30th Annual Meeting of the International Society for Pharmacoepidemiology
Taipei, Taiwan October 23, 2014

Confounding and Bias in Case-Control Studies

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Disclosures

- There is no potential conflict of interest relevant to this presentation
- Materials in this presentation are adopted from the lectures in this year provided by Dr. Tobias Gerhard!

Outline

- Bias that might occur in case-control studies
  - Selection Bias
  - Information Bias
- Summary

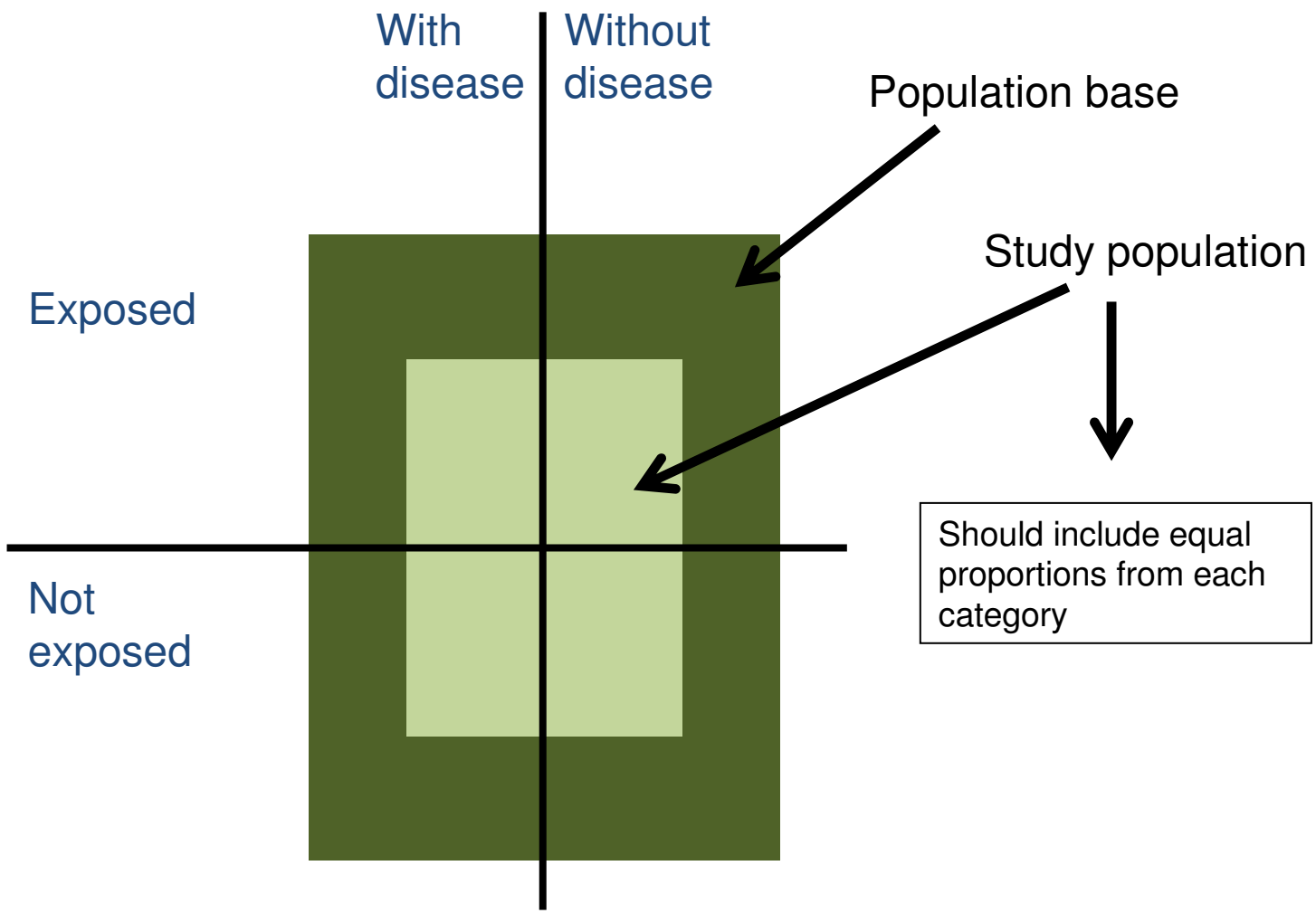
SELECTION BIAS

Selection Bias

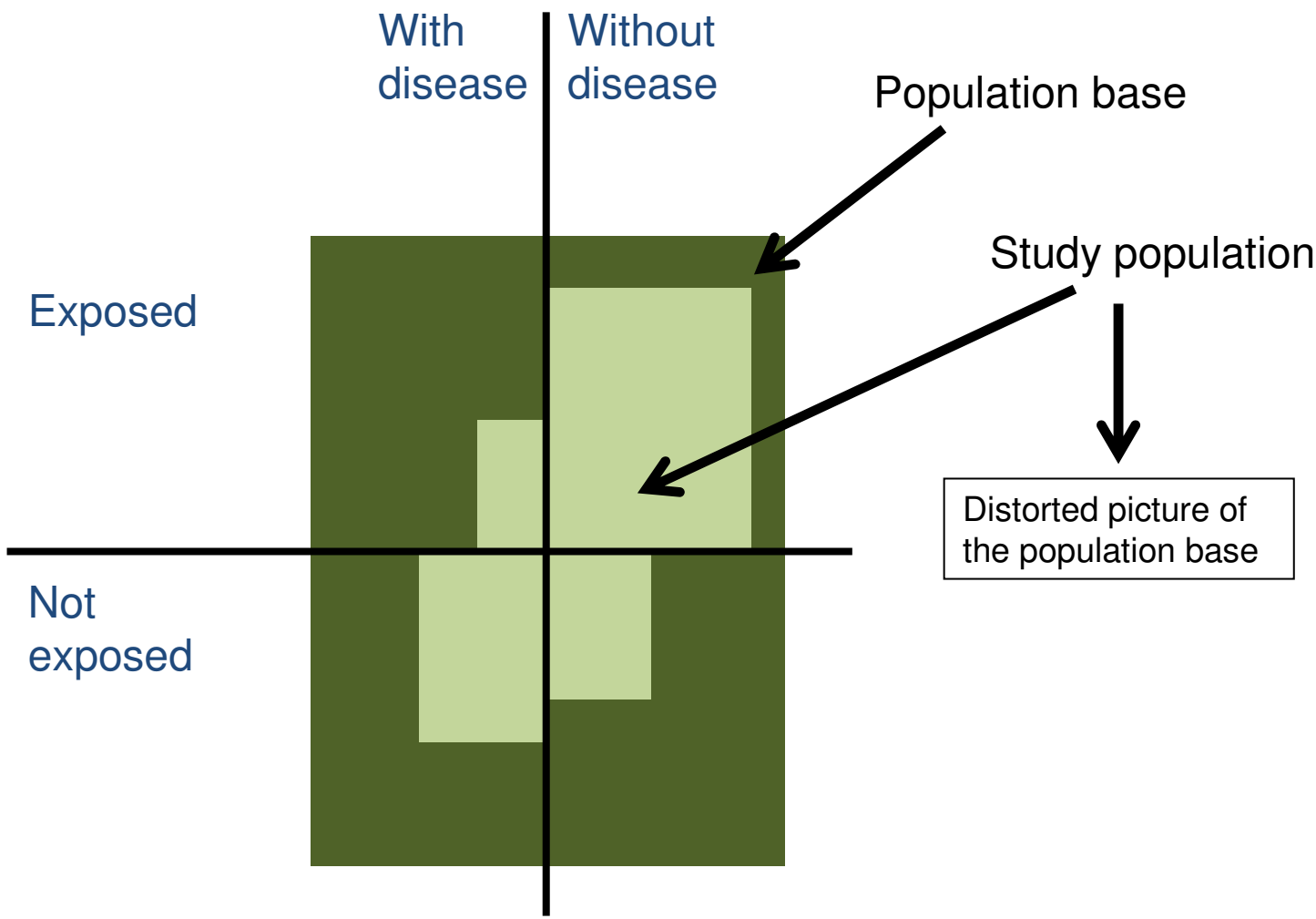
- Selection bias occurs when a systemic error in the ascertainment of cases or controls in case-control studies.

- If exposure status is differentially distributed between cases and controls, leading to a distortion of the exposure-disease association.

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
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

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

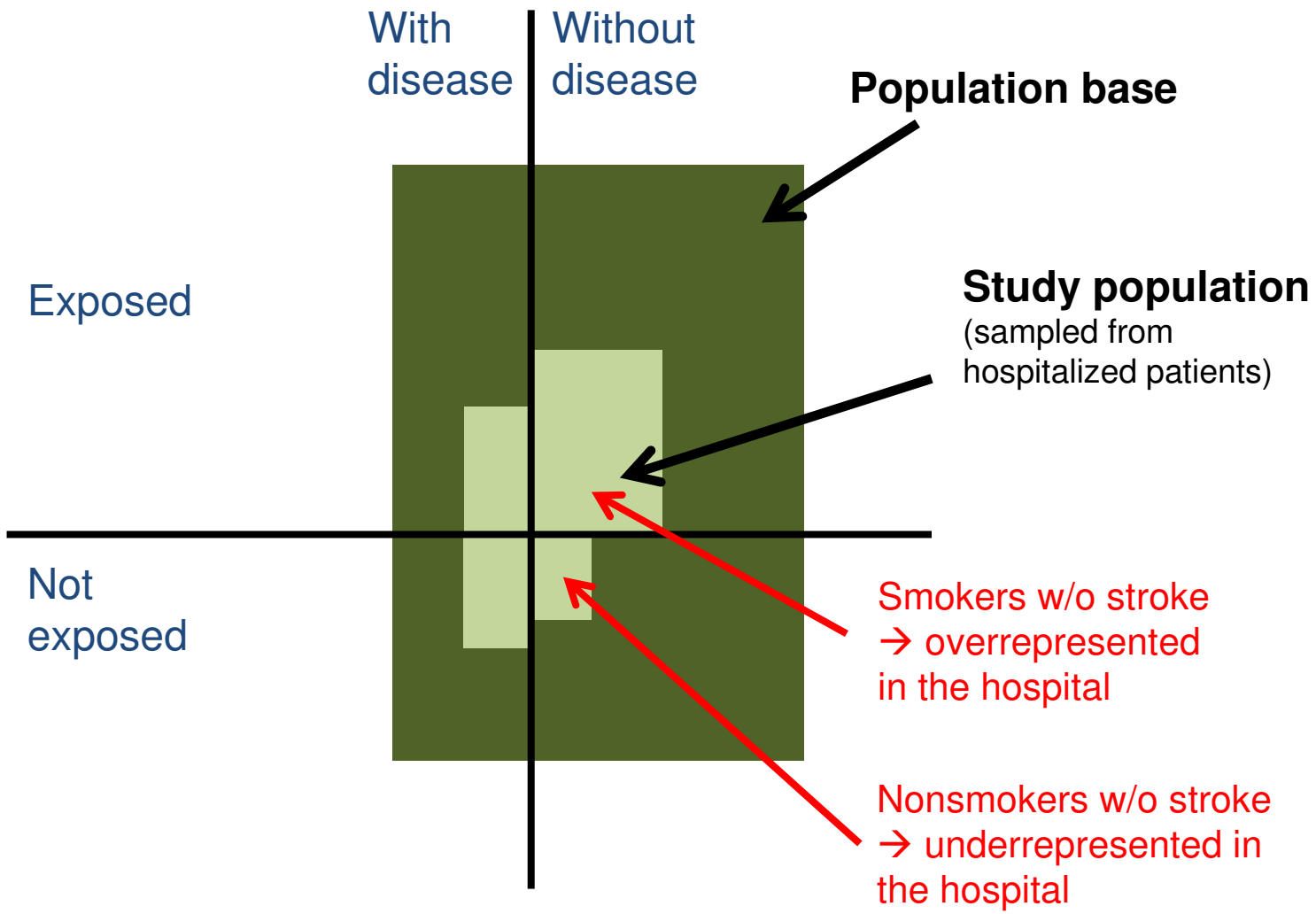
Study OR = 1.0

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

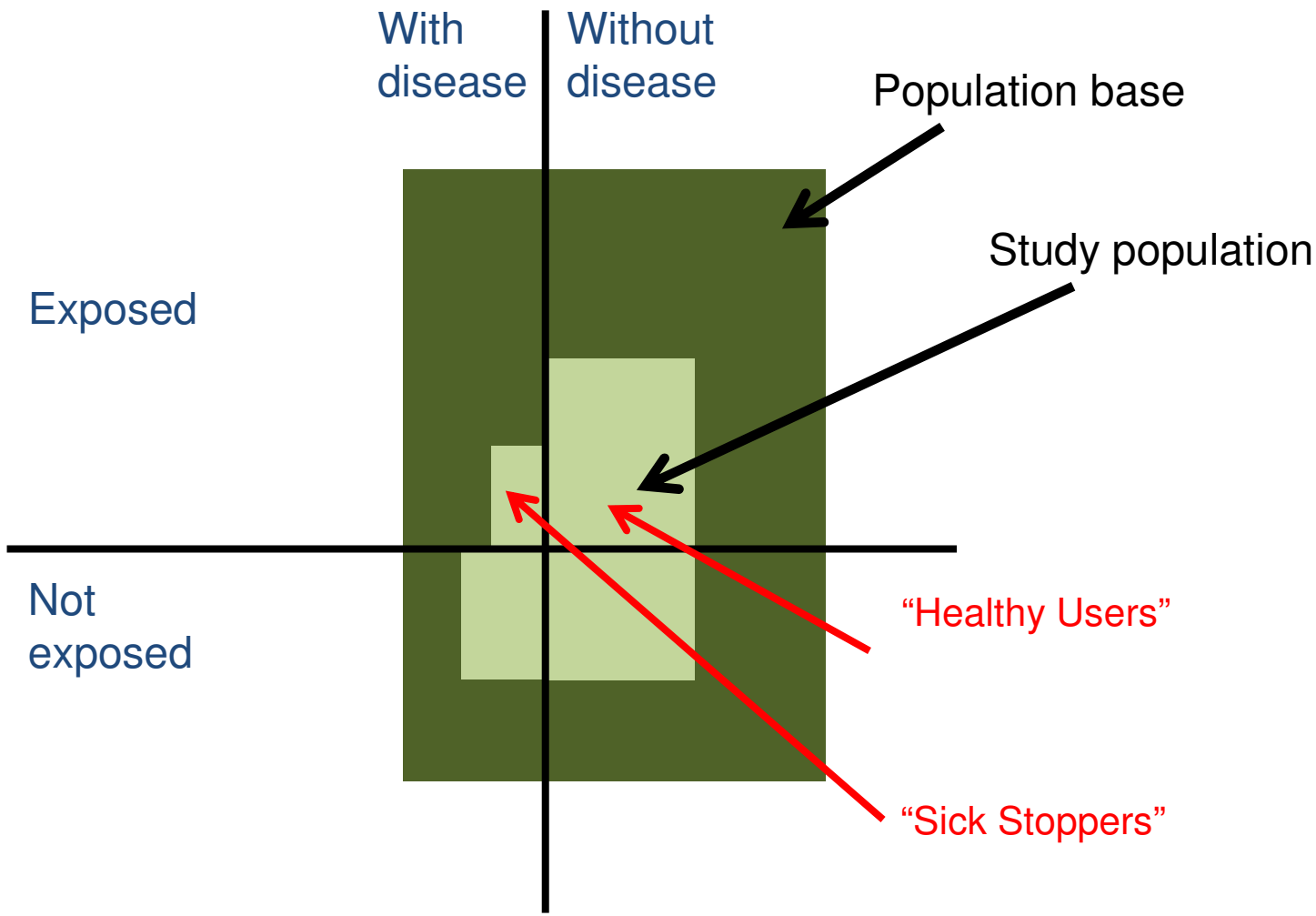


Example II – Prevalent User Bias

- Those who develop outcomes stop taking the drug (depletion of susceptibles, sick stoppers)
- Prevalent users tend to be healthy adherers and those that benefit from treatment (healthy users)
- 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*)
- 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

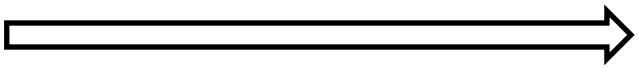
Non-differential misclassification of exposure

	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
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
	(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 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 1989
  - 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

In summary…

- Best remedy for bias is prevention!
- RCTs
  - Randomization
  - Blinding
  - Primary data collection
- Observational Studies
  - Sample selection
  - Choice of comparator
  - Use validated measures
  - Statistical analysis

Thank you

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