HPTN
HIV Prevention
Trials Network

Alternatives to Randomized Designs

Jim Hughes, PhD
SCHARP
HPTN Annual Meeting
April, 2017

Randomization

- Randomization "guarantees" that treatment and control groups are comparable
  - Individuals who select a treatment likely differ from those who don't ("confounding")
  - Provides estimate of causal effect
- Provides appearance of "fairness"

Randomization

- Not always possible to randomize
  - Unethical
  - Not feasible (e.g. intervention widely available)
  - Control group “unacceptable”
- Concerns about external validity of RCT
  - Trial participants are a selected group
  - May be more relevant for behavior interventions

Instrumental Variable

- Requires an “instrument” that affects intervention but not outcome (except through intervention);

$$Z \rightarrow T \rightarrow Y$$

  - The stronger the relationship between the instrument and intervention, the better
  - E.g. Smoking and health - tax rate on tobacco products may be an instrument

Instrumental Variable

Example (Oster, 2012, *J Health Economics*)

- **Question**: What is the relationship between HIV prevalence and sexual risk behavior in Africa?
  - Prediction: high HIV prevalence should lead to less risky sexual behavior
  - Observed: high HIV prevalence positively correlated with risky behavior (reverse causality?)
- **Instrument**: Distance from origin of HIV epidemic
  - Areas further from origin should have lower prevalence
- **Model**: Distance $\rightarrow$ Prevalence $\rightarrow$ Behavior
- **Results**: Using Distance as an IV, Oster found a negative relationship between HIV prevalence and risky sexual behavior

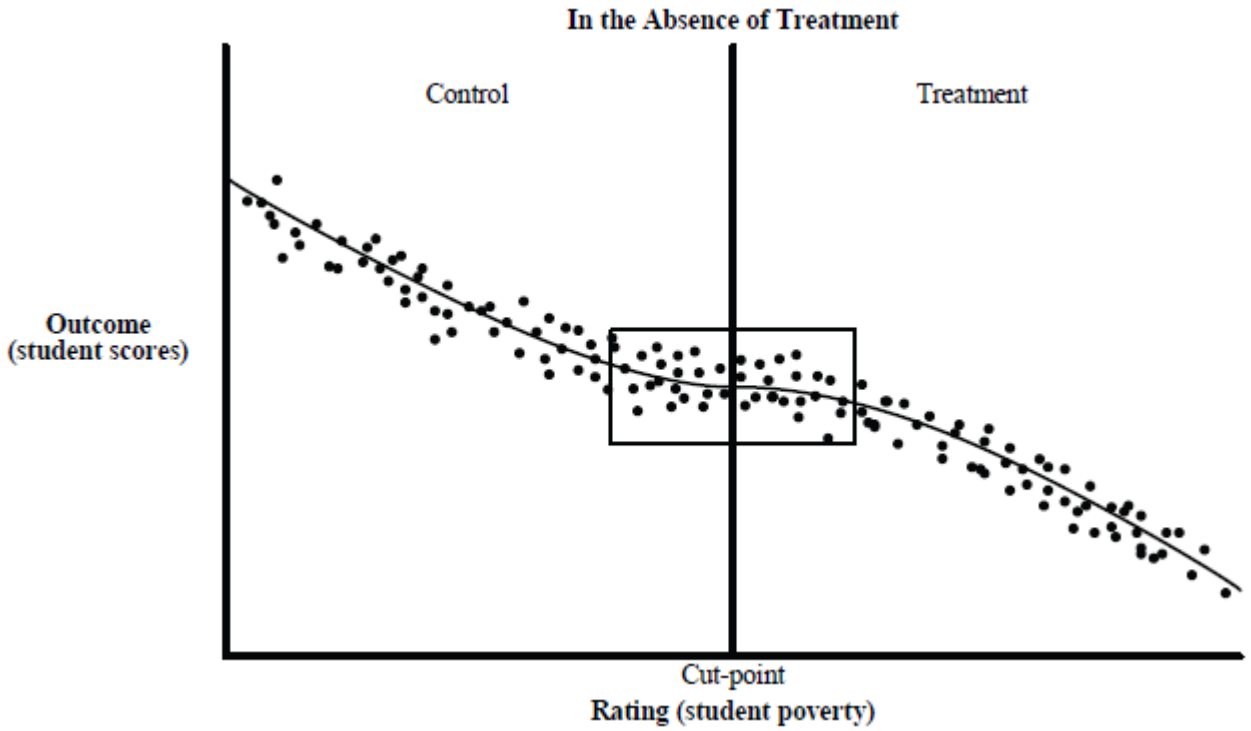
Instrumental Variable

- Requires detailed specification of causal diagram
- Instrumental variable often not available
  - Randomization is an ideal instrument!

Regression Discontinuity

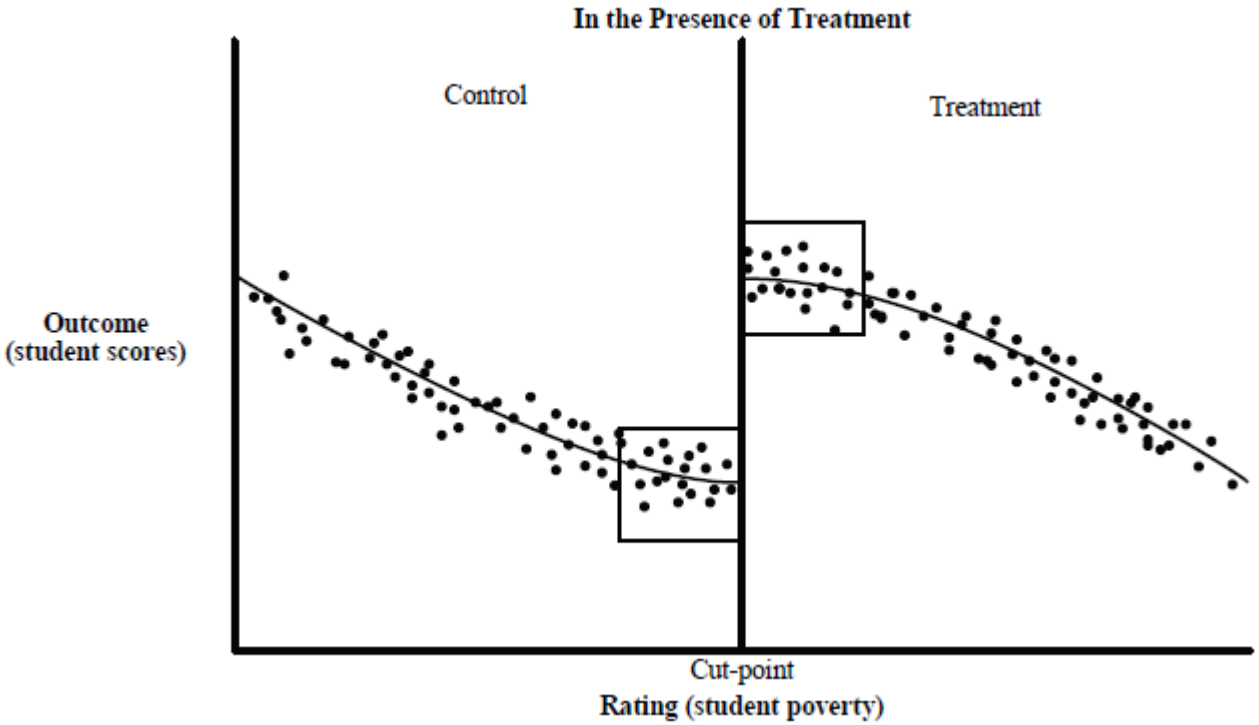
- Individuals assigned to treatment based on cut-off value of an “assignment score”
  - e.g. students with scores below a threshold on test receive remedial instruction
- Measure outcome
- Regress outcome on assignment scores
- Treatment effect is measured by a discontinuity in the regression line at the cutoff

REGRESSION DISCONTINUITY



Jacob R and Zhu P. A Practical Guide to Regression Discontinuity.

REGRESSION DISCONTINUITY



Jacob R and Zhu P. A Practical Guide to Regression Discontinuity.

Regression Discontinuity

- Assumptions:
  - Assignment score not influenced by treatment
  - Cut-point determined a priori
  - Treatment is the only factor that differs above and below cutpoint (control for other covariates possible)
  - Relationship between assignment score and outcome is continuous and correctly specified.

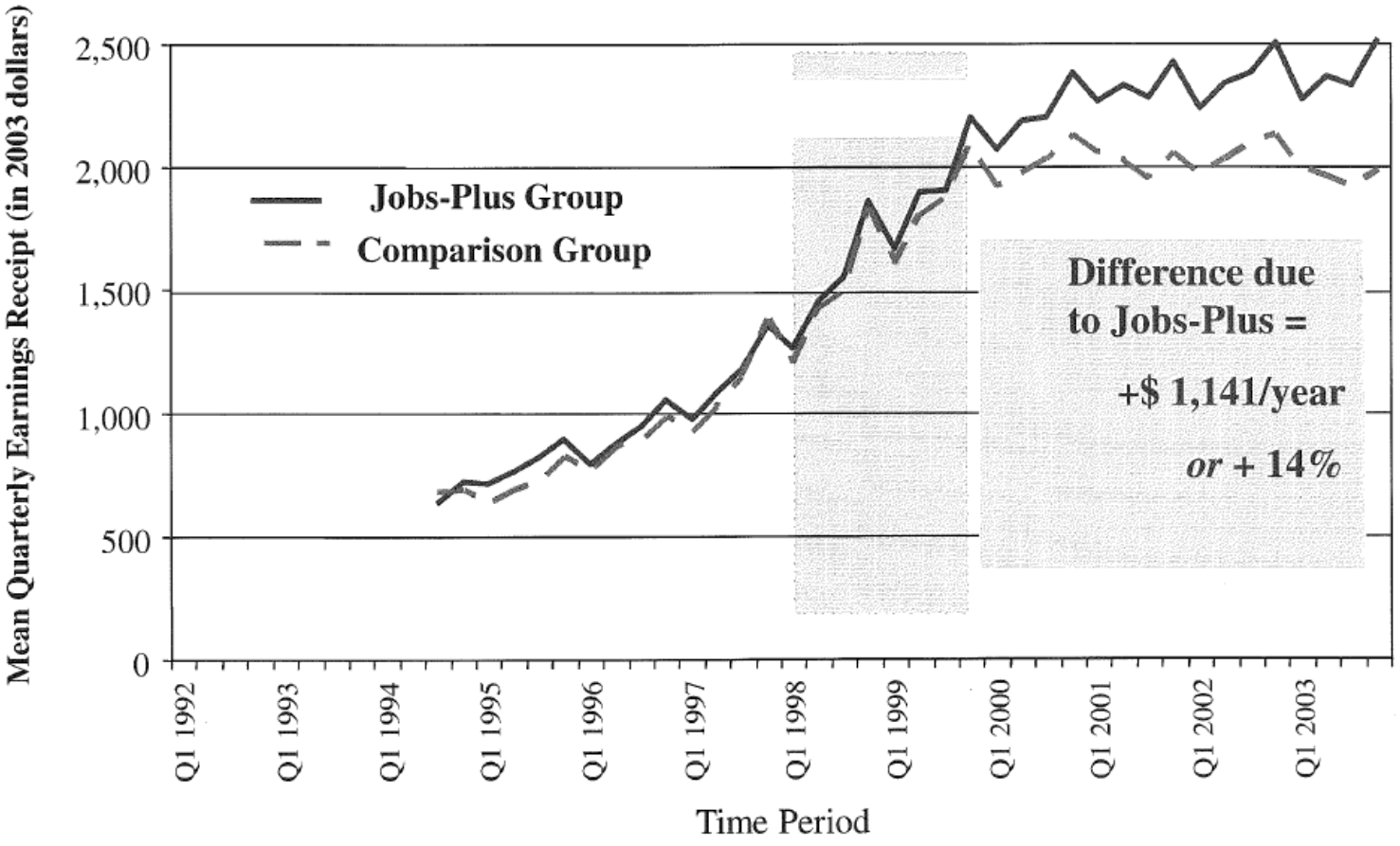
Regression Discontinuity

- Choose cutoff so it is “policy-relevant”
  - Treatment effect estimate may only be applicable to individuals with scores near the cutoff
- Strengthen design by adding a comparison group i.e. measure assignment score and outcome but don’t give intervention

Interrupted Time Series

- Compares values of an outcome before and after an intervention
  - e.g. Compare average earnings before and after job training program
- Useful for evaluating policy changes
- Strengthen design by adding comparison group where intervention was not applied

INTERRUPTED TIME SERIES



Bloom, H. A Short Comparative Interrupted Time-Series Analysis of the Impacts of Jobs-Plus

Interrupted Time Series

- Requirements
  - Outcome is measured consistently over time
  - Sufficiently long, stable baseline period
  - Impact of intervention is immediate
  - Other factors not changing during followup period

Interrupted Time Series

- May be used prospectively or retrospectively
- Often relies on administrative data
  - Aggregate or individual level
- Covariate adjustment may be used to account for changes in sample composition over time

Comparison Group

- Key idea: Compare outcomes in an intervention group to outcomes in a comparison group that did not receive intervention
- Need to ensure intervention group and comparison group are as similar as possible on baseline characteristics
  - Matching
  - Weighting (e.g. propensity score)
  - Regression adjustment

Comparison Group

- Key assumption: “No unmeasured confounders”
  - No differences between intervention and comparison groups (wrt factors affecting outcome) after balancing/adjusting for observed characteristics
- Assume that all participants COULD have received intervention or control
  - Exclude individuals not eligible for intervention

Comparison Group

Example (Donnell et al., 2010, *Lancet*)

- Compare (linked) HIV transmissions in discordant couples by ART status of HIV+ partner
  - ART not randomized
  - Those receiving ART tended to have lower CD4 levels
- Use regression adjustment
  - Unadjusted RR = .17
  - Adjusted RR = .08

Comparison Group

- Important considerations
  - Select comparison group carefully; understand why individuals did/did not get intervention
  - Measure variables same way in intervention and control groups
  - Large sample size in comparison group makes balancing easier
  - Do not adjust for/match on post-intervention measures

Summary

- Randomize when possible
  - Provides guarantee against confounding
  - Don’t dismiss randomization because it is “hard”
- All non-randomized designs involve untestable assumptions
  - Confounding is the major concern; measure as many potential confounders as possible
  - Understand the intervention assignment process
  - Assess sensitivity to assumptions

HPTN
HIV Prevention
Trials Network

ACKNOWLEDGEMENTS

The HIV Prevention Trials Network is sponsored by the National Institute of Allergy and Infectious Diseases, the National Institute of Mental Health, and the National Institute on Drug Abuse, all components of the U.S. National Institutes of Health.

Instrumental Variable

Example

- Preschool children encouraged to watch Sesame Street, or not (randomly assigned)
- Outcome: Letter recognition test
- Results:
  - 45% of not encourage watch; average test score 73
  - 80% of encouraged watch; average test score 76
- ITT: 76 – 73 = 3 point ↑ due to encouragement
- IV: 3/.35 = 8.6 point ↑ due to Sesame Street

INTERRUPTED TIME SERIES