Bias in Pharmacoepidemiology Studies

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Acknowledgement

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Outline

- Safety concerns in formal epidemiologic studies
  - Challenges
- Bias (systematic error) vs. chance (random error)
- Types of Bias
  - Selection bias
  - Information bias
  - Confounding
- Addressing bias in observational studies
- Examples

Goal and Steps of Analytic Studies for Drug Safety

Goal

- Assess the (causal) association between an exposure (drug) and outcome of interest (adverse event)
  - Risk ratio (relative risk) or risk differences

Steps

- Identify exposed group (users of drug A) and non-exposed group (non-users of drug A or users of comparison drug or therapy)
- Follow up both groups to identify outcomes
- Calculate the risk (frequency of adverse event or incidence rate of adverse event) in the two groups (exposed and unexposed groups)
- Compare risk in the two groups
  - Risk ratio (relative risk) or risk differences

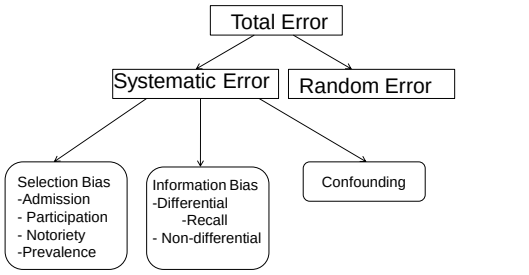
Challenges in Observational Studies

Type of Study	Purpose	Validity
RCT (explanatory) Gold standard': selected study population, unusual settings	Efficacy - Does it work in an ideal situation?	Internal (no bias)
RCT (pragmatic/large simple) Randomized: Usual setting of care, on-selected study population	Effectiveness - Does it work in the 'real world'?	External (Generalizability)
Observational Analytic Studies Cohort Study, Case-control Study, Nested Case-cohort Study, Case crossover Study		

BIAS (SYSTEMATIC ERRORS)

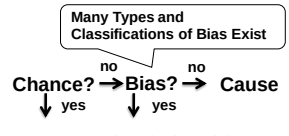
VS.

CHANCE (RANDOM ERROR)



Modified ICPE 2011

Chance vs. Causality



No causal Relationship

- **Selection Bias**
  - Referral Bias
  - Self-selection Bias
  - Prevalence Bias
  - Protopathic Bias
- **Information Bias**
- **Immortal-time Bias**
- **Confounding**

SELECTION BIAS

Selection Bias

- Definition:

  Distortions that result from procedures used to select subjects and from factors that influence study participation

  --Modern Epidemiology

- Case control study

  Selection of cases and controls was affected by exposure status

- Cohort study

  Selection of exposure and non-exposure group was affected by risks of outcome of interest

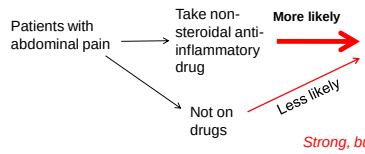
Examples of selection bias

In Pharmacoepidemiology, four types of section bias are particularly important:

- Referral bias
- Self Selection bias
- Prevalence bias
- Protopahtic bias

Referral Bias

Can occur if the reasons for referring a patient to the hospital, may be related to the drug exposure status



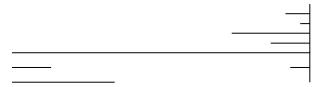
Strong, but biased, association between non bleeding gastric ulcers and the use of nonsteroidal anti-inflammatory drugs

Self Selection Bias

- Patients decide to participate or leave a study
- This decision may be related to both drug exposure and health status
- Problem of representativeness of the real association in the source population

Prevalence Bias

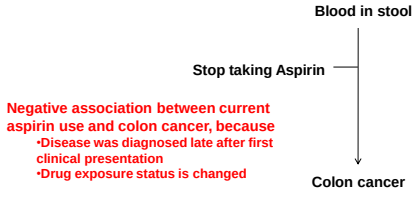
Occurs when prevalent cases rather than new cases are selected for a study



- Cannot identify outcomes that occur soon after the initiation of the exposure drug
- Those who developed the outcome stopped taking the exposure drug, leading to survivor bias
- Prevalent users tend to be healthy adherers, leading to compliance bias

Protopathic Bias

Occurs when a pharmaceutical agent is inadvertently prescribed for an early manifestation of a disease that has not yet been diagnostically detected



Negative association between current aspirin use and colon cancer, because

- **Disease was diagnosed late after first clinical presentation**
- **Drug exposure status is changed**

INFORMATION BIAS

Information Bias

Measurement error or classification error on

- *Exposure status*
- *Outcome status*
- *Confounding*

Can cause bias on the effect estimate

Non-Differential Misclassification Bias

- Degree of (or presence of) misclassification is not affected by exposure or outcome status
- Non-differential outcome misclassification
  - Example: typo in the coding of diagnosis, not likely associated with the use of drug
- Non-differential exposure misclassification
  - Example: Some patients forgot to take drug occasionally (such as during the holiday season), not likely to relate to the risk of developing diseases

The bias will underestimate the risk or benefit

Differential Misclassification

- The degree (or presence) of misclassification differ by exposure or outcome status
- Famous example of differential exposure misclassification - Recall Bias
  - Cases tend to recall exposure status better than controls in case-control studies

Direction of bias unknown (over or underestimation of the risk)

Immortal Time Bias

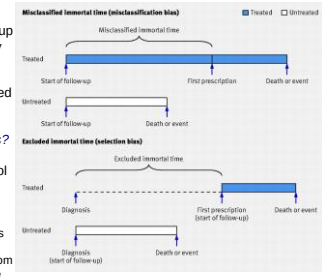
What is Immortal Time Bias?

- Immortal time refers to a period of follow-up during which, by design, death or the study outcome cannot occur
- In pharmacoepidemiological studies
  - Wait for a prescription to be dispensed
  - Wait for a treatment to be scheduled

How to Account for the Immortal Time Bias?

- Design: Time matched nested case control
- Analysis: Time dependent analysis

Examples: Immortal time bias is introduced in cohort studies when the period of immortal time is either incorrectly attributed to the treated group through a time fixed analysis (top) or excluded from the analysis because the start of follow-up for the treated group is defined by the start of treatment and is, by design, later than that for the untreated group (bottom).



Lévesque L E et al. BMJ 2010;340:bmj.b5087

CONFOUNDING

Confounding

- The quantitative association between exposure and outcome is distorted by a third factor with the following characteristics

1. *Is a risk factor for the outcome of interest*
2. *Is a predictor of the exposure of interest*
3. *Is not an intermediate factor on the causal pathway between exposure and outcome*

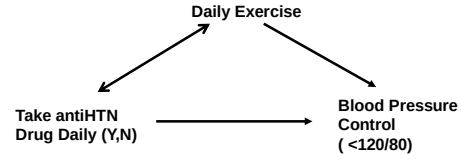
Criteria to be a confounder

The factor must:

- **be a cause of the disease or outcome, or a surrogate measure of a cause, in unexposed people; factors satisfying this condition are called risk factors**
- **be correlated, positively or negatively, with exposure in the study population. If the study population is classified into exposed and unexposed groups, this means that the factor has a different distribution (prevalence) in the two groups**
- **not be an intermediate step in the causal pathway between the exposure and the disease**

Example of Confounder

Among people diagnosed with high BP and prescribed antiHTN drug

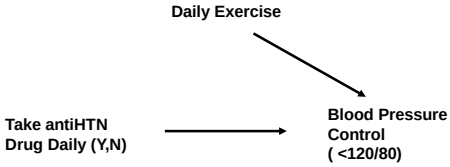


Compare Rates of BP Control:

Those who take drug daily
vs.
Those who take it less frequently

1. A "cause" of the outcome even in the unexposed group

Regular daily exercise contributes to lower blood pressure

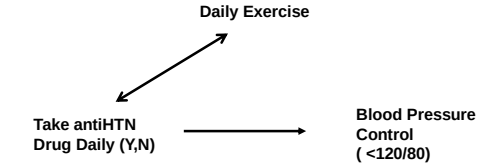


Compare Rates of BP Control:

Those who take drug daily
vs.
Those who take it less frequently

2. Correlated with Exposure

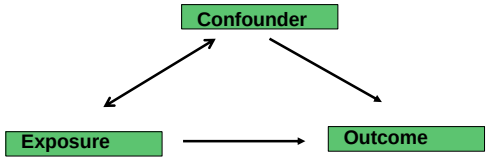
Regular daily exercisers are more likely to take their meds daily



Compare Rates of BP Control:

Those who take drug daily
vs.
Those who take it less frequently

Confounder Diagram



Drug Safety Studies

- We cannot observe the same population with and the without exposure
- The closest we can do is to compare two groups randomly assigned to exposure.
  - They are not the same population but similar in characteristics on average as a result of randomization
- However, RCT cannot answer every possible questions on drug safety
  - Ethnical concerns
  - Scarce resources
- But we do our best to conduct high quality observational analytic studies
  - Use real-world complex data
  - Employing clever way of designing and analyzing data
  - Considering and combating potential biases

Confounding by Indication or Severity

- Indication for an exposure drug or severity of the disease predict the use the exposure drug
- The indication or severity is also associated with the risk outcome of interest

Confounding by Indication

- Are ACEIs effective preventing MI patients with Hypertension?

ACEIs ← Hypertension

Vs.

Vs.

No ACEIs ← No Hypertension

Confounding by Severity

Are ACEIs effective preventing MI in patients with hypertension?

Everybody has Hypertension

ACEIs ← Hypertension with Diabetes and proteinuria

Vs.

Vs.

No ACEIs ← Uncomplicated Hypertension

Addressing Bias in observational Studies

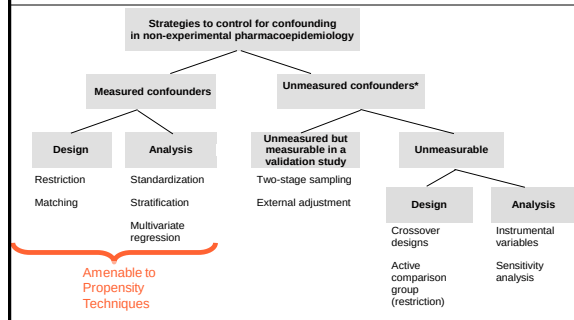
- Selection bias
  - Must be prevented at the design stage through:
    - Random sampling of subjects
    - Minimize loss to follow-up
    - Prevent self selection by implementing systematic recruitment
    - Reduce referral bias
    - Include only incident cases
    - Track drop outs
    - Random allocation of drug exposure
- Information bias
  - Blinding
  - Standardize the measurement process e.g. use of questionnaires etc.

Addressing Bias in observational Studies

Confounding

- Design
  - Randomization
  - Matching
  - Restriction
- Analysis
  - Standardization
  - Stratification
  - Multivariate analysis
  - Sensitivity analysis
  - Propensity scores

Epidemiologic Tools



Thanks to S. Schneeweiss

Propensity Score Matching (PSM)

What is the Propensity Score?

- Multivariable scoring method that collapses predictors of treatment into a single value
  - Probability that subject with given characteristics will receive therapy
  - Removes confounding by components of the score
  - Avoids the "curse of dimensionality"
- Used to remove confounding resulting from patient characteristics that lead to selection of one therapy over another
  - Stratification
  - Matching
  - Regression adjustment with the propensity score
  - Weighting

What is the PS?

Intuitive definition:

It is a measure of likelihood that a person would have been treated using only their covariate scores.

It can be thought as a balancing score, i.e., as a function *b (X)* of the observed covariates such that the conditional distribution of X given *b (X)* is the same for the treated (Z=1) and control (Z=0) subjects

What is the PS? (Cont'd)

Employs a predicted probability of group membership—e.g., treatment vs. control group--based on observed predictors, usually obtained from logistic regression to create a counterfactual group

Propensity scores may be used for matching or as covariates—alone or with other matching variables or covariates.

Why PSM?

Estimate of Treatment Effects

- "What would have happened to those who, in fact, did receive treatment, if they had not received treatment (or the converse)?"
- Counterfactuals cannot be seen or heard—we can only create an estimate of them.
- PSM is one "correction strategy" that corrects for the selection biases in making estimates.

Guo et al., Introduction to Propensity Score Matching: A New Device for Program Evaluation. University of North Carolina at Chapel Hill

Propensity Scores

Why estimate the probability that a subject receives a certain treatment when we already known what treatment they received?

Propensity Scores

By using the probability that a subject would have been treated (the propensity score) to adjust the estimate of the treatment effect, we create a **quasi-experiment.**

Find two subjects with the same propensity score, one treated, one a control. We can think of these two subjects as "*randomly assigned"* to each group, since they have the same probability of being in either group, given their covariates.

Theory: Propensity Score

- In 1983, Rosenbaum and Rubin proposed the use of the propensity score to adjust for observed covariates in observational studies
- The propensity score for an individual is the conditional probability of his or her treatment given the observed pretreatment covariates
- The propensity score is a probability and thus can take values between 0.0 and 1.0 (0.0<e(x)<1.0)
- The propensity score offers a one-dimensional summary of multidimensional covariates, such that when the propensity score is balanced across the treatment and control groups, the distribution of all the covariates are balanced in expectation across the two groups

Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. Biometrika 1983;70:41-55.

Propensity score analysis

Goal: Identify patients with the identical likelihood to receive treatment

- Some receive treatment others do not

Two steps:

- Step 1: Estimate propensity for treatment as a function of covariates:
  - Mimic prescribers decision process for treatment
  - Prevalent exposure allows for rich model
  - Collapse multiple variables into single variable
  - Predicted value is each patient's "propensity score"
- Step 2: Use propensity score to account for treatment selection:
  - Restriction
  - Stratification (quantiles)
  - Matching
  - Model adjustment
  - Weighting

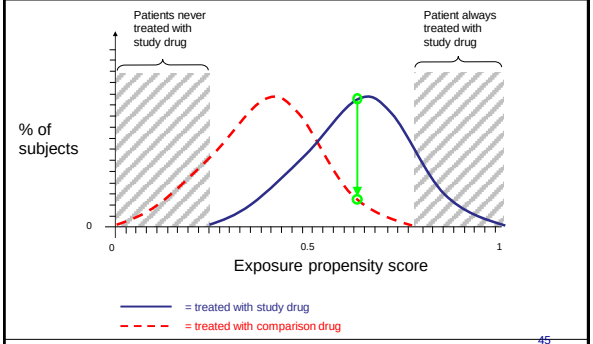
Population Cohorts

	Fentanyl TDS	LA Opioids
N	504	2,201
65+ years	29%	10%
Male	35%	49%
Periph Vasc Disease	4%	1%
Sx of Abd or Pelvis	18%	10%
> 2 hospitalztns 6 mo	9%	3%
30 days NonRx Costs	$1,136	$746

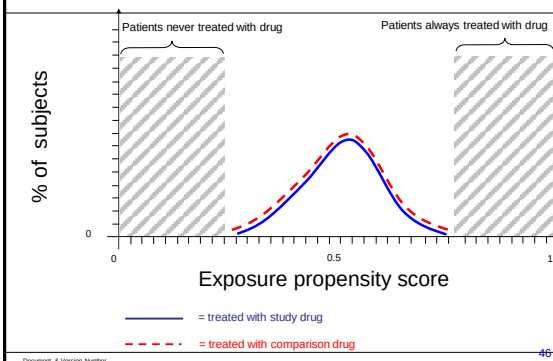
Loughlin JE, Cole JA, Dodd SL, et al. Pain Medicine 2002;3;47-55.

Propensity score matching

Example: Thrombolysis with tPA in patients with stroke



PS distributions after matching



General Procedure

Run Logistic Regression:

- Dependent variable: Y=1, if participate; Y = 0, otherwise.
- Choose appropriate conditioning (instrumental) variables.
- Obtain propensity score: predicted probability (p) or log[p/(1-p)].

⇒

Match Each Participant to One or More Nonparticipants on Propensity Score

- Nearest neighbor matching
- Caliper matching
- Mahalanobis metric matching in conjunction with PSM
- Stratification matching
- Difference-in-differences matching (kernel & local linear weights)

⇐

Multivariate analysis based on new sample

Guo et al., Introduction to Propensity Score Matching: A New Device for Program Evaluation. University of North Carolina at Chapel Hill

Principles of PS variable selection

Include all confounders

Include predictors of outcome ("risk factors") even if you think they are not associated with treatment

Including predictors of treatment that are not associated with outcomes

- Will lead to statistical inefficiency
- May amplify residual confounding bias by unobserved characteristcs

Brookhart MA, Schneeweiss S, Rothman K, Glynn RJ, Avorn J, Sturmer T. Variable selection in propensity score models. Am J Epidemiol 2006;163:1149-56.

Limited clinical information in admin databases

---------- 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 Descri ption
10/01/00	OFFICE	Family Practice	90658	INFLUENZA VIRUS VACC/SP	LIT	V048	VACC FOR INFLUEN
10/01/00	Rx	Pharmacy		CIPROFLOXACIN 500MG TAB	LETS		10
11/05/00	OFFICE	Family Practice	17110	DESTRUCT OF FLAT WARTS,	UP	0781	VIRAL WARTS
11/07/00	Rx	Pharmacy		CIPROFLOXACIN 500MG TAB	LETS		10
01/15/01	Rx	Pharmacy		CIPROFLOXACIN 500MG TAB	LETS		10
06/25/01	OFFICE	Emerg Clinic	99070	SPECIAL SUPPLIES		* 84509 E927	SPRAIN OF ANKLE 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 RIG	ID	* 72767	RUPT ACHILL TEND

Can we make better use of this information ?

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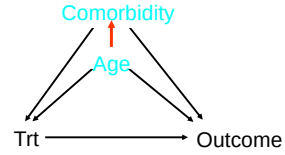
Document & Version Number

The power of proxies in claims data

Measured confounders (C) may serve as redundant proxies for unmeasured confounders (U):



Observable Proxy	Health State
Use of oxygen canisters	Very frail
Receiving a Dx of HTN during a hosp. stay	not too bad off
Annual checkup and colonoscopy	anal character trait, very compliant
Receiving the first statin at age 70	fairly healthy
Many drugs used, many visits	fairly sick

The more the better…

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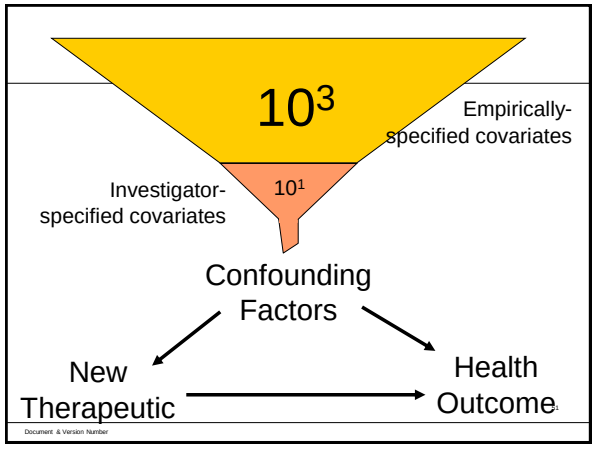

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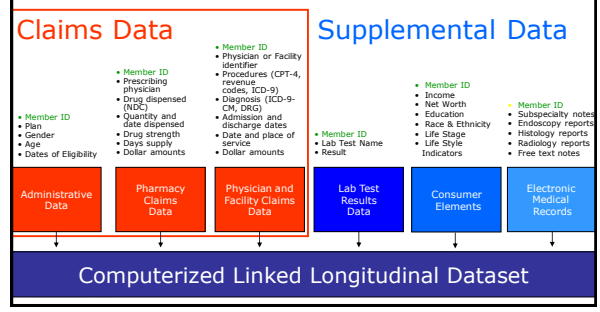
Electronic health care information in each Center

- Constant flow of data with little delay and at low cost
- Millions of patients with defined person–time denominator
- Data reflect routine care
- Generalizable to large population segments
- HIPAA compliance protects patient privacy



Under-adjustment is a bigger issue than "over-adjustment"

Because of the database limitations under-adjustment is a constant threat

Start out adjusting for as many covariates as possible, some of which may be proxies of unmeasured factors.

Unselect those rare variables that may cause bias after a large model is built (M-bias, Z-bias)

=> Variable un-selection

Brookhart et al. Med Care 2010

A Propensity Score-Matched Cohort Study of the Effect of Statins, Mainly *Fluvastatin*, on the Occurrence of Acute Myocardial Infarction

John D. Seeger, PharmD, DrPH, Alexander M. Walker, MD, DrPH, Paige L. Williams, PhD, Gordon M. Saperia, MD, and Frank M. Sacks, MD

This investigation quantified the effect of statins on acute myocardial infarction (AMI) in an observational setting where fluvastatin represented most of the statin use. The study applied propensity scores to match statin initiators to statin noninitiators and followed them for the occurrence of AMI. Serum low-density lipoprotein levels were reduced by statin therapy, and there were fewer incidents of AMI in statin initiators than in noninitiators. ©2003 by Excerpta Medica, Inc.

(Am J Cardiol 2003;92:1447–1451)

the risk of acute myocardial infarction (AMI).[2–7] Fluvastatin has beneficial low-density lipoprotein (LDL) effects, but randomized clinical trials have not established its efficacy for preventing AMI.[8] The objective of this investigation was to quantify the effect of statin therapy on the occurrence of AMI in an observational setting where formulary decisions, made independently of the study, had the effect that fluvastatin represented most statin use.

• • •

Members of the Fallon Community Health Plan (FCHP) with a recorded LDL >130 mg/dl at any time

An application of propensity score matching using claims data†

John D. Seeger PharmD, DrPH[1]*, Paige L. Williams PhD[2] and Alexander M. Walker MD, DrPH[1]

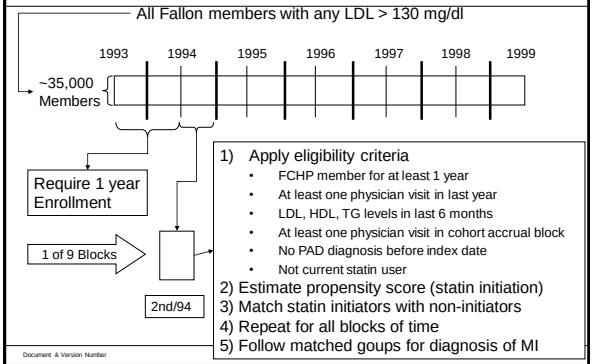
[1]*Ingenix Epidemiology, Auburndale, Massachusetts USA; Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts, USA*
[2]*Department of Biostatistics, Harvard School of Public Health, Boston, Massachusetts, USA*

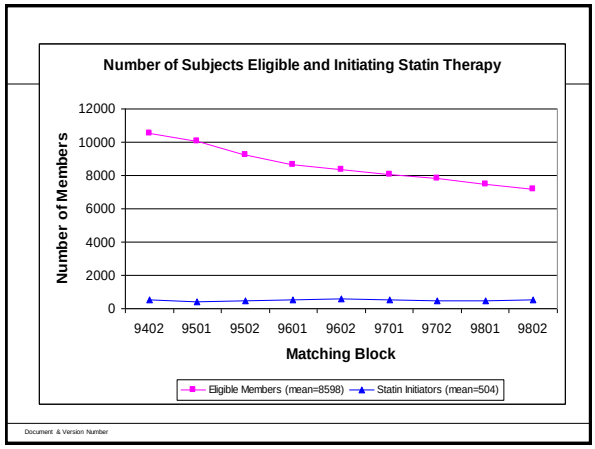
Pharmacoepidemiol Drug Saf. 2005 Jul;14(7):465-76.

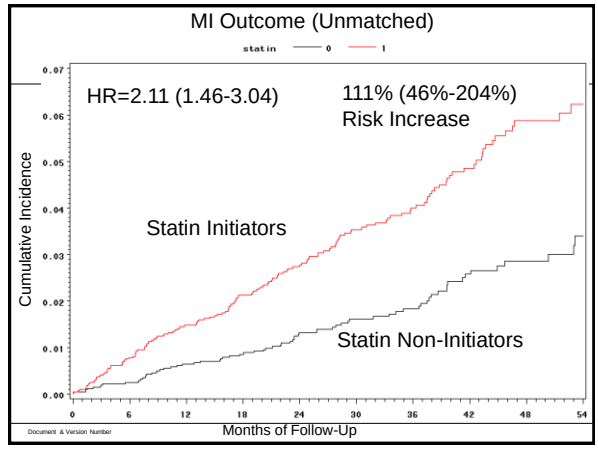
Data Source

- Fallon Community Health Plan
- Central Massachusetts HMO
- ~200,000 members
- Claims Data available on:
  - Enrollment (age, sex, date)
  - Ambulatory care visits
  - Hospitalization
  - Pharmacy dispensings (drug & quantity)
  - Laboratory tests (tests & results)

Schematic Representation of Study




Number of Subjects Eligible and Initiating Statin Therapy
Number of Members
12000
10000
8000
6000
4000
2000
0
9402
9501
9502
9601
9602
9701
9702
9801
9802
Matching Block
Eligible Members (mean=8598)
Statin Initiators (mean=504)
Document & Version Number


MI Outcome (Unmatched)
statin
0
1
HR=2.11 (1.46-3.04)
111% (46%-204%)
Risk Increase
Statin Initiators
Statin Non-Initiators
Cumulative Incidence
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0.00
0
6
12
18
24
30
36
42
48
54
Months of Follow-Up
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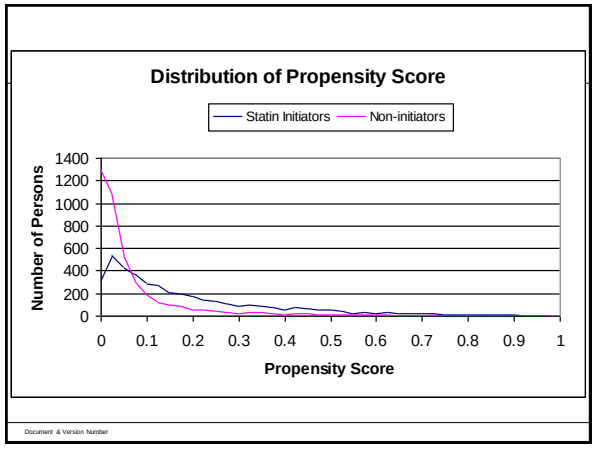
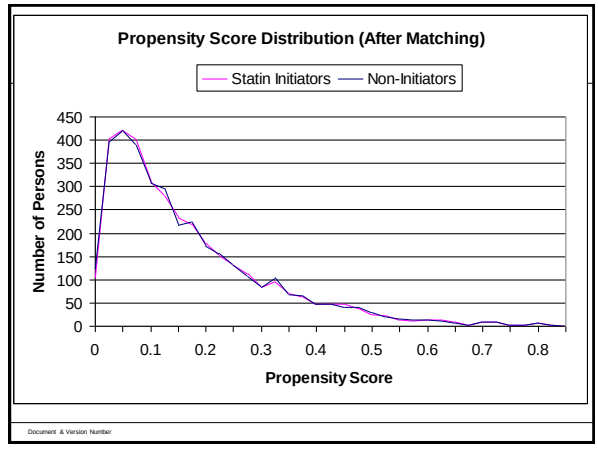
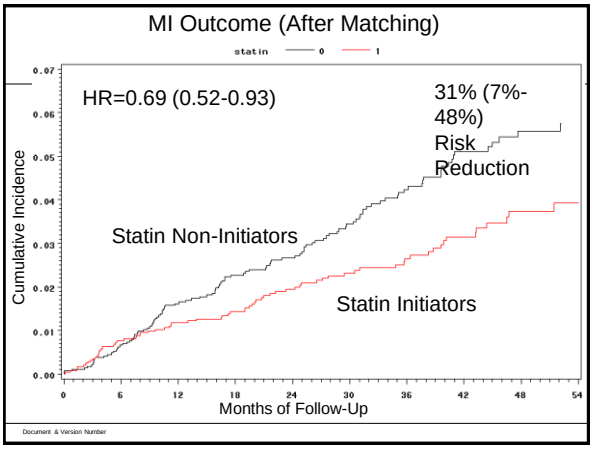

Distribution of Propensity Score
Statin Initiators
Non-initiators
Number of Persons
1400
1200
1000
800
600
400
200
0
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
Propensity Score
Document & Version Number


Propensity Score Distribution (After Matching)
Statin Initiators
Non-Initiators
Number of Persons
450
400
350
300
250
200
150
100
50
0
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
Propensity Score
Document & Version Number



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Summary of Steps

Define Population (statin initiators and eligible non initiators)

Define Exposure (statin initiation vs not)

Identify Factors That May be Correlates of Exposure (52 variables)

Estimate Propensity Score

Use Propensity Score
- Matching

Perform Outcome Analysis

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Other Important points

Coefficients are Interpretable and Informative

Continuous predictors require care

Be sure all predictors are included

Choice of predictors need not be a-priori
- but should make sense

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Case Study and Examples

Case Study 1

There have been recent news reports of kidney cancer among patients taking a newly marketed drug, Teragliptin (manufactured by Prozyme Biologics). Internal signal clarification assessment is inconclusive, but your safety surveillance team has decided to proceed with full evaluation of kidney cancer among patients prescribed Teragliptin. You are the Pharmacoepidemiologist responsible for pre- and post-marketing safety epidemiologic activities relating to Teragliptin, and have been asked by your safety team to conduct this study.

What are some initial considerations for the study?

Case Study 1 (next step)

You decide to conduct a cohort study using claims database with chart validation of outcomes.

What biases should you consider for this study?

How will you address these biases?

Case Study 1

List possible biases (measured and unmeasured)

List and discuss how you will control for bias and confounding

- Design features
- Analysis e.g. propensity scores etc.

Examples 1

Physicians may examine women who use oral contraceptives more often or more thoroughly than women who do not. If so, and if an association is observed between phlebitis and oral contraceptive use, the association may be due to

1. Selection bias
2. Interviewer bias
3. Surveillance bias
4. Non response bias
5. Recall bias

Reference: Gordis L., Epidemiology. 2nd edition

Examples 2

In a case-control study of the relationship of radiation exposure and thyroid cancer, 50 cases admitted for thryoid cancer and 100 "controls" admitted were studied. Only the cases were interviewed and 20 of the cases were found to have been exposed to x-ray therapy in the past, based on the interviews and medical records. The control were not interviewed, but a review of their hospital records when they were admitted for hernia surgery revealed that only 2 controls had been exposed to x-ray therapy in the past.

Based on the description given above, what source of bias is least likely to be present in this study?

1. Recall bias
2. Bias due to controls being nonrepresentative of the nondiseased population
3. Bias due to use of different methods of ascertainment of exposure in the cases and controls
4. Bias due to loss of subjects from the control group over time
5. Selection bias for exposure to x-ray therapy in the past

Reference: Gordis L., Epidemiology. 2nd edition

Examples 3

Cervarix™ Pregnancy Registry for Cervarix™ Human Papillomavirus Bivalent (Types 16 and 18) Vaccine, Recombinant is active in the United States and in the United Kingdom. To participate in this registry, registration should take place as early in the pregnancy as possible and prior to any knowledge of the pregnancy outcome.

The purpose of this request is to address,

1. Selection bias
2. Information bias
3. Confounding
4. Low enrollment

Reference: http://pregnancyregistry.gsk.com/Cervarix.html

Examples 4

Hagiwara M, Delea TE, Stanford RH. Retrospective Comparison of Early versus Late Treatment with Fluticasone Propionate/Salmeterol After an Asthma Exacerbation. J Asthma. 2011 Sep;48(7):721-8.

Background. The benefits of inhaled corticosteroids in asthma are well established. Early use of inhaled anti-inflammatories following and exacerbation could be beneficial.

Methods. A retrospective observational cohort study compared the risk of asthma-related exacerbations [hospitalization, emergency department visit, and/or treatment with systemic corticosteroid] in patients receiving treatment with fluticasone propionate/salmeterol in a single inhaler (FSC) within 90 days following an initial asthma-related exacerbation (early treatment) versus patients receiving the treatment subsequently (late treatment). Data were from a large health insurance claims database spanning from January 1998 to April 2008. Subjects included patients with ≥1 prescription for FSC ≤ 1 year after first asthma-related exacerbation. **Patients with early treatment were matched to those with late treatment by propensity score and compared in terms of healthcare utilization and costs after initiation of FSC.**

The reason to use propensity score matching method is to address

1. Selection bias
2. Information bias
3. Confounding
4. Internal validity
5. External validity

Thank you!
Questions?