INTRODUCTION TO PHARMACOEPIDEMIOLOGY

9 September 2012
University of South Australia, Adelaide

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With the growing availability of large healthcare databases, non-experimental studies of prescription medications are becoming increasingly common. However, appropriate design and analysis of such studies can be challenging. In this workshop we provide an intensive introduction to the field of pharmacoepidemiology. We review the data used in pharmacoepidemiology and the central threats to validity of studies medications, including the healthy user bias, immortal person time bias, and various types of confounding bias. We then discuss approaches to mitigate these biases through design and analysis. The workshop will cover the comparative new user design, self-controlled designs, propensity score methods, and instrumental variable approaches. We will also discuss some additional topics in the field, including studies of medication adherence, disparities, and active safety surveillance of medical products.

Timetable

Time	Topic
8:15-8:50	Registration
8:50-9:00	Welcome and introduction
9:00-9:30	**A brief introduction to pharmacoepidemiology**
9:30-10:40	**Confounding and other biases in non-experimental studies**
10:40-11:00	Coffee break
11:00-12:15	**Propensity scores**
12:15-1:15	Lunch
1:15-2:30	**Instrumental variable methods and natural experiments**
2:30-2:50	Coffee break
2:50-4:00	**Studies of prescribing and adherence, and general discussion**

Dr M. Alan Brookhart is an Associate Professor of Epidemiology and Medicine at the University of North Carolina at Chapel Hill. He completed a PhD in Biostatistics at the University of California, Berkeley, and held postdoctoral appointments at the Harvard Medical School and Brigham and Women's Hospital, Boston, before taking up his position at the University of North Carolina. His research is focused primarily on the development and application of new statistical methods and study designs for epidemiologic studies of medications using large clinical and healthcare utilization databases. In this area, he has made contributions to the development of quasi-experimental and instrumental variable approaches that can be used to estimate causal effects in the presence of unmeasured or poorly recorded confounding variables. He has also been involved with the development of propensity score and marginal structural model methodology and has also developed new epidemiologic approaches for studying medication adherence and use of healthcare services. Substantively, he is interested in the effects of medications in the elderly and patients with end-stage renal disease.

Date: **Sunday 9 September 2012** **9.00am – 4.00pm**

Venue: **Room C3-16, University of South Australia, City East Campus, Corner of North Terrace and Frome Road, Adelaide**

Introduction to Pharmacoepidemiology

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Learning Objectives

- To understand the scope of the field of pharmacoepidemiology
- To understand why we need observational/non-experimental studies of drugs
- To understand commonly used sources of data for pharmacoepidemiology

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Pharmacoepidemiology

- Study of the use of and the effects of drugs in large numbers of people

  Strom, Kimmel: Textbook of Pharmacoepidemiology 2006

Examples of Issues Addressed within Pharmacoepidemiology

- Drug utilization research/ quality of care
- Drug effects (effectiveness and safety)
- Analytic methods

Why do we need observational studies of drugs or medical products?

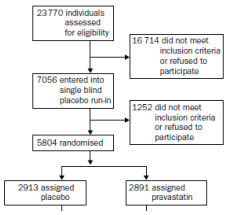
- Clinical trials provide gold standard evidence of drug effects
- Problems with clinical trials
  - Expensive
  - Small
  - Often drugs are compared against placebo
  - Exclude elderly, children, pregnant women, patients with important comorbidities
  - May be unethical
  - Not timely

MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20 536 high-risk individuals: a randomised placebo-controlled trial

- Enrolled patients 40-80 with some CV risk factors or diabetes
- Excluded patients with kidney disease, liver disease, life threatening condition (other than diabetes) such as COPD, cancer (other than non-malignant skin cancer)
- Excluded patient who might have a problem with compliance (psychiatric disorders, cognitive impairment, dementia, disabling stroke, etc)
- Less than 20% of patients were over 70

@ Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial

- Enrolled patients 70-82 with some vascular risk factors
- Excluded patients with cognitive impairment



Example of Need for Non-experimental CER: Antipsychotic Medications (APM) in the Elderly

- APMs approved to treat schizophrenia
- Widely used off-label to treat elderly patients with dementia
- Two broad classes: conventional (older drugs) versus atypical (newer drugs)
- Manufacturers of some of the atypicals conducted trials to assess effectiveness of the medications for controlling behavioral disturbances in elderly
- FDA meta-analysis: increased risk of mortality associated with atypical APMs (relative to placebo)
- FDA put a "black box" advisory on label of atypical APMs

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Clinical Dilemma

- Should physicians switch patients to the first generation APMs?
- Older APMs have many known side effects, poor safety profile
- Head-to-head trial will never be not be done
  - Practically difficult
  - Ethically impossible
- Question must be answered by analyzing existing data

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Increasing interest in "Comparative Effectiveness Research" in US

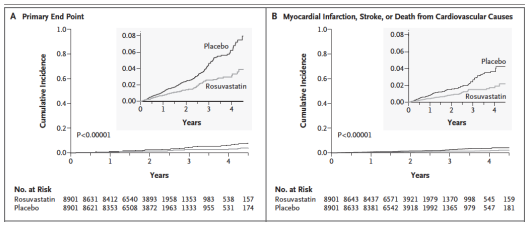
"Conduct and synthesis of research comparing the benefits and harms of different interventions and strategies to prevent, diagnose, treat and monitor health conditions in "real world" settings. The purpose of this research is to improve health outcomes by developing and disseminating evidence-based information to patients, clinicians, and other decision-makers, responding to their expressed needs, about which interventions are most effective for which patients under specific circumstances."

--Report to President and Congress, Federal Coordinating Council For CER

Most trial are placebo-controlled, rather than comparative

- JUPITER trial randomized 17,800 people with elevated high-sensitivity C-reactive protein, but normal lipids
- Patients assigned to receive placebo or high-potency rosuvastatin therapy

JUPITER results



Would other less expensive statins provide a similar benefit in this population?

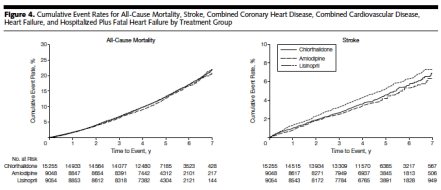
Ridker et al, Rosuvastatin to prevent vascular events in men and women with elevated C-reactive Protein. NEJM 2008

Randomized Comparative Studies

ORIGINAL CONTRIBUTION JAMA-EXPRESS

Major Outcomes in High-Risk Hypertensive Patients Randomized to Angiotensin-Converting Enzyme Inhibitor or Calcium Channel Blocker vs Diuretic
The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)

- 33,357 patient randomized to one of three antihypertensives: ACEIs, Thiazides, CCBs
- Patients had hypertension and at least one CV risk factor
- Followed between 3-8 years
- Outcome: Blood pressure and major CVD events



- Thiazide diuretics as good as or superior to ACE Inhibitors and CCBs for all outcomes
- Established guideline for management of hypertension that are still used
- AllHat took 8 years to complete and cost $130 million

Why do we need observational studies of drugs or medical products?

- Problems with clinical trials
  - Expensive
  - Small
  - Often drugs are compared against placebo
  - Exclude elderly, children, pregnant women, patients with important comorbidities
  - May be unethical
  - Not timely
  - > **we need observational studies of medications**
  - **85% of CER is nonexperimental**

What data can we use for non-experimental studies?

- Large cohort studies
  - Usually prospective or ongoing
- Healthcare and clinical database
- Disease registries
  - Cancer (SEER)
- Drug registries
  - E.g., antiretrovirals, biologics

Desired Qualities of a Database

- Representative
- Large
- Timely (i.e., up to date)
- Continuity
  - Individual observations
  - Calendar time
- Linkage on unique identifier
- Accessible
  - Without delay
  - Over prolonged periods (intimate knowledge of data)
  - To everyone

Desired Contents of Database

- All use of prescription drugs and over-the-counter (OTC) drugs
- Outpatient, inpatient, emergency care and reasons for visit
- Patient health-related behaviors
  - Smoking
  - Diet and exercise
- Indication for treatment
  - Clinical variables
  - Diagnoses
  - Laboratory
  - Radiographic
  - Function (RR, ejection fraction)
- Other determinants of treatment
  - Prescriber
  - SES
  - Frailty
- Cause-specific mortality
- Patient reported outcomes (QOL)

Healthcare and clinical databases

- Large N (often >> 1,000,000)
- Often population based
- No recall/interviewer bias
- Timely results
  - Regulatory
  - Commercial
  - Public Health
- Growing use to assess
  - Unintended and intended drug effects

Insurance Claims Databases

- Billing data from payors
- Closely audited
- Dispensed (filled) prescriptions
  - Best data on drug exposure in PE
- Diagnostic data potentially dependent on financial incentives (system/country specific!)
  - Inpatient DRGs
  - Outpatient procedures
- Age, sex
- Often race, income, mortality
- US e.g., MarketScan, IMS, i-3, Medicaid, Medicare

Examples of Claims Databases in US

- Medicaid
  - ~ 50 million lives
  - Low income pregnant women and families
  - Chronic disabilities (e.g., ESRF)
  - Low-income seniors
- Medicare
  - All 65+
  - Part D (drug insurance)
    - Since 1/1/2006
    - ~ 1/3 FFS (individual dispensed prescriptions)
    - Available to academic centers for research (UNC)
  - Pharmacy assistance programs

Limitations of Healthcare Databases

- Uncertain validity of diagnostic data
- Lack of data on confounders, but
  - Depending on specific hypothesis
  - Validation studies (external control)
  - Sensitivity analyses
- No OTC drugs
  - NSAIDs including aspirin
  - PPIs
  - Others (e.g., orlistat)
- US: High turnover of population < 65
- Formularies, deductibles
- Missing dispensing prescription drugs

Other Things to Worry About

- Outcome not reliably coming to medical attention
  - E.g., diabetes (vs. MI, stroke)
- Lethal outcomes (e.g., MI, suicide, injury)
- Immeasurable drug exposures
  - Inpatient
  - Nursing home
- Strong confounding
  - Association with exposure
  - Association with outcome
  - Prevalence
- Large OTC proportion
- Poorly defined outcomes

Electronic medical record databases

- Advantages
  - High validity of diagnostic data
  - Some information on lifestyle
  - Some test results (e.g., laboratory, RR)
- Disadvantages
  - Uncertain completeness of diagnostic data (out of system, hospital, specialist)
  - Prescribed drugs (not: filled – one step removed from taking)
  - Drug lists vs. e-prescribing
  - Various coding systems (including: none!)

EMR Databases US

- Group Health Cooperative (Washington)
  - ~ 500k lives
  - Health Maintenance Organization (HMO)
  - Pharmacy benefits management (PBM)
- Kaiser Permanente
  - ~ 8.2 million lives
- HMO Research Network
  - ~ 1 million lives(?)
- Regenstrief

Healthcare Databases from Outside US

- Canada
  - Saskatchewan
    - ~ 1 million lives (whole province)
    - Famous hole for drug data July 1987 – Dec 1988
  - Quebec
    - RAMQ (approx. 45% of adult population)
- Netherlands
  - PHARMO
    - ~ 500k lives covered
  - Rotterdam Study
    - Cohort with linked pharmacy records
- UK
  - GPRD
  - THIN
    - ~ 3 million lives covered
- Scotland
  - Tayside medicines monitoring unit (MEMO)
    - ~ 400 k lives covered
- Scandinavia (Denmark, Sweden, Norway)
  - Whole population
    - Several millions

Disease, Device, and Drug Registries

- Systems that collect data on patients with diagnosed with a disease, who have received a certain procedure, medical device, of medication
- Sometime these are simply include baseline data collected at the time of enrollment
- Sometimes these include detailed follow-up information, outcomes

Westphalian Stroke Registry

- Regional data bank in northwestern Germany
- All patients treated for stroke symptoms who were admitted to the participating 42 hospitals.
- Collected variables include sociodemographic characteristics, cerebrovascular risk factors, comorbidities, stroke type, and diagnostic data
- Treatment information
- Complications and discharge status

SEER Cancer Registry in US

- SEER=Surveillance, Epidemiology, and End Results
- Collecting data since 1973 from regions covering about 28% of US
- Collects data on patient demographics, primary tumor site, tumor morphology and stage at diagnosis, and first course of treatment
- No follow up other than date of death obtained from vital statistics

Many Other Examples

- Many countries have registries to track patients with artificial joints
- Many other device registries
- CABG and stent registries
- Transplant receipt registries
- Many drug registries in US are required as part of post-marketing surveillance

Registry Strengths

- Usually contain rich, clinically relevant baseline data
- Sometimes contain detailed clinical follow-up data

Registry Limitations

- Sometime these are simply include baseline data collected at the time of enrollment
- Follow-up data are often coarse, do not contain good information on treatment changes
- Drug device registries often lack a control group
- Available only on a segment of the population
- Often small

Future Directions

- Database linkage
  - Add claims data to cohort studies
    - Easy to get informed consent
    - E.g., ARIC, WHI, Rotterdam
  - Internal validation studies
    - Add additonal information for subgroup
    - E.g., Medicare Current Beneficiary Survey (MCBS)
  - Add disease registries to EMR data
    - E.g., cancer registry
  - Add PROs (collect during office visit)

-- notes --

Confounding and Other Source of Bias
The New User Design

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Learning Objectives

- To understand how confounding bias arises in studies of therapeutics
- To understand the characteristics of the new user design and how they mitigate many forms of confounding bias
- To recognize immortal and unexposable person time bias and know how to avoid these problems

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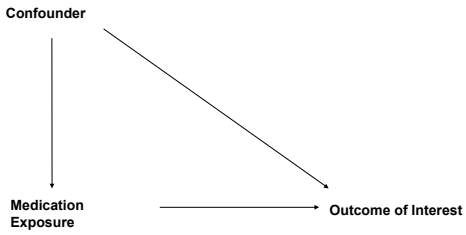
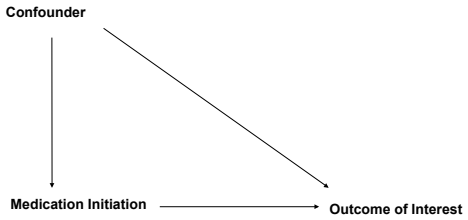
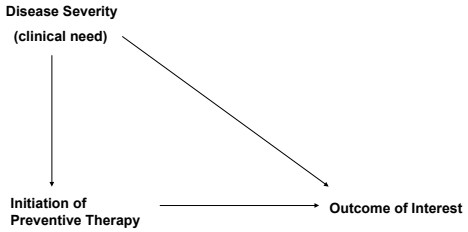
Confounding



Confounding During Treatment Initiation



Confounding by Indication / Disease Severity



Case Study: Statins and Primary Prevention of Myocardial Infarction

- Statins are safe and widely used cholesterol lowering agents
- Prescribed to patients at risk of CAD or with existing CAD
- Study among Medicare/PACE enrollees in PA, 1995-2002
  - All hospitalizations discharge data and physician office data (ICD-9 coded diagnoses and procedure codes)
  - Merged with pharmacy claims
- Identified 38,046 new users of statins (w/ no hx of MI)
- Matched these by calendar time 1-1 to non-users of statins (w/ no hx of MI)
- Outcome was time until hospitalization for acute MI (within one year)

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Unadjusted Results

- 805 events in “control” arm
- 1123 events statin arm
- Unadjusted hazard ratio = 1.36

- Do statins increase the one-year risk of MI by 36%?

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Multivariable Cox PH Model

- Next we adjusted for age, sex, and 30+ covariates abstracted from the claims data: history of co-morbid conditions, history of medication use, Charlson index, etc.

- Result: Hazard Ratio = 1.21 (95% CI 1.09-1.36)

- Clearly, residual confounding not controlled.

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SSRI Antidepressants and Suicide

- Fluoxetine (Prozac) the first SSRI-type anti-depressant (AD)
- Released in the US in 1988 and marketed as being safer and more effective than older ADs
- There were reports of suicide and violent behavior among patients recently started on Prozac (from older ADs) (Teicher MH, Glod C, Cole JO. 1990 Am J Psychiatry)
- Newly initiated patients were likely those that had failed on an older treatment
- Confounding by disease severity

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Protopathic Bias

- Closely related to CBI
- An early, undiagnosed form of disease leads to a treatment of early conditions
- Disease is subsequently recognized
- Exposure appears to cause disease

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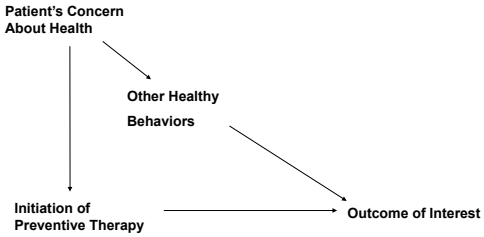
Confounding by The Healthy User Effect



Healthy Behaviors Often Associated with Benefits not Substantiated in RCTs

- Hormone Replacement Therapy
  - Observational Result: HRT associated with a 30% reduced risk of AMI
  - RCTs: HRT associated with a increased risk of MI, stroke, and breast cancer.
- Vitamin E in women
  - Observational research: 30%-40% decrease in risk of cardiovascular outcomes attributable to Vitamin E use
  - RCT: No benefit. (Lee et al, JAMA 2005)
- Many other examples

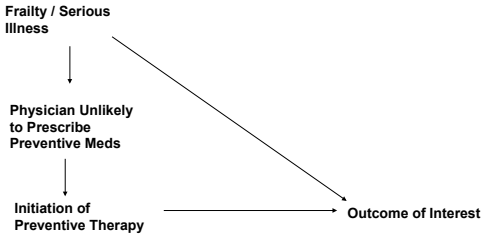
ORIGINAL CONTRIBUTIONS

Prior to Use of Estrogen Replacement Therapy, Are Users Healthier than Nonusers?

Karen A. Matthews,[1] Lewis H. Kuller,[2] Rena R. Wing,[1] Elaine N. Meilahn,[2] and Pamela Plantinga[2]

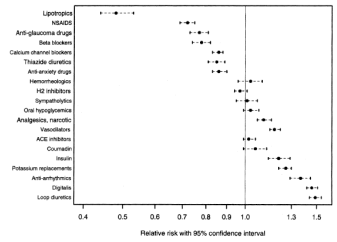
…women who use estrogen replacement therapy had a better cardiovascular risk profile than those who did not…

Confounding by Frailty / Serious Comorbidity

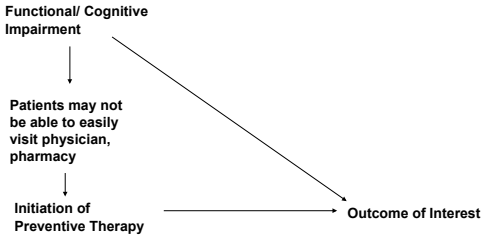


Paradoxical Relations of Drug Treatment with Mortality in Older Persons

Robert J. Glynn,[1,2] Eric L. Knight,[1] Raisa Levin,[1] and Jerry Avorn[1]



Confounding by Functional / Cognitive Status

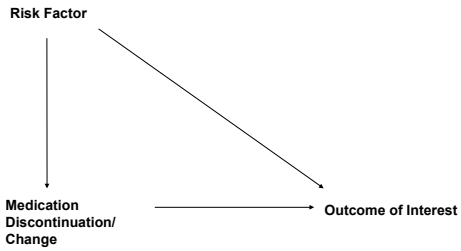


Functional status is a confounder of the association of influenza vaccine and risk of all cause mortality in seniors

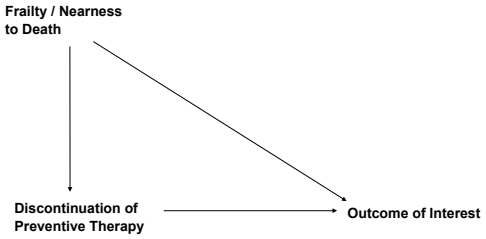
Lisa A Jackson,[1,2]* Jennifer C Nelson,[1,3] Patti Benson,[1] Kathleen M Neuzil,[4] Robert J Reid,[1] Bruce M Psaty,[1,2,4,5] Susan R Heckbert,[1,2] Eric B Larson[1,4] and Noel S Weiss[2]

- Influenza vaccine found to be associated with decreased mortality risk during *the non-flu season*
- Statistical adjustment for functional status attenuated this relation

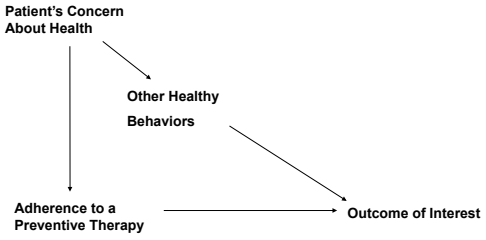
Confounding During Treatment Changes



Informative Treatment Changes: The Sick Stopper Effect



Informative Treatment Changes: The Healthy Adherer Effect "Compliance Bias"



Adherence to Placebo and Mortality Risk (Simpson, BMJ 2006)

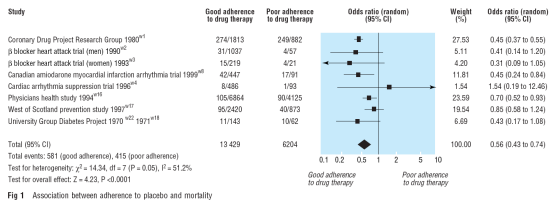


Fig 1 Association between adherence to placebo and mortality

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

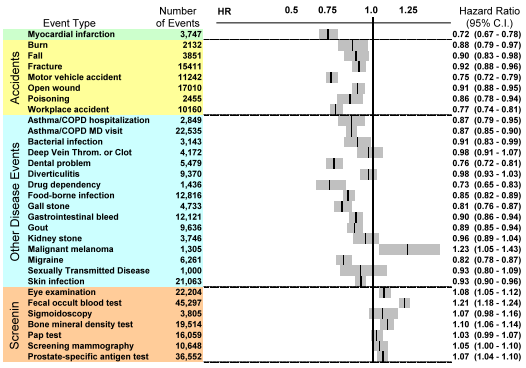
Epidemiology

Statin Adherence and Risk of Accidents
A Cautionary Tale

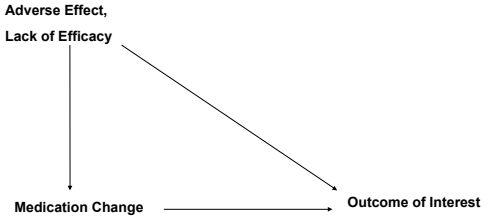
Colin R. Dormuth, ScD; Amanda R. Patrick, SM; William H. Shrank, MD; James M. Wright, MD, PhD; Robert J. Glynn, PhD, ScD; Jenny Sutherland, BSc; M. Alan Brookhart, PhD

- 145,000 new users of statins in British Columbia
- Examined association between statin adherence and both accidents and various clinical outcomes unlikely to affected by a statin

Associations Between Adherence to Statin Treatment and Health-Related Events



Informative Treatment Changes: Medication Intolerance / Treatment Failure



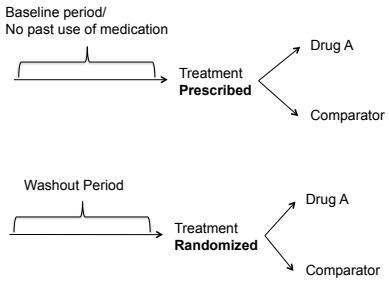
Summary

- Relative to non-users, prevalent users are more likely…
  - to have an indication for treatment
  - to follow a healthy lifestyle
  - to be cognitively and functionally intact
  - to not have other, serious comorbidities
  - to tolerate the medication and derive benefit from it

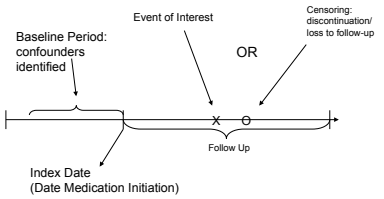
New User Design

- New User Design proposed by Ray et. 2003
- Compare new users of a medication of interest to new users of a comparator drug/no treatment
- Requires no use of either therapeutic or comparator drug
- Pairs naturally with propensity score methods to control confounding by baseline factors

New User Design Mimics A RCT



New User Design



New User Design

- Identify all people initiating treatment in a defined population (people and time)
- Define minimum period without drug exposure (wash-out) prior to t_0
  - *Make sure you would see drug (in system)!*
- Include everyone meeting these criteria
- Start follow-up as of this time t_0
- Define all covariates up to t_0
  - *You may want to include t_0*
  - *Use same length interval for covariate definition for everyone (e.g., wash-out)*

Permits Study of Early Events

- Period after initiation often associated with increased risk (Guess 89)
  - Benzodiazepines and falls
  - NSAID and peptic ulcer
  - ACE-inhibitors and angioedema
- Depletion of susceptibles
- Physiologic adaptation
- Selection (adherence) bias = healthy user

New User vs. First Time User

- First ever exposure would be ideal
- Possible with drugs new on the market
- Rarely ever possible with older drugs
- Wash-out period
  - Usually plausible
  - Not for serious acute events (anaphylaxis)
- Same problem as in RCT
- Make sure you mention that new users may not be first time users (drug naïve)

New Users Design Separates Confounders from Intermediates

- Confounders influence treatment choice
- Intermediates are affected by treatment and subsequently affect outcome No way of separating these in prevalent users cohort
- Example:
  - Statins and LDL
  - Antihypertensives and blood pressure

Disease Risk Factors

- New user design
  - Everything up to t_0 is a potential confounder
- Control for measured confounders
- Even more obvious with propensity scores
  - What affects treatment choice?
  - What risk factors affect treatment choice
- Everything after t_0 is a different animal
  - Ignore
  - Use other methods, e.g., MSM

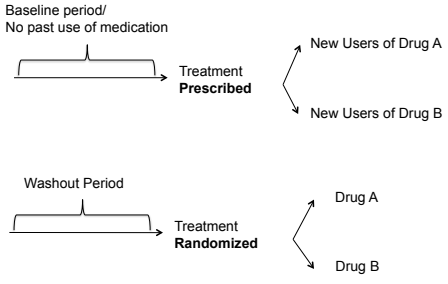
Follow-up

- Obvious timescale (t_0)
- Reduce healthy adherer (sick stopper) bias by using comparator drug if possible
- Decide on censoring for stopping/switching
  - Last prescription + days supply + grace period
  - No censoring
    - First exposure carried forward
    - Intention-to-treat
- Stratify by time on drug to detect time-varying hazard ratios

New User Design with Active Comparator

- Can either compare new users of a drug of interest to users of a comparator drug (active comparator)
- Often specified by research question (comparative effectiveness)
- "Is drug A safer or more effective than drug B?"
- Or can be a mechanism to control confounding

Limiting confounding by design: Comparative New User Design



Strengths of Active Comparator

- Reduce confounding by indication
  - Clinical alternative
  - Similar point in disease progression
  - Problem: step-up therapies (but reality often better than expected, e.g., TNF-α vs. MTX)
- Reduce confounding by frailty
  - Similar medicalization/access

Comparator Drug Examples

- Glargine vs. NPH insulin
- ARB vs. ACE
- TNF-α vs. MTX
- Rosiglitazone vs. Pioglitazone
- Sulfonureas vs. metformin
- Etc.

Problems: Many drug may not have a logical comparators

- Statins
- Vaccines
- One approach: use a drug with a different indication (e.g., anti-glaucoma drugs comparator for statins)
  - Reduce confounding by frailty, healthy user effect, etc
  - Problem indications are different, may not reduce confounding by indication
- Another approach: use the date of a physician visit

Strengths of the New Users Design

- Both groups are new users and thus similar:
  - Health seeking behavior, cognitive and physical functioning, etc
- Proper choice of a control can minimize confounding by indication
- Can study events that occur immediately after follow-up
- Groups are not enriched patients tolerant of medication
- Temporal separation of covariates and exposure

Limitations of the New Users Design

- Ideal for healthcare databases
  - Exposure and covariate information on day to day basis
- Difficult in cohort studies where exposure not well ascertained
- Limits sample size considerably, but
  - Less bias, wider CI
  - Much better coverage probability!
- Limits ability to assess long term effects
- Gives more weight to short term users

Alternative Design: follow-up begins after an index event

- Typically index date is a sentinel event, e.g., a diagnosis or hospitalization
- Interested in assessing effects of medication in patients who have experienced the event
- Post-MI medication use
  - Index date: discharge from hospital
  - Assess use of statins, ACE Inhibitors, etc
  - Examine effect on outcome

Common Source of Bias in Study Design

- Hypothetical study design
  - Identify post-MI patients
  - Determine whether they start post-MI meds in the thirty days after hospital discharge, classify them as exposed or unexposed
  - Examine survival by treated versus untreated

Immortal Time Bias

- Study design creates time in which an outcome could not occur
- Usually occurs before a subjects starts treatment
- Often unintentionally created by restricting on an event that happens during follow up

Solution to Immortal Time Bias

- Do not select cohort based on events occurring during follow-up
- Or apply selection to everyone
  - Create an exposure ascertainment period that everyone mu
- Have a common index date and make exposure time-varying

Immeasurable Time Bias

- Time when exposure cannot occur or be observed
  - Hospitalizations, acute care stays
- Often leads to exaggerated benefits of treatment

Counterfactuals and Propensity Score Methods

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UNC GILLINGS SCHOOL OF GLOBAL PUBLIC HEALTH

Learning Objectives

- To understand the concept of a counterfactual and a causal effect
- To understand how propensity scores can be used to estimate causal effects
- To understand a variety of practical issue involved with propensity score methods

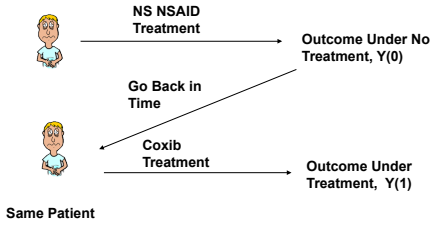
2

Ex: Non-steroidal anti-Inflammatory drugs and peptic ulcer disease risk in routine practice

- Compare risk of GI outcomes in between
  - Non-selective NSAIDs
  - COX-2 selective NSAIDs ("Coxibs")

  as they are used in a routine practice setting (the "real world")
- In trials, coxibs were slightly less likely to cause GI problems
- What is the benefit of Coxibs in a real world patient population?

Ideal Causal Experiment



Counterfactuals

- **Y(1)** and **Y(0)** are "counterfactual" or potential outcomes
- If we knew Y(1) and Y(0) for all patients, we could identify optimal treatment for everyone
- Unfortunately, we only observe one potential outcome – fundamental problem of causal inference
- Causal inference is similar to analysis of censored data
- Denote observed outcome **Y,** and observed treatment with **X**

Causal Parameters/Contrasts

- Let **Y** be an indicator of whether a patient experienced the outcomes during follow-up (a zero or one variable)
- Causal risk difference E[Y(1)] - E[Y(0)]
  - Interpretation: risk of outcome if everyone had been treated minus risk of outcome if nobody had been treatment
- Causal risk ratio E[Y(1)] / E[Y(0)]
  - Interpretation: risk of outcome if everyone had been treated divided by the risk of outcome if nobody had been treatment
- These tell us about treatment effects in a population but not individuals

Estimating Distributions of Counterfactuals

- We can estimate distributions of counterfactuals in idealized RCTs (fully blinded, perfect compliance, etc)
- No systematic difference between experimental units across arms of the trial

Y(1),Y(0) are independent of (unrelated to) treatment arm assignment

-> The distribution of Y(1) is the same as the distribution of Y among those randomized to receive treatment

Can estimate E[Y(1)] with the mean of Y among those assigned to treatment

Key Problem in Observational Studies

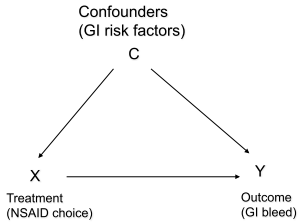
- In observational/non-randomized studies the key assumptions

Y(1),Y(0) are independent of (unrelated to) treatment arm assignment

does not hold.

- For example, Coxib treatment may be more likely to be assigned to patients at greater risk of GI complications
- We say that treatment is "**confounded.**"
- E[Y(1)] not necessarily equal to E[Y|X=1]

Confounding by Indication



Notation: X=treatment (0,1), C=vector of confounders, and Y=outcome

Causal Inference

- Causal inference is concerned with estimating readily interpretable causal contrasts from observational data
- In other words, estimating parameters that we would (or could) estimate in a randomized controlled trial
- As we will see, sometimes these cannot be easily estimated and we must settle for alternative quantities

Key assumption for causal inference
No unmeasured confounders / exchangeability

Y(1), Y(0) are independent of treatment (*X)* given the confounders (*C)*

C is a set of variables (age, sex, history of GI bleed, etc)

Among people with the same values for the confounders, treatment is effectively randomized.

Estimating Causal Effects by Stratification

Within small subgroups/strata of confounders (patients with a specific set of characteristics, we denote with C=c, e.g. Age=72, Gender=female, History of GI bleed=0, etc)

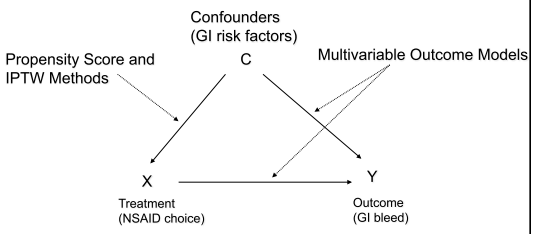
Under no unmeasured confounding, we can estimate within-strata causal effects

$E[Y|X=1,C=c]=E[Y(1)|C=c]$

$E[Y|X=0,C=c]=E[Y(0)|C=c]$

We can then average these to get average causal effects, e.g., E[Y(1)-Y(0)]

Controlling Confounding with Statistical Models



Notation: X=treatment (0,1), C=vector of confounders, and Y=outcome

Key Propensity Score Theory

Propensity score is the probability of receiving treatment given C

$$PS(C) = Pr(X=1|C)$$

If all confounders are measured, Rosenbaum and Rubin show

$Y(1), Y(0)$ are independent of X given $PS(C)$

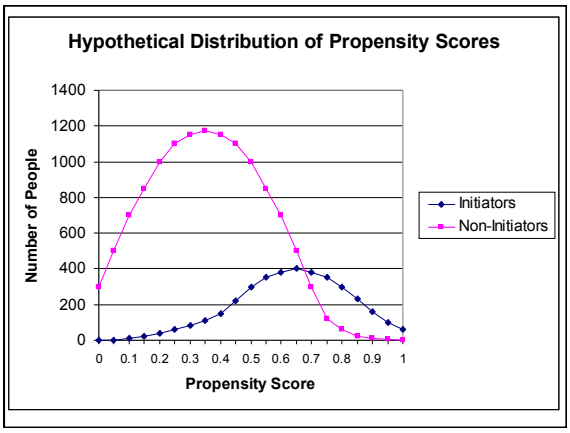
Among people with the same propensity score, treatment is effectively randomized.

Estimating the Propensity Score

Propensity scores are not know--must be estimated

$$Pr[X=1|C]=expit(b_0+b_1age + b_2sex +b_3CHD+\ldots)$$

For each patient a predicted probability of receiving treatment is computed -- the estimated PS



Methods of Using the PS

- Covariate adjustment (not optimal)
- Stratification on PS
- Matching on the PS
- Weighting on the PS (e.g., IPTW)
- Hybrid approaches: combine matching with multivariable regression (Cochran and Rubin) & doubly robust estimators (Robins)

Stratification on the Propensity Score

- Treatment effects are estimated within strata of PS
- Treatment effects averaged across strata
- This yields an estimate of the average effect of treatment
- Subject to residual bias within strata

Matching on the PS

- Match exposed to unexposed with similar PS
- Subjects who cannot be matched discarded
- Creates good balance of measured covariates
- Greedy matching techniques
  (http://www2.sas.com.proceedings/sugi26/p214-26.pdf)

Matching on the PS, cont.

- Limitation of matching
  - May lose many participants
  - Individuals in the tails of the distribution can be difficult to match
  - Generalizability: The effect of treatment may be different in those participants that cannot be matched.
  - Interpretability—not always a causal parameters

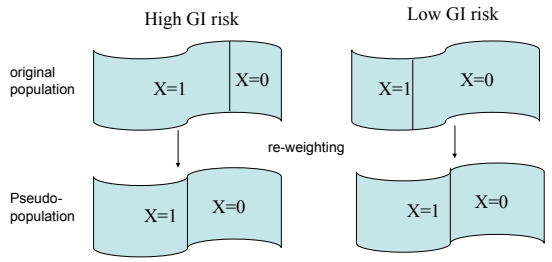
Inverse Probability of Treatment Weighting (IPTW)

- Each subject weighted by the inverse of the probability that they received their observed treatment
- Inverse probability of treatment (IPTW) estimator
  - Fit a standard regression, but weight by

    1/PS(X), in treated patients

    1/(1- PS(X)), in untreated patients

IPTW creates "pseudopopulation" in which treatment is unrelated to covariates



No association between NSAID use (X) and GI risk in pseudopopulation

IPTW estimates the average effect of treatment in the population

Absolute Scale (e.g., Risk Difference)

$RD = E[Y(1)] - E[Y(0)]$

Relative Scale (e.g., Risk Ratio)

$RR = E[Y(1)] / E[Y(0)]$

This contrasts with other treatment effects (treatment in the treated)

$RD_{TT} = E[Y(1)|X=1] - E[Y(0)|X=1]$

Experimental Treatment Assignment Assumption

- Everyone must have a non-zero probability of being treated or not

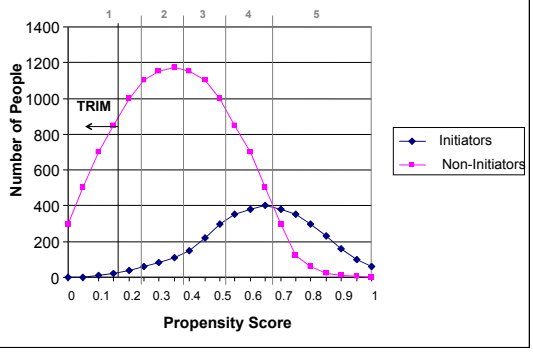
  $0 < Pr(X=1|C) < 1$

- Even small violations of this assumption can cause bias

Poorly Defined Populations

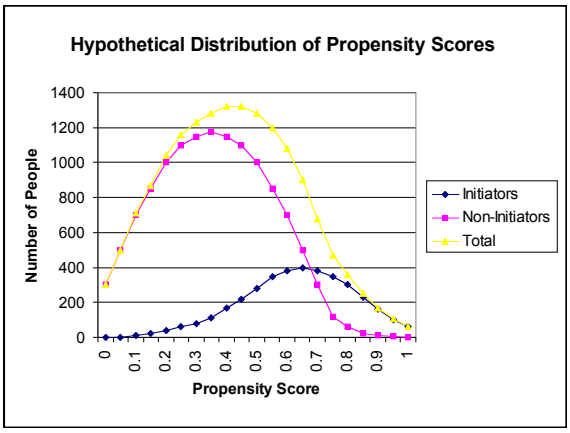
- Populations in pharmacoepi are often ill-defined
- If patients with contraindications are treated, may get hugely up-weighted
- Cause IPTW to give peculiar results

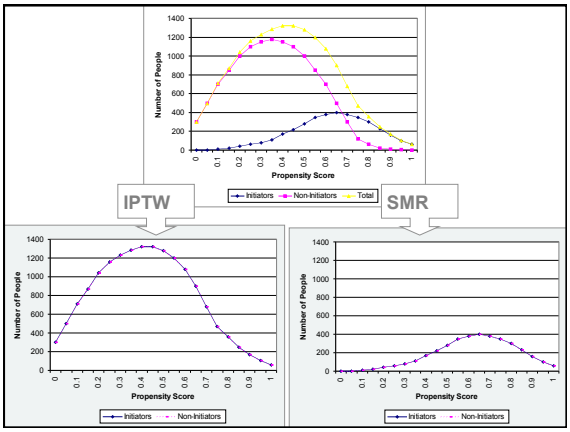
Hypothetical Distribution of Propensity Scores



SMR Weight

- Weighting method uses a standardized mortality/ morbidity ratio (SMR) weight :
  - Value of 1 in the treated
  - Propensity odds in the untreated, PS(X)/(1-PS(X))
- This weighting approach uses the treated group as the standard
- Yields the effect of “treatment among the treated.”
- E[Y(1)-Y(0)|X=1]





Doubly Robust Estimators

- Depends on both an outcome model and propensity score model
- More efficient than IPTW
- Estimate is consistent as long as at least one model is correctly specified!
- Does not depend on the experimental treatment assumption when outcome model is correct
- Emerging methodology: Targeted maximum likelihood

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

- Compare risk of GI outcomes in elderly between
  - Non-selective NSAIDs
  - COX-2 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 of confounding by indication

Data

- Population: Medicare beneficiaries in Pennsylvania eligible for a state run pharmaceutical benefit program (PACE)
  - Low to moderate income elderly
- Cohort of new users of COX-2 inhibitors or non-selective NSAIDs between Jan. 1, 1999 and Jul. 31, 2002
  - Yielded N=49,919
- Drug exposure came from pharmacy claims data, ITT analog
- Outcomes and covariates were derived from Medicare hospital claims data
- Outcome was defined as a hospitalization for peptic ulcer disease or GI bleeding during follow-up (60-days)

Characteristics of 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%

Counterfactuals

Y(0) outcome a patient would experience if given NS NSAIDs
Y(1) outcome a patient would experience if given Coxibs

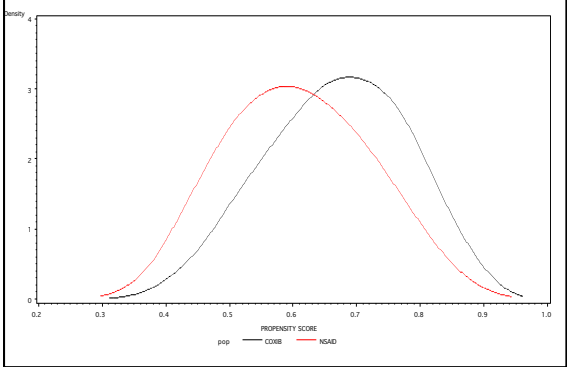
Treatment Effects on Absolute Scale (e.g., Risk Difference)
RD = E[Y(1)] - E[Y(0)]

Treatment Effects on Relative Scale (e.g., Risk Ratio)
RR = E[Y(1)] / E[Y(0)]

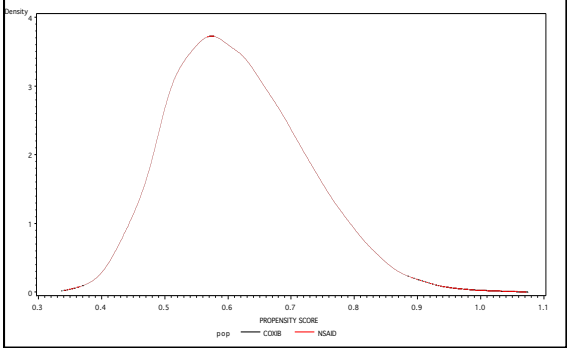
Example: Analysis

- Estimated PS using logistics regression
- Using 17 a priori selected covariates: GI risk factors and measures of frailty. Also included calendar year.
- PS Model yielded a c-statistic of 0.67
- Matched on estimated PS using a greedy matching algorithm to create a PS matched cohort (N=33,526)

Distribution of PS within Exposure Groups



Distribution of PS within Exposure Groups (Matched Cohort)



Assessing Balance Using Matching

	Unmatched (N=49,919)		PS Matched (N=33,526)	
Variable	Coxib Users (32,273)	NS NSAID Users (17,646)	Coxib Users (16,763)	NS NSAID Users (16,763)
Female Gender	86%	81%	82%	83%
Age > 75	75%	65%	68%	67%
Charlson Score>1	76%	71%	72%	71%
History of Hospitalization	31%	26%	26%	26%
History of Warfarin Use	13%	7%	7%	7%
History of Peptic Ulcer Disease	4%	2%	3%	3%
History of GI Bleeding	2%	1%	1%	1%
Concomitant GI drug use	5%	4%	4%	4%
History GI drug use	27%	20%	21%	21%
History of Rheumatoid Arthritis	5%	3%	3%	3%
History of Osteoarthritis	49%	33%	35%	35%

NSAIDs & GI Bleeds: Results

Statistical Method	RR (95% CI)
Unadjusted (Crude)	1.09 (0.91-1.30)
Multivariable Logistic Regression	0.96 (0.79 -1.15)
Including PS in Regression Model	0.95 (0.79-1.14)
PS Matching	0.95 (0.77-1.17)
Inverse Probability of Treatment Weighting	0.87 (0.71, 1.06)
SMR Weighted Estimator	0.83 (0.66, 1.03)

Example Paper with Treatment Effect Heterogeneity

American Journal of Epidemiology
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Vol. 163, No. 3
DOI: 10.1093/aje/kwf047
Advance Access publication December 21, 2005

Original Contribution

Results of Multivariable Logistic Regression, Propensity Matching, Propensity Adjustment, and Propensity-based Weighting under Conditions of Nonuniform Effect

Tobias Kurth[1,2,3], Alexander M. Walker[3,4], Robert J. Glynn[1,5,6], K. Arnold Chan[3,4], J. Michael Gaziano[1,2,7], Klaus Berger[8], and James M. Robins[3,6]

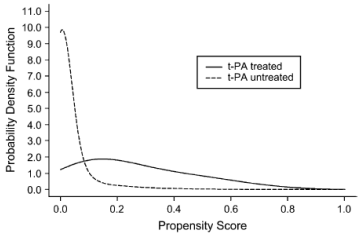

FIGURE 1. Probability density function of the propensity score for the 212 tissue plasminogen activator (t-PA)–treated and the 6,057 t-PA–untreated ischemic stroke patients registered in a German stroke registry between 2000 and 2001.

Thrombolysis and Mortality

TABLE 2. Proportion of deaths among 6,269 ischemic stroke patients registered in a German stroke registry between 2000 and 2001 who were treated or not treated with tissue plasminogen activator, according to percentiles of the propensity score for the entire study population

Percentile	Treated (n = 212)				Not treated (n = 6,057)				Empirical OR*
	Score†	No.	Deaths		Score†	No.	Deaths		
			No.	%			No.	%	
99 to 100	0.5809	36	3	8.3	0.5474	26	7	26.9	0.25
95 to <99	0.3143	73	13	17.8	0.2912	178	27	15.2	1.21
90 to <95	0.1393	55	8	14.6	0.1363	258	19	7.4	2.14
75 to <90	0.0585	31	3	9.7	0.0459	910	82	9.0	1.08
50 to <75	0.0115	10	4	40.0	0.0084	1,558	87	5.6	11.27
25 to <50	0.0017	5	2	40.0	0.0014	1,561	54	3.5	18.60
10 to <25	0.0004	2	1	50.0	0.000267	940	36	3.8	25.11
5 to <10		0	0	0	0.000066	313	6	1.9	
1 to <5		0	0	0	0.000027	251	8	3.2	
0 to <1		0	0	0	0.000007	62	1	1.6	
Overall	0.2521	212	34	16.0	0.0262	6057	327	5.4	3.35

* Propensity-stratum-specific-treatment–mortality odds ratio.
† Mean propensity score in percentile.

Kurth et al., AJE 2006

All cause mortality in stroke patients; Kurth T et al. AJE 2006

TABLE 4. Comparison of the estimated treatment effect of tissue plasminogen activator on death using multivariable logistic regression, propensity score–matched analysis, regression adjustment with the propensity score, inverse-probability-of-treatment-weighted, and standardized mortality ratio-weighted analyses for ischemic stroke patients registered in a German stroke registry between 2000 and 2001

	No.	OR*	95% CI*
Crude model	6,269	3.35	2.28, 4.91
Multivariable model†	6,269	1.93	1.22, 3.06
Matched on propensity score	406	1.17	0.68, 2.00
Regression adjusted with propensity score			
Propensity score, continuous	6,269	1.53	0.95, 2.48
Multivariable†	6,269	1.85	1.13, 3.03
Propensity score, deciles	6,269	1.76	1.13, 2.72
Multivariable†	6,269	1.96	1.20, 3.20
Weighted models			
IPTW*	6,269	10.77	2.47, 47.04
SMR* weighted	6,269	1.11	0.67, 1.84

* OR, odds ratio; CI, confidence interval; IPTW, inverse-probability-of-treatment weighted; SMR, standardized mortality ratio.
† Adjusted for age, gender, time from symptoms to hospital admission, Rankin scale, paresis, aphasia, state of consciousness, transportation to the hospital, admitting ward, admitting hospital, history of hypertension, diabetes, atrial fibrillation, other cardiac illnesses, previous history of stroke, and interaction terms for follow-up time and age, time from symptoms to admission to the hospital, and Rankin scale.

Coxib Example: Unmeasured Confounding

- Many GI risk factors are unmeasured in health care claims data files
  - Tobacco use
  - BMI / Obesity
  - Alcohol consumption
  - Aspirin use
- PS, IPTW methods cannot address this problem

An abundance of codes

---------- ID=********** dob=**/**/1948 sex=M eligdt=1/2000 indexdt=6/2001 ----------

Service Date	Site of Service	Prov Type	Drug or Procedure Code	Drug or Procedure Description		Diagnosis * Code	Diagnosis Description
10/01/00	OFFICE	Family Practice	90658	INFLUENZA VIRUS VACC/SPLIT		V048	VACC FOR INFLUEN
10/01/00	Rx	Pharmacy		CIPROFLOXACIN 500MG TABLETS			10
11/05/00	OFFICE	Family Practice	17110	DESTRUCT OF FLAT WARTS, UP		0781	VIRAL WARTS
11/07/00	Rx	Pharmacy		CIPROFLOXACIN 500MG TABLETS			10
01/15/01	Rx	Pharmacy		CIPROFLOXACIN 500MG TABLETS			10
06/25/01	OFFICE	Emerg Clinic	99070	SPECIAL SUPPLIES	*	84509	SPRAIN OF ANKLE
						E927	ACC OVEREXERTION
06/30/01	OFFICE	Orthopedist	99204	OV,NEW PT.,DETAILED H&P,LOW	*	72767	RUPT ACHILL TEND
06/30/01	OFFICE	Internist/Gener	99202	OV,NEW PT.,EXPD.PROB-FOCSD	*	84509	SPRAIN OF ANKLE
	OUTPT HP	Anesthesiologis	01472	REPAIR OF RUPTURED ACHILLES	*	84509	SPRAIN OF ANKLE
		Hospital	27650	REPAIR ACHILLES TENDON	*	84509	SPRAIN OF ANKLE
			85018	BLOOD COUNT; HEMOGLOBIN	*	84509	SPRAIN OF ANKLE
		Orthopedist	27650	REPAIR ACHILLES TENDON	*	84509	SPRAIN OF ANKLE
06/30/01	OFFICE	Orthopedist	29405	APPLY SHORT LEG CAST	*	72767	RUPT ACHILL TEND
07/30/01	OFFICE	Orthopedist	29405	APPLY SHORT LEG CAST	*	72767	RUPT ACHILL TEND
08/13/01	OFFICE	Orthopedist	L2116	AFO TIBIAL FRACTURE RIGID	*	72767	RUPT ACHILL TEND

➡ Search through these data to find claims codes that serve as proxies for previously unmeasured confounders.

Sources of codes

- Inpatient services
- Outpatient services
- Inpatient diagnoses (3, 4, 5-digit ICD)
- Outpatient diagnoses (3, 4, 5-digit ICD)
- Pharmacy fills (generic drug, drug class)
- Lab tests
- Lab values
- ...

Proxies in Claims

- Claims may contain proxies for unobserved confounders
- Lipid-testing important confounder in studies of statins (Seeger, Med Care)
- Can we identify important proxies in healthcare claims?

ORIGINAL ARTICLE

High-dimensional Propensity Score Adjustment in Studies of Treatment Effects Using Health Care Claims Data

Sebastian Schneeweiss, Jeremy A. Rassen, Robert J. Glynn, Jerry Avorn, Helen Mogun, and M. Alan Brookhart

Epidemiology • Volume 20, Number 4, July 2009

High-dimensional PS (hd-PS) Algorithm

- The approach:
  - Collect as many codes as possible
  - Identify those codes that could possibly bias the exposure/outcome relationship
  - Combine variables identified a priori with the "best" of these codes in a propensity score.
  - Use this "high dimensional propensity score" to adjust for confounding.
- Currently implemented in a SAS macro.

Detailed results of coxib study using hd-PS

Table 3: Variations in covariate adjustment and relative risk estimates for the association of selective cox-2 inhibitors and GI complications within 180 days of first medication use.

Model #	Covariates included in propensity score model	Number of covariates adjusted	Variables tested per data source	Data source granularity	Covariate prioriti-zation algorithm	c-statistic of PS model	Outcome model Relative risk	95% CI
							N = 49,653	
1	Unadjusted					-	1.09	0.91-1.30
2	Age, sex, race, year**	*d*=4				0.61	1.01	0.84-1.21
3	+ predefined covars (Table1)	*d*=4; *l*=14				0.66	0.94	0.78-1.12
4	+ empirical covariates	*d*=4;*l*=14;*k*=200	*n*=200	3-digit ICD	$Bias_{mult}$	0.69	0.86	0.72-1.04
5*	**+ empirical covariates**	***d*=4;*l*=14;*k*=500**	***n*=200**	**3-digit ICD**	**$Bias_{mult}$**	**0.71**	**0.88**	**0.73-1.06**
						Bootstrapped 95% CIs:		0.73-1.06
5b	Only demographics + empirical covariates	*d*=4; *k*=500	*n*=200	3-digit ICD	$Bias_{mult}$	0.71	0.87	0.72-1.05

Schneeweiss et al. Epidemiology, 2009.

Possible Explanations?

- Coxibs are not GI protective in this elderly population
- High non-adherence
- NS NSAIDs are co-prescribed with GI protective drugs
- Unmeasured confounding

Practical Guidelines

1) Importance of variable selection
   - Avoid entering variables not associated with outcome
   - Report % of exposed that could be matched to unexposed
2) Look for non-uniform effects over range of PS
   - Consider matching, range restrictions, trimming
   - Discuss residual confounding vs. treatment heterogeneity
3) Implementation of PS (modeling, stratification, matching, weighting) minor issue given uniform effects

Discussion / Questions

Multivariable Outcome Models

Usually to many confounders to stratify over and we must use a model.

Multivariable outcome models are models of an expectation (mean/average value) of an outcome given covariates and treatment.

Linear Regression

$E[Y|X,C]= b_0+b_1X + b_2C + b_3C*X$

Logistic Regression

$E[Y|X,C]=(1+exp\ (-b_0-b_1X - b_2C -b_3C*X)\ )^{-1}$

Causal Inference From Multivariable Outcome Models

If all confounders are measured (treatment if exchangeable) and model is correct, then model is estimating an expected value of a counterfactual given covariates

E[Y|X=1,C]=E[Y(1)|C], E[Y|X=0,C]=E[Y(0)|C]

One can then average these to get average causal effects (not conditional on C) – see appendix.

Validity depends on getting the model right!

Getting a more meaningful/interpretable estimate

E[Y(1)|C] is the expected value of Y(1) given a set of confounders

How do you get from a model for *E[Y(1)|C]* and *E[Y(0)|C]* to causal parameters/contrasts of interest?

For example, the causal risk difference

E[Y(1)] - E[Y(0)]

Marginalization ("G-computation")

If we have a single discrete covariate, C

$$E[Y(1)] = \sum_c E[Y(1) \mid C = c]\Pr(C = c)$$

Weighted average of "sub-group" effects, where the weights are the probability density

$$= \sum_c E[Y \mid A = 1, C = c]\Pr(C = c)$$

Estimate this with our fitted model and the empirical (observed) distribution of C

$$\sum_{i=1}^{n} \hat{E}[Y \mid A = 1, C = c_i](\frac{1}{n})$$

In English, please?

We can estimate causal parameters of interest using a fit multivariable model.

0) Fitting the multivariable model to the observed data
1) Create a dataset but set A=1 for all patients,
2) Using fit model generate predicted outcomes for all patients
3) Take the average of these to estimate *E[Y(1)]*
4) Repeat 1)- 3) but set A=0 for all patients to estimate *E[Y(0)]*
5) Estimate causal risk difference

$$RD = \hat{E}[Y(1)] - \hat{E}[Y(0)]$$

Fitted Model Allows Us to Estimate Other Parameters of Interest

- Can estimate the effect of treatment in the treated (on a risk difference scale)

  E[Y(1)|A=1]-E[Y(0)|A=1]

  (or relative scale)

  E[Y(1)|A=1]/E[Y(0)|A=1]
- Fit model to all patients
- Set treatment to zero for the treated patients, use model to predict outcome in patients, average these to get an estimate of *E[Y(0)|A=1]*
- Estimate *E[Y(1)|A=1]* using empirical (observed) rate of outcome in the treated

Can Estimate the Effects on a Population of "Treatment Rules"

- Define new counterfactuals

  Y("treat on if on warfarin")=outcome for a patient if he is only treated if he is on warfarin

  Y(1) = outcome if treated

  Y(0) = outcome if not treated

- Estimate

  E[Y("treat on if on warfarin")] – E[Y(0)]

How do we estimate this?

- To estimate *E[Y("treat on if on warfarin")]*
- Fit out multivariable model E[Y|X,C]
- Create a new dataset with treatment reassigned based on treatment rule
- Use fit model to generate predicted values of the outcome for all patients
- Average these to estimate *E[Y("treat on if on warfarin")]*
- Compare this to E[Y(0)] as previously estimated

We can use model to estimate counterfactuals in different populations

$$E[Y(1)] = \sum_c E[Y(1) \mid C = c]\Pr(C = c)$$

E[Y(1)] depends on the distribution of the covariates, *Pr(C=c)* …

What if the average age in the population were ten years older? We can plug-in an arbitrary distribution of *C, Pr*(C=c),* and estimate *E[Y(1)]*

$$\hat{E}[Y(1)] = \sum_c \hat{E}[Y \mid A = 1, C = c]\Pr^*(C = c)$$

Major limitation of "G-computation" based on an outcome model

- Outcome model must be correctly specified
  - Include all confounders
  - Including interactions between covariates
- Easy to inadvertently extrapolate model in to region where there is little covariate data
- Propensity score / inverse-probability of weighting methods

Derivation of IPTW

$$E\left[\frac{XY}{\Pr(X=1\mid C)}\right] = E\left[\frac{XY(1)}{\Pr(X=1\mid C)}\right]$$ By consistency assumption

$$= E\left[E\left(\frac{XY(1)}{\Pr(C=1\mid C)}\mid C, Y(1)\right)\right] = E\left[\frac{Y(1)}{\Pr(X=1\mid C)}E[X\mid C, Y(1)]\right]$$

$$= E[Y(1)]$$ By no unmeasured confounders

$$E\left[\frac{(1-X)Y}{1-\Pr(X=1\mid C)}\right] = E[Y(0)]$$

$$RD = E[Y(1)] - E[Y(0)] = E\left[\frac{XY}{\Pr(X=1\mid C)}\right] - E\left[\frac{(1-X)Y}{1-\Pr(X=1\mid C)}\right]$$

Derivation of IPTW, cont…

$$RD = E\left[\frac{XY}{\Pr(X=1\mid C)}\right] - E\left[\frac{(1-X)Y}{1-\Pr(X=1\mid C)}\right]$$

$$RD_{IPTW} = \frac{1}{n}\sum_{i=1}^{n}\frac{X_i Y_i}{PS(C_i)} - \frac{1}{n}\sum_{i=1}^{n}\frac{(1-X_i)Y_i}{1-PS(C_i)}$$

Natural Experiments and Instrumental Variable Methods

M. Alan Brookhart, Ph.D.
Department of Epidemiology,
UNC Gillings School of Global Public Health
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Learning Objectives

- To understand the assumptions and mechanics underlying instrumental variable estimation
- To understand how to evaluate an interpret an instrumental variable analysis
- To learn about some instrumental variable estimators that have been used in practice

2

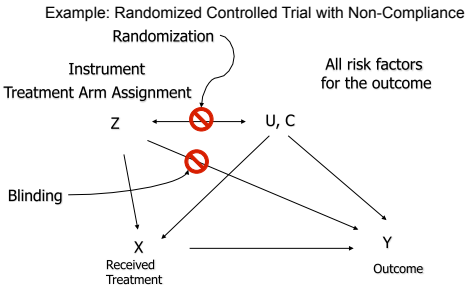
Donald Rumsfeld the Accidental Epidemiologist

"… there are known knowns; there are things we know we know. We also know that there are known unknowns; that is to say we know that there are some things we do not know. But there are also unknown unknowns – the ones we don't know we don't know. …, it is the latter category that tend to be the difficult ones."

Instrumental Variable Methods

- Developed and widely used by economists
- Can be used to bound and estimate treatment effects even when confounders are unmeasured
- IV methods depend on the existence of an instrumental variable ("instrument")

Causal Diagram of Structural IV Assumptions



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

IV Assumptions Informally

- Instrument should be correlated with treatment
- Instrument should be related to outcome only through association with treatment (often termed the exclusion restriction)
  - Empirically unverifiable, but can be explored in observed data.

Intention-to-treat (ITT) Approach

In RCTs with non-compliance, as-treated can be biased estimate of the effect of treatment.

ITT estimates the effect of Z on Y

$$ITT = \hat{E}[Y \mid Z = 1] - \hat{E}[Y \mid Z = 0]$$

In placebo-controlled trials, ITT estimates tend to be biased towards the null when there is non-compliance.

Classic IV estimator is a rescaled ITT estimator

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

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

Modeling Issues

- IVs can also be motivated as a solution to systems of equations (allows one to include cov)
  - A linear model for treatment (first-stage) that includes IV and covariates
  - A linear model for the outcome that includes exposure and covariates
  - System is solved by two-stage least-squares
- Many other variations
  - IV probit (implemented in Stata), probit models for both first and second stages

Weak Instruments

- Consistent: Wald estimator / 2SLS converges to true parameter but still biased in finite samples
- When instruments are weakly related to treatment (as quantified using a first-stage F statistic).
  - Residual bias in IV due to violations of assumptions is amplified
  - Variance in increased
  - 2SLS estimates biased toward OLS, even if IV is perfect
  - 2SLS confidence intervals are too narrow, particularly with many instruments and/or a first-stage F under 10.
  - Alternative estimation procedure (LIML: limited information maximum likelihood) is preferable.

See Staiger & Stock (1997)

Heterogeneous Treatment Effects

- Additional assumption required to justify IV estimator
- One example: 'Monotonicity'
  (Angrist, Imbens, and Rubin, JASA 1996)
  - In RCT example: 4 latent causal classes: always takers, never-takers, defiers, compliers
  - Monotonicity -> no defiers
  - If you took treatment in the placebo arm, you would receive treatment in active arm
  - **IV estimates the average effect of treatment in the compliers ('marginal' patients)**

ORIGINAL ARTICLE

Evaluating Short-Term Drug Effects Using a Physician-Specific Prescribing Preference as an Instrumental Variable

M. Alan Brookhart, Philip S. Wang, Daniel H. Solomon, and Sebastian Schneeweiss

- Goal: Use instrumental variable methods to estimate short-term risk of GI outcomes between
  - COX-2 selective NSAIDs versus
  - Non-selective NSAIDs
- Confounding: Coxibs are likely to be selectively prescribed to patients at increased GI risk

Characteristics of 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%

Unmeasured Variables

- Do not have data on
  - Lifestyle variables (e.g., diet, exercise, tobacco use)
  - Cognitive status
  - Physical functioning
  - Clinical variables (e.g., blood pressure, BMI)
  - Lab results (e.g., cholesterol levels)
  - Education level

Conventional Statistical Approach

- Parameter of interest is the risk difference
  Risk of GI bleed if given COX-2 – Risk of GI bleed if given a NS NSAID
- Conventional linear regression
  - Crude RD
  - Multivariable adjusted RD

Conventional Analysis: Results

Outcome Definition	Conventional Unadjusted Estimated RDx100 (95% CI †)	Conventional Adjusted Estimated RDx100 (95% CI †)
GI Event within 60 days	0.03 (-0.12, 0.18)	-0.04 (-0.20, 0.10)

We report the risk difference x 100

Possible Explanations?

- Coxibs are not GI protective in this elderly population
- High non-adherence
- NS NSAIDs are co-prescribed with GI protective drugs
- Unmeasured confounding

Unmeasured Indications for COX-2 Treatment

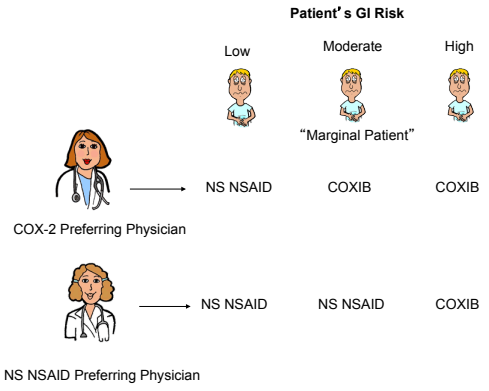
- These are selectively prescribed to patients at risk of GI complications
- Many GI risk factors are unmeasured in health care claims data files
  - Tobacco use
  - BMI / Obesity
  - Alcohol consumption
  - Aspirin use
  - Complaints to MD about stomach problems

What can we do?

- Sensitivity analysis
  - Requires assumptions about distributions of unknown confounders
- External adjustment, two-stage designs, multiple imputation, propensity score calibration
- Find an instrument!

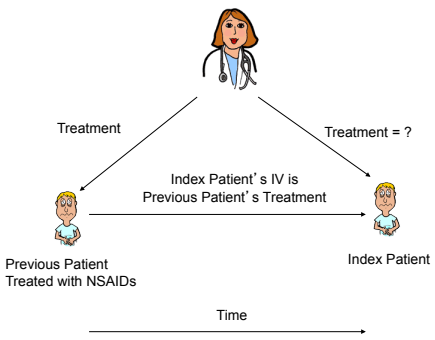
Physician as IV

- 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 is the natural experiment that we exploit



Estimating Preference

- Volume of NSAID prescribing varies considerably among physicians
- Our approach: use the type of the last NSAID prescription written by each physician as a measure of current preference
- If for last patient, physician wrote a coxib prescription, for the current patient he is classified as a "coxib preferring physician" other he is classified as an "non-selective NSAID preferring physician."



Re-Analysis of NSAID Data

Association between risk factors and treatment received

Variable	Coxib Users X=1	NS NSAID Users X=0
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%

Instrument should be unrelated to observed patient risk factors

Variable	Coxib Preference 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%

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%)

IV estimate of the effect of coxib exposure 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

Results: Estimated Risk of GI Complication

	Conventional Unadjusted	Conventional Adjusted*	Instrumental Variable Unadjusted	Instrumental Variable Adjusted
	Estimated RDx100 (95% CI †)	Estimated RDx100 (95% CI †)	Estimated RDx100 (95% CI †)	Estimated RDx100 (95% CI †)
GI Event within 60 days	0.03 (-0.12, 0.18)	-0.04 (-0.20, 0.10)	-0.92* (-1.74, -0.10)	-1.02* (-1.88, -0.16)

We report the risk difference x 100 * Significant at α=0.05

Comparison to RCT Results

	Risk Difference per 100 patients (95% CI)		
	60 days	120 days	180 days
IV Estimate (All Patients)	-0.92* (-1.74, -0.10)	-1.15* (-2.20, -0.09)	-0.94 (-2.14, 0.25)
VIGOR trial (Patients with RA)	-0.47 (-0.83, -0.12)	-0.65* (-1.08, -0.22)	-1.07* (-1.57, -0.57)
CLASS trial (Patients with OA or RA)	Not Reported	Not Reported	-0.96* (-1.74, -0.18)

Limitation:
Violations of Exclusion Restriction

- IV should affect outcome only through its association with treatment
- IV weakly associated age, Charlson score, history of arthritis, hospitalizations

-> Differences in patient case-mix

- IV weakly associated with past use of warfarin

-> Differences in medical practice or case-mix

Physicians who use coxibs see sicker patients, use medications that increase GI risk

Limitation:
Heterogeneous Treatment Effects

- When treatment effects are heterogeneous, IV estimator may be biased for ATE
- Under 'monotonicity' IV estimates average treatment effect in 'marginal' patients

Monotonicity Assumption

- In a randomized trial, coin flip encourages patients to take drug A or drug B
- Monotonicity states that there are no patients who would always do the opposite of what they were encouraged to do
- Monotonicity will not strictly hold in our setting

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Preference-Based Instrumental Variable Methods for the Estimation of Treatment Effects: Assessing Validity and Interpreting Results

M. Alan Brookhart* Sebastian Schneeweiss†

- If monotonicity doesn't hold, what is IV estimating in the presence of treatment effect heterogeneity?
- Weighted average of treatment effects, where the weight in a sub-group depends on the strength of the IV in the subgroup
- Can use subject matter knowledge to interpret…

Treatment effect heterogeneity: overuse of medications

- Coxibs are thought to be over-used, given to many patients who may not benefit from added GI protection
- High risk patients treated by most physicians
- IV is affecting treatment more in low risk patients

->IV estimate over-weights effect of treatment in low risk patients

- If low risk patients less likely to benefit, IV underestimates benefit of treatment at population-level (ATE)

Treatment effect heterogeneity underuse of medications

- Statins are widely thought to be underused, not given to many patients who might benefit
- Low risk patients not being treated by most physicians
- IV is affecting treatment more in high risk patients

->IV estimate over-weights effect of treatment in high risk patients

- If high risk patients more likely to benefit, IV overestimates benefit of treatment at population-level (ATE)

Treatment effect heterogeneity: misuse of medications (Contraindications)

- Physicians who infrequently use a medication may be more likely to misuse it
- Patients are at greater risk of adverse event if they see a physician who does not use medication
- Preference-based IV methods could make a drug appear to prevent a side effect that it causes

Exploring Possible Bias Due To Treatment Effect Heterogeneity

- Can look for evidence of possible treatment effect heterogeneity
- Does strength of the IV vary across sub-groups?
- Coxib study overall strength of IV was 24%
- In patients with a history of GI bleed, IV strength was 19%
- IV likely slightly underestimating average treatment effect (ATE)

Other examples of preference-based instrument

- 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)

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

ORIGINAL INVESTIGATION

ONLINE FIRST

Estimating Influenza Vaccine Effectiveness in Community-Dwelling Elderly Patients Using the Instrumental Variable Analysis Method

Kenny Wong, MPH; Michael A. Campitelli, MPH; Therese A. Stukel, PhD; Jeffrey C. Kwong, MD, MSc

ARCH INTERN MED PUBLISHED ONLINE FEBRUARY 27, 2012 WWW.ARCHINTERNMED.COM

- Used claims data from Ontario
- Used geographic region as an IV
- Found significant variation in vaccination rates across regions

Table 2. Selected Baseline Characteristics According to Receipt of Influenza Vaccine[a]

Characteristic	Patient Groups: Unvaccinated (n = 5 277 839)	Patient Groups: Vaccinated (n = 7 343 967)	Standardized Difference[b]
Demographics			
Age, mean (SD), y	74.5 (6.8)	75.5 (6.6)	14.5
Male sex	2 299 767 (43.6)	3 220 215 (43.8)	0.6
Rural residence	836 479 (15.8)	953 003 (13.0)	8.2
Neighborhood income quintile[c]			
1	1 097 456 (20.8)	1 405 066 (19.1)	4.2
2	1 117 164 (21.2)	1 579 953 (21.5)	0.8
3	1 030 921 (19.5)	1 466 779 (20.0)	1.1
4	992 881 (18.8)	1 405 877 (19.1)	0.8
5	1 028 765 (19.5)	1 476 807 (20.1)	1.5
Unknown	10 652 (0.2)	9485 (0.1)	1.8
Use of health care services			
No. of hospital visits in past 3 y, mean (SD)	0.44 (1.04)	0.48 (1.01)	4.0
No. of outpatient visits in past year, mean (SD)	13.31 (15.57)	17.52 (14.24)	28.4
Home care use in past 6 mo	306 562 (5.8)	424 239 (5.8)	0.1
Comorbidities			
Cancers	1 035 008 (19.6)	1 805 235 (24.6)	11.9
Cardiovascular diseases	1 652 785 (31.3)	2 939 387 (40.0)	18.2
Respiratory diseases	844 722 (16.0)	1 540 663 (21.0)	12.7
Anemias	516 317 (9.8)	936 881 (12.8)	9.3
Renal diseases	253 110 (4.8)	416 031 (5.7)	3.9
Diabetes mellitus	1 036 175 (19.6)	1 764 751 (24.0)	10.6
Immune disorders	29 614 (0.6)	45 361 (0.6)	0.7
Medications			
No. of medications in past year, mean (SD)	6.66 (6.05)	8.70 (6.10)	33.6
Statin use	1 532 049 (29.0)	2 858 214 (38.9)	20.9
ACE inhibitor use	1 492 016 (28.3)	2 691 436 (36.3)	15.0
β-Blocker use	1 112 200 (21.1)	1 934 863 (26.3)	12.3
Calcium channel blocker use	1 124 459 (21.3)	2 055 567 (28.0)	15.4
Procedures			
Stress test	935 052 (17.7)	1 619 046 (22.0)	10.8
Bone mineral density test	1 245 642 (23.6)	2 205 684 (30.0)	14.5
Echocardiography	1 067 008 (20.2)	1 869 532 (25.3)	12.1
Electrocardiography	3 367 340 (63.8)	5 335 538 (72.7)	19.2

Table 3. Selected Baseline Characteristics Across Quintiles of Regional Influenza Vaccine Coverage[a]

Characteristic	Quintile of Regional Influenza Vaccine Coverage: 1 (n = 2 548 688)	2 (n = 2 309 851)	3 (n = 3 806 662)	4 (n = 2 838 178)	5 (n = 2 574 443)
Mean influenza vaccine coverage, %	46.5	57.9	63.0	67.9	64.9
Mean predicted influenza season mortality, %[b]	1.09	1.00	1.04	0.94	1.08
Mean predicted influenza season P&I hospitalization or mortality, %	1.65	1.48	1.52	1.39	1.59
Demographics					
Age, mean (SD), y	74.84 (6.62)	74.84 (6.63)	75.23 (6.75)	75.01 (6.67)	75.24 (6.77)
Male, sex	1 142 438 (45.0)	1 053 133 (44.1)	1 325 627 (42.9)	886 124 (43.6)	1 112 660 (43.2)
Rural residence	882 357 (34.7)	234 284 (9.8)	153 421 (5.0)	171 433 (8.4)	347 957 (13.5)
Neighborhood income quintile[c]					
1	538 538 (21.2)	441 589 (18.5)	704 234 (22.8)	396 747 (17.6)	461 414 (17.9)
2	549 332 (21.6)	498 188 (20.9)	705 020 (22.8)	421 940 (20.8)	522 637 (20.3)
3	517 441 (20.4)	507 442 (21.2)	552 781 (17.9)	395 142 (19.5)	524 894 (20.4)
4	481 714 (19.0)	473 752 (19.8)	503 262 (16.3)	416 873 (20.6)	521 157 (20.2)
5	445 793 (17.5)	465 963 (19.5)	616 960 (20.0)	435 214 (21.4)	541 142 (21.0)
Unknown	7862 (0.3)	2317 (0.1)	4505 (0.1)	2854 (0.1)	2999 (0.1)
Use of health care services					
No. of hospital visits in past 3 y, mean (SD)	0.56 (1.15)	0.46 (1.02)	0.41 (0.96)	0.46 (1.00)	0.46 (1.00)
No. of outpatient visits in past year, mean (SD)	14.74 (14.32)	15.59 (14.89)	16.38 (15.64)	16.92 (14.99)	15.96 (14.71)
Home care use in past 6 mo	162 319 (6.4)	138 880 (5.8)	171 772 (5.6)	102 437 (5.0)	155 393 (6.0)
Comorbidities					
Cancers	573 859 (22.6)	508 236 (21.3)	669 285 (21.7)	459 260 (22.6)	629 604 (24.5)
Cardiovascular diseases	962 201 (37.5)	856 779 (35.9)	1 115 479 (36.1)	739 296 (36.4)	928 418 (36.1)
Respiratory diseases	497 997 (19.6)	433 179 (18.1)	581 725 (18.8)	380 549 (18.7)	491 996 (19.1)
Anemias	276 353 (10.9)	271 104 (11.3)	379 140 (12.3)	233 615 (11.5)	292 986 (11.4)
Renal diseases	122 455 (4.8)	126 696 (5.3)	184 927 (6.0)	105 643 (5.2)	129 420 (5.0)
Diabetes mellitus	540 588 (21.3)	536 476 (22.4)	732 882 (23.7)	438 661 (21.6)	552 319 (21.5)
Immune disorders	14 843 (0.6)	15 141 (0.6)	17 671 (0.6)	12 615 (0.6)	14 705 (0.6)
Medications					
No. of medications in past year, mean (SD)	7.63 (5.96)	7.89 (6.21)	8.16 (6.45)	7.76 (6.09)	7.71 (6.00)
Statin use	854 700 (33.6)	858 731 (35.9)	1 124 765 (36.4)	688 942 (33.9)	863 125 (33.5)
ACE inhibitor use	843 154 (33.2)	785 642 (32.9)	980 638 (31.8)	645 290 (31.8)	826 726 (32.2)
β-Blocker use	628 693 (24.7)	573 857 (24.0)	743 356 (24.1)	480 873 (23.7)	620 284 (24.1)
Calcium channel blocker use	627 424 (24.7)	613 355 (25.7)	810 076 (26.2)	507 752 (25.0)	621 419 (24.1)
Procedures					
Stress test	503 847 (19.8)	480 825 (20.1)	658 773 (21.3)	423 177 (20.8)	487 476 (18.9)
Bone mineral density test	549 060 (21.6)	697 701 (29.2)	979 151 (31.7)	570 520 (28.1)	654 834 (25.4)
Echocardiography	551 721 (21.7)	566 730 (23.7)	804 503 (26.1)	474 199 (23.4)	529 427 (20.6)
Electrocardiography	1 640 121 (64.6)	1 653 914 (69.2)	2 308 072 (74.8)	1 419 621 (69.9)	1 681 150 (65.3)

Table 4. Crude and Adjusted Association Between Influenza Vaccination and All-Cause Mortality Using Different Risk-Adjustment Methods

Influenza Season	Death During Influenza Seasons		Death During Post–Influenza Seasons	
	Crude OR (95% CI)	Adjusted OR (95% CI)[d]	Crude OR (95% CI)	Adjusted OR (95% CI)[d]
Logistic Regression Modeling				
2000-2001	0.76 (0.73-0.79)	0.74 (0.71-0.77)	0.87 (0.84-0.91)	0.82 (0.78-0.85)
2001-2002	0.80 (0.77-0.83)	0.77 (0.74-0.80)	0.92 (0.89-0.96)	0.87 (0.83-0.90)
2002-2003	0.61 (0.58-0.64)	0.59 (0.56-0.61)	0.93 (0.89-0.96)	0.84 (0.80-0.87)
2003-2004	0.53 (0.51-0.55)	0.51 (0.49-0.53)	0.91 (0.88-0.94)	0.84 (0.81-0.87)
2004-2005	0.74 (0.72-0.76)	0.68 (0.66-0.70)	0.95 (0.92-0.99)	0.87 (0.84-0.91)
2005-2006	0.82 (0.79-0.85)	0.74 (0.71-0.77)	0.91 (0.88-0.95)	0.82 (0.78-0.85)
2006-2007	0.72 (0.70-0.74)	0.66 (0.64-0.68)	0.96 (0.93-1.00)	0.87 (0.83-0.90)
2007-2008	0.73 (0.71-0.75)	0.66 (0.64-0.68)	0.93 (0.89-0.96)	0.83 (0.80-0.86)
2008-2009	0.76 (0.74-0.79)	0.70 (0.68-0.73)	0.98 (0.94-1.01)	0.88 (0.85-0.92)
Pooled	0.72 (0.67-0.77)	0.67 (0.62-0.72)	0.93 (0.91-0.95)	0.85 (0.83-0.86)
IV Analysis				
2000-2001	0.82 (0.71-0.95)	0.81 (0.68-0.97)	0.85 (0.74-0.98)	0.92 (0.78-1.10)
2001-2002	0.84 (0.74-0.95)	0.80 (0.69-0.94)	1.00 (0.87-1.15)	1.25 (1.05-1.49)
2002-2003	0.97 (0.83-1.13)	1.05 (0.86-1.27)	0.98 (0.86-1.13)	1.22 (1.03-1.45)
2003-2004	0.72 (0.63-0.82)	0.78 (0.66-0.91)	0.87 (0.76-0.99)	1.15 (0.97-1.35)
2004-2005	0.88 (0.79-0.97)	1.08 (0.95-1.23)	0.80 (0.71-0.91)	1.12 (0.96-1.31)
2005-2006	0.76 (0.68-0.85)	0.76 (0.66-0.88)	0.83 (0.73-0.93)	1.08 (0.92-1.26)
2006-2007	0.95 (0.84-1.07)	1.11 (0.95-1.30)	0.85 (0.75-0.97)	1.19 (1.01-1.41)
2007-2008	0.87 (0.79-0.96)	1.00 (0.89-1.13)	0.80 (0.71-0.91)	1.11 (0.95-1.29)
2008-2009	0.90 (0.81-1.00)	1.05 (0.92-1.19)	0.83 (0.73-0.93)	1.14 (0.98-1.33)
Pooled	0.85 (0.80-0.90)	0.94 (0.84-1.03)	0.86 (0.82-0.91)	1.13 (1.07-1.19)

Table 5. Crude and Adjusted Association Between Influenza Vaccination and the Composite Outcome of P&I Hospitalization or All-Cause Mortality Using Different Risk-Adjustment Methods

Influenza Season	P&I Hospitalization or Death During Influenza Seasons		P&I Hospitalization or Death During Post–Influenza Seasons	
	Crude OR (95% CI)	Adjusted OR (95% CI)[d]	Crude OR (95% CI)	Adjusted OR (95% CI)[d]
Logistic Regression Modeling				
2000-2001	0.85 (0.83-0.88)	0.80 (0.77-0.83)	0.94 (0.91-0.97)	0.86 (0.83-0.89)
2001-2002	0.87 (0.84-0.89)	0.79 (0.77-0.82)	0.88 (0.86-1.02)	0.91 (0.88-0.94)
2002-2003	0.72 (0.70-0.75)	0.67 (0.65-0.70)	0.98 (0.95-1.01)	0.87 (0.84-0.90)
2003-2004	0.67 (0.65-0.69)	0.61 (0.60-0.63)	0.96 (0.93-0.99)	0.87 (0.84-0.90)
2004-2005	0.83 (0.81-0.85)	0.75 (0.73-0.77)	1.00 (0.96-1.03)	0.90 (0.87-0.93)
2005-2006	0.91 (0.88-0.93)	0.80 (0.77-0.82)	0.97 (0.94-1.00)	0.86 (0.83-0.89)
2006-2007	0.81 (0.79-0.83)	0.72 (0.70-0.74)	1.02 (0.99-1.05)	0.90 (0.87-0.93)
2007-2008	0.83 (0.81-0.85)	0.72 (0.71-0.74)	0.99 (0.96-1.02)	0.87 (0.84-0.90)
2008-2009	0.87 (0.85-0.90)	0.77 (0.75-0.80)	1.04 (1.00-1.07)	0.92 (0.89-0.95)
Pooled	0.82 (0.77-0.87)	0.74 (0.70-0.78)	0.97 (0.94-1.00)	0.88 (0.87-0.90)
IV Analysis				
2000-2001	0.78 (0.69-0.89)	0.83 (0.71-0.96)	0.78 (0.69-0.88)	0.88 (0.76-1.02)
2001-2002	0.72 (0.65-0.80)	0.75 (0.66-0.85)	0.84 (0.74-0.96)	1.03 (0.89-1.19)
2002-2003	0.83 (0.73-0.94)	0.97 (0.82-1.13)	0.88 (0.78-0.99)	1.11 (0.96-1.29)
2003-2004	0.64 (0.57-0.71)	0.75 (0.65-0.85)	0.77 (0.69-0.87)	1.05 (0.91-1.21)
2004-2005	0.76 (0.70-0.83)	0.98 (0.88-1.10)	0.74 (0.66-0.82)	1.02 (0.89-1.18)
2005-2006	0.67 (0.61-0.74)	0.74 (0.65-0.83)	0.76 (0.69-0.85)	1.04 (0.91-1.19)
2006-2007	0.75 (0.68-0.83)	0.90 (0.79-1.03)	0.73 (0.65-0.82)	1.00 (0.87-1.16)
2007-2008	0.76 (0.70-0.83)	0.90 (0.81-1.00)	0.73 (0.65-0.81)	0.99 (0.87-1.14)
2008-2009	0.75 (0.68-0.82)	0.90 (0.81-1.01)	0.76 (0.68-0.84)	1.02 (0.90-1.17)
Pooled	0.74 (0.70-0.77)	0.86 (0.79-0.92)	0.77 (0.73-0.81)	1.02 (0.97-1.06)

INVITED COMMENTARY

ONLINE FIRST

The Influenza Vaccine in Elderly Persons

A Shot in the Dark?

M. Alan Brookhart, PhD
Leah McGrath, MS

- Results compatible with recent studies
- Should have used pre-flu season as a negative control
- Differences between regions in vaccine assessment might have biased results to null

Distance to Specialized Care As An Instrumental Variable

McClellan, M., B. McNeil and J. Newhouse, *JAMA*, 1994.
"Does More Intensive Treatment of Acute Myocardial Infarction Reduce Mortality?''

- Medicare claims data identify admissions for AMI, 1987-91
- Treatment: Cardiac catheterization (marker for aggressive care)
- Outcome: Survival to 1 day, 30 days, 90 days, etc.
- Instrument: Indicator of whether the hospital nearest to a patient's residence does catheterizations.

Are assumptions valid ?

1. Is IV associated with treatment?

   26.2% get cath if nearest hospital does caths
   19.5% get cath if nearest hospital does not do caths

2. Is IV associated with outcome other than through it effect on treatment?

   Can't be determined—but IV is unassociated with observed patient characteristics.

McClellan, et al. results

1. Conventional methods
   - 1-year mortality is 30% lower (17% vs. 47%) if catheterized
   - OLS estimate is -24%, adjusting for observable risk factors

2. IV estimator suggest catheterization associated with 10 percentage point reduction in mortality

$$\frac{E[Y|Z=1]-E[Y|Z=0]}{E[X|Z=1]-E[X|Z=0]} = \frac{-0.7\%}{6.7\%} = -10.4\%$$

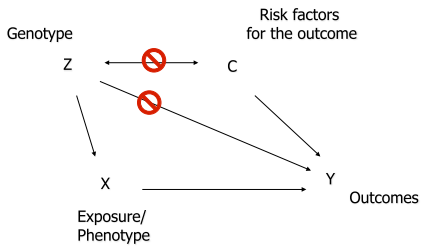
IVs can also be created

- 'Randomized encouragement' designs
- Randomized 'academic detailing' programs (Avorn and Soumerai)
- Designed delays (McClure M., Dormuth C; work in British Columbia)

Mendelian Randomization (Davey-Smith)

- Using genes as instruments for phenotypes or environmental exposures
- Mendel's Law of Independent Assortment: during gamete formation, segregation of alleles from one allelic pair is independent of the segregation of the alleles of another allelic pair

Mendelian Randomization



The effect of alcohol on HDL and hypertension
Davey-Smith and Ebrahim, BMJ 2005

- Studies of the effect of alcohol consumption are difficult
- Alcohol related to many lifestyle characteristics exposures that are hard to measure
- Enzyme aldehdye dehydrogenase (AD) responsible for alcohol metabolism
- 50% of Japanese are homozygous or heterozygous for a non-functional variant of the AD gene

Association between genotype and various characteristics

	Homozygous	Heterozygous	Functional Variant
Mean Alcohol Consumption (ml/day)	5.3	15.1	29.2
Mean Age	61.3	61.5	60.6
% Smokers	48.5	47.9	47.7
Mean HDL (mmmol/l)	1.24	1.35	1.4
% with Hypertension	40.6	37.7	46.9

Mendelian Randomization
Discussion

- Does this genotype seem like a valid instrument for the effect of alcohol?

ORIGINAL INVESTIGATION

Influenza Vaccine Effectiveness in Patients on Hemodialysis

An Analysis of a Natural Experiment

Leah J. McGrath, MHS; Abhijit V. Kshirsagar, MD, MPH; Stephen R. Cole, PhD; Lily Wang, PhD; David J. Weber, MD, MPH; Til Stürmer, MD, MPH; M. Alan Brookhart, PhD

- Controversy about effectiveness of vaccine in the elderly and patients with ESRD
- Receipt of vaccine appears to be a marker of good health
- Reports finding 50% reduced risk of mortality in vaccinated patients
- Year-to-year variation in vaccine match represent a natural experiment that we can exploit

Antigenic Distance – Vaccine Match

Table 2. Description of flu seasons

	1997	1998	1999	2001	2003
% Match	14%	90%	97%	100%	11%
Predominate strain	A(H3N2)	A(H3N2), B	A(H3N2)	A(H3N2), B	A(H3N2)
Start of flu season	1/24/1998	1/16/1999	12/18/1999	1/12/2002	10/25/2003
End of flu season	2/21/1998	4/10/1999	3/25/2000	4/27/2002	1/17/2004

Sketch of Design and Analysis

- Identified all hemodialysis patients prevalent on Sept. 1st 1997 and 1998
- Standard Analysis:
  - Vaccination status is a time-varying covariate
- Alternative analysis
  - Compared vaccinated in 1997 to vaccinated in 1998
  - Follow-up started on date vaccine was administered

Antigenic Distance – Vaccine Match

Table 2. Description of flu seasons

	1997	1998	1999	2001	2003
% Match	14%	90%	97%	100%	11%
Predominate strain	A(H3N2)	A(H3N2), B	A(H3N2)	A(H3N2), B	A(H3N2)
Start of flu season	1/24/1998	1/16/1999	12/18/1999	1/12/2002	10/25/2003
End of flu season	2/21/1998	4/10/1999	3/25/2000	4/27/2002	1/17/2004

Standard Analysis: Cox Proportional Hazards Model

Table 3. Estimates of Vaccine Effectiveness Comparing Vaccinated vs Unvaccinated Populations by Year

Year	No. of Events	No. of Cohort Lost to FU or Transplant	HR (95% CI)			
			Crude	Adjusted[a]	Adjusted in Preinfluenza Period[b]	Adjusted in Preinfluenza Period[c]
1997						
ILI	30 107	2807	0.95 (0.93-0.97)	0.89 (0.87-0.91)	0.90 (0.88-0.92)	0.76 (0.73-0.79)
Influenza/pneumonia hospitalization	16 081	3035	0.92 (0.89-0.95)	0.86 (0.83-0.89)	0.87 (0.85-0.90)	0.75 (0.70-0.80)
Death	23 397	3144	0.77 (0.75-0.79)	0.70 (0.68-0.72)	0.48 (0.46-0.51)	0.47 (0.44-0.49)
1998						
ILI	33 552	2848	0.94 (0.92-0.96)	0.88 (0.86-0.90)	0.77 (0.74-0.80)	0.74 (0.71-0.77)
Influenza/pneumonia hospitalization	17 969	3048	0.91 (0.88-0.94)	0.84 (0.81-0.87)	0.75 (0.71-0.80)	0.73 (0.68-0.78)
Death	25 768	3159	0.79 (0.77-0.81)	0.72 (0.70-0.74)	0.51 (0.48-0.53)	0.46 (0.44-0.49)
1999						
ILI	34 837	2783	0.94 (0.92-0.96)	0.87 (0.85-0.89)	0.67 (0.64-0.71)	0.62 (0.58-0.66)
Influenza/pneumonia hospitalization	18 893	3,020	0.90 (0.87-0.93)	0.84 (0.81-0.86)	0.63 (0.58-0.68)	0.56 (0.51-0.62)
Death	26 904	3150	0.76 (0.74-0.78)	0.70 (0.68-0.72)	0.36 (0.33-0.39)	0.28 (0.25-0.31)
2001						
ILI	40 768	3031	0.90 (0.88-0.92)	0.86 (0.84-0.88)	0.76 (0.73-0.79)	0.69 (0.66-0.72)
Influenza/pneumonia hospitalization	22 658	3280	0.87 (0.85-0.90)	0.82 (0.80-0.85)	0.71 (0.68-0.76)	0.64 (0.60-0.69)
Death	30 221	3417	0.76 (0.74-0.78)	0.70 (0.68-0.71)	0.46 (0.44-0.49)	0.40 (0.37-0.43)

Antigenic Distance – Vaccine Match

Table 4. RHR Estimates of Vaccine Effectiveness by Comparing Matched vs Mismatched Years Among Vaccinated vs Unvaccinated Populations

Variable	RHR (95% CI)						
	1998 vs 1997		1999 vs 1997		2001 vs 1997		Pooled vs 1997
	Crude	Adjusted[a]	Crude	Adjusted	Crude	Adjusted	Adjusted
ILI	1.03 (1.00-1.07)	1.03 (1.00-1.07)	1.01 (0.98-1.04)	1.00 (0.97-1.03)	0.97 (0.94-1.00)	0.98 (0.95-1.01)	1.00 (0.98-1.03)
Influenza/pneumonia hospitalization	1.02 (0.97-1.06)	1.01 (0.97-1.06)	1.00 (0.96-1.05)	0.99 (0.95-1.04)	0.95 (0.92-0.99)	0.95 (0.91-0.99)	0.98 (0.95-1.02)
Death	1.03 (0.99-1.06)	1.02 (0.99-1.06)	0.99 (0.96-1.03)	1.00 (0.96-1.03)	0.99 (0.96-1.03)	0.99 (0.96-1.03)	1.00 (0.97-1.03)

Abbreviations: ILI, influenza-like illness; RHR, ratio of hazard ratios.
[a] Adjusted for age, race, sex, cause of end-stage renal disease, vintage, adherence, hospital days, mobility aids, network, comorbidities, and oxygen use.

Conclusions

- Pharmacoepidemiology
  - Very large data sets
  - Limited ascertainment of confounders
- IV methods may be often indicated
- Key is finding good instruments!
- Care must be taken with
  - Study design
  - Evaluating assumptions
  - Interpreting/generalizing results

Discussion / Questions

Readings On Instrumental Variable Methods

Recommended Reading

Brookhart MA, Rassen JA, Schneeweiss S. Instrumental variable methods in comparative safety and effectiveness research. Pharmacoepidemiol Drug Saf. 2010

Angrist JD, Imbens GW, Rubin DB. Identification of causal effects using instrumental variables. *Journal of the American Statistical Association.* 1996;81:444-455.

Brookhart MA, Wang PS, Solomon DH, Schneeweiss S. Evaluating short-term drug effects using a physician-specific prescribing preference as an instrumental variable. *Epidemiology.* May 2006;17(3):268-275.

McClellan M, McNeil BJ, Newhouse JP. Does more intensive treatment of acute myocardial infarction in the elderly reduce mortality? Analysis using instrumental variables. *Jama.* Sep 21 1994;272(11):859-866.

Brookhart MA, Schneeweiss S. Preference-based instrumental variable methods for the estimation of treatment effects: assessing validity and interpreting results. *International Journal of Biostatistics.* 2007;3(1).

Smith GD, Ebrahim S. What can mendelian randomisation tell us about modifiable behavioral and environmental exposures? BMJ 2005

Fitting IVs in Stata
Two-Stage Linear Model

$X=a_0+ a_1Z+ a_2$ age + a_3 gender + … + e_x

$Y= b_0 + b_1 X+ b_2$ age + b_3 gender + … + e_y

System is solved by two-stage least-squares

Stata Code

Unadjusted Model (no covariates)

```
ivreg y (x=z), first
```

Adjusted Model (with covariates)

```
xi: ivreg y bleeding ulcer i.year i.gender ost_arthrit  (x=z),
  first
```

Stata Code

Unadjusted Model (no covariates)

```
ivreg y (x=z), first
```

Adjusted Model (with covariates)

```
xi: ivreg y bleeding ulcer i.year i.gender ost_arthrit  (x=z),
  first
```

Stata Code

Robust standard errors for IV estimator to account for within-physician clustering

```
ivreg y (x=z), first cluster(doctor)
```

IV Probit Model

```
ivprobit y (x=z), first
```

-- notes --

Studying Medication Adherence and Outcomes

M. Alan Brookhart, Ph.D.
Department of Epidemiology,
UNC Gillings School of Global Public Health
University of North Carolina at Chapel Hill

UNC GILLINGS SCHOOL OF GLOBAL PUBLIC HEALTH

Learning Objectives

- To understand how to measure and model medication adherence using pharmacy claims data
- To understand some challenges and potential approach to estimating the effects of adherence on outcomes

2

Everyone benefits from good adherence

- Stakeholders
  - Pharmaceutical companies
  - Physicians
  - Pharmacies
  - Patients

Overview of Lecture

- Introduction
- Measuring adherence
- Example: Adherence with Osteoporosis Medications
- Dynamic patterns of adherence
- Example: Statins in British Columbia
- The healthy user/adherer effect
- Adherence and comparative safety/effectiveness research

The Consequences of Nonadherence

- 125,000 deaths per year in U.S.[1]
- All medication-related hospital admissions in the United States, 33 to 69 percent are due to poor medication adherence.[4]
- Total cost estimates range from $100 billion[2] to $300 billion.[3]

[1] Cited by Haynes RB. *Compliance in Healthcare*, 1979; Blackwell B. *N Engl J Med*, 1973.
[2] Cited by Munger, Liu, Wertheimer, Whitcup, Berg, Ickovics, Burney, Biondi-zoccai
[3] DiMatteo, *Med Care*, 2004.
4 McDonnell PJ, Jacobs MR. Hospital admissions resulting from preventable adverse drug reactions. Ann Pharmacother 2002; 36:1331-6.

Why we need to study adherence

- To evaluate the magnitude of the problem
- To understand adherence
- To target interventions
- To help inform/interpret observational safety and effectiveness research of drugs

What do we know / do not know

- Many papers on
  - **How low** adherence is
  - **Patient groups at risk of becoming** nonadherent (people of lower education, socioeconomic status, depressed patients)
  - **Weak predictors of non-adherence** (medication regimen complexity, cost)
  - **Consequences** of nonadherence (somewhat questionable validity)
- Very little is known about
  - **Why** patients stop specific treatments
  - **How** to predict nonadherence at the patient level
  - **What** interventions will cause meaningful improvements

Table 1. Methods of Measuring Adherence.

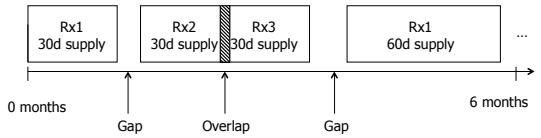
Test	Advantages	Disadvantages
Direct methods		
Directly observed therapy	Most accurate	Patients can hide pills in the mouth and then discard them; impractical for routine use
Measurement of the level of medicine or metabolite in blood	Objective	Variations in metabolism and "white-coat adherence" can give a false impression of adherence; expensive
Measurement of the biologic marker in blood	Objective; in clinical trials, can also be used to measure placebo	Requires expensive quantitative assays and collection of bodily fluids
Indirect methods		
Patient questionnaires, patient self-reports	Simple; inexpensive; the most useful method in the clinical setting	Susceptible to error with increases in time between visits; results are easily distorted by the patient
Pill counts	Objective, quantifiable, and easy to perform	Data easily altered by the patient (e.g., pill dumping)
Rates of prescription refills	Objective; easy to obtain data	A prescription refill is not equivalent to ingestion of medication; requires a closed pharmacy system
Assessment of the patient's clinical response	Simple; generally easy to perform	Factors other than medication adherence can affect clinical response
Electronic medication monitors	Precise; results are easily quantified; tracks patterns of taking medication	Expensive; requires return visits and downloading data from medication vials
Measurement of physiologic markers (e.g., heart rate in patients taking beta-blockers)	Often easy to perform	Marker may be absent for other reasons (e.g., increased metabolism, poor absorption, lack of response)
Patient diaries	Help to correct for poor recall	Easily altered by the patient
When the patient is a child, questionnaire for caregiver or teacher	Simple; objective	Susceptible to distortion

Osterberg and Blaschke, NEJM 2005

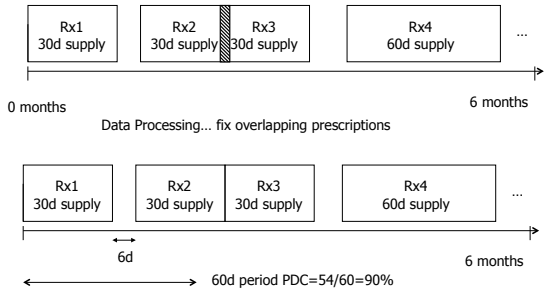
Typical Pharmacy Claims Data

- Date filled
- Agent (NDC code) & dose
- Days Supply
- Physician identifier
- Pharmacy identifier
- “Refill” indicator

Typical Pharmacy Refill Data

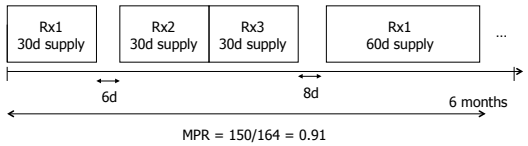


Percentage of Days Covered (PDC)

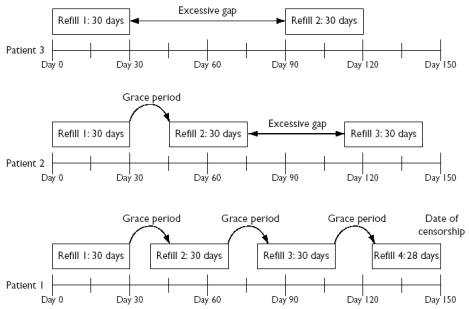


Medication Possession Ratio (MPR)

MPR is usually defined as the sum of the days' supply of medication divided by the number of days between the first fill and the last refill plus the days' supply of the last refill.



Measuring Persistence



Rishi Sikka, MD; Fang Xia, PhD; and Ronald E. Aubert, PhD, MSPH

(Am J Manag Care. 2005;11:449-457)

Arch Intern Med. 2005;165:2414-2419

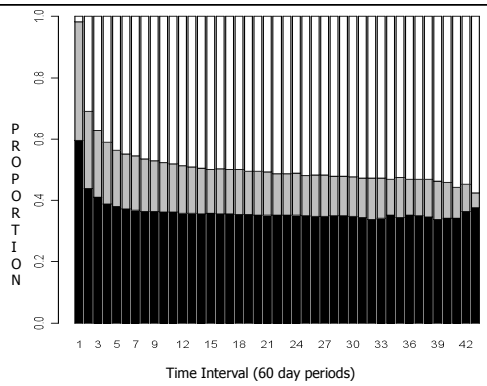
Compliance With Osteoporosis Medications

Daniel H. Solomon, MD, MPH; Jerry Avorn, MD; Jeffrey N. Katz, MD, MSc; Joel S. Finkelstein, MD; Marilyn Arnold, ScD; Jennifer M. Polinski, MPH; M. Alan Brookhart, PhD

- Selected all new user of osteoporosis medications who were Medicare beneficiaries and eligible for PACE from January 1, 1996, through December 31, 2002.
- Osteoporosis medications were bisphosphonates, HRT, raloxifene, and calcitonin.
- Follow-up was broken into 60-day intervals, percentage of days covered by medication was computed for each interval (patients were dropped from the denominator at death/censoring)
- Discontinuation was defined 120 days with no medication available.

Table 1. Characteristics of Patients in the 12 Months Before Initiating a Medication for Osteoporosis*

Characteristic	Value
No. of patients	40 002
Female sex	38 432 (96.1)
Age, y	79.9 ± 6.8
White race	38 480 (96.2)
No. of major comorbid conditions	2.2 ± 2.2
No. of different medications	9.1 ± 5.4
No. of physician visits	9.9 ± 6.8
Acute care hospitalization	15 110 (37.8)
Nursing home residence	4862 (12.2)
Fracture of the hip, wrist, humerus, or spine	7592 (19.0)
Bone mineral density testing	8557 (21.4)
Starting medications (monotherapy or combination)	
Bisphosphonate	18 751 (46.9)
Calcitonin	11 761 (29.4)
Hormone therapy	5285 (13.2)
Raloxifene hydrochloride	2578 (6.4)
Bisphosphonate and calcitonin	971 (2.4)
Other combinations	656 (1.6)



Black: PDC> 66%; Grey: 0%< PDC <=66%; White: PDC=0%.

***Persistence* is very poor**

One year after initiating treatment for osteoporosis, 45.2% of the 40,002 patients were not continuing treatment

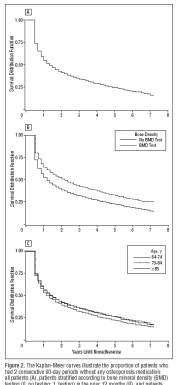


Figure 2. The Kaplan-Meier curves illustrate the proportion of patients who had 2 consecutive 60-day periods without any osteoporosis medication: all patients (A), patients stratified according to bone mineral density (BMD) testing (B; no testing, 1 testing, or ≥ the prior 12 months), and patients stratified according to age in years at the time of drug initiation (C).

Statistical Modeling of Adherence

- Modeled adherence in each 60-day interval via a repeated measures model
  - PDC as a continuous variable
  - Adherence as a dichotomous variables (PDC>66%)
- One model with baseline variables, one with time-varying covariates

Table 2. Adjusted Models of Compliance in Osteoporosis Medication Use, Dichotomous Outcome*

Characteristic	Relative Risk (95% Confidence Interval)	
	Full Model	Baseline Variables Only
Age, y		
65–74	1.00	1.00
75–84	0.96 (0.94–0.99)	0.96 (0.94–0.99)
≥85	0.88 (0.85–0.90)	0.87 (0.84–0.89)
Female sex	1.16 (1.08–1.25)	1.16 (1.08–1.25)
Race, nonwhite	0.83 (0.78–0.89)	0.83 (0.78–0.89)
Starting osteoporosis medication regimen		
Bisphosphonate	1.00	1.00
Calcitonin	0.55 (0.53–0.56)	0.55 (0.53–0.56)
Hormone therapy	0.82 (0.79–0.84)	0.82 (0.79–0.85)
Raloxifene hydrochloride	1.12 (1.08–1.16)	1.12 (1.08–1.16)
Bisphosphonate and calcitonin	0.94 (0.88–0.99)	0.94 (0.88–0.99)
Other combinations	1.21 (1.14–1.28)	1.21 (1.15–1.28)
During 12 mo before initiation of a medication for osteoporosis		
Comorbidity index, per condition	0.97 (0.96–0.97)	0.97 (0.96–0.97)
No. of physician visits†	0.99 (0.99–0.99)	0.99 (0.99–0.99)
No. of different medications‡	0.99 (0.99–0.99)	0.99 (0.99–0.99)
BMD testing	1.19 (1.16–1.22)	1.20 (1.17–1.23)
Fracture	1.10 (1.06–1.13)	1.10 (1.06–1.13)
Nursing home residence	1.09 (1.06–1.12)	1.08 (1.04–1.13)
During the course of osteoporosis medication use		
BMD testing	1.22 (1.19–1.25)	§
Fracture	1.13 (1.10–1.15)	§
Nursing home residence	0.59 (0.57–0.60)	§
Hospitalization	0.98 (0.97–0.99)	§

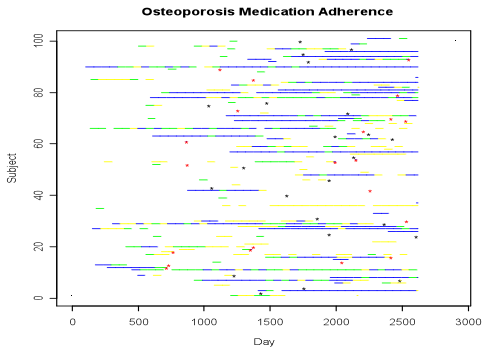
Table 3. Adjusted Models of Compliance in Osteoporosis Medication Use, Continuous Outcome*

Characteristic	Additional Days With Osteoporosis Medication (95% Confidence Interval)	
	Full Model	Baseline Variables Only
Age, y		
65–74	1.0	1.0
75–84	−1.4 (−2.0 to −0.80)	−1.4 (−1.9 to −0.8)
≥85	−3.6 (−4.5 to −3.2)	−3.9 (−4.5 to −3.2)
Female sex	3.3 (2.1 to 4.6)	3.4 (2.1 to 4.7)
Race, nonwhite	−3.7 (−4.4 to −3.1)	−3.8 (−4.9 to −2.6)
Starting osteoporosis medication regimen		
Bisphosphonate	1.0	1.0
Calcitonin	−9.0 (−9.5 to −8.4)	−9.0 (−9.5 to −8.5)
Hormone therapy	−5.3 (−6.0 to −4.5)	−5.3 (−6.0 to −4.5)
Raloxifene hydrochloride	3.4 (2.4 to 4.4)	3.4 (2.4 to 4.4)
Bisphosphonate and calcitonin	−0.4 (−1.9 to 1.1)	−0.36 (−1.8 to 1.1)
Other combinations	5.6 (3.8 to 7.3)	5.6 (3.9 to 7.7)
During 12 mo before initiation of a medication for osteoporosis		
Comorbidity index, per condition	−0.75 (−0.85 to 0.70)	−0.83 (−0.91 to 0.75)
No. of physician visits†	−0.07 (−0.10 to −0.03)	−0.06 (−0.10 to −0.02)
No. of different medications‡	−0.07 (−0.10 to −0.03)	−0.07 (−0.12 to −0.02)
BMD testing	4.6 (4.0 to 5.2)	4.7 (4.1 to 5.3)
Fracture	2.2 (1.5 to 2.8)	2.3 (1.7 to 3.0)
Nursing home residence	2.2 (1.4 to 3.1)	2.0 (1.1 to 2.8)
During the course of osteoporosis medication use		
BMD testing	7.5 (7.0 to 8.0)	§
Fracture	3.8 (3.3 to 4.3)	§
Nursing home residence	−7.7 (−8.1 to −7.3)	§

OP adherence study: Results

- Persistence is poor
- Clinical need predicts adherence
- Poor adherence was associated with non-white race, old age

Individual Time Series Plot: 100 randomly selected subjects
(blue dash=high adherence, green=medium, yellow=low
black star=censor, red=death



Gaps in Treatment Among Users of Osteoporosis Medications: The Dynamics of Noncompliance

M. Alan Brookhart, PhD, Jerry Avorn, MD, Jeffrey N. Katz, MD, MS, Joel S. Finkelstein, MD, Marilyn Arnold, ScD, Jennifer M. Polinski, MPH, Amanda R. Patrick, MS, Helen Mogun, MS, Daniel H. Solmon, MD, MPH

Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital/Harvard Medical School, Boston, Mass.

The American Journal of Medicine (2007) 120, 251-256

60% of patient who stop treatment for 60 days have restarted within two years....

Use of OP medications appears to be dynamic.

Positive interpretation: Adherence not quite as bad as we thought

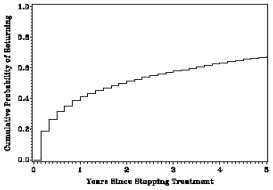


Figure 2 Kaplan-Meier estimate of the cumulative probability of returning to treatment.

Adherence as a Dynamic Process?

- The prevailing paradigm is that adherence is relatively static
- Many health-related behaviors are cyclical
  - Dieting
  - Exercise
- Is it useful to view adherence as a dynamic process?

ARCH INTERN MED/VOL 167, APR 23, 2007

Physician Follow-up and Provider Continuity Are Associated With Long-term Medication Adherence

A Study of the Dynamics of Statin Use

M. Alan Brookhart, PhD; Amanda R. Patrick, MS; Sebastian Schneeweiss, MD; Jerry Avorn, MD; Colin Dormuth, ScD; William Shrank, MD, MS; Boris L. G. van Wijk, PharmD; Suzanne M. Cadarette, PhD; Claire F. Canning, MA; Daniel H. Solomon, MD, MPH

- A study of 239,911 new users of statins in British Columbia, of whom 129,167 (53.8%) had a period of nonadherence that lasted for at least 90d.

- How many of these patients restart statin therapy?
- Can we identify predictors of re-initiation?

Re-initiation Rate

- Of patients who stopped therapy for at least 90d, an estimated 38% restarted treatment within one year and 52% restarted within two years.
- Statin use is dynamic

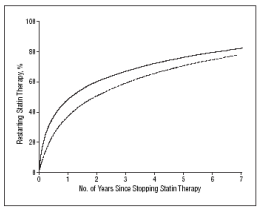
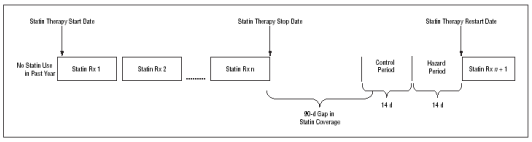


Figure 2. Kaplan-Meier estimate of the cumulative probability of returning to treatment. Solid line indicates the probability of restarting statin therapy in a cohort in which stopping therapy is defined as a period of at least 90 days after the completion of 1 prescription in which no refill for any statin medication was obtained. In this cohort, the index date is 90 days after the completion of the last prescription; dotted line, the probability of restarting statin therapy in a cohort in which the definition of stopping is extended to a period of at least 180 days after the completion of the last prescription.

Identifying Predictors of Re-initiation: a case crossover design



- Events
  - Cholesterol testing
  - Any physician visit
  - Visit with physician who started the patient on a statin
  - CAD-related hospitalization

Results

Table 2. Frequency of Events in Control Period* and Hazard Period† From Case-Crossover Analysis‡

Event	14-Day Control Period	14-Day Hazard Period	30-Day Control Period	30-Day Hazard Period
Physician visits				
Index physician§	12 818 (17.5)	34 603 (47.2)	18 734 (25.6)	39 548 (54.0)
Other physician	18 259 (24.9)	30 060 (41.0)	26 396 (36.0)	37 775 (51.5)
Any physician	28 127 (38.4)	57 494 (78.5)	38 307 (52.3)	63 853 (87.1)
Cholesterol testing	6689 (9.1)	15 180 (20.7)	6570 (9.0)	22 518 (30.7)
Hospitalizations				
Myocardial infarction	71 (0.1)	645 (0.9)	82 (0.1)	696 (1.)
Other cardiovascular disease	244 (0.3)	870 (1.2)	346 (0.5)	1100 (1.5)
Noncardiovascular	691 (0.9)	1195 (1.6)	1307 (1.8)	1909 (2.6)

Table 3. Results from Case-Crossover Analysis: Events Predicting Return to Adherence*

Event	14-Day Hazard and Control Periods	30-Day Hazard and Control Periods
Physician visits		
Index physician†	6.1 (5.9-6.3)	5.0 (4.8-5.2)
Other physician	2.9 (2.8-3.0)	2.4 (2.4-2.5)
Cholesterol testing	1.5 (1.4-1.5)	2.4 (2.4-2.5)
Hospitalizations		
Myocardial infarction	12.2 (8.9-16.9)	8.0 (6.2-10.3)
Other cardiovascular disease	3.6 (3.1-4.3)	3.0 (2.6-3.5)
Noncardiovascular	1.7 (1.5-1.9)	1.3 (1.2-1.4)

Statin Adherence Dynamics Study: Results

- Statin use is dynamic, once stopped does not mean always stopped
- "Fire-and-forget" approach to treatment not optimal
- Physician follow-up and provider continuity appear to be important components of adherence

Limitations

- Don't know why a patient stopped taking med
- Uncertainty about causal process
  - Do patients see a physician because they need a refill?
  - Physician urges patient to resume treatment

Adherence to Lipid-lowering Therapy and the Use of Preventive Health Services: An Investigation of the Healthy User Effect

M. Alan Brookhart[1], Amanda R. Patrick[1], Colin Dormuth[2], Jerry Avorn[1], William Shrank[1], Suzanne M. Cadarette[1], and Daniel H. Solomon[1]

American Journal of Epidemiology Advance Access published May 15, 2007

- Are patients who adhere to statins more likely to do other things that might affect outcomes?
- Sought to examine association between adherence and use of prevention-oriented health services
- Identified a cohort of new users of statins between 1996 and 2004 with no evidence of coronary heart disease (history of AMI, diabetes, angina, hypercholesterolemia)

Study Design

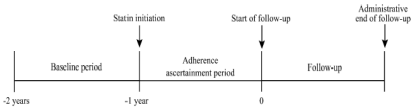


FIGURE 1. Schematic of study design used in a Pennsylvania cohort, 1996–2004.

- Dropped patients who died (602), lost eligibility (1,937), entered a nursing home (1,269) during ascertainment period -- 20,783 remained
- Outcomes: fecal occult blood test, influenza vaccination, pneumonia vaccination, mammogram, prostate specific antigen test, and bone mineral density test.

Healthy Adherer Results

TABLE 2. Hazard ratios of receiving various screening tests and vaccinations, along with two or more fills during the assessment period vs. a single statin fill, in a Pennsylvania cohort, 1996–2004*

Outcome	Unadjusted hazard ratio	95% confidence interval	Multivariable-adjusted hazard ratio†	95% confidence interval
Women only				
Bone mineral density test	1.04	0.84, 1.27	1.08	0.88, 1.33
Screening mammogram	1.22	1.09, 1.38	1.22	1.09, 1.38
Men only				
Prostate-specific antigen test	1.60	1.15, 2.24	1.57	1.17, 2.19
Both sexes				
Fecal occult blood test	1.29	1.10, 1.50	1.31	1.12, 1.53
Influenza vaccination	1.18	1.09, 1.28	1.21	1.12, 1.31
Pneumonia vaccination	1.44	1.15, 1.80	1.46	1.17, 1.83

* Subjects were censored at the end of follow-up, loss of Pharmaceutical Assistance Contract for the Elderly (PACE) eligibility, death, and nursing home admission.
† The analysis is stratified on age and sex. Multivariable adjustments were made for all the other covariates given in table 1.

Conclusion

- Patients who adhere to statins more likely to receive a range of prevention-oriented clinical service

Epidemiology

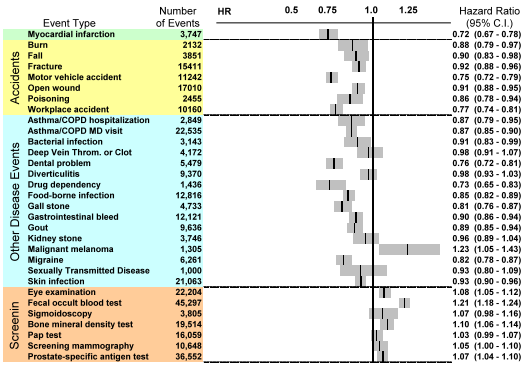
Statin Adherence and Risk of Accidents
A Cautionary Tale

Colin R. Dormuth, ScD; Amanda R. Patrick, SM; William H. Shrank, MD; James M. Wright, MD, PhD; Robert J. Glynn, PhD, ScD; Jenny Sutherland, BSc; M. Alan Brookhart, PhD

(Circulation. 2009;119:2051-2057.)

- Research Question: Are patients who are adherent to statins at lower risk of outcomes unlikely to be affected by statin exposure but likely to be related to healthy lifestyle?
- Population: All new users of statins in British Columbia with no evidence of existing heart disease

Associations Between Adherence to Statin Treatment and Health-Related Events



Conclusions

- Patients who adhere to statins more likely to receive a range of prevention-oriented clinical service at decreased risk of accidents and adverse health outcomes

Medication nonadherence is associated with a broad range of adverse outcomes in patients with coronary artery disease

P. Michael Ho, MD, PhD,[a,b,c] David J. Magid, MD, MPH,[b,c] Susan M. Shetterly, MS,[c] Kari L. Olson, PharmD, BCPS,[b,d] Thomas M. Maddox, MD,[a,b,c] Pamela N. Peterson, MD, MSPH,[b,c,e] Frederick A. Masoudi, MD, MSPH,[b,c,e] and John S. Rumsfeld, MD, PhD[a,b,c] Denver and Aurora, CO

- 15,767 patient with CAD
- Adherence dichotomized: PDC>80% in first 180 days
- Adherence associated with various outcomes during a 1-year follow-up period

Table I. Characteristics of the study population according to adherence category for each of the 3 medications

	•-Blocker (n = 11865)			Statin (n = 13596)			ACE inhibitors (n = 10021)		
Variables	Adherent (n = 8442)	Nonadherent (n = 3423)	P	Adherent (n = 10067)	Nonadherent (n = 3529)	P	Adherent (n = 7859)	Nonadherent (n = 2162)	P
Age	66.2 (10.5)	65.2 (11.0)	b.01	65.9 (10.0)	64.5 (10.9)	b.01	66.8 (10.1)	66.0 (11.1)	b.01
Female sex	32.7	30.9	.05	30.0	33.1	b.01	33.1	33.4	.81
Current smoker	21.2	22.3	.19	20.1	24.7	b.01	19.5	23.0	b.01
Atrial fibrillation	27.7	28.5	.40	26.9	23.9	b.01	31.4	32.1	.56
CABG surgery	46.8	51.0	b.01	49.5	46.1	b.01	48.9	47.8	.39
PCI	50.1	52.5	.02	49.0	50.1	.28	48.7	52.9	b.01
Myocardial infarction	46.7	48.6	b.05	43.6	42.4	.21	45.2	49.3	b.01
Hyperlipidemia	94.1	94.4	.47	97.2	97.0	.70	94.3	94.2	.87
Heart failure	36.5	38.4	.05	34.0	33.9	.91	43.6	47.7	b.01
Chronic obstructive pulmonary disease	27.3	29.8	b.01	28.3	29.8	.08	30.9	35.3	b0.01
Cerebrovascular disease	22.7	26.2	b.01	22.3	23.0	.42	24.3	28.1	b.01
Cancer	18.9	19.0	.92	19.0	18.2	.32	18.9	18.7	.84
Dementia	4.5	5.9	b.01	4.0	4.3	.32	4.5	6.4	b.01
Depression	28.6	35.3	b.01	28.4	32.9	b.01	30.4	36.1	b.01
Diabetes	37.7	36.7	.33	36.4	36.4	.99	45.8	45.2	.64
Hypertension	90.2	88.7	.01	87.2	86.1	.11	93.7	93.6	.89
Sleep apnea	11.7	12.0	.59	11.9	12.3	.53	13.4	13.5	.93

Main Results

Table II. Adjusted HRs between medication nonadherence and patient outcomes

	All-cause mortality (n = 1889)		CV mortality (n = 372)		CV hospitalization (n = 2008)		Coronary revascularization (n = 2377)	
	HR (95% CI)		HR (95% CI)		HR (95% CI)		HR (95% CI)	
Medication nonadherence	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted
• Blockers	1.60 (1.41-1.81)	1.50 (1.33 1.71)	1.62 (1.24-2.14)	1.53 (1.16-2.01)	1.18 (1.06-1.32)	1.10 (0.99-1.23)	1.20 (1.09-1.32)	1.15 (1.04-1.27)
Statins	1.82 (1.61-2.06)	1.85 (1.63, 2.09)	1.58 (1.21-2.07)	1.62 (1.24-2.13)	1.35 (1.22-1.51)	1.35 (1.21-1.50)	1.12 (1.02-1.24)	1.11 (1.01-1.22)
ACE inhibitors	1.92 (1.68-2.19)	1.74 (1.52-1.98)	1.83 (1.38-2.42)	1.66 (1.26-2.20)	1.50 (1.34-1.68)	1.40 (1.25-1.57)	1.39 (1.24-1.56)	1.32 (1.18-1.48)

Cardiovascular hospitalization, AMI or heart failure. Coronary revascularization, PCI or CABG.

- Very strong effects
- Effect weaker for more specific outcomes

Sensitivity Analysis

Table III. Adjusted HRs between nonadherence to proton pump inhibitors or H2 antagonists and patient outcomes

Medication nonadherence	All-cause mortality (n = 1889)	CV mortality (n = 372)	CV hospitalization (n = 2008)	Coronary revascularization (n = 2377)
	HR (95% CI, P)	HR (95% CI, P)	HR (95% CI, P)	HR (95% CI, P)
Proton pump inhibitors or H2 antagonists	1.14 (0.97-1.33, P = .10)	1.10 (0.78-1.57, P = .53)	1.02 (0.87-1.18, P = .83)	1.07 (0.92-1.23, P = .39)

CV, Cardiovascular.

- Acid reflux disease is symptomatic
- PPI, H2 blockers often not used chronically
- Confounding: angina often confused for reflux disease
- Fewer people are adherent

Effectiveness of Statin Therapy in Adults With Coronary Heart Disease

Timothy J. Wilt, MD, MPH; Hanna E. Bloomfield, MD, MPH; Roderick MacDonald, MS; David Nelson, PhD; Indulis Rutks, BS; Michael Ho, MD; Gregory Larsen, MD; Anthony McCall, MD, PhD; Sandra Pineros, MPH; Anne Sales, PhD

- Meta-analysis of 19 placebo-controlled statin trials in secondary prevention
- All cause mortality reduced by 16% (vs 85%)
- CHD mortality and non-fatal MI by 25% (vs 35% CV hospitalization 62% CV Death)

(REPRINTED) ARCH INTERN MED/VOL 164, JULY 12, 2004 WWW.ARCHINTERNMED.COM
1427

- Estimation of the benefits of adherence appears to be overstated
- What else can we do to estimate the effect of adherence?

Approaches to Control the Healthy User Bias: Better Adjustment

- Variables
  - Healthy behaviors
  - Unhealthy behaviors
  - Education
  - Use of other medications
  - Cognitive and functional status
  - Access to care
- These variables are not available in most pharmacoepidemiologic databases in US
- High-dimensional "proxy" adjustment

Approaches to the Healthy User Bias: Active Comparator Group

- Compare adherent new initiators of statins to adherent new users of other preventive medications

  What medications?

  You want something that does not affect the outcome.

- What about an instrumental variable?

Drug Copayment and Adherence in Chronic Heart Failure: Effect on Cost and Outcomes

J. Alexander Cole, D.Sc., M.P.H., Heather Norman, M.A., Lisa B. Weatherby, M.S., and Alexander M. Walker, M.D., Dr.P.H.

- Hard to study effects of medication adherence
- Use copayment as an instrument for the effect of adherence of BB and ACEI in heart failure
- Does this seems like a reasonable IV?
- How would you interpret the results?

Table 2. Predicted Medication Possession Ratios and Predicted Costs and Risks of Hospitalization for Chronic Heart Failure According to Group and Copayment

Group, Copayment ($)	Predicted Medication Possession Ratio, 2002 (%)	Predicted Medical Cost, 2003 ($)	Predicted Frequency of Hospitalization, 2003 (%)
ACE inhibitor			
5	94.5	7583	13.0
10	93.2	7554	13.3
15	91.9	7524	13.7
20	90.7	7495	14.0
25	89.4	7466	14.4
30	88.1	7437	14.7
β-Blocker			
5	94.3	8903	10.0
10	93.5	8779	10.4
15	92.6	8657	10.8
20	91.7	8536	11.2
25	90.8	8417	11.7
30	89.9	8300	12.1

ACE = angiotensin-converting enzyme.

Rationale and design of the Post-MI FREEE trial: A randomized evaluation of first-dollar drug coverage for post–myocardial infarction secondary preventive therapies

Niteesh K. Choudhry, MD, PhD,[a] Troyen Brennan, MD, JD, MPH,[b] Michele Toscano, MS,[b] Claire Spettell, PhD,[b] Robert J. Glynn, ScD, PhD,[a,c] Mark Rubins, MHA, RPh,[b] Sebastian Schneeweiss, MD, ScD,[a] Alan M. Brookhart, PhD,[a] Joaquim Fernandes, MS,[b] Susan Mathew, MPH,[b] Blake Christiansen, MS, RPh,[b] Elliott M. Antman, MD,[d] Jerry Avorn, MD,[a] and William H. Shrank, MD, MSHS[a] *Boston, MA; and Hartford, CT*

- Half of Aetna beneficiaries who experienced an AMI were randomized to receive free cardiovascular drugs ($0 copay)
- Other received usual benefit
- Hypothesis: Reducing copays will improve adherence, and save money and lives

The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL ARTICLE

Full Coverage for Preventive Medications after Myocardial Infarction

Niteesh K. Choudhry, M.D., Ph.D., Jerry Avorn, M.D., Robert J. Glynn, Sc.D., Ph.D., Elliott M. Antman, M.D.,

- 6,000 patients randomized
- Rates of adherence were slightly higher in the free drugs arm (6%)
- Rates of primary outcome (first major vascular event) not reduced
- Rates of all vascular event were lower in free drugs arm HR=0.89
- Costs were not different between groups

Final Lesson: Antipsychotic Medications (APM) in the Elderly

- APMs approved to treat schizophrenia
- Widely used off-label to treat elderly patients with dementia
- Two broad classes: conventional (older drugs) versus atypical (newer drugs)
- Manufacturers of some of the atypicals conducted trials to assess effectiveness of the medications for controlling behavioral disturbances in elderly
- FDA meta-analysis: increased risk of mortality associated with atypical APMs (relative to placebo)
- FDA put a "black box" advisory on label of atypical APMs

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Psychiatric News May 6, 2005
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CLINICAL & RESEARCH NEWS

FDA Orders New Warning On Atypical Antipsychotics

Jim Rosack

The FDA has linked off-label prescribing of antipsychotic drugs to an increased risk of death in the elderly, adding yet more text to the black-box warnings on the drugs' labels.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Risk of Death in Elderly Users of Conventional vs. Atypical Antipsychotic Medications

Philip S. Wang, M.D., Dr.P.H., Sebastian Schneeweiss, M.D., Jerry Avorn, M.D., Michael A. Fischer, M.D., Helen Mogun, M.S., Daniel H. Solomon, M.D., M.P.H., and M. Alan Brookhart, Ph.D.

Table 1. Characteristics of 22,890 New Users of Conventional and Atypical Antipsychotic Medications.

Characteristic	Users of Conventional Antipsychotic Medications (N=9142)	Users of Atypical Antipsychotic Medications (N=13,748)	P Value
	%	%	
Age (mean)	83.2	83.5	<0.001
Sex			
Female	77.6	83.0	<0.001
Male	22.4	17.0	
Race†			
White	92.8	94.7	<0.001
Nonwhite	7.2	5.3	
Diagnosis			
Cardiac arrhythmia	1.4	1.4	0.87
Cerebrovascular disease	29.1	30.9	0.003
Congestive heart failure	32.6	31.1	0.01
Diabetes	25.8	26.8	0.10
Myocardial infarction	3.5	3.5	0.85
Other ischemic heart disease	29.3	24.4	<0.001
Other cardiovascular disorders	12.7	12.3	0.39
Cancer	15.6	14.0	<0.001
HIV infection	<0.1	<0.1	0.36
Dementia	40.8	52.5	<0.001
Delirium	12.2	16.1	<0.001
Mood disorders	22.2	36.3	<0.001
Psychotic disorders	21.3	24.7	<0.001
Other psychiatric disorders	5.9	8.3	<0.001
Use of other drugs			
Antidepressants	28.0	43.5	<0.001
Other psychotropic medications	11.5	13.5	<0.001
Total no. of drugs used (mean)	6.8	7.9	<0.001
Hospitalization in previous 180 days	51.2	53.5	<0.001
Nursing home residence in previous 180 days	15.9	21.4	<0.001
Death within 180 days of index prescription for antipsychotic medication	17.9	14.6	<0.001

Ideally results from different approaches will agree

- APM Study comparing risk of death of new users atypicals to new users of conventionals
- Used various analytical approaches
  - Used COX-PH regression adjusting covariates
  - Sub-classification on the propensity scores
  - Instrumental variables based on prescribing physician
  - Established a dose-response relation within each APM group
  - Restricted to different populations (with and without dementia diagnosis, current nursing home resident)
  - Sensitivity analysis suggested there would have to be tremendous unmeasured confounding to change our conclusion
- All results suggested that conventional APMs have a higher short-term risk of death than atypical APMs

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TO THE EDITOR: Wang et al. attempted to estimate the risk of death from the use of conventional antipsychotic medications. Their adjustment methods reduced the estimate from 1.51 to 1.37, confirming confounding; this adjustment is probably insufficient. The authors were severely constrained in their ability to correct for confounding. Diagnoses obtained or inferred from claims data are variably reliable, and risk factors such as cigarette smoking and alcohol consumption are not included. Although users of conventional antipsychotic agents had poorer prognoses, users of atypical agents were more likely to have been in hospitals or nursing homes, giving more opportunities for diagnoses to be reported. The authors also did not account for differences in severity within diagnostic categories.

The ability to remove confounding can be tested by showing how much of the observed mortality within each treatment group can be explained. If the data cannot fully explain within-group mortality, it is likely that substantial confounding remains. Improved methods of estimating mortality could narrow, eliminate, or reverse differences in mortality.

Published randomized, controlled trials of conventional antipsychotic medications in patients with dementia have not included data on mortality; such information would be welcome.

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TO THE EDITOR: Although we agree with the conclusions of Wang et al., we recommend using caution in the interpretation of the results of a retrospective cohort study. The method of looking at prescriptions written and filled can be misleading, because it can extract erroneous conclusions from static data obtained from a decision tree unknown to the investigators.

Although the authors cite concern regarding confounding variables, we have several additional questions that could alter the interpretation of the results. First, did the group receiving atypical antipsychotic agents have a built-in protective — and possibly a selection — bias, since they were more likely than users of conventional agents to be white and female and less likely to have certain life-threatening diseases (congestive heart failure, ischemic heart disease, or cancer)? Second, did the higher rate of use of antidepressants (P<0.001) in the group receiving atypical agents confer a protective effect with regard to the outcome? Third, did the fact that persons with neuropsychiatric disorders preferentially received more atypical agents (P<0.001) have a salutary effect on the outcome?

We would welcome input from the authors with regard to the elaboration and clarification of other factors that have been considered, or that could be considered, in a follow-up analysis of their original data.

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TO THE EDITOR: The article by Wang et al. suggests that the use of conventional antipsychotic medications, as compared with the use of atypical agents, is associated with an increased risk of death. However, confounding according to indication might have biased the analysis, because in real-life conditions, conventional antipsychotic agents are more often prescribed than are atypical agents as add-on medications for severely ill patients.[1] In addition, Table 1 of the article shows that atypical agents were prescribed more often than were conventional agents for persons with affective disorders, who received more prescriptions for other psychotropic medications that might have had a protective role.[2]

The authors adjusted for the presence of a number of physical conditions associated with death, but not for the severity of medical illness. In addition, we do not know whether exposure variables were equally distributed in terms of the number of conventional and atypical agents actually prescribed during the follow-up period, the concomitant use of two or more agents, and history of use of antipsychotic agents. Given that the baseline risk of death in this cohort of subjects was very high, we suspect that these limitations might have hampered the validity of the conclusions.

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TO THE EDITOR: Wang et al. (Dec. 1 issue)[1] report that, as compared with atypical antipsychotic medications, the use of conventional antipsychotic agents increased the death rate among elderly users. Although we appreciate the instrumental-variable analysis, we have two concerns. First, it seems as though confounding would still be possible if the instrumental variable (a physician's choice of a conventional antipsychotic medication as his or her most recent prescription) was independently associated with the outcome (risk of death of the index patient). This confounding could happen if physicians who choose conventional antipsychotic medications also tend to care for very sick patients or to be less aggressive than other physicians in prolonging those patients' lives. Second, in the instrumental-variable analysis, the authors report an increase of 7.3 percent in the absolute risk of death within six months with conventional antipsychotic medications, whereas for the primary analysis, they report only a 3.3 percent increase in this risk. Since the instrumental variable (the type of antipsychotic agent the physician most recently prescribed before the index prescription) is an imperfect measure of the exposure of interest (the type of antipsychotic agent the index patient received), why isn't the difference in risk in the instrumental-variable analysis biased toward 0 — that is, lower than 3.3 percent?

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1. Wang PS, Schneeweiss S, Avorn J, et al. Risk of death in elderly users of conventional vs. atypical antipsychotic medications. N Engl J Med 2005;353:2335-41.

TO THE EDITOR: The article by Wang et al. suggests that the use of conventional antipsychotic medications, as compared with the use of atypical agents, is associated with an increased risk of death. However, confounding according to indi-

RESEARCH

Risk of death associated with the use of conventional versus atypical antipsychotic drugs among elderly patients

Sebastian Schneeweiss, Soko Setoguchi, Alan Brookhart, Colin Dormuth, Philip S. Wang

- AHRQ DEcIDE-funded study
- Same design, same analysis, done using claims data from the British Columbia Ministry of Health
- 37,241 elderly patients
- Same finding: 32% increased risk among new users of the conventional APM
- Similar finding reported in Ontario, CA (Gill, et al Ann of Int Med, 2007)

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CLINICAL & RESEARCH NEWS

FDA Extends Black-Box Warning to All Antipsychotics

Jun Yan

New studies and label warnings about the risks of all antipsychotics have not made clinical decisions any easier for physicians, patients, and caregivers.

Increased Mortality in Elderly Patients with Dementia-Related Psychosis — Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear.

In the absence of regulatory action, the final jury is the prescriber

"….More analysis of these drugs (anti-psychotics) clearly needs to be done before any firm conclusions emerge. In the meantime, we should temper our bias that older treatments are de facto safer because they have been on the market longer. As the old saying goes, you don't know what you don't know."

Medical Progress, Dec. 9th 2005

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If done well, non-experimental research can contribute useful information about comparative safety and effectiveness of therapeutics

- "… While many clinicians have shied away from using atypical antipsychotics, this study offers strong (although not convincing) evidence that conventional antipsychotics are even more dangerous. …it is wise to limit the use of antipsychotics in general, and if they are used, atypicals are likely to be safer."
  - -Ashish K. Jha, MD MPH
  - Outcomes Research in Review

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