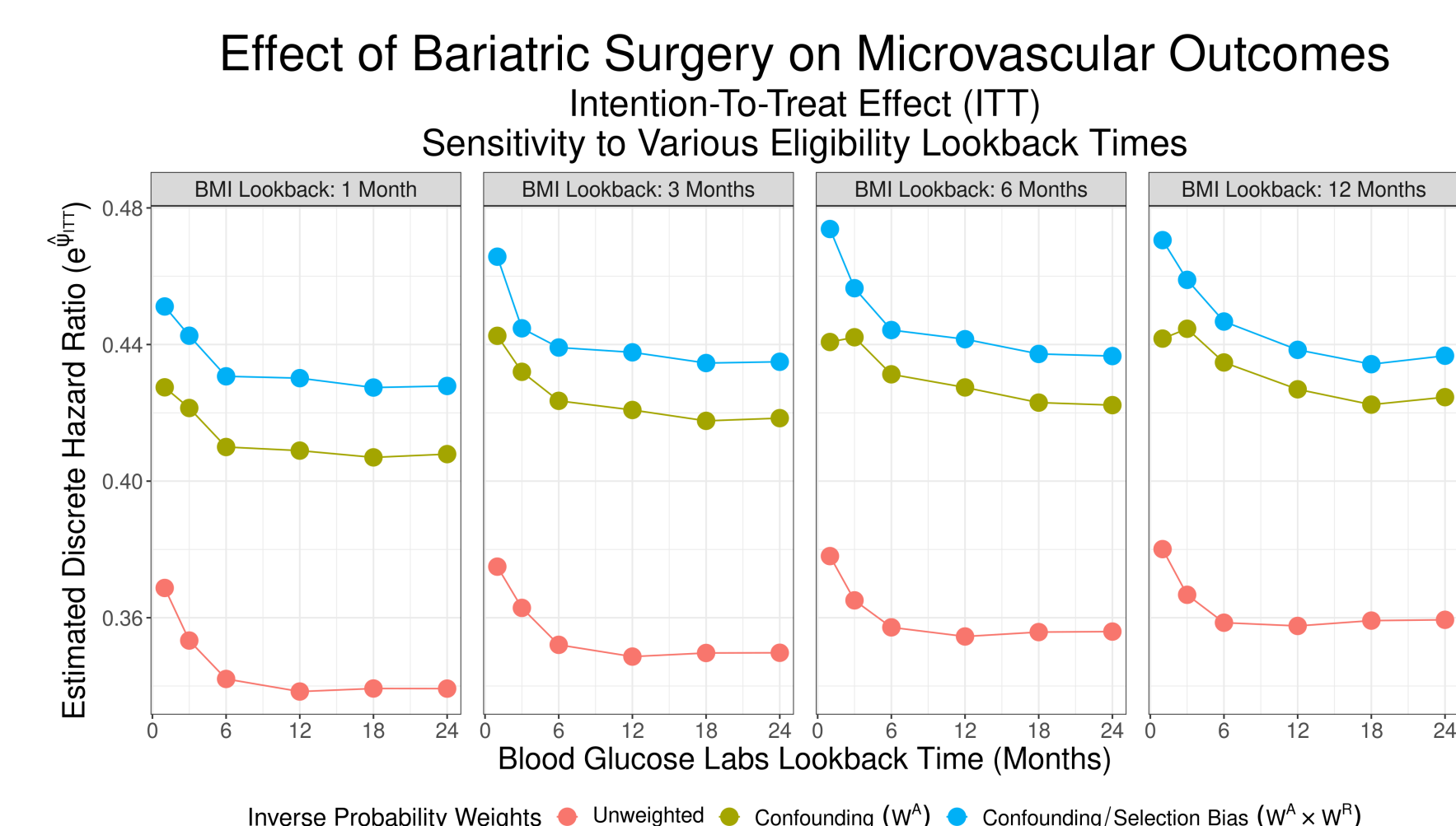


Figure 4: Discrete hazard ratio estimates for the effect of bariatric surgery on microvascular outcomes. Estimates are reported using various combinations of inverse probability weights.

Results

- Difficulty ascertaining eligibility for subjects might cause researchers to lookback further in time to ascertain eligibility (Figure 2).
- Even in longest lookback eligibility missing for close to 50% of patients in EHR (Figure 3).
- Strong evidence that bariatric surgery is protective against incident microvascular disease among T2DM patients (Figure 4).
- Intention to treat (ITT) estimates show some degree of sensitivity to lookback length (Figure 4).
- Accounting for possible selection bias attenuates estimates 5-10% towards the null, even after accounting for confounding (Figure 4).

Summary

- Missing data often overlooked issue relative to confounding.
- Excluding patients with missing eligibility data makes analyses susceptible to selection bias.
- Inverse probability of ascertainment weights can mitigate the potential for selection bias.
- Method integrates seamlessly into existing TTE methods for dealing w/ confounding, adherence, and censoring via IPW.

Learn More



- Paper:** Benz, L., et al. "Adjusting for Selection Bias Due to Missing Eligibility Criteria in Emulated Target Trials." *American Journal of Epidemiology*, 2024.
- Code:** https://github.com/lbenz730/missing_eligibility_tte