Fighting Noise with Noise

Causal Inference with Many Candidate Instruments

Dehan Kong
University of Toronto

Pacific causal inference conference
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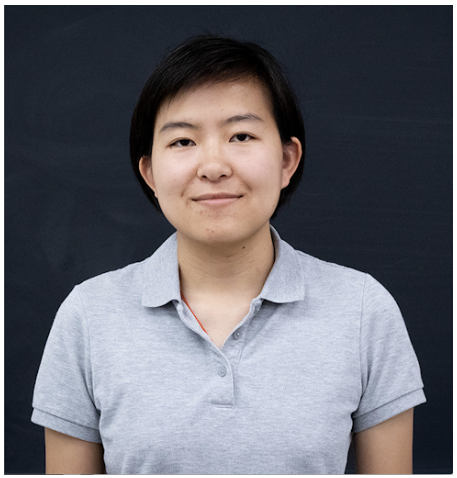
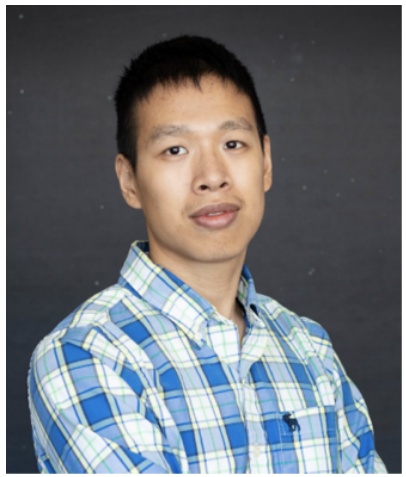
Acknowledgements



Cindy Zhang



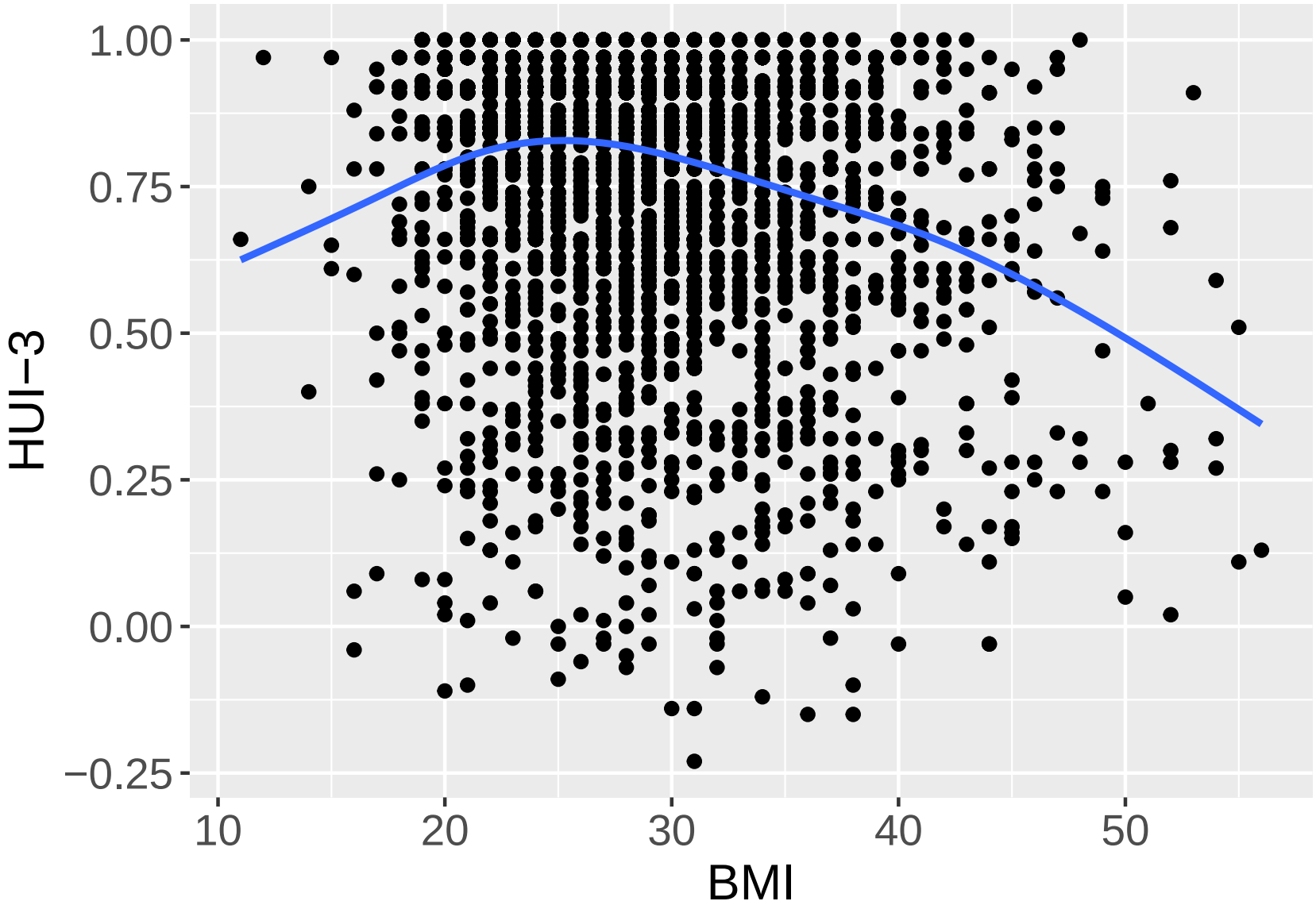
Linbo Wang

Stanislav Volgushev

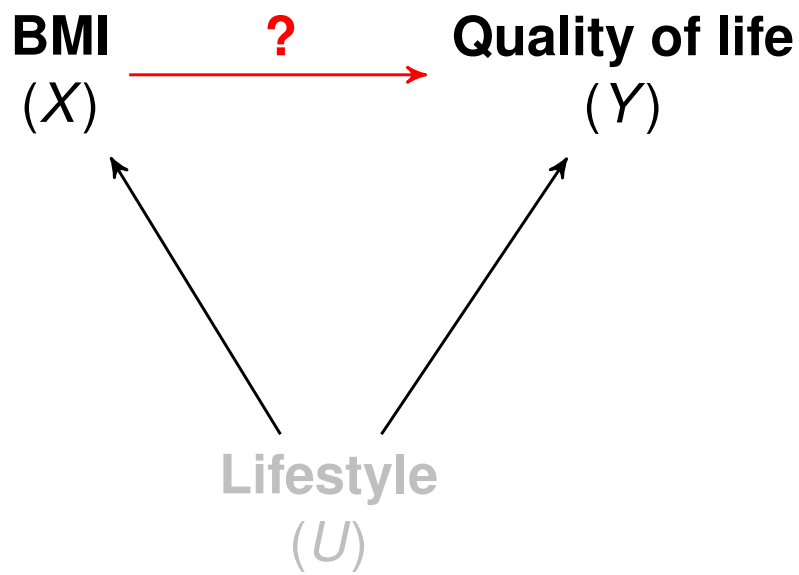
McLAUGHLIN CENTRE

Overweight

Overweight is associated with Quality of Life

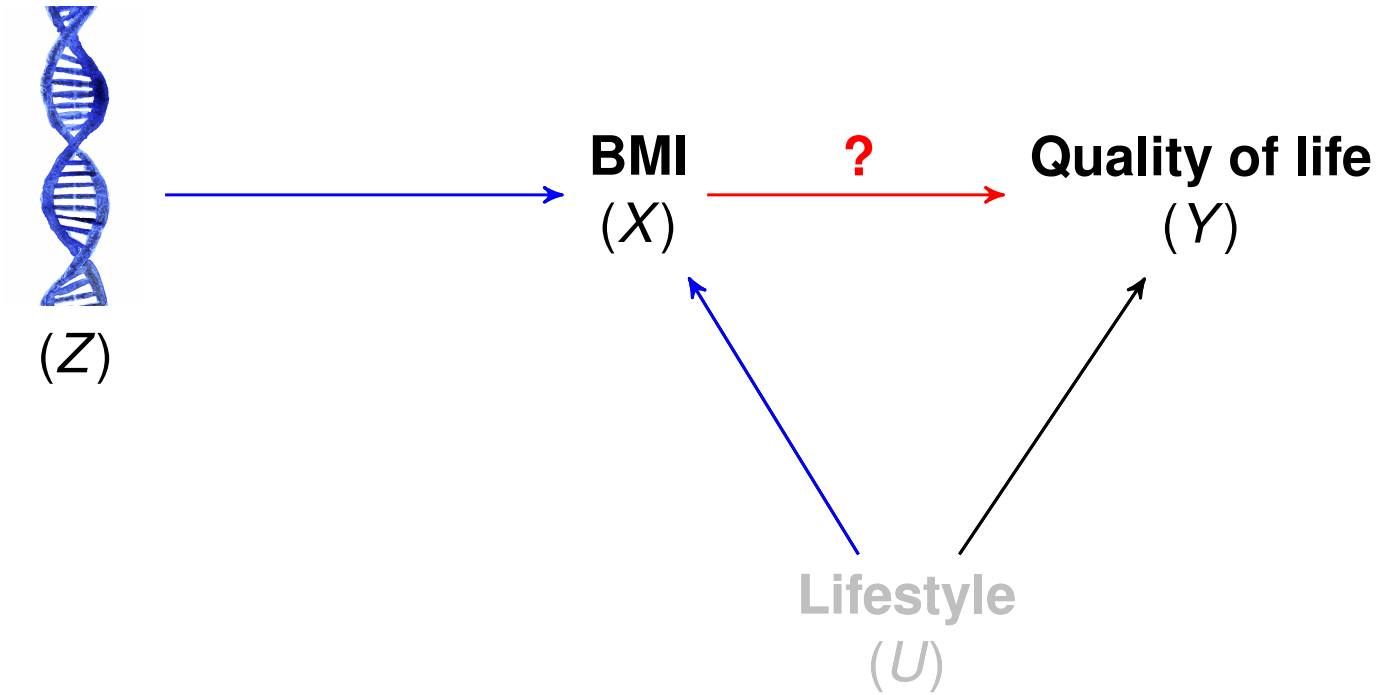


Is this association causal?



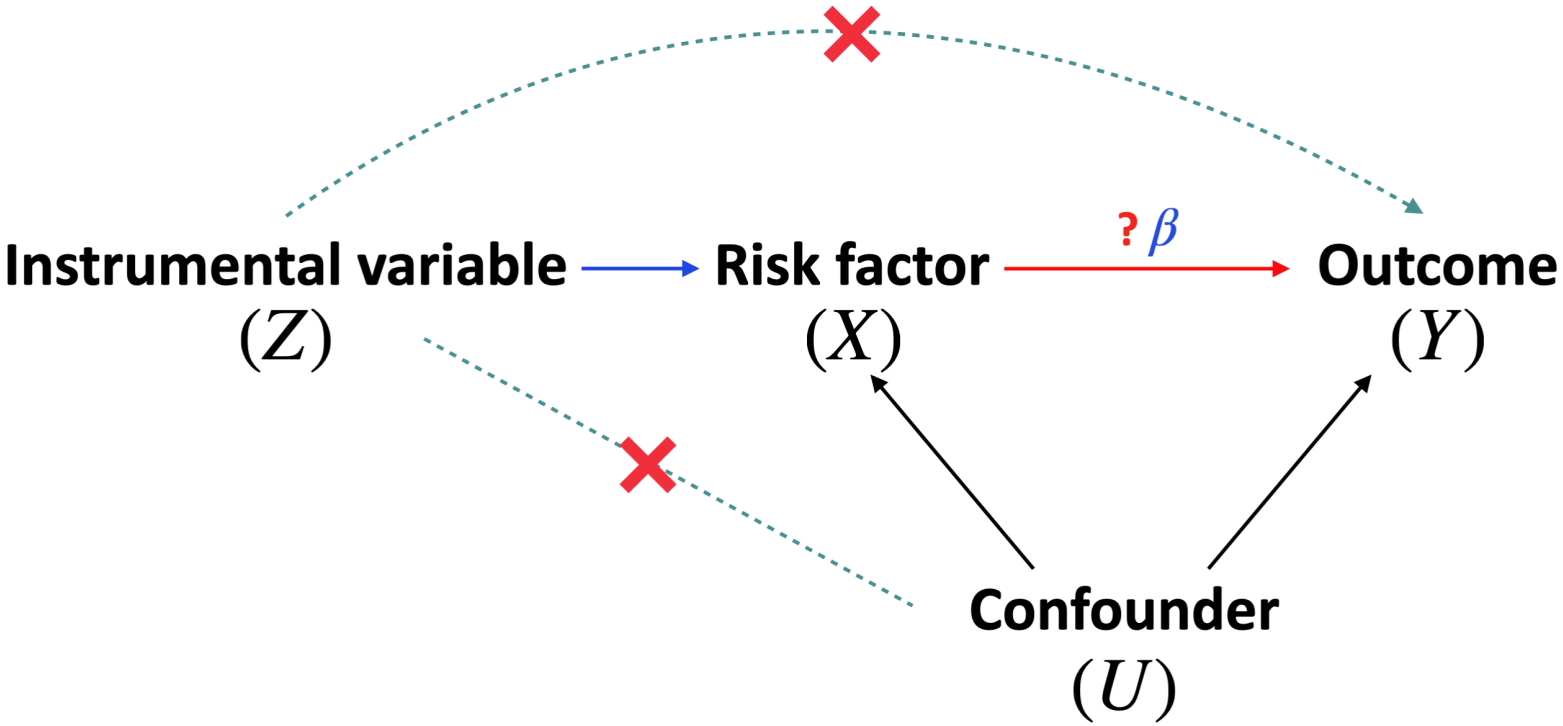
☛ **Unmeasured confounding!**

Mendelian randomization (MR)



Nature rolls the dice!

The math behind



IV1. $Z \to X \neq 0$
IV2. $Z \to Y = 0$
IV3. $\text{cov}(Z, U) = 0$

$\Longrightarrow$

$$Z \to X \to Y = (Z \to X) \times \underbrace{(X \to Y)}_{\beta}$$

$$X \to Y = \frac{Z \to X \to Y}{Z \to X}$$

Natural experiments are imperfect!

1. Most genetic variants are irrelevant!
   - In the past: rely on expert knowledge

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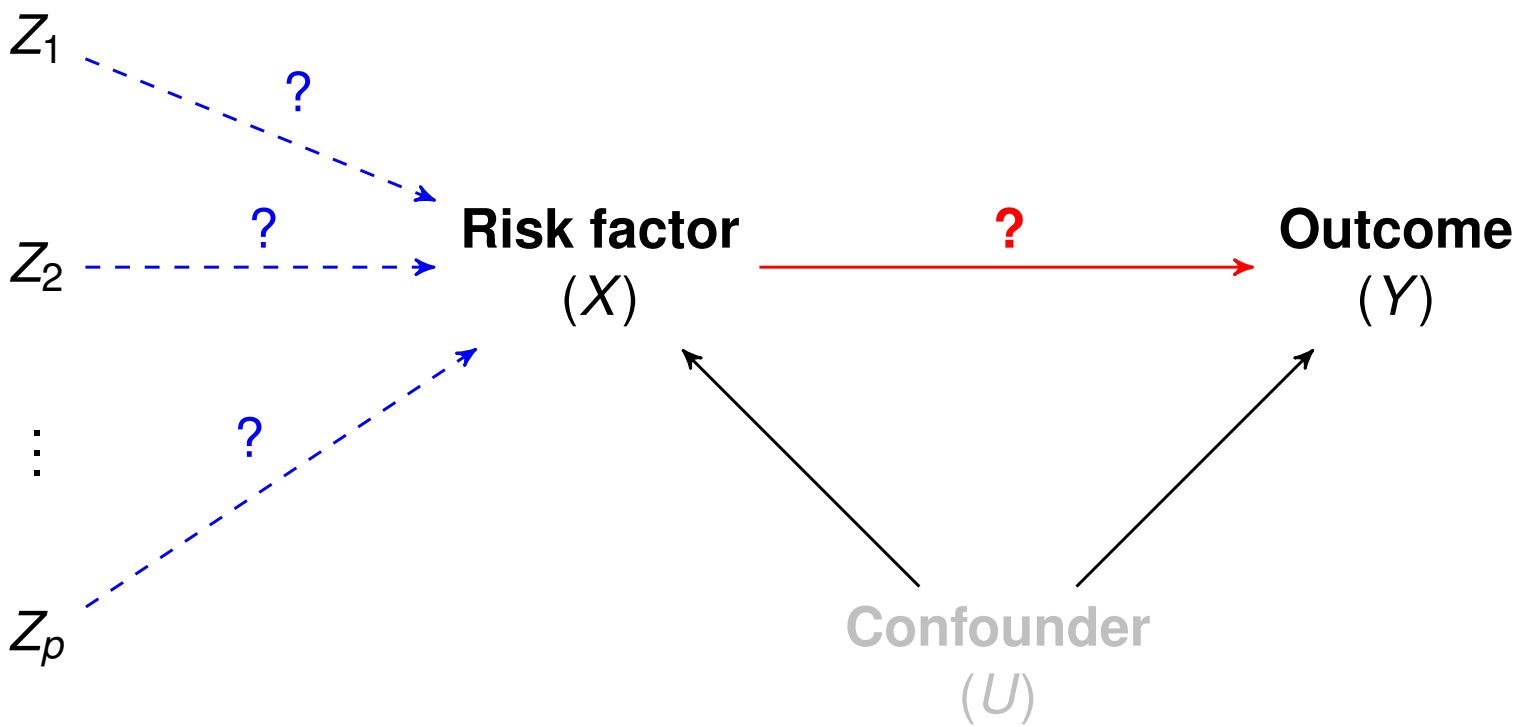
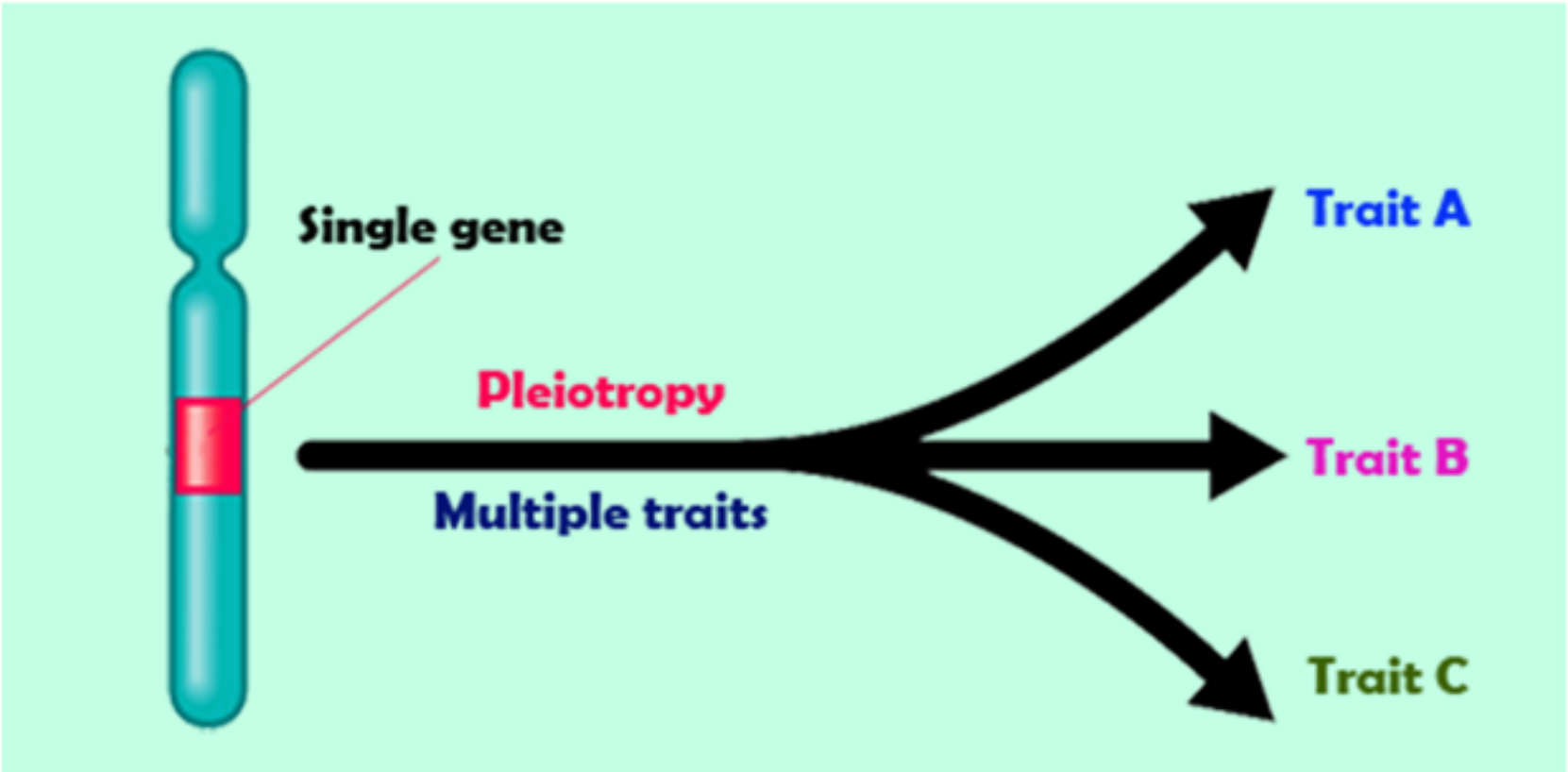
Modern approach: GWAS



Natural experiments are imperfect!

2 Some of SNPs that pass the GWAS test may still be invalid due to pleiotropy



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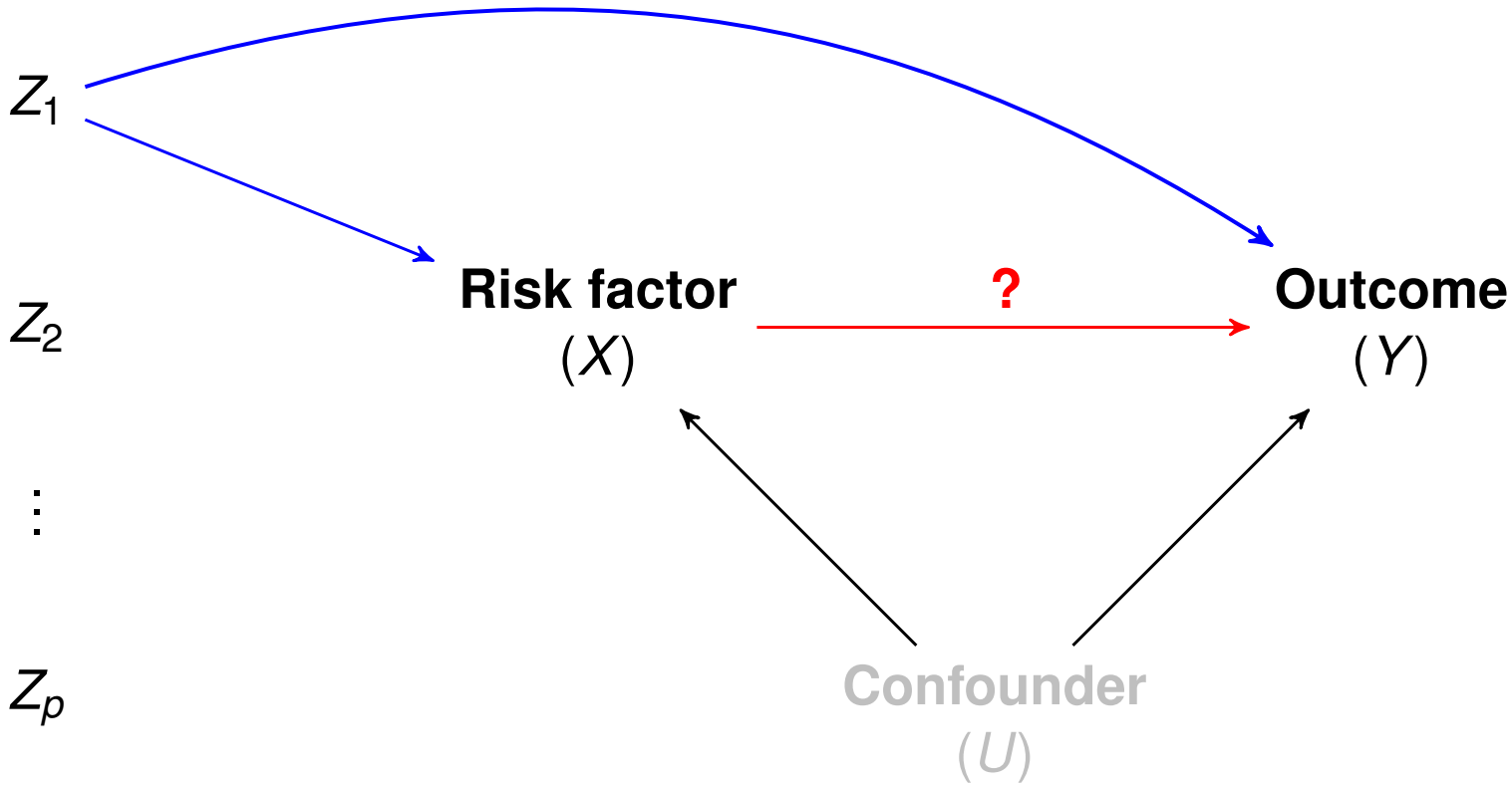


Natural experiments are imperfect!

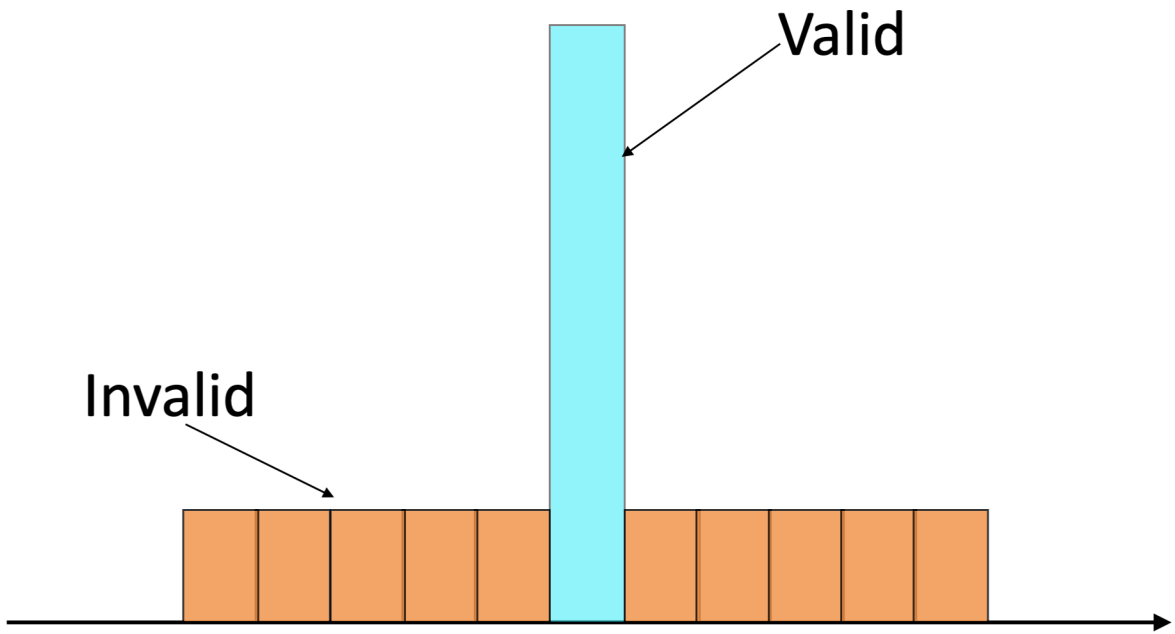
2 Some of SNPs that pass the GWAS test may still be invalid due to pleiotropy

Existing solution: Valid causal inference with some invalid instruments (Bowden et al. [2015], Kolesár et al. [2015], Kang et al. [2016], Hartwig et al. [2017], Guo et al. [2018], Hartford et al. [2020])

Valid causal inference with some invalid instruments

Solution:

All happy instruments are alike;
each unhappy instrument is unhappy in its own way



Plurality rule: Guo et al. , 2018

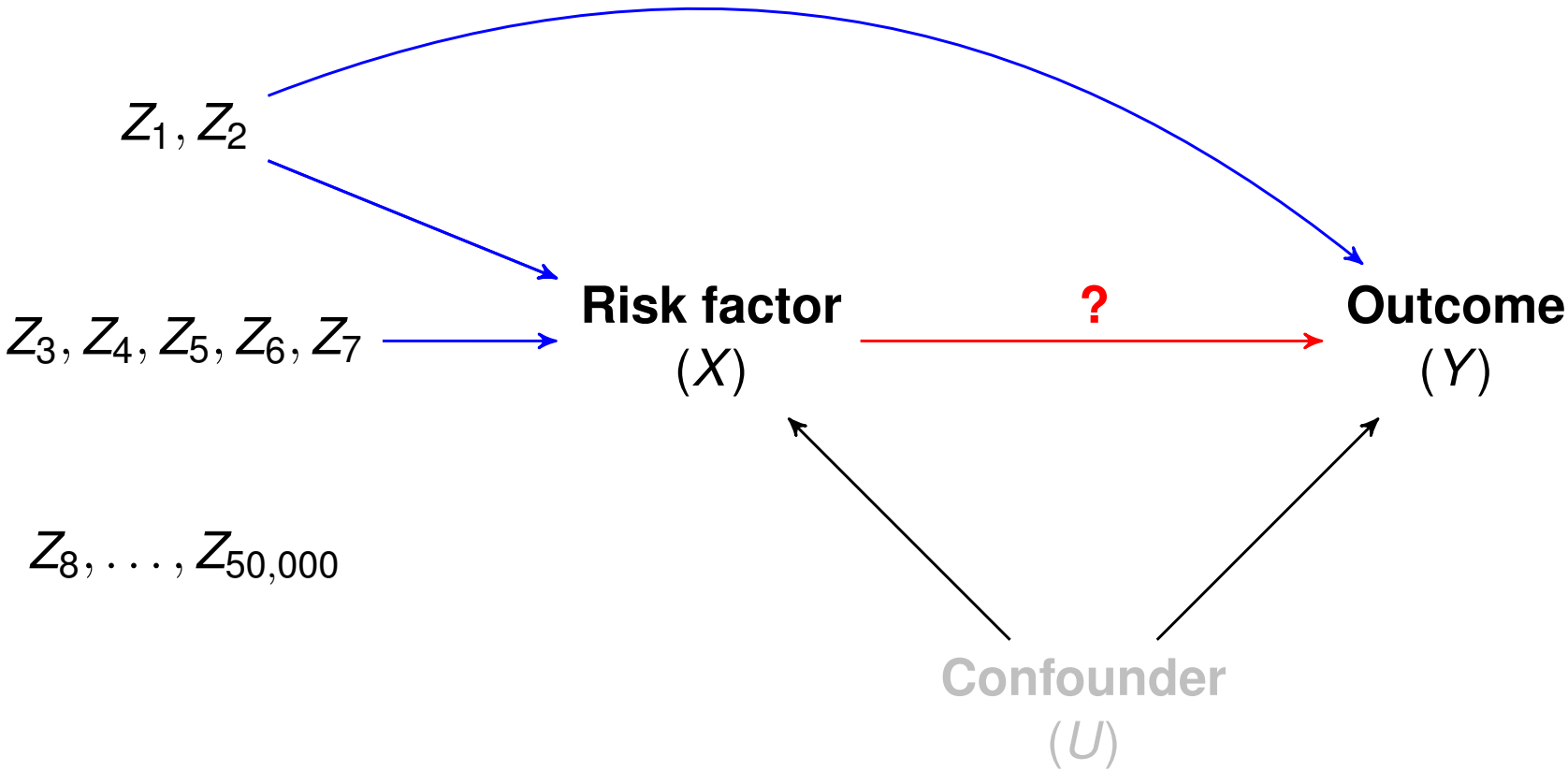
Summary of existing solutions

Step 1 GWAS based on strength of the links $Z_j \to X, j = 1, \ldots, p$

Step 2 Apply a mode-finding algorithm to identify the valid IVs

Step 3 Use the valid IVs to estimate the causal effect

A toy simulation



- Sample size = 500
- $Z_j, j = 1, \ldots, 50,000, U \sim N(0, 1)$
- Linear models
- True causal effect $X \rightarrow Y$ is 2

Step 1: GWAS

Step 1.1 (Marginal screening): Select the top 500 candidate IVs $\boldsymbol{Z}_r$ based on the marginal correlation

$$|Cor(Z_j, X)|, j = 1, \ldots, 50,000$$

Step 1.2 (Joint thresholding): Fit a debiased Lasso model

$$X \sim \boldsymbol{Z}_r$$

Result: On average left with 21 candidate IVs

☺ Include the 7 relevant IVs (5 valid, 2 invalid) every single time!

Step 2: Mode-finding

Solution:

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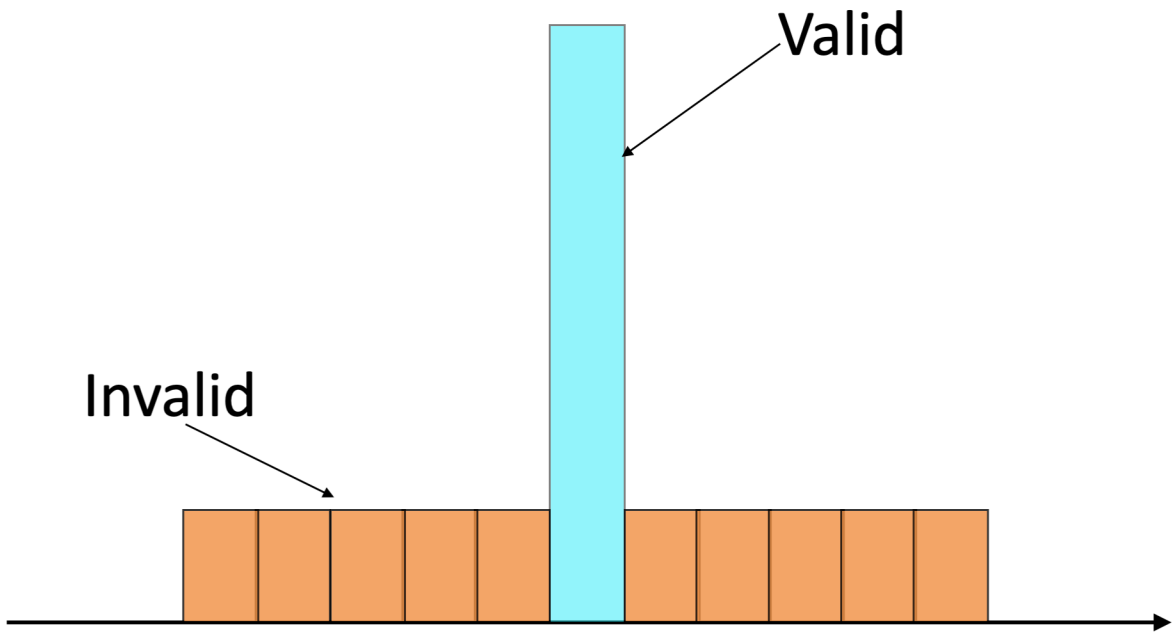

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Step 3: Causal effect estimation

☹ The causal effect estimates are biased!

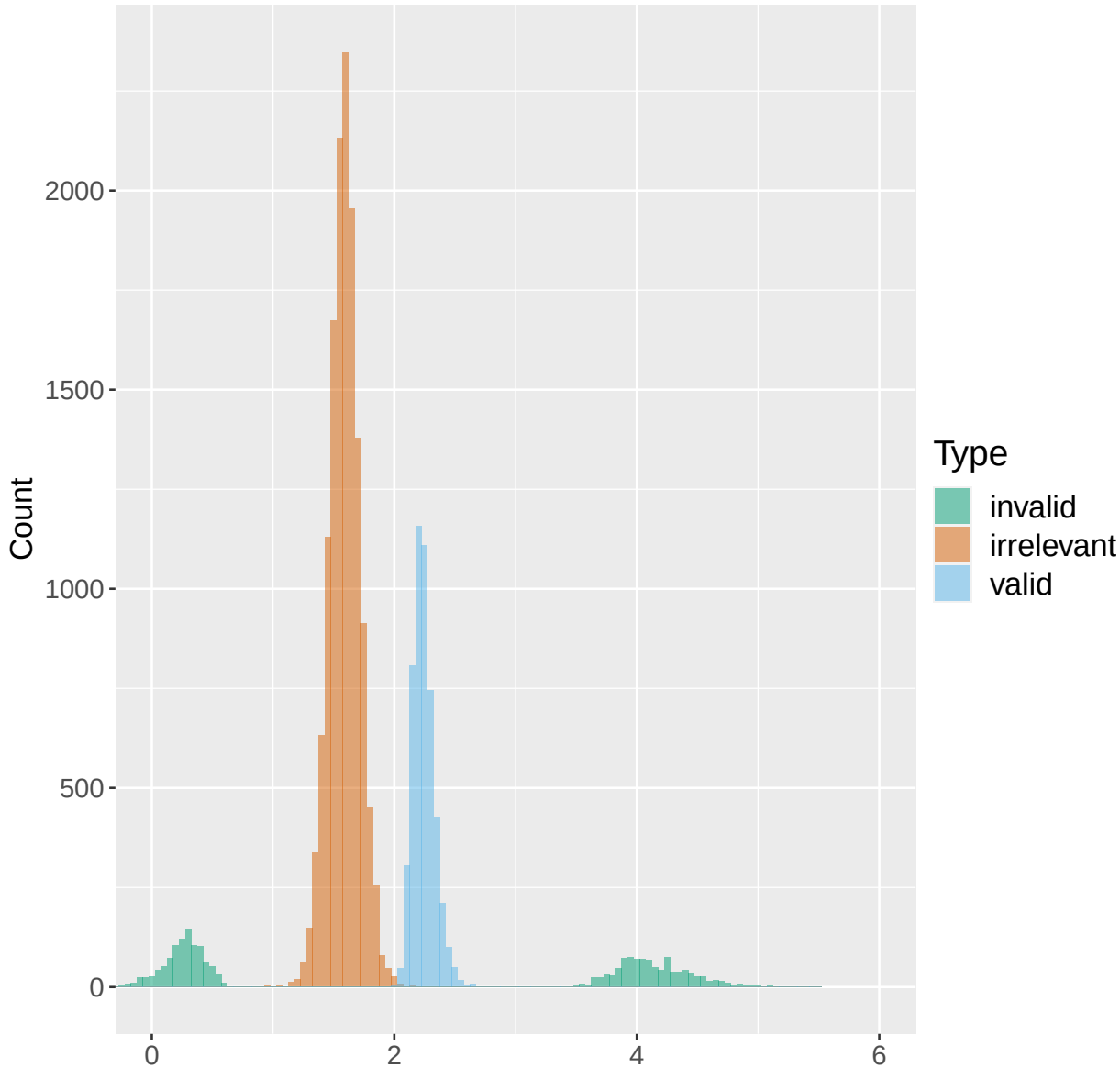
- Bias = -0.22 (SE = 0.02)
- Coverage probability = 0.07 (nominal = 0.95)

What went wrong?

Recall in Step 1: Select 21 candidate IVs

- 5 valid
- 2 invalid
- **14 irrelevant with spurious correlation**

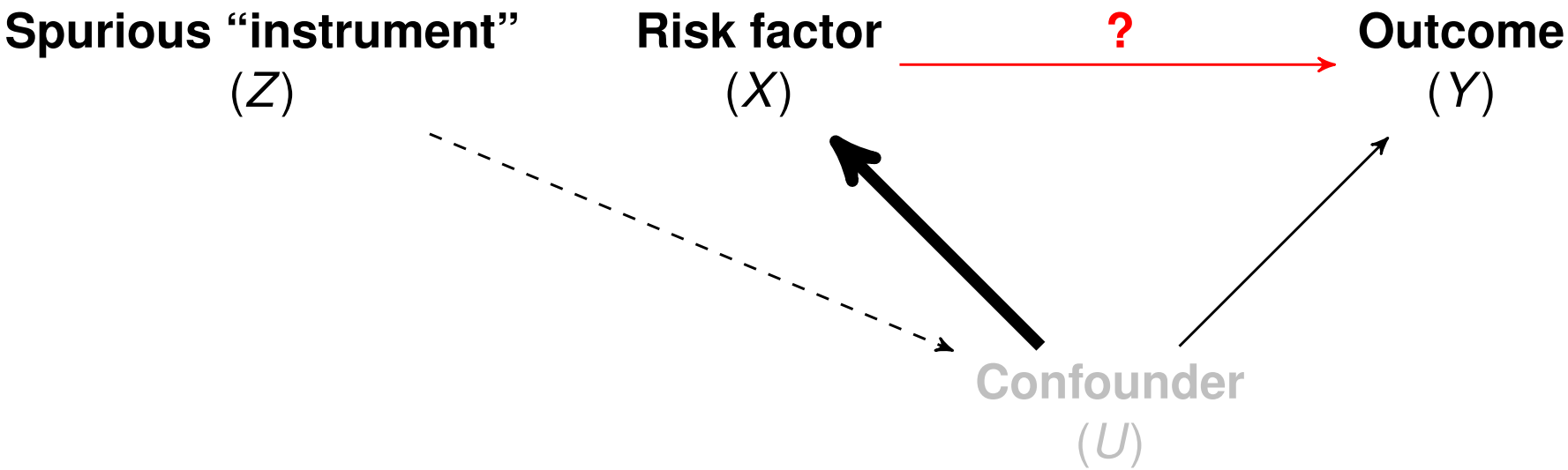
What happened in Step 2



Distribution of causal effect estimates for candidate IVs passing joint thresholding across 1000 Monte Carlo runs

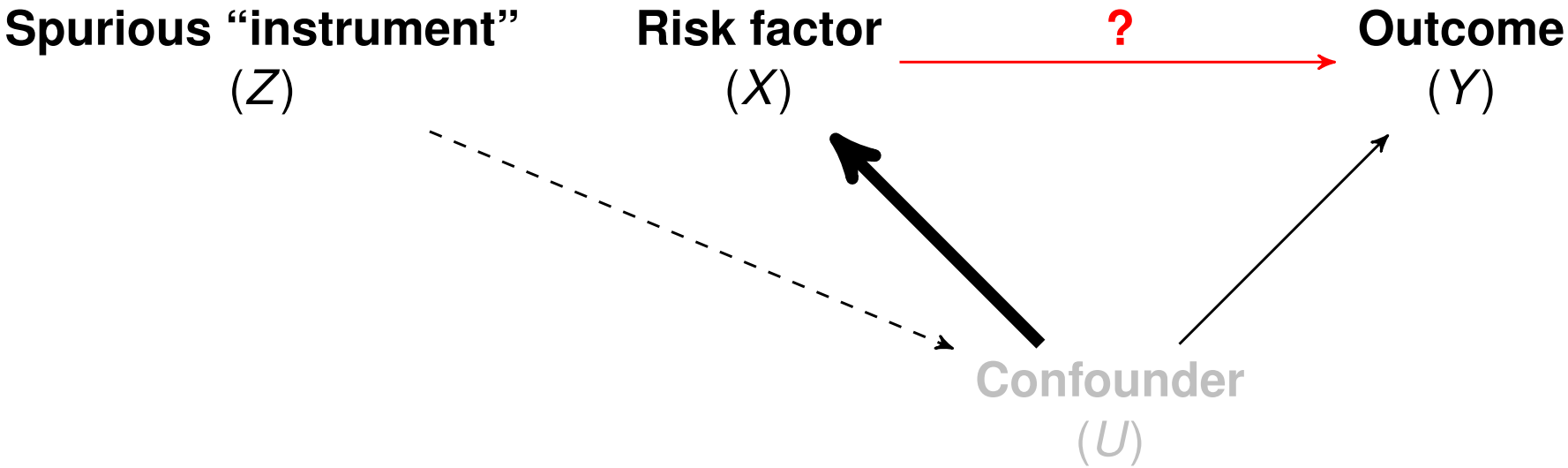
All irrelevant “instruments” are alike. Why?

The simplest case (extreme confounding)



- Single unmeasured confounder U
- X is only determined by U

The simplest case (extreme confounding)



Recall that under the IV framework,

$$X \to Y = \frac{Z \to X \to Y}{Z \to X} = \frac{Cov(Z, Y)}{Cov(Z, X)}$$

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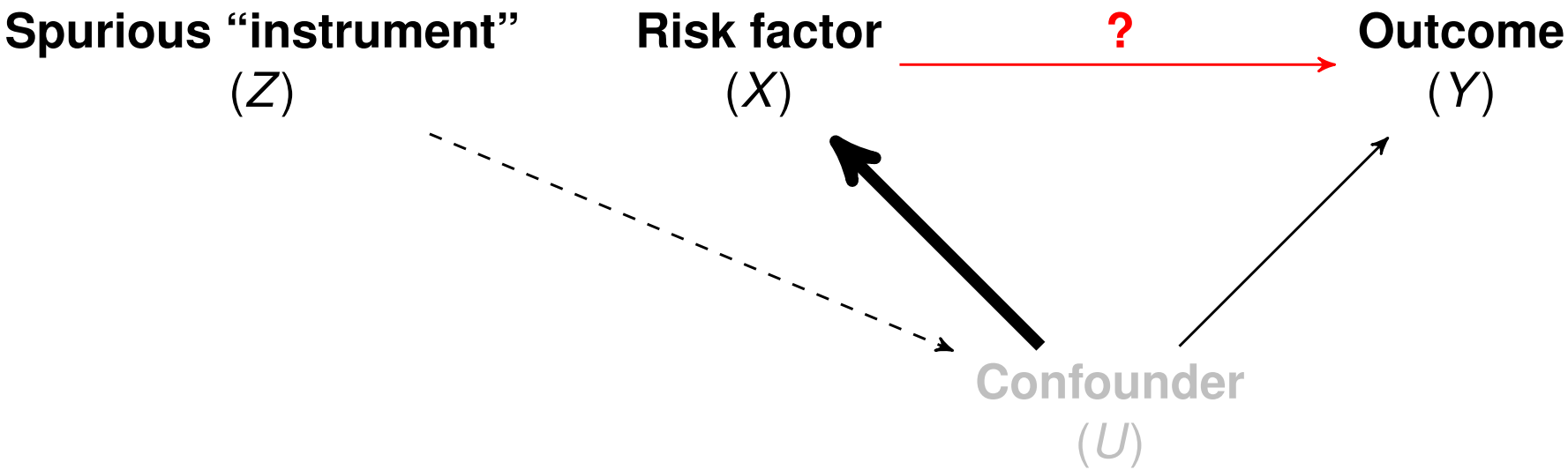

In the case of irrelevant "instrument,"

- $Cov(Z, Y) = Z \to U \to X \to Y \quad + \quad Z \to U \to Y$
- $Cov(Z, X) = Z \to U \to X$

$$\text{So} \quad \frac{Cov(Z, Y)}{Cov(Z, X)} = X \to Y \quad + \quad \frac{U \to Y}{U \to X}$$

The bias is the same for all irrelevant "instruments"!

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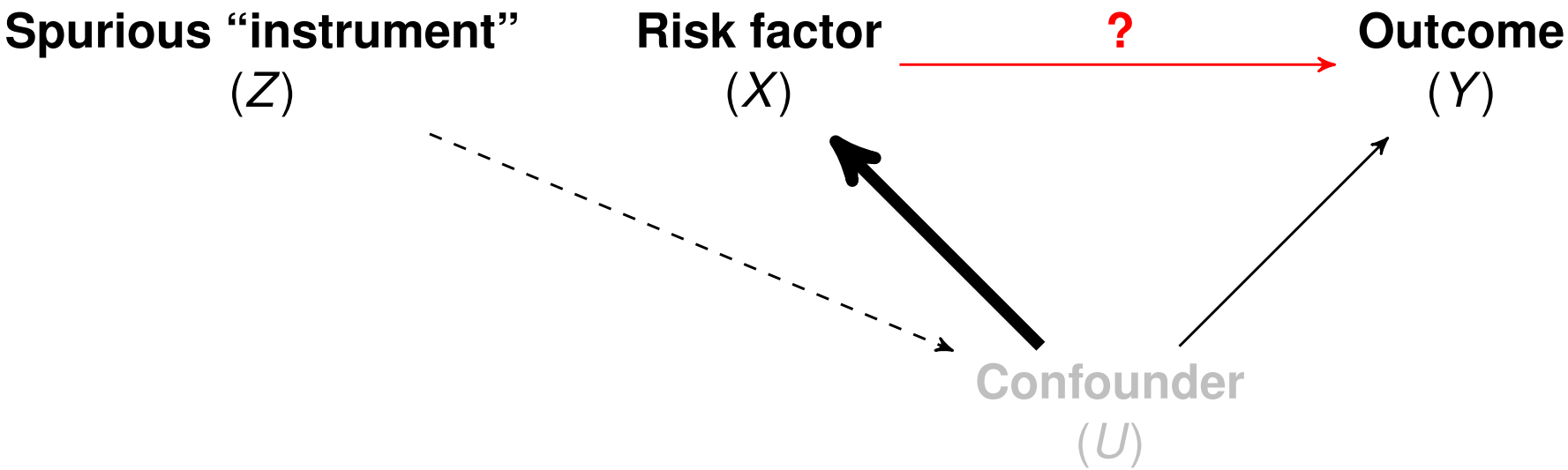

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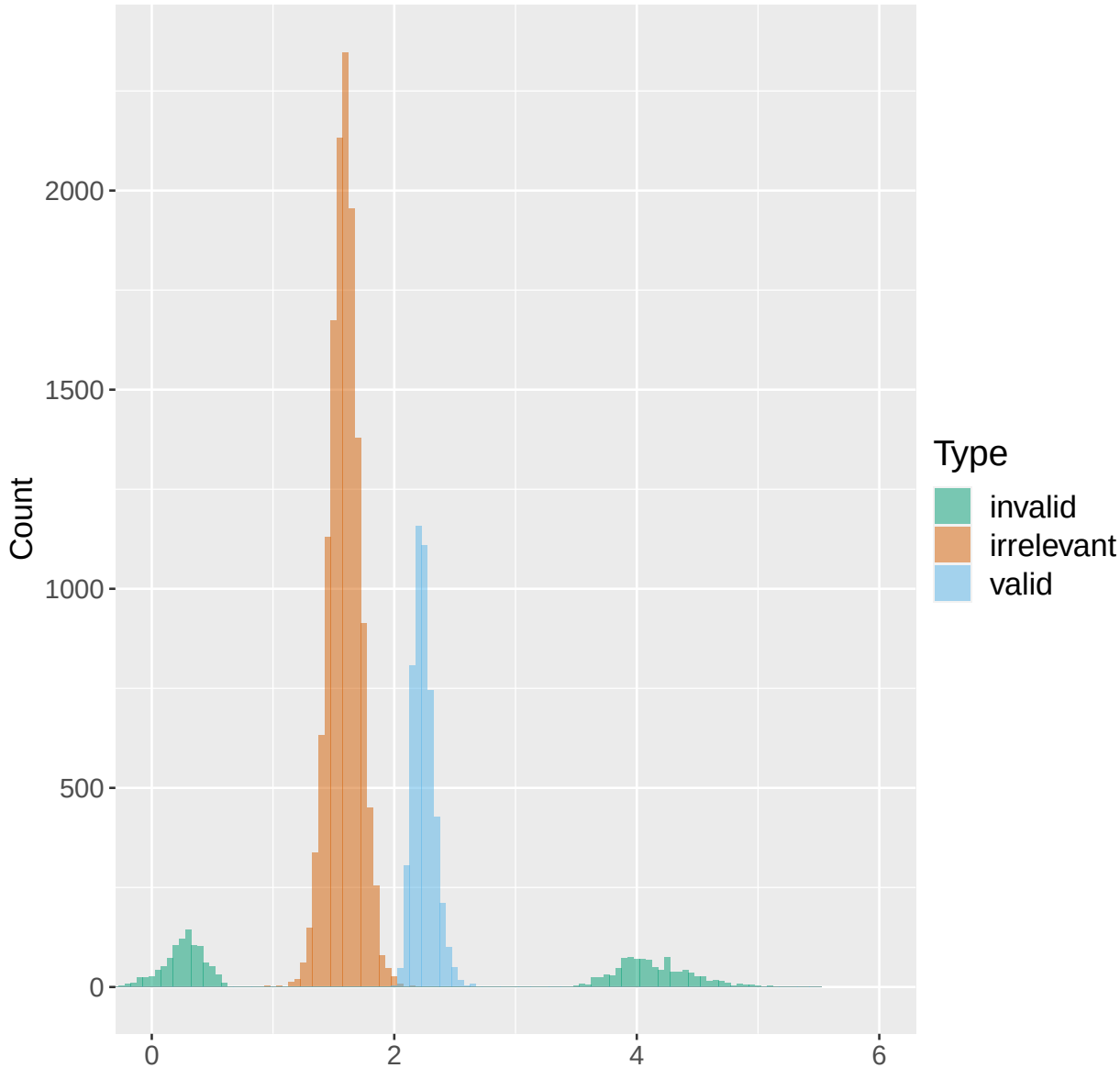
The bias is the same for all irrelevant "instruments"!

- In fact, also same as the bias from $Y \sim X$

What happened in Step 2



Distribution of causal effect estimates for candidate IVs passing joint thresholding across 1000 Monte Carlo runs

What we know so far:

- **All valid instruments are alike**
- **All irrelevant instruments are alike**
- Invalid instruments are different from each other

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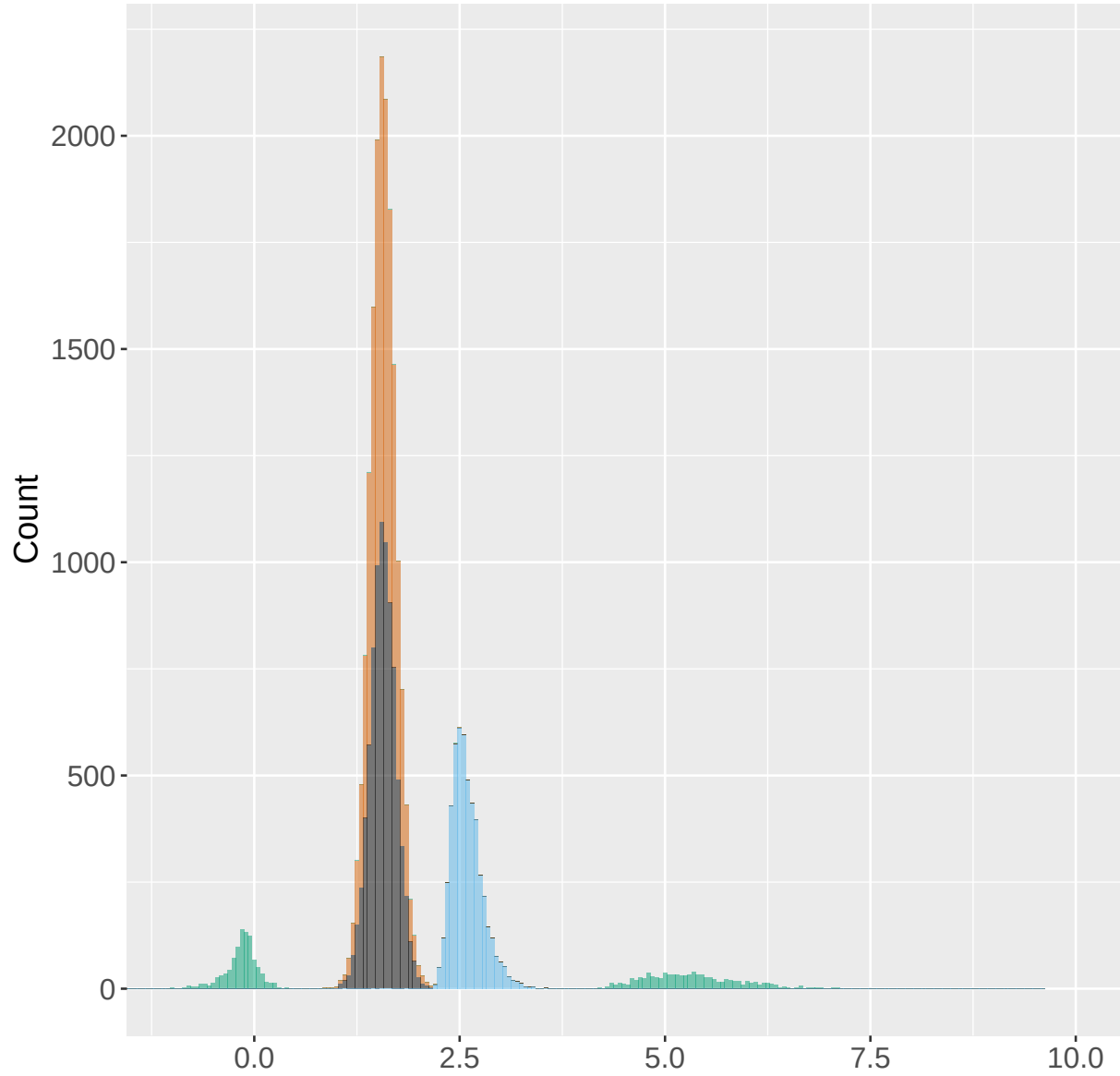
How to distinguish valid instruments from irrelevant ones?

Key idea: Generate pseudo variables by permuting rows of Z, denoted by Z^*

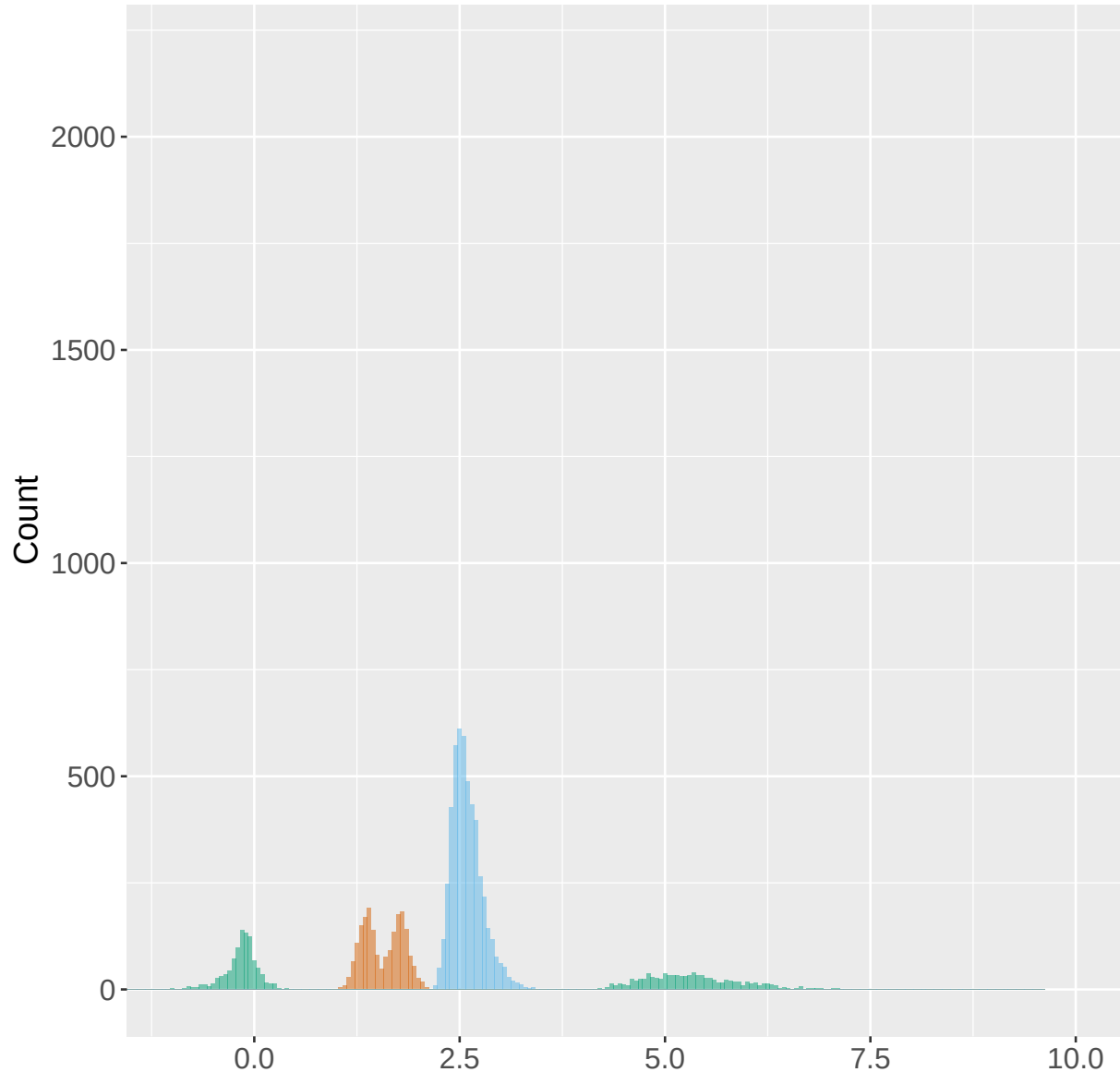
- **Group 1: valid instruments in Z**
- **Group 2: invalid instruments in Z**
- **Group 3: irrelevant instruments in Z**
- **Group 4: irrelevant instruments in Z^***

Groups 3 and 4 are alike! We can track variables in Group 4.



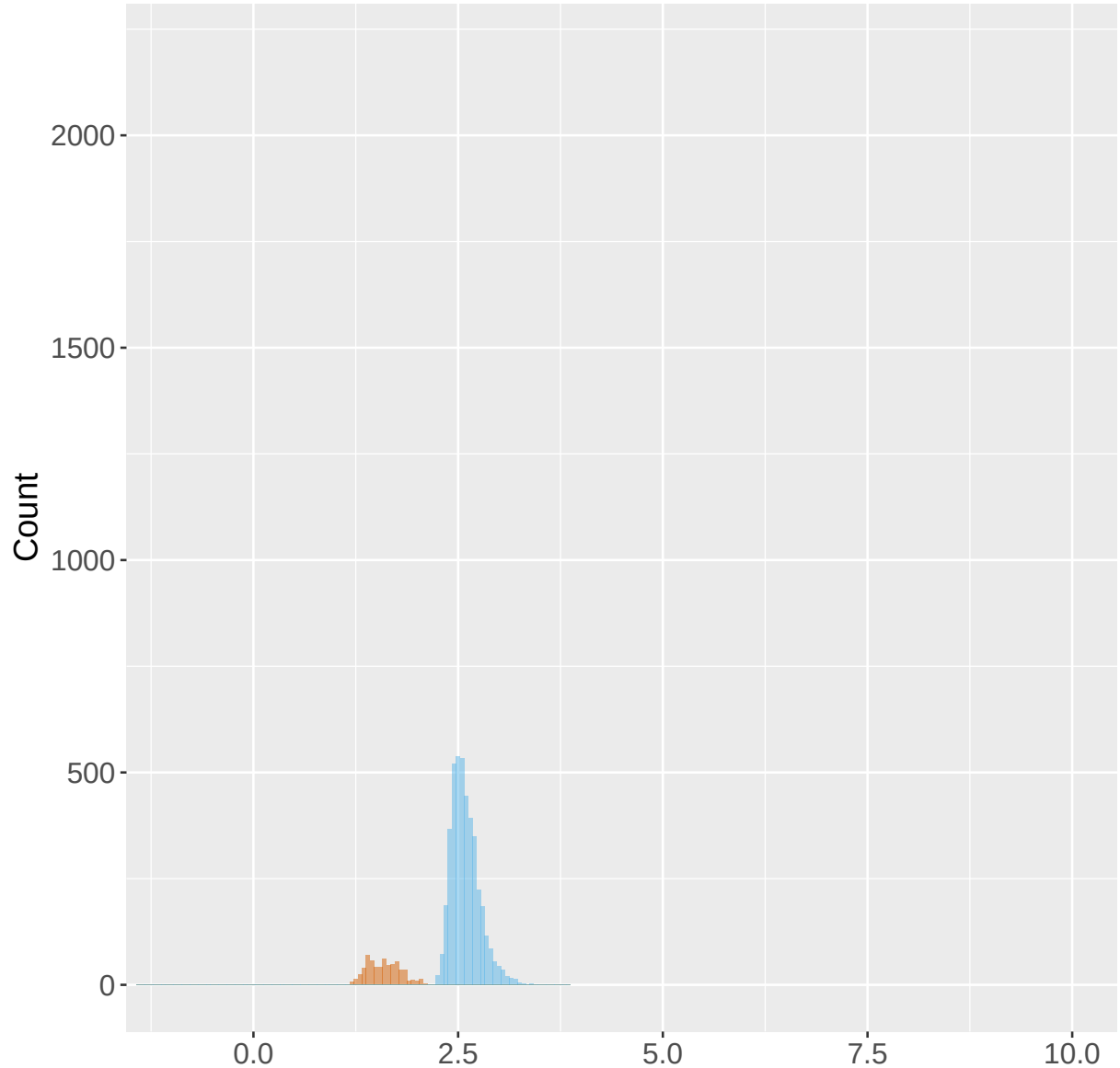
Distribution of causal effect estimates for candidate IVs passing joint thresholding across 1000 Monte Carlo runs

Step 2: Remove causal effect estimates inside the range of pseudo effect estimates



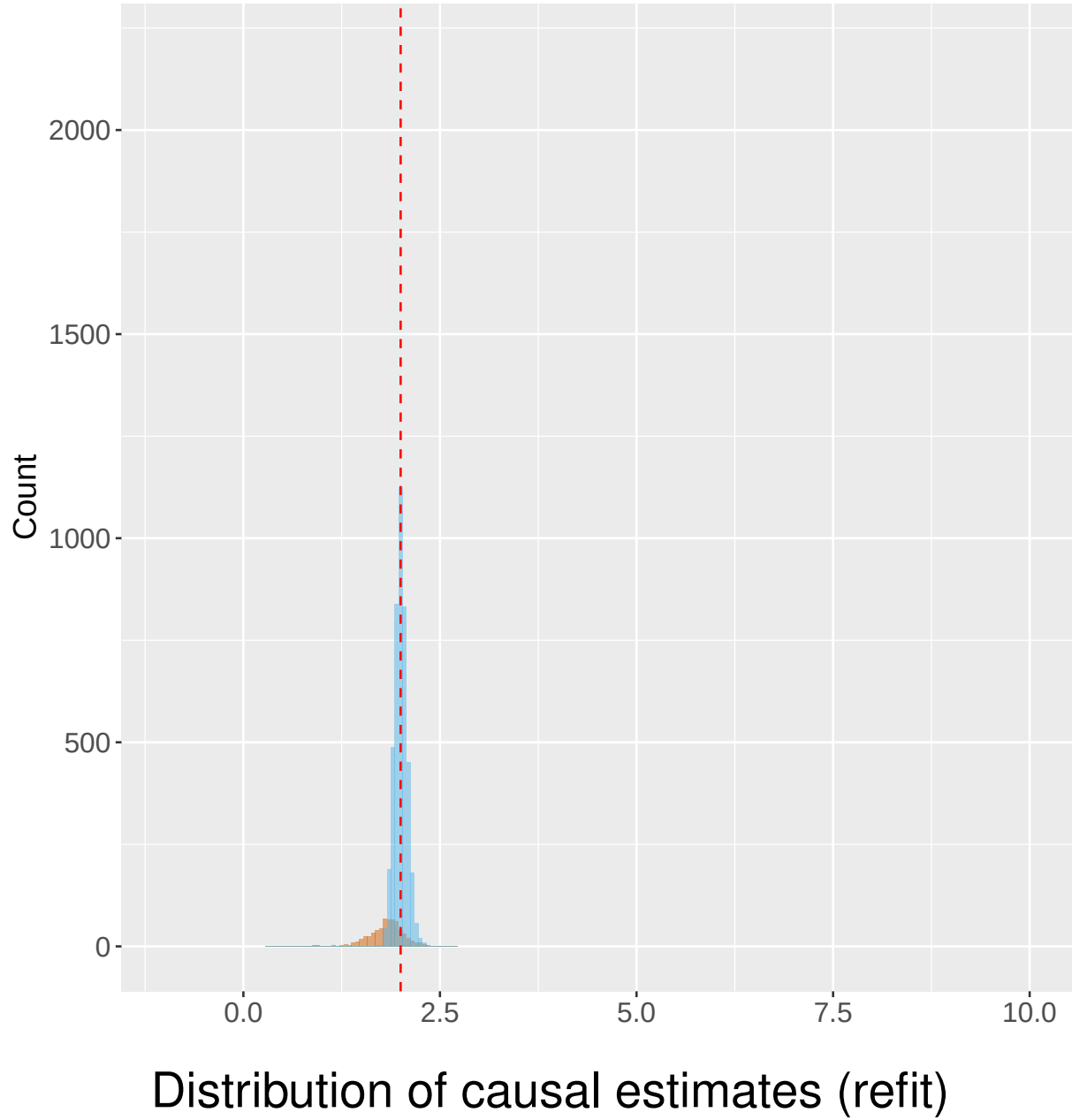
Distribution of causal estimates after removing spurious IVs

Step 3: Develop a mode-finding algorithms to identify the valid instruments



Distribution of causal estimates after mode-finding

Step 4: Use the selected valid instruments to estimate the causal effects



Theoretical guarantees

Theorem 1 (Zhang et al., 2022)

(Spurious IV) Under some regularity conditions, with probability tending to 1, causal estimates for spurious IVs are concentrated within

$$[\beta^* + C_* - d,\ \beta^* + C_* + d]$$

for $d > L\left(\omega, \sigma_X^2, \sigma_u^2, \sigma_Y^2, \alpha_X^*, \alpha_Y^*\right)$, where $C_* = (\alpha_Y^* \alpha_X^* \sigma_u^2)/(\alpha_X^{*2} \sigma_u^2 + \sigma_X^2)$.

Theorem 2 (Zhang et al., 2022)

(Valid IV) Under some regularity conditions, with probability tending to 1, causal estimates for valid IVs are concentrated around β^*.

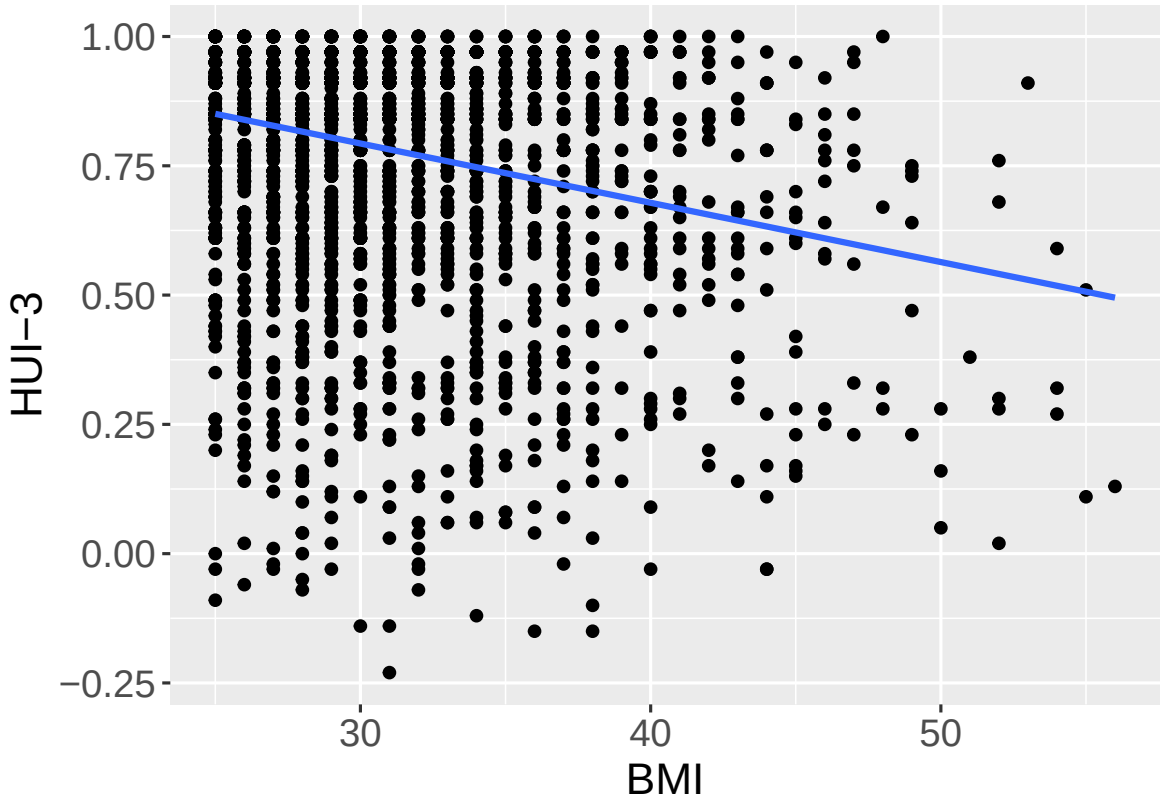
Separation: If $d < |C_*|$, then spurious IVs and valid IVs are separable.

Easier separation if stronger U OR sufficiently large ω

Wisconsin Longitudinal Study

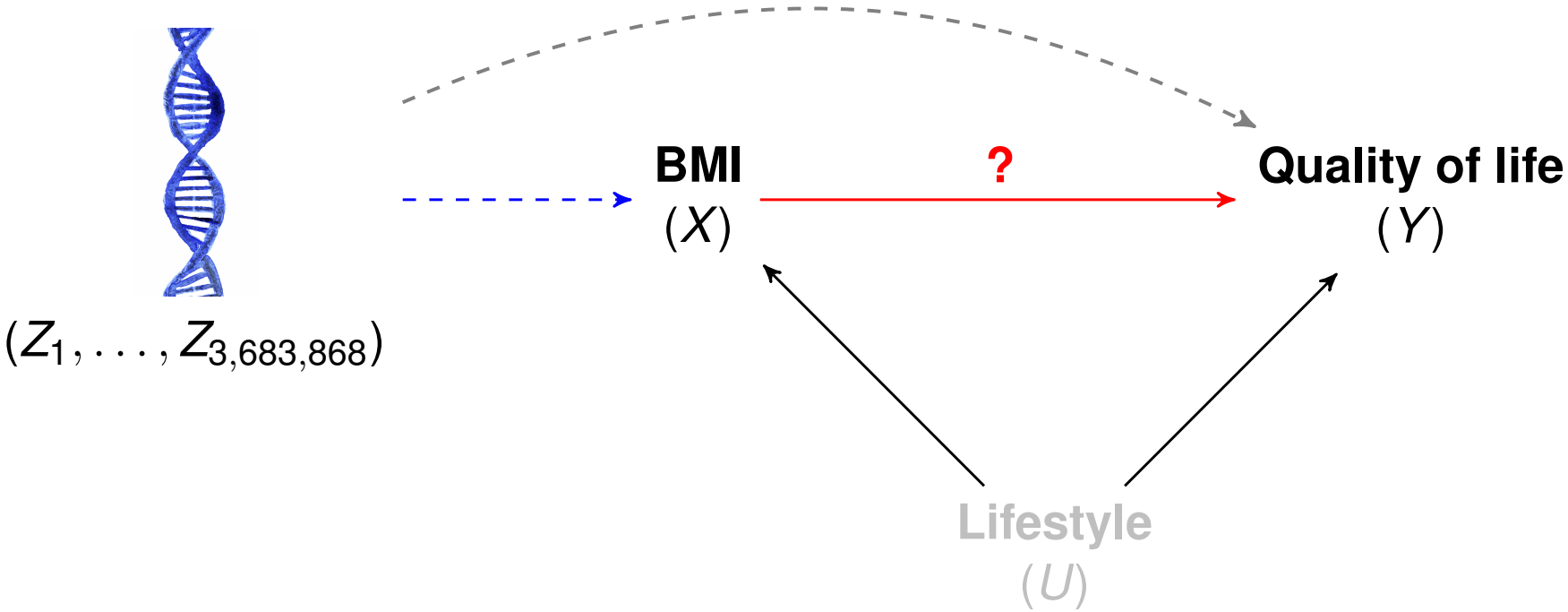
- Participants were graduates from Wisconsin high schools in 1957 and their siblings
- Use 3023 unrelated individuals re-interviewed in 2011
- Exposure: BMI (only those ≥ 25)
  - mean (SD): 30.6 (4.9)
- Outcome: Health Utility Index Mark 3 (HUI-3)
  - between -0.22 and 1
  - mean (SD): 0.79 (0.23)

Crude analysis



After adjusting for age, gender and education, one unit BMI increase associated with 0.011 unit decrease in HUI-3 (95% CI = [0.009, 0.013])

Conceptual Mendelian randomization model

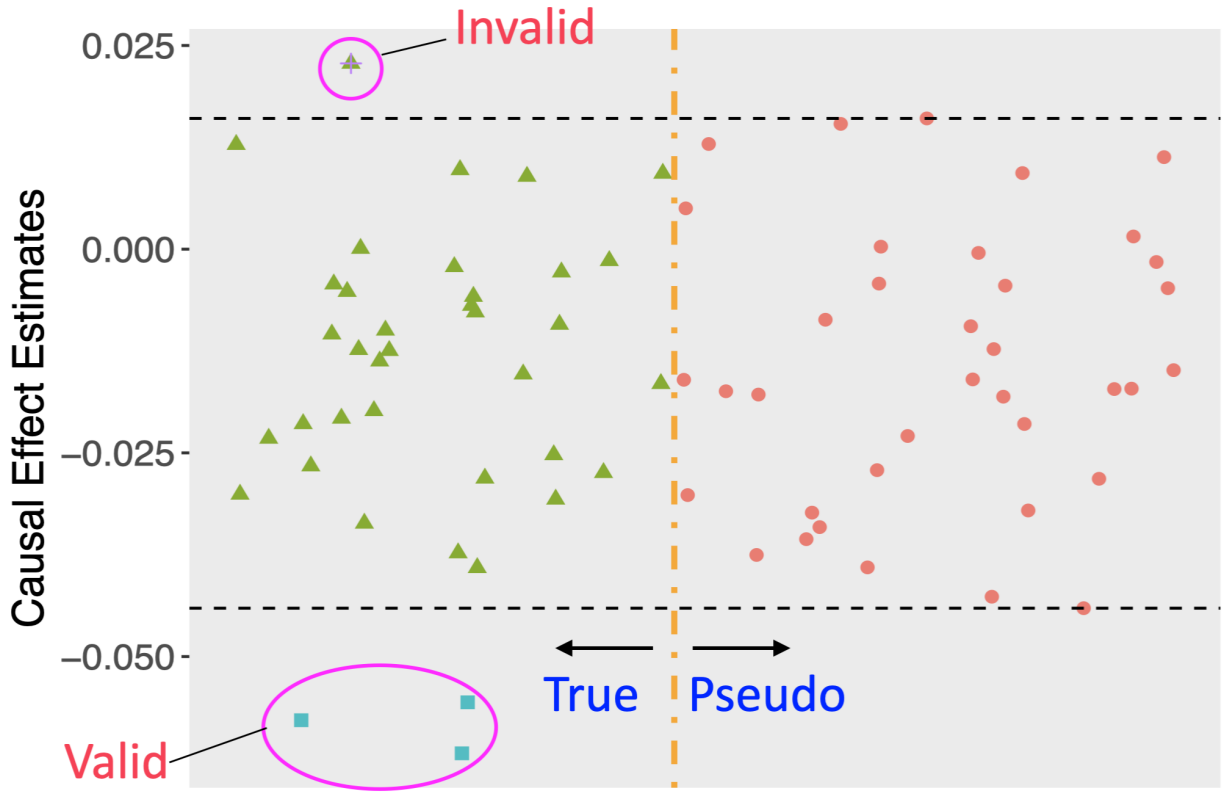


- Consider baseline covariates including age, gender, education and population stratification (top 6 principal components)

Data analysis: Prepossessing + Step 1

- Quality control ☞ 3,683,868 SNPs left
- Generate the same number of pseudo SNPs by permuting the rows of the Z matrix
- After GWAS: 44 SNPs $+$ 42 pseudo

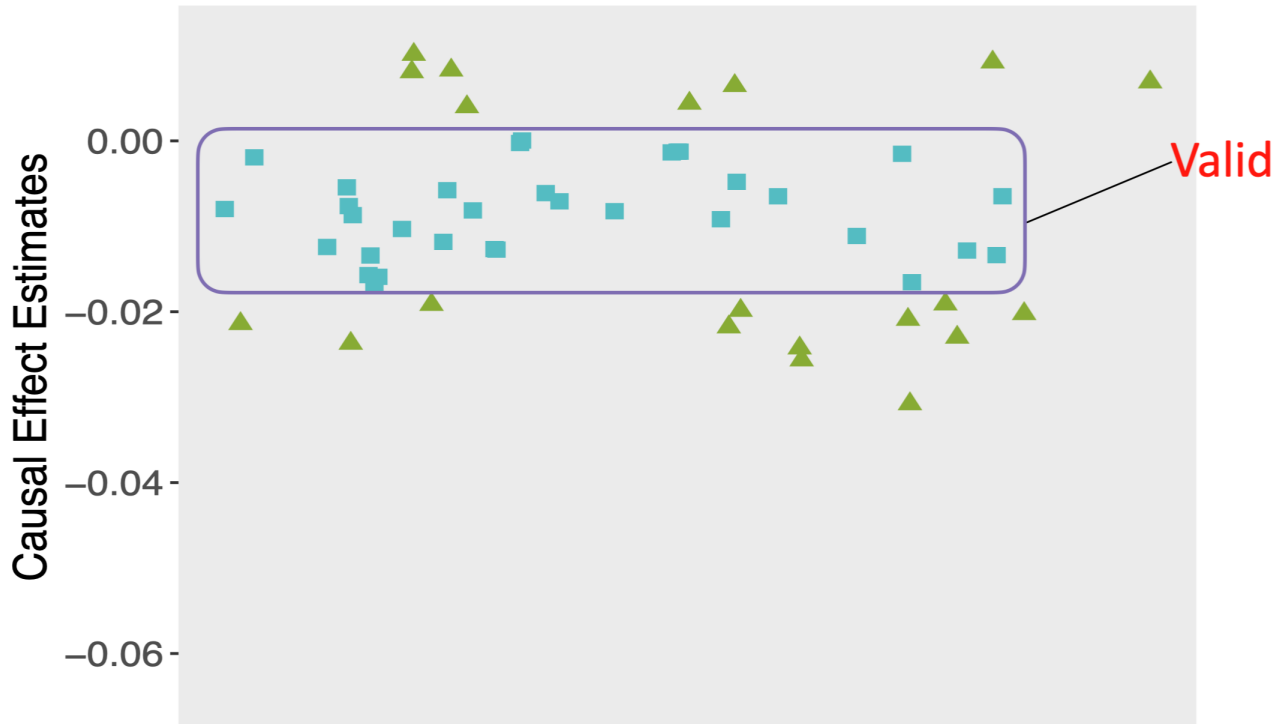
Data analysis: Steps 2-4



Causal estimate: one unit increase in BMI will result in 0.039 unit decrease of HUI-3 (95% CI $= [-0.052, -0.025]$)

Data analysis: Ignoring spurious instruments

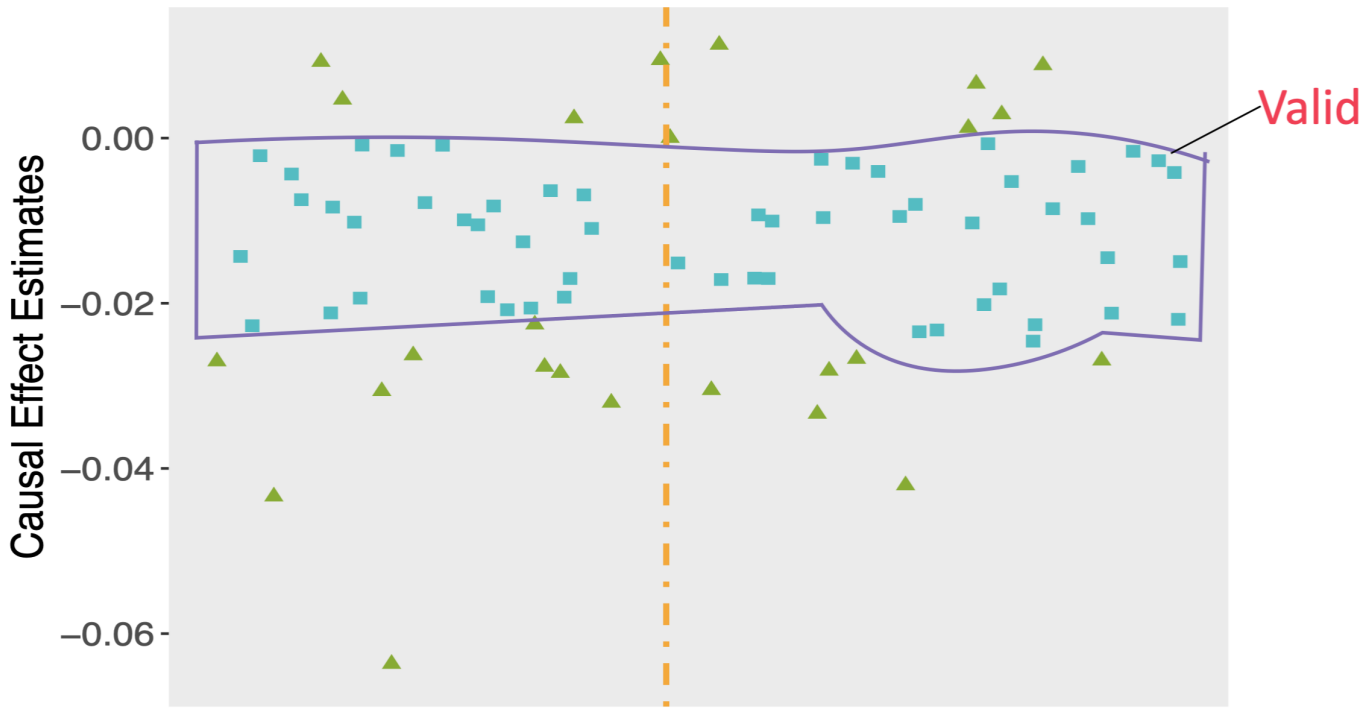
Two-stage hard thresholding with voting (Guo et al., 2018): true SNPs only



Causal estimate: one unit increase in BMI will lead to 0.008 unit decrease in HUI-3 (95% CI $= [-0.013, -0.003]$)

Data analysis: Ignoring spurious instruments

Two-stage hard thresholding with voting (Guo et al., 2018): same data set as the proposed (true + pseudo)



Causal estimate: one unit increase in BMI will lead to 0.011 unit decrease in HUI-3 (95% CI $= [-0.015, -0.008]$)

Comparison of results

Proposed:

1 SD increase in BMI leads to 1 SD (roughly) decrease in HUI-3

Guo et al. (2018)'s method (ignore spurious instruments; true only):

1 SD increase in BMI leads to 0.2 SD (roughly) decrease in HUI-3

Guo et al. (2018)'s method (ignore spurious instruments; true + pseudo):

1 SD increase in BMI leads to 0.2 SD (roughly) decrease in HUI-3

Crude analysis (OLS):

1 SD increase in BMI is associated with 0.2 SD (roughly) decrease in HUI-3

Summary

- Mendelian randomization is a powerful tool for causal effect estimation
- Challenges for MR studies
  - Find relevant IVs ☞ GWAS
  - Deal with pleiotropy ☞ find the mode of effect estimates
  - **Bias due to spurious variables in GWAS**
- Spurious IV bias is potentially a serious problem
  - Ignoring Spurious IV bias has a similar effect as ignoring unmeasured confounding bias
- **Fight noise with noise**
  - Use pseudo variables to correct for Spurious IV bias

References I

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