

Using an Instrumental Variable (IV) to deal with unmeasured confounding

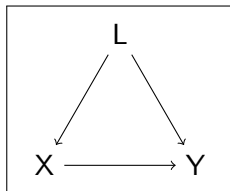
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A Short Course on Concepts and Methods in Causal Inference
V Edition



- X is a *binary* exposure X ($X = 1$ for the exposed; 0 for the unexposed), Y the outcome (binary or continuous) and L a set of confounders.
- If all confounders L are measured, apply standardization (for example) to estimate the *Average Treatment Effect* (ATE):

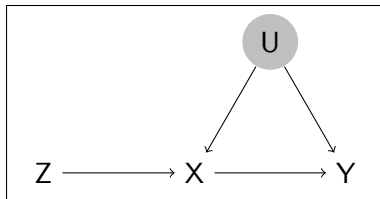
$$ATE = E(Y^1 - Y^0),$$

where Y^x is the potential outcome for $x \in \{0, 1\}$.

- **What if L is unmeasured?**

1. Definition of Instrumental Variables (IVs).
2. Identification of causal effects and Principal Stratification
3. Two-Stage Least-Squares (2SLS) approaches.
4. What can go wrong?
5. Extensions and other approaches.

Definition of an IV: core conditions

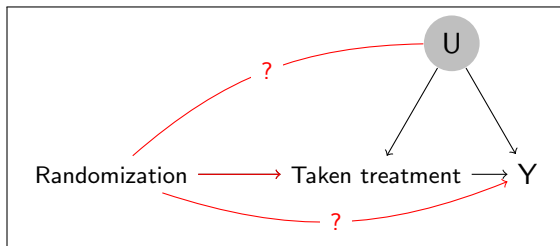


A *binary* variable Z is an **instrumental variable** if:

- 1 Z affects assigned treatment X (*Inclusion Restriction*):
 $E(X^1 - X^0) \neq 0$
where X^z is the potential treatment under $Z = z$
- 2 Z has no direct effect on Y (*Exclusion Restriction*):
 $Y^{z,x} = Y^x$ for all $z, x = 0, 1$
- 3 Z is independent of all confounders (*Randomization*):
 $Z \perp\!\!\!\perp \{X^0, X^1, Y^0, Y^1\}$

(Baioocchi, 2014)

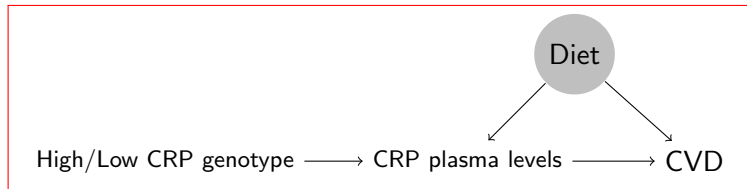
Example I - A double-blind RCT with non-compliance



- ① (*Inclusion Restriction*) Does randomized treatment assignment affect which treatment is taken?
Yes, by the experimental design.
- ② (*Exclusion Restriction*) Does randomized assignment affect the outcome only by determining which treatment is taken?
Yes, by blinding conditions.
- ③ (*Randomization*) Is randomized assignment independent of all confounders?
Yes, by random assignment.

(Greenland, 2000)

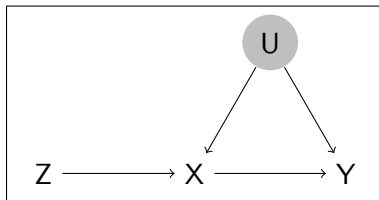
Example II - Mendelian randomization



- Rationale (Mendel's laws): parents genotype \rightarrow random assortment of alleles \rightarrow offspring genotype \rightarrow offspring characteristics (phenotype).
- Example: C-reactive protein (CRP) and CVD.
- Core conditions must be supported from available genomic knowledge (e.g. no pleiotropy, no gene linkage).

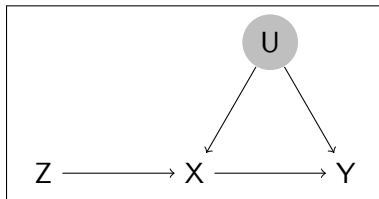
(Lawlor, 2008)

Example III - Other IVs in observational studies



- Many other IVs were considered in observational settings (Baiocchi, 2014):
 - physician's preferences;
 - calendar time;
 - geographic area;
 - distance to specialty care provider;
 - copayment amount;
 - ...
- Core conditions must be assessed from background knowledge.
- Observational study + valid IV = “natural experiment” (Angrist, 2001).

Identification of causal effects with IVs



- With a valid IV we can:
 - test the null hypothesis of no treatment effect (as in an intention-to-treat analysis):
 $X \perp\!\!\!\perp Y|U \Rightarrow Z \perp\!\!\!\perp Y$;
 - test for the presence of unmeasured confounders (Guo, 2014);
 - bound the value of the ATE (Balke, 1997);
- ... but we cannot estimate the causal effect of X without further assumptions!
- We will use **Principal Stratification** to understand two identifiability conditions.

Principal Stratification (1)

- Classify subjects according to their **principal strata** or **compliance classes**:

X^0	X^1	Compliance class (C)
0	0	<i>Never Takers (NT)</i>
1	1	<i>Always Takers (AT)</i>
0	1	<i>Compliers (CO)</i>
1	0	<i>Defiers (DE)</i>

- Compliance-Class-specific treatment Effects (CCEs):*

$$CCE_c = E(Y^1 - Y^0 | C = c) \quad c \in \{CO, NT, AT, DE\}.$$

- CC_{CO} is called the *Compliers Average Casual Effect (CACE)* or the *Local Average Treatment Effect (LATE)*.

(Frangakis, 2002)

Principal Stratification (2)

Decomposition of the ATE

Denote with $\pi_c = P(C = c)$ the proportion of subjects in the compliance class $c \in \{CO, NT, AT, DE\}$. Then:

$$ATE = \sum_c CCE_c \cdot \pi_c$$

Proof

Use the Law of Total Expectation:

$$\begin{aligned} ATE &= E(Y^1 - Y^0) \\ &= \sum_c E(Y^1 - Y^0 | C = c) P(C = c) \\ &= \sum_c CCE_c \cdot \pi_c \end{aligned}$$

The no treatment-effect heterogeneity assumption (1)

No treatment-effect heterogeneity assumption (NTEH).

On average, all subjects respond to treatment in the same way:

$$CCE_{CO} = CCE_{AT} = CCE_{NT} = CCE_{DE}$$

- Under NTEH, decomposition of the ATE implies $ATE = CCE_c$ for all $c \in \{CO, NT, AT, DE\}$.

Theorem 1 (Identification of the ATE under NTEH)

If Z is an IV (i.e. satisfies the core conditions) and the NTEH assumption holds, then the ATE is identified and equal to

$$W = \frac{E(Y|Z=1) - E(Y|Z=0)}{E(X|Z=1) - E(X|Z=0)} = \frac{ITT_{ZY}}{ITT_{ZX}}$$

The no treatment-effect heterogeneity assumption (2)

Proof of Theorem 1

For individuals with $Z = z$, we observe $X = X^z$ and, by the exclusion restriction, $Y = Y^{X^z}$ ($z = 0, 1$).

Hence:

$$\begin{aligned} ITT_{ZY} &= E(Y|Z = 1) - E(Y|Z = 0) \\ &= E(Y^{X^1}|Z = 1) - E(Y^{X^0}|Z = 0) \\ &= E(Y^{X^1} - Y^{X^0}) && \text{(by randomization)} \\ &= \sum_c E(Y^{X^1} - Y^{X^0}|c)\pi_c \\ &= E(Y^1 - Y^0|CO)\pi_{CO} + E(Y^1 - Y^1|AT)\pi_{AT} \\ &\quad + E(Y^0 - Y^0|NT)\pi_{NT} + E(Y^0 - Y^1|DE)\pi_{DE} \\ &= CCE_{CO} \cdot \pi_{CO} - CCE_{DE} \cdot \pi_{DE} \end{aligned}$$

The no treatment-effect heterogeneity assumption (3)

Proof of Theorem 1 (cont.)

Similarly:

$$\begin{aligned} ITT_{ZX} &= E(X|Z=1) - E(X|Z=0) \\ &= E(X^1|Z=1) - E(X^0|Z=0) \\ &= E(X^1 - X^0) && \text{(by randomization)} \\ &= E(1-0|CO)\pi_{CO} + E(1-1|AT)\pi_{AT} \\ &\quad + E(0-0|NT)\pi_{NT} + E(0-1|DE)\pi_{DE} \\ &= \pi_{CO} - \pi_{DE} && (\neq 0 \text{ by incl. restr.}) \end{aligned}$$

The no treatment-effect heterogeneity assumption (4)

Proof of Theorem 1 (cont.)

We found that:

$$ITT_{ZY} = CCE_{CO} \cdot \pi_{CO} - CCE_{DE} \cdot \pi_{DE}$$

$$ITT_{ZX} = \pi_{CO} - \pi_{DE}$$

$$W = \frac{ITT_{ZY}}{ITT_{ZX}} = \frac{CCE_{CO} \cdot \pi_{CO} - CCE_{DE} \cdot \pi_{DE}}{\pi_{CO} - \pi_{DE}}$$

However, by the NTEH assumption, $CCE_{CO} = CCE_{DE} = ATE$, so:

$$\begin{aligned} W &= \frac{ATE \cdot \pi_{CO} - ATE \cdot \pi_{DE}}{\pi_{CO} - \pi_{DE}} \\ &= \frac{ATE \cdot (\pi_{CO} - \pi_{DE})}{\pi_{CO} - \pi_{DE}} \\ &= ATE \end{aligned}$$

The no treatment-effect heterogeneity assumption (5)

- The NTEH assumption allows us to identify the ATE.
- It is true whenever treatment has no real effect, but in general it may be biologically implausible (Hernán, 2006).
- Example: never-treated may have a serious contraindication.
- We are going to look at a less stringent but weaker assumption.

The monotonicity assumption (1)

The monotonicity assumption

There are no defiers: $\pi_{DE} = 0$

- Equivalently: $X^1 \geq X^0$ (defiers have $X^1 = 0 < X^0 = 1$).
- Less stringent than NTEH (we assume nothing about AT and NT) but weaker because **the ATE is not identified...**
- ... **but the CACE is!**

Theorem 2 (Identification of the CACE by IVs)

If Z is an IV (i.e. satisfies the core conditions) and the monotonicity assumption holds, then the CCE_{CO} (i.e. the CACE) is identified and equal to

$$W = \frac{E(Y|Z=1) - E(Y|Z=0)}{E(X|Z=1) - E(X|Z=0)} = \frac{ITT_{ZY}}{ITT_{ZX}}$$

The monotonicity assumption (2)

Proof of Theorem 2

Recall from proof of Theorem 1:

$$ITT_{ZY} = CCE_{CO}\pi_{CO} - CCE_{DE}\pi_{DE}$$

$$ITT_{ZX} = \pi_{CO} - \pi_{DE}$$

$$W = \frac{ITT_{ZY}}{ITT_{ZX}} = \frac{CCE_{CO} \cdot \pi_{CO} - CCE_{DE} \cdot \pi_{DE}}{\pi_{CO} - \pi_{DE}}$$

Hence, by the monotonicity assumption:

$$\begin{aligned} W &= \frac{CCE_{CO} \cdot \pi_{CO} - CCE_{DE} \cdot 0}{\pi_{CO} - 0} \\ &= CCE_{CO} \end{aligned}$$

The Wald estimator

- The quantity W could be estimated by substituting expectations with sample means or model-based estimates:

$$\widehat{W} = \frac{\widehat{E}(Y|Z=1) - \widehat{E}(Y|Z=0)}{\widehat{E}(X|Z=1) - \widehat{E}(X|Z=0)}$$

- Example (using sample means):

$$\widehat{W}_{Wald} = \frac{\bar{Y}_1 - \bar{Y}_0}{\bar{X}_1 - \bar{X}_0}$$

is **Wald's estimator**.

- Wald's estimator is also equal to $\widehat{W}_{Wald} = \widehat{Cov}(Z, Y) / \widehat{Cov}(Z, X)$.

(Baioocchi, 2014)

Example: a trial of Vitamin A supplements

- Data from an RCT assessing the efficacy of Vitamin A supplements in reducing the risk of one-year mortality among 23,682 pre-school Indonesian children (Greenland, 2000):

Assigned Vit. A (Z)	Received Vit. A (X)	N (%)	Deaths	Risk (per 100,000)
1 (Yes)	1	9,675 (80%)	12	124
	0	2,419 (20%)	34	1406
	Total	12,094 (100%)	46	380
0 (No)	1	0 (0%)	0	-
	0	11,588 (100%)	74	639
	Total	11,588 (100%)	74	639

$$\widehat{W}_{Wald} = \frac{380 - 639}{0.80 - 0} = \frac{-259}{0.80} = -323 \text{ (per 100,000)}$$

- S.E.s and conf. intervals by the δ -method or the bootstrap.

Two-Stage Least Squares (2SLS) (1)

- Generally W is estimated by a two-stage procedure:
 - ① Regress X on Z using a standard linear model by OLS:

$$E(X|Z) = \alpha_0 + \alpha_1 Z \quad (1st\ stage)$$

- ② Regress X on the predicted values $\hat{X} = \hat{\alpha}_0 + \hat{\alpha}_1 Z$, again using OLS:

$$E(Y|\hat{X}) = \beta_0 + \beta_1 \hat{X} \quad (2nd\ stage)$$

- The estimated regression coefficient $\hat{\beta}_1$ in the second stage regression is a consistent estimator of W .

(Baiocchi, 2014)

Two-Stage Least Squares (2SLS) (2)

Why does 2SLS work?

From the definition of W :

$$E(Y|Z = 1) - E(Y|Z = 0) = W \cdot (E(X|Z = 1) - E(X|Z = 0))$$

For each $Z = 0, 1$, this is equivalent to:

$$\begin{aligned} E(Y|Z) - E(Y|Z = 0) &= W \cdot (E(X|Z) - E(X|Z = 0)) \\ E(Y|Z) &= \underbrace{(E(Y|Z = 0) - W \cdot E(X|Z = 0))}_{\beta_0} + \underbrace{W}_{\beta_1} \cdot E(X|Z) \end{aligned}$$

$$E(Y|Z) = \beta_0 + \beta_1 \cdot E(X|Z)$$

- Regressing Y on $E(X|Z)$ yields a consistent estimator of $\beta_1 = W$.
- In 2SLS, we substitute $E(X|Z)$ with its consistent estimator \hat{X} .

Example: a trial of Vitamin A supplements (again)

- Data from an RCT assessing the efficacy of Vitamin A supplements in reducing the risk of one-year mortality among 23,682 pre-school Indonesian children (Greenland, 2000):

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- Using PROC REG in SAS:

1st stage $E(X|Z) = 9.52743\text{E-}17 + 0.79998 \cdot Z$

2nd stage $E(Y|\hat{X}) = 0.00639 - 0.00323 \cdot \hat{X}$

- $\hat{\beta}_{1,2\text{nd stage}} = -323/100,000 = \hat{W}_{Wald}$
- For binary IV and exposure (as in our setting): $\hat{\beta}_{1,2\text{nd stage}} = \hat{W}_{Wald}$.

Two-Stage Least Squares (2SLS) (3)

- Inference in 2SLS:
 - S.E. from second-stage regression are **NOT** valid!
 - How can we get valid S.E.s?
 - exact S.E.s from 2SLS theory for continuous outcomes with homoschedastic errors (Angrist, 2008);
 - robust asymptotic S.E.s from Generalized Method of Moments (GMM) theory for general continuous or binary outcomes (Baum, 2003);
 - bootstrapping;
- 2SLS is available in many statistical softwares:
 - STATA `ivregress`
 - SAS `PROC SYSLIN` (requires SAS/ETS)
 - R `ivreg` (in the AER package)
- 2SLS is amenable to several generalizations (later).

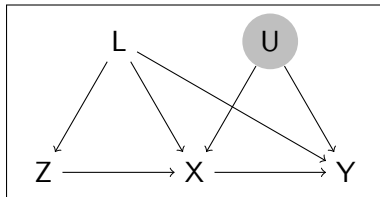
What can go wrong?

- Violation of the core assumptions introduces bias. See, for example, (Baiocchi, 2014), (Brookhart, 2007), and (Angrist, 1996) for a discussion of the introduced biases and related sensitivity analysis methods.
- **Weak instrument bias:** instruments weakly associated with exposure are more prone to bias (even when the core conditions are met) and provide less efficient estimators (Baiocchi, 2014).
- Example: if the denominator in Wald's estimator is small, the variability and bias of the numerator will be amplified.

$$\widehat{W}_{Wald} = \frac{\widehat{E}(Y|Z=1) - \widehat{E}(Y|Z=0)}{\widehat{E}(X|Z=1) - \widehat{E}(X|Z=0)}$$

- In 2SLS, if the partial F statistic for Z in the first-stage regression is $F \geq 10$, then the IV is usually regarded as sufficiently strong.

Extention 1: IVs and measured covariates



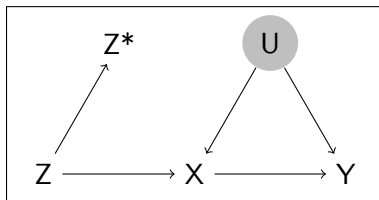
- The core conditions can hold *within the strata of the measured covariates* L .
- Principal stratification can be performed in each strata of L .
- If there is no X - L and $Z - L$ interaction, then 2SLS is still applicable:

$$E(X|Z) = \alpha_0 + \alpha_1 Z + \alpha_2 L \quad (\text{first stage})$$

$$E(Y|\hat{X}) = \beta_0 + \beta_1 \hat{X} + \beta_2 L \quad (\text{second stage})$$

(Baioocchi, 2014)

Extention 2: surrogate IVs



- The definition of IVs can be relaxed and a surrogate instrument Z^* can be used in place of the true instrument Z .
- 2SLS is still applicable:

$$E(X|Z^*) = \alpha_0 + \alpha_1 Z^* \quad (\text{first stage})$$

$$E(Y|\hat{X}) = \beta_0 + \beta_1 \hat{X} \quad (\text{second stage})$$

(Hernán, 2006)

Extention 3: other approaches

- Methods to estimate causal effects via IVs are still a hot research topic.
- Other approaches:
 - For binary, continuous or more general outcomes:
 - 2-Stage Residual Inclusion - (Terza, 2008)
 - Generalized Method of Moments estimation - (Johnston, 2008)
 - (Generalized) Structural Mean Models - (Hernán, 2006), (Vansteelandt, 2003)
 - For time-to-event outcomes:
 - Structural Accelerated Failure Time models - (Robins, 1991)
 - Structural Cox model - (Loeys, 2003)
 - ... and many more; see (Baiocchi, 2014) for other references.
- Each method makes specific modeling and identifiability assumptions (possibly different than NTEH or monotonicity) and so target a specific causal estimand.

- We have seen how IVs can help in estimating causal effects even in presence of unmeasured confounders.
- IV methods trade one untestable assumption (no unmeasured confounders) with other untestable assumptions (the core conditions plus identifiability assumptions).
- The point is: the IV assumptions can be more plausible than the no-unmeasured-confounders assumption in light of the available background knowledge.
- When assumptions are met, IV methods should be incorporated in the analyses.

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