Causal Inference

Vanessa Didelez, Robin Evans, Karla Diaz-Ordaz
BIPS, University of Bremen (Germany), University of Oxford, UCL (UK)

September 2025
APTS — Southampton

Appendix II:

Instrumental Variables (IVs)

IVs: Motivation

Unobserved cofounding present

Often in observational studies: assumption of sufficient covariates (or 'no unmeasured confounders') not realistic.

Alternative: can sometimes use an **instrumental variable (IV)** to identify, at least partially, desired causal effect

IV: similar to 'nature is randomising' (or some other external source of randomness)

IVs still rely on **assumptions**, but different ones...

Instrumental Variables

Notation

$G =$ instrumental variable (e.g. genetic marker)

$A =$ exposure of interest (e.g. alcohol consumption)

$U =$ unobserved confounders (e.g. life-style)

$Y =$ outcome of interest (e.g. cardiovascular disease)

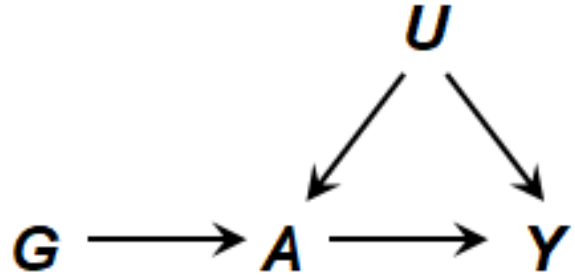
Mostly: target in terms of $E(Y|\text{do}(A = a))$

Sometimes in terms of potential outcomes $Y(a)$

Assumptions of IV

G is IV for the effect of A on Y if there is a U with

1. $G \perp\!\!\!\perp U$
2. $G \not\perp\!\!\!\perp A$
3. $G \perp\!\!\!\perp Y \mid (A, U)$.



Structural assumptions:

$$p(y|u,a) = p(y|u;\mathsf{do}(a)), \quad p(g) = p(g|\mathsf{do}(a)), \quad p(u) = p(u|\mathsf{do}(a))$$

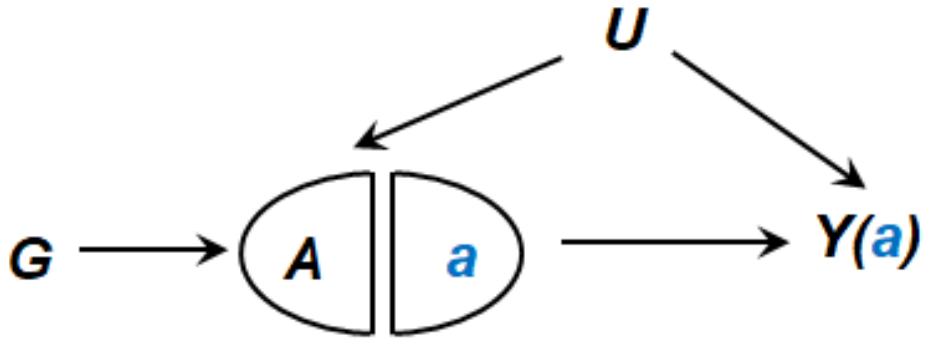
i.e. (cond.) distributions not changed by intervention in A.

(Greenland, 2000; Hernán & Robins, 2006, Didelez & Sheehan, 2007)

Assumptions of IV – with SWIG

Alternatively write assumptions as

1.' $Y(a) \perp\!\!\!\perp G$
2. $G \not\perp\!\!\!\perp A$



Note: many other versions of IV
$\rightarrow$ subtle differences in estimands

Examples:
'exclusion restriction' $Y(a, g) = Y(a)$;
'monotonicity' $A(G = 1) \geq A(G = 0)$ (where $A(g)$ PO of A under setting of G).

Examples for IVs

- In randomised trials with partial compliance:

  IV = treatment assignment, $A =$ actual treatment taken, $Y =$ health outcome.

- In epidemiology: IV = genetic variant, $A =$ exposure (often phenotype), $Y =$ health outcome

  $\Rightarrow$ **Mendelian randomisation**

- In observational studies / econometrics:
  - physicians drug preference,
  - accessibility of facilities,
  - birth date for years of education,
  - weather conditions for availability of fish / cereal etc.
  - lottery situations etc.

Use of IVs?

Testing:

check if $Y \perp\!\!\!\perp G$ — this is (roughly) testing whether there is a causal effect at all.

Estimation:

(1) when all observable variables are discrete, we can obtain bounds on causal effects without further assumptions.

(2) for point estimates need some (semi–)parametric / structural assumptions, as well as clear definition of target causal parameter.

But first, will discuss IV assumptions.

'Untestable' Assumptions

The assumptions

1. $G \perp\!\!\!\perp U$
3. $G \perp\!\!\!\perp Y \mid (A, U)$.

do not imply that $G \perp\!\!\!\perp Y | A$ or $G \perp\!\!\!\perp Y$ — check!!.

However, when all variables discrete, they impose inequality restrictions on the joint distribution $p(y, a|g)$ — these can easily be checked and provide a test against *gross violations* of the above assumptions. (Balke & Pearl, 1994)

Structural assumptions cannot be tested and may even depend on the particular intervention you have in mind.

$\Rightarrow$ Justify IV assumptions with **expert background** knowledge!

Justifying IV Assumptions

Example: Partial Compliance

In randomised trials with partial compliance: G = treatment assignment, $A =$ actual treatment taken, $Y =$ health outcome.

Treatment assignment is randomised $\Rightarrow G \perp\!\!\!\perp U$ seems very plausible.

Most subjects comply with treatment assignment $\Rightarrow G \not\perp\!\!\!\perp A$.

$Y \perp\!\!\!\perp G | (U, A)$ usually only plausible in a double–blind randomised trial!

Justifying IV Assumptions

Example: Effect of alcohol consumption

Genotype: ALDH2 determines blood acetaldehyde, the principal metabolite for alcohol.

Two alleles/variants: wildetype *1 and “null” variant *2.

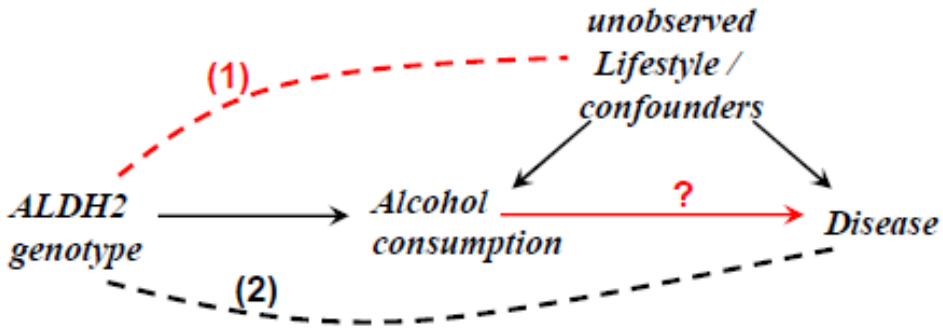
*2*2 homozygous individuals suffer facial flushing, nausea, drowsiness and headache after alcohol consumption.

$\Rightarrow$ *2*2 homozygous individuals have low alcohol consumption *regardless* of other lifestyle behaviours – Mendelian randomisation

IV–idea: check if these individuals have a different risk than others for alcohol related health problems!

Justifying IV Assumptions

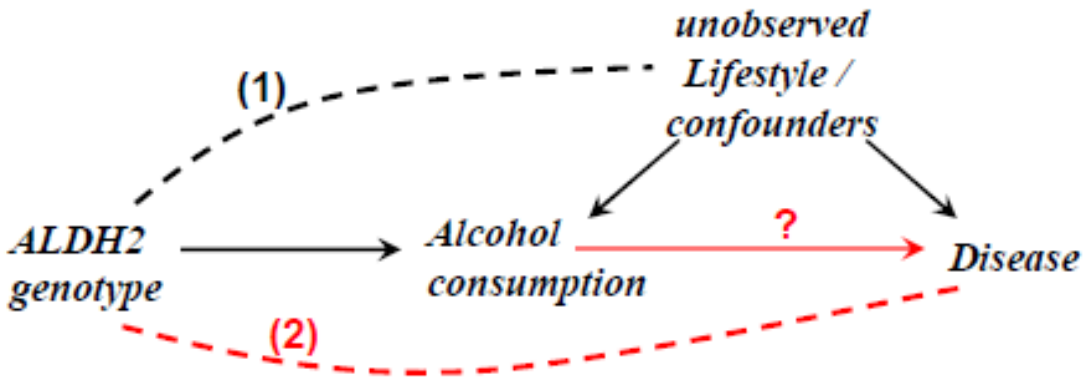
Example: Effect of alcohol consumption



Note 1: due to random allocation of genes at conception, can be fairly confident that genotype is not associated with unobserved confounders (subpopulation structure can be a problem).
Further evidence: in extensive studies no evidence for association with *observed* confounders, e.g. age, smoking, BMI, cholesterol. (see e.g. Davey Smith et al., 2007)

Justifying IV Assumptions

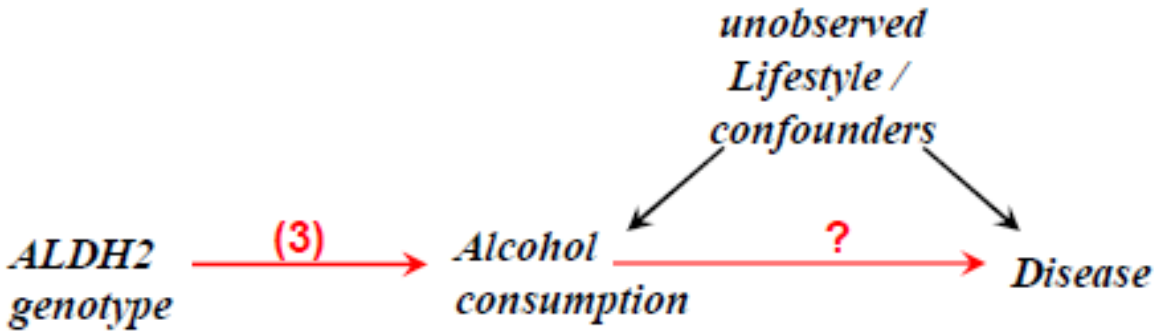
Example: Effect of alcohol consumption



Note 2: due to known 'functionality' of ALDH2 gene, we can exclude that it affects the typical diseases considered by *another* route than through alcohol consumption.
$\Rightarrow$ important to use well studied genes as instruments!

Justifying IV Assumptions

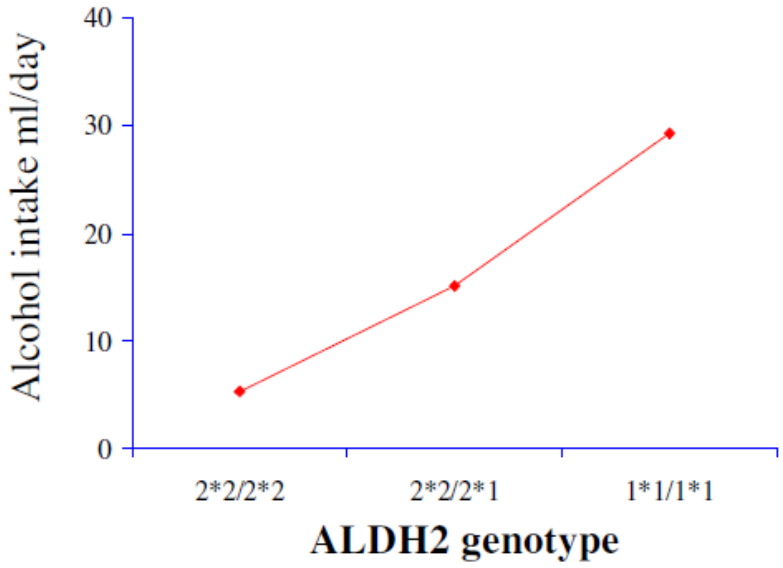
Example: Effect of alcohol consumption



Note 3: association of ALDH2 with alcohol consumption well established, strong, and underlying biochemistry well understood.

Justifying IV Assumptions

Example: Effect of alcohol consumption



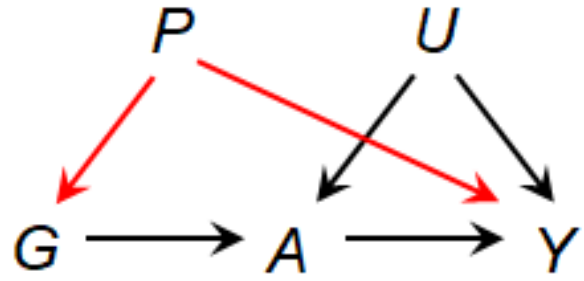
Note 3: association of ALDH2 with alcohol consumption well established, strong, and underlying biochemistry well understood.

Violation of IV Assumptions

Example: Mendelian randomisation

Population stratification occurs when there exist population subgroups that experience both, different disease rates (or different distributions of phenotypes) and have different frequencies
of alleles of interest.

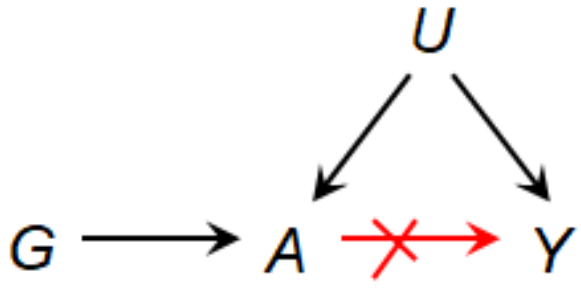
$\Rightarrow$ might violate condition
$Y \perp\!\!\!\perp G | (A, U)$.



Solution?

Testing for Causal Effect with IV

No causal effect "$\Leftrightarrow$" G independent of Y.



Here: take causal null-hypothesis as 'no $A \to Y$ edge'

Note: not the same as $ACE = 0$.

Example: Alcohol Consumption

Findings: (Meta-analysis by Chen et al., 2008)

Blood pressure on average 7.44mmHg higher and
risk of hypertension 2.5 higher
for ALDH2*1*1 than for ALDH2*2*2 carriers (only males).
$\Rightarrow$ mimics the effect of *large versus low* alcohol consumption.

Blood pressure on average 4.24mmHg higher and
risk of hypertension 1.7 higher
for ALDH2*1*2 than for ALDH2*2*2 carriers (only males).
$\Rightarrow$ mimics the effect of *moderate versus low* alcohol consumption.

Testing for Causal Effect with IV

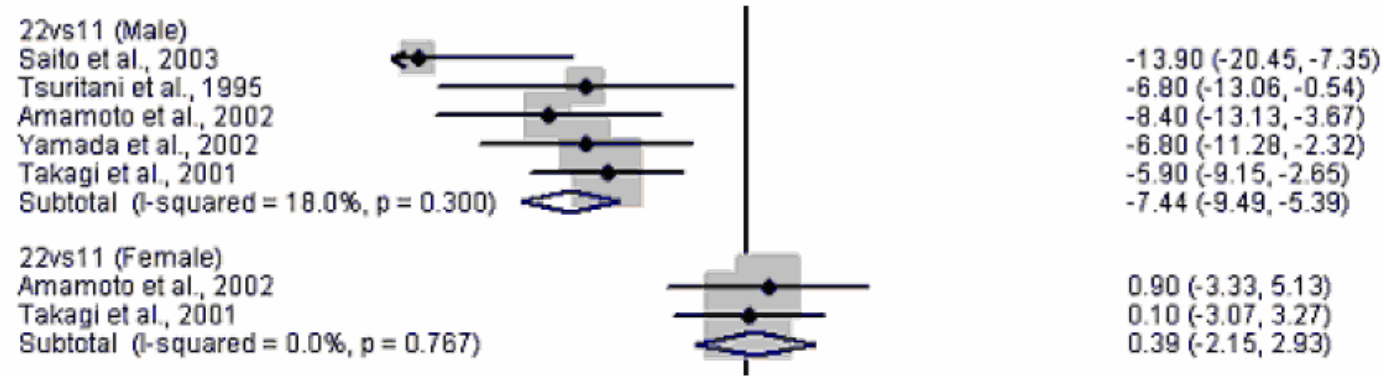
Results of Meta-analysis by Chen et al. (2008) suggest that **even moderate** alcohol consumption is **harmful**.

Note: studies mostly in Japanese populations (where ALDH2*2*2 is common), where women drink only little alcohol in general.

$\Rightarrow$ use women as 'negative control' group.

Example: Alcohol Consumption

Is condition $Y \perp\!\!\!\perp G|(A, U)$ satisfied?



Some indication

Women in Japanese study population did not drink. ALDH2 genotype in women not associated with blood pressure $\Rightarrow$ there does not seem to be another pathway creating a G–Y association here.

Bounds on Causal Effect

The all–binary case

Without parametric assumptions we cannot normally identify any *population* causal effect parameters.

But with A, Y, G all binary (or all discrete) we can derive upper and lower **bounds** on the causal effect (e.g. ACE).

(Balke & Pearl, 1994)

The derivation exploits restrictions on joint distribution of A, Y, G due to the conditional indepedencies involving U.

Interpretation of bounds: for a given observed frequency table on A, Y, G there exist different causal models that agree with these frequencies and can give causal effects anywhere within these bounds.

Bounds on Causal Effect

Y, A and G are **all binary**;
$ACE = E(Y|\text{do}(A = 1)) - E(Y|\text{do}(A = 0))$.

Let $p_{yx.g} = p(y, a|g)$. Then we have

$$\left.\begin{array}{c} p_{11.1} + p_{00.0} - 1 \\ p_{11.0} + p_{00.1} - 1 \\ p_{11.0} - p_{11.1} - p_{10.1} - p_{01.0} - p_{10.0} \\ p_{11.1} - p_{11.0} - p_{10.0} - p_{01.1} - p_{10.1} \\ -p_{01.1} - p_{10.1} \\ -p_{01.0} - p_{10.0} \\ p_{00.1} - p_{01.1} - p_{10.1} - p_{01.0} - p_{00.0} \\ p_{00.0} - p_{01.0} - p_{10.0} - p_{01.1} - p_{00.1} \end{array}\right\} \leq \text{ACE} \leq \left\{\begin{array}{c} 1 - p_{01.1} - p_{10.0} \\ 1 - p_{01.0} - p_{10.1} \\ -p_{01.0} + p_{01.1} + p_{00.1} + p_{11.0} + p_{00.0} \\ -p_{01.1} + p_{11.1} + p_{00.1} + p_{01.0} + p_{00.0} \\ p_{11.1} + p_{00.1} \\ p_{11.0} + p_{00.0} \\ -p_{10.1} + p_{11.1} + p_{00.1} + p_{11.0} + p_{10.0} \\ -p_{10.0} + p_{11.0} + p_{00.0} + p_{11.1} + p_{10.1} \end{array}\right.$$

$\Rightarrow$ can easily be estimated by observed relative frequencies.

Note: bounds are *sharp* — for given frequencies on (A, Y, G) there always exists joint distributions on (A, Y, U, G) for which the bounds are attained.

Notes on Bounds

- In most realistic scenarios: bounds are very wide and include 'no–causal–effect,' i.e. include $ACE = 0$.
- **Interpretation:** if $ACE = 0$ included, there is always another model, where A has no causal effect on Y, that could generate the same data.
- Width of bounds depends on strength of IV and amount of confounding.
- Still, bounds should always be calculated to assess how informative the data 'alone' are.
- Stata / R package `bpbounds` (Palmer et al., 2011, 2018); various IV methods: R package `ivtools` (Sjølander, 2018)

IV Estimation

ETT

The binary case — Effect of treatment on the treated (ETT)

With a key parametric assumption, we can identify the causal effect within a *subgroup* of the population, the treated

Assume structural mean model (SMM)

$$E(Y(1) - Y(0)|A = 1, G = g) = \psi$$

IV Estimation

ETT

Assume: **no effect modification** by the IV G (NEM)

$$E(Y(1) - Y(0)|A = 1, G = g) = \psi$$

It can then be shown that

$$E(Y(1) - Y(0)|A = 1) = \frac{E(Y|G = 1) - E(Y|G = 0)}{E(A|G = 1) - E(A|G = 0)}.$$

$\Rightarrow$ 'ratio estimator' (Wald-estimator)

With $E(Y(1) - Y(0)|U) = E(Y(1) - Y(0))$, i.e. no effect modification by U (on additive scale), the above equals population ACE.

IV Estimation

All binary: other target parameters, e.g.

'Wald type' IV estimators for RR and OR (Y and G binary)

$$WaldRR = \hat{RR}(Y|G)^{1/\Delta} \qquad WaldOR = \hat{OR}(Y|G)^{1/\Delta}$$

where $\Delta = \hat{E}(A|G=1) - \hat{E}(A|G=0)$.

WaldRR consistent for CRR if (Didelez et al, 2010)
– log-linearity of Y in A
– no A-U interaction on Y on log-linear scale
– $A|(G,U)$ normally distributed.

WaldOR approximation to WaldRR for rare disease.

Advantages: WaldOR can be used in case–control studies.

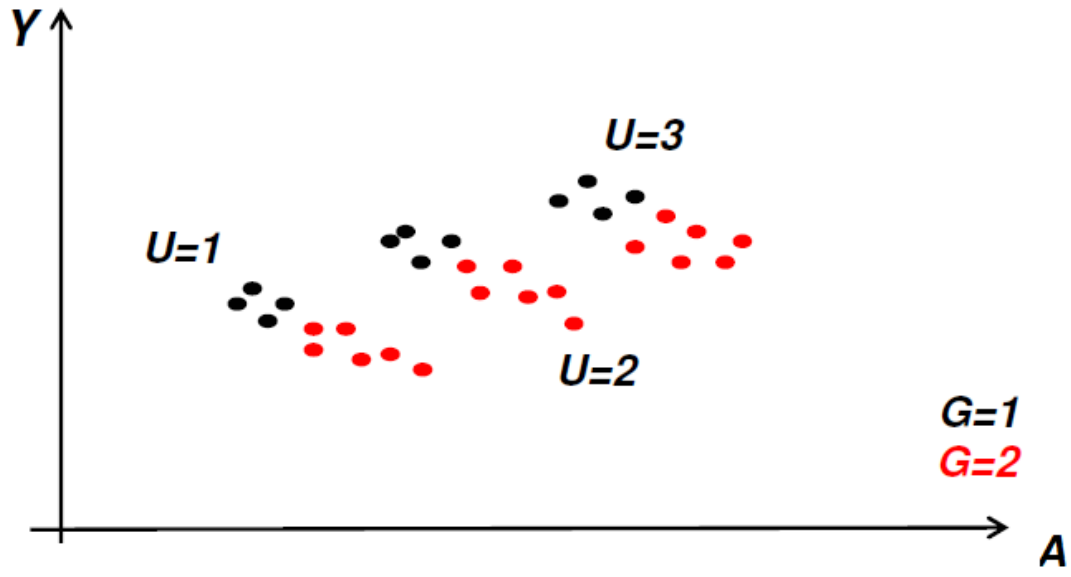
IV Estimation: 2SLS

The linear case: two-stage-least-squares (2SLS)

Some intuition first!

IV Estimation: 2SLS

Linear models



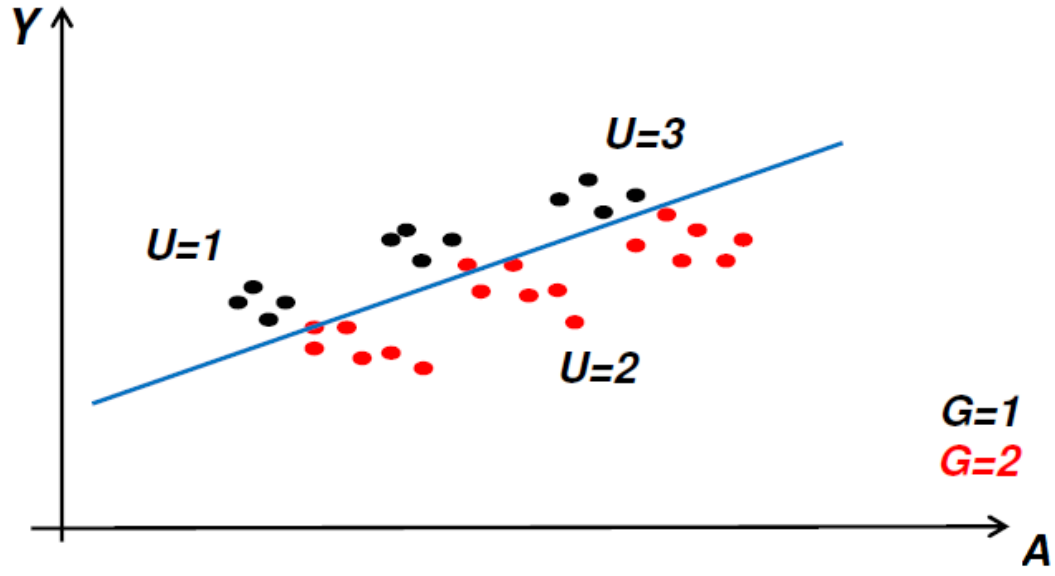
Positive confounding: larger values of U induce larger Y and larger A.

But conditional on (unobservable) U we have that Y and A have negative association.

Different colours = different values of IV.

IV Estimation: 2SLS

Linear models

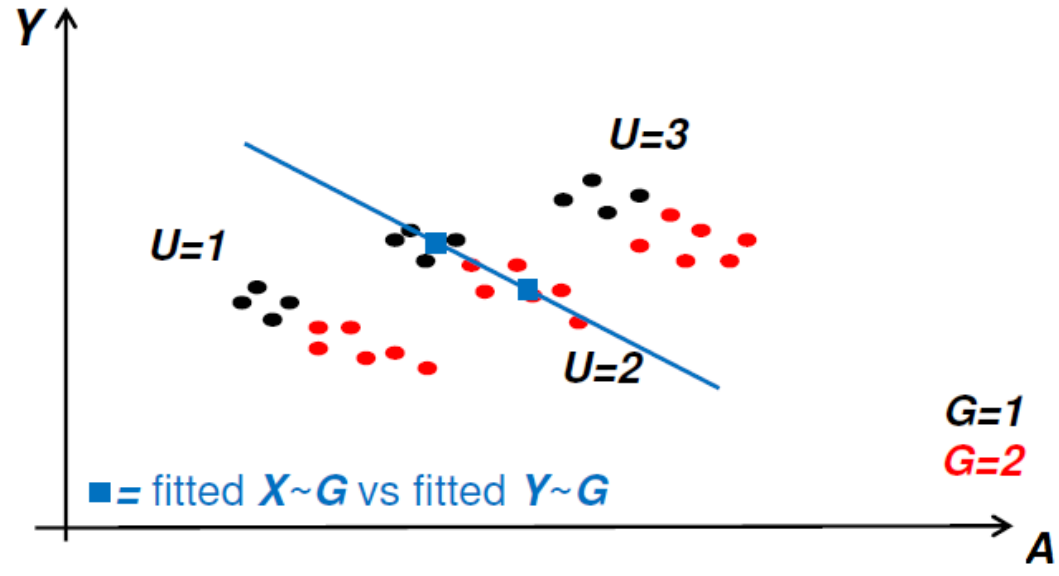


Regression of Y on A (ignoring U and G) results in positive slope.

Due to role of (unobservable!) U, biased estimate of causal effect.

IV Estimation: 2SLS

Linear models



With instrument: regress of A on G and Y on G and divide slopes.

This recovers the negative slope without knowing U.

IV Estimation in LSEM

Written as LSEM:

two endogenous variables

$$Y = \beta_0 + \beta A + \xi_Y(U)$$

$$A = \alpha_0 + \alpha G + \xi_A(U)$$

where $\xi_Y(U), \xi_A(U)$ are **correlated errors**.

G as IV is exogenous variable.

Econometrics: various approaches to estimating such (and more general) systems of equations (Bowden & Turkington, 1984)

IV Estimation in LSEM

$$Y = \beta_0 + \beta A + \xi_Y(U)$$

$$A = \alpha_0 + \alpha G + \xi_A(U)$$

Path-tracing results in:

– total effect of G on A is α

– total effect of G on Y is $\alpha\beta$

$\Rightarrow \beta =$ ratio of coefficients from OLS regr. Y on G and A on G.

Or: regress Y on $\hat{A}$, predicted from OLS $A|G$.

IV Estimation: 2SLS

Alternative: **weaker** model assumption — linear SMM.

A, Y, G arbitrary scale. Assume

$$E(Y|U = u; \text{do}(A = a)) = E(Y|u, a) = \mu_Y + \beta a + h(u)$$

Note, no (A, U)-interaction on linear scale.

Then $ACE = \beta$.

Can show

$$\beta = \frac{Cov(Y, G)}{Cov(A, G)}$$

i.e. β is identified from obs. data on A, Y, G.

IV Estimation: 2SLS

The linear case

Hence, consistent estimator for β given by ratio of estimated coefficients from regression of Y on G and from A on G

$\Rightarrow$ called IV–estimator or two–stage–least–squares (2SLS):

$$\hat{\beta}_{IV} = \frac{\hat{\beta}_{Y|G}}{\hat{\beta}_{A|G}}$$

where $\hat{\beta}_{Y|G}$, $\hat{\beta}_{A|G}$ least squares regression coefficients.

Note: denominator: weak IV (weak G-A association)
$\Rightarrow$ unstable *and also biased* IV estimators.

Notes on 2SLS

- popular, very simple to implement (many softwares)
- surprisingly robust towards misspecification

  (Vansteelandt & Didelez, 2017)
- can be generalised to multiple IVs, multiple exposures, multiple outcomes; but **weak** IV problem quickly becomes more serious in higher dimensions
- can also be used in 2-samples situation with separate (A, G)-data and (Y, G)-data.

Instrumental Variables

Summary

In presence of unobserved confounding: hope to find IV

- 'natural' experiment – genes, year of birth etc;
- can be used for testing for causal effect, or bounds;
- *estimation* requires more assumptions (e.g. NEM, linearity or other);
- recent work: inference with multiple instruments, some of which may be *invalid* (Bowden et al., 2015; Guo et al, 2018)

Natural Experiments

When suspicious of unobserved confounding: look for ‘natural experiments’

- regression discontinuity designs (RDD);
- interrupted time-series (e.g. policy changes) / difference-in-differences / before-after-design;
- negative controls;
- differences in difference;
- twin / sibling studies etc.

Unobserved Confounding

Absence of instruments / natural experiments?
$\Rightarrow$ sensitivity analysis!

See book: Lash et al (2009)

– needs some assumption on plausible confounding

– ad-hoc adjustment formulas or

– MC methods or

– Bayesian approaches (Gustafson et al, 2010)

Thank You!

www.leibniz-bips.de/en

Contact
Vanessa Didelez
Leibniz Institute for Prevention Research
and Epidemiology – BIPS
Achterstraße 30
D-28359 Bremen
didelez@leibniz-bips.de