



# Some Thoughts about the Merits of Observational Research

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# Data Quality And Research Design Are Related But Not Identical

- A Simple Hierarchy of Evidence
  - Randomized Trials
  - Quasi-Experimental Design
  - Observational data with no controls
- Everything else equal, randomized designs provide the most reliable evidence for drawing inferences irrespective of how we define the population in which we are estimating the treatment effect
  - e.g., carefully controlled trial for product approval or a pragmatic trial with no inclusion/exclusion criteria.

# Trouble is, everything else is rarely equal

- Inclusion/exclusion criteria of most trials define patient study cohorts who are very different from populations who actually end up taking the medications.
  - Irony of the selection bias issue.
  - Internal versus external validity
- Distorts payer decisions because efficacy and safety data from trials don't translate well to real-world
- Trials are often underpowered or too short in duration to detect rare safety events or economic endpoints.
- Often of limited use in evaluating how a product will perform in the real world

# Who are we talking about?

- Randomized designs don't necessarily guarantee that studies will produce results that drive the best policy development and treatment guidance
- In general, efficacy data from trials probably overstate real world efficacy and understate the size of populations that will ultimately utilize the medication. Not terribly informative from a payer perspective.
- On otherhand, randomized studies can be hugely influential—e.g., WHI study.

# Antidepressant Treatment in Adolescents

- Case control studies in the area of adolescent antidepressant treatment have been equally influential
- Several studies showing increased risk of suicidal ideation and suicide attempt resulted in FDA black box warning on antidepressants for children and adolescents

# Data Quality versus Study Design Again

- It's true that many observational studies make use of data collected for a different purpose and that can create some severe problems of missing variables that may be impossible to overcome.
- But there is nothing that prevents the collection of data elements in observational studies that are needed to answer a specific research question-e.g., clinical scores to measure differences in real world effectiveness of treatment.

# Statistical Analysis of Observational Data

- Good methods for developing well-matched control groups but no magic bullets--e.g., propensity score.
- These methods control only for observables.
- Do not control for endogeneity or confounding.

# The Problem of Endogeneity

- Endogeneity occurs when one or more regressors (independent variables) is correlated with the residual.
- Residuals capture effects of all omitted (or imperfectly measured) variables.
- Any correlation between a regressor and the residuals will introduce bias

# Some sources of endogeneity

- In outcomes research many equate endogeneity with the problem of sample selection bias
  - Omitted variables in treatment selection that are also correlated with outcomes
- In reality, problem is much broader in observational studies. Also includes
  - Measurement error
  - Simultaneity
  - Correct functional form, etc.

# Structural Simultaneity

Suppose drug use patterns affected the risk of hospitalization and that the converse was also true:

$$U = XB_1 + DB_2 + YB_3 + \varepsilon_1$$

$$Y = XC_1 + UC_2 + \lambda C_3 + \varepsilon_2$$

Where Y is hospitalization and U is drug use.

# Instrumental Variables

- We need to find an observable variable  $Z$  *not* in the outcome equation that satisfies two conditions:
  - $\text{Cov}(Z,u)=0$
  - $\lambda$  is not  $=0$
- Where  $\lambda$  is the partial correlation between  $Z$  and  $X_k$
- From the reduced form equation:

$$X_k = C_0 + C_1 X_1 + C_2 X_2 + \dots + C_{k-1} X_{k-1} + \lambda Z + \hat{e}$$

Wooldridge, J. 2002. *Econometric Analysis of Cross Section and Panel Data*. Cambridge, MA: MIT Press.

# Instrumental Variables Estimation

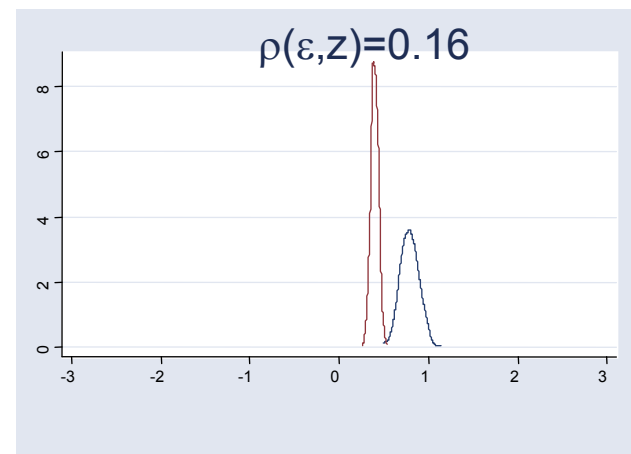
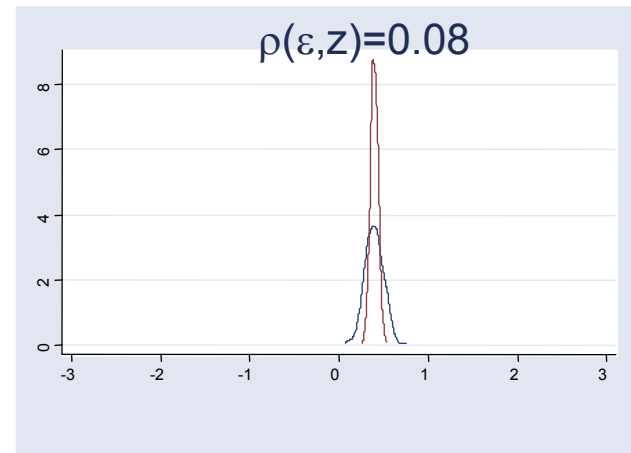
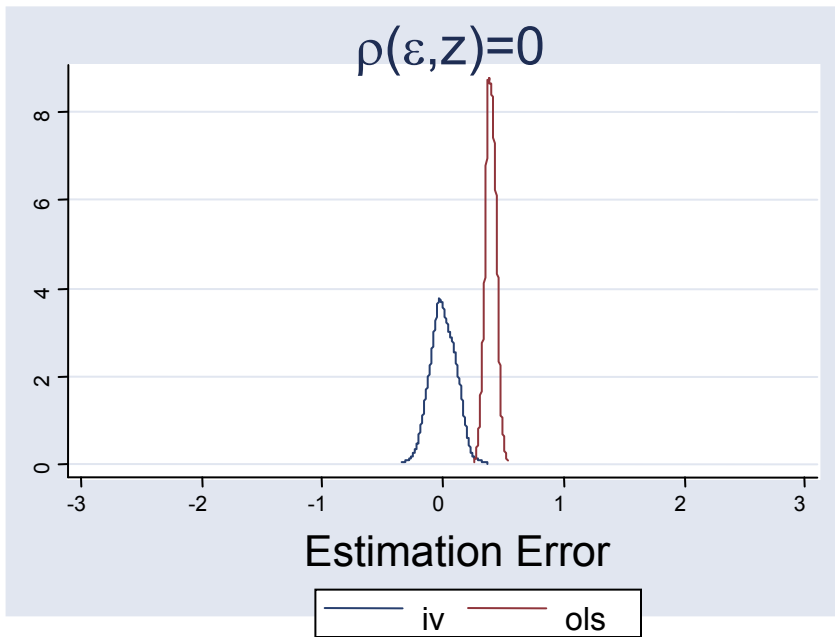
- Estimate the endogenous variable as a function of all exogenous variables—including those that are associated with the endogenous variable but not with outcomes.
- Substitute this reduced form into structural model for outcomes.
- This becomes reduced form for outcomes.
- Two Stage Least Squares (2SLS)
  - Most statistical packages have special commands for 2SLS
  - Avoid doing the second stage manually as standard error are not valid

# Instrumental Variables--Challenges

- Finding good instruments is really, really hard.
- What happens if the instruments are less than perfect?
  - Bound, Jaeger, and Baker, 1995
  - Henk, VanNess, Crown, 2007

# Distribution of Estimation Error

$\rho(T,z)=0.4$  &  $\rho(T,e)=0.4$ ,  $N=2000$



# Well-designed Observational Studies can Yield Results Similar to RCTs

- Benson K, Hartz AJ. A Comparison of Observation Studies and Randomized, Controlled Trials. N Engl J Med 2000; 342: 1878-86
- Concato J, Shah N, Horwitz RI. Randomized, Controlled Trials, Observation Studies and the Hierarchy of Research Designs. N Engl J Med 2000; 342: 1887-92

# Conclusions

- No doubt that RCTs are superior research design but:
  - Rarely conducted on real world patient populations.
  - Have selection bias issues of their own
  - Often too small or too short to detect safety events or health economic endpoints
- Observational studies conducted on convenience samples often need to confront serious endogeneity/confounding issues
- All of the fancy econometrics in the world cannot overcome lousy data.
- But carefully designed observational studies with good data can answer the *right* question if you are interested in treatment effects in real world practice.

# References

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- Olfson M, Marcus SC, Shaffer D. *Arch Gen Psychiatry* 2006 63: 865-872
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- Bound, J., D. A. Jaeger, et al. (1995). "Problems with instrumental variables estimation when the correlation between the instruments and the endogenous explanatory variable is weak." *JASA* 90(430): 443-450.