Introduction to Pharmacoepidemiology

Confounding and Bias

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• No other conflict of interest to declare.

Conflict of Interest Declaration

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
- **Validity** → degree of systematic error
- **Accuracy** = Precision + Validity

**Accuracy**

Accuracy = 1 / Total 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**

- 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
  - Hospital based recruitment to study NSAIDs & abdominal pain
  - Risk of AE → Cohort
  - 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)

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\[
\text{True OR} = 2.25 \\
\frac{(20 \times 90)}{(80 \times 10)}
\]

\[
\text{Estimated OR} = 1.60 \\
\frac{(26 \times 82)}{(74 \times 18)}
\]

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

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\[
\text{True OR} = 2.25 \\
\frac{(20 \times 90)}{(80 \times 10)}
\]

\[
\text{Estimated OR} = 3.63 \\
\frac{(24 \times 92)}{(76 \times 8)}
\]

Bias away from, or towards the null

### 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.
**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**

- NSAIDs
- Stomach Pain
- Coxib
- UGIB

**DB**

- NSAIDs
- Stomach Pain
- Coxib
- UGIB

**Confounding - Characteristics**

- Drug use (Exposure)
- Outcome (AE)
- Confounder

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, ß-agonists & Death)

• Comedication and/or Cofactors (e.g., Placebo, Compliance & Death)

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Crude OR = 9.5
\[
\frac{77 \times 52}{23 \times 148} = 9.5
\]

Stratified OR = 4
\[
\frac{5 \times 128}{5 \times 32} = 4
\]

Stratified ORs are equal, but both are \# from the crude OR

Adjustment

Possible Solutions for Confounding

Design
• Randomization
• Matching
• Restricting (e.g., age population) \(
\rightarrow \text{May reduce generalization}
\)

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

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
Muchas Gracias!

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