INSTRUMENTAL VARIABLE ESTIMATION (I)

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Learning objectives
At the end of this lecture you will be able to

- Define an instrumental variable
- Define the standard instrumental variable estimator
- Provide examples of commonly used instruments

□ Key concepts

- Instrument
- Surrogate instrument
- Two-stage least squares estimator

Our goal: To estimate the average causal effect of treatment A on outcome Y

- For example
  - the effect of aspirin (A) on blood pressure (Y)
  - the effect of smoking cessation (A) on weight gain (Y)

- The average causal effect is the difference of counterfactual means $\mathrm{E}[Y^{a=1}] - \mathrm{E}[Y^{a=0}]$

To validly estimate causal effects we will generally need to adjust for confounding

For example

- Individuals with history of coronary heart disease are more likely to receive aspirin (A) and also to have higher blood pressure (Y)
- Heavy smokers are less likely to quit smoking (A) and also less likely to gain weight (Y)

Methods to adjust for confounding

- Stratification/Regression
- Matching
- Stratification/matching based on propensity scores
- Standardization/G-formula
- IP weighting
- G-estimation

- All these methods require one unverifiable condition…

The measured confounders L are sufficient to control all confounding

"No unmeasured confounding" condition

Requires **conditional exchangeability**

- the outcome distribution in the treated if untreated is the same as the outcome distribution in the untreated, and vice versa, within levels of L

$$Y^a \perp\!\!\!\perp A | L = l \qquad \text{for all } a$$

Conditional exchangeability is necessary for all the above methods, but…

… it is also empirically **unverifiable**

- Data to test this condition are, by definition, unavailable

- For example:
  - We cannot prove that individuals who take and do not take aspirin are comparable after conditioning on the measured confounders
  - because these individuals may still not be comparable with respect to unmeasured confounders

Meet instrumental variable (IV) estimation

- We can identify causal effects using IV estimation even if we do not measure the confounders!

- Sounds like magic?
  - Economists have used IV methods for a long time
  - Epidemiologists are increasingly using IV methods

The "magic" of IV estimation applies to treatment-outcome confounders only

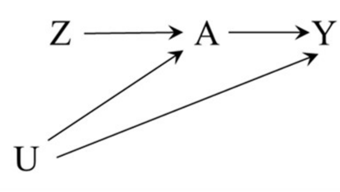
- For example, if there is time-varying selection bias (e.g., because of differential loss to follow-up), then additional adjustment is necessary
  - Such adjustment requires additional data
  - e.g., data on joint predictors of censoring and outcome to estimate IP weights and then implement IV estimation in the pseudo-population

Z is an instrument if it meets the 3 instrumental conditions

i. Z is associated with treatment A
  - relevance condition

ii. Z affects the outcome Y only through treatment A
  - exclusion restriction

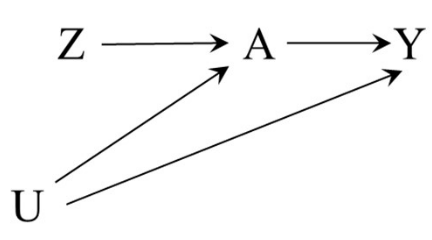
iii. Z does not share causes with the outcome Y
  - no confounding for Z



Outline

1. IV estimation in randomized experiments
2. IV estimation in observational studies
3. Application to smoking cessation study
   - Standard IV estimator
   - Two-stage estimator
4. Limitations of IV estimation
5. Conclusions

Example:
Double-blind randomized experiment



- Z: assigned treatment
  - Aspirin (1: yes, 0: no)
- A: actual treatment
  - Aspirin (1: yes, 0: no)
- Y: outcome
  - Blood pressure
- U: unmeasured factors
  - Healthy lifestyle

The Z-A association is a valid estimator of the effect of Z on A

0

True

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False

0%

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The Z-Y association is a valid estimator of the effect of Z on Y

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False

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We can estimate the intention-to-treat effect

- That is, the effect of being assigned to aspirin vs. no aspirin
  - regardless of whether trial participants adhered to their assignment
  - this is the effect of Z on Y
- However, the intention-to-treat effect is hard to interpret because it critically depends on the degree of adherence
  - the effect of Z on A

We would like to estimate the per-protocol effect

- That is, the effect of actually receiving aspirin vs. no aspirin
  - the effect if trial participants adhered to their assignment
  - this is the effect of A on Y

The A-Y association is a valid estimator of the effect of A on Y

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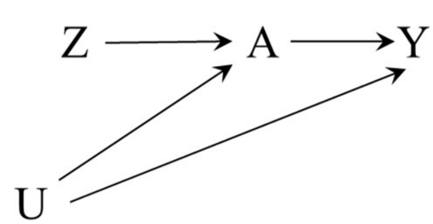
IV estimation to the rescue



- IV estimation can be used to estimate the effect of A on Y as long as we have an instrument Z
  - even if no confounders U are measured

How can IV estimation work?

- By taking advantage of two average causal effects that can be estimated without bias
  - The effect of Z on Y
  - The effect of Z on A

Two effects can be directly estimated because they are unconfounded

Effect of Z on Y

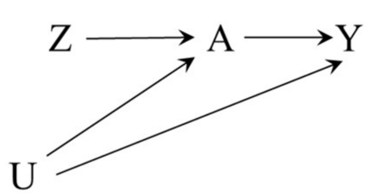
$E[Y|Z=1] - E[Y|Z=0]$

- on additive scale
- Intention-to-treat effect

Effect of Z on A

$E[A|Z=1] - E[A|Z=0]$

- on additive scale
- Adherence (compliance)



The average causal effect of A on Y $\mathrm{E}[Y^{a=1}] - \mathrm{E}[Y^{a=0}]$ is the standard IV estimand

$$\frac{\text{Effect of } Z \text{ on } Y}{\text{Effect of } Z \text{ on } A} = \frac{\text{ITT effect}}{\text{Adherence}} = \frac{\mathrm{E}[Y|Z=1] - \mathrm{E}[Y|Z=0]}{\mathrm{E}[A|Z=1] - \mathrm{E}[A|Z=0]}$$

- Intention-to-treat effect in the numerator is inflated by a measure of adherence in the denominator
  - If full compliance, the denominator is 1 and the intent-to-treat effect equals the effect of A on Y
  - See Chapter 16 for a proof under additional conditions

IV estimand**s** for the average causal effect of A on Y

- The standard IV estimand measures the effect on the additive scale for a dichotomous instrument
  - Difference of means or risks

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

- Other IV estimands yield the effect on the multiplicative scale
  - Ratio of means or risks

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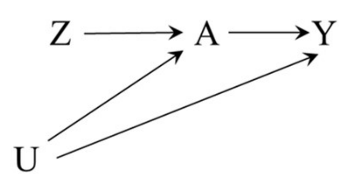
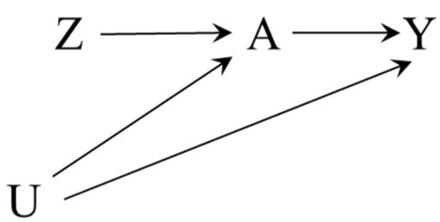
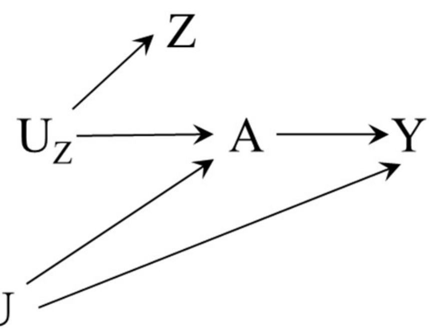


Instrument Z

Causal instrument



Surrogate instrument



For surrogate instruments, the Z-A association is a valid estimator of the effect of Z on A 0

True 0%

False 0%

For surrogate instruments, the Z-Y association is a valid estimator of the effect of Z on Y 0

True

0%

False

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For surrogate instruments, the A-Y association is a valid estimator of the effect of A on Y 0

True

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False

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A surrogate instrument Z can also be used for IV estimation

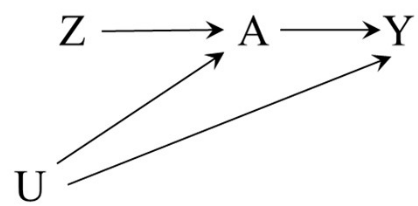
i. Z is associated with treatment A
   - It is OK if the Z - A association is not a valid estimator of the effect of Z on A
   - As long as the causal instrument U_Z is

ii. Z affects the outcome Y only through treatment A
   - It is OK if Z does not affect the outcome Y through A
   - As long as the causal instrument U_Z only affects the outcome through treatment A

iii. Z does not share causes with the outcome Y
   - It is OK if Z and Y share the causal instrument U_Z as a cause
   - U_Z cannot share common causes with outcome Y

Proposed instruments in observational studies Genetic variants

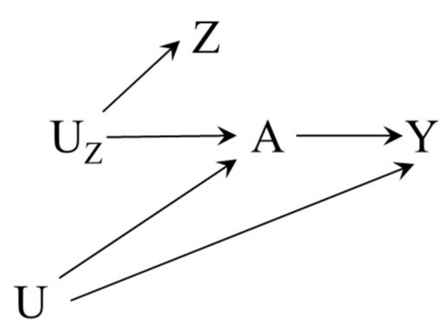
- A: Alcohol intake (1: heavy drinking, 0: mild/no drinking)
- Y: Coronary heart disease
- Z: Genetic variants associated with alcohol metabolism, e.g., ALDH2 polymorphisms in Asian populations



- Mendelian randomization
  - Katan 1986, Davey Smith and Ebrahim 2004, Chen et al 2008…

Proposed instruments in observational studies Genetic variants (surrogate)

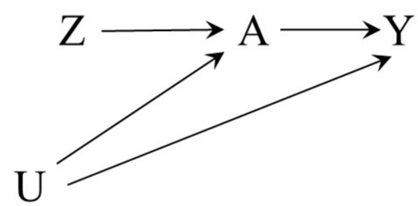
- A: Dietary calcium
- Y: Osteoporosis
- U_Z: Lactose intolerance gene
- Z: Self-reported lactose intolerance



- Causal instrument U_Z is unmeasured, instrument Z is a proxy for U_Z

Proposed instruments in observational studies Preference

- Lung cancer patients
  - A: Type of chemotherapy
  - Y: 5-year mortality
  - Z: Physician's preference for type of chemotherapy



- Pharmacoepidemiology / Outcomes research
  - Korn and Baumrind 1998, Earle et al 2001, Brookhart et al 2006…

Just out of curiosity, do you think this proposed instrument is a valid instrument? 0

(A) Yes — **0%**

(B) No — **0%**

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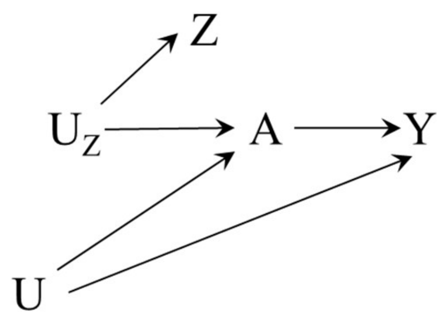
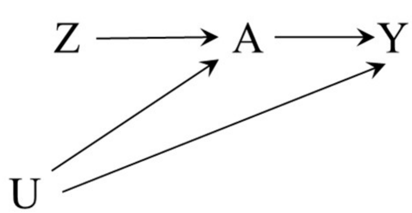
Proposed instruments in observational studies Preference (surrogate)

- Lung cancer patients
  - A: Type of chemotherapy
  - Y: 3-year mortality
  - U_Z: Physician's preference for type of chemotherapy
  - Z: Proportion of patients recently treated by that physician who received A=1
- Causal instrument U_Z is unmeasured, instrument Z is a proxy for U_Z



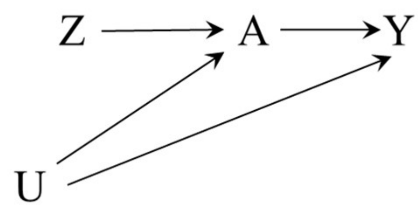
Proposed instruments in observational studies Access: physical distance

- Patients with myocardial infarction
  - A: Invasive procedures
  - Y: Mortality
  - Z: Distance from patient's residence to hospital with capability for invasive procedures
    - McClellan et al 1994



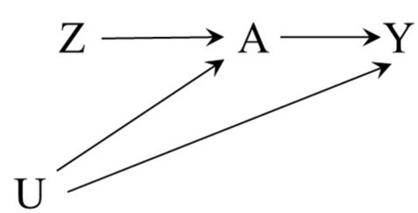
Proposed instruments in observational studies Access: price

- Patients with myocardial infarction
  - A: Cigarette smoking cessation
  - Y: Health outcome (physical functional status)
  - Z: Cigarette price
    - Leigh and Schembri 2004



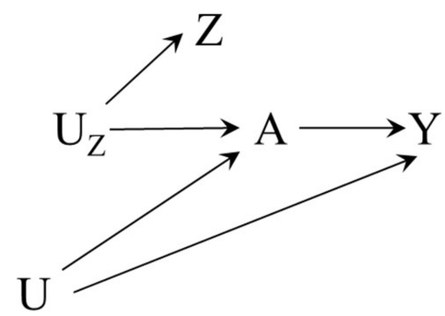
Proposed instruments in observational studies Access: calendar time

- HIV-infected patients
  - A: Type of antiretroviral therapy (monotherapy, combination therapy, cART)
  - Y: AIDS or death
  - Z: Calendar period (1990-93, 1994-95, 1996-97)
    - Hoover et al 1994, Detels et al 1998



Proposed instruments in observational studies Access (surrogate)

- Physical distance, price, calendar period, can also be seen as surrogates of the causal instrument accessibility U_Z
  - Distance Z is an approximation to actual driving time (e.g., traffic patterns may be important too)
  - Cigarette price in a state Z is an approximation to price at the closest store
  - Calendar time Z is an approximation to accessibility to a treatment because there might be a fuzzy boundary of availability



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Study population

- 1629 cigarette smokers
- Aged 25-74 years when interviewed in 1971-75 (baseline)
- Interviewed again in 1982
- Known sex, age, race, weight, height, education, alcohol use, and smoking intensity at both baseline and follow-up visits, and who answered the general medical history questionnaire at baseline

Key variables

Treatment A	Quit smoking between baseline and 1982 1: yes, 0: no
Continuous outcome Y	Weight gain, kg Weight in 1982 minus baseline weight Available for 1566 individuals
Proposed instrument Z	Price of a pack of cigarettes in 1982 in the state of birth in 2008 US dollars 1: greater than $1.50, 0: $1.50 or lower
Y and Z available for 1476 individuals	For simplicity, IV analysis restricted to them

Reminder

- Average causal effect of A on Y is $\mathrm{E}[Y^{a=1}] - \mathrm{E}[Y^{a=0}]$
  - on the additive scale
- where
  - $\mathrm{E}[Y^{a=1}]$ is the mean weight gain if everybody had quit smoking
  - $\mathrm{E}[Y^{a=0}]$ is the mean weight gain if nobody had quit smoking

Data analysis
Standard IV estimator

- $\hat{\mathrm{E}}[Y|Z=1] - \hat{\mathrm{E}}[Y|Z=0]$
  - $= 2.686 - 2.536 = 0.1503$
- $\hat{\mathrm{E}}[A|Z=1] - \hat{\mathrm{E}}[A|Z=0] =$
  - $0.2578 - 0.1951 = 0.0627$
- The IV estimate of $\mathrm{E}[Y^{a=1}] - \mathrm{E}[Y^{a=0}]$ is
  - 0.1503 / 0.0627 = 2.4 kg *See iv.R, lines 6-11*

Data analysis
Two-stage least-squares estimator

- Stage 1: Fit a linear model for treatment
  - $\mathrm{E}[A|Z] = \alpha_0 + \alpha_1 Z$
  - Generate the predicted values $\hat{\mathrm{E}}[A|Z]$ for each individual
- Stage 2: Fit a linear model for the outcome
  - $\mathrm{E}[Y|Z] = \beta_0 + \beta_1 \hat{\mathrm{E}}[A|Z]$
- The parameter estimate of β_1 is the IV estimate
  - 2.4 kg; 95% CI (-36.5, 41.3) *See iv.R, lines 16-24*

Standard estimator and two-stage estimator are equivalent IV estimators

- But the two-stage estimator is more frequently used because it makes it easier to
  - introduce covariates
  - handle continuous treatments
  - consider multiple instruments simultaneously
- However, the two-stage estimator makes strong parametric assumptions
  - Robins's g-estimators of structural mean models avoid some of those assumptions but have been rarely used

Isn't it amazing?

- NO DATA on confounders are needed!
- If we find an instrument
  - conditional exchangeability of the treated and untreated is not necessary for causal inference from observational data
- Why have we wasted our time with confounding adjustment methods that require exchangeability?

Progress report

1. Introduction to modeling
2. Stratified analysis:
   - outcome regression
   - propensity scores
3. Standardization
4. Inverse probability weighting
   - Marginal structural models
5. Instrumental variable estimation

   to be continued…