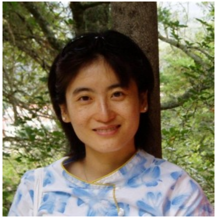
Robust and efficient estimation in the presence of a randomly censored covariate

Brian Richardson

November 12, 2024

Acknowledgements

Seong-Ho Lee, PhD	Yanyuan Ma, PhD	Karen Marder, MD	Tanya Garcia, PhD
			
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Huntington's Disease

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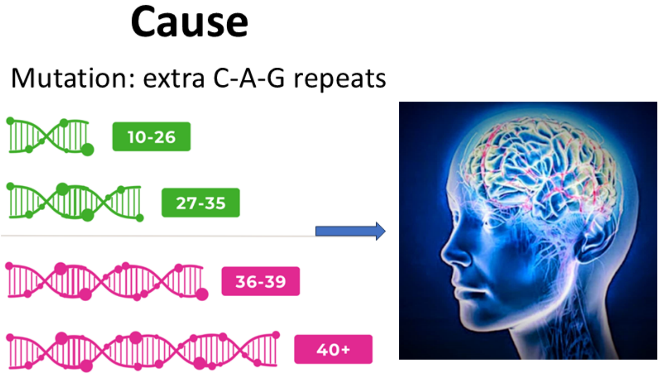

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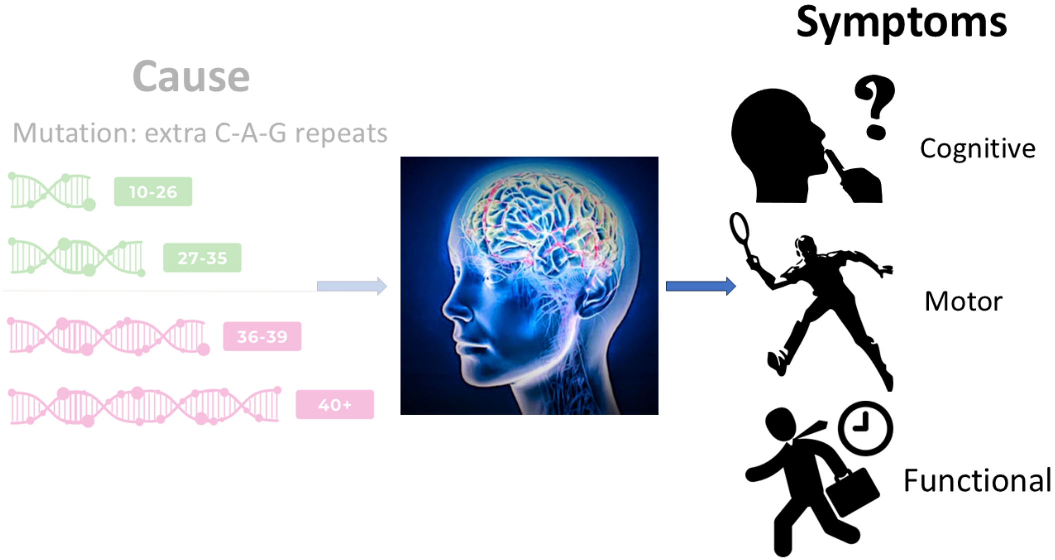

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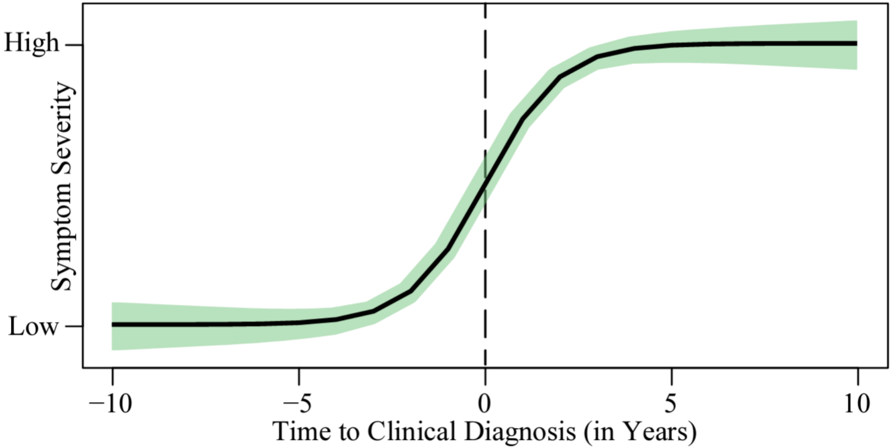

(Lotspeich et. al., 2024)

Censoring in Huntington's Disease Studies

- **model**: $\mathrm{E}(Y|X) = m(X, \beta)$

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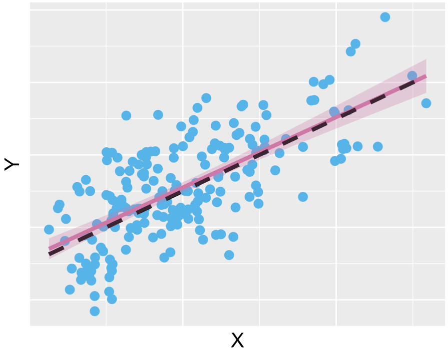
"Humans are precious"

Want methods that are **robust** and **efficient**

Censored Covariates: a Simple Example



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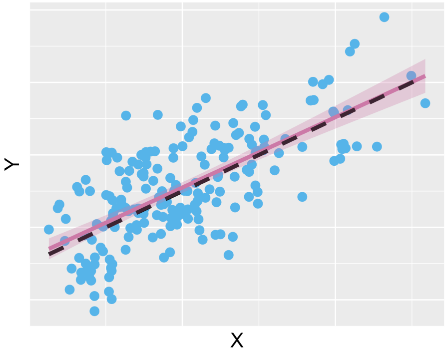

- Regression model: $\mathrm{E}(Y|X) = \beta_0 + \beta_1 X$
- Estimate $\boldsymbol{\beta} = (\beta_0, \beta_1)^T$ with least squares/maximum likelihood
- Solve estimating equation $\sum_{i=1}^{n}(Y_i - \beta_0 - \beta_1 X_i)(1, X_i)^T = \mathbf{0}$

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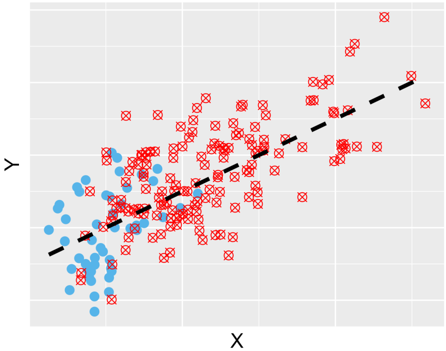

Problem: X is censored by a **random censoring time** C

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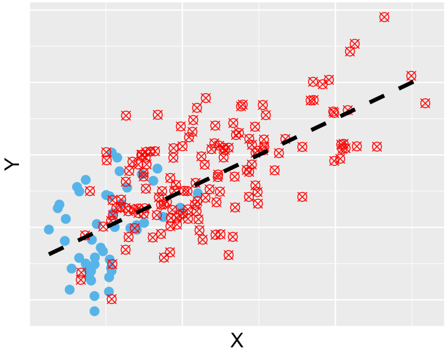

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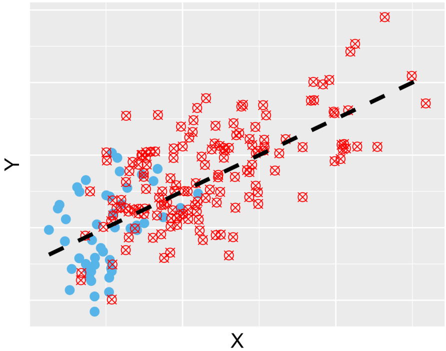
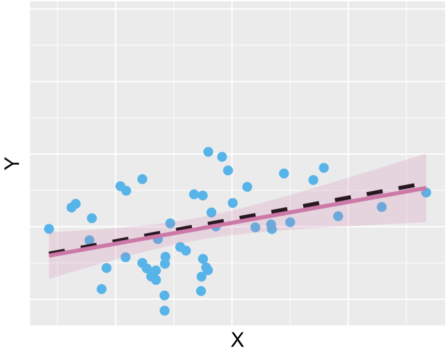


Problem: X is censored by a **random censoring time** C

- $W = \min(X, C)$
- $\Delta = I(X \leq C)$
- assume: $C \perp\!\!\!\perp (X, Y)$

Complete Case Analysis



Only use *uncensored* observations

Solve estimating equation
$\sum_{i=1}^{n} \Delta_i (Y_i - \beta_0 - \beta_1 W_i)(1, W_i)^T = \mathbf{0}$

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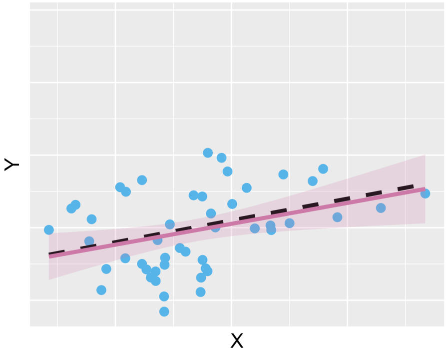

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✓ Consistent

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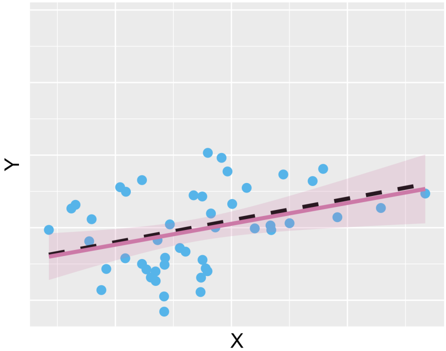

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- ✓ Consistent
- ✗ Inefficient

Maximum Likelihood Estimation (MLE)

$$f_{Y,W,\Delta}(y, w, \delta, \boldsymbol{\beta}, \boxed{\boldsymbol{\alpha}}) \propto \underbrace{\{f_{Y|X}(y, w, \boldsymbol{\beta})\}^{\delta}}_{\text{uncensored}} \underbrace{\left\{\int_{w}^{\infty} f_{Y|X}(y, x, \boldsymbol{\beta}) \boxed{f_X(x, \boldsymbol{\alpha})} dx\right\}^{1-\delta}}_{\text{censored}}$$

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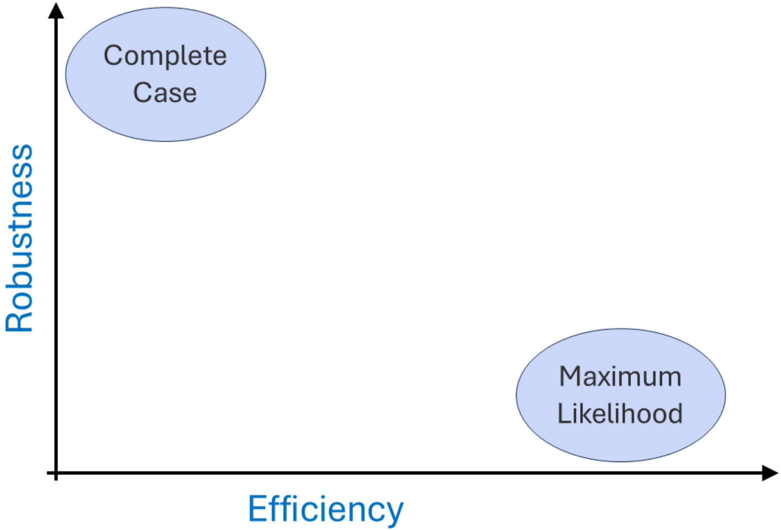
✗ inconsistent when model for f_X is incorrect

Existing Opportunity



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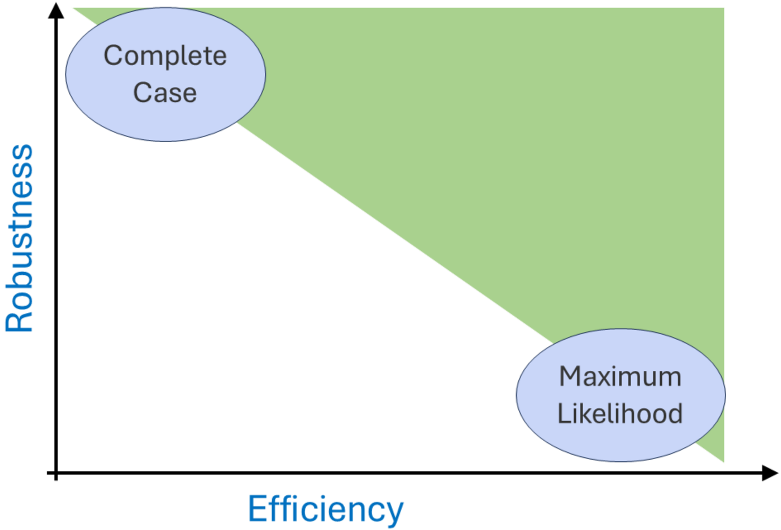

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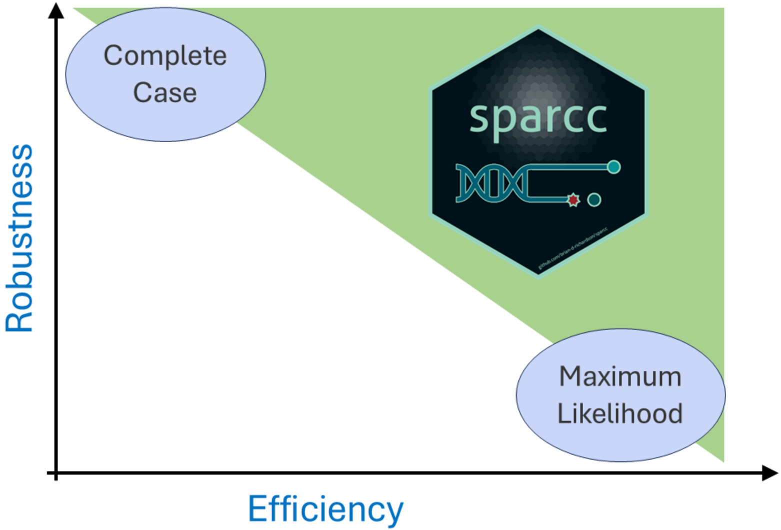

The Semiparametric Recipe

- **model**: $\mathrm{E}(Y|X) = \beta_0 + \beta_1 X$

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- **goal:** derive the SPARCC estimator

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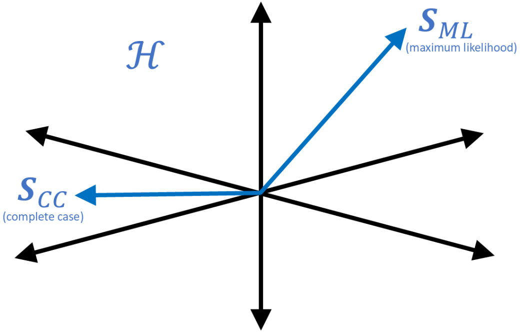

- **Hilbert space** of estimating functions

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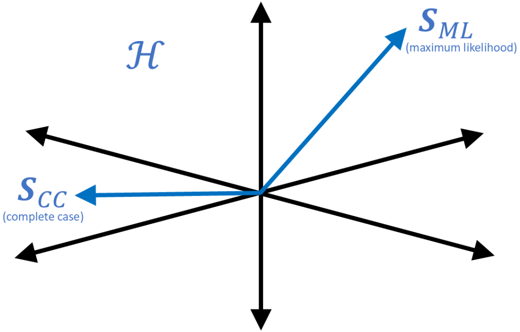

- **Hilbert space** of estimating functions
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  $\langle \boldsymbol{h}, \boldsymbol{g} \rangle \equiv \mathrm{E}(\boldsymbol{h}^T \boldsymbol{g})$

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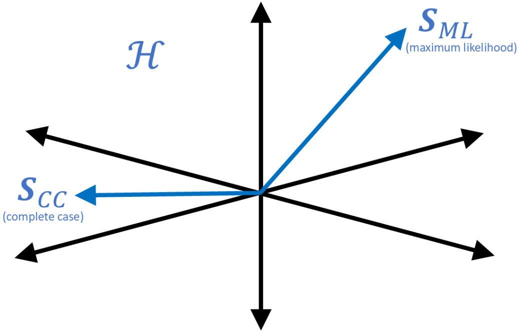
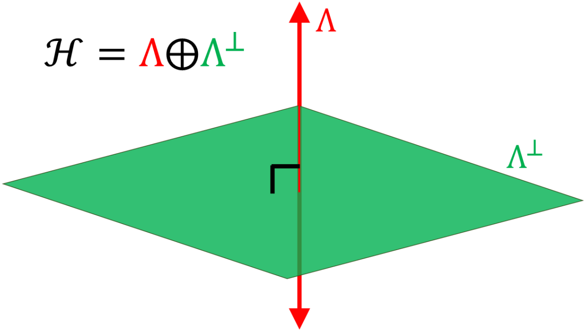


- **Hilbert space** of estimating functions
- **covariance inner product**
  $\langle \boldsymbol{h}, \boldsymbol{g} \rangle \equiv \mathrm{E}(\boldsymbol{h}^T \boldsymbol{g})$
- **orthogonal** $\Leftrightarrow$ **uncorrelated**

$$\boldsymbol{h} \perp \boldsymbol{g} \iff \langle \boldsymbol{h}, \boldsymbol{g} \rangle = 0$$

The Semiparametric Recipe

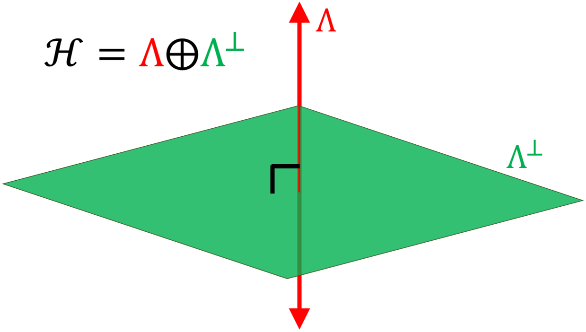
$$\mathcal{H} = \Lambda \oplus \Lambda^{\perp}$$



- construct Λ using **nuisance scores**

$$\partial \log f_{Y,W,\Delta}(y, w, \delta, \boldsymbol{\beta}, \boldsymbol{\eta}) / \partial \boldsymbol{\eta}$$

The Semiparametric Recipe



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- orthogonal complement $\Lambda^{\perp}$

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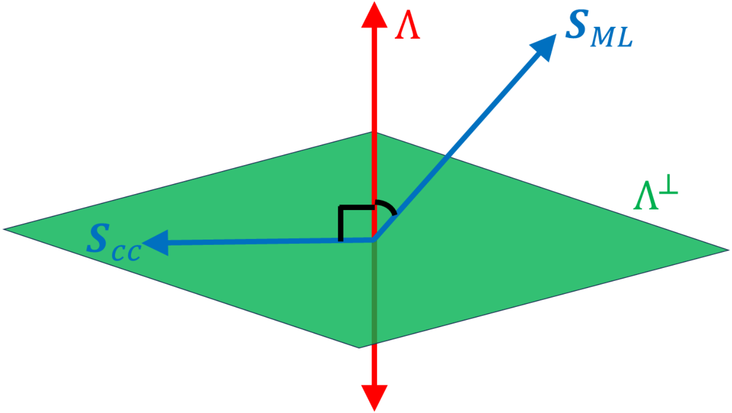

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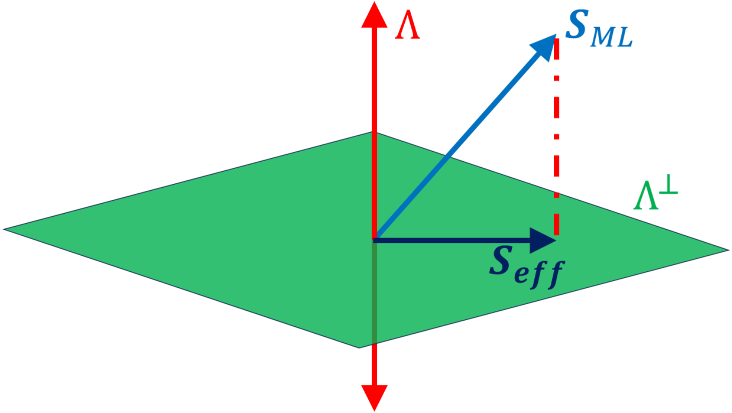

Implementing the SPARCC Estimator

The **SPARCC Estimator** $\widehat{\beta}$ is the solution to

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Can be modeled either **parametrically** or **nonparametrically**

Properties of the SPARCC Estimator

With **parametric** f_X, f_C, $\widehat{\beta}$ is:

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With **nonparametric** f_X, f_C, $\widehat{\beta}$ is:

- ✓ **consistent**
- ✓ **semiparametric efficient**

Simulation Setup

$$\underbrace{Y}_{\text{outcome}} |X, Z \sim N(\beta_0 + \beta_1 X + \beta_2 Z, \sigma^2)$$

Simulation Setup

$$Y | \underbrace{X}_{\text{censored}}, Z \sim N(\beta_0 + \beta_1 X + \beta_2 Z, \sigma^2)$$

Simulation Setup

$$Y|X, \underbrace{Z}_{\text{uncensored}} \sim N(\beta_0 + \beta_1 X + \beta_2 Z, \sigma^2)$$

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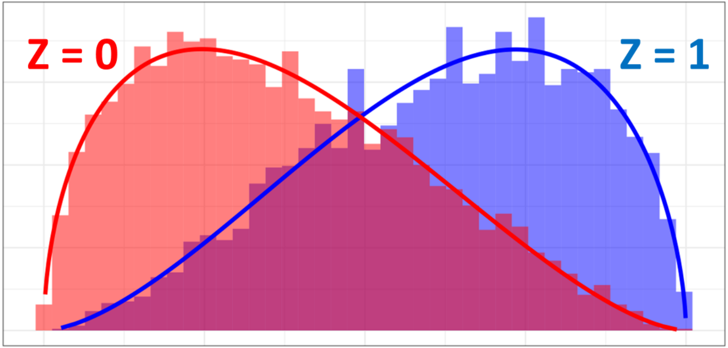
$$Y|X, Z \sim N\Big(\underbrace{\beta_0 + \beta_1 X + \beta_2 Z, \sigma^2}_{\text{parameter of interest: } (\beta_0, \beta_1, \beta_2, \sigma^2)}\Big)$$

Simulation Setup: Nuisance Distributions

$$\boldsymbol{\eta} = (f_{X|Z}, f_{C|Z})$$

Simulation Setup: Nuisance Distributions

$f_{X|Z}$ correct parametric:



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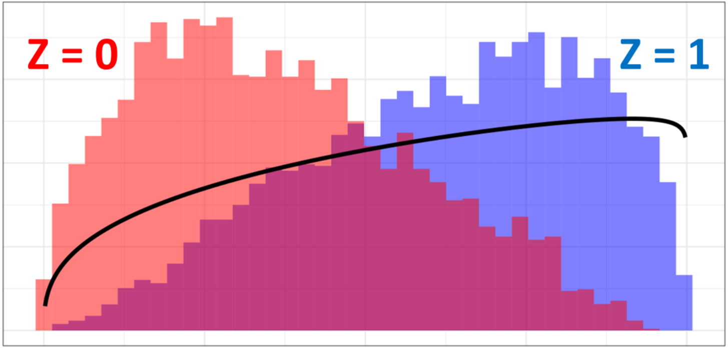

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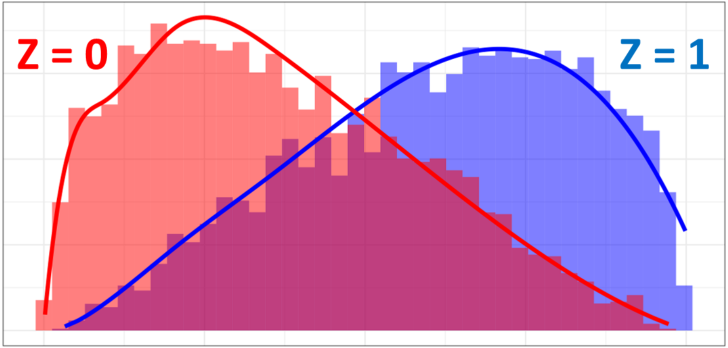
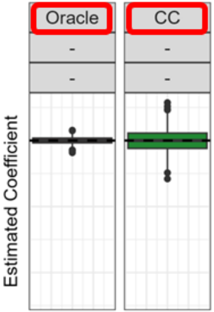


Simulation Results: Robustness



(censoring proportion $q = 0.8$)

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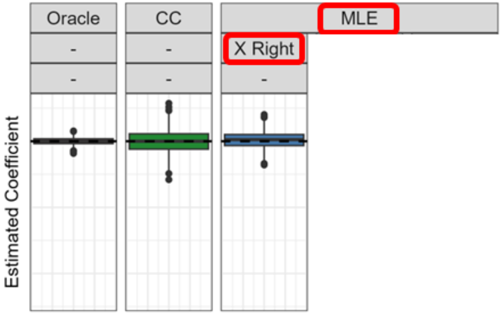

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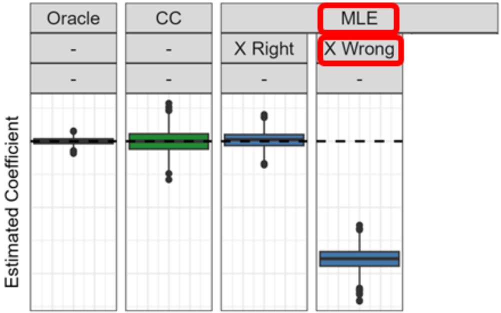

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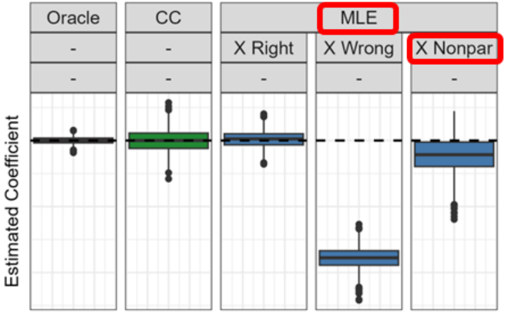

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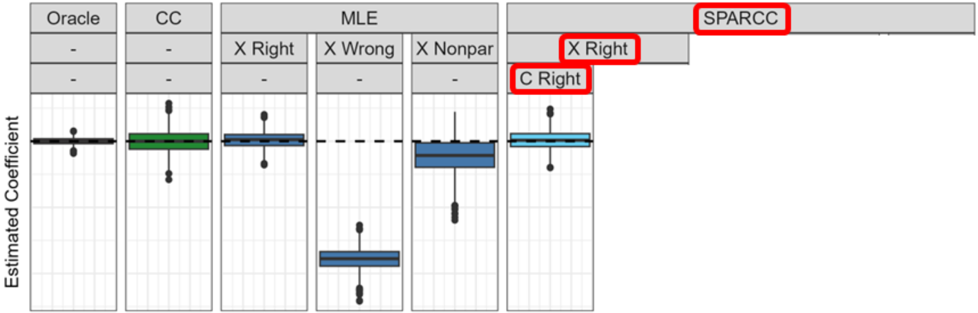

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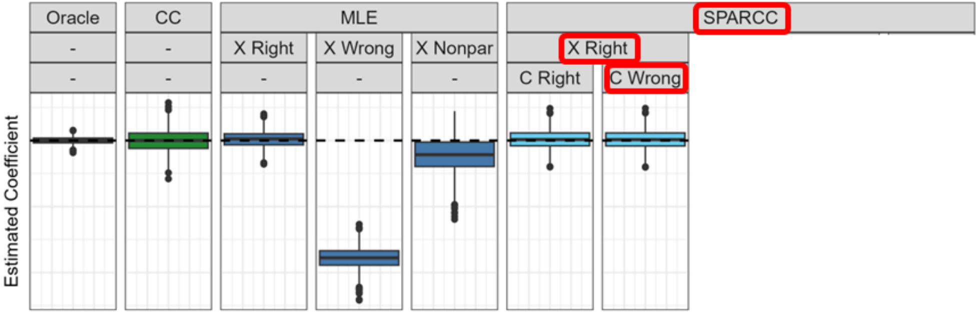

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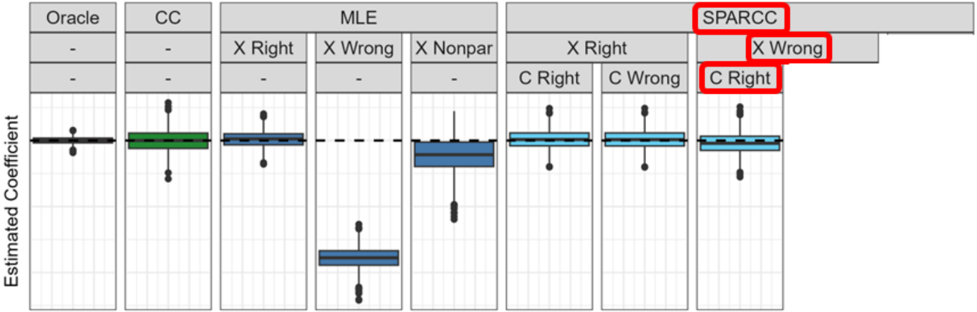

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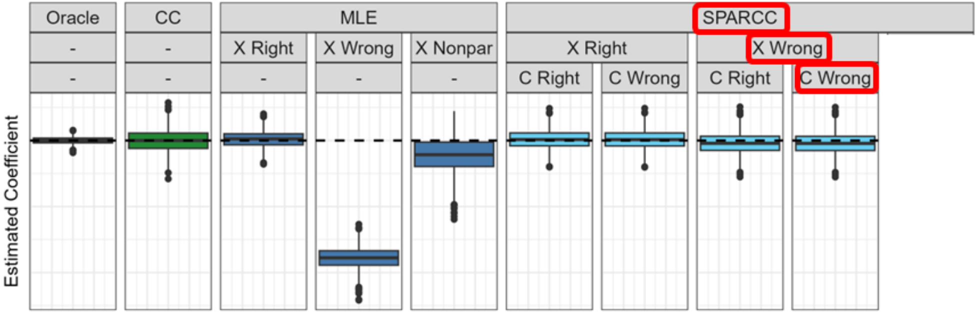

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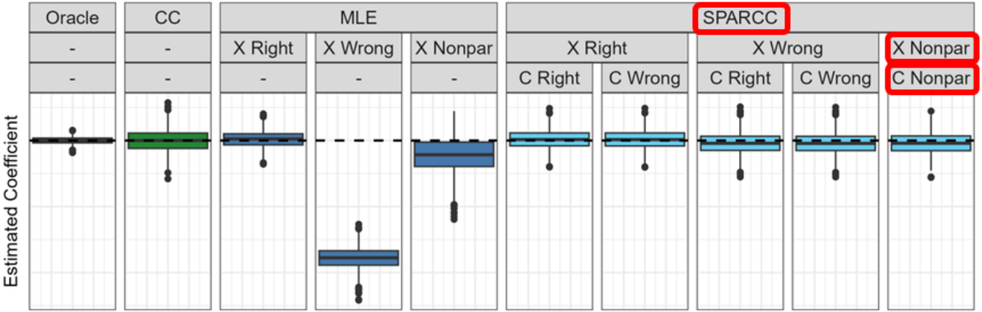

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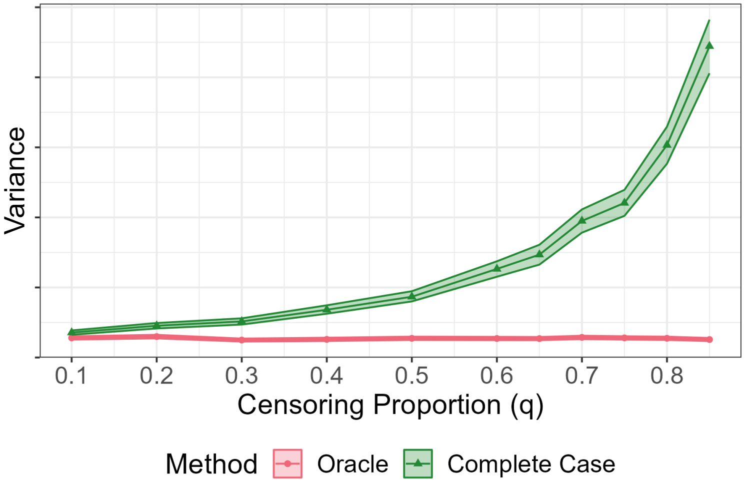
Simulation Results: Efficiency



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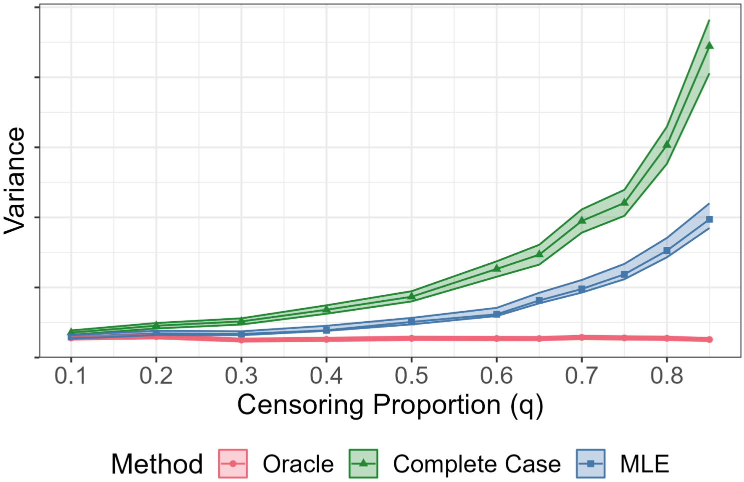

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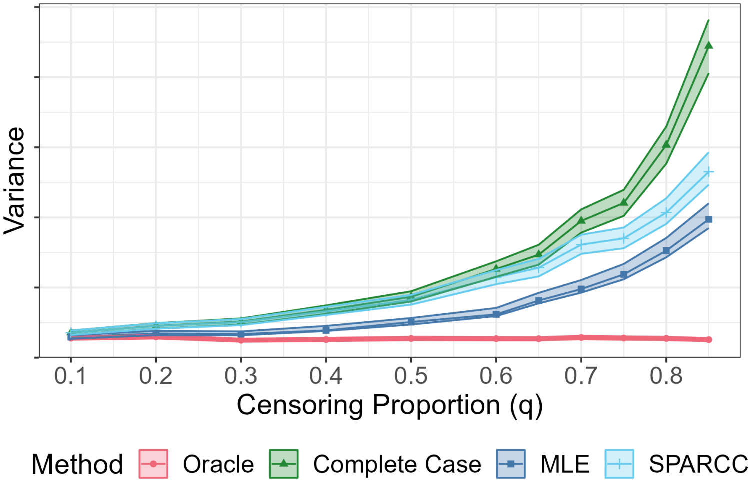

ENROLL-HD Study

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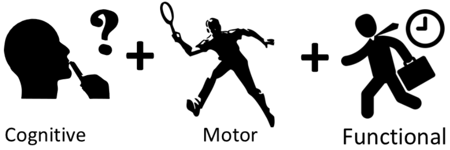
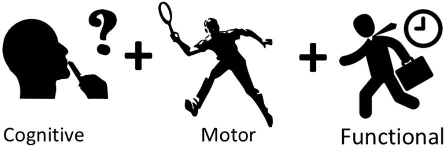


ENROLL-HD Study

- large, observational study of people with Huntington's disease or mutation
- **composite Unified Huntington Disease Rating Scale (cUHDRS) score**



- **CAP** Score: product of age and mutation severity

Huntington's Disease Application

$$\underbrace{Y}_{\text{cUHDRS}} | X, Z \sim N(\beta_0 + \beta_1 X + \beta_2 Z, \sigma^2)$$

Huntington's Disease Application

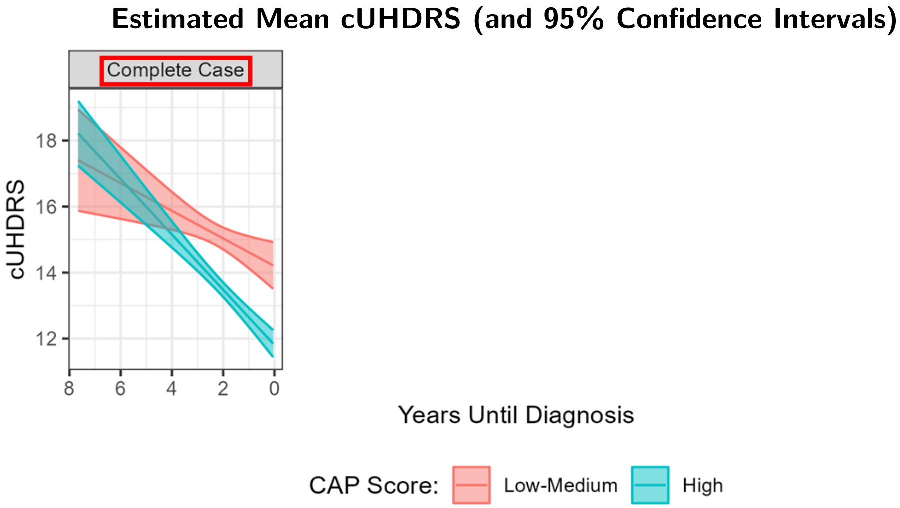
$$Y \mid \underbrace{X}_{\text{time to diagnosis}}, Z \sim N(\beta_0 + \beta_1 X + \beta_2 Z, \sigma^2)$$

Huntington's Disease Application

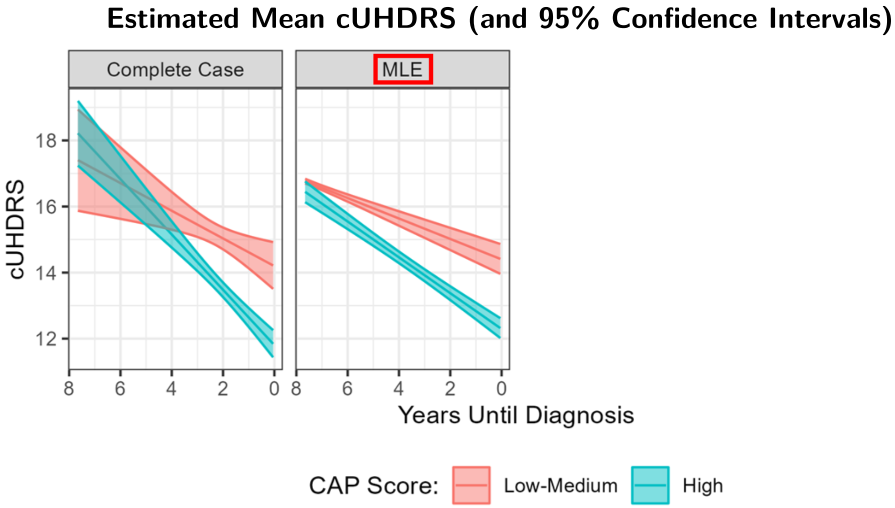
$$Y | X, \underbrace{Z}_{\text{CAP group}} \sim N(\beta_0 + \beta_1 X + \beta_2 Z, \sigma^2)$$

- **sample size**: $n = 4530$
- **censoring rate**: $q = 81.9\%$

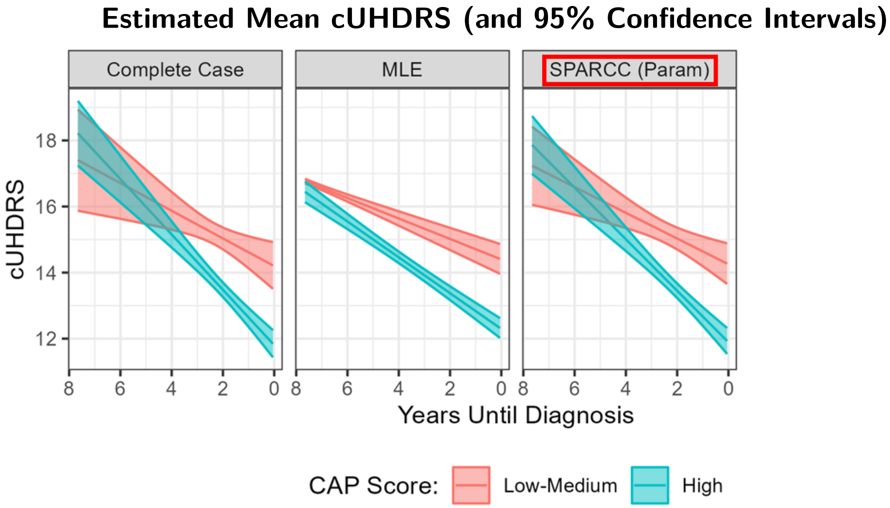
Huntington's Disease Results



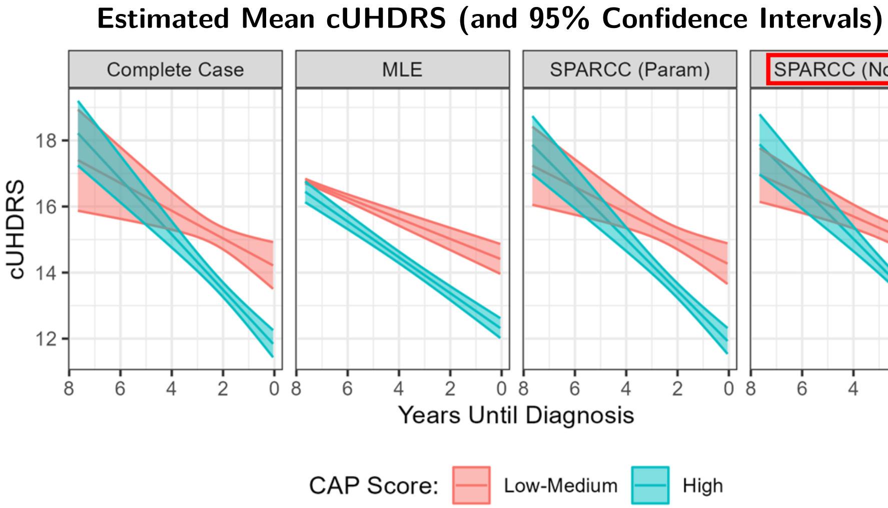
Huntington's Disease Results



Huntington's Disease Results



Huntington's Disease Results



Discussion

Robustness and **efficiency** matter when studying humans

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Proposed **SPARCC** estimator has these properties

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Future Work:

- implementation and computation for general models

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Future Work:

- implementation and computation for general models
- longitudinal extension

SPARCC: **S**emi**par**ametric **C**ensored **C**ovariate Estimation

Paper on arXiv

GitHub R package