Causal inference in medicine and public health
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Instrumental Variables

Elizabeth Stuart

JHSPH

Instrumental Variables

Outline

1. Section A: The quantity of interest
2. Section B: Defining and estimating the CACE
3. Section C: Two-sided noncompliance
4. Section D: More details on CACE estimation

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A new method: Instrumental variables

- Moving to another approach for estimating causal effects: instrumental variables
  - "Natural experiments"
  - "Randomized encouragement" designs
- Useful for dealing with noncompliance in randomized trials, as well as estimation of causal effects in non-experimental settings
- Will first motivate in experimental setting; can use as a framework for non-experimental settings too

Noncompliance

- A common complication in randomized trials is that people don't always do what they're told
  - Treatment group members may not take the treatment
  - Control group members may find a way to take it
- Interest is in effect of telling people to take a particular treatment, as well as in the "biologic efficacy" of a treatment: what is the effect if someone actually takes it?
- What to do about this?
- For now, consider only "one-sided noncompliance:" assume control group does not have access to the treatment

What is the "instrument"?

- Note: The randomization is the "instrument"
- Idea is that we randomize something, but not the thing we're really interested in
- Really interested in the effect of actually taking the treatment, but we couldn't randomize that
- But we can use the randomization of the "instrument" to help us estimate the effect we really want

Motivating example: Sommer and Zeger (1991)

- Study estimating the effect of Vitamin A on child mortality
- Carried out in Indonesia
- Villages randomized to receive vitamin A supplements or not
- Not all children in Vitamin A villages actually got Vitamin A
- No children in control villages got Vitamin A (not available)
- For simplicity, will ignore village clustering and treat as if children randomly assigned (village indicators not available anyway)

Two types of people: compliers and non-compliers

- Can think of there being two types of people:
  - Compliers: take the treatment if assigned to, don't take it if not assigned to
  - Non-compliers: don't take the treatment either way
- Observe compliance status in treatment group
- Don't observe compliance status in control group
  - We don't know what the controls would have done if they had been in the treatment group
- Note: Compliance status defined just with respect to this particular trial (not a more general personality trait)

Sommer and Zeger data

Row	True Compliance Type	Treatment Assigned (T)	Treatment Received (D)	Dead (1) or Alive (0) (Y_{obs})	Number of Children
1	?	0	0	0	11,514
2	?	0	0	1	74
3	N	1	0	0	2,385
4	N	1	0	1	34
5	C	1	1	0	9,663
6	C	1	1	1	12
					23,682

How do we deal with noncompliance?

What are some strategies (good and bad) for dealing with the noncompliance? Two potential quantities of interest:

- The effect of being told (randomized) to take Vitamin A
- The effect of actually taking it

The intent-to-treat (ITT) effect

- This is the standard estimate in randomized trials
- Ignores the compliance (what treatments people actually took) and just uses the randomization
- Gives a valid (unbiased) estimate of the effect of being assigned to the treatment group (being told to take the treatment)
- Compares mortality rates among all treatment group members with mortality rates among all control group members
  - Rows 3,4,5,6 vs. Rows 1,2
- In this example:

$$\text{ITT} = \frac{12 + 34}{2,385 + 34 + 9,663 + 12} - \frac{74}{11,514 + 74} = -0.0026$$

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Row	True Compliance Type	Treatment Assigned (T)	Treatment Received (D)	Dead (1) or Alive (0) (Y_{obs})	Number of Children
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As-treated analysis

- Compares the people who actually received the treatment with those who actually received the control
- Ignores the randomization (what people were assigned to)
- Not a valid estimate of a causal effect
  - Compares the compliers in the treatment group with the non-compliers in the treatment group and the full control group
  - Rows 5,6 vs. Rows 1,2,3,4
  - Since compliers and non-compliers likely quite different from each other, this not a valid comparison
- In this example:

$$\text{As} - \text{treated} = \frac{12}{9,663 + 12} - \frac{74 + 34}{11,514 + 74 + 2,385 + 34} = -0.0065$$

Sommer and Zeger data

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Per protocol analysis

- Compares the outcomes of those people who appeared to comply with their assigned treatment
- Not a valid estimate of a causal effect
  - Compares the people in the treatment group who took the treatment with people in the control group who didn't take the treatment
  - In this case it compares the compliers in the treatment group with the full control group
  - Rows 5,6 vs. Rows 1,2
  - Again, since compliers and non-compliers likely different from each other, this is not a valid comparison
- In this example:

$$\text{Per} - \text{protocol} = \frac{12}{9,663 + 12} - \frac{74}{11,514 + 74} = -0.0052$$

Sommer and Zeger data

Row	True Compliance Type	Treatment Assigned (T)	Treatment Received (D)	Dead (1) or Alive (0) (Y_{obs})	Number of Children
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Review of Section A

- Goal of estimating the "biologic" effect of taking a treatment (not just of being assigned to take it)
- Discussed problems with standard approaches
- Intent-to-treat estimate valid for the effect of the randomization, but not for what we're interested in
- Per-protocol, as-treated estimators not valid for anything; not valid causal comparisons
- Will move on now to a better approach . . . estimating the "complier average causal effect" (CACE)

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The IV/CACE estimate

- None of these provide an estimate of what we really want: the biologic effect of taking Vitamin A on mortality
- Can use instrumental variables/complier average causal effect methods to estimate this effect
- Because there are two types of people in the population (compliers and non-compliers), can express the overall effect as the average of the effects for those two groups:

$$ACE = p_c * CACE + p_n * NACE$$

- For compliers, the effect of being told (randomized) to take the treatment is the same as actually taking the treatment
- So the effect of interest is the "complier average causal effect" (CACE)

So how to estimate the CACE?

- The ITT provides an unbiased estimate of the total effect of randomization across the population (the overall average causal effect)
- The proportions of people in each group (p_c and p_n) can be estimated from the data:
  - p_c is the proportion of treatment group members who took the treatment ($\frac{9663+12}{9663+12+2385+34} = .8$)
  - Since treatment assigned randomly, that estimates the % compliers in the population
  - $p_n = 1 - p_c = .2$

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Solving an equation . . .

- Now have an equation with two unknowns

$$ACE = p_c * CACE + p_n * NACE$$

$$-0.0025 = .8 * CACE + .2 * NACE$$

- Assume that being assigned to the treatment doesn't affect outcomes if it doesn't affect behavior (NACE=0)

$$-0.0025 = .8 * CACE$$

$$CACE = -0.0025/.8 = -0.0031$$

- This is the instrumental variables/CACE effect estimate
- More on the underlying assumptions later . . .

Review of Section B

- Defined complier average causal effect (CACE) as the quantity of interest
  - For compliers, effect of being randomized the same as the effect of actually taking the treatment
- Talked briefly about how to estimate it, at least in a simple setting
- Will now move on to more complex two-sided noncompliance

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The more general setting: Two-sided noncompliance

- If control group has access to the treatment, compliance can go both ways
- So now think about 3 types of "non-compliers:"
  - Defiers
  - Always-takers
  - Never-takers
- Main interest still in the CACE, but more complicated to get to it

Motivating example: Effectiveness of flu shots

- Interest in estimating effect of flu shots on hospitalizations among the elderly
- Not ethical to randomly assign people to get flu shots or not
- Instead, randomly assign *encouragement* to get flu shots
  - Send doctors letters to encourage a randomly selected sample of their patients to get flu shots
  - Consider compliance/participation just at the patient level
- Hirano et al. (2000)

More broadly: Encouragement designs

- An example of a randomized encouragement design
- Useful when can't actually randomize treatment of interest (or can't deny the program to some individuals)
- Instead, randomize something that will affect whether people get that treatment
  - Encouragement to get a flu shot
  - More intensive invitation to participate in the program

The flu shot data

- Two covariates available: Age, and chronic obstructive pulmonary disease (COPD)
- Outcome: Flu-related hospitalization

	No letter	letter	No flu shot	Flu shot
Letter	0	1	0.475	0.631
Flu shot	0.19	0.307	0	1
Hospitalization	0.092	0.078	0.085	0.084
Age	65.0	65.4	64.7	66.8
COPD	0.29	0.277	0.264	0.343

There are now 4 compliance types

- Now 4 types of people, defined by compliance behavior under treatment and under control
  - Compliers (c): Do as they're told (take treatment if in treatment group; don't if in control group)
  - Defiers (d): Do the opposite of what they're told (don't take the treatment if in treatment group; do if in control group)
  - Always-takers (at): Take the treatment whether in treatment or control group
  - Never-takers (nt): Don't take the treatment whether in treatment or control group

What this means

- Makes the calculations more complicated (and requires more assumptions)
- Think of these as like baseline characteristics: they are intrinsic characteristics of individuals
  - Not affected by treatment assignment
  - (As opposed to OBSERVED compliance behavior, which is affected by assignment)

Behavior of the four types

Type	Treatment assigned (Z)	Treatment received (D(Z))
Compliers	0	0
	1	1
Defiers	0	1
	1	0
Always-takers	0	1
	1	1
Never-takers	0	0
	1	0

Trying to identify types from observed behavior

Treatment assigned (Z)	Observed treatment received (D(Z))	Possible types
0	0	Compliers or never-takers
0	1	Defiers or always-takers
1	0	Defiers or never-takers
1	1	Compliers or always-takers

Estimating the CACE

- Fundamental idea still the same:

$$ACE = p_c * CACE + p_d * DACE + p_{at} * AACE + p_{nt} * NACE$$

- Estimate ACE by the ITT effect:

$$ITT = 0.078 - 0.092 = -0.014$$

  - A 15% reduction in flu-related hospitalizations ($\frac{.078-.092}{.092} = .15$)
- Note: patients with COPD more likely to receive flu shot than patients without COPD, implying that compliers and non-compliers are different
- (Always-takers look sicker than the other groups)

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Assumptions needed to estimate the CACE

1. SUTVA
2. Encouragement increases participation for some people: there are some compliers ($p_c > 0$)
3. Treatment assignment (encouragement) does not affect outcomes if it does not affect the treatment actually received
   - i.e., no effects of encouragement for always-takers or never-takers
   - $NACE = 0$, $AACE = 0$
   - The "exclusion restrictions"
4. Encouragement (the "instrument") was assigned randomly (or at least is unconfounded)
5. No defiers ("monotonicity")
   - Encouragement can only increase the probability that someone gets a flu shot

Hernan and Robins (2006) description of an instrument

Three conditions for an instrument:

- Has a causal effect on the treatment of interest (i.e., $p_c > 0$)
  - (there are some compliers)
- Affects the outcome only through the treatment received
  - (exclusion restrictions)
- Does not share common causes with the outcome
  - instrument (encouragement) was assigned randomly

Review of Section C

- Extended thinking to case with two-sided noncompliance
- Now 4 types of people
- Still interested in the CACE
- Discussed assumptions underlying the standard estimator
- Next will discuss more details of the estimation

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So how do we actually estimate it?

$$ACE = p_c * CACE + p_d * DACE + p_{at} * AACE + p_{nt} * NACE$$

- No defiers $=>$ $p_d = 0$
- Exclusion restrictions $=>$ $AACE = NACE = 0$
- People in treatment group who don't get flu shot must be never-takers $=>$ $p_{nt} = 1 - .307 = .693$
- People in control group who get the flu shot must be always-takers $=>$ $p_{at} = .19$
- The remaining people must be compliers: $p_c = 1 - .693 - .19 = .12$
- ITT estimates the ACE: $ITT = -0.014$
- $ACE = p_c * CACE => CACE = ACE/p_c =>$ $CACE = -0.014/.12 = -0.12$

What is this doing?

Redistributes the overall effect to only the compliers

Person	Compliance status	Effect under ITT	Effect under IV
1	Complier	-0.014	-0.12
2	Complier	-0.014	-0.12
...	...	...	...
12	Complier	-0.014	-0.12
13	Never-taker	-0.014	0
14	Never-taker	-0.014	0
...	...	...	...
99	Always-taker	-0.014	0
100	Always-taker	-0.014	0
Average		-0.014	-0.014

What about the exclusion restrictions?

- Exclusion restrictions often the most questionable assumptions
- Never-takers: being encouraged to get a flu shot might prompt them to change other behaviors (e.g., washing hands)
- Always-takers: being encouraged may prompt them to also change other behaviors, or get the shot earlier
- Can relax these assumptions through alternate model assumptions (Jo 2002) or Bayesian methods (Hirano et al. 2000)
- In this example, some evidence that the exclusion restriction does not hold for always-takers

Another way of writing the IV/CACE effect

$$CACE = ITT/p_c$$

is the same as

$$\frac{E(Y|T=1) - E(Y|T=0)}{E(D|T=1) - E(D|T=0)}$$

- (The effect of treatment assignment on Y divided by the effect of treatment assignment on the treatment received)
- Implies that the IV estimate will always be larger than the ITT estimate
- The more non-compliers there are, the larger this will be (in comparison to the ITT estimate)
- Called the Wald estimator or Bloom's estimate in education

Historical note

- This basic idea popped up in a number of fields
  - Education/public policy: Bloom (1984) ["Bloom's estimate"]
  - Public health: Sommer and Zeger (1991)
  - Economics: Haavelmo (1943)
- Economists tend to describe the assumptions very differently, in terms of model specification and relationships between error terms
- Angrist, Imbens, and Rubin (1996) brought these ideas together
  - Developed framework presented here of compliers, always-takers, etc.
  - Way to describe assumptions in meaningful way

Interpretation of CACE

- The estimate that we get is the effect of treatment for the compliers
- Technically only applies to them
  - Kind of like the people around the cut-off in an RD design
  - They are the only people for whom the instrument changes the treatment received
- CACE sometimes called the "local average treatment effect" (LATE)
- Angrist and Fernandez-Val (2010)

Two-stage least squares

- CACE estimate above very simple: does not allow for predictors, does not incorporate uncertainty in p_c
- More generally, people use "two-stage least squares" (TSLS) to estimate these IV/CACE effects
- "Two-stage" refers to two models:
  - Treatment received (as a function of treatment assigned–the "instrument")
  - Outcome, given the treatment received
- Allows the incorporation of predictors in both models (will increase precision)

Conclusions

- CACE estimation allows us to estimate the effect of actually taking some treatment
- Relies on assumptions such as the exclusion restrictions and "no defiers"
- Exclusion restrictions ("no direct effects") often the most troublesome
- Useful for dealing with noncompliance in randomized experiments
- Next time will see that this framework also useful for estimating causal effects in non-experimental studies
  - Think of as a randomized encouragement design
- Will also discuss other complications and extensions

For more information

- Angrist, J., Imbens, G. W., & Rubin, D. B. (1996). Identification of causal effects using instrumental variables. Journal of the American Statistical Association, 91, 444472. doi:10.2307/2291629.
- Grootendorst, P. (2007). A review of instrumental variables estimation of treatment effects in the applied health sciences. Health Services and Outcomes Research Methodology 7:159-179.
- Hernan, M.A. and Robins, J.M. (2006). Instruments for causal inference: An epidemiologists dream? Epidemiology 17: 360-372.
- Stuart, E.A., Perry, D.F., Le, H-N., & Ialongo, N.S. (2008). Estimating intervention effects of prevention programs: Accounting for noncompliance. Prevention Science 9(4): 288-298