Selecting Genetic Variants Using Knockoff Under Collider Bias

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A motivating question

- Severe mental illnesses overlap in symptoms and share some genetic risks

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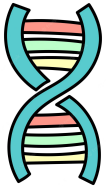

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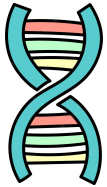

Symptoms
& Diagnosis

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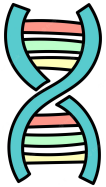

Symptoms & Diagnosis

Neurocognitive function

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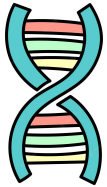

Symptoms & Diagnosis

Neurocognitive function

- Demographics
- Medication
- Substance use
- …

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Case-control study design

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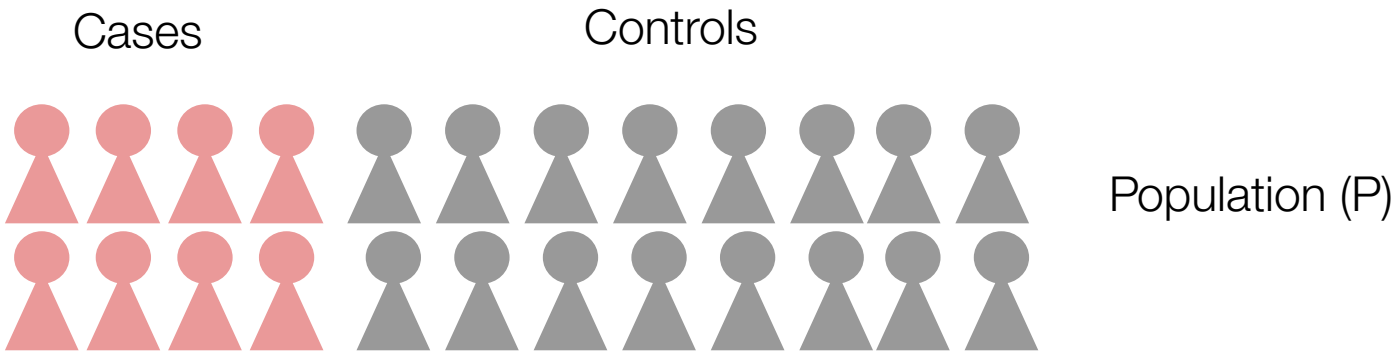

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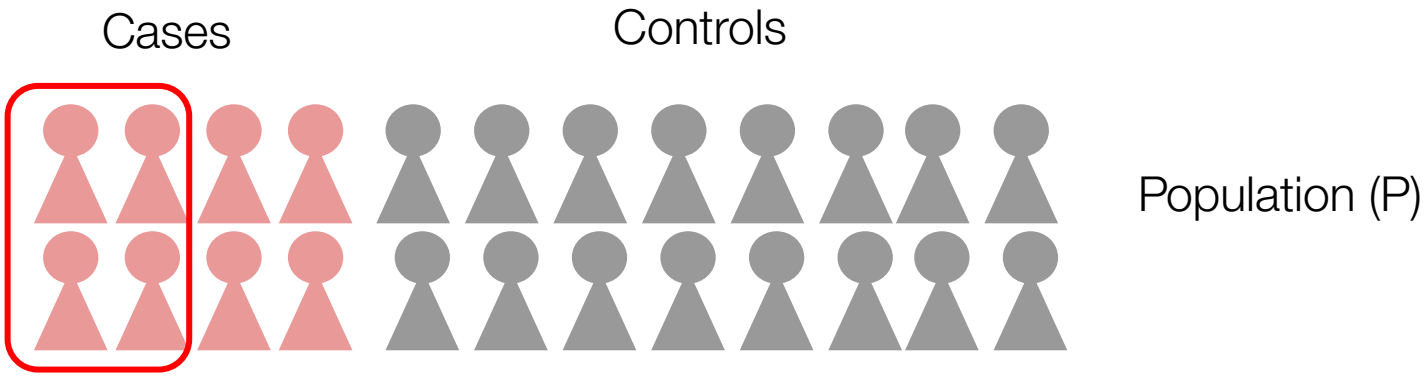

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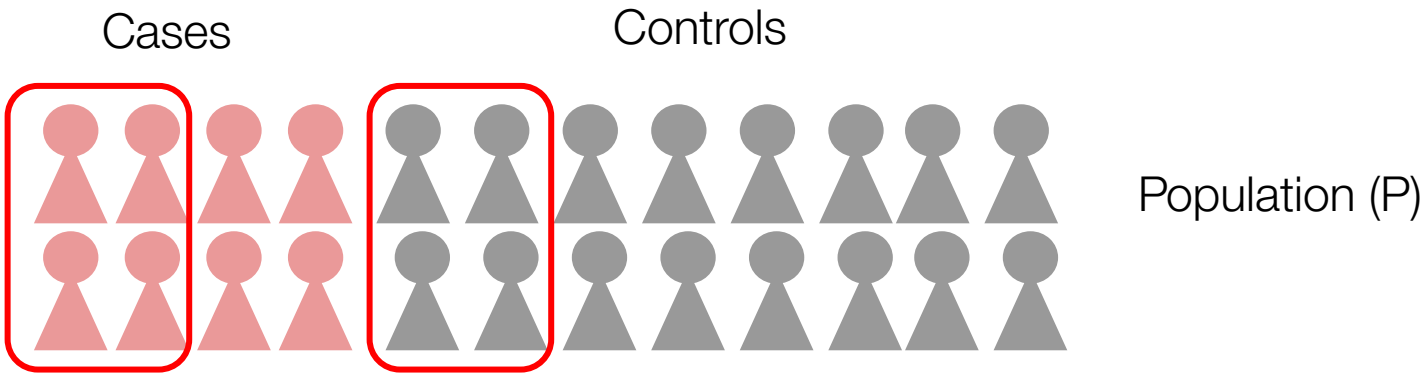

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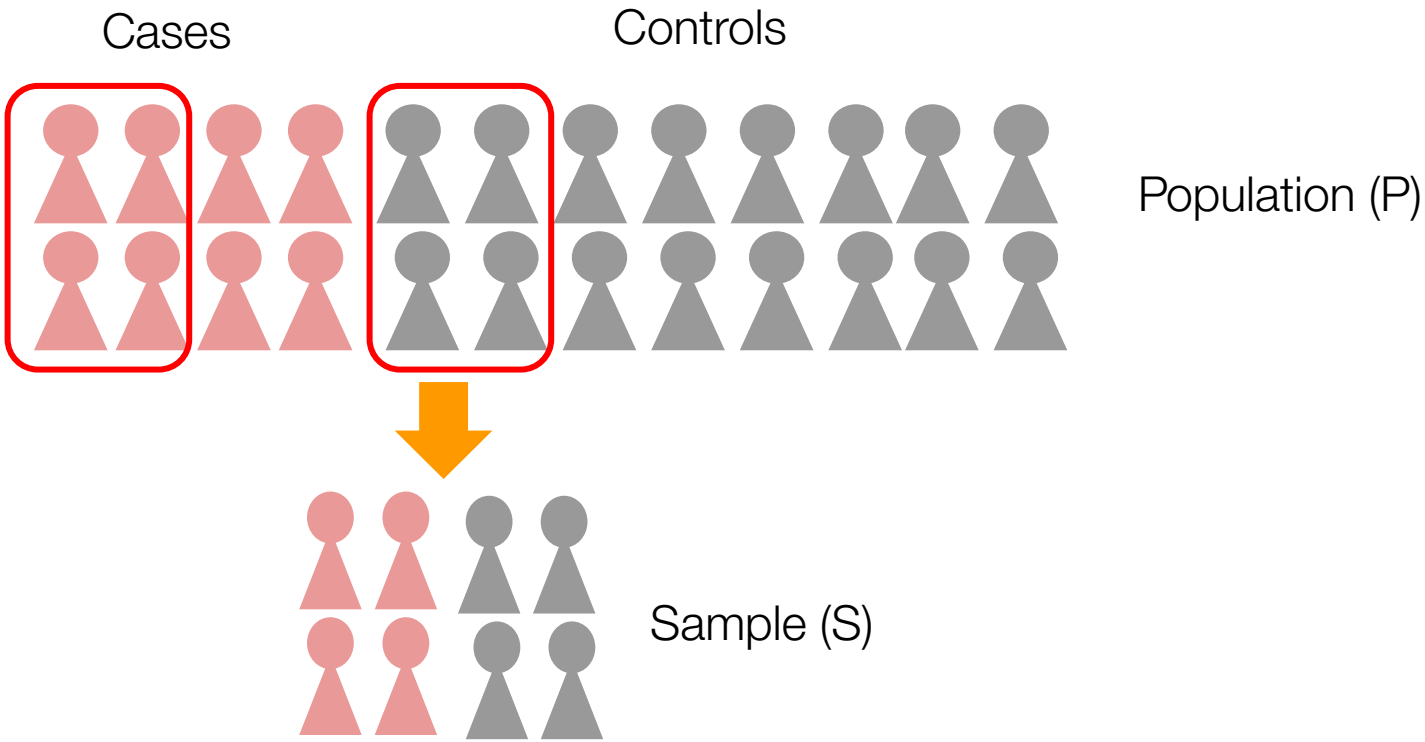

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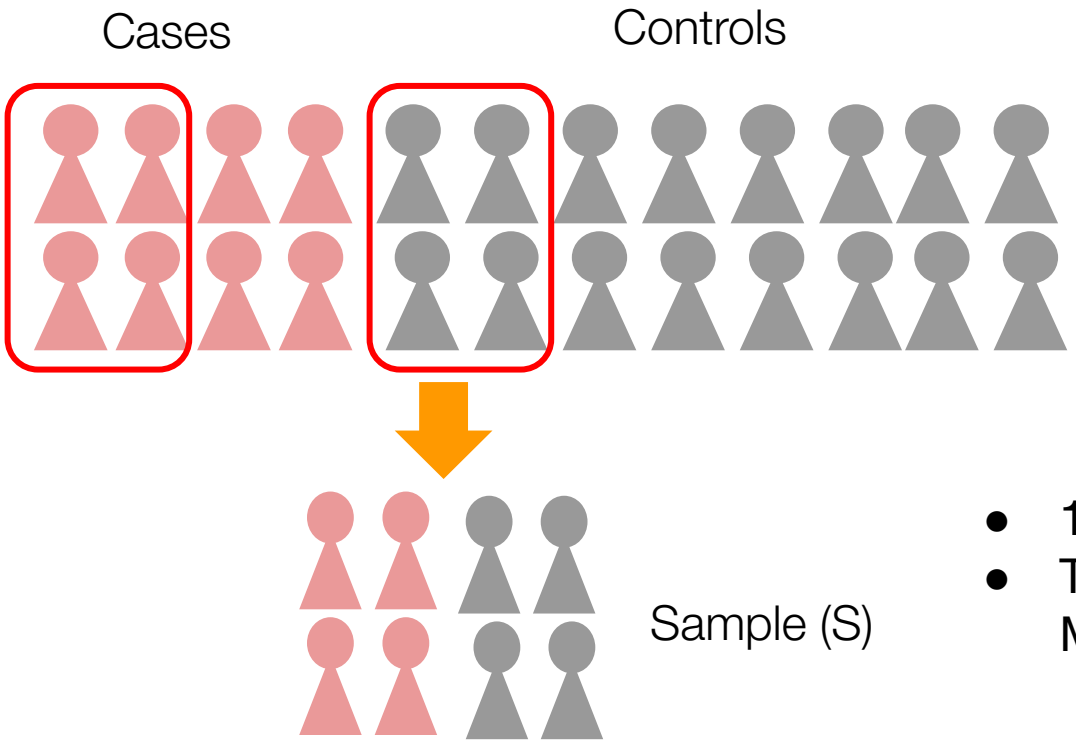


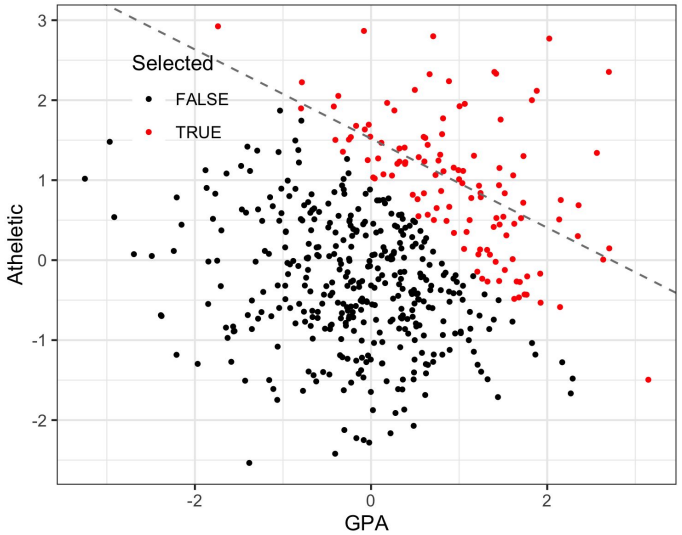
- 1119 Controls; 7246 Cases
- Three locations: Manizales, Medellin, Bello in Columbia

Example: Is academic ability associated with athletic ability?

Academic Ability (X)

Athletic Ability (Y)

Population P(X,Y)
(Red + Black points)



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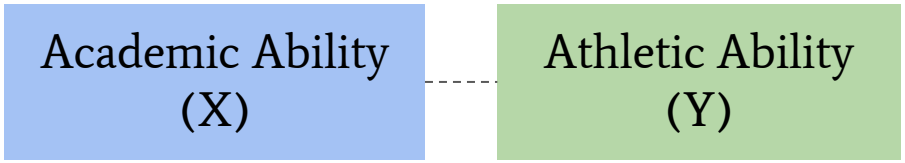

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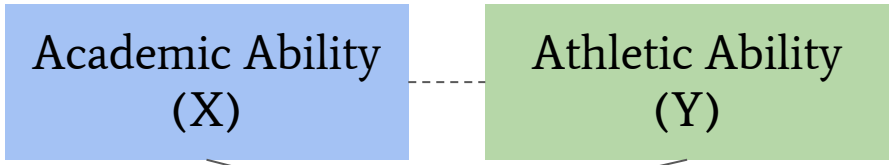
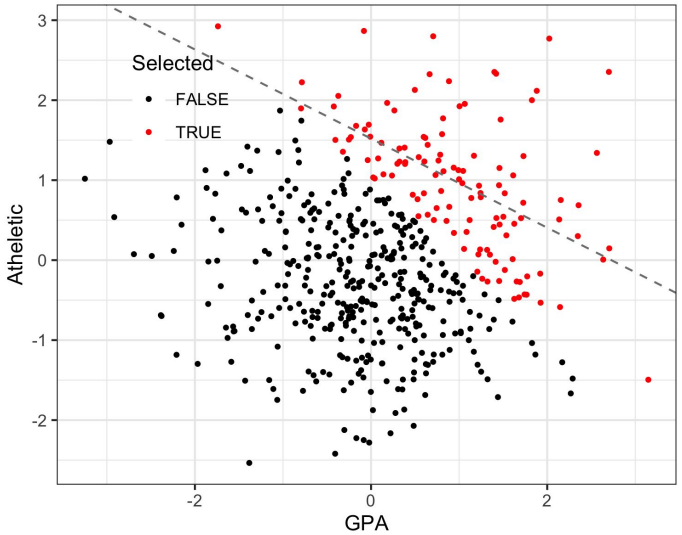
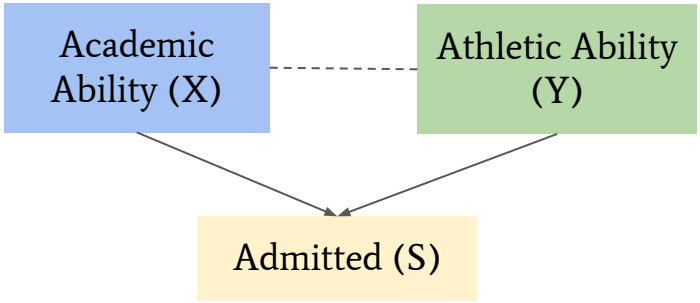


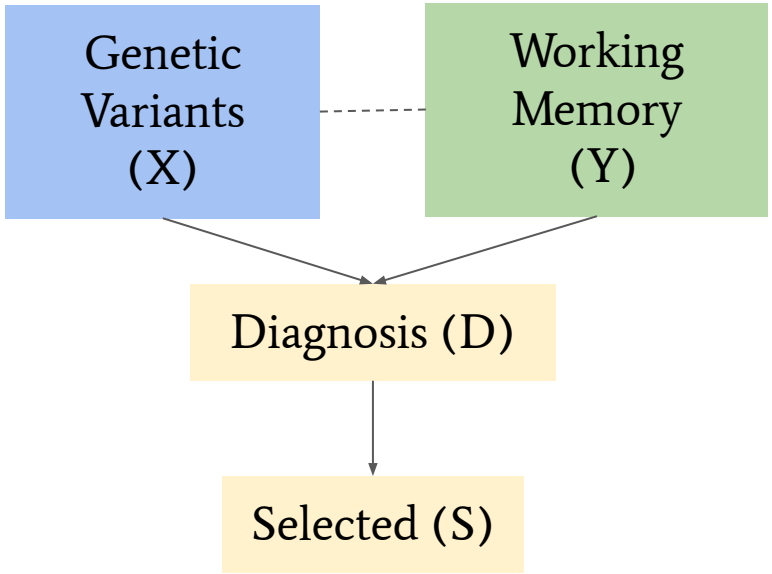
Sample L(X, Y) = P(X, Y|S=1)
(red points)



Collider Bias



Case-control study



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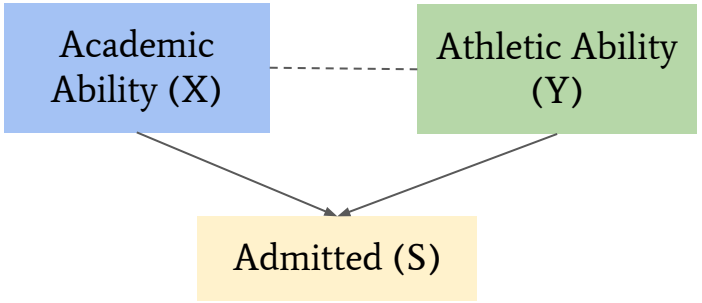

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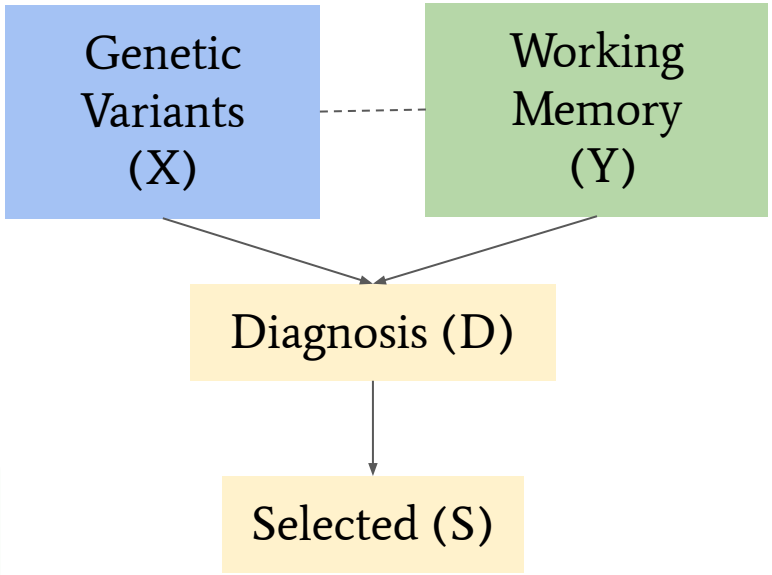

Can we test if X affects Y in the population (P) using case case-control sample (S)?

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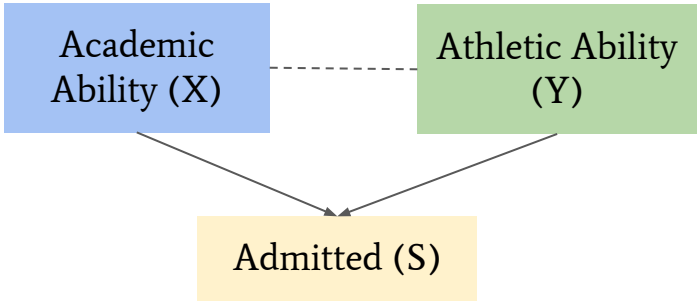

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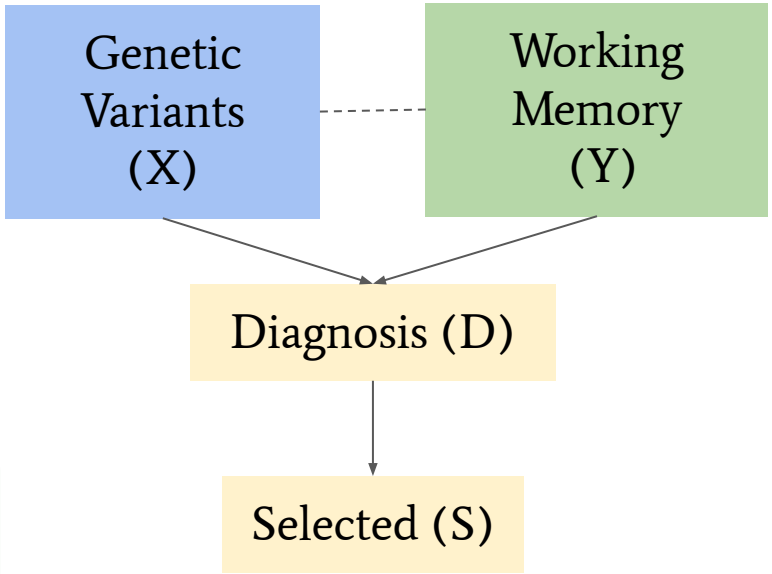
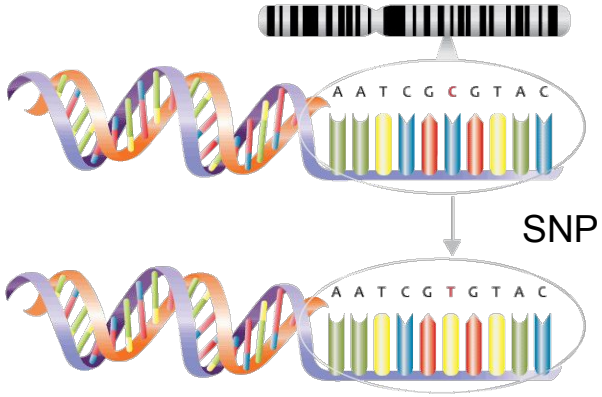


Current approaches usually do not apply when the number of variables is large!

A knockoff approach to select variables in the high-dimensional setting



$(X_1, X_2, \ldots, X_{10})$

- Single nucleotide polymorphisms (SNP) are alterations in a single nucleotide (A, T, G, C) in the DNA sequence.
- Denote the SNPs as

$$(X_1, X_2, \ldots, X_p)$$

- Denote the endophenotype as Y.
- Identify important SNPs by testing

$$\mathcal{H}_j : X_j \perp\!\!\!\perp Y \mid X_{-j}$$

Figure source

The knockoff method

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- The knockoff method is a variable selection procedure that controls the false discovery rate

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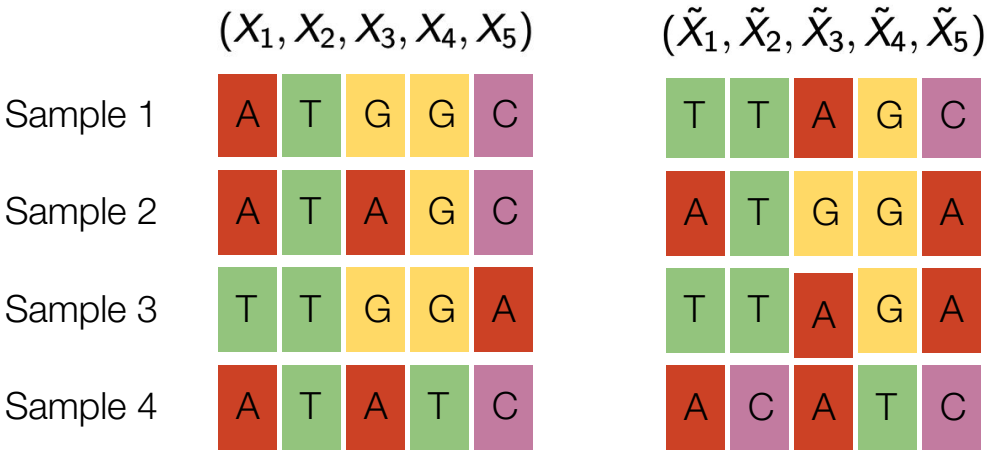
- The knockoff method is a variable selection procedure that controls the false discovery rate
- For every observation $(X_1, X_2, \ldots, X_p)$
  We construct **knockoff variables** $(\tilde{X}_1, \ldots, \tilde{X}_p)$
  Such that

$$(X_1, \ldots, X_p, \tilde{X}_1, \ldots, \tilde{X}_p)_{\text{Swap S}} \stackrel{d}{=} (X_1, \ldots, X_p, \tilde{X}_1, \ldots, \tilde{X}_p)$$

  For every set S containing only **null** variables

The knockoff method



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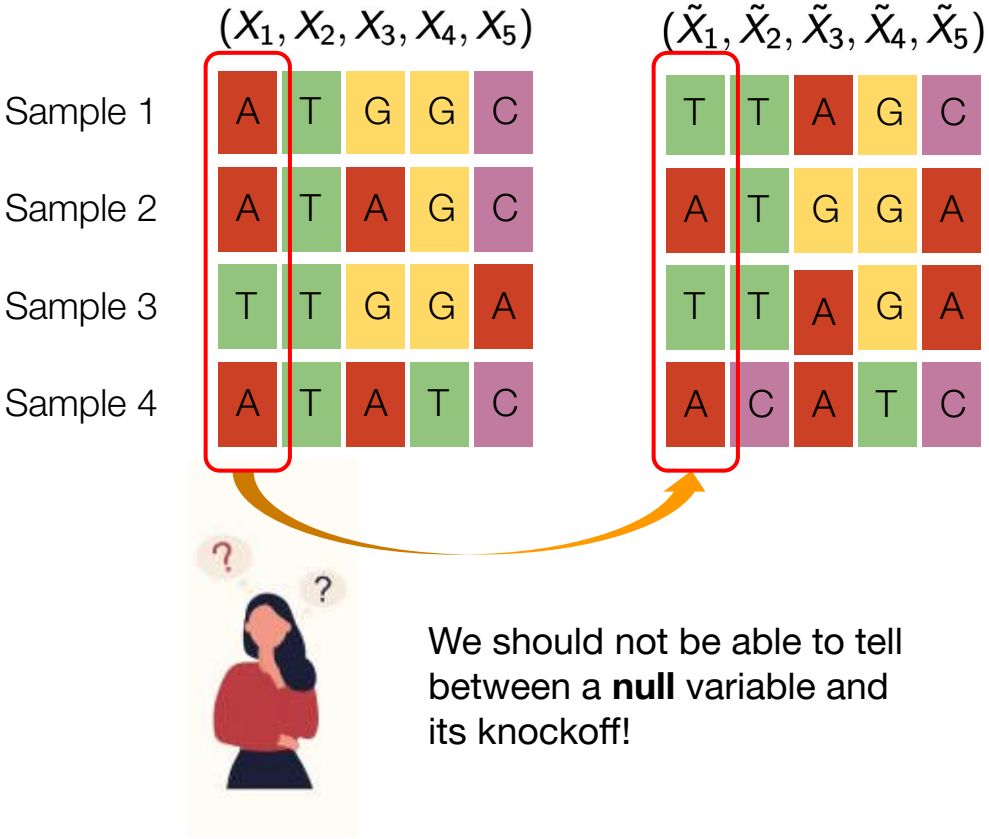

We should not be able to tell between a **null** variable and its knockoff!

The knockoff method

	$(X_1, X_2, X_3, X_4, X_5)$					$(\tilde{X}_1, \tilde{X}_2, \tilde{X}_3, \tilde{X}_4, \tilde{X}_5)$				
Sample 1	A	T	G	G	C	T	T	A	G	C
Sample 2	A	T	A	G	C	A	T	G	G	A
Sample 3	T	T	G	G	A	T	T	A	G	A
Sample 4	A	T	A	T	C	A	C	A	T	C

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Feature importance statistics

$$(Z_1, Z_2, \ldots, Z_5, \tilde{Z}_1, \tilde{Z}_2, \ldots, \tilde{Z}_5)$$

E.g. LASSO regression coefficients

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Scores

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A list of selected variables

How do we construct knockoff variables?

$$(X_j, X_{-j}, \tilde{X}_j, \tilde{X}_{-j}, Y) \stackrel{d}{=} (\tilde{X}_j, X_{-j}, X_j, \tilde{X}_{-j}, Y)$$

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User defined!

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$$\mathrm{P}(X_j, X_{-j})\, \mathrm{P}(S = 1 | X_j, X_{-j}, Y)$$

We can use this distribution instead!

(Selection probability)

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We can use this distribution instead!

$$\propto \mathrm{P}(X_j | X_{-j}, Y, S = 1)$$

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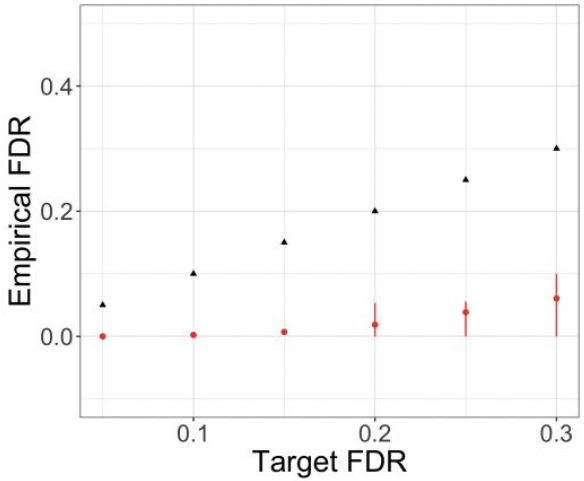

If

$$\mathrm{P}(X_j, X_{-j})\,\mathrm{P}(S = 1 | X_j, X_{-j}, Y)$$

Is multivariate Gaussian, then we can sample knockoffs from another multivariate Gaussian.

Number of cases = Number of controls = 1,000; Number of variables = 200; X is from a multivariate Gaussian distribution where the covariance matrix is block diagonal (block size = 10); Y is from a linear model where 10% of the variables are non-nulls;

$\mathrm{P}(D = 1|X, Y) = e^{-v^2/2}$, $v = \gamma_0 Y + X^\top \gamma$.

Conclusion and remaining challenges

- Collider bias can occur in many studies!
- We describe one way to adjust the knockoff sampling procedure to select variables that controls the false discovery rate (1) in high-dimensions (2) under collider bias

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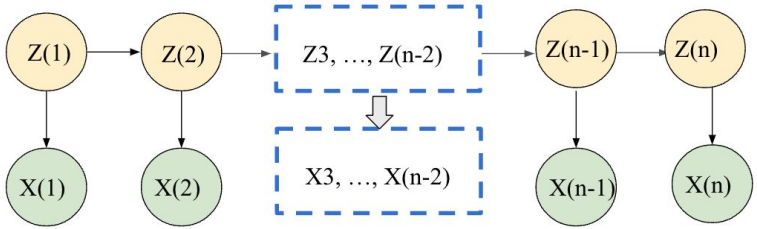

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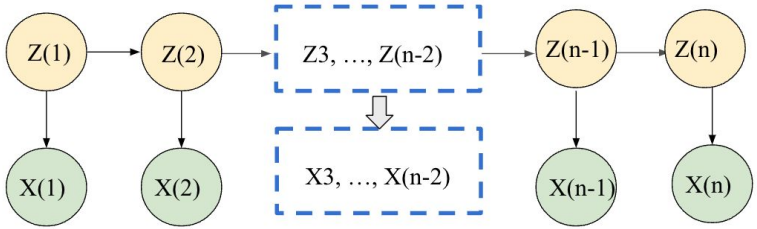
- One idea: approximate $\mathrm{P}(X_j, X_{-j})\,\mathrm{P}(S = 1 | X_j, X_{-j}, Y)$ by another distribution for which we know Q



Thank you! Questions?