CIMPOD 2017 – Day 2
Instrumental Variable (IV) Methods

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Big picture overview

- Motivation for IV methods

- Key assumptions for identifying causal effects with IVs
  - Day 1: Per-protocol effects in trials with non-compliance
  - Day 2: Effects of initiating treatment in observational studies

- IV estimation and tools for understanding possible threats to validity
  - Day 1: Bounding, instrumental inequalities…
  - Day 2: Weak IVs, bias component plots…

- Extensions and further considerations

- Summary and Q&A

Some disclaimers

- My emphasis will be on addressing the following questions

  1. What are we hoping to estimate, and what can we actually estimate?

  2. Are the assumptions required to interpret our estimates as causal effects reasonable?

  3. Under plausible violations of these assumptions, how sensitive are our estimates?

- Provided R code will emphasize #2 and #3, as well as examples of how to implement IV estimation

- Ask questions!

Case study (Day 1): Swanson 2015 *Trials*

TRIALS

METHODOLOGY

Open Access

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Bounding the per-protocol effect in randomized trials: an application to colorectal cancer screening

Sonja A. Swanson[1,2*], Øyvind Holme[3,4], Magnus Løberg[3,6], Mette Kalager[2,3,5], Michael Bretthauer[2,3,6], Geir Hoff[3,5,7], Eline Aas[3] and Miguel A. Hernán[2,8,9]

Case study (Day 2): Swanson 2015 *PDS*

ORIGINAL REPORT

Methodological considerations in assessing the effectiveness of antidepressant medication continuation during pregnancy using administrative data[†]

Sonja A. Swanson[1]*, Sonia Hernandez-Diaz[1], Kristin Palmsten[2], Helen Mogun[3], Mark Olfson[4] and Krista F. Huybrechts[3]

Overview

- Motivation for IV methods

- Key assumptions for identifying causal effects with IVs

- IV estimation and tools for understanding possible threats to validity

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Motivation for IV methods

- Most methods for causal inference rely on the assumption that there is no unmeasured confounding
  - Regression, propensity score methods, and other forms of stratification, restriction, or matching
  - G-methods (inverse probability weighting, parametric g-formula, usual form of g-estimation of structural nested models)
- HUGE assumption
- Dream with me: what if we could make causal inferences without this assumption?
- More specifically…

Problem #1: trials with non-compliance

- First, consider a hypothetical double-blind, placebo-controlled, single-dose randomized trial with complete follow-up
    - But with non-compliance
- We can readily estimate the intention-to-treat (ITT) effect
    - The effect of randomization
- But the ITT effect is hard to interpret because it critically depends on the degree of adherence

Problem #1: trials with non-compliance and estimating per-protocol effects

- We may be interested in a per-protocol effect
  - The effect of following the protocol (i.e., of actual treatment)
- How can we estimate a per-protocol effect?
  - This effect is confounded!
  - Usual strategies analyze the randomized trial data like an observational study, adjusting for measured confounders
  - IV methods offer an alternative strategy

$$Z \longrightarrow A \longrightarrow Y$$
$$U \nearrow \qquad \nearrow$$
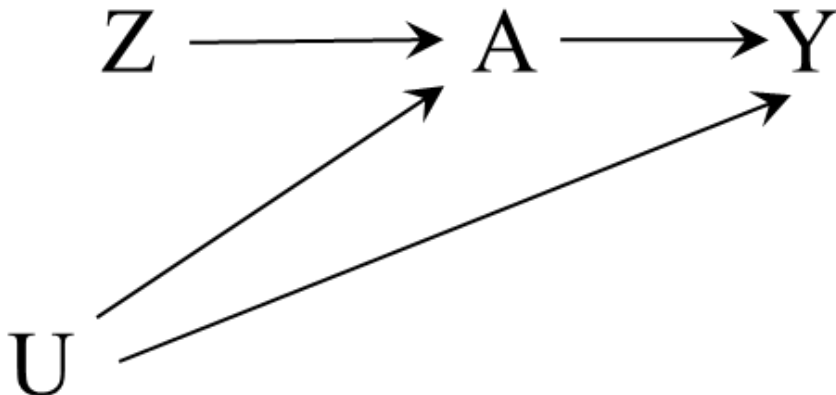
Problem #1: trials with non-compliance and our case study

- Consider the NORCCAP pragmatic trial of colorectal cancer screening vs. no screening
  - We may be interested in a per-protocol effect of screening versus no screening
- How can we estimate a per-protocol effect?
  - This effect is confounded!
  - Usual strategies analyze the randomized trial data like an observational study, adjusting for measured confounders
  - IV methods offer an alternative strategy

Problem #2: observational studies with unmeasured confounding

- Often observational studies are our only hope for estimating treatment effects

- Treatment effects can be confounded (e.g., by indication)

  - Usual methods for analyzing treatment effects in observational studies rely on measuring and appropriate adjusting for confounders

  - IV methods offer an alternative strategy

Problem #2: observational studies with unmeasured confounding and our case study

- Suppose we want to estimate the risks and benefits of continuing antidepressant medication use during pregnancy among women with depression
  - Observational studies may be our best hope
- Treatment effects could be confounded by depression severity, healthy behaviors, etc.
  - Usual methods for analyzing treatment effects would require we measure (or come very close to approximating) these confounders
 - IV methods offer an alternative strategy

Overview

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Some notation

- *Z*: proposed instrument (defined on next slide)

- *A*: treatment

- *Y*: outcome

- *U, L*: unmeasured/measured relevant covariates

- Counterfactual notation: $E[Y^a]$ denotes the average counterfactual outcome *Y* had everybody in our study population been treated with *A=a*

IV conditions

1. Instrument and treatment are associated
2. Instrument causes the outcome only through treatment
3. Instrument and outcome share no causes
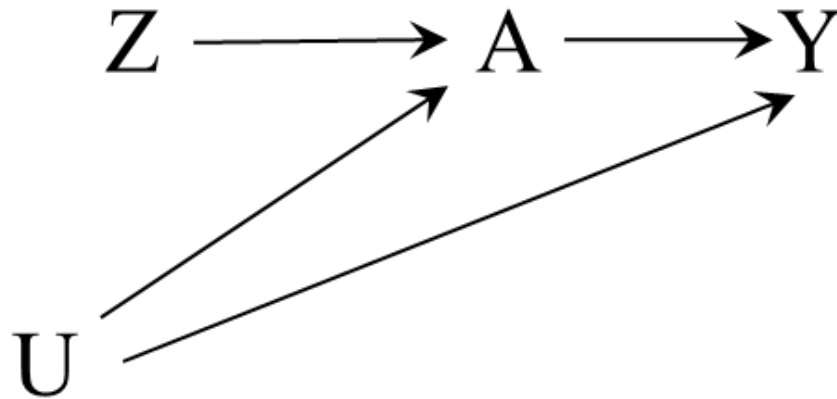
IV conditions

1. Instrument and treatment are associated
2. Instrument causes the outcome only through treatment
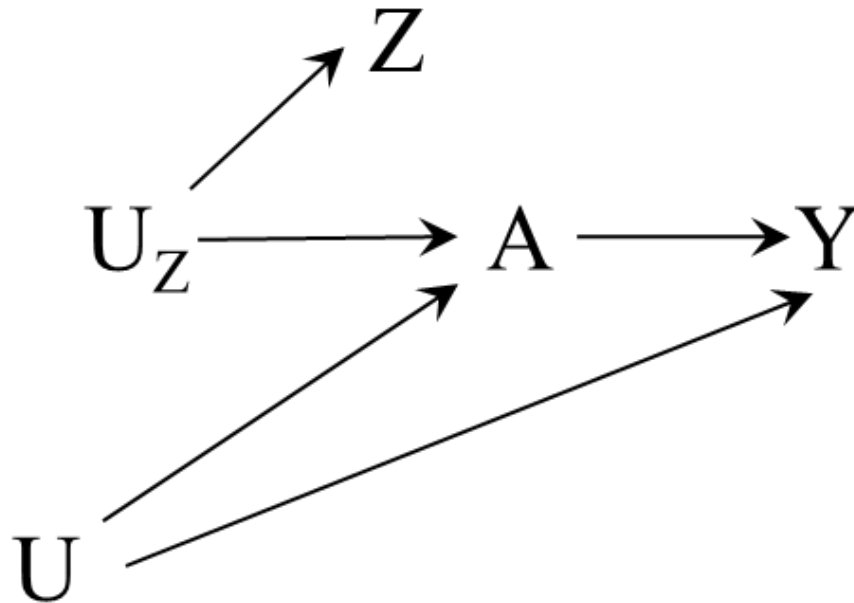3. Instrument and outcome share no causes

IV conditions

1. Instrument and treatment are associated

2. Instrument causes the outcome only through treatment

3. Instrument and outcome share no causes

Under these conditions, we can use the standard IV ratio or related methods to identify treatment effects

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

IV methods in randomized trials

The randomization indicator as a proposed instrument to help estimate a per-protocol effect (focus of Day 1)

1. Randomization indicator and treatment are associated
2. Randomization indicator causes the outcome only through treatment
3. Randomization indicator and outcome share no causes
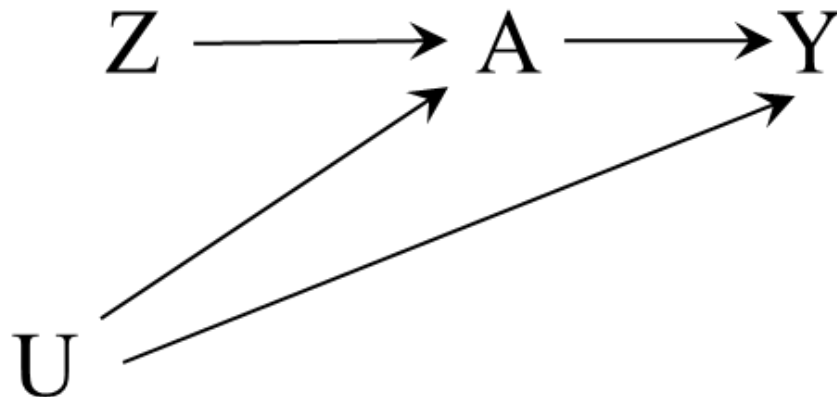
IV methods in observational studies

- Propose/find a "natural experiment" measured in your observational study that meets the IV conditions (focus of Day 2)

- Commonly proposed IVs in PCOR

  - Physician or facility preference

  - Calendar time

  - Geographic variation

Example of a proposed IV: preference

Propose physician/facility preference (e.g., as measured via prescriptions to prior patients) as an IV

1. Preference and patients' treatments are associated
2. Preference affects outcomes only through treatment
3. Preference and outcome share no causes

Example of a proposed IV: geographic variation

Propose geographic variation as an IV

1. Location and patients' treatments are associated
2. Location affects outcomes only through treatment
3. Location and outcome share no causes

Example of a proposed IV: calendar time

Propose pre- versus post-warning calendar period as an IV

1. Calendar period and patients' treatments are associated

2. Calendar period related to patient outcomes only through treatment

3. Calendar period and outcome share no causes

The ideal: calendar time as a proposed IV

Hypothetical Treatment Probability by Calendar Time
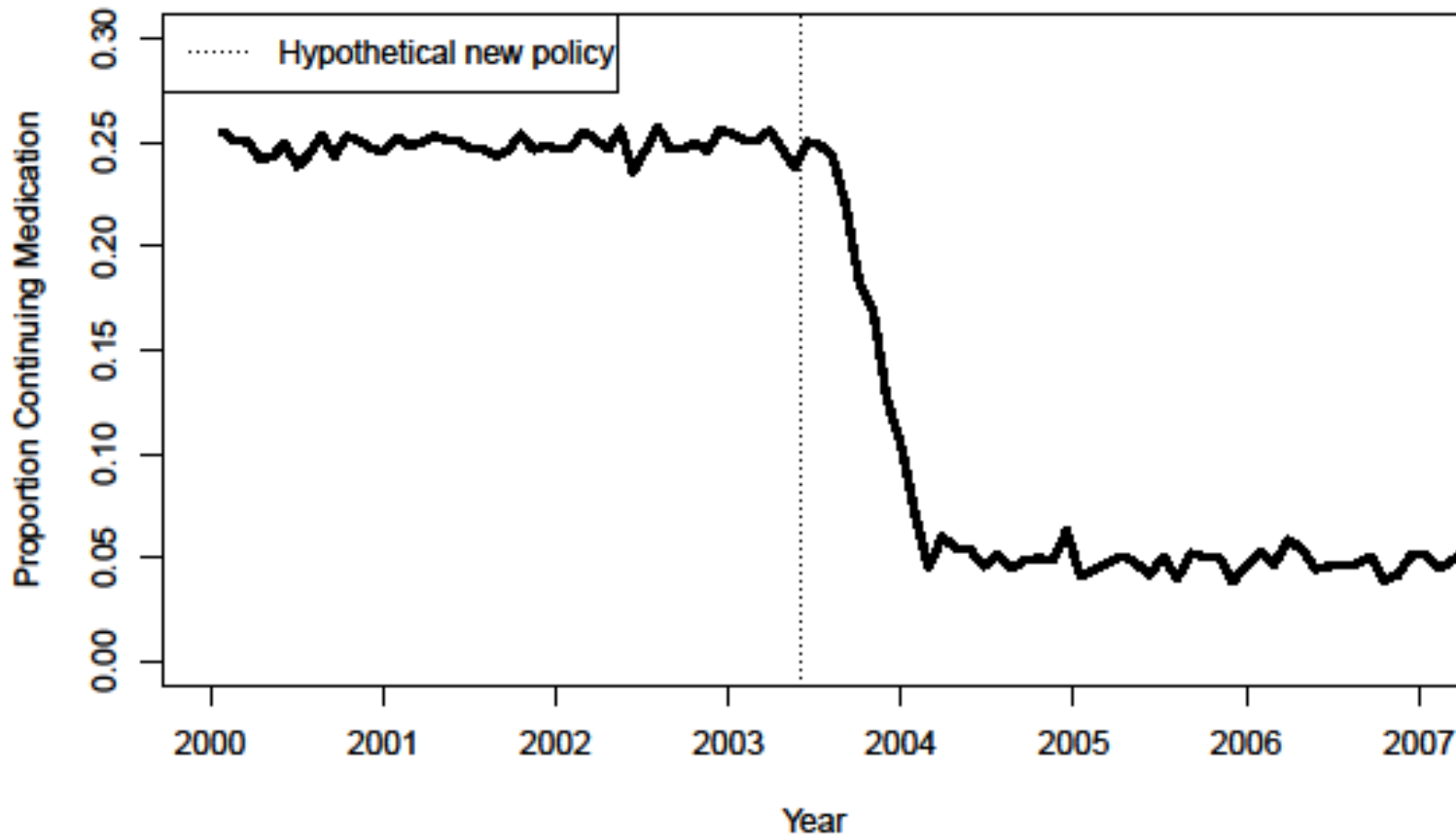
The reality: calendar time as a proposed IV

Treatment Continuation Probability by Calendar Time
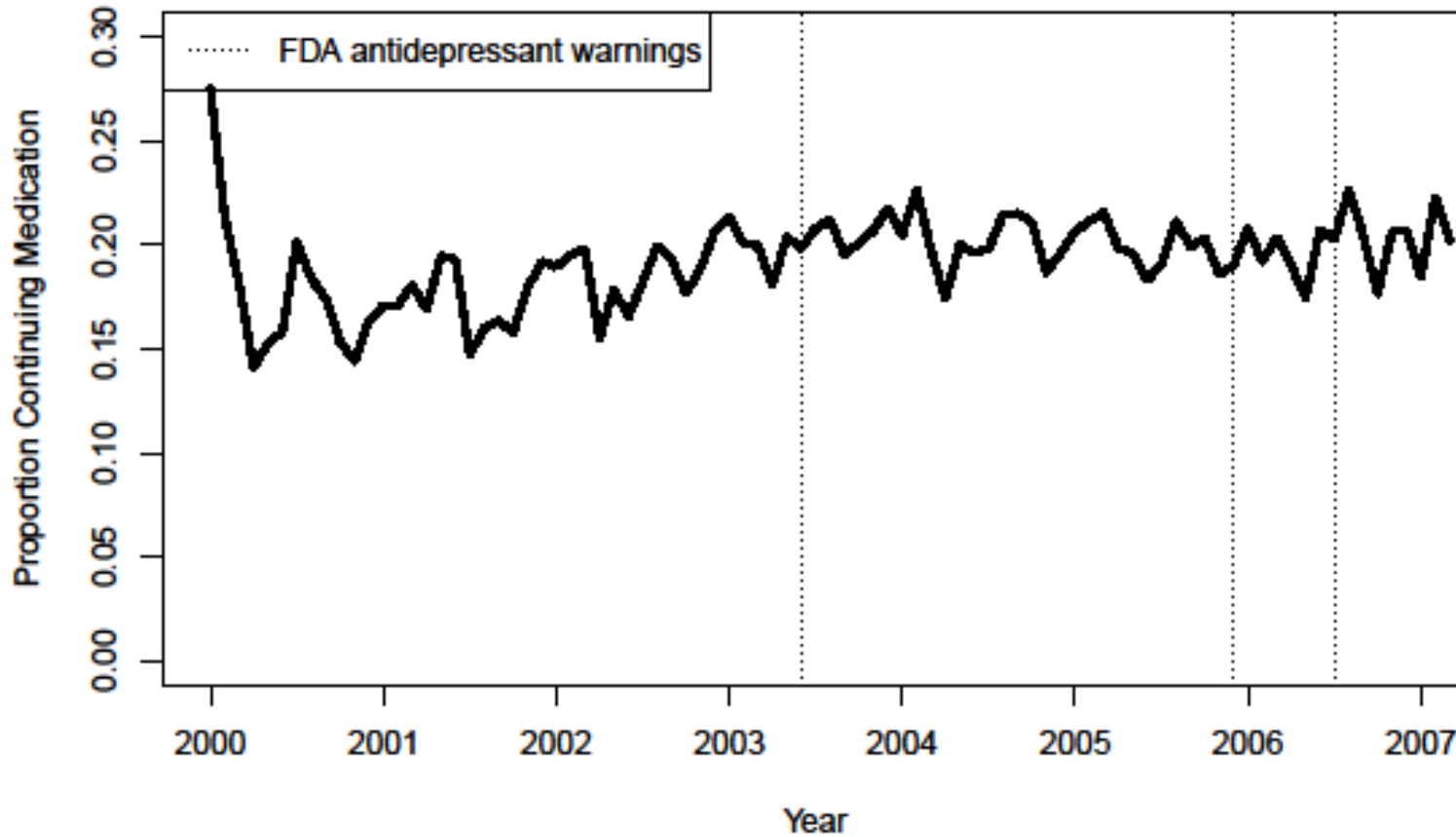
However, an IV not enough

- With only these three conditions that define an IV, we cannot generally obtain a point estimate for a causal effect
  - Can estimate "bounds"

- What does the standard IV methods estimate then?
  - Depends on what further assumptions we are willing to make

"Fourth" assumptions: homogeneity

- Under strong homogeneity assumptions, IV methods estimate the average causal effect

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

- Most extreme type of homogeneity assumption: constant treatment effect

  - $Y^{a=1} - Y^{a=0}$ is the same for all individuals

- Less extreme (but still strong) version: no additive effect modification by the IV among the treated and untreated

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

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

"Fourth" assumptions: monotonicity

- Under a monotonicity assumption, IV methods estimate a causal effect in only a subgroup of the study population
  - Local average treatment effect (LATE)
  - Complier average causal effect (CACE)

Angrist, Imbens, & Rubin 1996 *JASA*

Compliance types in the context of a trial

Randomized to treatment arm ($Z=1$)

		Treated ($A^{z=1}=1$)	Not treated ($A^{z=1}=0$)
Random-ized to placebo arm ($Z=0$)	Treated ($A^{z=0}=1$)	**Always-taker** ($A^{z=0}=A^{z=1}=1$)	**Defier** ($A^{z=0}>A^{z=1}$)
	Not treated ($A^{z=0}=0$)	**Complier** ($A^{z=0}<A^{z=1}$)	**Never-taker** ($A^{z=0}=A^{z=1}=0$)

Compliance types: any causal IV Z

$Z=1$

	$A^{z=1}=1$	$A^{z=1}=0$
$Z=0$ $A^{z=0}=1$	**Always-taker** $(A^{z=0}=A^{z=1}=1)$	**Defier** $(A^{z=0}>A^{z=1})$
$A^{z=0}=0$	**Complier** $(A^{z=0}<A^{z=1})$	**Never-taker** $(A^{z=0}=A^{z=1}=0)$

Compliance types: preference

Prefers treatment ($Z=1$)

		Treated ($A^{z=1}=1$)	Not treated ($A^{z=1}=0$)
Prefers no treatment ($Z=0$)	Treated ($A^{z=0}=1$)	**Always-taker** ($A^{z=0}=A^{z=1}=1$)	**Defier** ($A^{z=0}>A^{z=1}$)
	Not treated ($A^{z=0}=0$)	**Complier** ($A^{z=0}<A^{z=1}$)	**Never-taker** ($A^{z=0}=A^{z=1}=0$)

Compliance types: geographic variation

| | | Location with high treatment rate ($Z=1$) | |
		Treated ($A^{z=1}=1$)	Not treated ($A^{z=1}=0$)
Location with low treatment rate ($Z=0$)	Treated ($A^{z=0}=1$)	**Always-taker** ($A^{z=0}=A^{z=1}=1$)	**Defier** ($A^{z=0}>A^{z=1}$)
	Not treated ($A^{z=0}=0$)	**Complier** ($A^{z=0}<A^{z=1}$)	**Never-taker** ($A^{z=0}=A^{z=1}=0$)

Compliance types: calendar time

Post-warning period ($Z=1$)

		Treated ($A^{z=1}=1$)	Not treated ($A^{z=1}=0$)
Pre-warning period ($Z=0$)	Treated ($A^{z=0}=1$)	**Always-taker** ($A^{z=0}=A^{z=1}=1$)	**Defier** ($A^{z=0}>A^{z=1}$)
	Not treated ($A^{z=0}=0$)	**Complier** ($A^{z=0}<A^{z=1}$)	**Never-taker** ($A^{z=0}=A^{z=1}=0$)

Monotonicity and the LATE

- Under the IV conditions plus assuming there are no defiers (monotonicity), we can estimate the effect in the compliers

  - The local average treatment effect (LATE)
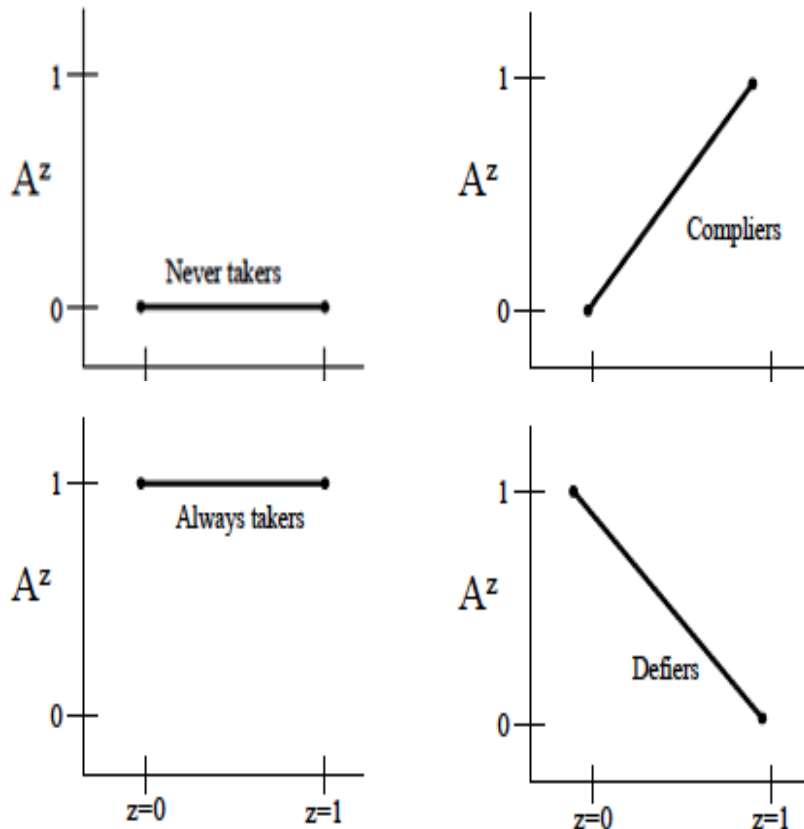
$$E[Y^{a=1} - Y^{a=0} | A^{z=0} < A^{z=1}]$$

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

Identification of LATE: sketch of proof (1)

- The ITT effect is a weighted average of the ITT effects in our four compliance types

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

$$\mathrm{E}[Y^{z=1} \text{-} Y^{z=0} | A^{z=0} < A^{z=1}] \mathrm{Pr}[A^{z=0} < A^{z=1}] \qquad \text{(compliers)}$$

$$+ \mathrm{E}[Y^{z=1} \text{-} Y^{z=0} | A^{z=0} = A^{z=1} = 1] \mathrm{Pr}[A^{z=0} = A^{z=1} = 1] \qquad \text{(always-takers)}$$

$$+ \mathrm{E}[Y^{z=1} \text{-} Y^{z=0} | A^{z=0} = A^{z=1} = 0] \mathrm{Pr}[A^{z=0} = A^{z=1} = 0] \qquad \text{(never-takers)}$$

$$+ \mathrm{E}[Y^{z=1} \text{-} Y^{z=0} | A^{z=0} > A^{z=1}] \mathrm{Pr}[A^{z=0} > A^{z=1}] \qquad \text{(defiers)}$$

Identification of LATE: sketch of proof (2)

- Because an always-taker would always take treatment regardless of what she was randomized to, the effect of randomization in this subgroup is 0

$$E[Y^{z=1}\text{-}Y^{z=0}|A^{z=0}=A^{z=1}=1] = E[Y^{a=1}\text{-}Y^{a=1}|A^{z=0}=A^{z=1}=1] = 0$$

- Similar logic applies to the never-takers

$$E[Y^{z=1}\text{-}Y^{z=0}|A^{z=0}=A^{z=1}=0] = E[Y^{a=0}\text{-}Y^{a=0}|A^{z=0}=A^{z=1}=0] = 0$$

Identification of LATE: sketch of proof (3)

- Because a complier would take the treatment she was randomized to, the effect of randomization in this subgroup is exactly the average causal effect of the treatment in this subgroup

$$\mathrm{E}[Y^{z=1}\text{-}Y^{z=0}|A^{z=0}<A^{z=1}] = \mathrm{E}[Y^{a=1}\text{-}Y^{a=0}|A^{z=0}<A^{z=1}]$$

Identification of LATE: sketch of proof (4)

- Let's return to our ITT effect to see what happens if zero defiers

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

$$\mathrm{E}[Y^{z=1}\text{-}Y^{z=0}|A^{z=0}<A^{z=1}]\mathrm{Pr}[A^{z=0}<A^{z=1}] \quad\quad \text{(compliers)}$$

$$+\ \mathrm{E}[Y^{z=1}\text{-}Y^{z=0}|A^{z=0}=A^{z=1}=1]\mathrm{Pr}[A^{z=0}=A^{z=1}=1] \quad \text{(always-takers)}$$

$$+\ \mathrm{E}[Y^{z=1}\text{-}Y^{z=0}|A^{z=0}=A^{z=1}=0]\mathrm{Pr}[A^{z=0}=A^{z=1}=0] \quad \text{(never-takers)}$$

$$+\ \mathrm{E}[Y^{z=1}\text{-}Y^{z=0}|A^{z=0}>A^{z=1}]\mathrm{Pr}[A^{z=0}>A^{z=1}] \quad\quad \text{(defiers)}$$

Identification of LATE: sketch of proof (4)

- Let's return to our ITT effect to see what happens if zero defiers

$$E[Y^{z=1} - Y^{z=0}] =$$

$$E[Y^{z=1} - Y^{z=0} | A^{z=0} < A^{z=1}] Pr[A^{z=0} < A^{z=1}] \quad \text{(compliers)}$$

$$+ 0 \quad \text{(always-takers)}$$

$$+ 0 \quad \text{(never-takers)}$$

$$+ 0 \quad \text{(defiers)}$$

Identification of LATE: sketch of proof (5)

- By randomization and monotonicity, we have:

$$\mathrm{E}[Y^{z=1}\text{-}Y^{z=0}] = \mathrm{E}[Y|Z=1] - \mathrm{E}[Y|Z=0]$$

$$\mathrm{Pr}[A^{z=1}<A^{z=0}] = \mathrm{E}[A|Z=1] - \mathrm{E}[A|Z=0]$$

- Thus, we have:

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

$$= \mathrm{E}[Y^{a=1}\text{-}Y^{a=0}|A^{z=0}<A^{z=1}](\mathrm{E}[A|Z=1] - \mathrm{E}[A|Z=0])$$

- Rearranging terms, we have identified the LATE:

$$\mathrm{E}[Y^{a=1}\text{-}Y^{a=0}|A^{z=0}<A^{z=1}]$$

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

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- Motivation for IV methods

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Introducing our data setting

- Suppose our (simulated) dataset came from a study that is similar to the observational study in our case study paper

- Specifically, suppose our data come from a cohort of pregnant women with depression on antidepressant medications pre-pregnancy

  - Treatment of interest is continuing versus discontinuing medication during pregnancy

  - Outcome of interest is a continuous measure of change in depression severity score

  - Complete follow-up (for illustrative purposes)

  - Three proposed IVs

- See R code for data

Computing effect estimates with proposed IVs

- We can use the standard IV ratio to compute treatment effect estimates based on our three proposed IVs

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

- Our three proposed IVs lead to three effect estimates

  - More on modeling procedures (and obtaining confidence intervals) in the R code and later in the lecture
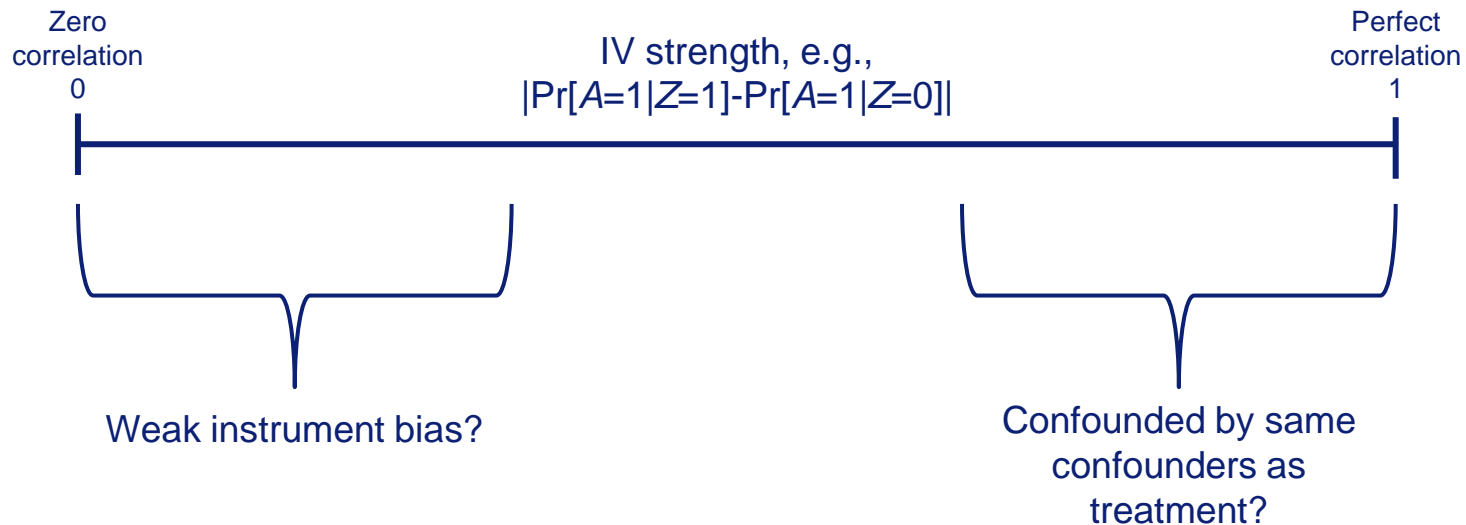
- Are we done?

Reporting guidelines

Swanson & Hernan 2013 *Epi*
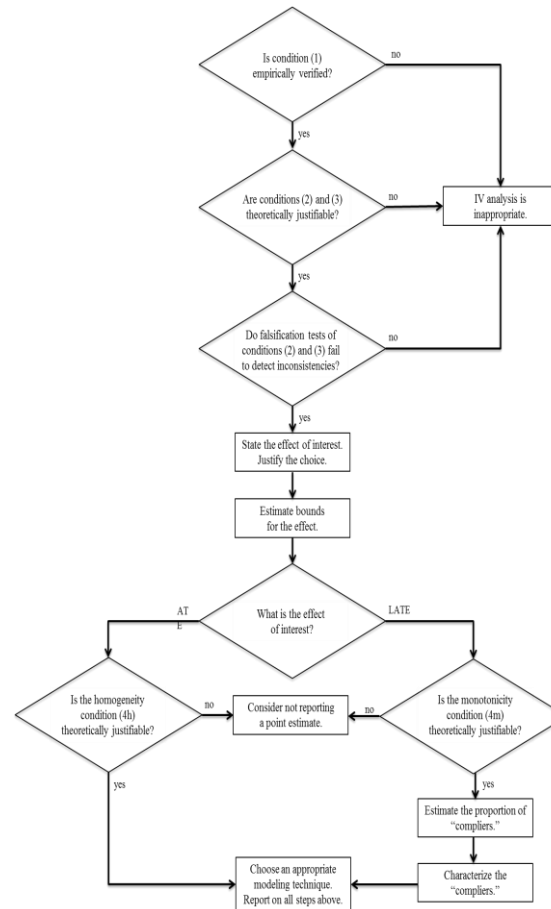
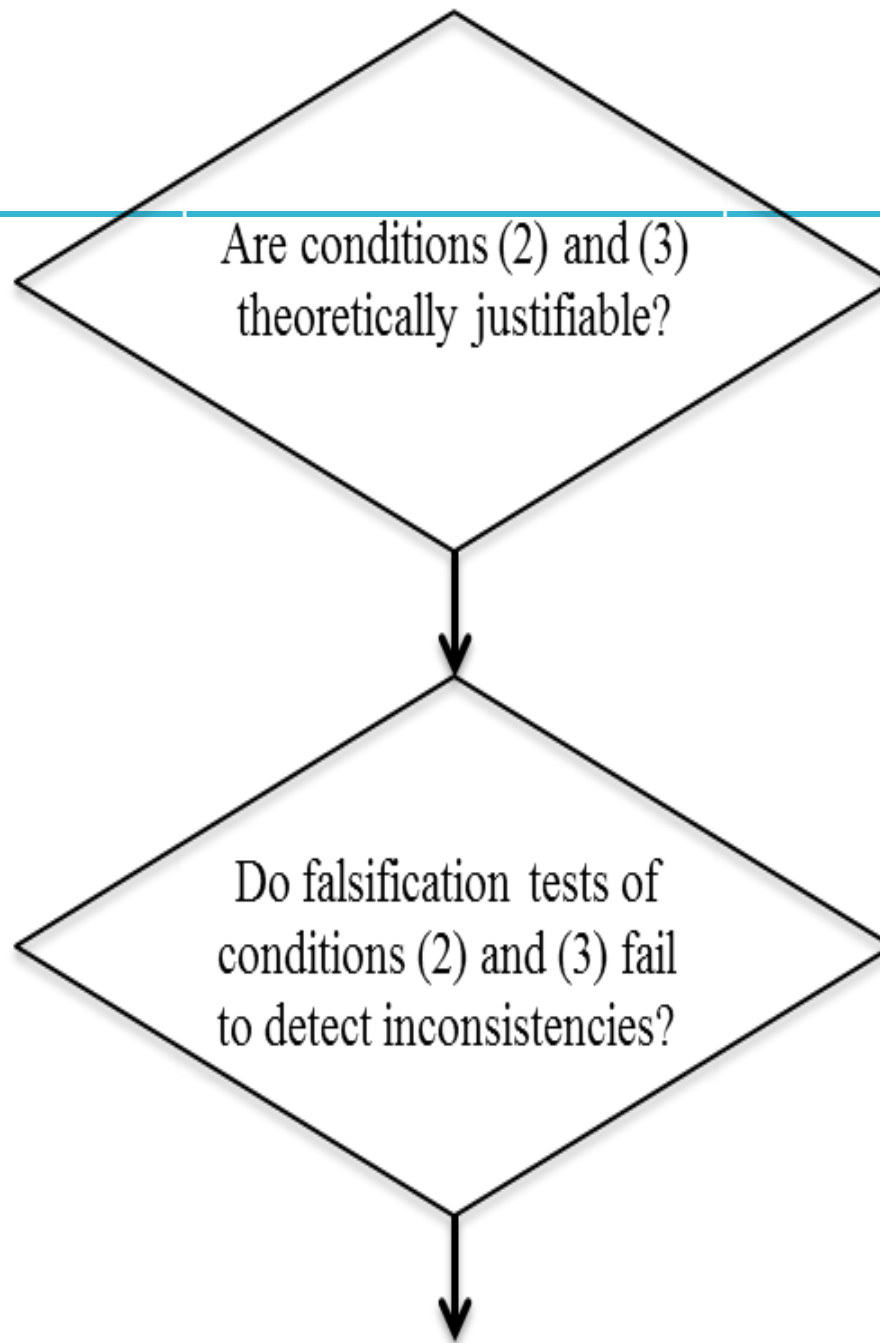Is condition (1)
empirically verified?

Checking IV strength

- Condition (1) is empirically verifiable

    - Check in our data: $\Pr[A{=}1|Z{=}1] \neq \Pr[A{=}1|Z{=}0]$?

    - Can use common statistical tools (non-zero RD, F-statistic, R^2)

    - See R code

- Condition (1) can be satisified but the strength of the association also matters (be cautious of "weak" IVs)

- Problems with weak IVs

    - Weak IVs imply uncertainty (wide 95% CIs)

    - Weak IVs amplify bias due to violations of conditions (2)-(3)

    - Even in large samples, weak IVs introduce bias and result in underestimation of variance

Bound et al. 1995 *JASA*

# Considering IV strength in CER

- ## For discussion:

  - ### Is there an ideal "strength" for an IV?

  - ### When choosing between multiple proposed IVs, how do we compare the trade-offs between strong vs. weak IVs?

Zero correlation
0

IV strength, e.g.,
$|Pr[A=1|Z=1]-Pr[A=1|Z=0]|$

Perfect correlation
1

Weak instrument bias?

Confounded by same confounders as treatment?

Are conditions (2) and (3) theoretically justifiable?

Do falsification tests of conditions (2) and (3) fail to detect inconsistencies?

Subject-matter justifications of conditions (2)-(3)

- For discussion: when are these conditions more or less likely to be reasonable for commonly proposed IVs (e.g., calendar time, geographic variation, preference)?
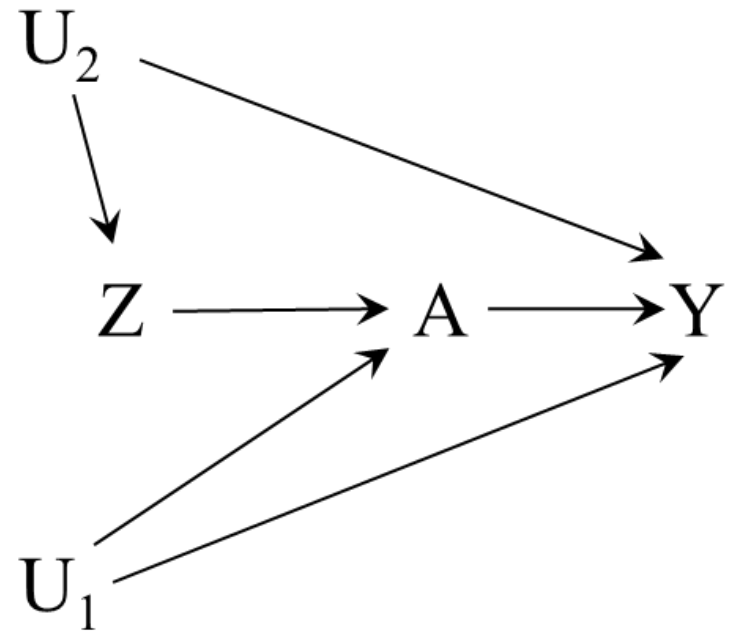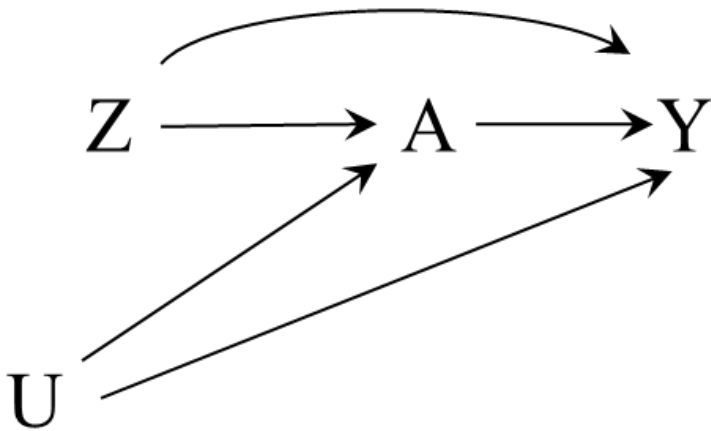
Be aware of subtle violations of (2)-(3)…

- Forms of collider-stratification biases

    - E.g., "selecting on treatment"

- Forms of measurement error that induce these biases

- Violations for an unmeasured causal IV or for the measured non-causal IV?

Vanderweele et al. 2014 *Epi*; Swanson et al. 2015 *AJE*; Swanson 2015 *EJE*

Falsification of conditions (2)-(3)

- Various types of falsification tests, e.g.:
  - Assessing inequalities that can detect extreme violations
  - Leveraging specific prior causal assumptions
  - Comparing estimates from several potential IVs

- Unfortunately, these tests may fail to reject a proposed instrument even if conditions (2)-(3) are violated

Glymour et al. 2012 *AJE*

Falsification example: IV inequalities

- For dichotomous *Z, A, Y*, the IV conditions imply certain constraints on the observed data
  - See R code
  - IV inequalities also for some non-binary settings
- Can be used to detect extreme violations of the IV conditions

Balke & Pearl 1997 *JASA*; Bonet 2001 *PUAI*; Glymour et al. 2012 *AJE*

Falsification example: over-identification

- Key logic behind "over-identification" assessments: if all proposed IVs were valid and targeting the same effect, then estimates should be equal (ignoring sampling variability)

- Some limitations of these approaches:
  - Estimates may differ because one (or more) proposed IVs are not valid, or because the proposed IVs are identifying effects in different subgroups
  - Because each IV estimate can have a lot of uncertainty, assessments have low power
  - If important differences are found, generally do not know which estimates (if any) are valid

Falsification example: direction of bias

- Consider the crude non-IV estimate in our dataset and our estimates from the three proposed IVs (see R code)

- For discussion:
    - Because of residual confounding by indication, what direction would we expect bias in the non-IV estimate?
    - How does this compare to our IV estimates?
    - Based on these comparisons, what (if anything) can we conclude about the validity of our IV estimates or our prior beliefs about the direction of bias?

Covariate balance

- A common practice is to present the balance of measured covariates by levels of treatment and the proposed IV

  - Key logic: imbalance in measured covariates (which can be adjusted for) may alert us to unmeasured/residual confounding

- Comparisons may help give a sense of relative bias in an IV versus a non-IV approach

  - If IV strength is taken into account

Brookhart & Schneeweiss 2007 *IJB*; Vanderweele & Arah 2011 *Epi*; Jackson & Swanson 2015 *Epi*

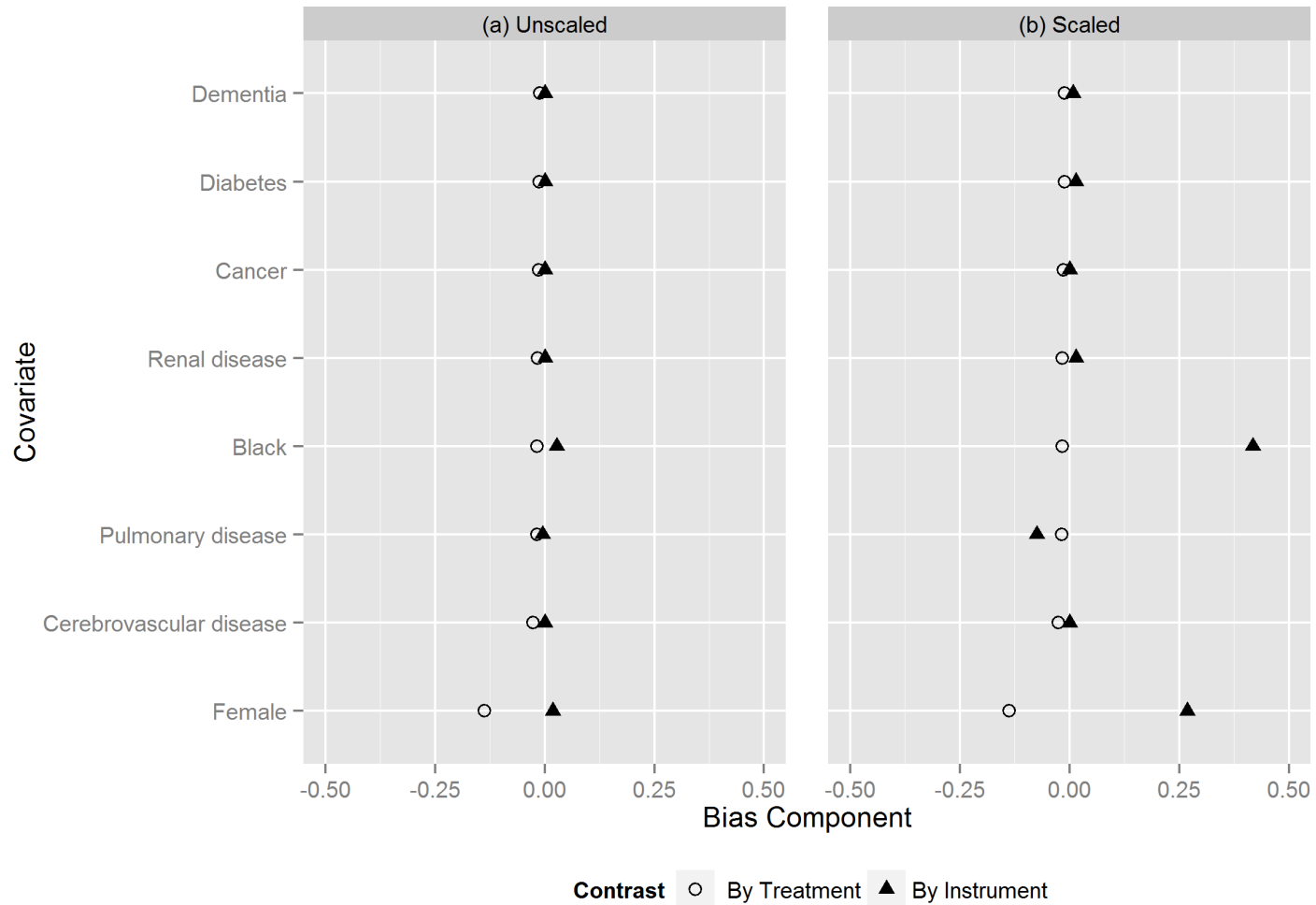# Confounding bias in IV and non-IV approaches

- Why does IV strength matter when comparing relative bias of an IV and a non-IV approach?

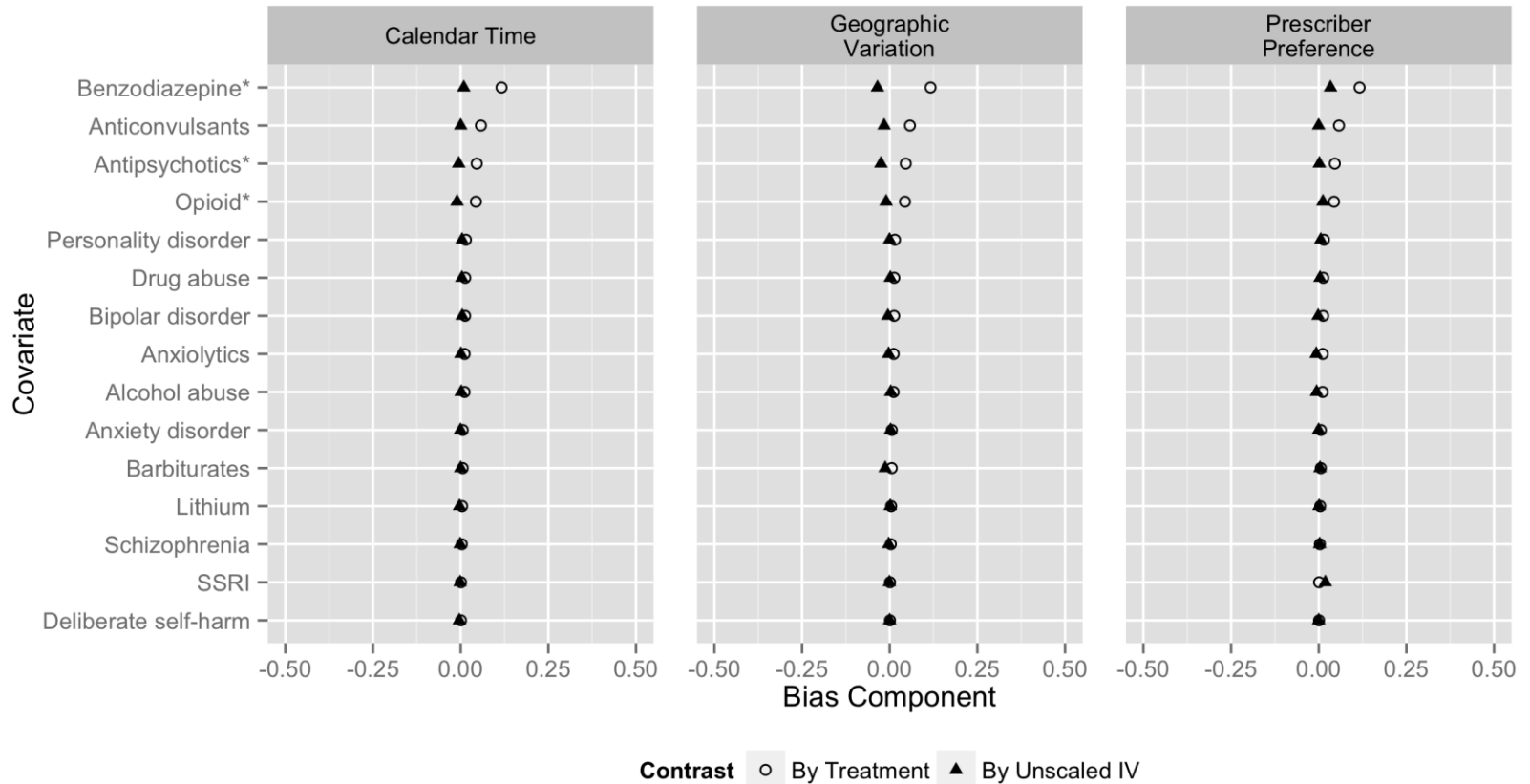$$\frac{E[Y|Z = 1] - E[Y|Z = 0]}{E[A|Z = 1] - E[A|Z = 0]}$$

If the numerator is off by a little bit, this will get amplified by the denominator

- Confounding bias from *U* is a function of:
    - Non-IV approaches: *U-Y, U-A*
    - IV approaches: *U-Y, U-Z,* <u>and</u> *Z-A*
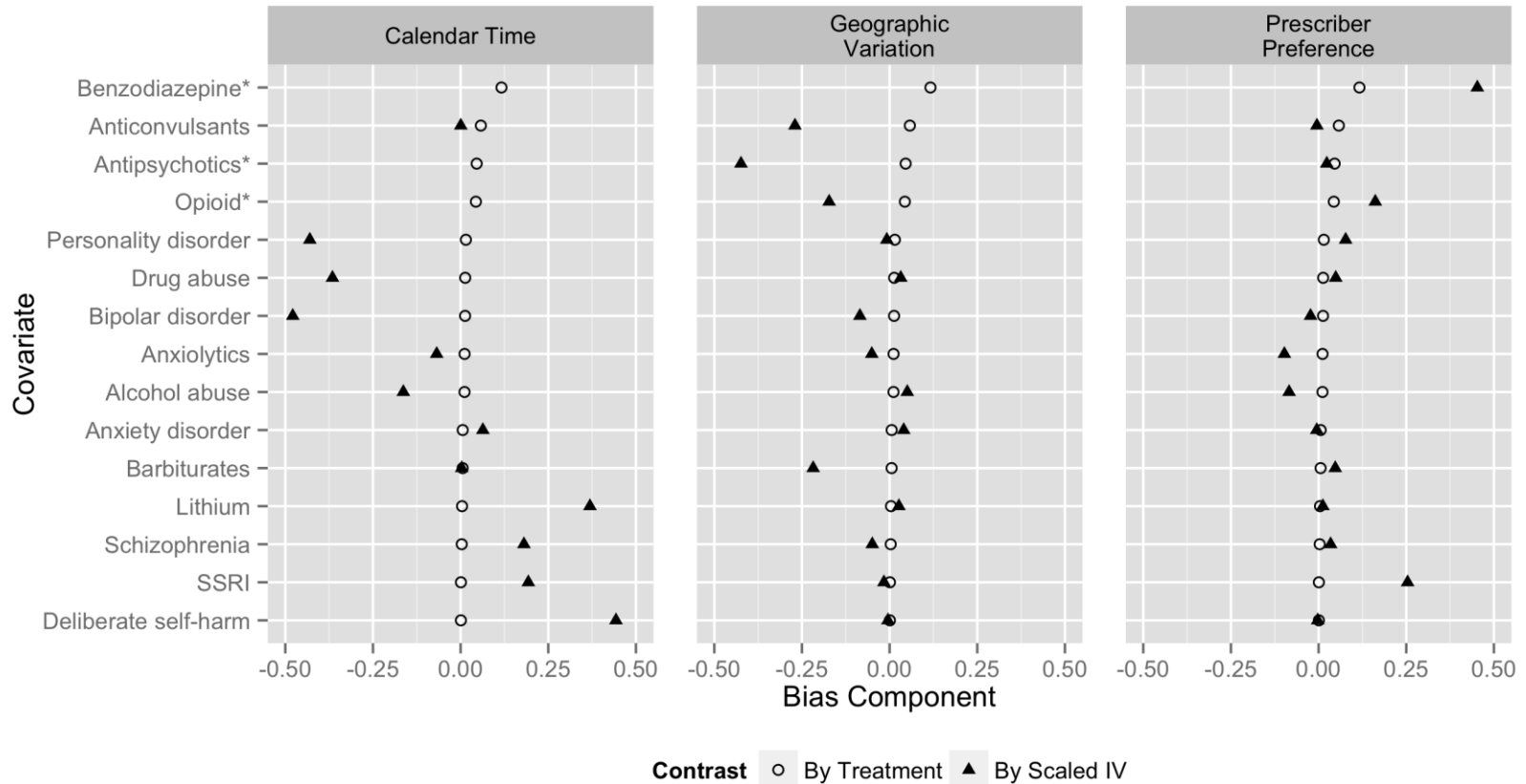
Brookhart & Schneeweiss 2007 *IJB*; Vanderweele & Arah 2011 *Epi*; Jackson & Swanson 2015 *Epi*

Bias component plot example: McClellan 1994

McClellan et al. 1994 *JAMA*; Jackson & Swanson 2015 *Epi*

Unscaled plot example: our case study

Swanson et al. 2015 *PDS*; Jackson & Swanson 2015 *Epi*

Bias component plot example: our case study
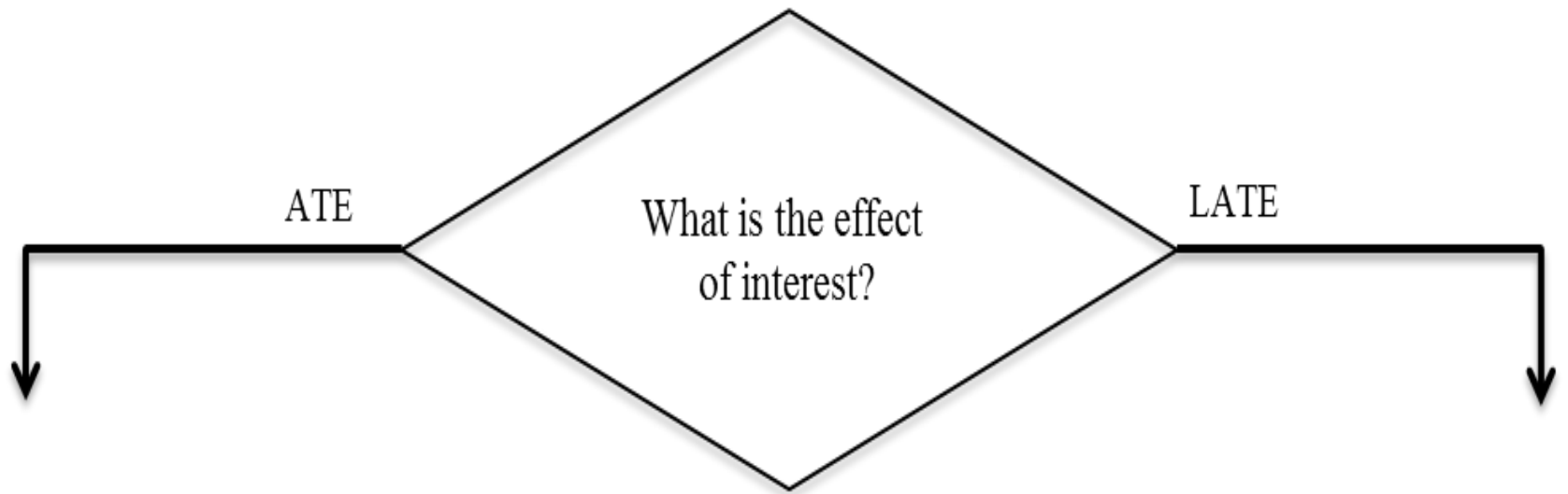
Swanson et al. 2015 *PDS*; Jackson & Swanson 2015 *Epi*

State the effect of interest.
Justify the choice.

Estimate bounds
for the effect.

For bounds, see Day 1
R code and notes!

ATE

What is the effect
of interest?
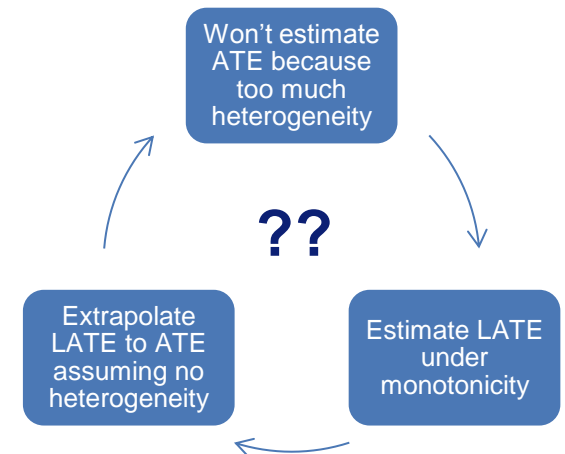
LATE

Choice of LATE versus ATE

- Typically, published epidemiologic studies are vague regarding the definition of the treatment effect they are estimating

- When explicit, the provided rationale for their choice is usually based on:
  - Whether the effect is of clinical/policy interest
  - Whether the requisite conditions for valid identification are reasonable
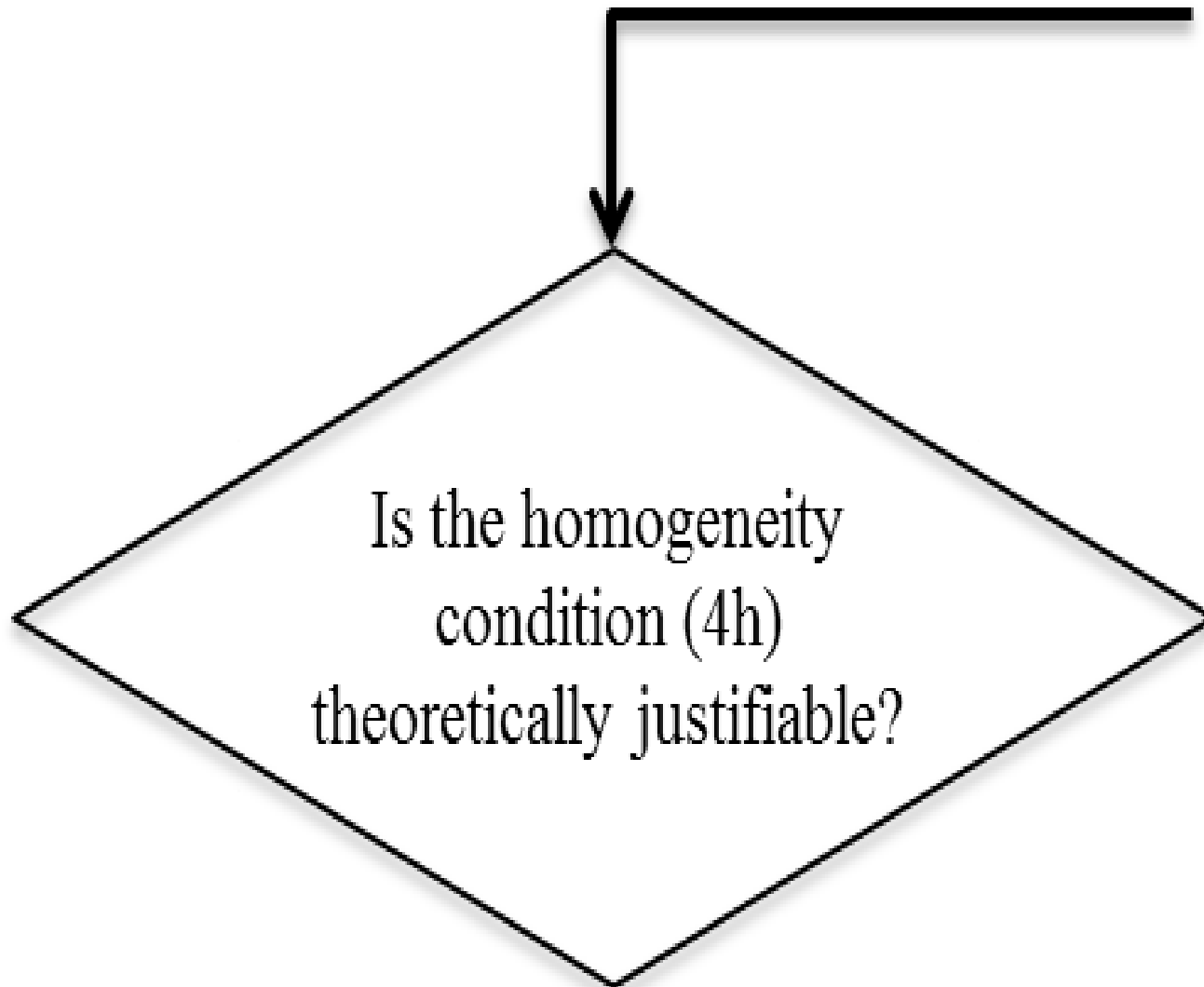
LATE: the effect only pertains to a subgroup…

- "So what? We often estimate effects only in subgroups. Should we disregard results from a male-only randomized trial?"

- Two reasons we may be interested in the result of a male-only study

    1. We want to apply the policy to men only

    2. We think the effect in men and women are likely similar and want to apply the policy to both sexes

- Is this reasoning appropriate for the subgroup of compliers?

LATE: not of direct policy/clinical relevance

- Even when well-defined, the compliers are a subgroup we can't target policies toward

- Nor should we extrapolate from the compliers
  - The whole reason we introduced "local" effects is because we expect heterogeneity!

- Some mitigating factors: we can describe the proportion and characteristics of compliers

Won't estimate ATE because too much heterogeneity

??

Estimate LATE under monotonicity

Extrapolate LATE to ATE assuming no heterogeneity

ATE

Is the homogeneity
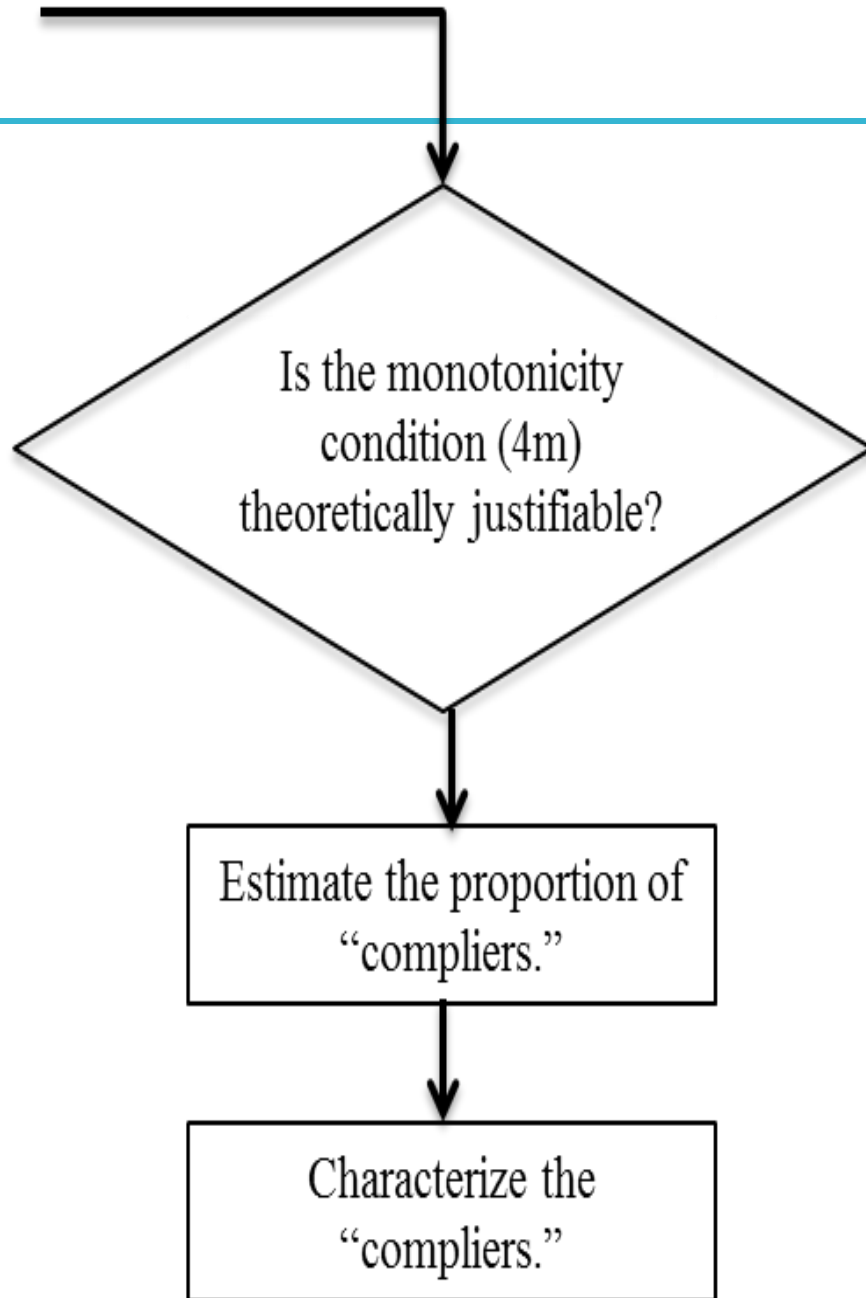condition (4h)
theoretically justifiable?

Plausibility of homogeneity conditions

- Recall the homogeneity conditions that are required for idenitfying the average treatment effect

  - E.g., no additive effect modification by the IV among the treated and the untreated

- A difficult condition to interpret what it means causally and to evaluate its plausibility in a given study

- A simpler way is to consider the sufficient condition: if U modifies the effect of A on Y (on the additive scale)

Theoretical justification of homogeneity?

- For discussion: what are some reasons homogeneity may or may not be a reasonable assumption for a given proposed IV in a given study?

LATE

Is the monotonicity condition (4m) theoretically justifiable?

Estimate the proportion of "compliers."

Characterize the "compliers."

Theoretical justification of monotonicity?

- For discussion: what are some reasons monotonicity may or may not be a reasonable assumption for a given proposed IV in a given study?

Two physicians with different preferences…

- Physician A: usually prefers to prescribe treatment, but makes exceptions for patients with diabetes
- Physician B: usually prefers to prescribe no treatment, but makes exceptions for physically active patients
- What happens if a patient is diabetic and physically active?

		Physician A	
		Treated	Not Treated
Physician B	Treated	**Always-taker**	**Defier**
	Not Treated	**Complier**	**Never-taker**

Multiple versions of the proposed IV

- But wait: there are more than two physicians in the world!

    - Multiple versions of the IV

- Depending on which pair of physicians we are considering, a specific individual could be conceptualized as a complier, always-taker, never-taker, or defier

Swanson & Hernan 2014 *Stat Sci*; Swanson et al. 2015 *Epi*

Survey of preference to assess monotonicity

- Although monotonicity cannot usually be verified, what if we surveyed physicians?

- Feasible study (Swanson et al. 2015 *Epidemiology*)

  - Presented 20 hypothetical patients eligible for the treatment decision, and asked physicians for their likely treatment plan

  - Measured preference via multiple proxies (e.g., reported medication prescribed to prior patient)

Consider the following hypothetical patient, JW. In your most likely treatment approach, would you prescribe any antipsychotic medication? *

An 88 year-old female, JW, with a probable Alzheimer's diagnosis presents with new symptoms of hallucinations and paranoia. JW has exhibited escalating dementia symptoms for five years, and moved to a nursing home last year when she could no longer care for herself. Nursing home staff report she has become violent when agitated. Behavioral interventions and redirection have been tried, and have not succeeded in reducing her periods or severity of agitation. JW has a BMI of 18, and a family history of osteoporosis. Other than what is noted here, she has no noteworthy family or personal medical history.

○ Yes, I would prescribe a conventional antipsychotic medication

○ Yes, I would prescribe an atypical antipsychotic medication

○ No, I would not prescribe an antipsychotic medication

Design of the feasibility study

- Identified 4800 active antipsychotic prescribers using the Xponent prescription database and AMA Physician Masterfile
    - >10 antipsychotic prescriptions written in 2011
    - Relevant medical specialty (family or internal medicine; psychiatry)
    - Valid email address
- Twice emailed these providers with a description of the study and a link to the online survey
- N=53 completed the survey

Results of the feasibility study

- Evidence of multiple versions of the instrument
  - Physicians with same preference made different decisions

- Evidence of monotonicity violations
  - Pairs of physicians with different preferences who both prescribed a hypothetical patient contrary to their preference

- Demonstrated use of survey results to adjust for possible bias in the IV estimates

Angrist, Imbens, & Rubin 1996 JASA; Richardson & Robins 2010; Swanson et al. 2015 *Epi*
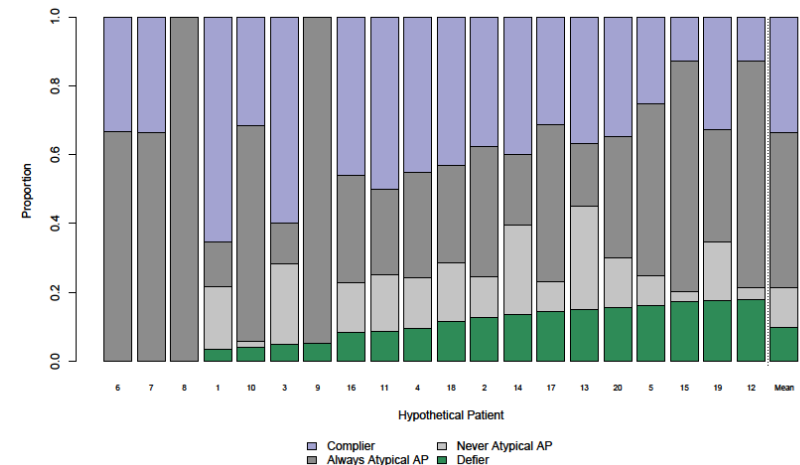
Lessons from feasibility study

- In practice, monotonicity violations (and multiple versions of the IV) may be likely when preference is used as an IV

- A survey of physicians may help quantify the degree of violations and resulting bias, under certain conditions

Characterizing the compliers

- Under the IV conditions plus monotonicity, can estimate the proportion of compliers

- Under the IV conditions plus monotonicity, can describe the relative prevalence of a measured covariate in the compliers (compared to the full study population)

- See R code

Choose an appropriate
modeling technique.
Report on all steps above.

IV estimation

- The two-stage estimator is frequently used, while IV g-estimators of structural mean models are less common approaches

- Benefits/extensions of these modeling approaches:
  - Introduce covariates
  - Handle continuous treatments
  - Consider multiple instruments simultaneously

- See R code for examples

Two-stage least squares estimation

- Stage 1: Fit a linear model for treatment

  - $E[A|Z] = \alpha_0 + \alpha_1 Z$

  - Generate the predicted values $\hat{E}[A|Z]$ for each individual

- Stage 2: Fit a linear model for the outcome

  - $E[Y|Z] = \beta_0 + \beta_1 \hat{E}[A|Z]$

- The parameter estimate of β_1 is the IV estimate

Appropriate modeling techniques

- Options covered in R code:

  - Standard IV ratio

  - Two-stage least squares regression

  - G-estimation of an additive structural mean model

- Some considerations/extensions:

  - Binary or failure-time outcomes

  - Non-binary proposed IVs

  - Combining with inverse probability weighting (e.g., to address loss to follow-up)

Reporting guidelines
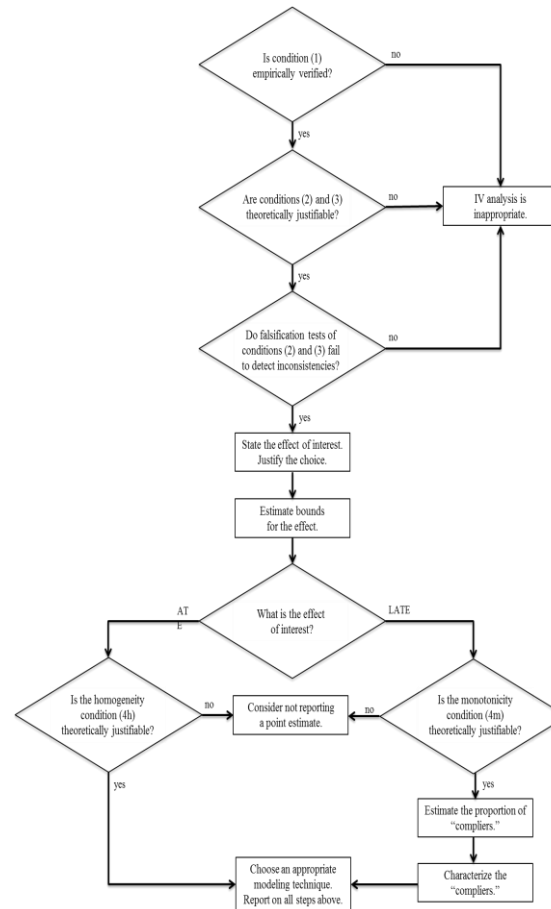
Swanson & Hernan 2013 *Epi*

Overview

- Motivation for IV methods

- Key assumptions for identifying causal effects with IVs

- IV estimation and tools for understanding possible threats to validity

- Extensions and further considerations

- Summary and Q&A

Further points for consideration

- Bounding approaches
  - IV conditions alone, relaxations of the IV conditions, etc.
- Proposing IVs conditional on measured covariates
- Possible collider stratification biases
- Causal versus non-causal proposed IVs
- Non-binary proposed IVs, treatments
- Binary or failure-time outcomes

Overview

- Motivation for IV methods

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Summary: key conditions

- IV methods require strong, untestable assumptions
  - Three IV conditions for bounding
  - Three IV conditions plus additional conditions for point estimation
- Applying IV methods requires concerted efforts to attempt to falsify assumptions and quantify possible biases
- Under these key conditions, IV methods offer opportunities for estimating:
  - Per-protocol effects in randomized trials
  - Treatment effects in observational studies

Summary: transparent reporting

- Transparent reporting is a key component of PCOR

- Major themes in reporting guidelines apply to both IV and non-IV studies

  - Should always clearly state and discuss assumptions
  - Should always state the effect we are estimating

- IV reporting also needs to address unique challenges

  - Requires applying different subject matter expertise
  - Seemingly minor violations of assumptions can result in large or counterintuitive biases
  - Interpreting "local" effects requires special care

Q&A

- Email: s.swanson@erasmusmc.nl