Individual treatment effect estimation in the presence of unobserved confounding using proxies

a cohort study in stage III non-small cell lung cancer

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Wouter A.C. van Amsterdam, MD, PhD

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Affiliations & Collaborators

- University Medical Center Utrecht
    - Joost Verhoeff, MD PhD*
    - Netanja Harlianto
    - Gijs Bartholomeus
    - Pim de Jong, MD PhD*
    - Tim Leiner, MD PhD*
    - Anne van Lindert, MD
    - Rene Eijkemenas, PhD
- New York University
    - Aahlad Puli
    - Rajesh Ranganath, PhD*
- Me
    - Then: PhD student at UMCU
    - Now: Sr. research scientist at Babylon Health
    - 2023: Assistent Prof. at UMCU

*PhD advisors

Introduction

Motivation

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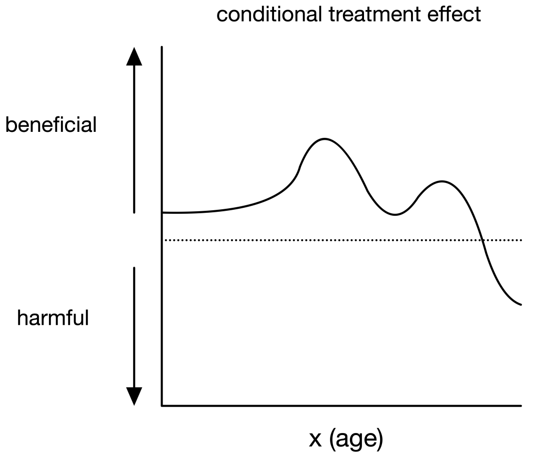
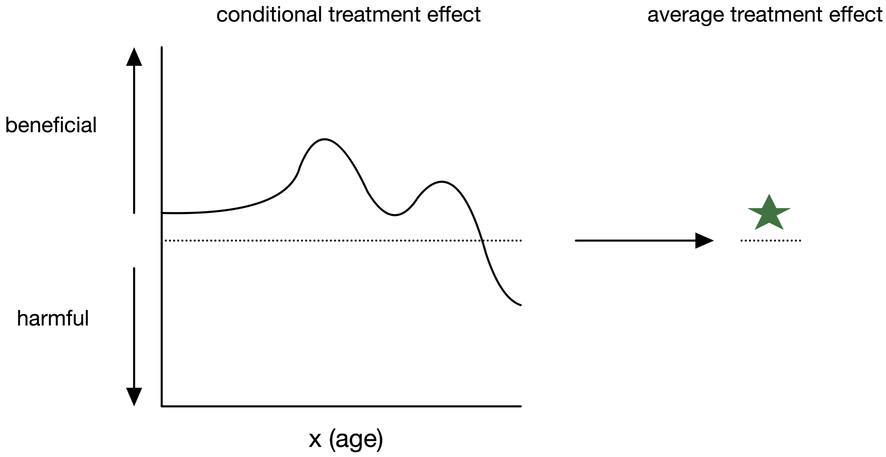
- weigh probability of benefit versus probability of harm for available treatments
- (relative) efficacy of treatments determined in RCTs for a certain population (average treatment effect: ATE)
- for personalized treatment decision making, want to known treatment effect conditional on patient characteristics X (conditional average treatment effect: CATE)

Ideal scenario: CATE known



RCT estimates average treatment effect, which is average CATE



Why estimate CATE in observational data

CATE estimation requires too many randomized participants to have sufficient power

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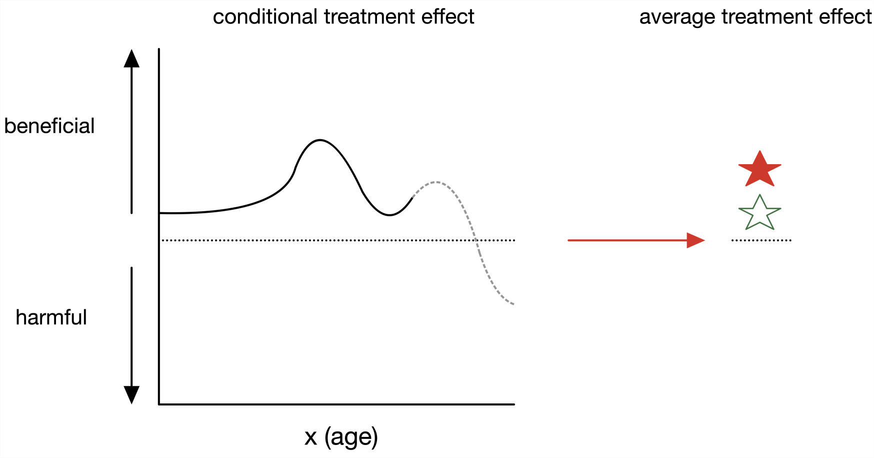
RCT gives us ATE in selected population



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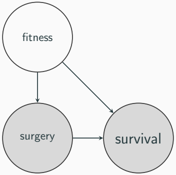
Wider population than RCT

Confounding: surgery vs chemoradiation



- Surgical treatment is preferred for patients who are fit for surgery

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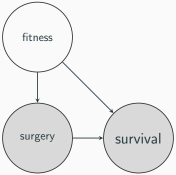

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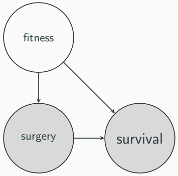

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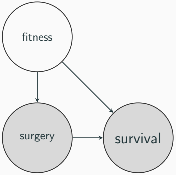

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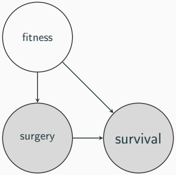

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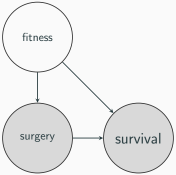
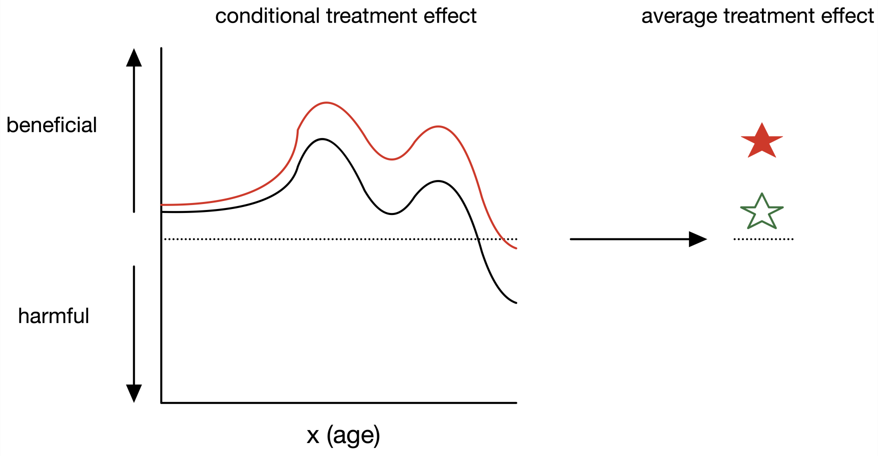


- Per-fitness group survival estimation resolves confounding bias (stratified / standardized / conditional / adjusted / back-door / point-treatment g-formula)
- **Requires measurement of overall fitness**

CATE estimation from observational data when some confounders are unknown



Causal inference from observational data requires (additional) assumptions

- Confounders known and measured (conditional ignorability)
- Positivity: $0 < p(t|x) < 1$

Randomization ensures this

The cost of causal inference

RCTs:

- time

Observational:

Always:

The cost of causal inference

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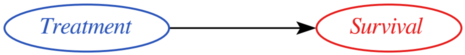
Always:

- causal inference in practice is costly,
- **but it's because we're acquiring something of value**

PROTECT

DAG: Directed Acyclic Graph



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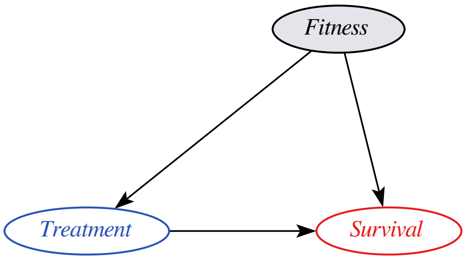

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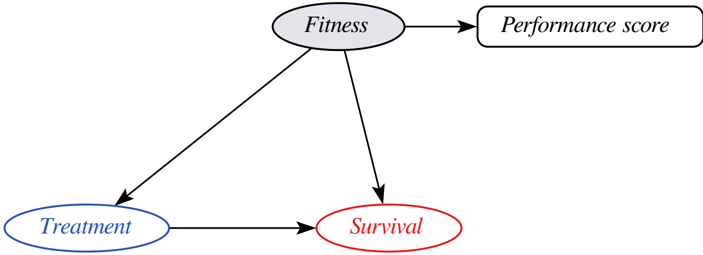

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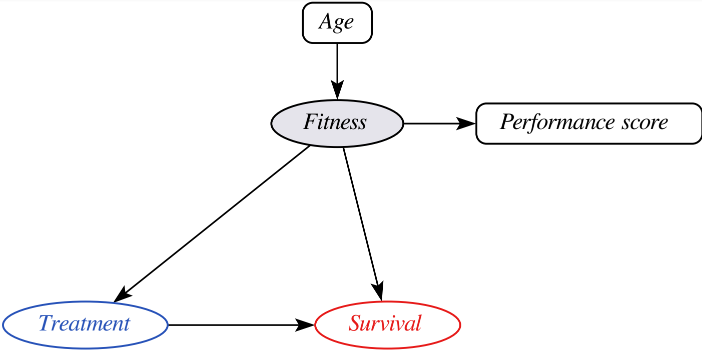

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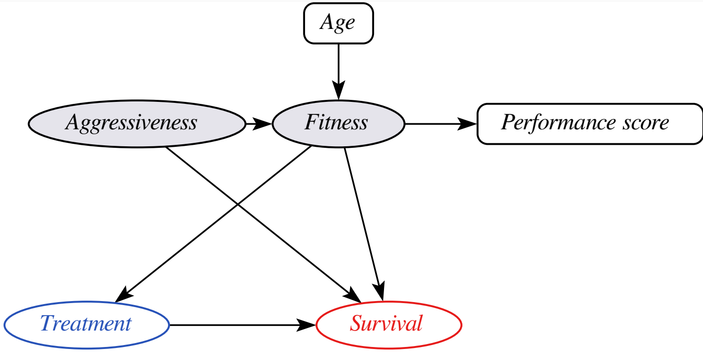

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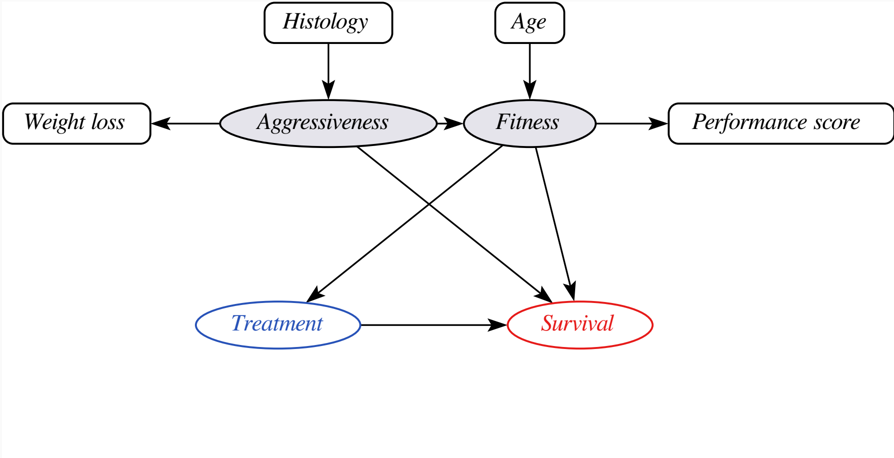

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- Estimate latent variable model $\Pr(Y|\text{do}(T), X) = E_{F|X} \Pr(Y|\text{do}(T), X, F) = E_{F|X} \Pr(Y|T, X, F)$
- Question 1: is treatment effect identified?

Identification, definition

Definition 3.2.3 (Identifiability)
Let $Q(M)$ be any computable quantity of a model M. We say that Q is identifiable *in a class $\mathbf{M}$ of models if, for any pairs of models M_1 and M_2 from $\mathbf{M}$, $Q(M_1) = Q(M_2)$ whenever $P_{M_1}(v) = P_{M_2}(v)$. If our observations are limited and permit only a partial set F_M of features (of $P_M(v)$) to be estimated, we define Q to be* identifiable from F_M *if $Q(M_1) = Q(M_2)$ whenever $F_{M1} = F_{M2}$.*

Loosely:

- Defined with respect to model family M

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Loosely:

- Defined with respect to model family M
- If models $m_1, m_2 \in M$ fit the data equally well
- m_1, m_2 agree on the treatment effect

Identification, our case

Here:

- Not identified given data and DAG

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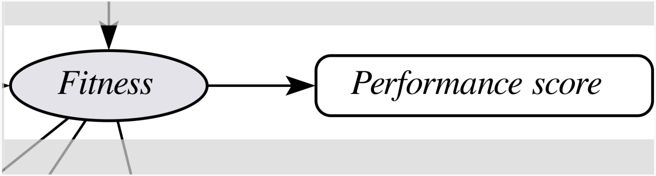
- Naturally expressed as (parts-of) the data generating process

PROTECT step 2: add parametric assumptions



Assumption

- expected WHO performance score always higher with higher fitness

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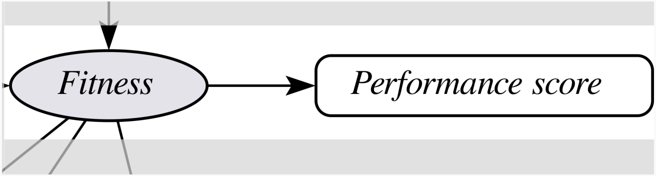

Assumption

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- e.g. logistic regression, fix sign of Fitness

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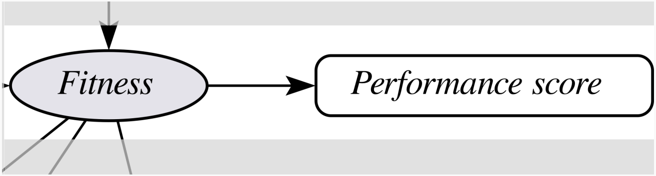

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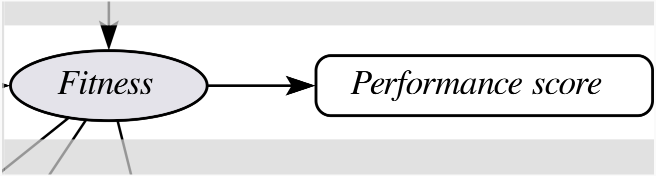

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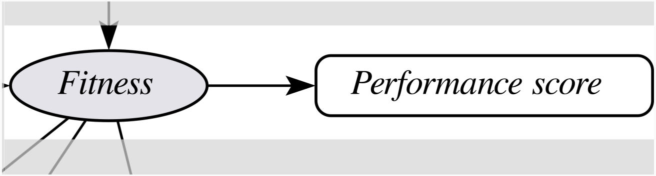

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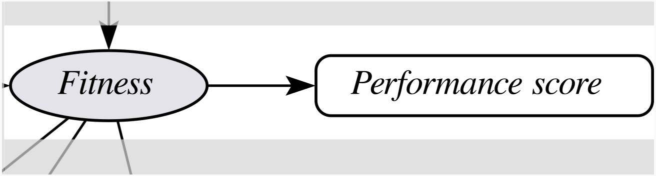

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- 'buying' identification with assumptions we're comfortable with making

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- Identification criterion: unimodal posterior over treatment effect (necessary, not sufficient)

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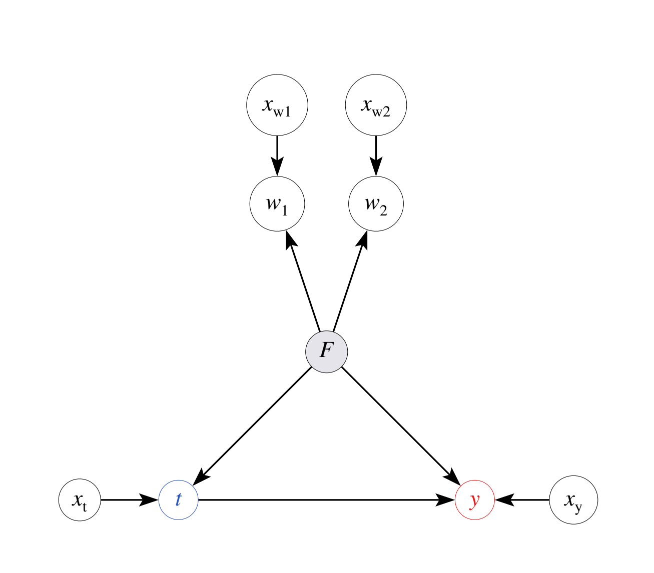
PROTECT DAG model selection assumed



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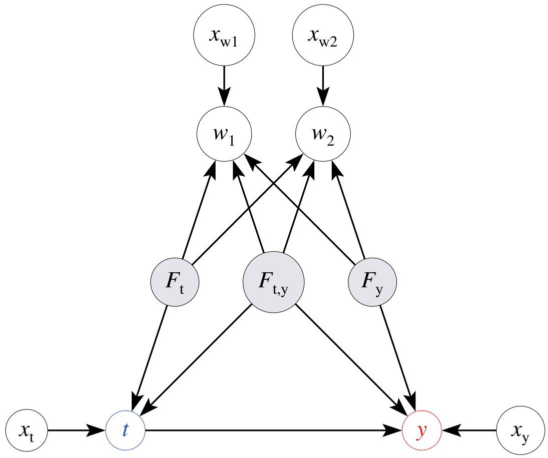

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Final inference

Given models m_j, Bayesian Model Average for all models that pass the tests

PROTECT: proxy based individual treatment effect modeling in cancer

PROTECT has three steps:

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3. follow model selection procedure

Application to state III non-small cell lung cancer

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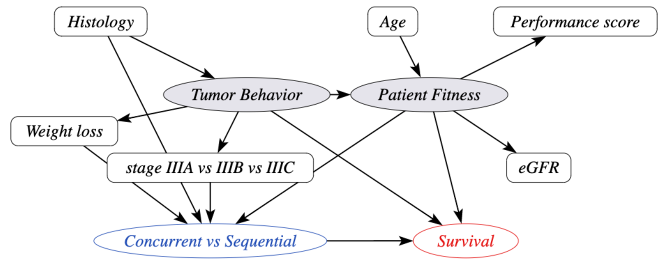
  - 'intention-to-treat' treatment
  - age, sex, eGFR, weight loss, performance score, stage IIIA/IIIB/IIIC, histology type

PROTECT step 1: add proxies / causes of fitness and aggressiveness



PROTECT step 2: specify parametric assumptions for all arrows in the DAG

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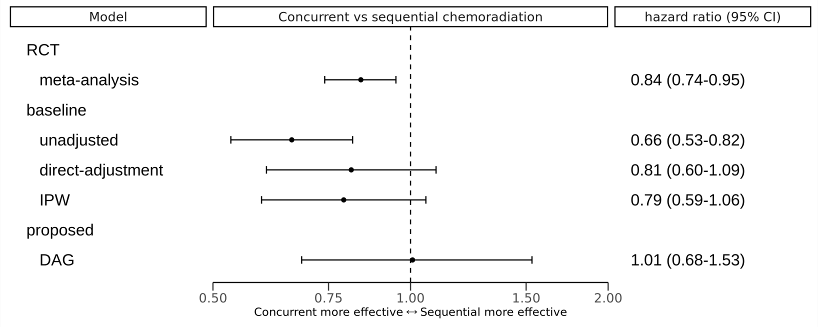
- estimation details:
  - dealing with missing data
  - marginalized DAG (no latent factor for behavior)

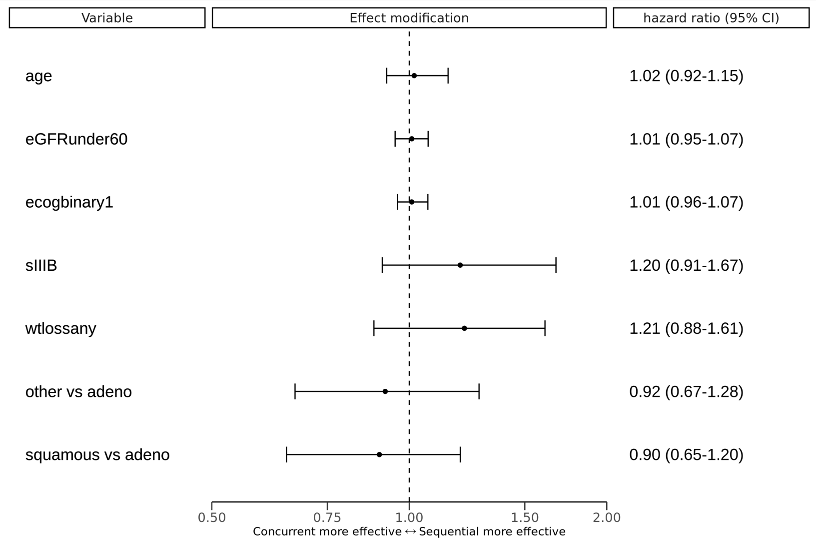
Estimation details

- HMC (NUTS)
- 16 chains
- converged chains (Rhat)
- few divergent transitions (false positives)
- unimodal posterior

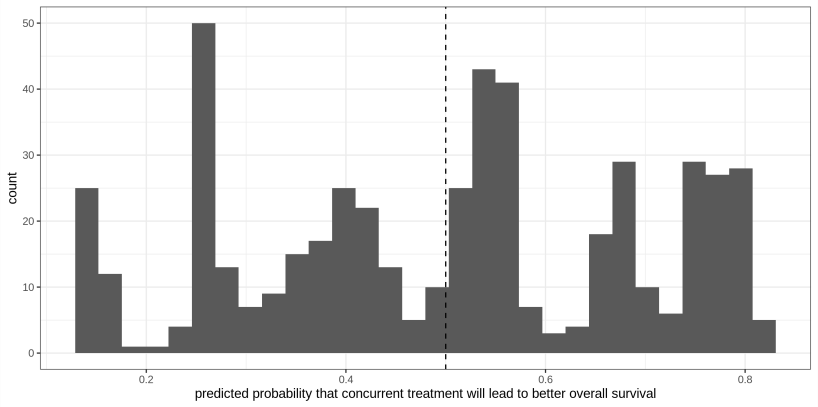
Results: Average Treatment Effects



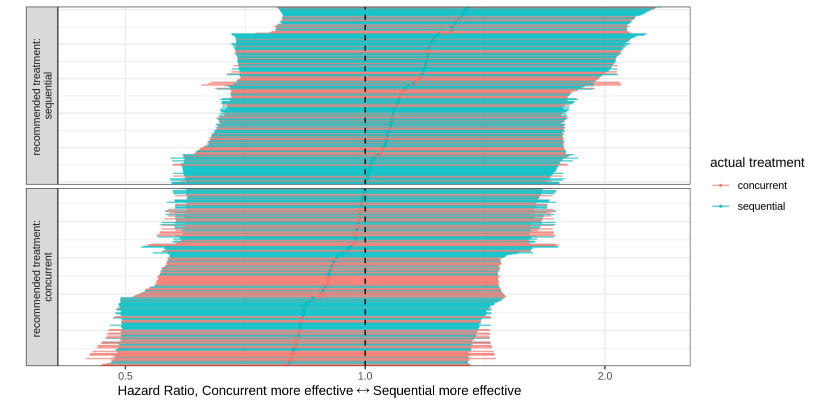
Results: (Friedman) Treatment Effect Modification



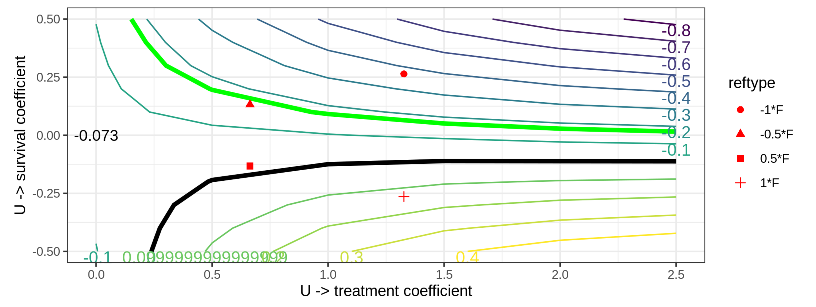
Results: Should treat probabilities



Results: Individual treatment effect estimates



sensitivity to unobserved confounder



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- for NSCLC: treatment effect estimates more credible than standard adjustment, but large confidence intervals

Conclusion

- PROTECT: treatment effect estimation with proxies
- for NSCLC: treatment effect estimates more credible than standard adjustment, but large confidence intervals
- point estimate smaller than RCT estimate, robust to unobserved confounders of reasonable strength

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