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Confounding and Bias

Tobias Gerhard, PhD

Assistant Professor, Ernest Mario School of Pharmacy and
Institute for Health, Health Care Policy, and Aging Research

Rutgers University

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Conflict of Interest

- The views and opinions expressed in this presentation are solely mine and do not represent the position or opinion of ISPE or any other institution.
- I have no conflicts of interest to declare.
- I have freely plagiarized lecture materials from previous years. Many thanks to my predecessors!

Outline

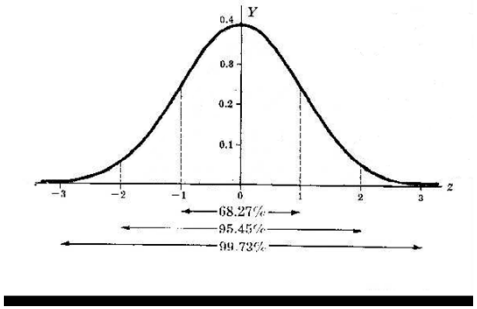
- Bias – General Concepts
- Types of bias and what to do about it
  - Confounding Bias
  - Selection Bias
  - Information Bias
- Summary and Implications

"MY FATHER SAYS, THESE INTELLIGENCE TESTS ARE BIASED TOWARD THE INTELLIGENT."

Bias and Chance

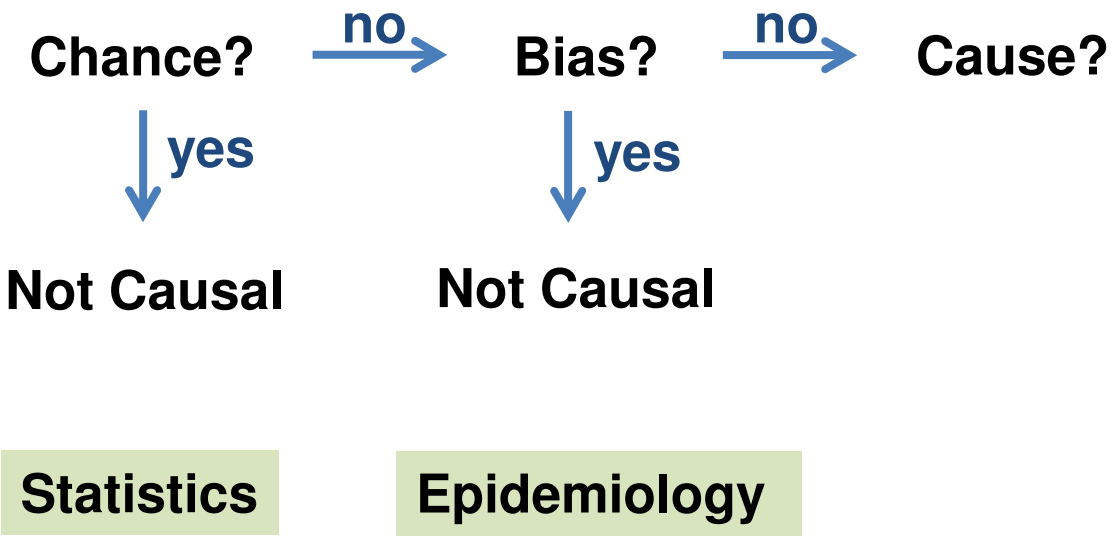
- **Bias = Systematic Error**
  - Unaffected by study size
  - Many specific biases have been described but generally all biases can be classified into one of three types: **(1) confounding**, **(2) selection bias**, and **(3) information bias**.

- **Chance = Random Error**
  - Decreases as study size increases
  - Confidence intervals, p-values



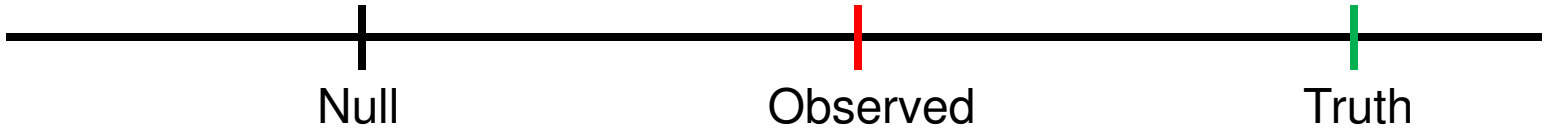
Bias, Chance, and Causality

- Risk estimate differs from null value. What now?

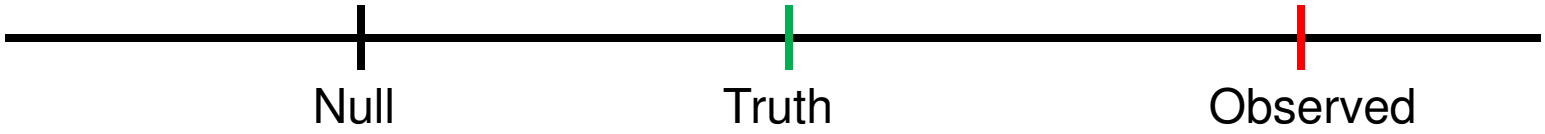


Bias – General Concepts

- Bias can affect all types of studies though observational studies are particularly vulnerable.
- Bias has a direction
  - **Bias towards the null** – observed value is closer to the null hypothesis than the true value



  - **Bias away from the null** – observed value is farther from the null hypothesis than the true value



Null: 1 for ratio estimates, 0 for difference estimates

Types of Bias

- **Confounding**

  Bias due to a third factor that distorts the association between exposure and outcome. Mixing of effects (from lat. confundere).

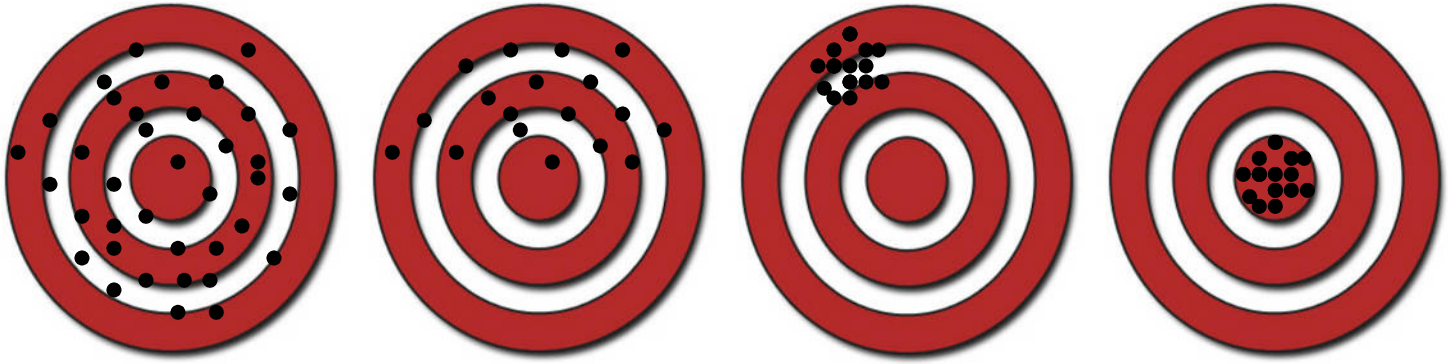
- **Selection Bias**

  Bias that results from the selection and retention of the study population.

- **Information Bias**

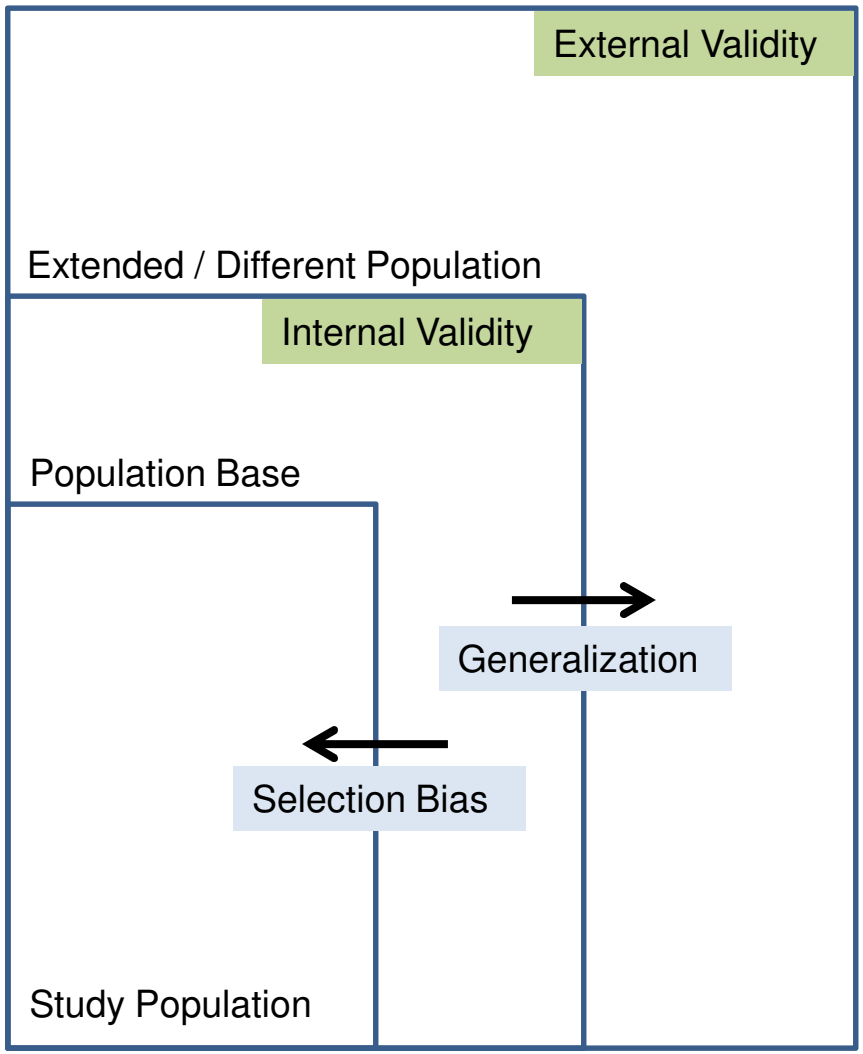
  Bias that results from poor measurement of study variables - exposure, outcome, confounders.

Precision and (Internal) Validity



Random Error	large	large	small	small
Systematic Error	small	large	large	small
Terminology	imprecise, valid	imprecise, invalid	precise, invalid	**precise, valid → accurate**

External Validity



CONFOUNDING

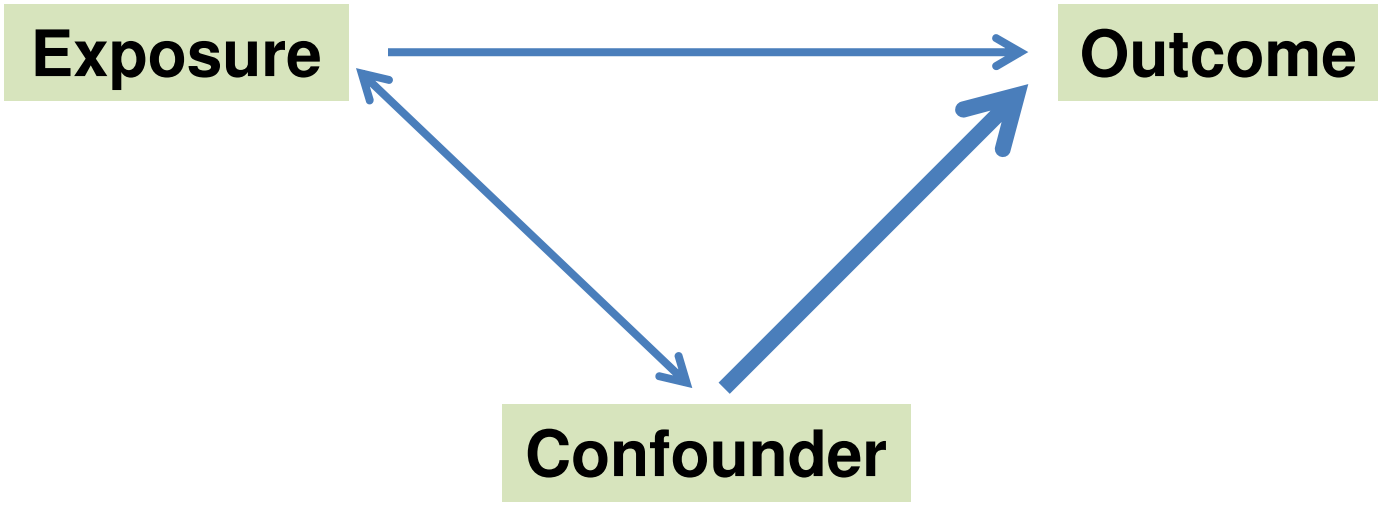
Confounding

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

The confounder is

- **a risk factor for the outcome**
- **associated with the exposure (better: a direct or indirect predictor of the exposure)**
- **not an intermediate on the causal pathway between exposure and outcome**

Confounding



The confounder is

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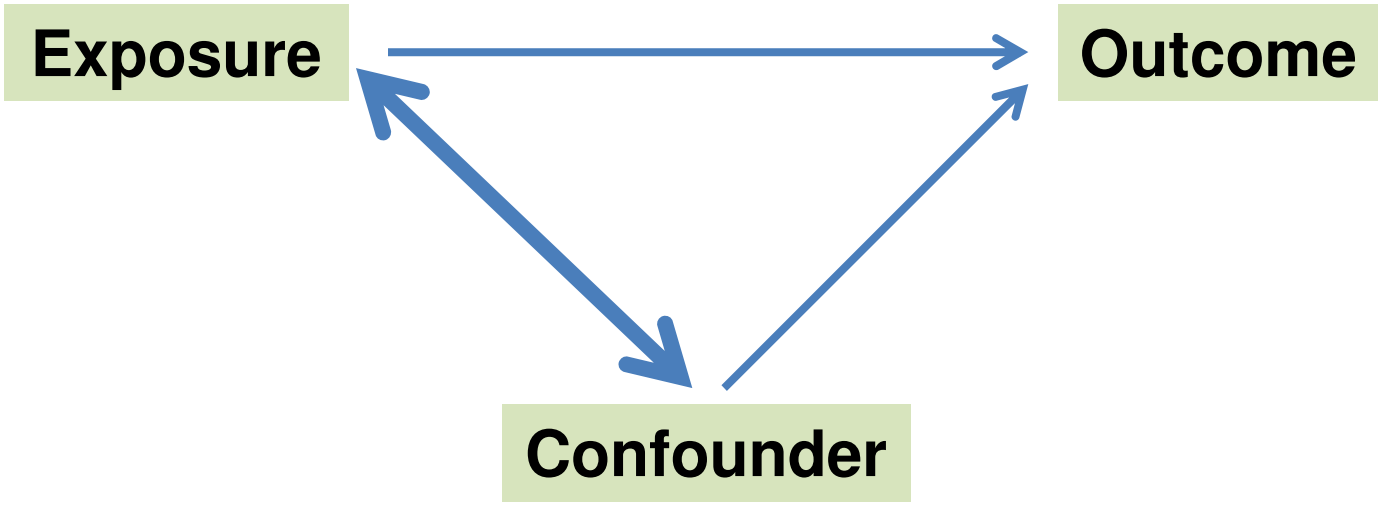
- **not an intermediate**

Confounding



The confounder is

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Confounding

The confounder is

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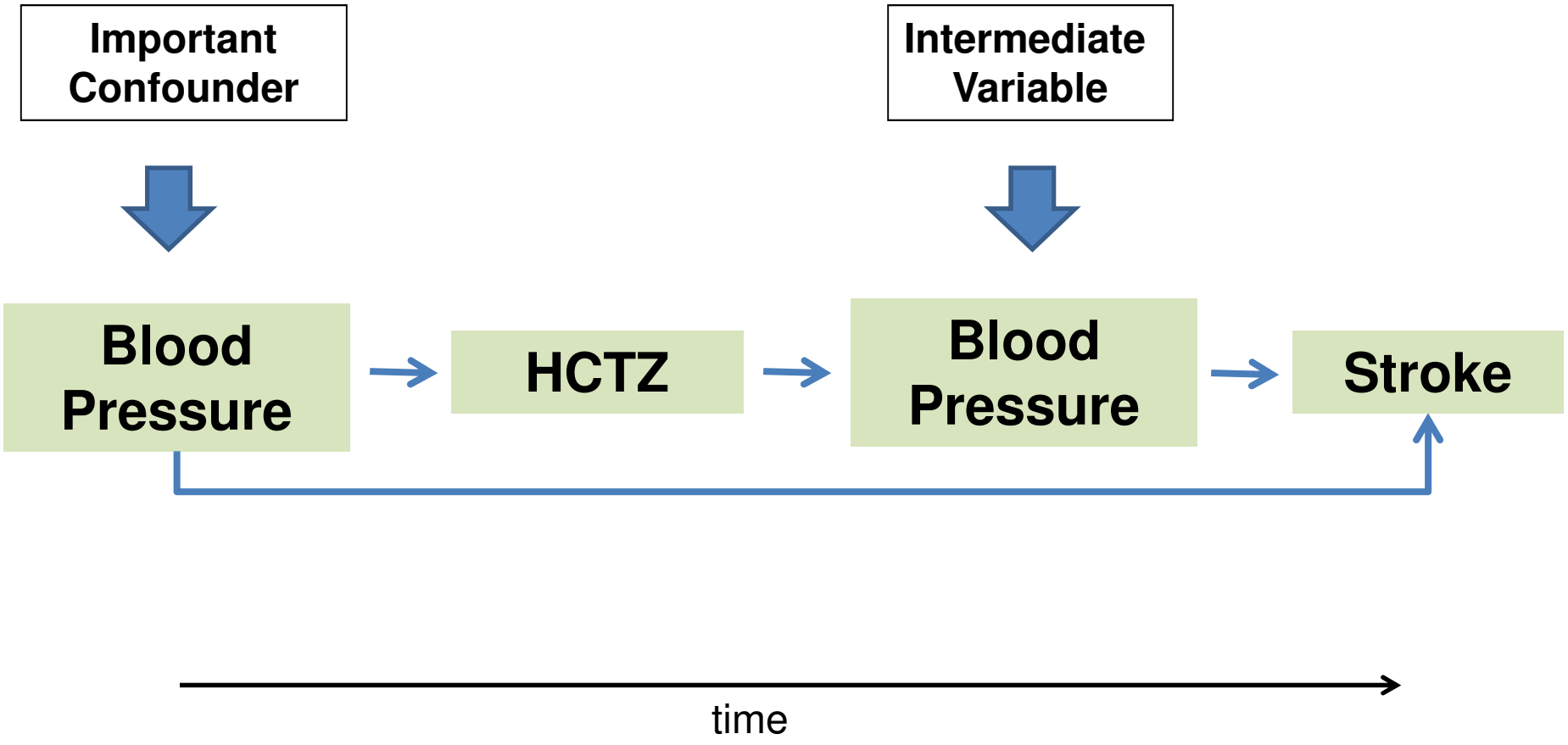
- **associated with the exposure**
- **not an intermediate**

Confounding – Timing Matters



Confounding - Example

Does drinking coffee cause cancer?

	Cancer+	Cancer-	Total
Coffee+	105	11395	11500
Coffee-	45	8455	8500

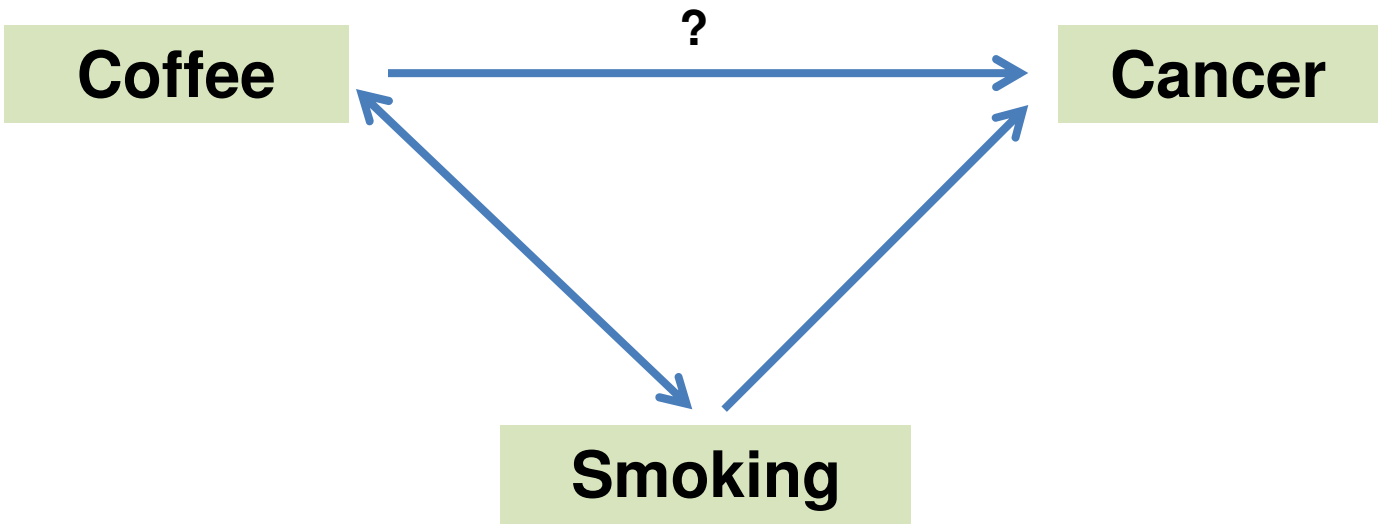
Observed RR = 1.72

(105/11500)/(45/8500)

Confounding - Example

Does drinking coffee cause cancer?

…or could there be confounding



Confounding - Example

Stratified analysis:

(Separation of factors so any mixture of their effect is removed)

Full Cohort (N=20,000)

	Cancer+	Cancer-	
Coffee+	105	11395	11500
Coffee-	45	8455	8500

Observed RR = 1.72

(105/11500)/(45/8500)

Non Smokers (N=15,000)

Smoker-	Cancer+	Cancer-	
Coffee+	25	7475	7500
Coffee-	25	7475	7500

Observed RR = 1.0

(25/7500)/(25/7500)

Smokers (N= 5,000)

Smoker+	Cancer+	Cancer-	
Coffee+	80	3920	4000
Coffee-	20	980	1000

Observed RR = 1.0

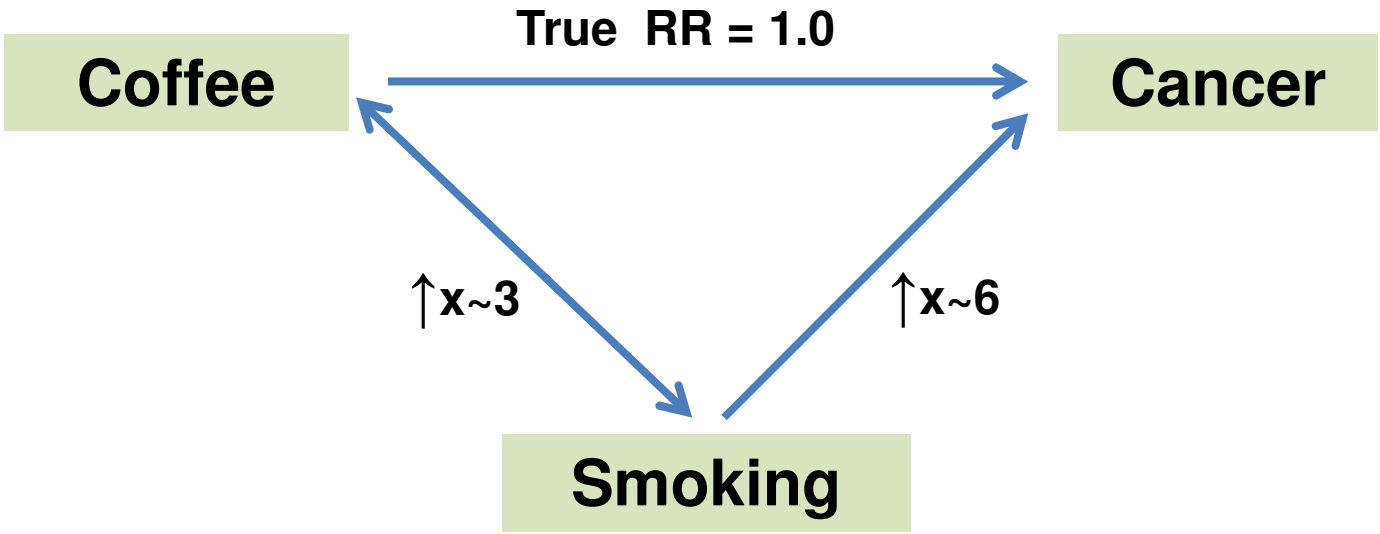
(80/4000)/(20/1000)

Confounding - Example

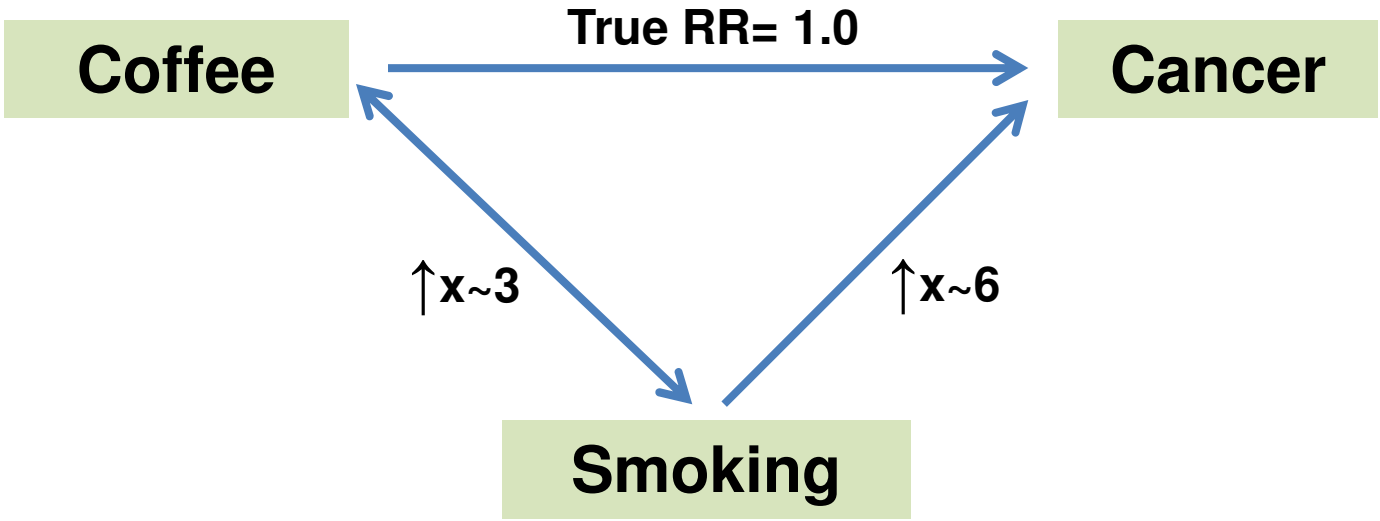
Does drinking coffee cause cancer? – Observed RR = 1.72

→ smoking(coffee+): 35% vs. smoking(coffee-): 12%

→ cancer(smoking+): 2% vs. cancer (smoking-): 0.33%



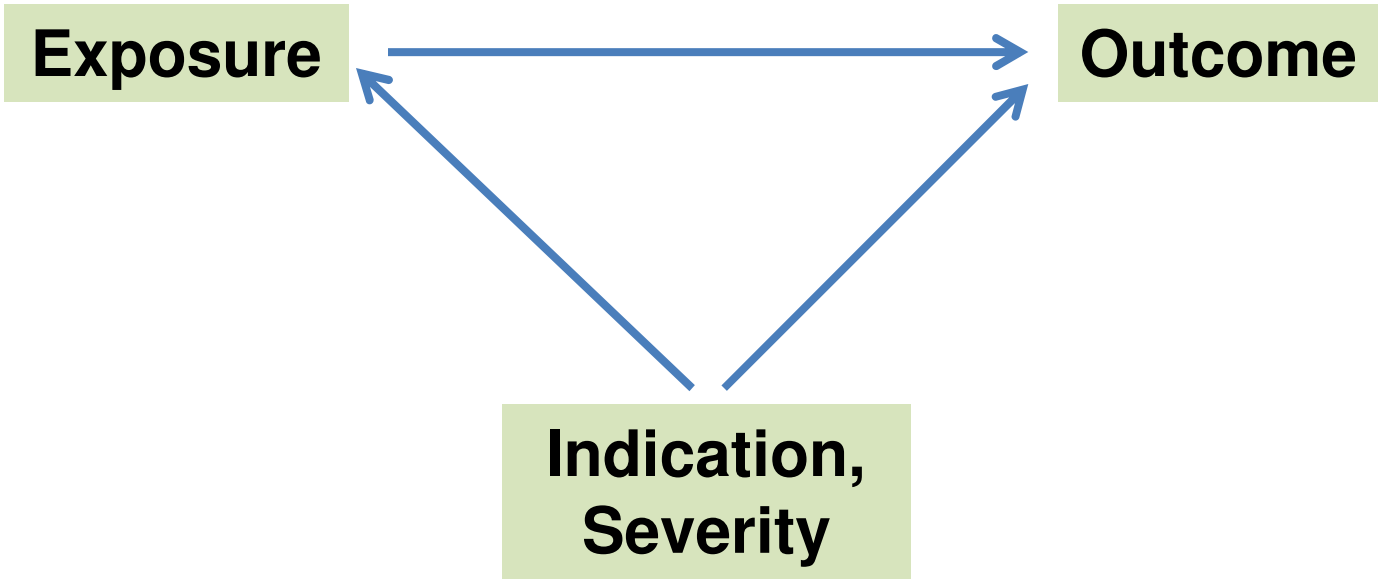
Confounding - Example



Smoking acts as a confounder in our study of cancer risk from coffee drinking. Without controlling for this confounder, it appears that coffee drinkers are ~70% more likely to develop cancer. After stratification by smoking status, the analysis shows no increased risk of cancer for coffee drinkers. The apparent association resulted from the fact that (1) coffee drinkers are more likely to smoke and (2) smoking is a strong risk factor for cancer.

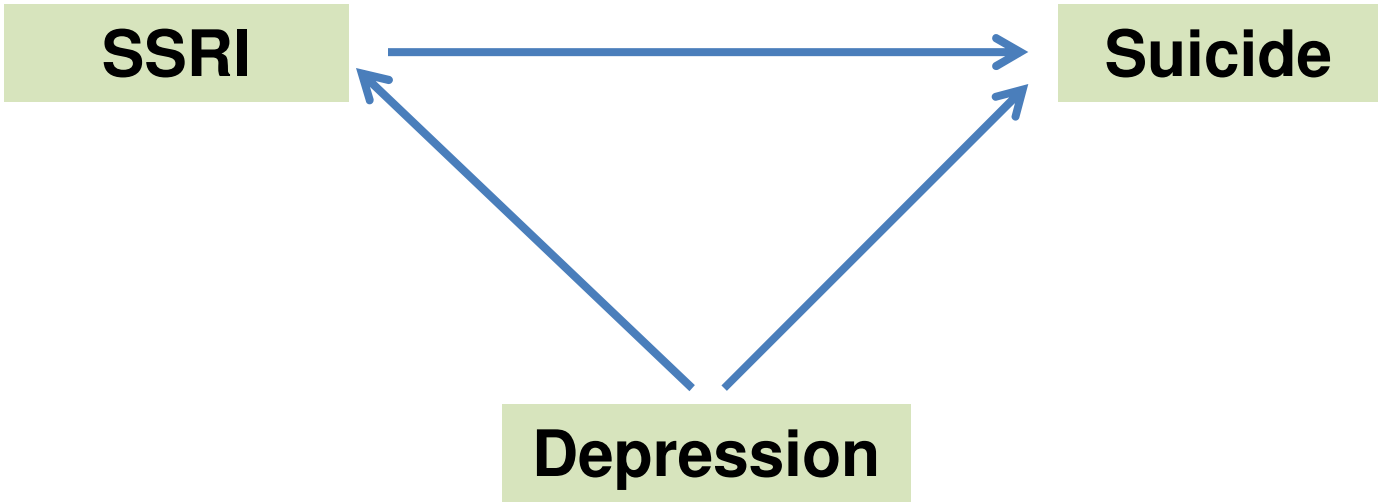
Confounding by Indication

- **Good prescribing creates confounding**
  - Indication for treatment or severity of disease commonly predict the initiation of treatments
  - Indication for treatment and disease severity are associated with the outcome of interest



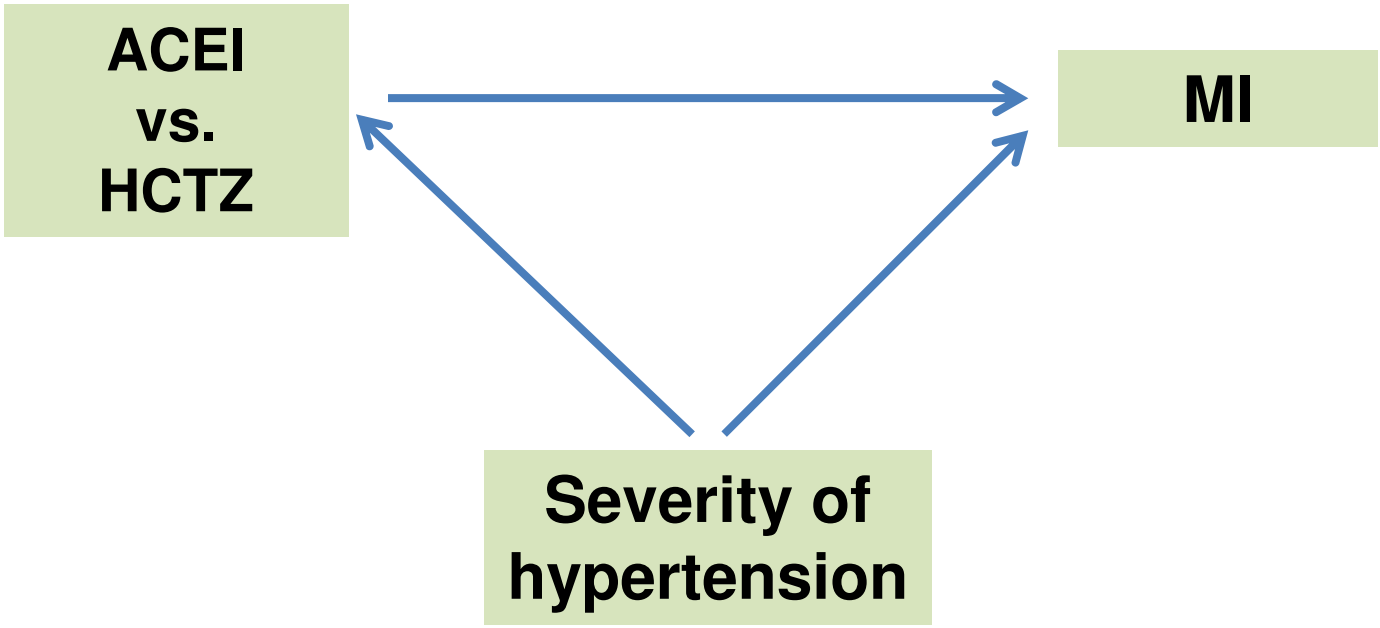
Confounding by Indication

- **Good prescribing creates confounding**
  - **Indication** for treatment or severity of disease commonly predict the use or choice of treatment
  - **Indication** for treatment and disease severity are associated with the outcome of interest

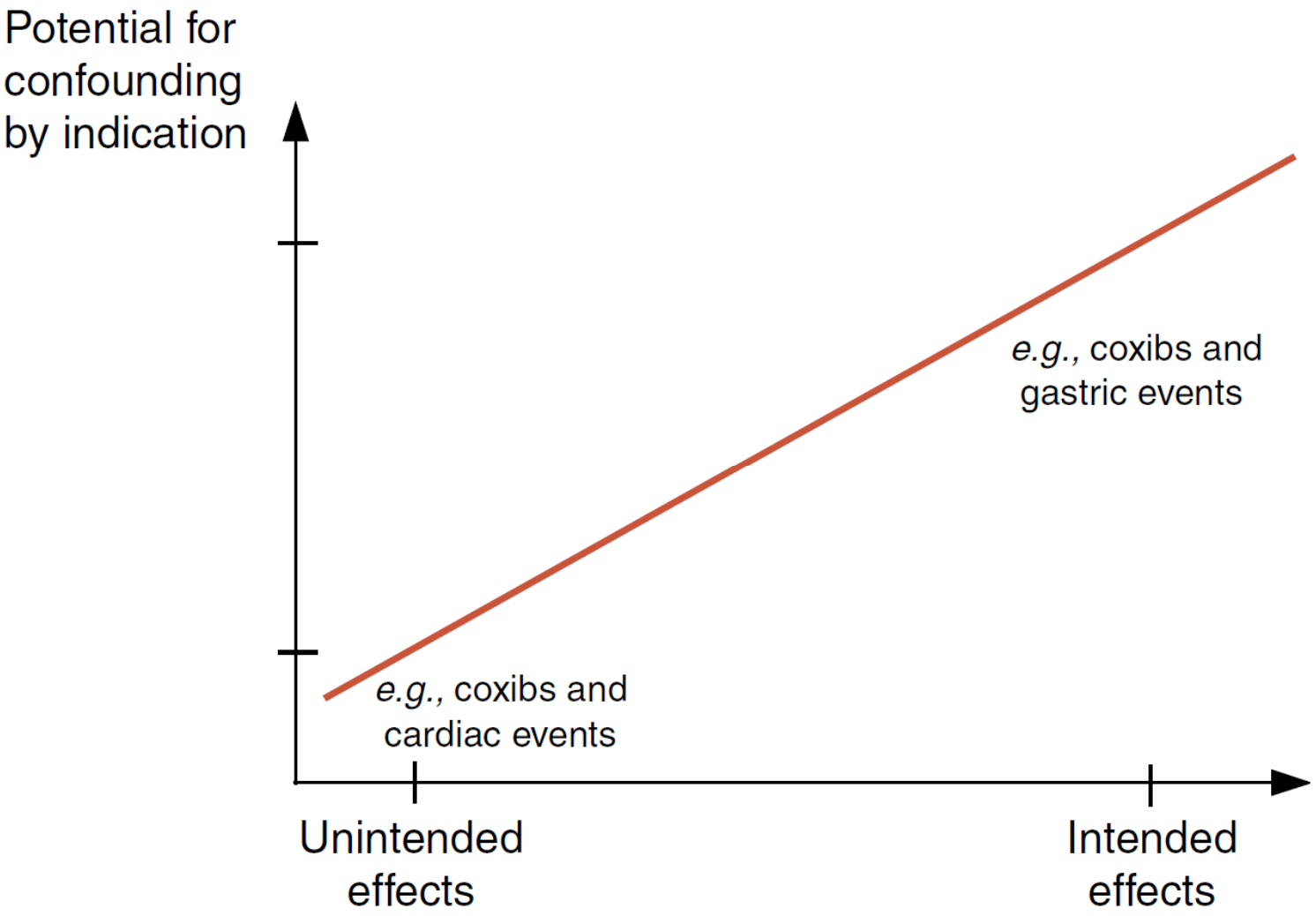


Confounding by Indication

- **Good prescribing creates confounding**
  - Indication for treatment or **severity** of disease commonly predict the use of
  - Indication for treatment and disease **severity** are associated with the outcome of interest



Confounding and Outcome of Interest



Schneeweiss, CPT 2007

Confounding and Choice of Comparator

- Choice of comparator directly affects the presence and magnitude of confounding
- Non-use is generally a poor comparator (↑confounding)
- Potential for confounding smaller for comparators with
  - Same indication
  - Similar contraindications
  - Same treatment modality
  - Similar adverse effects
- Comparator choice can be used to minimize confounding. Make sure that the clinical question remains relevant!

Setoguchi and Gerhard, AHRQ CER User Guide, Chapter 5, 2013

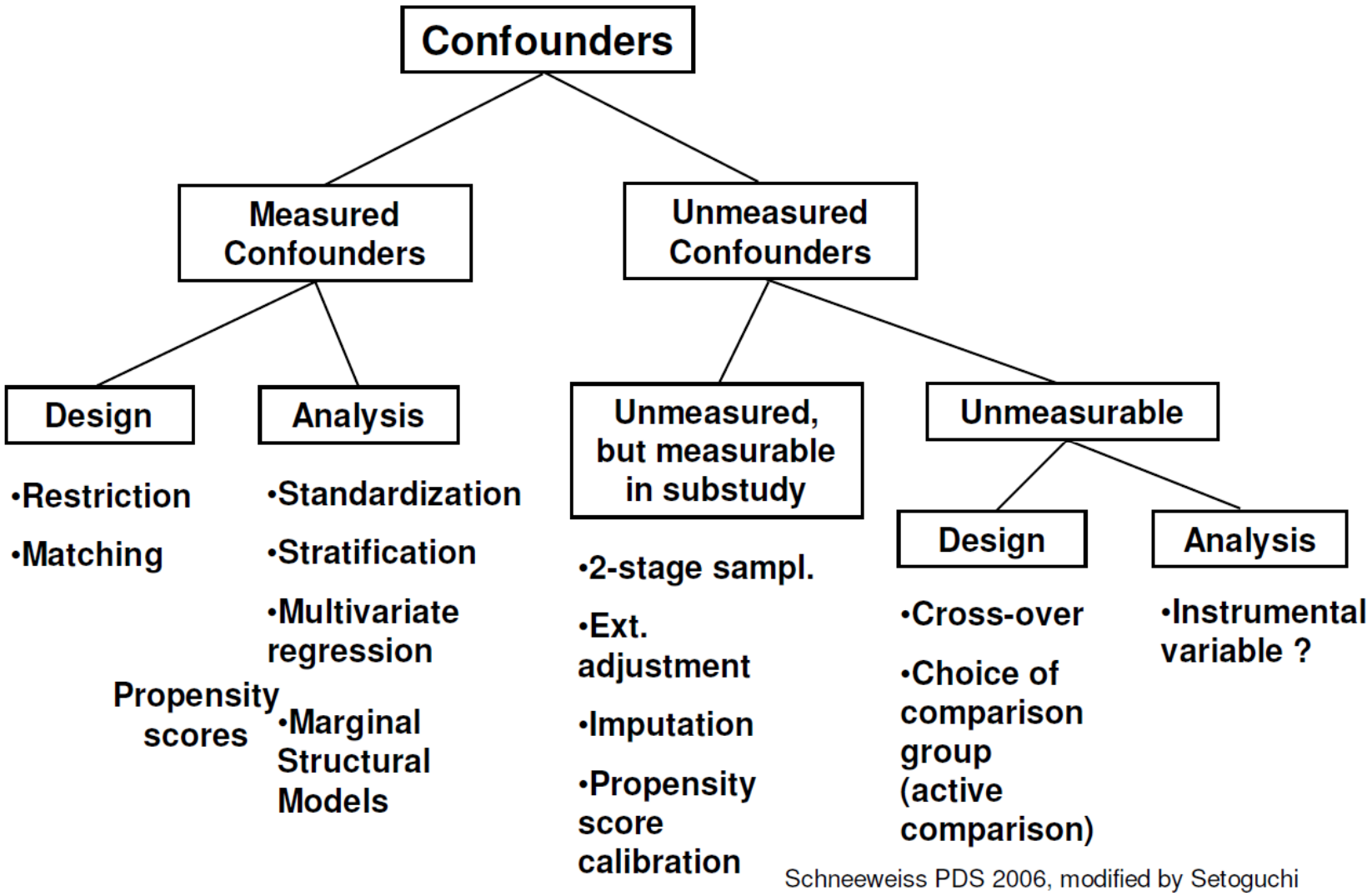
Addressing Confounding

- **Identify potential confounders** → learn about determinants of treatment in your population

Addressing Confounding

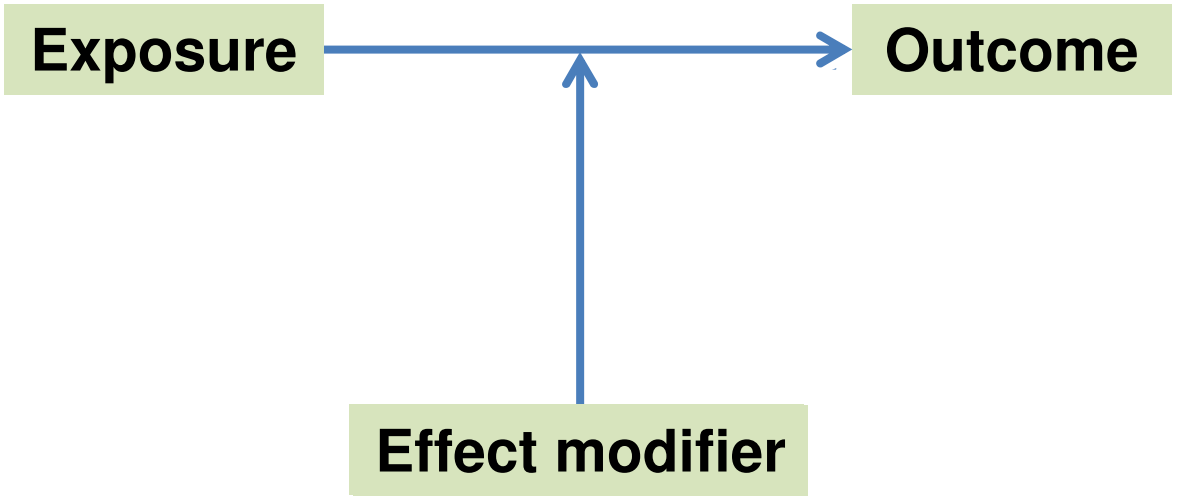
- **Identify potential confounders** → learn about determinants of treatment in your population
  - Cannot solely be done from guidelines, literature
  - Misleading if obtained from (academic) super-specialists
  - Might vary in different populations (countries, health plans, etc)
  - Important role for drug utilization studies
- Confounders may be **measured** or **unmeasured**
- **Measured confounders:** Restriction, matching, stratification, multivariate analysis

Addressing Confounding



Schneeweiss PDS 2006, modified by Setoguchi

Confounding vs. Effect Modification



Effect Modification

- Also called treatment effect heterogeneity
- Occurs when the effect of the exposure is different in different (sub)groups of the population
- Examples include genetics, age, sex
- There is no average ‘true effect’
- Results are best presented stratifies
- Facilitates personalized medicine

Effect Modification - Example

- **Effect of exposure differs by carrier status of a specific SNP:**

Stratified analysis:

Full Cohort (N=2,000)

	AE+	AE-	
Exp+	30	370	400
Exp-	160	1440	1600

Observed RR = 0.75
(30/400)/(160/1600)

SNP- (N=1,600)

SNP+	AE+	AE-	
Exp+	20	180	200
Exp-	140	1260	1400

Observed RR = 1.0
(20/200)/(140/1400)

SNP+ (N=400)

SNP-	AE+	AE-	
Exp+	10	190	200
Exp-	20	180	200

Observed RR = 0.5
(10/200)/(20/200)

- **Treatment highly protective in SNP+**
- **No effect in SNP-**
- **Average treatment effect misleading**

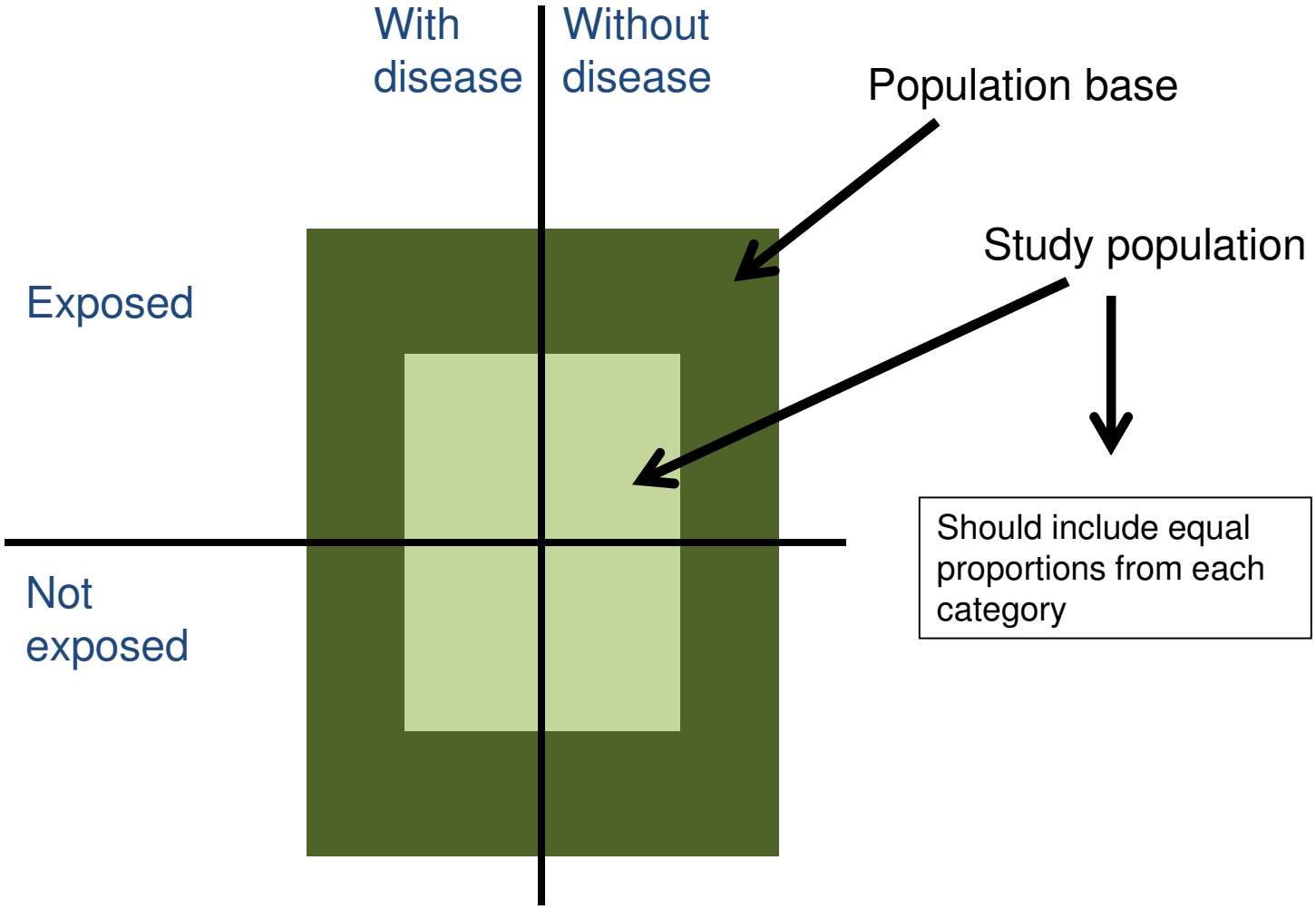
SELECTION BIAS

Selection Bias

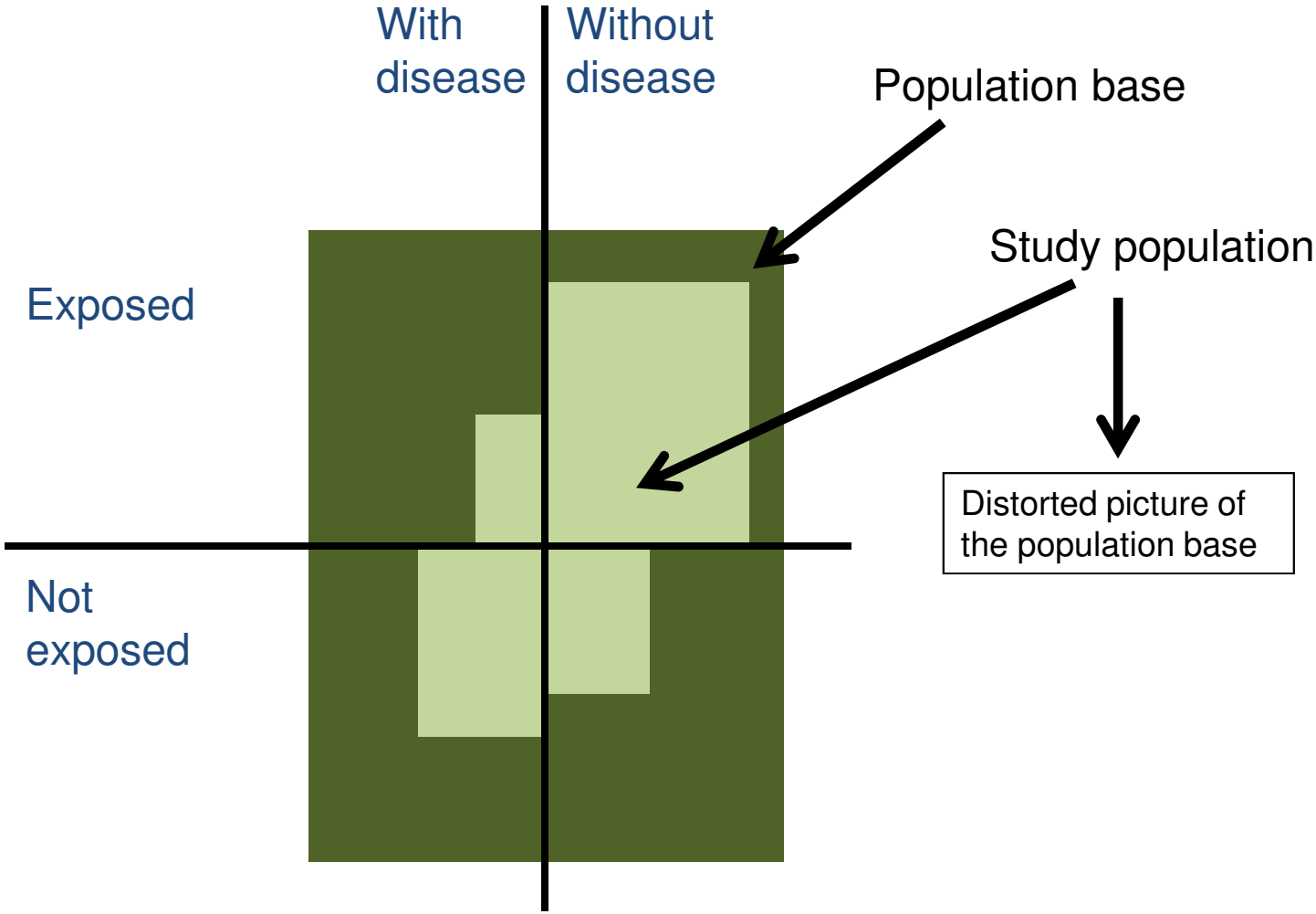
- Distortions that result from procedures used to select subjects and from factors that influence participation/retention in the study. A distortion in the estimate of the effect due to the manner in which subjects are selected for the study.

- Bias of the estimated effect of an exposure on an outcome due to conditioning on a common effect of the exposure and the outcome (or of causes of the exposure and the outcome)

Selection Bias



Selection Bias



Example I: Selection Bias in Case Control Studies

- Imagine a cumulative case-control study conducted in one large hospital. The study aims to explore whether smoking increases the risk of experiencing a stroke. Cases are patients admitted for stroke, controls are patients admitted for everything else. In order to have an unbiased result, the controls need to be representative of the non-cases in the source population, particularly in regards to the exposure of interest (smoking). However, because smokers are also at higher risk for other diseases that lead to hospitalizations than non-smokers (lung cancer, COPD, etc), smoking is more common among hospitalized non-cases than among non-cases in the source population. This will result in an underestimation of the effect of smoking on stroke risk.

Unbiased Control Selection

Source Population (Exposure odds in non-cases = 0.5)

	Stroke (Cases)	No Stroke (Controls)
Smoker	60	30000
Non-Smoker	40	60000

True OR = 3.0

Random Sample

Cumulative Case-Control Study (4:1); (Exposure odds in non-cases = 0.48)

	Stroke (Cases)	No Stroke (Controls)
Smoker	60	130
Non-Smoker	40	270

Estimated OR = 3.1

Biased Control Selection

Source Population (Exposure odds in non-cases = 0.5)

	Stroke (Cases)	No Stroke (Controls)
Smoker	60	30000
Non-Smoker	40	60000

True OR = 3.0

Hospitalization

Hospitalized Population

	Stroke (Cases)	No Stroke (Controls)
Smoker		
Non-Smoker		

Biased Control Selection

Source Population (Exposure odds in non-cases = 0.5)

	Stroke (Cases)	No Stroke (Controls)
Smoker	60	30000
Non-Smoker	40	60000

True OR = 3.0

Hospitalization

All cases are hospitalized

Hospitalized Population

	Stroke (Cases)	No Stroke (Controls)
Smoker	60	
Non-Smoker	40	

Biased Control Selection

Source Population (Exposure odds in non-cases = 0.5)

	Stroke (Cases)	No Stroke (Controls)
Smoker	60	30000
Non-Smoker	40	60000

True OR = 3.0

Hospitalization

Among the possible controls (i.e. the source population) smokers are more likely to be hospitalized than non smokers (1.8% vs. 0.6%).

Hospitalized Population

	Stroke (Cases)	No Stroke (Controls)
Smoker	60	540
Non-Smoker	40	360

Biased Control Selection

Source Population (Exposure odds in non-cases = 0.5)

	Stroke (Cases)	No Stroke (Controls)
Smoker	60	30000
Non-Smoker	40	60000

True OR = 3.0

Hospitalization

Among the possible controls (i.e. the source population) smokers are more likely to be hospitalized than non smokers (1.8% vs. 0.6%).

Hospitalized Population **(Exposure odds in non-cases = 1.5)**

	Stroke (Cases)	No Stroke (Controls)
Smoker	60	540
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Biased Control Selection

Source Population (Exposure odds in non-cases = 0.5)

	Stroke (Cases)	No Stroke (Controls)
Smoker	60	30000
Non-Smoker	40	60000

True OR = 3.0

Hospitalization ↓

Among the possible controls (i.e. the source population) smokers are more likely to be hospitalized than non smokers (1.8% vs. 0.6%).

Hospitalized Population → **sample controls for study**

	Stroke (Cases)	No Stroke (Controls)
Smoker	60	540 → 240
Non-Smoker	40	360 → 160

Biased Control Selection

Source Population (Exposure odds in non-cases = 0.5)

	Stroke (Cases)	No Stroke (Controls)
Smoker	60	30000
Non-Smoker	40	60000

True OR = 3.0

Hospitalization

Among the possible controls (i.e. the source population) smokers are more likely to be hospitalized than non smokers (1.8% vs. 0.6%).

Study Population **(Exposure odds in non-cases = 1.5)**

	Stroke (Cases)	No Stroke (Controls)
Smoker	60	240
Non-Smoker	40	160

Biased Control Selection

Source Population (Exposure odds in non-cases = 0.5)

	Stroke (Cases)	No Stroke (Controls)
Smoker	60	30000
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True OR = 3.0

Hospitalization

Among the possible controls (i.e. the source population) smokers are more likely to be hospitalized than non smokers (1.8% vs. 0.6%).

Study Population **(Exposure odds in non-cases = 1.5)**

	Stroke (Cases)	No Stroke (Controls)
Smoker	60	240
Non-Smoker	40	160

Study OR = 1.0

Biased Control Selection

Source Population **(Exposure odds in non-cases = 0.5)**

	Stroke (Cases)	No Stroke (Controls)
Smoker	60	30000
Non-Smoker	40	60000

True OR = 3.0

Hospitalization

Exposure distribution in study controls ≠ exposure distribution in source population controls

Study Population **(Exposure odds in non-cases = 1.5)**

	Stroke (Cases)	No Stroke (Controls)
Smoker	60	240
Non-Smoker	40	160

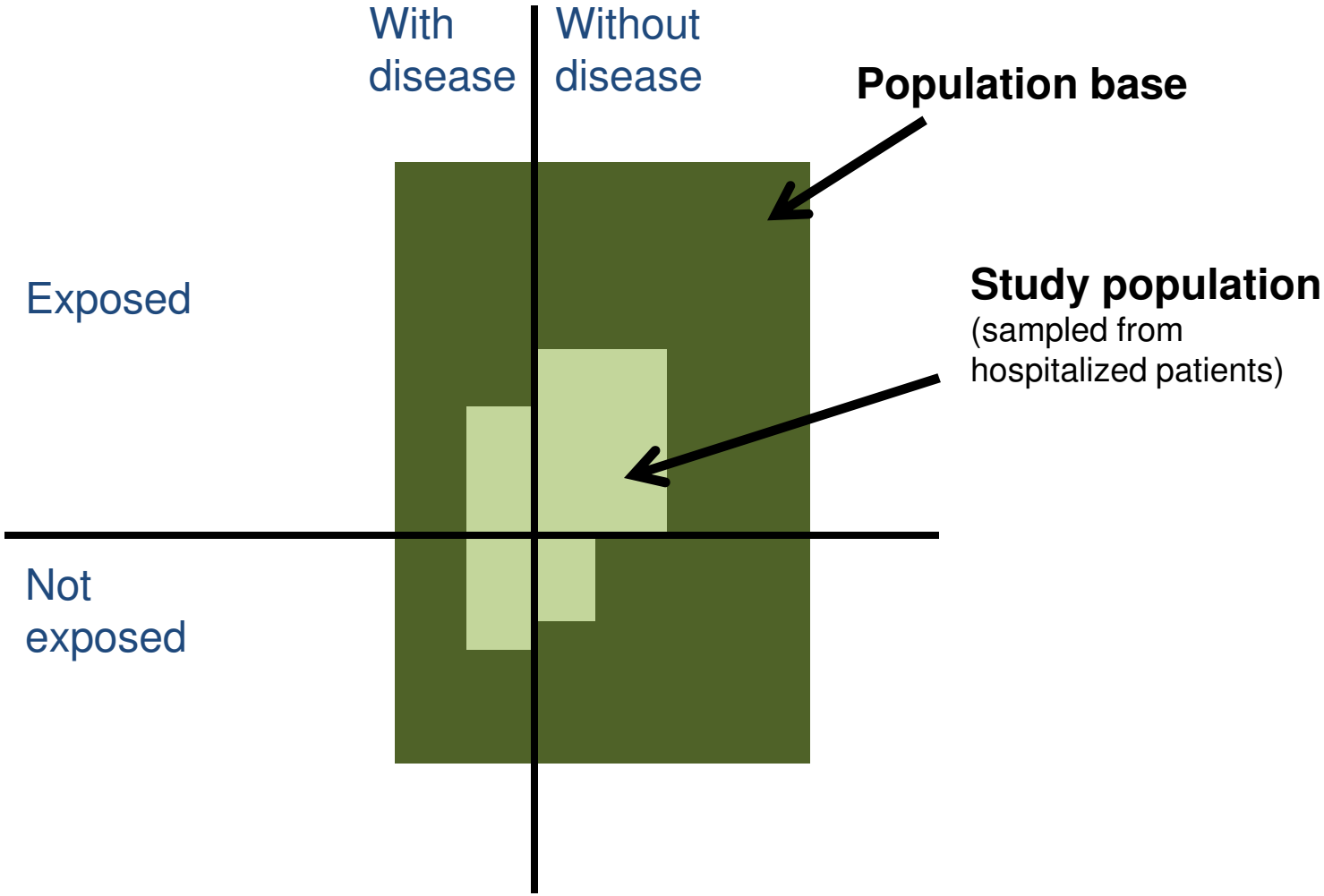
Study OR = 1.0

Selection Bias in Case Control Studies

- In the example, the selection process for the controls – sampled from hospitalized patients instead of randomly sampled from the non-cases in the source population – changed the distribution of the exposure of interest (smoking) in the control patients of the study from the true distribution in the source population.

Solution → Population-based sampling of controls

Selection Bias in Case Control Studies

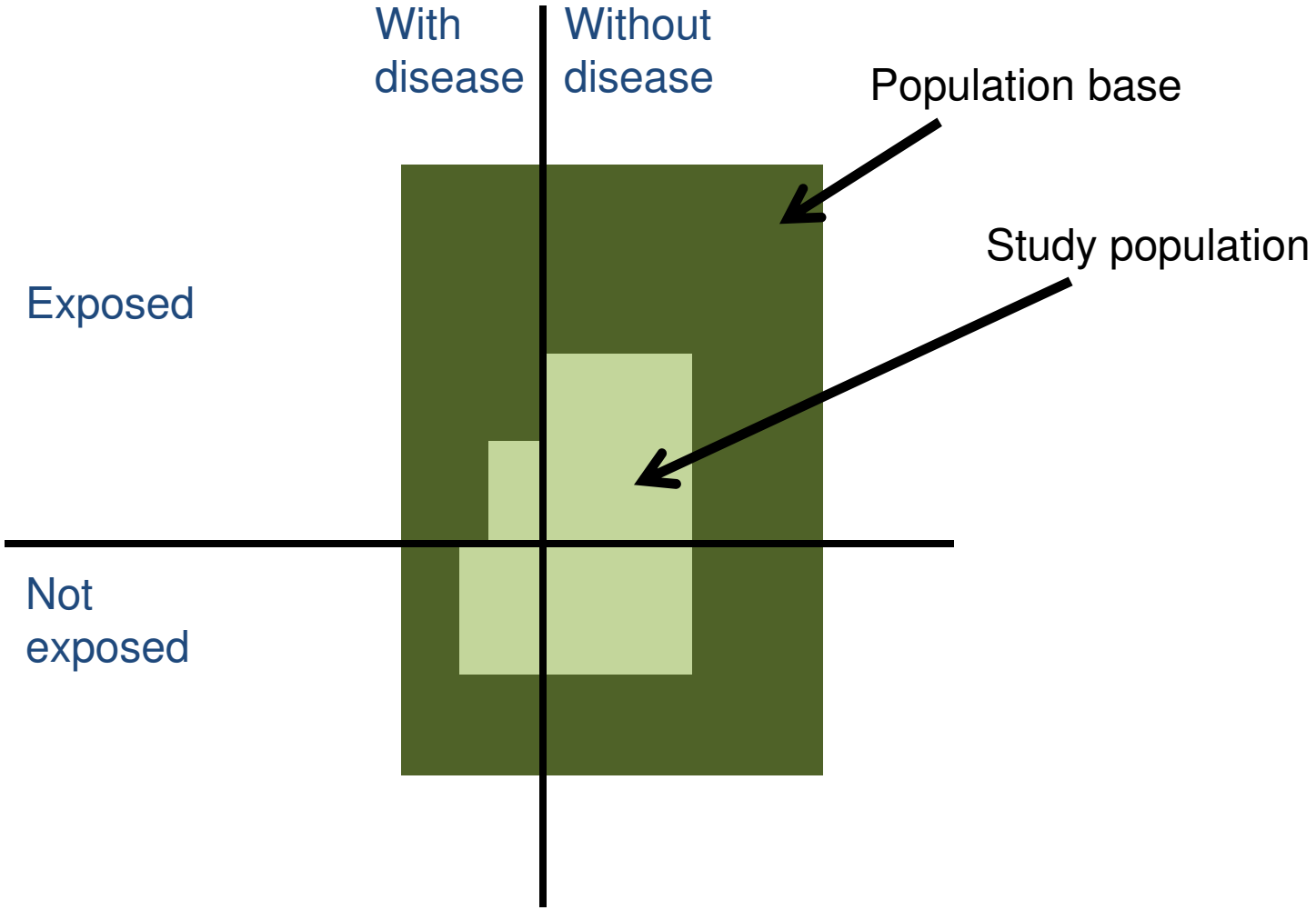


Example II – Prevalent User Bias

- Those who develop outcomes stop taking the drug (depletion of susceptibles)
- Prevalent users tend to be healthy adherers and those that benefit from treatment
- In sum, inclusion of prevalent users will distort the study population (oversampling of subjects / person time at low risk) and result in underestimation of harms and overestimation of benefits

Solution → New user design

Selection Bias – Prevalent User Bias



INFORMATION BIAS

Information Bias

- Often referred to as measurement bias
- Occurs due to poor measurement (classification) of study variables (*exposure*, *outcome*, *confounders*)
- Particularly problematic when using secondary data
  - Primary data: collected for research purposes
  - Secondary data: collected for clinical, administrative, or payment purposes
- Distinguish two basic types of information bias
  - **Non-differential**
    - Misclassification between groups is approximately equal
  - **Differential**
    - Amount of misclassification differs between groups

Misclassification of Exposure

- **Binary, non-differential** → Bias towards the null
  - 20% of exposed subjects classified as unexposed (used OTC version of the drug)
  - 10% of unexposed subjects classified as exposed (non-compliers)

Truth

	AE+	AE-
Exp+	20	10
Exp-	80	90

Non-differential misclassification of exposure

	AE+	AE-
Exp+	20 ↓4	10 ↓2
Exp-	80 ↑8	90 ↑9

Observation

	AE+	AE-
Exp+	24	17
Exp-	76	83

True OR = 2.25
(20x90)/(80x10)

Estimated OR = 1.54
(24x83)/(76x17)

Misclassification of Exposure

- **Binary, differential** → Direction of bias is unpredictable

Truth

	AE+	AE-
Exp+	20	10
Exp-	80	90

True OR = 2.25
(20x90)/(80x10)

Differential exposure misclassification I (e.g., recall bias)

	AE+	AE-
Exp+	20	10 ↓3
Exp-	80	90
	(0%)	(30%)

Observation I

	AE+	AE-
Exp+	20	7
Exp-	80	93

Estimated OR = 3.32
(20x93)/(80x7)
Bias away from null

Differential exposure misclassification II

	AE+	AE-
Exp+	20	10
Exp-	80	90 ↑9
	(0%)	(10%)

Observation II

	AE+	AE-
Exp+	20	19
Exp-	80	81

Estimated OR = 1.07
(20x81)/(80x19)
Bias towards null

- **Exposure not binary** → Direction of bias is unpredictable

Misclassification of Outcome

- Analogous to misclassification of exposure
- Detection bias (differential misclassification of the outcome) often occurs when diagnostic procedures necessary for outcome classification are influenced by exposure
- **Notable special case:** Incomplete sensitivity in outcome ascertainment does not cause bias in *risk ratio* if specificity is 100%

Truth

	AE+	AE-	
Exp+	80	920	1000
Exp-	40	960	1000

True RR = 2.0
(80/1000)/(40/1000)

	AE+	AE-	
Exp+	80 → 40 (50%)	920	1000
Exp-	40 → 20 (50%)	960	1000

Non-differential misclassification of the outcome. Specificity = 100%

Observation

	AE+	AE-	
Exp+	40	960	1000
Exp-	20	980	1000

Estimated RR = 2.0
(40/1000)/(20/1000)

Misclassification of Confounders

- Adjustment with a binary non-differentially misclassified confounder reduces bias and produces a partially adjusted effect estimate that falls between the crude and true effect – residual confounding

  Greenland and Robins, AJE 1985

  - Residual confounding decreases with increasing sensitivity and specificity of the misclassified confounder

    Savitz and Baron, AJE 1986

  - Necessary assumption (likely to hold in most applications in epidemiology) – Effect of the confounder on the outcome is in the same direction among the treated and the untreated (i.e., there is no qualitative interaction between the treatment and the confounder)

    Ogburn and VanderWeele, Epidemiology 2012

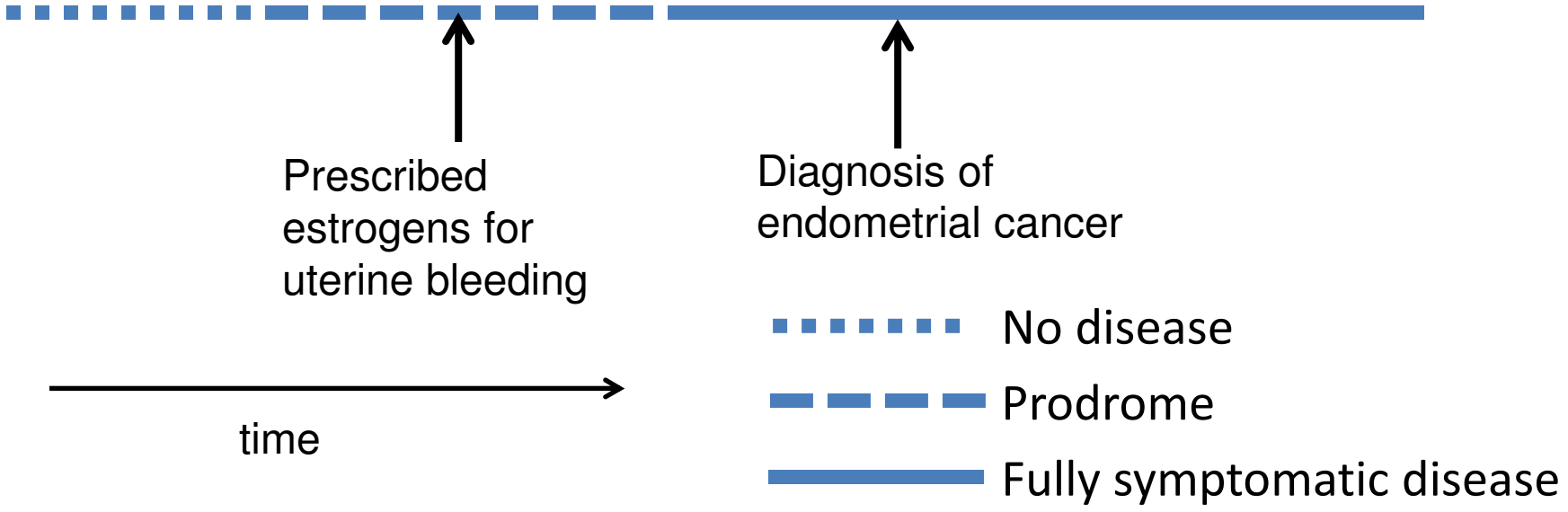
Addressing Misclassification

- Prospective studies with primary data collection
  - Ensure accurate measurement (instruments, procedures, quality control, etc)
- Studies that rely on secondary data
  - Use validated measures for exposure, outcome, and confounding factors
  - Rule out recall and detection biases

PROTOPATHIC BIAS

Protopathic Bias

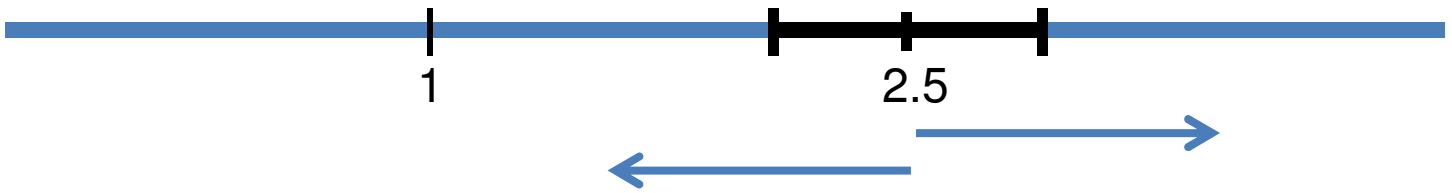
- **First symptoms** of the outcome of interest are the **reason** for the **prescription** of the drug under study **and** the **outcome**.
- Reverse causation



SUMMARY

In Conclusion…

- **Best remedy for bias is prevention!**
- Frame your question in a way that minimizes biases
- Design your study well to minimize biases
- Carefully analyze your results to control for confounding
- Understand the potential effects of residual bias and confounding on the risk estimate. Perform sensitivity analyses.
  - What is the magnitude of the bias?
  - In which direction is the estimate pulled?



Addressing Bias: RCTs

- **Confounding**
  - → **Randomization**
- **Selection Bias**
  - → **Randomization**
  - → **Maximize protocol adherence/minimize attrition**
  - → **Intent-to-treat analysis**
- **Information Bias**
  - → **Primary data collection**
  - → **Blinding**

RCTs are explicitly designed to minimize bias.

That does not mean that all RCTs do a good job with it!

Addressing Bias: Observational Studies

- **Confounding**
  - → **Restriction** (e.g., patients with hypertension; certain age range; free of contraindications)
  - → **Choice of comparator** (non-use vs. active treatment; same vs. different class/indication); e.g., healthy user effect!
  - → **Statistical control** (multivariate models, propensity scores, etc)
- **Selection Bias**

→ **New user design**

→ **Population-based data / sampling**

- **Measurement Bias**

→ **Use validated measures**

→ **Rule out differential misclassification** (recall & detection bias)

If there are significant biases that can't be addressed, don't do the study!

Thank you for your attention!

Contact:
tgerhard@rci.rutgers.edu