Extended Instrumental Variables Methods

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Introduction

- Definition
  - Estimation of effects based on
    - Complex ordered systems of variables
      - Most naturally depicted graphically
    - Effects based on combination/integration of effects from component parts
    - Instrumental variables (IV) used to estimate (some of) component effects

Overview

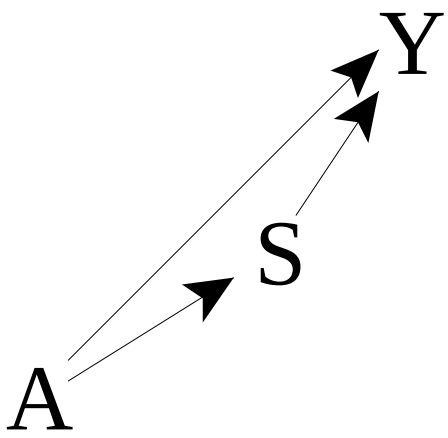
- Motivating example
  - Vascular access (VA) in hemodialysis
- Show relationships among variables
  - Explain why IV methods inadequate
- Sketch alternative approach(es)
- Alternative estimands
- Other examples: gene expression
- Mediation analyses
- Further work/extensions

Vascular access in hemodialysis

- Hemodialysis
  - One of main treatment options in end-stage renal disease (ESRD)
  - Requires access to vascular system
- Three main types
  - Catheter
  - Synthetic material
  - Native arteriovenous fistula (AVF)

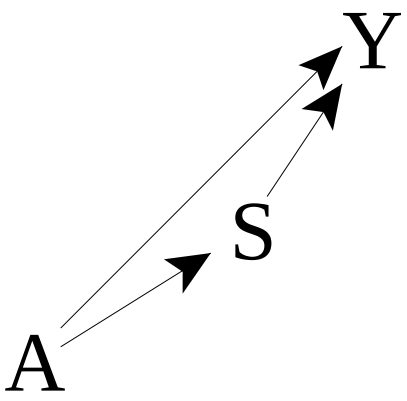
Vascular access (cont'd)

- Type of VA (*A*) partially determines dose of dialysis (DD; *S*)
  - Native AVF allows larger doses than catheter
  - DD may affect outcomes (e.g., mortality)
- VA may have effects on outcome (*Y*) not mediated by dose (e.g., infection)
- Incomplete directed acyclic graph (DAG) of key variables



Estimand of interest

- To gauge impact of type of VA, interested in overall effect
  - Involves both
    - Direct effect (*A->Y*)
    - Indirect effect (*A->S->Y*)
- Formulate in terms of potential outcomes:



Y^{a}

$$Y^{a_1} - Y^{a_0} \quad \text{singly indexed}$$

$$= Y^{a_1 S^{a_1}} - Y^{a_0 S^{a_0}} \quad \text{doubly indexed}$$

$$\text{direct effect:} \quad Y^{a_1 S^{a_0}} - Y^{a_0 S^{a_0}}$$

$$\text{indirect effect:} \quad Y^{a_1 S^{a_1}} - Y^{a_1 S^{a_0}}$$

Confounding by indication

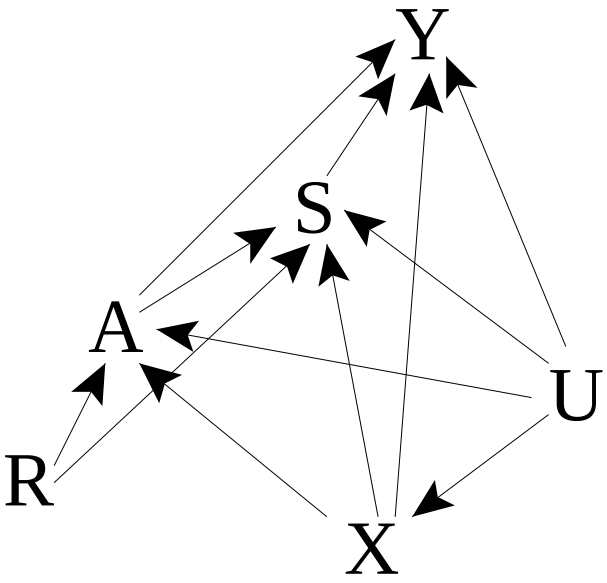
- AVFs given preferentially to healthier subjects
- Results in confounding by indication
  - Often difficult to control using standard methods based on ignorable treatment assignment
  - Variety of treatments of dialysis patients in which standard approaches based on ignorability lead to implausible results
- DD choice also nonignorable

Instrumental variables

- Alternative approach for estimation
- Need to find instrumental variable (*R*)
  - Associated with treatment of interest (*A*)
  - Shares no common cause with outcome (*Y*)
  - Has no direct effect on outcome (exclusion restriction)
- Practice at which dialysis provided reasonable candidate
  - Used for various analyses in Dialysis Outcomes and Practice Patterns Study (DOPPS)
    - Large, international study with hundreds of practices
- Will assume that holds jointly for VA, DD

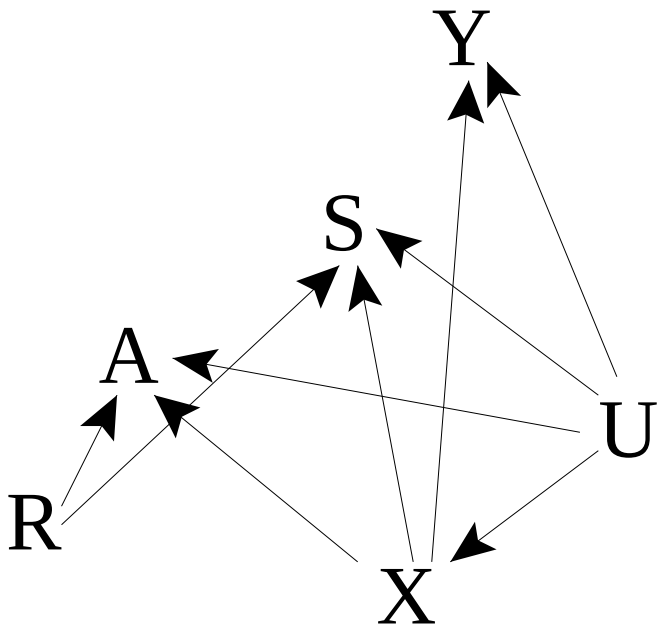
Revise DAG

- Need to elaborate DAG
- Include
  - instrument/center (*R*)
  - Measured (*X*) and unmeasured (*U*) common causes of variables of interest
- Is *R* an instrument?



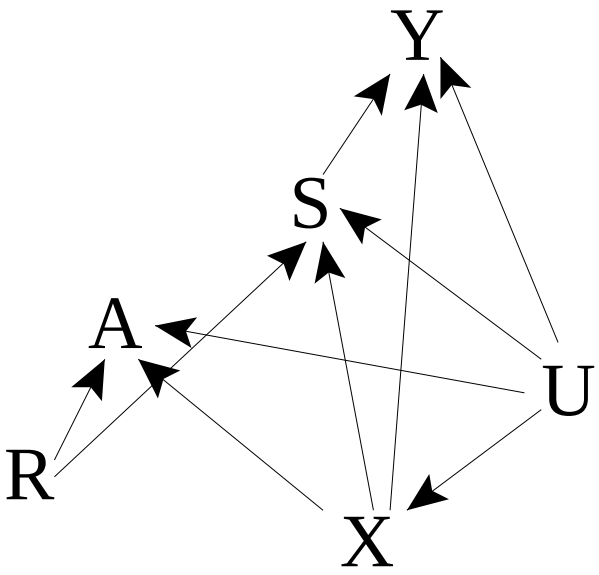
Graphical criteria for instrument

- Remove effect of treatment(s) of interest
- Check whether *R* independent of/D-separated from *Y*
- Consider first for joint effects of *A*, *S*
- No directed path from *R* to *Y*
- Criterion satisfied



Overall effect of VA

- Remove effect of treatment of interest
- Check whether *R* independent of/D-separated from *Y*
- Directed path *R->S->Y*
- Criterion not satisfied
- Upshot: *R*
  - Not instrument for overall effect of *A*
  - Instrument for joint effects of *A*, *S*

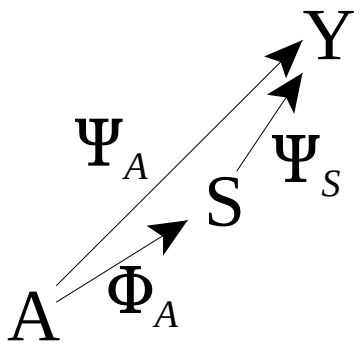


Estimation

- For overall effects, can't use
  - Standard methods based on ignorability
  - Instrumental variables methods
- Sketch two approaches for estimation
  - Two-step (based on above graphs)
  - One-step (simplify graphs, remove *S*)
  - Compare approaches/extensions

Two-step approach

- Estimate joint effect of *A*, *S* on *Y*
- Estimate effect of *A* on *S*
- Combine to obtain overall effect
- In systems of linear models, overall effect is sum of
  - Direct effect of *A*: ψ_A
  - Indirect effect of *A*: $\psi_S \Phi_A$



Two-step approach (1st step)

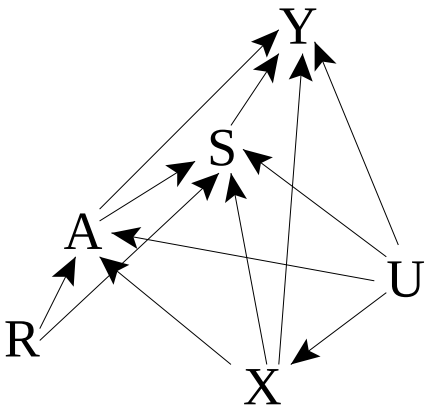
- Center (R) instrument for joint effect of A, S
- Use IV method to estimate effect
- Y^{as} potential outcome
- Model for joint effect:
  - $Y^{as} = Y^{00} + a\psi_A + s\psi_S$
  - Rank-preserving/deterministic formulation
- Model for observables
  - $E(Y|X,R) = E(Y^{AS}|X,R) = E(Y^{00}|X,R) + E(A|X,R)\psi_A + E(S|X,R)\psi_S = g(X) + E(A|X,R)\psi_A + E(S|X,R)\psi_S$

Two-step approach (1st step; cont'd)

- Estimation:
  - Model:
    - $E(Y|X,R)=g(X)+E(A|X,R)\psi_A+E(S|X,R)\psi_S$
  - 2-stage least squares
    - Estimation requires that $E(A|X,R)$, $E(S|X,R)$, $g(X)$ not collinear
  - Maximum likelihood
  - G-estimation (semiparametric); leave $g(X)$ unspecified

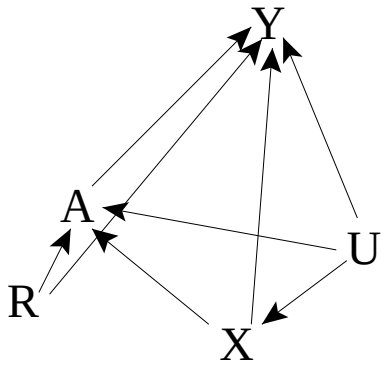
Two-step approach (2nd step)

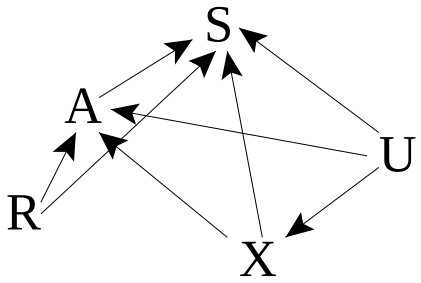
- Under assumptions
  - Effect of *A* on *S* confounded
  - *R* not instrument for effect of *A* on *S*
- Consider alternative
  - Linear model for joint effect of *R*, *A*
  - $S^{ra} = S^{00} + r\Phi_R + a\Phi_A$
- Model for observables
  - $E(S|X,R) = E(S^{00}|X) + R\Phi_R + E(A|X,R)\Phi_A$
- Estimation: 2SLS, G-estimation, etc.
- 2SLS requires full-rank design matrix
- Estimation sensitive to causal model misspecification (interactions of *X* with *A*, *S*)



One-step approach

- Estimator of effect of *A* on *S* does not require either standard ignorability or IV
- Can we do same for overall effect of *A* on *Y*?
- Remove *S* from graph, redraw diagram
- Graph identical to original graph removing *Y*
- Use same methods of estimation for effect of *A* on *S*





Compare approaches

- Both make no-interaction assumptions
- One-step approach
  - Simpler to apply
  - Fewer models to misspecify
- Two-step approach
  - Effect of misspecification of non-IV model potentially less serious
  - Mechanistic understanding
  - Alternative estimands

Alternative estimands

- Assumed that interested in overall effect
  - VA (*A*) inevitably affects DD (*S*)
    - Type of VA limits possible dose
- However, may be possible to alter DD
- Interested in
  - Effect of DD
  - Effect of VA if affects DD in different fashion from under current practice

Alternative estimands (cont'd)

- Show altered effect, new intervention on DAG
- Formulate in terms of potential outcomes

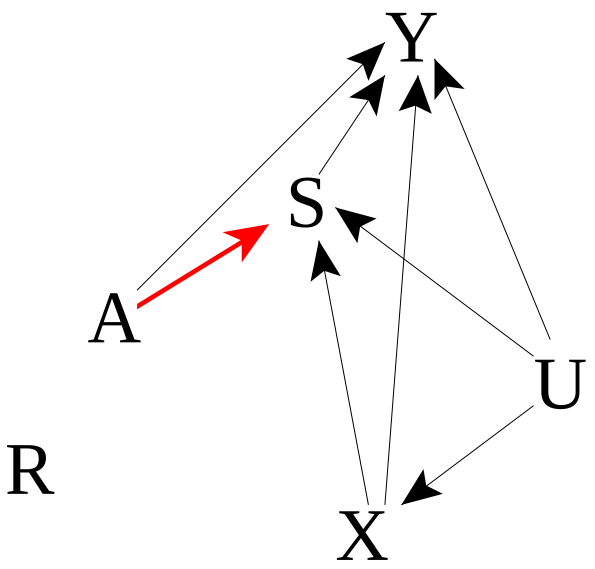
  $S^{g,a}$ target level of S

  under treatment a, plan g

  $E(Y^{aS^{g,a}})$ expected of Y level

  under treatment a, plan g

- Contrast for different levels of treatment



Alternative estimands (cont'd)

- Defining intervention on *S*
  - Individualize target levels of *S*
    - e.g., base on maximum tolerated DD
    - Insufficient information in established databases (e.g, DOPPS)
  - Set target level of *S* based on *A*, covariates *X*
    - Currently little information to set target levels
    - Available covariate information may be insufficient to determine whether particular DD feasible for individual

Alternative estimands (cont'd)

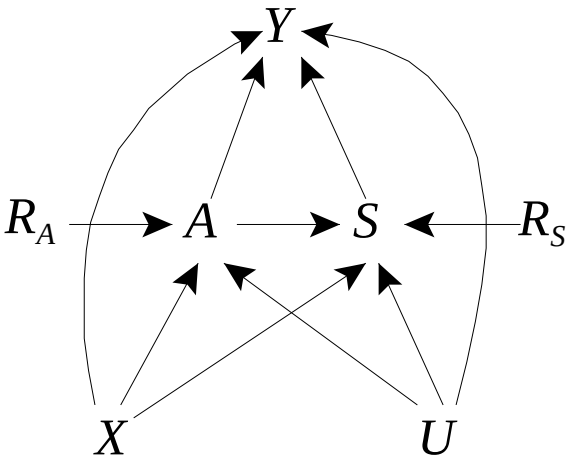
- Defining intervention on *S*
  - Speculate about feasible interventions on *S* at aggregate level
    - Consider effects of *A* on *S* under those interventions; i.e., propose value for Φ_S^*
    - Compute overall effect from component effects: $\psi_A+\psi_S\Phi_A^*$
    - Perform sensitivity analysis for values of Φ_A^*

Alternative estimands (cont'd)

- Intervene jointly on *A*, *S*
- Akin to search for optimal dynamic treatment regime (Murphy, Robins, etc.)
  - Search for *a*, *s* which maximizes Y^{as}
    - Choice of optimal treatment may depend on prior covariate, treatment history
  - Less information available in our problem
  - Challenge to people working with dynamic regimes to formalize problem
- Two-stage approach facilitates
  - Facilitates mechanistic understanding & thereby
  - Examination of broader range of questions, estimands

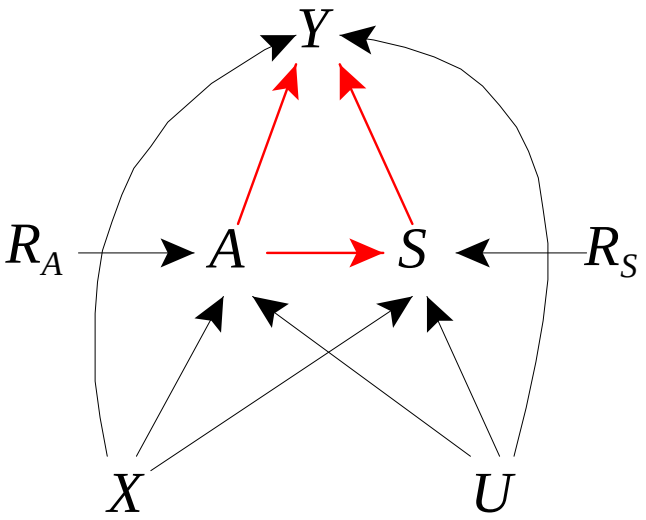
Other settings: gene expression

- Effects of multiple genes on outcomes
- R_A, R_S genes
  - presumed to share no common causes with other variables
    - Mendelian randomization
- A, S biochemical variables, gene products
- Y outcome of interest
- X, U confounders of A,S



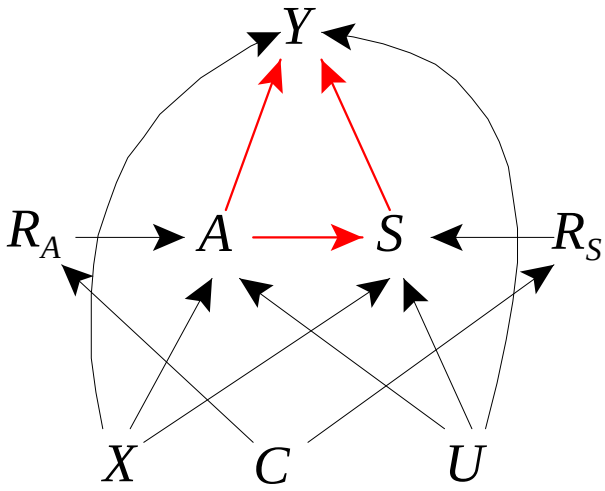
Gene expression (cont'd)

- R_A instrument for A (and S)
- R_S instrument for S
- R_A, R_S instrument for joint effects of A, S
- Effects of A, S confounded
- Can use IV methods to estimate
  - Component, joint effects, overall effect (2-step approach)
  - Overall effect of A (1-step approach)



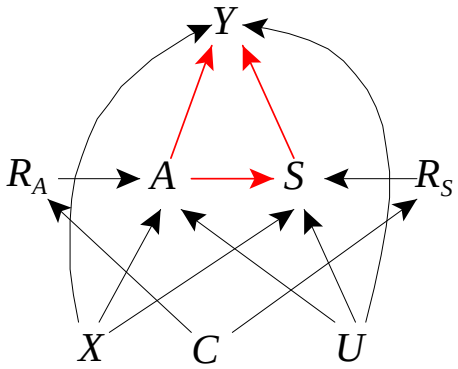
Gene expression (cont'd)

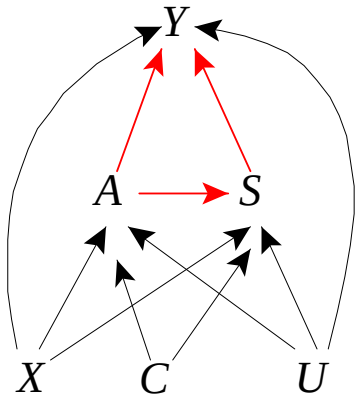
- Suppose genes not independent
  - Linkage disequilibrium
  - On same chromosome (*C*)
- R_A instrument for effect of *A* (on *S*, overall on *Y*) and *S* conditional on R_S or *C*
- R_S instrument for *S* conditional on R_A or *C*
- R_A, R_S (or R_A, C, or R_S, C) jointly instrument for joint effects of *A*, *S*
- Can use IV methods to estimate
  - Component, joint effects, overall effect (2-step approach)
  - Overall effect of *A* (1-step approach)



Gene expression (cont'd)

- Suppose further that only C (or only R_A or R_S) measured
  - Typically don't measure all genes on chromosome (tag-SNPs)
- Remove unmeasured genes (R_A, R_S) from graph, redraw
- Same structure as original graph for VA (substituting C for R)





Gene expression (cont'd)

- Same methods of inference valid in principle for gene expression, VA
- Difference:
  - VA problem: center (R) had many levels
  - Gene expression: may have more limited variation in measured levels of C
- Model for observable Y:
  - $E(Y|X,R)=g(X)+E(A|X,R)\psi_A+E(S|X,R)\psi_S$
  - Require full rank design matrix, noncollinearity
    - If R/C has 2 levels, require X to be non-null, interactions of R, X in models for A, S
    - If R/C has many levels, don't in general require
    - If few levels of R/C, expect intermediate
      - Need to formalize

Mediation

- Basic ideas
  - Break down effects into component parts, mechanistic understanding
  - Encompasses
    - Direct effects
    - Indirect effects
    - Overall effects
    - Joint effects
  - Naturally expressed graphically; useful for
    - Expressing relationships among variables
    - Deriving (conditional) independencies implied by assumptions

Limitations of graphical approach

- Does poor job of representing interactions
  - Can lead to casually assuming no interactions
    - Typical in path analytic literature
- Typically do not formally define causal estimands
  - Require more explicit consideration of (hypothetical) interventions, potential outcomes

Interactions

- No-interaction assumptions in models
  - $Y^{as} = Y^{00} + a\psi_A + s\psi_S$
  - No interaction of
    - *a* and *s*
    - *a* and *X*
    - *s* and *X*
    - Individuals and effects of treatment
    - Treatment(s) received and effects of treatment(s)
  - Consider in turn

Interactions among model variables

- Elaborate model $Y^{as} = Y^{00} + a\psi_A + s\psi_S$
  - $Y^{as} = Y^{00} + aq_1(X)\psi_A + sq_2(X)\psi_S + as\psi_{AS}$
- Model for observables
  - $E(Y^{as}|X,R)$ $= E(Y^{00}|X) + E(A|X,R)q_1(X)\psi_A + E(S|X,R)q_2(X)\psi_S$ $+ E(AS|X,R)\psi_{AS}$
  - Can estimate with 2SLS, etc.
  - Requires design matrix in regression be full rank
  - May require interactions in 1st stage models

Other interactions (1)

- Model as formulated: $Y^{as} = Y^{00} + a\psi_A + s\psi_S$
- Effect of *a*, *s* same for all subjects
  - Deterministic effects/rank-preservation
- Assumptions can be relaxed
  - Structural nested distribution models (Robins)
    - Maps distributions of potential outcomes under different treatments
    - Rank preservation imposes no restrictions on observable data beyond model
  - Structural nested mean models (Robins)
    - Weaker models/fewer assumptions
- Can continue using same estimation procedures

Other interactions (2)

- Treatment(s) received and effects of treatment(s)
- Have assumed no interaction
- Current treatment interaction (Robins) for *s* (in mean model):
  - $E(Y^{As}|X,A,S=s)-E(Y^{A0}|X,A,S=s) - E(Y^{As}|X,A,S=s^*)-E(Y^{A0}|X,A,S=s^*)$
  - Need to make untestable assumptions about this in order to predict what would happen if set *S* for all subjects
- Careful consideration of how treatment effects vary with subgroups important
  - also done (in finer partition of data in principal stratification framework)

Interactions in 2-step procedures

- Covariate (X) by treatment (a,s) interactions
  - ψ_{AX} effect of A on Y at covariate level X (etc.)
  - Easy to estimate X-specific overall (indirect) effects $\psi_{AX}+\psi_{SX}\Phi_{AX}$ ($\psi_{SX}\Phi_{AX}$)
  - Aggregate/average effects: average over distribution of X

Interactions in 2-step procedures (2)

- Interactions of *A* by *S*
  - Overall effect uniquely defined
    - $\psi_A+(\psi_S+\psi_{AS})\Phi_A+S^0\psi_{AS}$
  - Direct/indirect effects not uniquely defined
    - Can compute from model
- Further developments needed for
  - Non-rank-preserving models
  - Presence of current treatment interaction

Other issues

- Models/extensions already considered in some details
  - Failure-time outcomes
  - Time-varying *S*
- Extensions required
  - Binary outcomes (e.g., logistic regression, etc.)
  - More general nonparametric formulation of
    - problems
    - estimation procedures

Acknowledgements

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- Discussions with:
  - Mike Elliott
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Papers

- Joffe, M. M., Small, D., Brunelli, S., Ten Have, T., and Feldman, H. I. (2008), "Extended Instrumental Variables Estimation for Overall Effects," *International Journal of Biostatistics*, 4.
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Papers (cont'd)

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