EPID 765
Pharmacoepidemiology

Lesson 10

Instrumental Variables

(some slides adapted from Alan Brookhart)

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Motivating Example:
Observational Study of Non-steroidal Anti-Inflammatory Drugs and GI bleeding risk in an elderly population

- Compare short-term risk of GI outcomes between
  - COX-2 selective NSAIDs
  - Non-selective NSAIDs
- Coxibs are slightly less likely to cause GI problems
- Coxibs are likely to be selectively prescribed to patients at increased GI risk
- Classic problem: confounding by indication

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Characteristics of Medicare New User Cohort

Variable	Coxib	NS NSAID
Female Gender	86%	81%
Age > 75	75%	65%
Charlson Score>1	76%	71%
History of Hospitalization	31%	26%
History of Warfarin Use	13%	7%
History of Peptic Ulcer Disease	4%	2%
History of GI Bleeding	2%	1%
Concomitant GI drug use	5%	4%
History GI drug use	27%	20%
History of Rheumatoid Arthritis	5%	3%
History of Osteoarthritis	49%	33%

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Unmeasured Indications for COX-2 Treatment

- Cox-2 selectively prescribed to patients at risk of GI complications
- Many GI risk factors are unmeasured in health care claims data files
  - Tobacco use
  - BMI / Obesity
  - Alcohol consumption
  - Aspirin & warfarin use
  - Complaints to MD about stomach problems

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What Can We Do About These?

- Sensitivity analysis
  - Requires assumptions about distributions of unknown confounders
- External adjustment, two-stage designs, multiple imputation, propensity score calibration
- Instrumental variable methods

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Natural Experiment / Instrumental Variable (IV) Methods

- Natural experiment creates an allocation of exposure similar to a randomized study
- IV can be used to bound and estimate treatment effects in the presence of a natural experiment (even when confounders are unmeasured)
- IV methods depend on the existence of an instrumental variable ("instrument")

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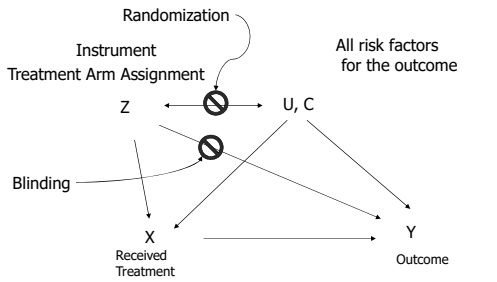
Causal Diagram of Structural Instrumental Variable Assumptions

Example: Randomized Controlled Trial with Non-Compliance



Note: Z can be a valid IV under less restrictive conditions

Note 2: Double headed arrow represents association due to direct causal relation between Z -> C or C <- Z or an assoc. due to a common cause

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IV Assumptions Informally

- Instrument should affect treatment
- Instrument should affect outcome only through its effect on treatment (exclusion restriction)
  - Empirically unverifiable, but can be explored in observed data

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Classic IV estimator is a rescaled ITT estimator

$$\hat{\alpha}_{IV} = \frac{\hat{E}[Y \mid Z=1] - \hat{E}[Y \mid Z=0]}{\hat{E}[X \mid Z=1] - \hat{E}[X \mid Z=0]}$$

Y is outcome
Z is instrument
X is received treatment

- Numerator is the intention to treat (ITT) estimate of the risk difference
- Denominator is estimate of the effect of the instrument on treatment on the risk difference scale

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Heterogeneous Treatment Effects

- IV estimate does not always generalize to the entire population
- Under 'monotonicity', IV estimates the average effect of treatment in the
  - Compliers
  - 'Marginal' patients
  - Those whose treatment would be affected by IV
  - These are unidentifiable!
  - But their characteristics can be described

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Physician as IV

- Coxib prescribing is driven strongly by MD preference (Solomon DH, et. al. 2003)
- Implication: Some patients would be treated with coxibs by some physicians and with non-selective NSAIDs by others
- Differences in coxib prescribing patterns across physicians is the **natural experiment** that we exploit

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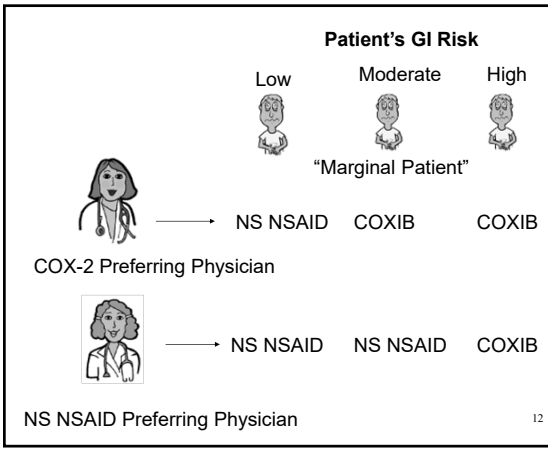

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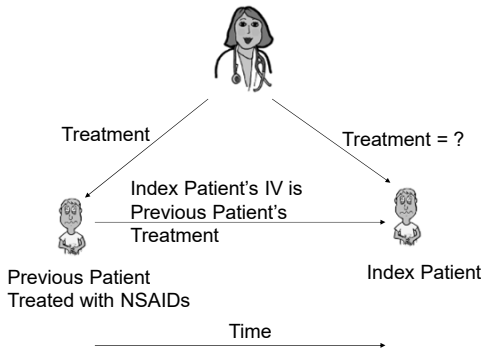

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Instrument should be unrelated to observed patient risk factors

Variable	Coxib Pref Z=1	NS NSAID Pref Z=0
Female Gender	84%	84%
Age > 75	73%	72%
Charlson Score > 1	75%	73%
History of Hospitalization	29%	27%
History of Warfarin Use	12%	10%
History of Peptic Ulcer Disease	3%	3%
History of GI Bleeding	1%	1%
Concomitant GI drug use	5%	5%
History GI drug use (e.g., PPIs)	25%	24%
History of Rheumatoid Arthritis	4%	4%
History of Osteoarthritis	45%	41%

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Instrument should be related to treatment

Last NSAID Prescription (IV)	Current Prescription (Actual Treatment)	
	Coxib X=1	**Non-Selective NSAID X=0**
Coxib Z=1	(73%)	(27%)
Non-Selective NSAID Z=0	(50%)	(50%)

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IV estimate of the effect of coxib vs. NSAID on GI outcome

$$\frac{E[Y|Z=1]-E[Y|Z=0]}{E[X|Z=1]-E[X|Z=0]} = \frac{-0.21\%}{22.8\%} = -0.92\%$$

- Numerator is the intention to treat (ITT) estimate of the risk difference
- Denominator is estimate of the effect of the instrument on treatment on the risk difference scale

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Other Examples of Preference-Based IVs

- Explicit clinician preference (Korn, Stat. Sci.)
- Clinic, hospital as IV (Johnston, J Clin Epi)
- Geographic region as instrument (Wen, J Clin Epi, Brooks et al, HSR, Stuckel T, et. al JAMA)
- Dialysis clinic

-> All attempt to estimate treatment effects by using difference in practice patterns as a quasi-experiment

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Other Potential IVs

- Calendar time
  - Policy or formulary changes
  - Guideline changes
  - Regulatory (black box) warnings
  - Rapid diffusion after approval
- Designed delays (Maclure M., et al)

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Calendar Time IVs

- New chemotherapy (FOLFOX) shown to be superior to standard therapy (5-FU) in patients with stage III colon cancer
- New therapy more aggressive (neutropenia, neuropathy)
- Few patients over age 75 enrolled in RCT
- Majority of patients with stage III colon cancer older adults (age > 70)
- CER in older adults important, but likely confounding by frailty

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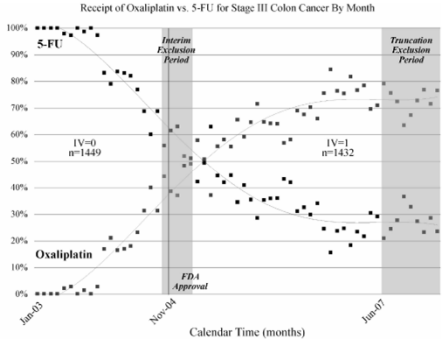
Switchover of Standard Treatment



Mack CD, Brookhart MA, Glynn RJ, Meyer AM, Carpenter WR, Sandler RS, Stürmer T. Comparative Effectiveness of Oxaliplatin Versus 5-flourouricil in Older Adults: An Instrumental Variable Analysis. Epidemiology. 2015 Sep;26(5):690-9

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Calendar Time IVs

- DPP4i versus TZD
- Both alternative second line Rx in DM type 2
- Much interest in CER of CVD outcomes
- Good exchangeability (after CHF exclusion)
- TZD associated with bladder cancer
- Rapid switchover from TZD to DPP4i
- IV?

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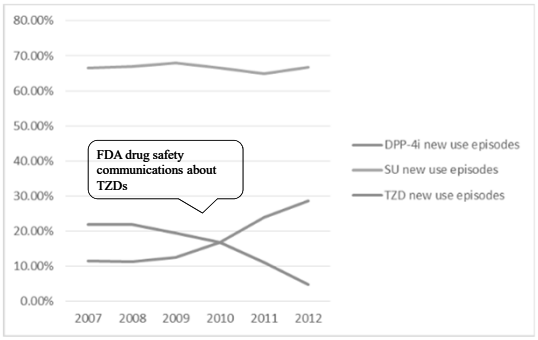
Switchover of Alternative Treatments



Gokhale et al. Pharmacoepidemiol Drug Saf 2018

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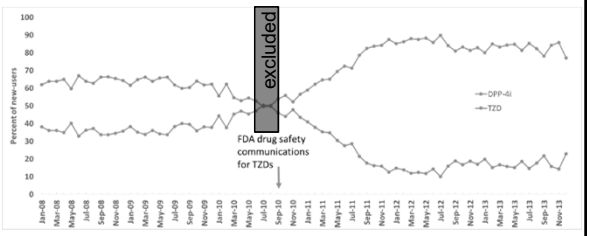
DPP4i versus TZD



DPP-4i treatment 37% pre vs. 77% post
=> 40% compliance (strong IV!)

Gokhale et al. Pharmacoepidemiol Drug Saf 2018

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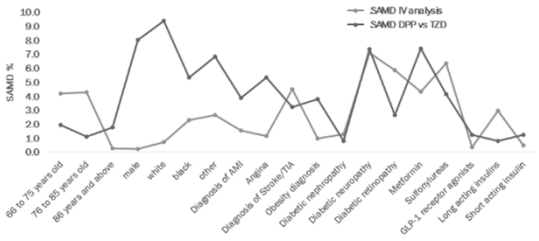
Balance of Measured Covariates: IV (Blue) Versus Actual Treatment (Red)



Standardized Absolute Mean Difference (SAMD)
Cave: needs to scaled for IV to be fair (here: unscaled)

Gokhale et al. Pharmacoepidemiol Drug Saf 2018

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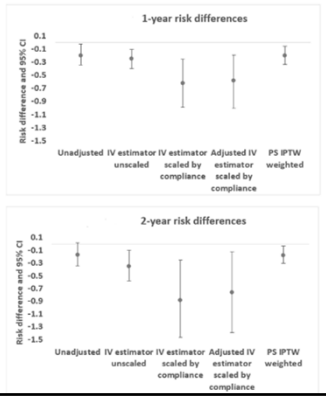
DPP-4i vs TZD: Comparison of Results



Gokhale et al.
PDS 2018

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Conclusions IVs

- Observational CER / outcomes research
  - Very large data sets
  - Limited ascertainment of confounders
- IV methods may be often indicated
- Key is finding good instruments
- Tremendous variability in medical practice in US
  - Preference-based IVs useful in some circumstances (lots of confounding, strong preference, big *n*)
- Care must be taken with
  - Evaluating assumptions
  - Interpreting results
- Weigh IV assumptions against alternative assumption of no unmeasured confounding

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