Instrumental Variables & Other Methods for Addressing Unmeasured Confounding in Observational Studies

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A Little About Me

- Trained as a health services researcher & health economist
- Research focus: identifying high value services & systems of care for persons with complex chronic illness
- Answering questions about value often entails using secondary data and observational study designs

Presentation Outline

1. Unmeasured confounding in observational studies – what's the problem, and why is it a problem?
2. 1 potential solution: instrumental variables
3. Example of a study that used instrumental variables to address unmeasured confounding
4. A few words about other solutions
5. Summary

Quick Poll Question

- Which type of study design to do you most typically use in your research?
  - Randomized controlled trial (RCT)
  - Observational study
  - Both

Estimating Causal Effects

- Regardless of your preferred study design, a common aim is estimating a causal effect
  - What is the effect of [treatment] on [outcome]?
- RCTs are ideal for estimating causal effects but not always possible
- Alternative approach: regression analysis using observational data…
  - …if we can adequately address 1 key problem: unmeasured confounding

Linear Regression Model

$$Y_i = \beta_0 + \beta_1 X_i + e_i$$

- Y: outcome variable of interest
- X: explanatory variable of interest
- e: error term
  - e contains any other factors besides X that determine the value of Y
- β_1: the change in Y associated with a unit change in X

- Key elements for causal effect of X on Y:
  - β_1 must be an unbiased estimate
  - X must be exogenous

Exogenous vs. Endogenous

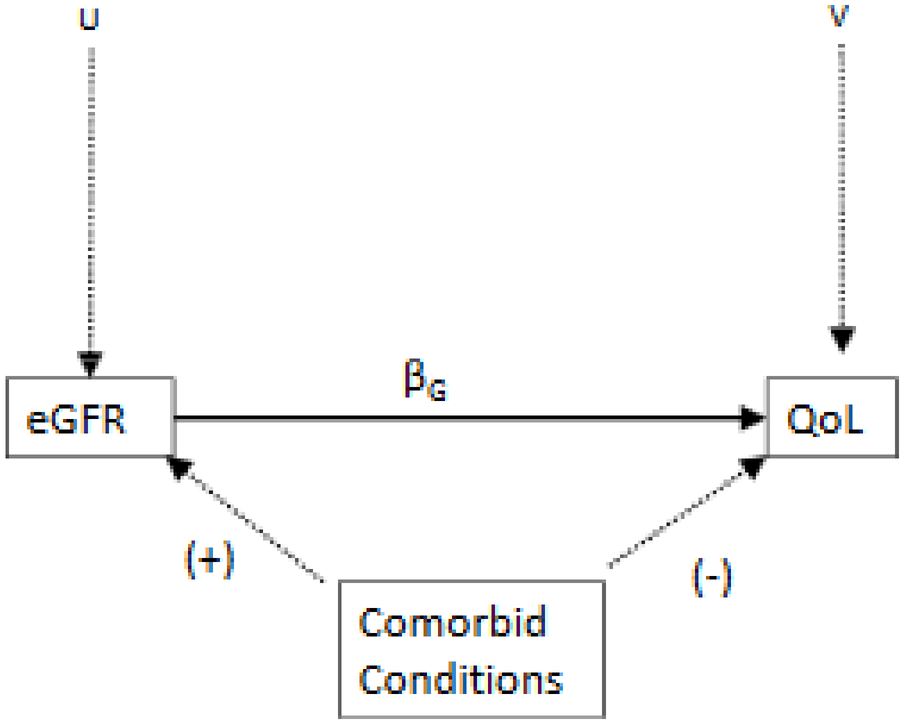
- Exogenous: caused by something outside the system
- Endogenous: caused by something inside the system
- Whether a variable is exogenous or endogenous depends upon your conceptual model and perspective
  - E.g., Medicare reimbursement amount for dialysis is exogenous to dialysis facilities but endogenous to the Centers for Medicare & Medicaid Services

What is Bias? What is an Unbiased Estimate?

- In our previous regression equation, β_1 is considered a biased estimate of the effect of X on Y if the estimated value of β_1 isn't equal to the true value of β_1
  - Unbiased estimate is one where the estimated value = true value
- Cause of bias:
  - X is correlated with e (i.e., X is endogenous)
  - Unmeasured confounder(s)
  - In an observational study, these problems lead to selection bias
    - The treated group and the "non-treated" group may differ in ways that will also affect their difference in outcomes
- Consequence of a biased estimator = incorrect estimate of treatment effect

Selection Bias Example

- Suppose you want to estimate effect of eGFR upon dialysis initiation on quality of life (QoL)
- People with more comorbid conditions are more likely to start dialysis with higher eGFR and more likely to have lower QoL
- If comorbid conditions are unmeasured and excluded from model, β_G will be biased



Solving the Endogeneity Problem

- Variation in X has 2 components:
  - 1 component is correlated with e
    - Causes endogeneity
  - Other component is not correlated with e
    - “Exogenous” variation
- Need to use only the exogenous variation in X to estimate β_1
- We need to add a variable to the regression model that isolates the exogenous variation in X that is uncorrelated with e
  - That variable is called an instrumental variable or an instrument

2 Key Requirements for a Valid Instrument

- Relevance
- Exogeneity

Instrument Relevance

- An instrument (Z) must be correlated with the treatment variable (X)
- Variation in Z must explain variation in X
- If so, Z is "relevant"

Instrument Exogeneity

- The instrument Z must be uncorrelated with the error term e
- Z must also be uncorrelated with all other factors, besides X, that determine outcome Y
- Z doesn't affect Y, except via X
- If these statements are all true, then Z is "exogenous"

An Intuitive Example of an Instrument

$$Outcome_{\mathrm{i}} = \beta_0 + \beta_1 Treatment_i + \mathrm{e}_{\mathrm{i}}$$

- Suppose treatment is assigned via a coin flip
  - Heads: patient gets treatment
  - Tails: patient doesn’t get treatment
- Is the coin flip a valid instrument for treatment?
  - Does the coin flip affect whether a patient receives treatment? *Yes, so it’s relevant.*
  - Does the coin flip directly affect the outcome? *No, so it’s exogenous.*
  - *Therefore, a coin flip is a valid instrument for treatment.*
- Variation in an instrument mimics the role played by randomization in an RCT

What Kinds of Variables Make For Good Instruments?

Instrument Type	Instrument	Treatment -> Outcome
Distance	Distance to nearest hospital with cardiac catheterization[1]	Acute myocardial infarction (AMI) treatment -> mortality
Physician Preference	Prescribing MD's preference for conventional or atypical antipsychotics, as indicated by most recent new Rx[2]	Antipsychotic medication type -> mortality
Geography	Regional catheterization rate[3]	Invasive cardiac management -> AMI survival
Health policy	Medicare geographic adjustment factor, used to calculate fees paid for breast cancer treatments[4]	3 early-stage breast cancer treatments -> 3-year post-treatment survival

[1]McClellan 1994; [2]Wang 2005; [3]Stukel 2007; [4]Hadley 2003

Analytic Approaches When Using IVs

- 4 options
  - **2 stage least squares (2SLS)**
  - Generalized method of moments
  - 2 stage residual inclusion
  - Bivariate probit with correlated errors

2SLS – 1st Stage

- Regress X on Z:

$$X_i = \pi_0 + \pi_1 Z_i + \gamma_i$$

- Predict X:

$$\hat{X}_i = \hat{\pi}_0 + \hat{\pi}_1 Z_i$$

2SLS – 2nd Stage

- Regress Y on $\hat{X}$:

$$Y_i = \beta_0^{TSLS} + \beta_1^{TSLS}\hat{X}_i + error_i$$

- Estimate β_1^{TSLS} (the instrumented treatment effect)
  - $\hat{X}$ is uncorrelated with e from the original regression model $Y_i = \beta_0 + \beta_1 X_i + e_i$
  - β_1^{TSLS} is an unbiased estimate of β_1

Instrumental Variable Example

McClellan, McNeil, & Newhouse 1994

Does More Intensive Treatment of Acute Myocardial Infarction in the Elderly Reduce Mortality?

Analysis Using Instrumental Variables

Mark McClellan, MD, PhD; Barbara J. McNeil, MD, PhD; Joseph P. Newhouse, PhD

Objective.—To determine the effect of more intensive treatments on mortality in elderly patients with acute myocardial infarction (AMI).

Design.—Analysis of incremental treatment effects using differential distances as instrumental variables to account for unobserved case-mix variation (selection bias) in observational Medicare claims data (1987 through 1991).

Main Outcome Measures.—Survival to 4 years after AMI.

Results.—Patients who receive different treatments differ in observable and unobservable health characteristics, biasing estimates of treatment effects based on standard methods of adjusting for observable differences. Patients' differential distances to alternative types of hospitals are strong independent predictors of how intensively an AMI patient will be treated and appear uncorrelated with health status. Thus, differential distances approximately randomize patients to different likelihoods of receiving intensive treatments. Comparisons of patient groups that differ only in differential distances show that the impact on mortality at 1 to 4 years after AMI of the incremental ("marginal") use of invasive procedures in Medicare patients was at most 5 percentage points; this gain was achieved during the first day of hospitalization and therefore appears attributable to treatments other than the procedures. Admission to a hospital treating a high volume of AMI patients was associated with an effect on mortality at 4 years of less than 1 percentage point, again arising on day 1. Patients living in rural areas experienced acute mortality that was an additional 0.6 percentage-point higher, after controlling for less access to intensive treatments.

Conclusions.—For elderly patients with AMI, the aspects of treatment most affecting long-term survival relate to care within the first 24 hours of admission. The survival benefits from greater use of catheterization and revascularization procedures appear minimal in marginal patients.

(*JAMA*. 1994;272:859-866)

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Purpose of Paper + a Few Design Details

- To estimate the effect of 3 different acute myocardial infarction (AMI) treatments – cardiac catheterization, angioplasty, coronary artery bypass graft [CABG] – on mortality 4 years after AMI
- Study cohort: most Medicare beneficiaries age 65+ who had an AMI in 1987 but not in 1986 (n=205,021)
- Data source: Medicare claims & enrollment data
  - AMI treatment could be ascertained at both individual and hospital levels

Analytic Problem

- Model:

$$mortality_i = \beta_0 + \ \beta_1 treatment_i + e_i$$

- Problem: whether or not a patient receives a particular treatment is correlated with many unmeasured factors that may also affect mortality
  - E.g., health status, patient or physician preferences

Endogeneity Problem #1

Table 1.—Characteristics of Elderly Patients With Acute Myocardial Infarction in 1987*

Characteristic	All Patients (N=205 021)	No Catheterization Within 90 d (n=158 261)	Catheterization Within 90 d (n=46 760)
Demographic Characteristics			
Female	50.4	53.5	39.7
Black	5.6	6.0	4.3
Mean age, y (SD)	76.1 (7.2)	77.4 (7.3)	71.6 (5.0)
Urban	70.5	69.6	73.8
Comorbid Disease Characteristics			
Cancer	1.9	2.2	0.8
Pulmonary disease, uncomplicated	10.7	11.1	9.3
Dementia	1.0	1.2	0.1
Diabetes	18.0	18.3	17.1
Renal disease, uncomplicated	1.9	2.3	0.7
Cerebrovascular disease	4.8	5.4	2.8

What Instrument to Use?

- Idea:
  - Patients who live closer to hospitals that have capacity to perform more intensive treatments are more likely to receive those treatments (*relevance*)
  - The distance a patient lives from a given hospital should be independent of her/his health status and mortality risk (*exogeneity*)
- Instrument (for intensive treatment): differential distance to catheterization & revascularization hospitals

What Impact Did the Instrument Have?

Table 4.—Patient Characteristics by Differential Distance to a Catheterization or Revascularization Hospital*

Characteristic	Differential Distance ≤2.5 Miles (n=102 516)	Differential Distance >2.5 Miles (n=102 505)
Comorbid Disease Characteristics		
Cancer	1.9	1.9
Pulmonary disease, uncomplicated	10.4	10.9
Dementia	0.99	0.94
Diabetes	18.1	18.0
Renal disease, uncomplicated	2.0	1.9
Cerebrovascular disease	4.8	4.8
Treatments		
Initial admit to catheterization hospital†	34.4	5.0
Initial admit to revascularization hospital†	41.7	10.7
Initial admit to high-volume hospital†	67.1	36.5
Catheterization within 7 d	20.7	11.0
Catheterization within 90 d	26.2	19.5
CABG‡ within 90 d	8.6	6.9
PTCA§ within 90 d	6.4	4.3

Results (1 of 2)

Table 7.—Instrumental Variable Estimates of the Effects of Patient Location, High-Volume Hospital, and Catheterization on Mortality at Indicated Time Intervals After Acute Myocardial Infarction

Average Effect	Time After Acute Myocardial Infarction, Percentage-Point Change (SE)						
	1 d	7 d	30 d	1 y	2 y	3 y	4 y
Catheterization within 90 d							
Cumulative	−8.8 (2.0)	−11.5 (2.5)	−7.4 (2.9)	−4.8 (3.2)	−5.4 (3.3)	−5.0 (3.2)	−5.1 (3.2)

Table 2.—Estimated Cumulative Effect of Catheterization, Not Accounting for Selection Bias

Adjustment for Observable Differences Using ANOVA*	Percentage-Point Changes in Mortality Rates (SE)					
	1 d	7 d	30 d	1 y	2 y	4 y
None (unadjusted differences)	−9.4 (0.2)	−18.7 (0.2)	−19.2 (0.3)	−30.5 (0.3)	−34.0 (0.3)	−36.8 (0.3)
After adjustment for demographic and comorbidity differences	−6.8 (0.2)	−13.5 (0.2)	−17.9 (0.3)	−24.1 (0.3)	−26.6 (0.3)	−28.1 (0.3)

- IV estimates of the effect of catheterization on mortality are much smaller than estimates that didn’t account for the endogeneity problem

Results (2 of 2)

Table 7.—Instrumental Variable Estimates of the Effects of Patient Location, High-Volume Hospital, and Catheterization on Mortality at Indicated Time Intervals After Acute Myocardial Infarction

	Time After Acute Myocardial Infarction, Percentage-Point Change (SE)						
Average Effect	1 d	7 d	30 d	1 y	2 y	3 y	4 y
Catheterization within 90 d							
Cumulative	−8.8 (2.0)	−11.5 (2.5)	−7.4 (2.9)	−4.8 (3.2)	−5.4 (3.3)	−5.0 (3.2)	−5.1 (3.2)

- Catheterization within 90 days of AMI reduces mortality by 5 percentage points at 1-4 years post-AMI

- Caveats:
  - Validity of these results hinge on the instrument's validity
  - This is an estimate of the marginal effect of catheterization (for patients who wouldn't have otherwise received treatment if they lived differentially far from a catheterization or revascularization hospital)
  - This estimate is an upper bound of the effect of catheterization
    - If C&R hospitals offer better care (e.g., more specialists) other than more intensive procedures, then mortality should be lower at those hospitals

Cautions about Instrumental Variables

- Weak instruments (i.e., those that are weakly correlated with treatment) can accentuate bias and provide unreliable estimates
- Rule of thumb to check if an instrument is weak:
  - From 1st stage of 2SLS, compute the F-statistic testing the hypothesis that the instrument's coefficient equals 0
  - "Rule of Ten": F-statistic > 10 indicates the instrument isn't weak
  - Remember that you still need a convincing argument the instrument is relevant; the instrument should have good face validity
- Assumption that the instrument is uncorrelated with error term in the outcome equation is untestable

Alternatives to IVs When You Have Unmeasured Confounding

- Difference in differences (DiD; Angrist & Pischke, 2008):
  - Using data from 2 points in time, separately calculate the difference in t_2 and t_1 outcomes within the treatment group and within the comparison group; the difference between those two differences will reflect the treatment effect, subject to assumptions
  - Uses regression with period-treatment interaction term
- Prior event rate ratio (Lin & Henley, 2016)
  - Analogous to DiD method for time-to-event or rate data
- Streeter et al 2017 describes other rarely used alternatives

Summary

- Instrumental variables regression is a useful approach for estimating causal effects when you have unmeasured confounding
- Valid instrument must be
  - Relevant: the instrument must affect treatment
  - Exogenous: the instrument must be uncorrelated with all other factors that may affect outcomes
- Good instruments are hard to find
- Using a weak instrument will provide meaningless results
- Beyond testing for instrument validity, must have a good story for why your instrument is relevant & exogenous

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Thank you for inviting me.

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