Introduction to Pharmacoepidemiology

Confounding and Bias

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Conflict of Interest Declaration

• The opinions expressed in this presentation are those of the presenter and do not necessarily reflect those of the *Université de Montréal* or the *Government of Canada*.

• No other conflict of interest to declare.

Definitions

Confounding (Lat. *confundere*, to mix together) is the distortion of a measure of the effect of an exposure on an outcome due to the association of the exposure with other factors that influence the occurrence of the outcome.

Bias is the systematic deviation of results or inferences from the truth

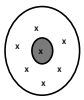
Dictionary of Epidemiology (5th ed)
M Porta 2008

Bias is a systematic error in sampling or measurement that leads to an incorrect conclusion.

Quantitative Methods for Health Research
Bruce N et al. 2008

Precision, Validity & Accuracy

Precision → degree of random error



Accuracy = Precision + Validity

Validity → degree of systematic error

Accuracy

Accuracy = Precision + Validity

Accuracy = 1 / Total Error

Accuracy = 1 / Random Error + 1 / Systematic Error

Random Error
- *p* values
- Confidence Intervals
- Study power

Systematic Error
- Study Estimations vs. Real Value Differences
- Methodological Issues (Study Design)

NB: Increased sample size improve precision but not necessarily validity

Bias and Confounding

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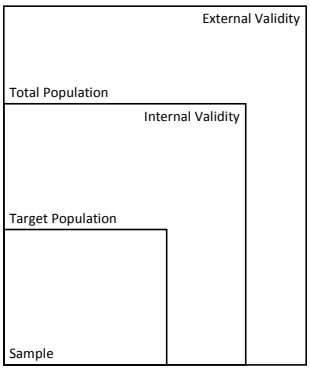
Increase Systematic Error

⇩

Affect Validity

⇩

Decrease Accuracy



Bias - General Concepts

- Although observational studies are particularly vulnerable to bias, it can occur in all type of studies
- Bias may be introduced at any point of a study
- Improving study design is the main (only) way to minimise or control bias

Types of Bias

- Several types (e.g. referral, recall, differential, non-differential, etc.)
- It is usually subdivided into

1) Selection Bias: Related to study subject recruitment or retention procedures
2) Information Bias: Related to procedures used to measure the information about study variables
3) Confounding: Distortion caused by other variables to both exposure & outcome

- The risk of Protopathic Bias (Reverse Causality) is believed to occur only in PE studies.

Selection Bias - Definition

• 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)

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

Selection Bias - Examples

• Subject selection is influenced by

Exposure → Case-Control
Q) Are cases & controls selected from the same population?
- Hospital based recruitment to study NSAIDs & abdominal pain

Risk of AE → Cohort
Q) Does recruitment of exposed and non-exposed relate to their likely development of the outcome of interest?
-A recent publication may condition and increase the probability of diagnostic testing of “interesting cases”.

• Includes Referral, Self-Selection and Prevalence Bias

Information Bias - Definition

• A flaw in measuring exposure, covariate or outcome variables that results in different quality (accuracy) of information between comparison groups. It may not be independent of the occurrence of selection bias.

Information Bias - Examples

• Non-differential (random) misclassification → may affect statistical significance
- Commonly mentioned as limitation of PE studies
- Somehow difficult to control (… the "unknowns")
- e.g. Non-validated diagnostic criteria (medical services DB); Exposure ascertainment (prescription vs. actual drug use; choice of time point vs. previous exposure history)

10% Non-differential misclassification of Exposures

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

	AE +	AE -
Exp+	20 ↓2	10 ↓1
Exp-	80 ↑8	90 ↑9

	AE +	AE -
Exp+	26	18
Exp-	74	82

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

Estimated OR = 1.60
(26x82)/(74x18)

Bias towards null

Information Bias - Examples

• Differential (systematic) misclassification
- When knowledge of exposure (cohort), or outcome (case-control), influences validity of the information collected
- e.g. Differential recall; differential detection

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

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

Differential misclassification of Exposures

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

(5%) (20%)

	AE +	AE -
Exp+	24	8
Exp-	76	92

Estimated OR = 3.63
(24x92)/(76x8)

Bias away from, or towards the null

	AE +	AE -
Exp+	20 ↓3	10 ↓1
Exp-	80 ↑10	90 ↑7

(12%) (8%)

	AE +	AE -
Exp+	27	16
Exp-	73	84

Estimated OR = 1.94
(27x84)/(73x16)

Confounding - Definition

• Distortion of a measure of the effect of an exposure *(Drug use)* on an outcome *(Adverse Event)* due to the association of the exposure with other factors *(Confounders)* that influence the occurrence of the outcome.

Protopathic Bias

Definition

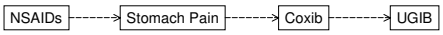
A type of bias that occur if the first symptoms of the outcome of interest are the reasons for using the treatment under study (i.e. to become exposed).

If there is a delay between the first symptoms of an AE (for Drug A) and the diagnosis

The AE (for Drug A) may be incorrectly associated to the Drug B, which was prescribed to replace it (or to treat the symptoms)

Protopathic Bias - Example

Truth



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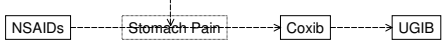
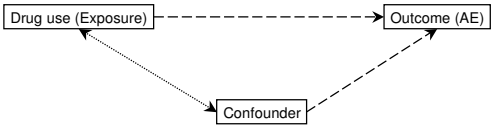


Confounding - Characteristics



The Confounder is:
- an independent risk factor (AE)
- associated with exposure
- not an intermediate between exposure and outcome

Confounding - Examples

- **Reason for Prescription**
  - Indication (e.g. Depression, Suicide & Anti-depressants)
  - Channelling (e.g. Coxibs, NSAIDs, & UGIB)
  - Disease severity (e.g. Asthma, β-agonists & Death)
- **Comedication and/or Cofactors** (e.g. Placebo, Compliance & Death)

	AE +	AE -
Exp+	77	52
Exp-	23	148

Crude OR = 9.5
(77x148)/(23x52)

	AE +	AE -
Exp+	5	32
Exp-	5	128

Stratified A OR = 4
(5x128)/(5x32)

	AE +	AE -
Exp+	72	20
Exp-	18	20

Stratified B OR = 4
(72x20)/(18x20)

Stratified ORs are equal, …but both are ≠ from the crude OR

Adjustment

Possible Solutions for Bias

Selection
- Random sampling of cases & controls (exposed & non-exposed)
- Systematic recruiting
- Minimizing lost to follow-up
- Investigating drop-outs
- Selecting only incident cases
- Random allocation of exposures

Information
- Blinding
- Standardization of measurement procedures
- Definition criteria of exposure & outcome (objective, prior

Possible Solutions for Confounding

Design
- Randomization
- Matching
- Restricting (e.g. age population) → May reduce generalization

Analysis
- Standardization of rates
- Stratification
- Multivariate analysis & mathematical modelling (sample size and adequacy of data are important limiting factors)

Large Databases
- Propensity Scores
- Sensitivity Analysis

Muchas Gracias !

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