Negative ICC?

- From: http://faculty.umb.edu/peter_taylor/09b.pdf
- ICC refers to a number of quantities, but the simplest form is the usual linear (Pearson product-moment) correlation among a set of pairs of values when the order in each pair is arbitrary. That would be the case if we wanted to know the correlation of heights in same sex couples or the agreement of two independent ratings of an exam done by a set of students (where the two raters differed from one student to the next) -
- Harris (1913; as described in Haggard 1958) showed that it is equivalent to finding the ratio of the variance of the means of the classes to the variance of the entire set of values, which is easier to calculate
- As a ratio of variances, the ICC should be in the interval [0,1]. Yet, without comment, negative estimates are included in Field's (2005) encyclopedia entry.
- In fact, as best I can tell, the ICC calculated with the variance component formula is identical to the rho calculated as the correlation between individuals in a cluster *unless* the rho is negative, in which case the ICC goes to null

http://biostats.bepress.com/cgi/viewcontent.cgi?article=1255&context=ucbbiostat

For next 2 classes

- For Kara Rudolph:
- http://biostats.bepress.com/cgi/viewcontent.cgi?article=1255&context=ucbbiostat
- And install R: http://cran.r-project.org/
- - When running a regression model to do analysis, what should we be worried about?
- - Why use TMLE instead of regression?
- - Why use TMLE instead of inverse probability of treatment weighting?
- - Are there instances when we wouldn't want to use TMLE?
- - What are marginal effects? What are conditional effects? Which do we usually report? Which are the most useful?
- - Can you think of applications in your field in which TMLE might be helpful?

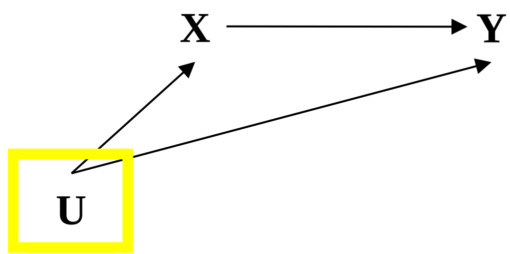
For next 2 classes

- For Sander Greenland: 3 readings – did all receive?

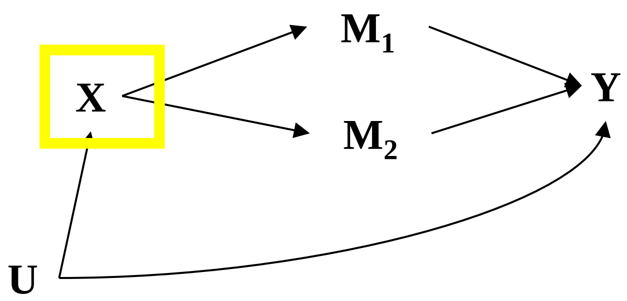
Instrumental Variables: Randomization andPseudoRandomization

Demonstrating Causation

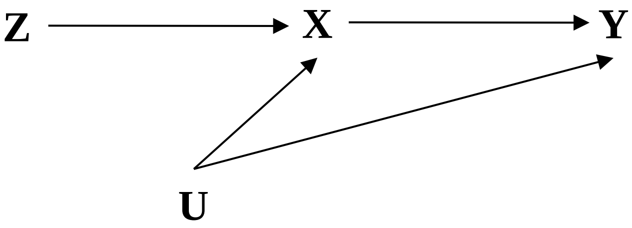
- Condition on all CPCs



- Measure all pathways



- Use an instrument



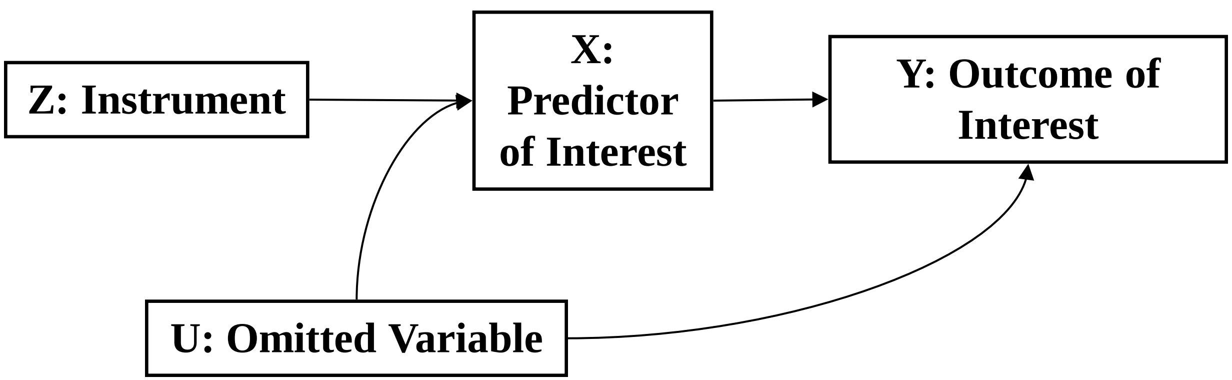
Motivations for IV Analyses

- Avoid confounding if a plausible natural experiment is available
- Estimate the effect of *receiving* treatment (IV) instead of being *assigned* treatment (ITT)
- Estimate the effect of treatment on the "marginal patient" or the compliers

Instrument Assumptions

Z is an instrument for the influence of X on Y if:

- Z is not an effect of X
- Z and X are associated
- every unblocked path between Z and Y has an arrow into X



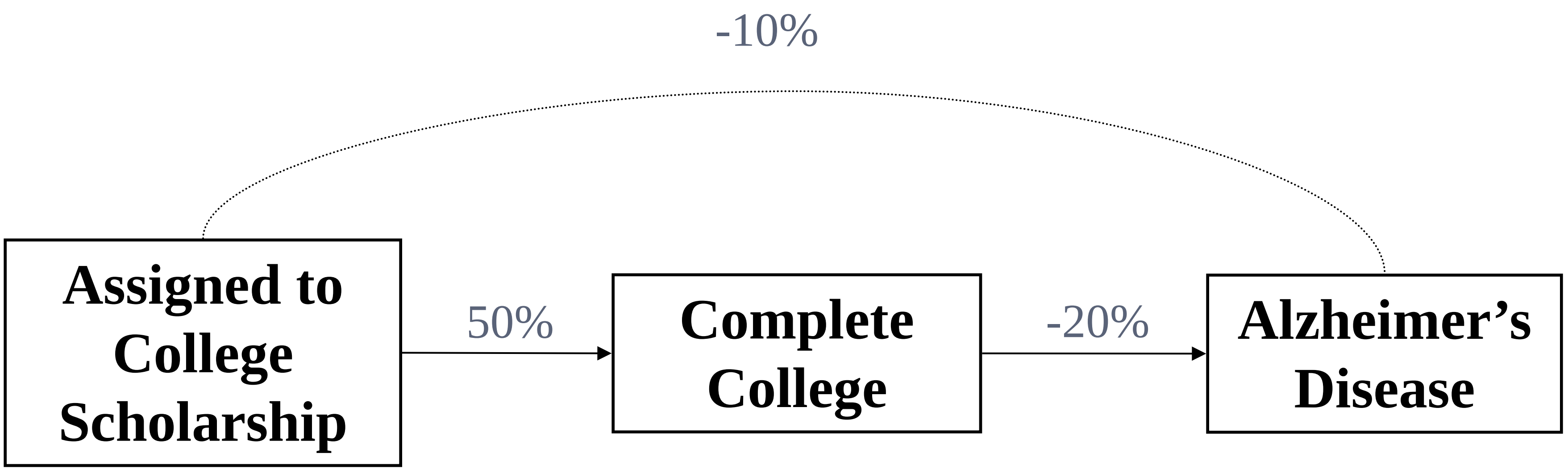
Familiar Instruments

- Instruments arise in the context of experiments
  - Randomized controlled trials
  - Natural experiments
  - Mendelian randomization
- Intent to treat analyses estimate the relation between treatment *assignment* and the outcome
- IV analyses estimate the relation between treatment and the outcome
  - Similar to correction for non-compliance
  - Estimates the effect of treatment on those who were treated because of their assignment
  - NOT a comparison of the treated to the untreated

Why are natural experiments important to epidemiology?

- Epidemiologists have long considered RCTs the "gold standard" for causal inference.
- Recent results call into question the reliability of causal inference from observational studies.
- Some exposures cannot be tested in RCTs.
- We must seek all approaches to bolster observational evidence.

IV Effect Estimates



Obtaining IV Estimates

Wald Estimates:

$$\text{Effect} = \frac{\text{(Difference in Avg Outcome Score between Instr Groups)}}{\text{(Difference in Avg Exposure Level between Instr Groups)}}$$

Two Stage Least Squares Estimates:

$\hat{e}\text{xposure} = \beta_0 + \beta_1 \text{Instrument} + \beta_k \text{Other Covariates}$

$\text{Outcome} = \beta_0 + \beta_1 \hat{e}\text{xposure} + \beta_k \text{Other Covariates}$

Generalized Method of Moments: Use assumption that residuals are independent of exposure

Obtaining IV Estimates

Wald Estimates:

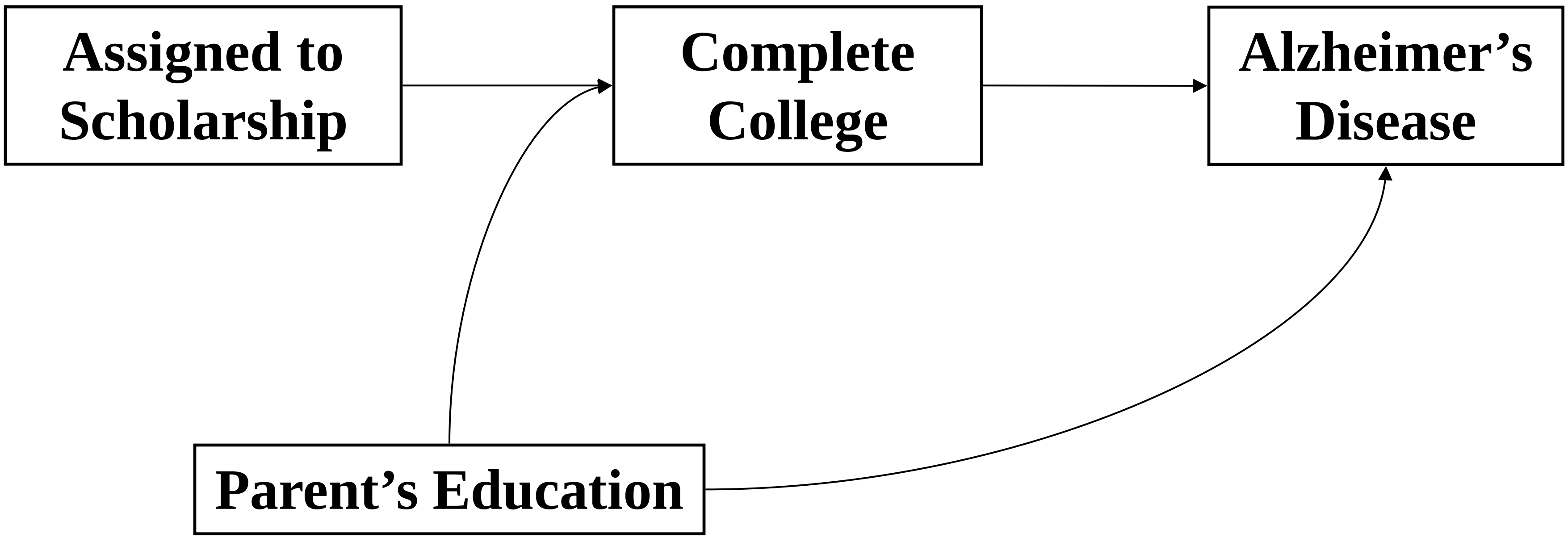
$$\text{Effect} = \frac{\text{(Difference in Avg Outcome Score between Instr Groups)}}{\text{(Difference in Avg Exposure Level between Instr Groups)}}$$

Note that the Wald Estimate is essentially the Intent to Treat effect estimate in the numerator

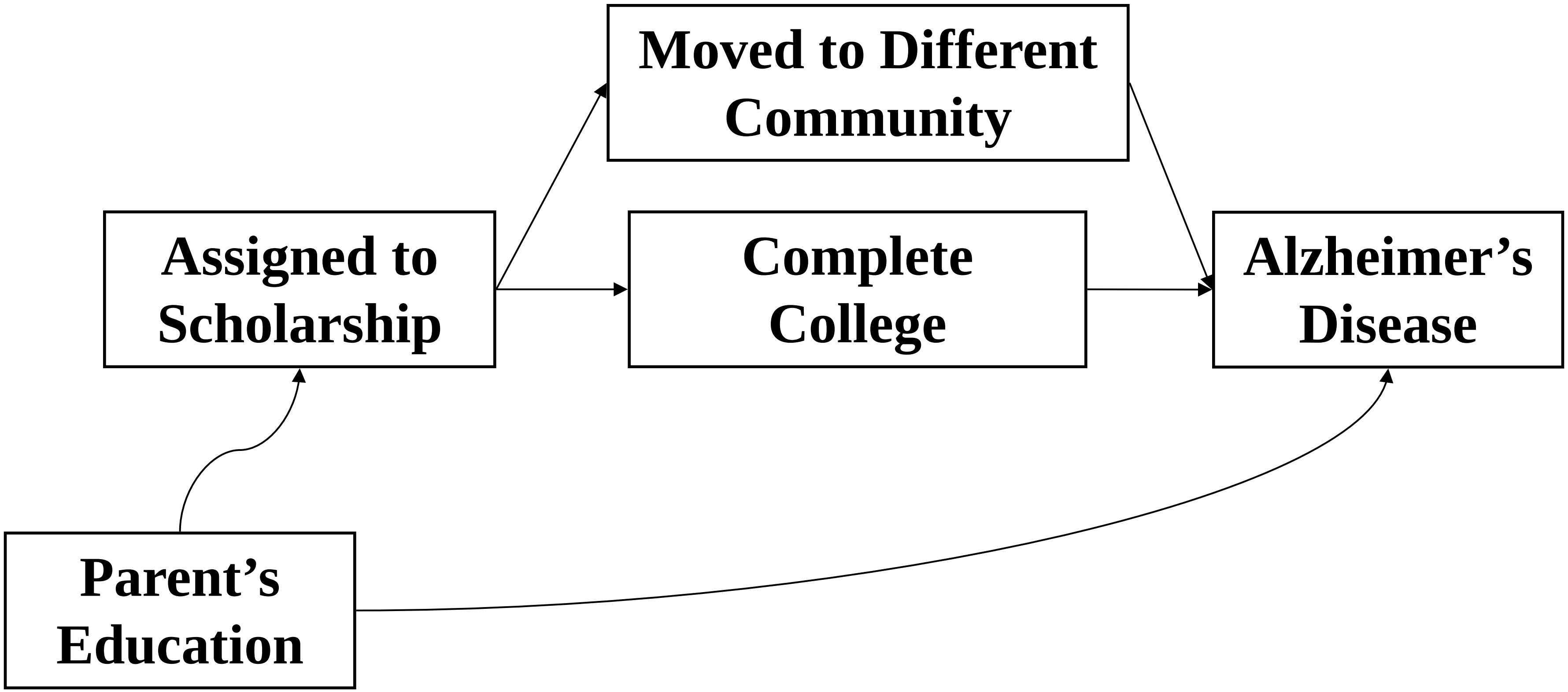
Divided by the effect of randomization on adherence in the denominator

Both ITT and adherence can be estimated without bias in an RCT, so you can use these two unbiased estimates to derive the estimated effect of exposure on outcome.

What's Neat About IV



Biggest concern in the violation



What IV Analyses Estimate

- Must assume monotonicity: the instrument does not have *opposite* effects on individuals within the population.
  - "no contrarians"
  - This is violated if increasing mandatory school increases Joe's educational attainment, but *decreases* Earl's educational attainment.
- IV analyses estimate the effect of the treatment on people induced to receive the treatment because of the instrument
- This may or may not equal the population average effect.

Whose Causal Effect?

Response if assigned to treatment B:

Response if assigned to treatment A:

	Take A	Take B
Take A	Never-Takers	Compliers
Take B	Contrarians	Always Takers

Variations on the Definition

- Standard econ:
  - If you are interested in estimating $Y_i=\beta X_i+e_i$ then Z is an instrument if "Z_i is correlated with X_i but not with ε_i" (Greene 2000, pg 370)
- Counterfactual:
  - Z is independent of Y_x (the counterfactual value of Y under any given value of X), and
  - Z is not independent of X. (Pearl, 2000, pg 248)
- AIR 1994 (developed originally for dichotomous Z, X):
  - SUTVA
  - Random assignment of Z
  - Exclusion: Y(Z,X)=Y(Z′,X) for all X, Z and Z′
  - Z has to have some effect on the probability of X
  - Montonicity: X(Z=1)≥ X(Z=0) for everyone in the population

Economists' Account of IV

This [instrument] is a new independent variable which must have two characteristics. First, it must be contemporaneously uncorrelated with the error; and second, it must be correlated (preferably highly so) with the regressor for which it is to serve as an instrument.

Economists' Account of Confounding

$$Outcome_i = \beta_0 + \beta_1\, exposure_i + \beta_k\, Other\ Covariates_i + \varepsilon_i$$

Consider estimating the above as a structural (causal) equation. If the errors are correlated with exposure, the estimate of β_1 is biased.

Why would ε_i be correlated with exposure?

Because of a common cause of exposure and the outcome

Or in econ parlance, because of a variable that should be included in the structural equation but has been omitted. Omitted variable bias=Confounding.

Assessing Instrument Validity

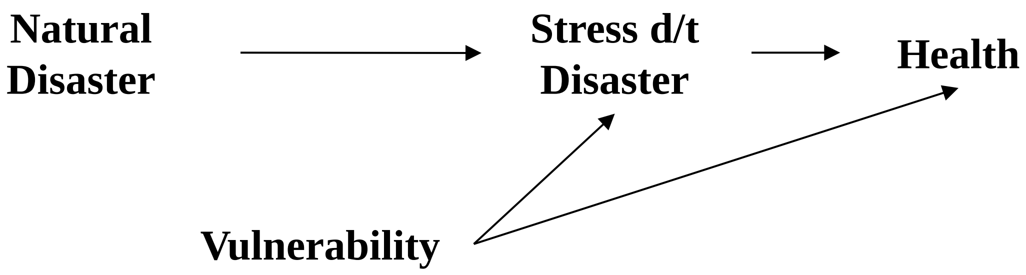
- Compare effect estimates from multiple instruments.
- Test whether first stage is specific to population likely to be affected.
- Look at relation of instrument to outcome, conditional on endogenous variable (but… collider bias may be an issue)
- Weak instruments: special caution ; F~>10

Separate Samples

- Sometimes, the exposure and the outcome are not available in the same data set
- If there are two data sets,
  - One with instrument and exposure
  - One with instrument and outcome
- You can estimate the IV effect

Common Confusions

- Is an instrument a confounder?
- Is 2sls like a propensity score model?
- If variation was induced by a natural experiment… do I compare the exposed to the unexposed?

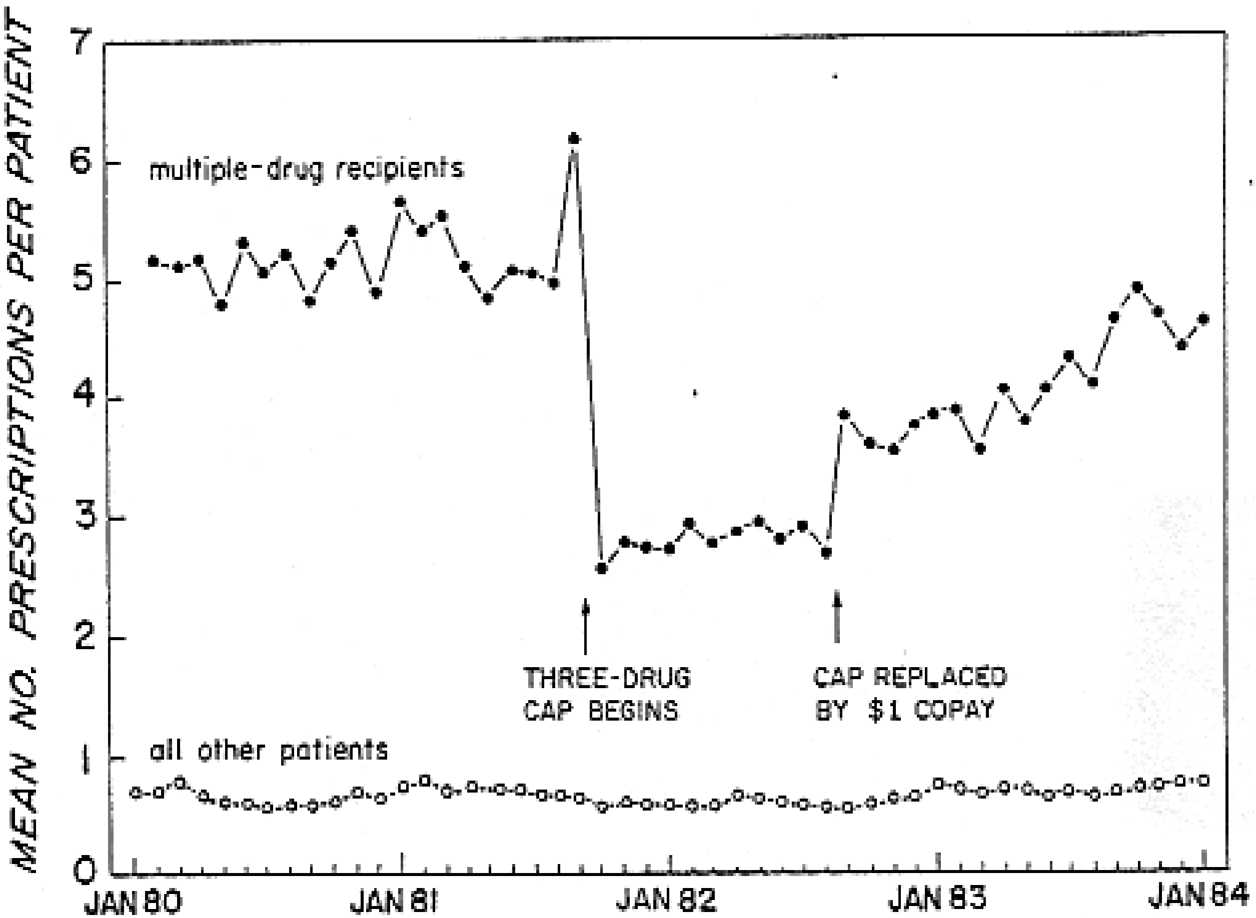


IV and related methods

- IV Analyses are a tool to combine information on Z-Y and Z-X to estimate X-Y.
- Sometimes used informally when people didn't measure X and possible only to test the null that X has no effect on Y.
- Often the null or the ITT is of most interest.
  - Policy makers: the instrument is the policy
  - For an RCT: not everyone will take up the drug, so what's the effect of availability?

IV and related methods

- Conceptualize a group of methods that are about moving a step back from a direct correlation (or regression) of exposure and outcome, using something that influences exposure to test the null
- Regression discontinuity: "in a highly rule based world, some rules are arbitrary and therefore provide good experiments"
- RDs often strengthened with a comparison group, otherwise risk being pre-post comparisons (remember threats to validity, e.g., history, maturation, regression)
- Can distinguish between "sharp" and "fuzzy" RD



STEPHEN B. SOUMERAI, SC.D., JERRY AVORN, M.D.,
DENNIS ROSS-DEGNAN, SC.D., AND STEVEN GORTMAKER, PH.D.
New England Journal of Medicine 317:550-556 (August 27), 1987

IV and related methods

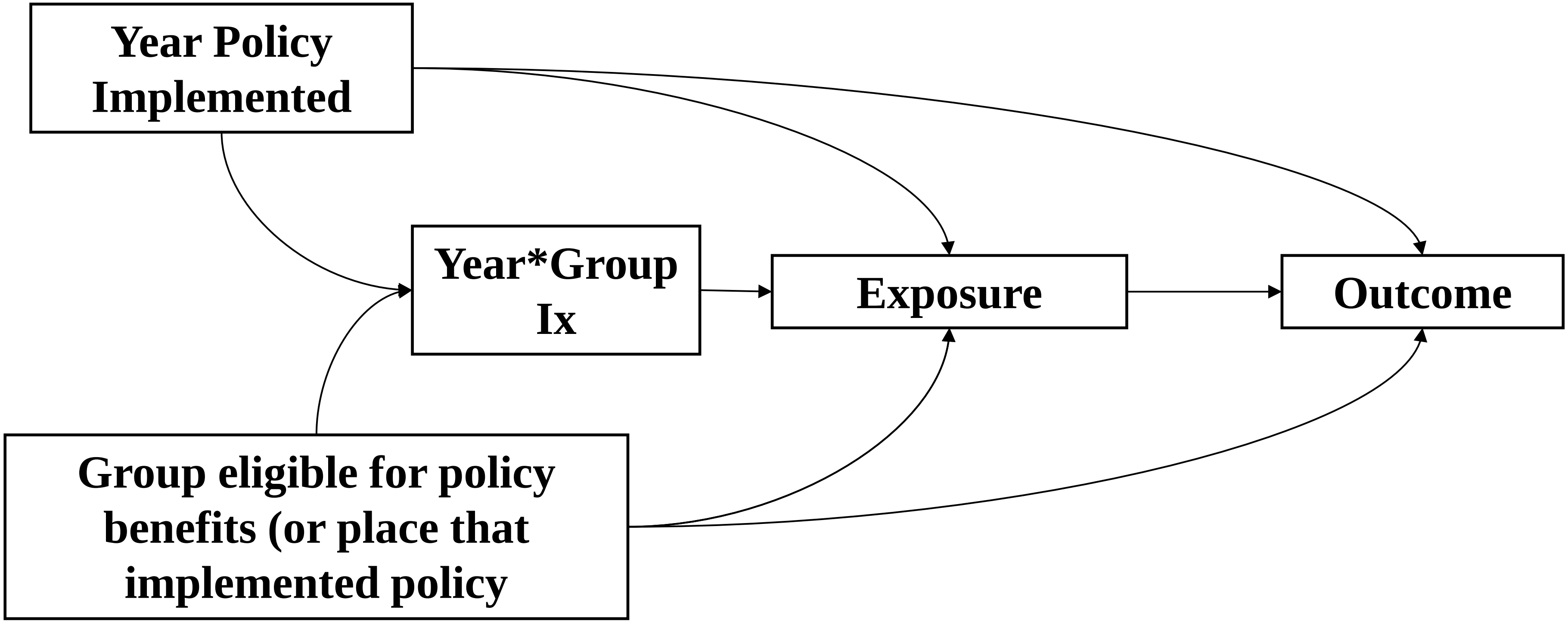
- "sharp" RD
- Exposure is a deterministic function of an underlying continuous characteristic
  - Test score (college eligibility)
  - Date (policy implementation)
  - Class size (additional class resources)
  - Weeks of gestation (abortion access)
  - Income (Medicaid eligibility)
  - BP (? Receive medications)
- X_i=1 if z_i>=cutoff
- X_i=0 if z_i<cutoff
- $\text{Outcome}_i=\beta_0+\beta_1(Z_i>=\text{cutoff})+\beta_2 Zi+\beta_k \text{Other Covariates}+\varepsilon_i$
- β_1 now corresponds with the effect of X.

IV and related methods

- “fuzzy” RD
- Exposure is influenced by an underlying continuous characteristic
  - Mandatory school dropout age or work permit age
  - Amount of $ your MD received in marketing incentives
  - Distance from specialized care facility (probability receiving specialized care)
  - Blood type (transplant waiting time)
- These are almost equivalent to IVs as we have discussed above.
- Economists used to think of these as separate – conceptualization merging.

Regression Discontinuity/Fixed Effects

- Caveat controversy over whether this is a valid DAG, so consider it a heuristic.

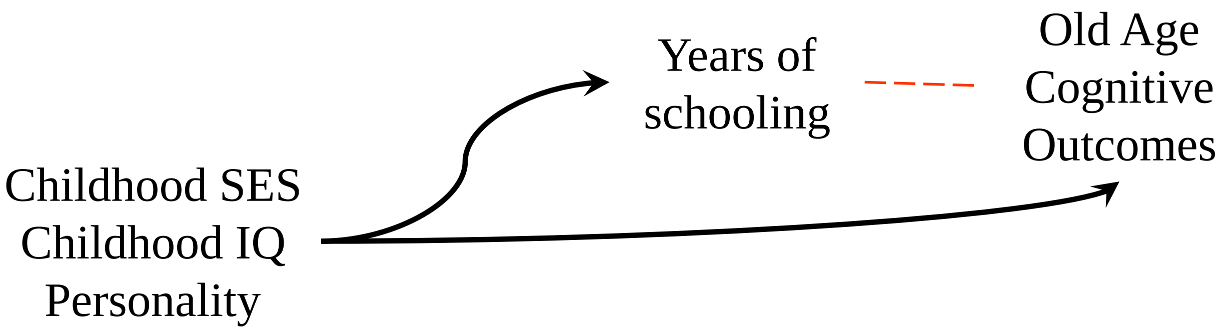


An example: CSLs and education

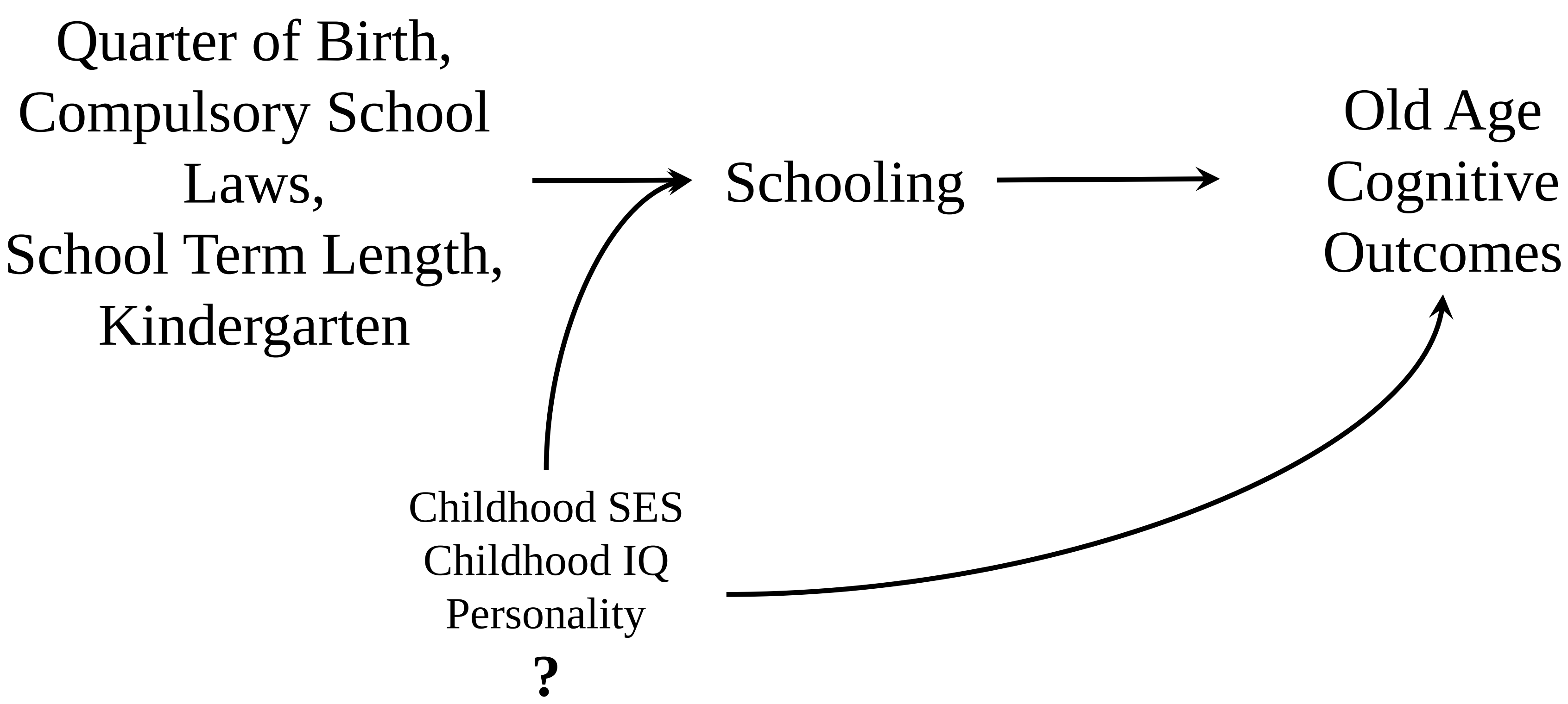
Substantive Question

Multiple studies show that years of education predicts old age cognitive function, cognitive change, and dementia.

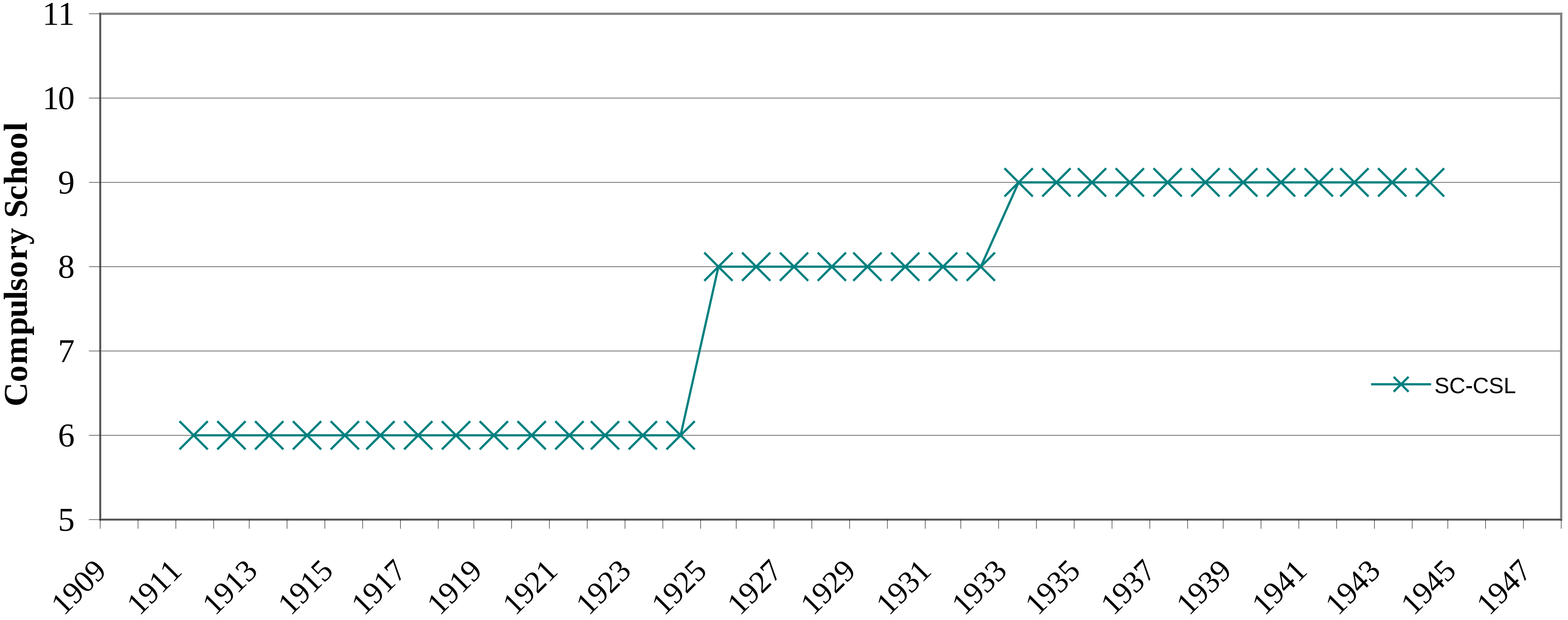
Causality questionable.



Natural Experiments for Education



Early 20th Century CSL Changes



Hypotheses

Variation in schooling is induced by CSLs, CSL-Ws

&

these instruments also predict old age cognitive test scores.

IV Analyses

- State schooling policies
  - Compulsory school to drop out (CSL) or receive a work-permit (CSL-W)
  - Based on policy in state of birth when school-age
  - 2-Sample least squares analysis
- Exposure (endogenous) variable:
  - Years of education (self-report)

Data Set: 1st Stage

- IPUMS (Census) 5% 1980 sample,
- Birth years 1900-1947
- Years of education linked to CSLs and CSL-Ws based on state of birth
- Link predictions from 1st stage regression model to individual data in the 2nd stage based on state of birth and all covariates.

Data Set: 2nd stage

- Health & Retirement Study, 1992-2000: panel enrollment by birth cohort (whites only due to evidence on enforcement)
- Cognitive assessments and state of birth on 21,041 individuals born 1900-1947
- CSLs and CSL-Ws

Two-Sample Least Squares

Sample 1:
5% Census sample.

CSLs in each state and year, 1906-1961.

Stage 1:
Regress education on CSLs, with other covariates.

Predicted education (Ê).

Sample 2:
HRS data.

Stage 2:
Regress health outcomes on Ê, with other stage 1 covariates.
Regression coefficient for Ê is the IV effect estimate.

Outcomes

- Immediate and delayed word list recall
  - Z-scores averaged over all years of interviews (1-5)
- Combined cognitive score
  - Modified telephone interview for cognitive status + serial-7 subtractions
  - Z-scores averaged over all years of interviews (1-4)

Covariates

1 - Unadjusted

- Sex

2 - Birthyear (indicators for every year)

- State of birth indicators

3

- State characteristics: age 6 % black, % urban, and % foreign born; age 14 manufacturing jobs
4 per capita and wages per manufacturing job

HRS Sample

	n	%
n	11,439	100
Male	4,862	43
Birth Year		
<1914	1,278	11
1914-1921	2,078	18
1922-1930	2,656	23
1931-1941	4,241	37
1942-1947	1,186	10
Years of schooling		
<6	308	3
6-8	1,706	15
9-11	2,677	23
12	6,719	59

Distribution of Instruments

CSLs

	n	%
Not Restricted	115	1
< 7 years	323	2
7 years	1,481	7
8 or 9 years	12,928	60
10 years	1,461	7
11 years	76	0
12 or more years	5,056	24

CSL-Ws

	n	%
Not Restricted	174	1
< 6 years	406	2
6 years	2,645	12
7 years	5,562	26
8 or more years	12,653	59

Social and Economic Characteristics of States

	CSL		CSL-W	
	rho	**p**	**rho**	**p**
% Urban at age 6	0.15	<0.01	0.11	<0.01
% Foreign-born at age 6	0.01	0.65	-0.10	<0.01
% Black at age 6	-0.09	<0.01	0.06	0.01
% Manufacturing jobs at age 14	0.05	0.02	0.07	<0.01
Manufacturing wages per job	0.38	<0.01	0.36	<0.01
CSL-W	0.49	<0.01	-	-

Do the Instruments Predict Education?

First stage regression results (from IPUMS 5% sample)

	1. Unadjusted Model	2. Birthyear and sex	3. Model 2 + state of birth	4. Model 3 + state condns
CSLs	0.238 (0.236, 0.240)	0.110 (0.108, 0.112)	0.062 (0.059, 0.064)	0.037 (0.034, 0.040)
CSL-Ws	0.143 (0.146, 0.141)	-0.032 (-0.034, -0.029)	0.063 (0.060, 0.066)	0.044 (0.040, 0.048)
CSL-Ws UNR	-1.397 (-1.429, -1.365)	-0.282 (-0.315, -0.249)	-0.204 (-0.238, -0.17)	0.034 (0.000, 0.069)

How Strong is the 1st Stage?

	1. Unadjusted Model	2. Birthyear* and sex.	3. Model 2 + state of birth indicators	4. Model 3 + state characteristics#
	β 95% CI	β 95% CI	β 95% CI	β 95% CI
Model r^2 without instrumental variables	0.0000	0.1080	0.1599	0.1626
Model r^2 including instrumental variables	0.0465	0.1127	0.1613	0.1631
Variance explained by instrumental variables	0.0465	0.0047	0.0014	0.0005

Not technically “weak” instruments, but clear that a small violation of the IV assumptions could introduce a large amount of bias.

IV Estimates for Education: CSLs

Estimated effect of 1 year ed'n on cognitive test scores.

Model covariates	Memory β_{IV}	Memory 95% CI^	Cognition β_{IV}	Cognition 95% CI^
1. Unadjusted	0.33	(0.27, 0.39)	0.19	(0.12, 0.26)
2. Birthyear, and sex	0.30	(0.14, 0.46)	0.34	(0.05, 0.63)
3. Model 2 + birth state	0.18	(0.02, 0.33)	0.03	(-0.22, 0.27)
4. Model 3 + state condns	0.34	(0.11, 0.57)	-0.06	(-0.37, 0.26)
5. OLS estimates	0.09	(0.08, 0.10)	0.15	(0.14, 0.16)

Sensitivity Analyses

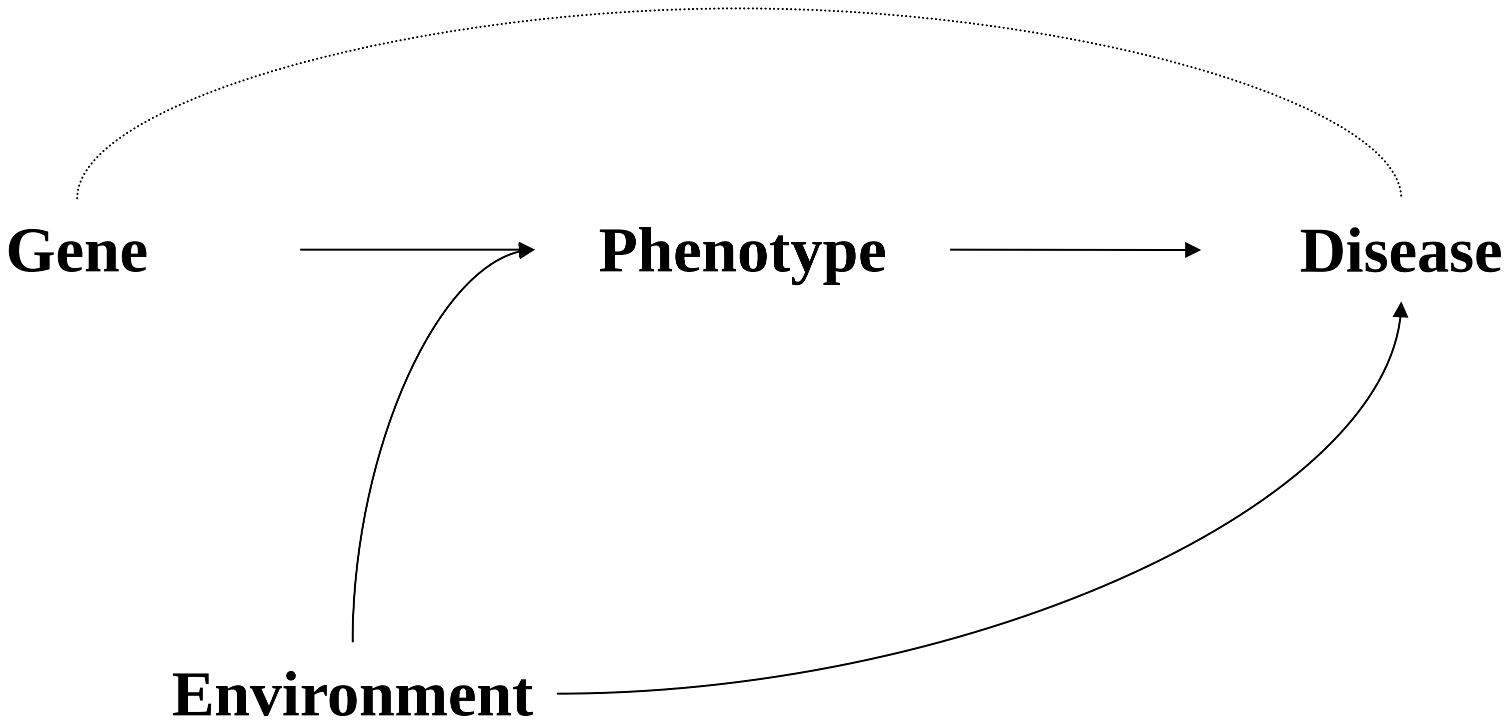
- Including education >13 years
  - β_{IV} (memory, model 3): 0.15 (-0.01, 0.31)
- Restricting to education > 13 years
  - Instruments do not predict education or memory for individuals with >13 years of school
  - β_{IV} (memory, model 3): -1.04 (-3.70, 1.62)
- Inverse probability weighted for missing Memory (parental SES, self-report chronic condns at baseline)
  - β_{IV} (memory, model 3): 0.19 (0.03, 0.36)

Conclusions

- CSLs and CSL-Ws applicable in state of birth predicted years of education completed.
- IV estimates of the effect of education on Memory score were significant and larger than OLS estimates.
- IV estimates of the effect of education on cognition were uninformative: CIs included OLS estimates and the null.
- Other state characteristics are plausible confounders, but must change in tandem with CSLs and affect only those with <13 years of education.

Mendelian Randomization

Mendelian Randomization & IV



Invalid Instruments in MR

- Canalization
- Pleiotropy

Direct pathways from the instrument to the outcome

- Population stratification
- Linkage disequilibrium

Common prior causes of the instrument and the outcome

Thinking of Instruments

- Often ecological
- Policy changes
- Policy discontinuities
- Differences in "expert" opinion
- Encouragement designs: randomize the incentive
- **Ask: What is the process that determines exposure? Is any part of this process arbitrary/random?**

Doubting Instruments

- Do they have other pathways to the outcome?
  - *Quarter of birth*
- Is there a common cause of the instrument and the outcome?
  - *State of birth*
- Do they actually affect anyone's exposure?
  - *Tax policies*

Conclusions

- Honest epidemiologists tend to be worried epidemiologists
- Abandon the difficult questions?
  - Or learn what we can from fraught methods?
- IV adds:
  - A way forward with observational data
  - Sometimes a parameter estimate of special interest
  - Pushes us to identify interventions that change exposures