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INSTRUMENTAL VARIABLE ESTIMATION

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LEARNING OBJECTIVES.

By the end of the session, you will be able to:

1. Define an instrumental variable
2. Describe the standard IV estimator
3. Identify the limitations of IV estimation
4. Conduct an IV analysis using R.

PLAN FOR TODAY: IV ESTIMATION.

1. Recap
2. Instrumental variables
3. IV estimation in a randomized trial
4. IV estimation in an observational study
5. Limitations of IV methods
6. Additional considerations for IV

RECALL: CAUSAL QUESTION OF INTEREST.

1. What is the effect of quitting smoking on weight gain?
2. What is the effect of quitting smoking on risk of death?

We can define the causal effects of interest as:

$$\mathrm{E}[Y^{a=1}] - \mathrm{E}[Y^{a=0}]$$

RECALL: METHODS TO ADJUST FOR CONFOUNDING.

So far, we have covered:

- Stratification/regression
- Propensity scores
- Inverse probability weighting
- Standardization

All of these methods rely on the unverifiable assumption that we have adequately identified and adjusted for all confounders

- "No unmeasured confounding"
- Conditional exchangeability, $Y^a \perp\!\!\!\perp A|L$, holds

INSTRUMENTAL VARIABLE ESTIMATION.

- IV estimation is unlike any method we've discussed so far
- Can identify the casual effect of a treatment on an outcome *even in the presence of unmeasured confounding*
- IV trades the conditional exchangeability assumption for a different set of assumptions (more on this later)

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PLAN FOR TODAY: IV ESTIMATION.

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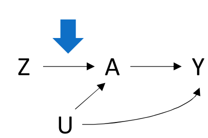
INSTRUMENTAL VARIABLES.

For any instrumental variable (IV) analysis, we need a variable Z (referred to as an instrument or an instrumental variable) that meets three conditions:

1. The instrument is associated with the exposure. (Relevance)



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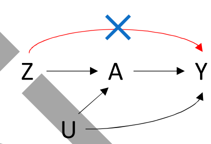
2. The instrument does not affect the outcome except through its potential effect on the exposure. (Exclusion restriction)



9 IV Estimation - Shi

INSTRUMENTAL VARIABLES.

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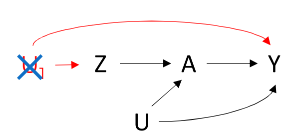
2. The instrument does not affect the outcome except through its potential effect on the exposure. (Exclusion restriction)
3. The instrument and the outcome do not share common causes. (Independence)



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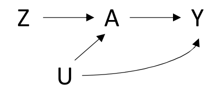
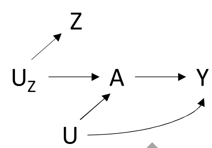
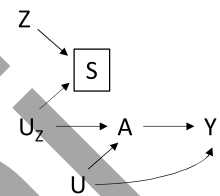
SURROGATE INSTRUMENTS.

The DAG on the previous slides shows a causal instrument.



You can also have instruments that do not cause the exposure. These are referred to as surrogate instruments.





All paths from Z or U_Z to Y must go through the $A \rightarrow Y$ path.

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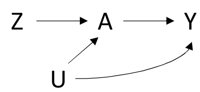
LET'S CONSIDER A RANDOMIZED TRIAL.

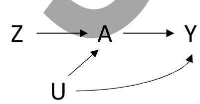


Z: randomization to taking statins (1: yes, 0: no)
A: actually taking statins (1: yes, 0: no)
Y: cardiovascular disease (1: yes, 0: no)
U: treatment-outcome confounders

There are two types of causal effects we might be interested in:

1. Intention-to-treat effect: effect of Z on Y
2. Per-protocol effect: effect of A on Y

RANDOMIZATION AS AN INSTRUMENT.



Z: randomization to taking statins
A: actually taking statins
Y: cardiovascular disease
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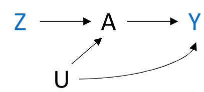
Let's consider randomization, Z, as our instrument.
Recall the three instrumental conditions:

1. Randomization is associated with taking statins.
   We expect (some) people to follow their assigned treatment arm.
2. Randomization does not affect CVD except through its potential effect on taking statins.
   We expect this to hold in a blinded trial.
3. Randomization and CVD do not share common causes
   We expect this to hold because there are no causes of randomization.

POLL QUESTION.



Z: randomization to taking statins
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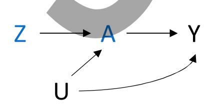
In our randomized trial, the association between Z and Y is an unbiased estimate for the effect of Z on Y.

A. True

B. False

POLL QUESTION.



Z: randomization to taking statins
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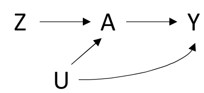
In our randomized trial, the association between Z and A is an unbiased estimate for the effect of Z on A.

A. True

B. False

IV ESTIMATION.



Z: randomization to taking statins
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IV estimation takes advantage of the fact that we can estimate two quantities without bias:

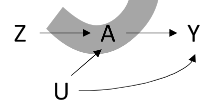
1. Effect of Z on Y (the intention-to-treat effect): effect of being randomized to take statins on the incidence of CVD
2. Effect of Z on A (the level of adherence): effect of being randomized to take statins on actually taking statins

The conventional IV estimator:

$$\frac{\text{intention}-\text{to}-\text{treat effect}}{\text{level of adherence}}$$

With perfect adherence (denominator = 1), the ITT effect is equal to the per-protocol effect

IV ESTIMATION.



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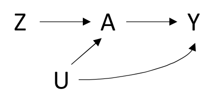

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$$\frac{\mathrm{E}[\mathrm{Y}|\mathrm{Z}=1]-\mathrm{E}[\mathrm{Y}|\mathrm{Z}=0]}{\mathrm{E}[\mathrm{A}|\mathrm{Z}=1]-\mathrm{E}[\mathrm{A}|\mathrm{Z}=0]}$$

IV ESTIMATION IN RANDOMIZED TRIALS.

- In double-blind randomized trials, we have, by design, a variable (i.e. randomization) which is expected to meet all the instrumental conditions
- Ideal setting for IV analysis
- Identify the per-protocol effect without adjusting for confounders
- What about applications in observational studies?

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IV ANALYSIS IN OBSERVATIONAL STUDIES.

We no longer have randomization, so identifying an instrument is not as straightforward.

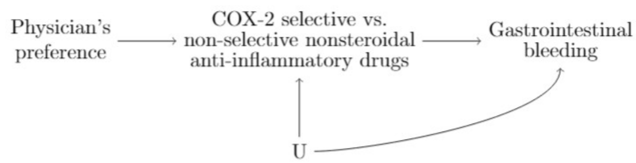
Our proposed instrument still needs to meet the three instrumental conditions:

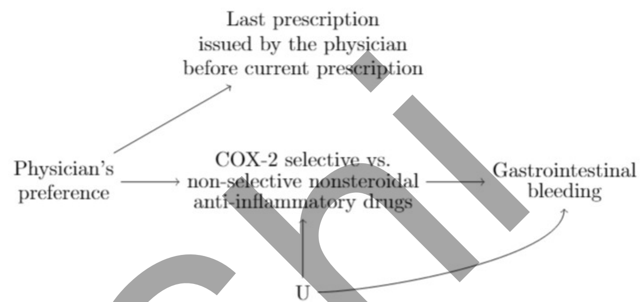
1. The instrument is associated with the exposure.
2. The instrument does not affect the outcome except through its potential effect on the exposure.
3. The instrument and the outcome do not share common causes.

IV EXAMPLE: PHYSICIAN'S PREFERENCE.

Physician's preference influences prescribed treatment A without directly affecting the outcome Y.

Physician's preference is generally unmeasured, so may use past prescription patterns as a surrogate.

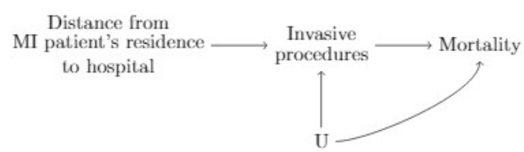


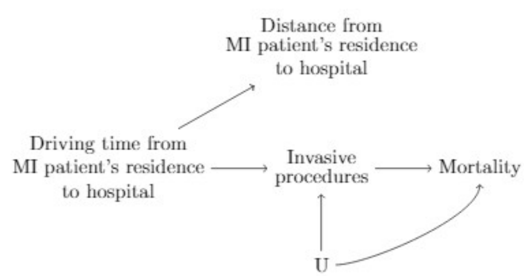


IV EXAMPLE: ACCESS.

Access to a treatment affects the use of treatment A but without directly affecting the outcome Y.

Examples of measures of access include:
- Physical distance (or travel time)
- Calendar period
- Price/cost of treatment

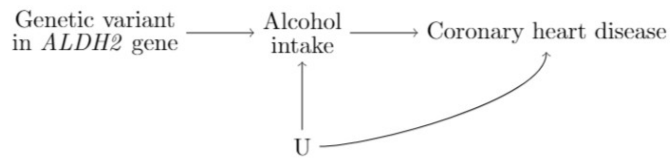




(McClellan et al., 1994)

IV EXAMPLE: MENDELIAN RANDOMIZATION.

A genetic variant that is associated with treatment A and is only related to the outcome Y through the treatment.

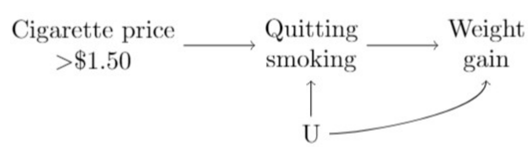


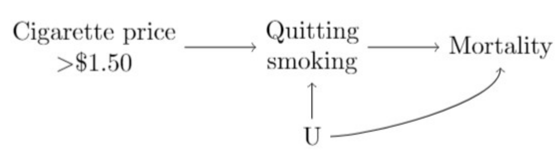
IV ANALYSIS IN THE NHEFS DATASET.

Proposed instrument:

- Price of a pack of cigarettes in 1982 (adjusted for inflation to 2008 US dollars) in the state in which the participant was born
- Dichotomized at >$1.50

Let’s try it in R!





ALTERNATIVE ESTIMATORS FOR IV.

In practice, people often do not use the standard IV estimator:

$$\frac{\mathrm{E}[\mathrm{Y}|\mathrm{Z}=1]-\mathrm{E}[\mathrm{Y}|\mathrm{Z}=0]}{\mathrm{E}[\mathrm{A}|\mathrm{Z}=1]-\mathrm{E}[\mathrm{A}|\mathrm{Z}=0]}$$

Rather, they use an estimator called two-stage least squares:

- Can accommodate continuous instruments
- Can accommodate multiple instruments
- Can add other covariates
- Provide 95% confidence intervals

TWO-STAGE LEAST SQUARES ESTIMATOR.

Two-stage least squares involves running two linear regression models:

1. Model 1: Regress the treatment on the instrument
$$\mathrm{E}[A|Z]=\alpha_0+\alpha_1 Z$$
2. Model 2: Regress the outcome on the predicted values obtained from model 1
$$\mathrm{E}[Y|Z]=\beta_0+\beta_1\hat{\mathrm{E}}[A|Z]$$

With a dichotomous treatment and instrument, this will give you the same answer as the standard IV estimator.

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LIMITATION OF IV METHODS.

We just estimated the effect of quitting smoking on weight gain without having to worry about any confounders!

What's the catch?

We'll highlight 3 limitations of IV methods:

1. The instrumental conditions may not hold, especially in observational studies.
2. Weak instruments can create and inflate bias.
3. The three instrumental conditions are not enough.

THE INSTRUMENTAL CONDITIONS MAY NOT HOLD...

Recall our three instrumental conditions:

1. The instrument is associated with the exposure.
2. The instrument does not affect the outcome except through its potential effect on the exposure.
3. The instrument and the outcome do not share common causes.

If any of those three conditions do not hold, then our IV estimate will be biased.

Let's evaluate the three instrumental conditions in our NHEFS example.

POLL QUESTION.

Can we use our data to empirically verify whether the first instrumental condition holds?

1. Yes
2. No

Recall: The first instrumental condition states "*The instrument is associated with the exposure.*"

THE FIRST INSTRUMENTAL CONDITION.

Recall the first instrumental condition:

The instrument is associated with the exposure.

We can verify this using our data!

Recall the IV estimator:

$$\frac{E[Y|Z=1]-E[Y|Z=0]}{E[A|Z=1]-E[A|Z=0]}$$

- The denominator is a measure of the association between our instrument and exposure
- We calculated 0.06 as the denominator in our NHEFs example
  - Probability of quitting smoking is 6 percentage points higher among people with high cigarette prices (>$1.50) compared to people with low cigarette prices (≤$1.50)

POLL QUESTION.

Can we use our data to empirically verify whether the second instrumental condition holds?

1. Yes
2. No

Recall: The second instrumental condition states "*The instrument does not affect the outcome except through its potential effect on the exposure.*"

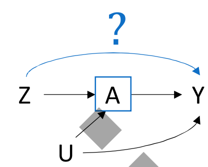
THE SECOND INSTRUMENTAL CONDITION.

Recall the second instrumental condition:

The instrument does not affect the outcome except through its potential effect on the exposure.

We cannot verify this using our data.

Can we check for the presence of an arrow from Z to Y by blocking the path through A (i.e., from Z to A to Y)?



No, because A is also a collider, so we opened the path Z to A to U to Y.

Can you think of how this condition might be violated in our NHEFS example?

POLL QUESTION.

Can we use our data to empirically verify whether the third instrumental condition holds?

1. Yes
2. No

Recall: The third instrumental condition states "*The instrument and the outcome do not share common causes.*"

THE THIRD INSTRUMENTAL CONDITION.

Recall the third instrumental condition:

The instrument and the outcome do not share common causes.

- We can never guarantee that there is no confounding
  - True for exposure-outcome confounding, and for instrument-outcome confounding
- If we have data on the Z-Y confounders, we can adjust for them in the analysis (using the two-stage least squares estimator)

Can you think of how this condition might be violated in our NHEFS example?

LIMITATION 1: THE INSTRUMENTAL CONDITIONS MAY NOT HOLD.

If we cannot verify the second and third instrumental conditions, what can we do?

- Use our expert knowledge to pick an appropriate instrument
- Adjust for Z-Y confounders (for the third instrumental condition); let's see how to do this in R
- Try to falsify the instrumental conditions (see Labrecque and Swanson, 2018)
  - Can conduct tests that prove the 2nd or 3rd conditions don't hold
  - "Passing" these tests does not prove that these conditions hold

LIMITATION 2: WEAK INSTRUMENTS CAN CREATE AND INFLATE BIAS.

- With weak instruments, the denominator of our IV estimator is closer to 0:

$$\frac{\mathrm{E}[\mathrm{Y}|\mathrm{Z}=1]-\mathrm{E}[\mathrm{Y}|\mathrm{Z}=0]}{\mathrm{E}[\mathrm{A}|\mathrm{Z}=1]-\mathrm{E}[\mathrm{A}|\mathrm{Z}=0]}$$

- Any bias due to violations of the 2nd or 3rd instrumental conditions are captured in the numerator, and get inflated by the denominator

How strong of an instrument should we have?

- Many people use a cut-off of F-statistic >10 (but this is arbitrary and sample size-dependent)
- Let's check the F-statistic in our NHEFS example

LIMITATION 2: WEAK INSTRUMENTS CAN CREATE AND INFLATE BIAS.

For weak instruments, we should be concerned that Z and A are associated by chance.

Suppose we randomly generate data for Z so that Z and A are independent:

- The Z-A association will be zero
- Denominator of the IV estimand is zero and therefore the IV estimate is undefined

With finite data:

- Z-A association will be small but not exactly zero
- IV estimate will be incorrectly inflated (i.e., biased)

LIMITATION 2: WEAK INSTRUMENTS CAN CREATE AND INFLATE BIAS.

Let's re-examine our instrument in the NHEFS dataset

- Dichotomizing price of cigarettes at $1.50 was an arbitrary decision
- What if we chose a different cutoff?

Cutoff of $1.60: 41.3 kg

Cutoff of $1.70: -40.9 kg

Cutoff of $1.80: -21.1 kg

Cutoff of $1.90: -12.8 kg

Cutoff of $2.00: -682.5 kg

- Price of cigarettes behaves as a randomly generated variable

LIMITATION 3: THE INSTRUMENTAL CONDITIONS ARE NOT ENOUGH.

- Even if we have a variable that meets all three instrumental conditions, that's not enough
- Fourth assumption is needed
- Depending on the type of fourth assumption we use, the interpretation of our IV estimate differs:
  - Homogeneity
  - Monotonicity

HOMOGENEITY.

- There are many versions of the homogeneity assumption
- If *any* of them hold, then the IV estimate represents the marginal causal effect:

$$\mathrm{E}[Y^{a=1}] - \mathrm{E}[Y^{a=0}] = \frac{\mathrm{E[Y|Z=1]-E[Y|Z=0]}}{\mathrm{E[A|Z=1]-E[A|Z=0]}}$$

Version 1:

The effect of A on Y is the same for every individual.

- Referred to as "constant treatment effect"
- Too strong of an assumption

POLL QUESTION.

Homogeneity (version 1) states: "*The effect of A on Y is the same for every individual.*"

Can we empirically test this assumption?

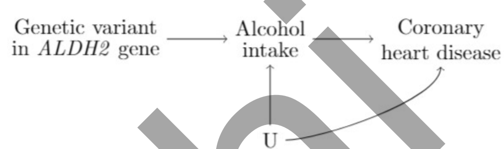
1. Yes
2. No

HOMOGENEITY: VERSION 2.

Version 2:

The effect of A on Y (on the additive scale) is not modified by Z (or by U_Z).

- This must hold true among the treated and the untreated, separately
- Example of violation:



- *ALDH2* affects alcohol intake, but it also affects alcohol metabolism; could modified the effect of alcohol intake

POLL QUESTION.

Homogeneity (version 2) states: "*The effect of A on Y (on the additive scale) is not modified by Z (or by U_Z).*"

Can we empirically test this assumption?

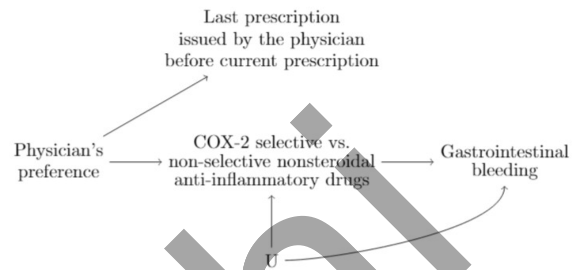
1. Yes
2. No

HOMOGENEITY: VERSION 3.

Version 3:

The effect of A on Y (on the additive scale) is not modified by U.

- Example of violation:



- If U is response to past treatment, it could act as a modifier
- Also cannot be empirically tested

HOMOGENEITY: VERSION 4.

Version 4:

The association between Z and A (on the additive scale) is constant across levels of the exposure-outcome confounders.

- If we've measured some of the confounders between exposure and outcome, we could test this assumption
- Unless we've measured all exposure-outcome confounders, we cannot guarantee that this assumption holds

HOMOGENEITY: MORE GENERALIZED.

More generally, we can consider homogeneity to hold if:

Modifiers for the effect of treatment A on the outcome Y on the additive scale

are unrelated to

Modifiers of the Z-A association on the additive scale

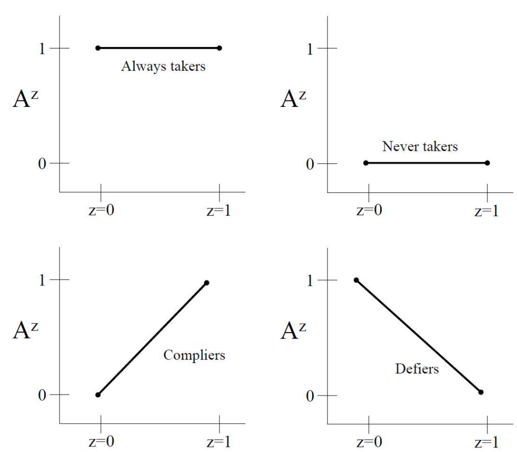
Homogeneity versions 3 and 4 are special cases of this generalized definition of homogeneity.

MONOTONICITY: AN ALTERNATIVE TO HOMOGENEITY.

Monotonicity: For all participants, the level of treatment A that an individual would take if given a level of the instrument Z is a monotone increasing function of the level Z.

What does this mean?

- Consider a randomized trial, where Z (randomization) is our instrument
- Four types of people: always-takers, never-takers, compliers, defiers



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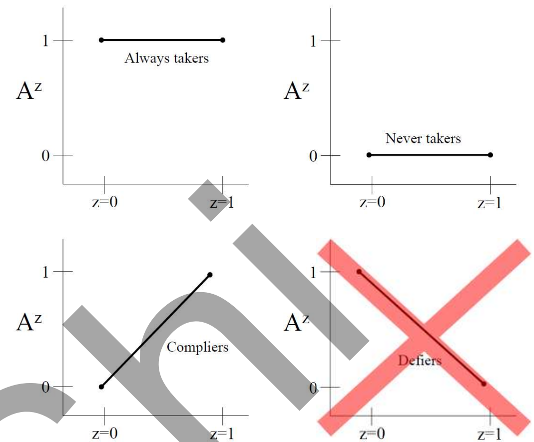
What does this mean?

- Consider a randomized trial, where Z (randomization) is our instrument
- Four types of people: always-takers, never-takers, compliers, defiers
- Monotonicity means there are no defiers



POLL QUESTION.

Can the monotonicity assumption be empirically verified?

1. Yes
2. No

PLAUBILITY OF THE MONOTONICITY ASSUMPTION.

- Monotonicity cannot be empirically verified
- In a randomized trial, it is a reasonable assumption
- In an observational study, it will depend on the study question

- In the NHEFS example, monotonicity means there is no one who:
  - Would quit smoking if price of cigarettes was low (≤$1.50)
  - Would *not* quit smoking if price of cigarettes was high (>$1.50)

INTERPRETATION OF THE IV ESTIMATE UNDER MONOTONICITY.

Under monotonicity, the IV estimate cannot be interpreted as the marginal causal effect.

Rather, it is the average causal effect of A on Y among the compliers

- Local average treatment effect (LATE)
- Complier average causal effect (CACE)

WHO ARE THE COMPLIERS?

- We cannot identify *who* the compliers are
- Our estimate applies to an unidentifiable subgroup of the study population

- When treatment is dichotomous, we *can* calculate the proportion of people who are compliers in our study population
  - Equal to the denominator of the standard IV estimator:

$$\frac{E[Y|Z=1]-E[Y|Z=0]}{E[A|Z=1]-E[A|Z=0]}$$

- Recall in our NHEFS example, the denominator was 0.06 (i.e., only 6% of our study population are compliers)

POLL QUESTION.

Do you think monotonicity is a reasonable assumption to make in the NHEFS dataset?

1. Yes
2. No

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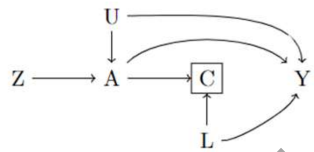
IV ESTIMATION & SELECTION BIAS.

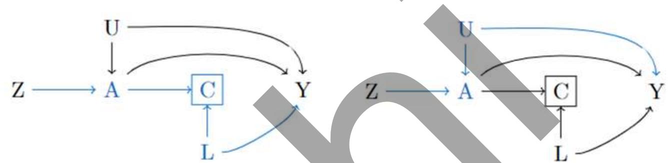
- IV estimation only addresses confounding between treatment A and outcome Y
- Still susceptible to selection bias
- We described the third instrumental condition as: "*The instrument and the outcome do not share common causes.*"
  - Oversimplification
  - More correct to say "*The instrument and the outcome do not share common causes or <u>other sources of lack of exchangeability</u>*"
- Selection bias is a source of lack of exchangeability between the instrument and the outcome

IV ESTIMATION AND SELECTION BIAS EXAMPLE

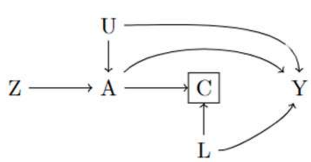
Consider our DAG for selection bias due to loss to follow-up:



Conditioning on C creates a source of lack of exchangeability between Z and Y:

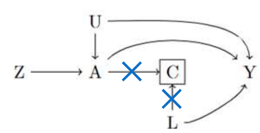


IP WEIGHTING AND IV ESTIMATION.

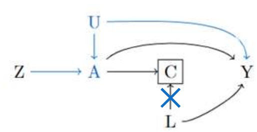


Need to use inverse probability of censoring weights to address this

- Need data on variables related to selection
- Using *unstabilized* weights will remove $A \rightarrow C$ and $L \rightarrow C$ arrows



- Cannot use *stabilized* weights because there is still bias if the $A \rightarrow C$ arrow is present



- tsls function in R will not allow us to calculate robust variances; will need to bootstrap to get 95% CI

IV ESTIMATION: SUMMARY.

- The three instrumental conditions:
  - Associated with exposure
  - Does not affect the outcome except through its potential effect on exposure
  - Does not share common causes with outcome
- A fourth assumption of homogeneity or monotonicity
  - Interpretation of IV estimate varies depending on this 4th assumption

By using IV, we trade one unverifiable assumption…

(i.e., no unmeasured treatment-outcome confounding)

…for other unverifiable assumptions.

(i.e., no unmeasured instrument-outcome confounding, no direct effect of the instrument, homogeneity/monotonicity)

LEARNING OBJECTIVES.

By the end of the session, you will be able to:

1. Define an instrumental variable
2. Describe the standard IV estimator
3. Identify the limitations of IV estimation
4. Conduct an IV analysis using R.