

# Methods for Selection Bias in the UK Biobank

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# Unrepresentativeness in the UK Biobank

## UK Biobank

- **Goal:** Study exposures and outcomes that affect aging populations
- 500,000+ participants aged 40-70 when recruited between 2006 and 2010
- *Not representative of the UK general population* (Fry et al. 2017)

## UK Biobank imaging cohort

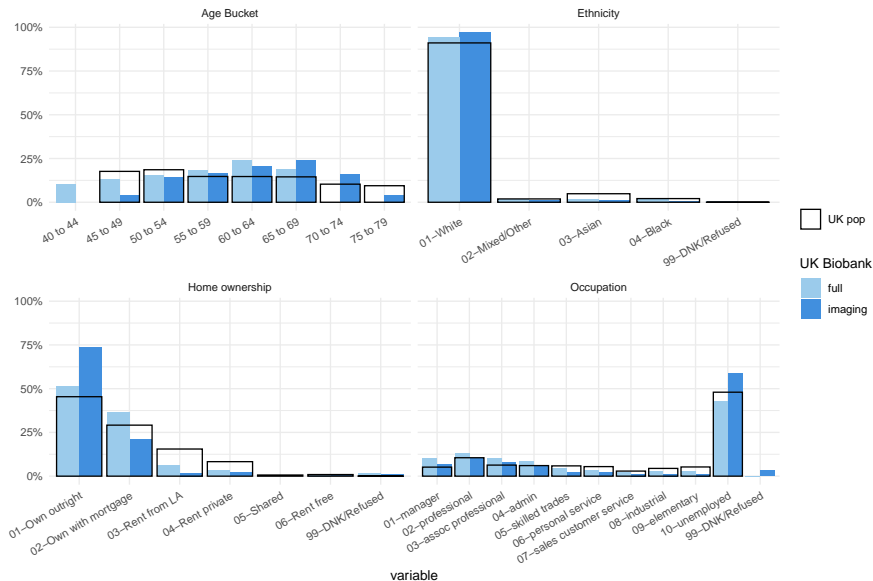
- Subset of UKB participants, undergo additional imaging exams
- 21,407 complete, valid T1 structural MRIs (4% of UKB)

## 2016 Health Survey for England

- Designed to estimate prevalence of health outcomes (e.g. smoking, obesity, high blood pressure)
- 2016 survey contains 10,067 respondents, 4,318 aged 45-80

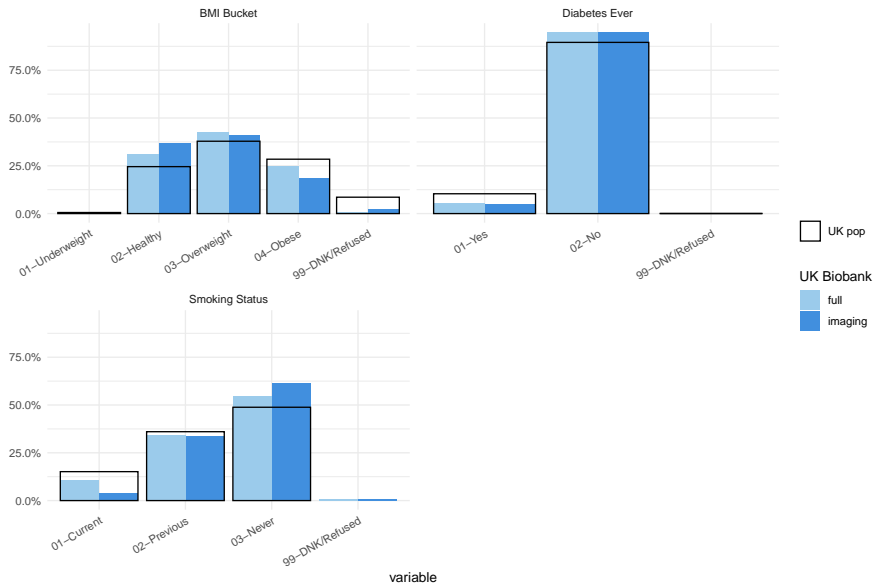
# Quantifying unrepresentativeness of the UKB

## Demographic covariates



# Quantifying unrepresentativeness of the UKB

## Health covariates

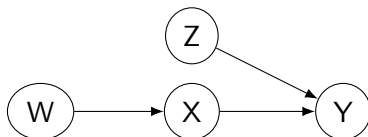


Why is unrepresentativeness a problem?

# Quick note on structural causal models (SCMs)

SCMs use directed acyclic graphs (DAGs) as “a mathematical language for integrating statistical and subject-matter information,” specifically information about dependence structures (Pearl 1995)

- **nodes** represent *physical mechanisms*
- **edges** represent *direct causal pathways*

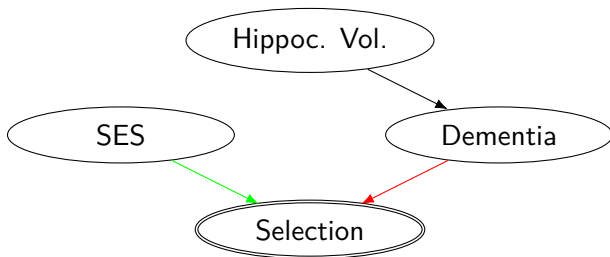


Things we can say:

- there is a *direct* causal pathway from  $X$  to  $Y$
- there is an *indirect* causal pathway from  $W$  to  $Y$
- $X$  *d-separates*  $W$  and  $Y$ , such that  $W \perp\!\!\!\perp Y|X$



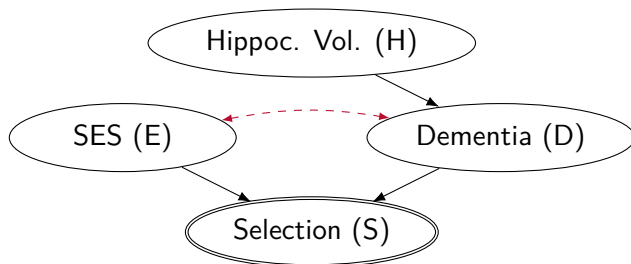
# SCM Example



- SES and participation in UKB are **positively** correlated
- Dementia and participation are **negatively** correlated
- No causal relationship between SES and hippocampal volume (no edge)

Are SES and Dementia independent?

# Collider bias



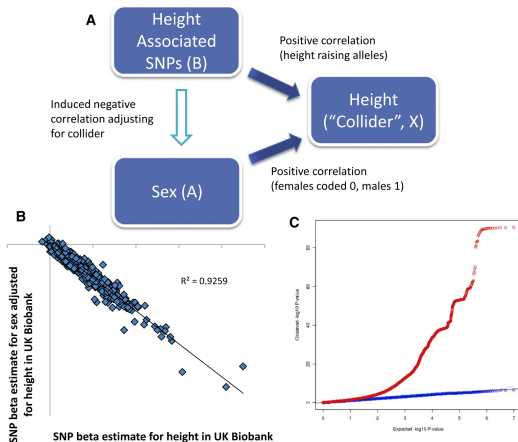
**Collider bias:** “When two variables independently influence a third variable, and that third variable is conditioned upon” (Munafò et al. 2018)

Opens a *backdoor path* (spurious association) between E and H.

- Want to know  $P(H|E)$
- But only observe  $P(H|E, S = 1)$
- And, because  $H$ ,  $E$  are *not* independent of  $S$ , those are not the same

# Collider bias example

Day et al. (2016): GWAS using 142,630 observations from the UKB, induced strong collider bias



**Figure 1. Induced Collider Bias between Genetic Variants, Height, and Sex**

(A) Schematic diagram of the scenario in which collider bias can occur between genetic variants, height, and sex.

(B) Spurious autosomal SNP-effect estimates for sex, created by adjusting for height as a covariate, are almost perfectly correlated with SNP-effect estimates for height. In this scenario of collider bias, adjustment for the collider height creates biologically implausible sex associations for the 694 previously identified genome-wide significant autosomal SNPs for height.

(C) A quantile-quantile plot of genome-wide autosomal test statistics for sex  $\sim$  SNP (shown in blue) and sex  $\sim$  SNP + height (shown in red).

Can we recover from selection bias?

# Formal conditions for recovery

Consider the *association* between  $X$  and  $Y$ ,  $P(y|x)$

We can recover from selection bias **if and only if**  $P(y|x)$  can be written in terms of the quantities observed under selection; use *auxiliary variables*  $\mathbf{Z}$

- if  $Y \perp\!\!\!\perp S | \{\mathbf{Z}, X\}$ , then

$$P(y|x) = \sum_{\mathbf{z}} P(y|x, \mathbf{z}, S = 1) P(\mathbf{z}|x)$$

- If  $\{Y \cup X\} \perp\!\!\!\perp S | \mathbf{Z}$ , then

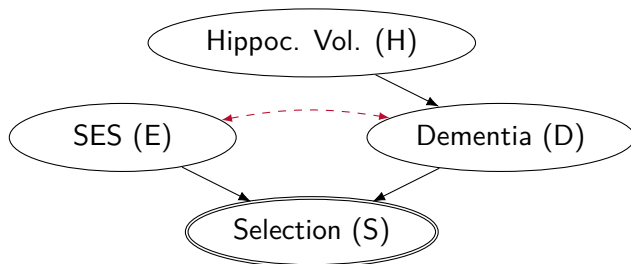
$$P(y|x) = \sum_{\mathbf{z}} P(y|x, \mathbf{z}, S = 1) P(\mathbf{z})$$

**The key:** conditioning on  $\mathbf{Z}$  (and maybe  $X$ ) makes  $Y$  *conditionally independent of selection*  $S$

$P(\mathbf{z})$  and  $P(\mathbf{z}|x)$  are population distributions

# Example

Back to our example. . .



✗  $\{H \cup E\} \perp\!\!\!\perp S|D$

✓  $H \perp\!\!\!\perp S|D, E$

So, can only recover  $P(H|E)$  as

$$P(H|E) = \sum_D P(H|E, D, S = 1)P(D|E)$$

*as long as we observe  $P(D|E)$*

- ① Must assume we have correctly represented the dependence structures (and have correctly identified all necessary elements of  $\mathbf{Z}$ ). This is **hard** to do in practice.
- ② Don't always observe  $P(\mathbf{Z}|X)$  or  $P(\mathbf{Z})$  in full. *Can we estimate it?*
- ③ Can only condition on a limited number of discrete variables  $\mathbf{Z}$  before this breaks down. *What happens when an element of  $\mathbf{Z}$  is continuous?*

# Methods for recovering from selection bias



# Two main methods for recovery

Classes of methods for estimating effects, associations, prevalence in the presence of selection bias:

- **Inverse probability weighting (IPW)**: weight each observed unit by the inverse of the probability of selection,  $w_i \propto 1/P(S = 1|Z_i)$ 
  - **pro**: weights are independent of  $Y$  and  $X$
  - **con**: not always clear how to incorporate into estimators
  - **con**: hard to correctly estimate standard errors of weighted estimators
- **Regression methods**: directly model the outcome of interest  $P(Y|X)$ , accounting for confounders/auxiliary variables
  - **con**: have to estimate separate model for each outcome

# Inverse probability weighting (IPW)

Can be derived exactly from (causal) recovery conditions (Correa, Tian, and Bareinboim 2018):

$$P(\mathbf{y}|do(\mathbf{x})) = \sum_{\mathbf{z}} P(\mathbf{y}|\mathbf{x}, \mathbf{z}, S = 1)P(\mathbf{z} \setminus \mathbf{z}^T|\mathbf{z}^T, S = 1)P(\mathbf{z}^T) \quad (1)$$

$$= \sum_{\mathbf{z}} \frac{P(\mathbf{y}, \mathbf{x}, \mathbf{z}|S = 1)}{P(\mathbf{x}|\mathbf{z}, S = 1)} \frac{P(S = 1)}{P(S = 1|\mathbf{z}^T)} \quad (2)$$

- $P(\mathbf{y}, \mathbf{x}, \mathbf{z}|S = 1)$ , joint distribution of  $\mathbf{Y}$ ,  $\mathbf{X}$  and  $\mathbf{Z}$  under selection bias
- $P(\mathbf{x}|\mathbf{z}, S = 1)$ , the probability of treatment given covariates in the selection-biased sample data
  - related to the *propensity score*  $P(X|\mathbf{Z})$
- $P(S = 1)/P(S = 1|\mathbf{z}^T)$ , the *inverse probability-of-selection weight*

But how should we estimate  $P(S = 1|\mathbf{Z})$ ?

# Estimating $P(S = 1|\mathbf{Z})$

Things to think about when comparing methods for estimating  $P(S = 1|\mathbf{Z})$ :

- ① Weighted **marginal distribution** of  $\mathbf{Z}$  should match that of the population
- ② Avoid extreme weights that inflate the **variance** of estimators (have to account for the additional uncertainty of weights)
- ③ **Computational complexity** of the method
- ④ How well does the method account for interactions between elements of  $\mathbf{Z}$

# Methods: summary

Classic weighting methods:

- ① *Post-stratification*: adjust to the joint distribution of  $\mathbf{Z}$
- ② *Raking*: iteratively adjust the marginal distributions of elements in  $\mathbf{Z}$
- ③ *Calibration*: raking, but with continuous variables as well as discrete variables

Less-common methods:

- ④ *Logit*: estimate the probability of selection directly
- ⑤ *LASSO*: use a LASSO to select variables and interactions for raking

New method:

- ⑥ *BART + raking*: use a Bayesian Additive Regression Tree (BART) to estimate the probability of selection, then rake such that key marginal distributions match those of the population

# Application to the UK Biobank

- ① Generate a probability of missingness  $p_i$  for all 21,407 imaging subjects in the UKB
  - $p_i$  depends on covariates that we know to be related to brain volume (mainly age) so that samples are biased
- ② For sample sizes in  $n_{sim} = 21,407 \times (0.01, 0.02, 0.04, 0.05, 0.075, 0.1, 0.25)$ :
  - ① Draw sample of size  $n_{sim}$  from imaging cohort with probability proportional to  $p_i$
  - ② Weight sample to  $P(\mathbf{Z})$  defined by UKB imaging cohort using each of 6 methods
  - ③ Perform steps 2.1-2.2 1000 times

# Simulation overview

Evaluate methods based on:

- **design effect:** measures the decrease in effective sample size (ESS) from weighting

$$\text{deff}(\mathbf{w}) = 1 + \text{Var}(\mathbf{w})$$

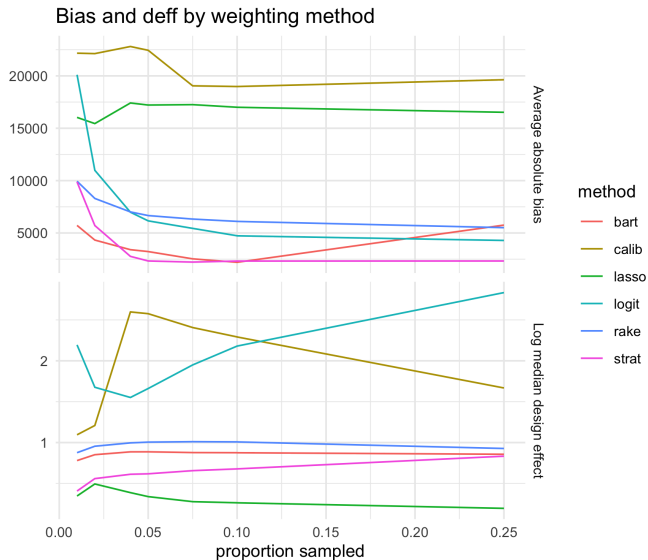
$$ESS = \frac{n}{\text{deff}(\mathbf{w})}$$

- **Absolute bias** of estimated average total brain volume

$$\text{bias} = |\bar{Y}^w - \mu|$$

$$\bar{Y}^w = \frac{1}{n_{sim}} \sum_{i=1}^{n_{sim}} Y_i \hat{w}_i$$

# Simulation results

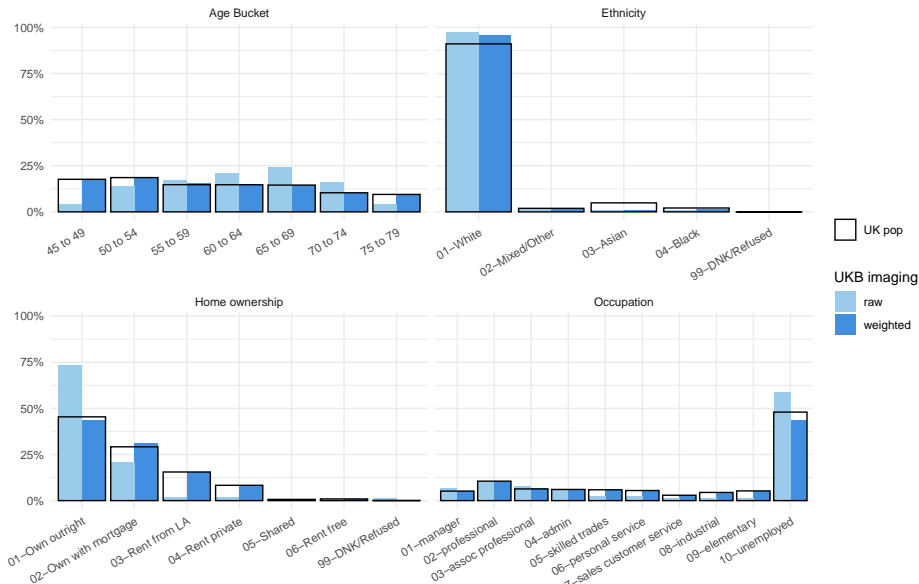




- *Post-stratification* performs surprisingly well, likely due to the size of the data set
  - note that stratification variables chosen with a random forest (not the standard implementation)
- *BART + raking* outperforms other methods at the smallest sample sizes (which is probably the most realistic setting)
- *Calibration* performs very poorly - fails to correct bias and has large variance (likely from sensitivity to age distribution)
- Directly predicting  $P(S = 1|\mathbf{Z})$  with *logistic regression* corrected bias well, but at a rather large cost in variance
- *LASSO* has smallest deff, but also fails to correct bias (variable selection not working well)

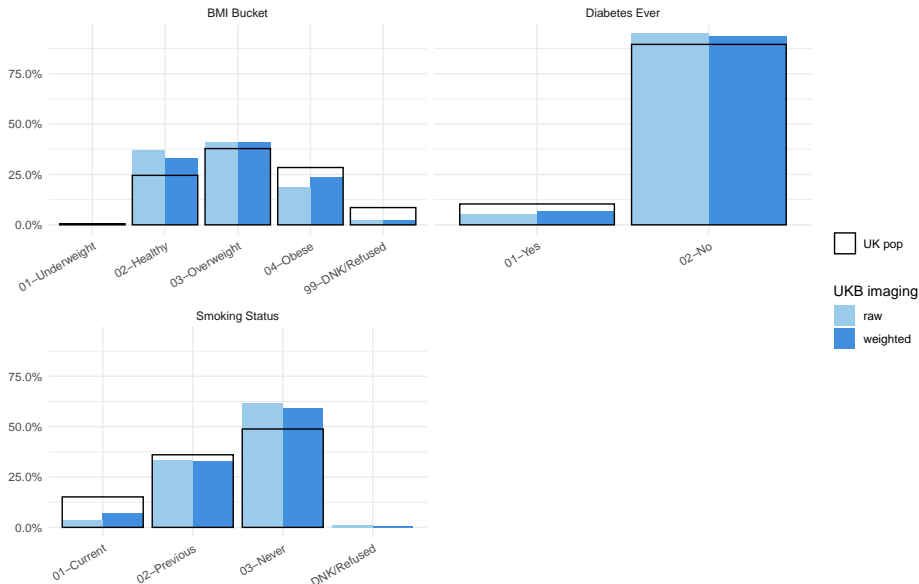
# Application to UK Biobank imaging cohort

## Weighted demographic distributions



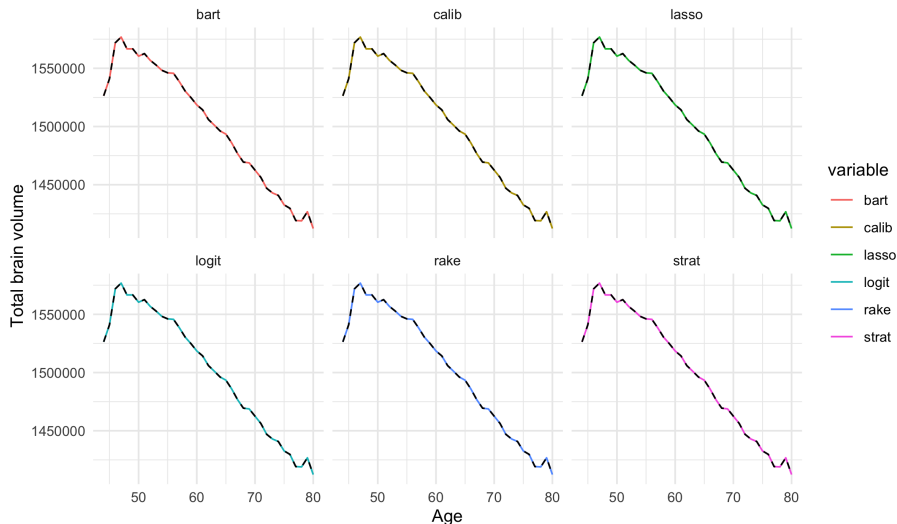
# Application to UK Biobank imaging cohort

## Weighted health outcome distributions



# Application to the UK Biobank imaging cohort

Total brain volume by age



- Be wary of collider bias when estimating associations in the UK Biobank!
- SCMs are a good framework for thinking about dependence structures, potential sources of bias, and if that bias can be corrected
- **inverse probability weighting** can be used to adjust for selection bias, many different ways to estimate weights
- Weighting the UKB imaging cohort corrects most of the bias in the demographic covariates, but only some of the bias in health outcomes

# Appendix

# Method 1: Post-stratification

Adjust to the *joint* distribution of  $\mathbf{Z}$ . This is exactly the definition for recovery (i.e. a sum over all combinations of levels of  $\mathbf{Z}$ )

- 1 Define strata based on the full joint distribution of  $\mathbf{Z}$
- 2 Calculate the probability of selection for each stratum
- 3 Apply stratum-level estimates to individuals

Example:

sex	age	N (sample)	N (pop)	$\hat{P}(S = 1 \mathbf{Z})$	$w^s$
Male	under 50	35	320	$\frac{35}{320} = 0.109$	$\frac{0.1}{0.109} = 0.917$
Male	50 plus	11	133	0.083	1.20
Female	under 50	41	355	0.115	0.870
Female	50 plus	13	192	0.068	1.47

where  $P(S = 1) = 0.1$

Then, all men under 50 in the study are given  $w^s = 0.917$

# Method 1: Post-stratification

## Pros:

- quick, closed-form solution
- weighted joint distribution of  $\mathbf{Z}$  exactly matches that of the population

## Cons:

- $\mathbf{Z}$  must be discrete
- can only consider a limited number of  $\mathbf{Z}$  before the strata get too small



## Method 2: Raking

*Iterative proportional fitting*; iteratively adjust the *marginal* distributions of auxiliary variables **Z**

- 1 Post-stratify to the population sex distribution
- 2 Post-stratify the *weighted* sample to the population age distribution and update the weights
- 3 Post-stratify the *new weighted* sample to the population sex distribution and update weights

...

Stop when weights stabilize (according to a tolerance threshold  $\epsilon$ )

# Method 2: Raking

## Pros:

- Weights are more stable, less extreme than post-stratification
- Can consider a large set of variables  $\mathbf{Z}$

## Cons:

- Iterative (may never converge)
- Not considering interactions between variables

(Basically the opposite of post-stratification)

## Method 3: Calibration

A generalization of raking that allows for continuous  $\mathbf{Z}$

Instead of iterating over marginal distributions of elements in  $\mathbf{Z}$  (i.e.  $P(\text{sex})$  and  $P(\text{age})$ ), we iterate over the totals of each level of each element in  $\mathbf{Z}$  (i.e. female, male, under 50, over 50).

With this formulation, we can also enforce constraints (weight) on **continuous** variables. \* e.g. we constrain the mean age of the sample

*Con:* can be very finicky, even less likely to converge than raking

## Method 4: Directly estimate $\hat{P}(S = 1|\mathbf{Z})$ with regression

We use logistic regression to estimate  $\hat{P}(S_i = 1|\mathbf{Z}_i)$  because selection is binary ( $S = 1$  if observed, 0 otherwise):

$$\hat{P}(S_i = 1|\mathbf{Z}_i) = \text{logit}^{-1}(\beta\mathbf{Z}_i)$$

### Pros:

- Can account for a large  $\mathbf{Z}$ , including continuous variables and interactions
- Don't need custom weighting tools, just logistic regression

### Cons:

- Weighted distribution of  $\mathbf{Z}$  will almost certainly not match population distributions (making results much less interpretable)
- Requires individual-level population data

## Method 5: Raking with LASSO variable selection

**Problem:** Both raking and post-stratification can fail when  $\mathbf{Z}$  is too large

**Solution:** Select significant subsets of  $\mathbf{Z}$  using LASSO, then rake to those marginals (Caughey and Hartman 2017)

General procedure:

- 1 Specify all levels of  $\mathbf{Z}$  and subsets to consider (i.e. all first-order terms, and maybe two-way interactions)
- 2 Fit LASSO to  $S_i = \text{logit}^{-1}(\beta \mathbf{Z}_i)$
- 3 Fit LASSO to  $Y_i = f(\beta \mathbf{Z}_i)$  ( $f$  depends on likelihood of  $Y$ )
- 4 Rake to marginal distributions of all levels of  $\mathbf{Z}$  for which the corresponding  $\beta \neq 0$  in either of the LASSOs

**Caution:** Highly dependent on LASSO performance

## Method 6: BART + raking

**Intuition:** Use **Bayesian additive regression tree (BART)** to estimate  $P(S = 1|\mathbf{Z})$ , then rake to selected  $\mathbf{Z}$  so that marginal distributions match (for interpretability)

Why a BART?

- Trees are great for interactions
- Some parallels to post-stratification

(but could use any method)

**Caution:** Computation time much greater than other methods

# References I

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