Bias and confounding

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The accuracy of a result is determined by the degree of absence of systematic variation (validity), and the degree of absence of random variation (precision).

**Variation**

- Random variation
  - precision
- Systematic variation
  - internal validity
    - BIAS
    - CONFOUNDING

Generalizability

- external validity
Two cohort studies of the same research question

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Diseased</th>
<th>Healthy</th>
<th>Total</th>
<th>IP (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+</td>
<td>40</td>
<td>160</td>
<td>200</td>
<td>20</td>
</tr>
<tr>
<td>-</td>
<td>20</td>
<td>180</td>
<td>200</td>
<td>10</td>
</tr>
<tr>
<td>Study 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+</td>
<td>10</td>
<td>26</td>
<td>36</td>
<td>28</td>
</tr>
<tr>
<td>-</td>
<td>5</td>
<td>31</td>
<td>36</td>
<td>14</td>
</tr>
</tbody>
</table>

Study 1: RR = 2.0  p = 0.005  95% CI = 1.23 - 3.25
Study 2: RR = 2.0  p = 0.14   95% CI = 0.79 - 5.10

Random variation

- Can be reduced by increasing the number of study participants thereby increasing the statistical precision
- Dependent on methodological choices
- For a given result, the degree of chance variability is quantified by the confidence interval
Bias in epidemiologic studies

Bias in selection or measurement

Chance

Confounding

Cause

True value of factor

Biological variation

True value of factor at the point of measurement

Performance of the instrument used to measure the factor
Bias due to the influence of the subjects being assessed
Bias due to the influence of the observers

Recording and computation of the results

Value of the variable used in the study
Bias

Definition

- Deviation of results or inferences from the truth, or processes leading to such deviation. Any trend in the collection, analysis, interpretation, publication, or review of data that can lead to conclusions that are systematically different from the truth” (Murphy)

Bias

Nomenclature

“Popularity bias, centripetal bias, referral filter bias, diagnostic access bias, diagnostic suspicion bias, unmasking bias, mimicry bias, previous opinion bias, wrong sample size bias, admission rate bias, prevalence-incidence bias, diagnostic vogue bias, diagnostic purity bias, procedure selection bias, missing clinical data bias, non-contemporaneous control bias, starting time bias, migrator bias, membership bias, non-respondent bias, volunteer bias, insensitive measure bias, underlying cause bias, end-digit preference bias, unacceptability bias, obsequiouness bias, expectation bias, substitution bias, family information bias, exposure suspicion bias, recall bias, attention bias, instrument bias”

(Sackett, 1979)
Bias

nomenclature

- SELECTION BIAS

- INFORMATION BIAS

Selection Bias

- Selection of study groups (on the basis of exposure or outcome) is influenced by the other study axis (exposure or outcome)
- Selective recruitment of study subjects with specific characteristics related to exposure and outcome
  - *i.e, the relation between exposure and outcome is different for those who participate and those who were theoretically eligible for study but were not chosen to participate*

*Bias occurring outside the study material*
Selection bias in cohort studies

➢ The selection or classification of exposed and non-exposed individuals is related to the outcome

Ex:

▪ Retrospective cohort study
▪ “Healthy worker/patient effect”
▪ “Protopathic bias” (“reverse causation”)
▪ Depletion of susceptibles
▪ Confounding by indication

Retrospective cohort study

➢ In the late 1970s, the Centers for Disease Control, USA, wished to assess whether exposure to atmospheric nuclear weapons testing in Nevada in the mid-1950s had caused an increase in leukaemia (and other cancers) among troops who had been present at the particular tests

➢ 76% of the troops were enrolled in the study. Of these, 82% were traced by the investigators, while 18% contacted the investigators on their own initiative

➢ Problems?

Caldwell et al. Leukemia among participants in military maneuvers of a nuclear bomb-test: a preliminary report. JAMA 1980; 244: 1575-8
Retrospective cohort study

- From the service records of the Royal New Zealand Navy, Pearce et al* identified 500 servicemen who had participated in nuclear weapons testing in the Pacific area in 1957-58. Personnel from three ships that were in service during that time but not involved in the nuclear testing were selected as controls.
- Follow-up of index- and control persons through 1987 was performed by linkage to the national cancer registry and death certificates.
- Mortality was similar in the two groups, but there was an excess of leukaemias in servicemen involved in the nuclear tests.

**Strengths:** Participation independent on outcome, nearly complete follow-up.

**Limitations:** Limited information on confounders, including radiation exposure other than from the nuclear tests.

*Pearce et al. Follow-up of New Zealand participants in British atmospheric nuclear weapons tests in the Pacific. BMJ 1990, 300, 1161-1162

Protopathic bias

- “Reverse causation”
- The exposure, typically for a drug, changes as a result of early disease manifestations:
  - The first symptoms of the outcome of interest are the reasons for prescription of the drug.

**Ex:**
- Use of analgesics (NSAIDs) for back pain caused by undiagnosed cancer, e.g., prostate or pancreas cancer.
- Use of NSAIDs for joint pain occurring prior to exacerbation and diagnosis of Crohn's disease.
- Changes in lifestyle and/or dietary habits because of early disease symptoms (e.g. gastrointestinal discomfort).
Protopathic bias

Risk of stomach cancer among users of proton pump inhibitors (acid suppressive drug)

<table>
<thead>
<tr>
<th></th>
<th>IRR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>First year follow-up</td>
<td>9.0</td>
<td>6.9-11.7</td>
</tr>
<tr>
<td>1-14 year</td>
<td>1.2</td>
<td>0.8-2.0</td>
</tr>
</tbody>
</table>


Hazard function

"Depletion of susceptibles"
Start of study

- Start of treatment (n=300)
  - Follow-up
  - Remained on treatment (n=150)
  - Stopped treatment/developed disease/adverse event/died (n=150)
  - Study population (n=150)
  - Follow-up

Ideal

Survival cohort

Solution

- Restrict the study to persons who start a course of treatment within the study period
- Apply an appropriate “treatment-free washout period”, with a time window depending on the given treatment(s) and indication(s)
- Primarily an option in register-based studies with continuous information on treatment and other relevant variables

Limitations:

- Reduced sample size (study power)
- High representation of individuals in short-term treatment
- Limited long-term follow-up
- Overrepresentation of “poor/non-compliers” and patients with poor effect of earlier/other treatment

Selection bias in case-control studies

- Selection of cases or controls into a study is related to their exposure status

**Ex:**
- “Diagnostic bias”
  - referral
  - self-selection
- Non-participation/non-response
- Selection of control group

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>a = fA</td>
<td>b = gB</td>
</tr>
<tr>
<td>-</td>
<td>c = fC</td>
<td>d = gD</td>
</tr>
<tr>
<td>Total</td>
<td>a+c = f (A+C)</td>
<td>b+d = g (B+D)</td>
</tr>
</tbody>
</table>

f = sampling fraction for cases = (a+c)/(A+C)
g = sampling fraction for controls = (b+d)/(B+D)

The sampling fractions f and g must be identical for exposed and nonexposed individuals.
Selection bias in case-control studies

If the assessment of the diagnosis is influenced by the history of exposure, there is risk of selection bias in a case-control study.

<table>
<thead>
<tr>
<th>Eligible study population</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposure</td>
<td>Case</td>
<td>Control</td>
<td>Total</td>
</tr>
<tr>
<td>+</td>
<td>107</td>
<td>193</td>
<td>300</td>
</tr>
<tr>
<td>-</td>
<td>143</td>
<td>557</td>
<td>700</td>
</tr>
<tr>
<td>Total</td>
<td>250</td>
<td>750</td>
<td>1000</td>
</tr>
<tr>
<td>OR = 2.2</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Examined study population</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposure</td>
<td>Case</td>
<td>Control</td>
<td>Total</td>
</tr>
<tr>
<td>+</td>
<td>96</td>
<td>139</td>
<td>235</td>
</tr>
<tr>
<td>-</td>
<td>103</td>
<td>401</td>
<td>504</td>
</tr>
<tr>
<td>Total</td>
<td>199</td>
<td>540</td>
<td>739</td>
</tr>
<tr>
<td>OR = 2.7</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Non-participation/response</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposure</td>
<td>Case</td>
<td>Control</td>
</tr>
<tr>
<td>+</td>
<td>10% (11)</td>
<td>28% (54)</td>
</tr>
<tr>
<td>-</td>
<td>28% (40)</td>
<td>28% (156)</td>
</tr>
<tr>
<td>20% (51)</td>
<td>28% (210)</td>
<td></td>
</tr>
</tbody>
</table>
Selection of controls  
Case-control design

- The control group should provide an estimate of the exposure distribution in the source population for cases ("study base")
- "The controls should represent the population of nondiseased persons who would have been eligible for inclusion as cases had they developed the disease of interest"

"check list"
- Would controls be cases if they had developed the disease?
- Are controls healthy or diseased?
- Is the exposure associated with the probability of being selected as control?

Ex:
- High testosterone level and risk of prostate cancer. The controls were men with benign prostate hyperplasia
- Hormone replacement therapy (HRT) and risk of endometrial cancer. The controls were women undergoing diagnostic evaluation for endometrial cancer, but subsequently determined not to have cancer
Selection of controls

Case-control design

Why then use patients as controls?

- Study base cannot be identified
- Minimize impact of selection factors applying to cases
- Reduce information bias
- Reduce non-participation/non-response
- Need for blood samples and other “invasive” tests
- Logistic considerations

Information bias

➢ DIFFERENTIAL

Systematic differences between study groups in the collection, interpretation, or reporting of information on the other study axis (exposure or outcome)

➢ NON-DIFFERENTIAL

Misclassification of exposure or outcome independent of the other study axis
Information bias in cohort studies

- **Ascertainment of outcome is different for exposed and non-exposed individuals**

**Ex:**
- “Diagnostic bias”
  - Women presenting with symptoms of thromboembolism are more likely to be hospitalised (and diagnosed) if they use oral contraceptives
  - Smokers may be more likely to seek medical attention for smoking-related diseases
- Loss to follow-up

<table>
<thead>
<tr>
<th>Eligible study population</th>
<th>Exposure</th>
<th>Disease</th>
<th>Healthy</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+</td>
<td>107</td>
<td>193</td>
<td>300</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>143</td>
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<td>700</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td>250</td>
<td>750</td>
<td>1000</td>
</tr>
</tbody>
</table>

**RR = 1.7**

<table>
<thead>
<tr>
<th>Examined study population</th>
<th>Exposure</th>
<th>Disease</th>
<th>Healthy</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+</td>
<td>96</td>
<td>139</td>
<td>235</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>103</td>
<td>401</td>
<td>504</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td>199</td>
<td>540</td>
<td>739</td>
</tr>
</tbody>
</table>

**RR = 2.0**

<table>
<thead>
<tr>
<th>Loss to follow-up</th>
<th>Exposure</th>
<th>Disease</th>
<th>Healthy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+</td>
<td>10% (11)</td>
<td>28% (54)</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>28% (40)</td>
<td>28% (156)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td>20% (51)</td>
<td>28% (210)</td>
</tr>
</tbody>
</table>
Information bias in case-control studies

- Ascertainment of exposure status is different for cases and controls

Ex:

- recall bias
- “interviewer” bias
  - An interviewer who is aware of the disease status and hypothesis of the study may tend to “probe” more intensively for exposure history among cases
  - Data abstractors with knowledge of disease status and study hypothesis may tend to scan records of cases with more scrutiny

In a case-control study, the investigators examined the association between alcohol use and liver cirrhosis.

- Cases and (population) controls were interviewed to obtain detailed information on alcohol use.
- Problems?
Information bias in case-control studies

Recall bias

- Exposure experience reported differently by cases and controls
  - over- or underreporting depending on research question
    - Interest in seeking explanation
    - “Sensitive question”

*Ex:* Mothers of children with congenital malformations may recall drug use and other exposures during pregnancy better than controls.

Diseases with long latency are particularly prone to recall bias (e.g. sun exposure during childhood and melanoma).

Non-differential misclassification

- Theoretical definition
- Empirical definition
- Measurement error
Disagreement between theoretical and empirical definition?

Ex:
- ‘Vitamins’ and ‘cancer’
- ‘Passive smoking’ and ‘heart disease’
- ‘Aspirin’ and ‘heart disease’

Precise criteria for ascertainment of exposure and outcome

Non-differential misclassification

- Misclassification of exposure or outcome is independent on the other study axis (exposure or outcome)
- Most often “conservative” bias (risk estimate towards the null)

Ex:
- Study of the association between alcohol use and cancer risk during a short observation period
- Drugs prescribed for one person are not used or used by another person
- Register-based ascertainment of exposure and outcomes (e.g. administrative registers)
Advantages with record linkage studies

Data specificity and sensitivity

Non-differential misclassification

Important considerations

- Theoretical versus empirical definition
  - ex: diet/cancer
- Induction time
  - relevant exposure time window?
  - ex: drug use/cancer, smoking/AMI, smoking/lung cancer
- Exposure
  - type
  - pattern
  - timing
  - duration
  - ex: dietary fat/AMI
- Disease
  - criteria?
  - stroke (ex: hemorrhagic vs. thrombotic)
Confounding

“Thus it is easy to prove that the wearing of tall hats and the carrying of umbrellas enlarges the chest, prolongs life, and confers comparative immunity from disease; for the statistics show that the classes which use these articles are bigger, healthier, and live longer than the class which never dreams of possessing such things”

George Bernard Shaw:
Preface to *The Doctor’s dilemma* (1906)

Confounding

*Mixture of an effect of exposure on outcome with the effect of a third factor*

... mixing of effects ..

latin: “confundere” = to mix/blend
### Confounding

A **confounder** is a variable that is associated with both the exposure and the outcome, but is not a direct cause of the outcome. Confounders can distort the apparent relationship between exposure and outcome. They do not represent an intermediate link between exposure and outcome. Instead, they are independent predictors of the studied outcome.

1. **Exposure** → **Outcome**
2. **Exposure** → **Confounder**
3. **Confounder** → **Outcome**

**Alcohol**

- Crude OR = 2.1
- True OR ~ 1.0

**Lung cancer**

- Smokers have, independent of their alcohol consumption, an increased risk of lung cancer

- The association between alcohol use and lung cancer risk is due to a higher prevalence of smoking among drinkers
- The association do not reflect a causal relationship but a correlation between alcohol consumption and smoking
Confounding in a cohort study

<table>
<thead>
<tr>
<th>AMI</th>
<th>PY</th>
<th>IR (per 1000)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table A: All study subjects (n=8000)**

| Low physical activity | 105 | 4000 | 26.25 |
| High physical activity | 25  | 4000 | 6.25  |

RR = \(\frac{26.25}{6.25} = 4.2\)

**Sub-table B1: Overweight**

| Low physical activity | 90  | 3000 | 30.0 |
| High physical activity | 10  | 1000 | 10.0 |

RR = 3.0

**Sub-table B2: Normal weight**

| Low physical activity | 15  | 1000 | 15.0 |
| High physical activity | 15  | 3000 | 5.0  |

RR = 3.0

Confounding in a cohort study

Low physical activity → AMI

Positive association

Crude RR = 4.2
True RR = 3.0

Crude RR = 3.3
True RR = 2.0

Obesity
Women who take OCTs have – on average - lower BMI than non-users

Obesity is an independent risk factor for DVT

• Example of “negative confounding”
• Important always to consider the size and direction of potential confounders, especially for confounders for which adjustment are not possible in neither design or analysis

Confounding

A factor representing an intermediate step in the causal chain from exposure to outcome will:

• fulfill the two first criteria for a confounder
• if treated as a confounder result in bias toward the null hypothesis

Ex.

Alcohol use in relation to risk of cardiovascular disease, with adjustment for serum level of HDL cholesterol
Control of confounding

IN DESIGN
- Randomization
- Restriction
- Matching

IN ANALYSIS
- Standardization
- Stratification
- Multivariate analysis

Confounder control in design

Randomization

Study subjects are randomly allocated to “exposure therapy” or to “comparison therapy”. Study outcome(s) of interest are subsequently registered in each study arm.

Ex: Patients are randomly allocated to therapy with a new drug or to placebo

- “Golden standard” in studies of intended effects (e.g. drugs)
- Controls for known as well as unknown or unmeasurable confounders
- Often demands considerable resources
- Logistic/ethical considerations depending on the scientific question
Confounding control in design

**Restriction**

The study includes individuals with specific characteristics, thus avoiding (minimizing) potential confounding by these characteristics.

**Ex:** A study of physical activity and cardiovascular disease included only men aged 50-60 years.

- Risk of residual confounding if restriction is too broad
- Reduce the number of eligible study subjects, potentially yielding low statistical precision
- Reduces generalizability
- May alternatively be applied in the analysis

Confounder control in design

**Matching**

- For each exposed individual, one (or more) non-individual(s) are selected matched on specific characteristics to the exposed individual
- Intuitively an imitation of the randomized trial
Confounder control in analysis

Aims

- To evaluate the effect of the exposure(s) in relation to the outcome(s) adjusted for other predictors of the studied outcome(s)
- To evaluate potential interaction/effect modification

Confounder control in design

Standardization

- **Indirect standardization**
  - Stratum-specific rates from a reference population are applied to the studied (exposed) population
  - Is the number of outcomes in the studied population higher (or lower) than would be expected if the incidence rates in the studied population were the same as in the reference population?

- **Direct standardization**
  - Rates from the studied population are applied to a reference population (non-exposed population or external population)
    - Intuitively simple methods
    - Can only incorporate few variables
Confounder control in analysis

*Stratification*

The material is stratified into categories (strata) of each potential confounder.

Risk estimates are computed for each strata that may be combined to summary estimates.

- Intuitively simple
- Becomes complicated if many strata

<table>
<thead>
<tr>
<th>Physical activity and mortality</th>
<th>Level of activity</th>
<th>Deaths</th>
<th>Person-years</th>
<th>Incidence per 10000</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low to moderate</td>
<td>532</td>
<td>65000</td>
<td>81.8</td>
<td>3.4</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>66</td>
<td>27700</td>
<td>23.8</td>
<td>1.0 (ref)</td>
</tr>
<tr>
<td><em>Table 81</em> 35-45 yrs</td>
<td>Low to moderate</td>
<td>3</td>
<td>5900</td>
<td>5.1</td>
<td>1.1</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>4</td>
<td>8300</td>
<td>4.8</td>
<td></td>
</tr>
<tr>
<td><em>Table 82</em> 45-55 yrs</td>
<td>Low to moderate</td>
<td>62</td>
<td>17600</td>
<td>35.2</td>
<td>1.9</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>20</td>
<td>11000</td>
<td>18.2</td>
<td></td>
</tr>
<tr>
<td><em>Table 83</em> 55-65 yrs</td>
<td>Low to moderate</td>
<td>183</td>
<td>23700</td>
<td>77.2</td>
<td>1.7</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>34</td>
<td>7400</td>
<td>45.9</td>
<td></td>
</tr>
<tr>
<td><em>Table 84</em> 65-75 yrs</td>
<td>Low to moderate</td>
<td>284</td>
<td>17800</td>
<td>159.6</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>8</td>
<td>1000</td>
<td>80.0</td>
<td></td>
</tr>
</tbody>
</table>

*Mantel-Haenszel RR, adjusted for age = 1.8*
Confounder control in analysis

Multivariate analysis

Data are analyzed by statistical modelling, typically in regression analyses [linear, logistic, proportional hazards (Cox), Poisson], which allow simultaneous control for a number of variables

- Can incorporate large number of variables
- “Black box approach” if conducted with insufficient knowledge of the methods and the underlying statistical assumptions
- Should not be presented alone

CONFOUNDING

“Can only be controlled for if you have thought of it!”
Effect modification

Exposure → Outcome

Effect modifier

- The effect of one factor on outcome is modified by levels of another factor
- Important to present and discuss
- A factor may be both a confounder and an effect modifier
Effect modification

Case-control study of physical activity and risk of acute myocardial infarction, stratified according to gender

<table>
<thead>
<tr>
<th>Gender</th>
<th>Physical activity index (kcals)</th>
<th>Cases</th>
<th>Controls</th>
<th>OR, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>2500+</td>
<td>141</td>
<td>208</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;2500</td>
<td>144</td>
<td>112</td>
<td><strong>0.53</strong> (0.38-0.73)</td>
</tr>
<tr>
<td>Women</td>
<td>2500+</td>
<td>49</td>
<td>58</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;2500</td>
<td>32</td>
<td>45</td>
<td><strong>1.19</strong> (0.65-2.16)</td>
</tr>
<tr>
<td>Total</td>
<td>2500+</td>
<td>190</td>
<td>266</td>
<td><strong>0.64</strong> (crude)</td>
</tr>
<tr>
<td></td>
<td>&lt;2500</td>
<td>176</td>
<td>157</td>
<td><strong>0.62</strong> (adj. for gender)</td>
</tr>
</tbody>
</table>

Confounding by indication

The indication(s) for treatment or the reason(s) for choosing one treatment in preference to another are associated with the risk of the studied outcome(s)

- Confounding by disease (being treated)
- Confounding by severity/prognosis
- (Shared risk factors)
- (Proopathic bias/reverse causation)
Confounding by indication

*A few examples*

- Red car & accidents, RR~1.2
- Blood transfusion & 24 h mortality, RR~6
- Blood transfusion & Hepatitis, RR~6
- Aspirin & Mortality
- Calcium channel blockers & Myocardial infarction
- HRT & Myocardial infarction

**INTERPRETATION?**

Are the disease being treated associated with the outcome?

- Yes or unknown
- Can potentially compare to undiseased or diseased

Is disease severity associated with the outcome?

- Can disease severity be measured?
Confounding by indication

- Confounding by indication is the Achilles heel of pharmacoepidemiology
- Observational studies only provides measures of associations
- “Risk ratio” should be interpreted as “association ratio”
- Evaluate any relation between indication and outcome of interest, determinants of treatment of choice (“the art of medicine”), shared risk factors, and potential protopathic bias

### Confounding by severity

**Hypothetical cohort study**

<table>
<thead>
<tr>
<th></th>
<th>Death</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>A</strong></td>
<td>202</td>
<td>898</td>
</tr>
<tr>
<td><strong>B</strong></td>
<td>8</td>
<td>102</td>
</tr>
<tr>
<td><strong>RR = 18%/7% = 2.5</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Severe disease**

<table>
<thead>
<tr>
<th></th>
<th>Death</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>A</strong></td>
<td>200</td>
<td>800</td>
</tr>
<tr>
<td><strong>B</strong></td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td><strong>RR = 20%/40% =0.5</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Mild to moderate disease**

<table>
<thead>
<tr>
<th></th>
<th>Death</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>A</strong></td>
<td>2</td>
<td>98</td>
</tr>
<tr>
<td><strong>B</strong></td>
<td>4</td>
<td>96</td>
</tr>
<tr>
<td><strong>RR = 2%/4% = 0.5</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Miettinens exercise

Anticoagulants and DVT

Exposure: Use of anticoagulants
Outcome: Deep venous thrombosis (DVT)
True rate ratio (RR): <1
Analysis adjusted for age and gender: RR = 27
Analysis adjusted for age, gender and other known risk factors for DVT: RR = 4

Miettinens exercise

Conclusions

Confounding by indication can be very strong
Often impossible to fully adjust for confounding by indication in studies with non-randomized design

Immortal person-time

- Immortal time in epidemiology refers to a period of cohort follow-up time during which death cannot occur.

Rothman-KJ. Modern Epidemiology, 2nd Edition

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Immortal time bias

- Immortal time bias can arise when the period between cohort entry and time of exposure definition, e.g., for a drug, is either misclassified or simply excluded and not accounted for in the analysis.

Suissa-S. Immortal time bias in observational studies of drug effects. Pharmacoepidemiology and Drug Safety 2007; 16: 241-9
The overall RR for an ED visit among those who received intranasal corticosteroids, adjusted for..., was 0.7 (95% CI, 0.59–0.94)

..., current use of statins was associated with a significant reduced fracture risk (adjusted OR, 0.55; 95% CI, 0.44–0.69) compared with nonuse of lipid-lowering drugs
Illustration of bias

- Base cohort
  - Saskatchewan Health Insurance Database 1980-1997
  - Persons >55 år treated for chronic obstructive pulmonary disease (COPD)

- Study cohort
  - COPD patients hospitalized for cardiovascular disease (CVD)

- Exposures
  - Beta2-agonists (IBA)
  - Gastrointestinal drugs (GID) [unrelated to risk of CVD]

- Outcome
  - Death from any course during 1-year follow-up following discharge from their CVD hospitalization

Suissa-S. Pharmacoepidemiology and Drug Safety 2007; 16: 241-9
Illustration of bias (3)

Misclassification of "immortal time"

- Cohort entry defined as the date of discharge from the CVD hospitalization

<table>
<thead>
<tr>
<th>Misclassified approach</th>
<th>Number of Subjects</th>
<th>Number of deaths</th>
<th>Person-years</th>
<th>Rate (per 100 per year)</th>
<th>Rate ratio (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No IBA during 180-day period</td>
<td>771</td>
<td>148</td>
<td>674.6</td>
<td>21.9</td>
<td>Reference</td>
</tr>
<tr>
<td>IBA during 180-day period</td>
<td>771</td>
<td>114</td>
<td>713.0</td>
<td>16.0</td>
<td>0.73 (0.57-0.93)</td>
</tr>
</tbody>
</table>

Correctly classified approach

<table>
<thead>
<tr>
<th></th>
<th>Number of Subjects</th>
<th>Number of deaths</th>
<th>Person-years</th>
<th>Rate (per 100 per year)</th>
<th>Rate ratio (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unexposed to IBA</td>
<td>1642</td>
<td>148</td>
<td>777.0</td>
<td>19.2</td>
<td>Reference</td>
</tr>
<tr>
<td>No IBA during 180-day period</td>
<td>771</td>
<td>148</td>
<td>674.6</td>
<td>19.2</td>
<td>Reference</td>
</tr>
<tr>
<td>Exposed after IBA prescription</td>
<td>771</td>
<td>114</td>
<td>610.6</td>
<td>18.7</td>
<td>0.98 (0.77-1.25)</td>
</tr>
</tbody>
</table>

Suissa-S. Pharmacoepidemiology and Drug Safety 2007; 16: 241-9

Illustration of bias (4)

Exclusion of "immortal time"

- Exposed cohort entry taken as the date of the first dispensed prescription for the study drug within one year from the hospitalization for CVD

<table>
<thead>
<tr>
<th>Excluded immortal time approach</th>
<th>Number of subjects</th>
<th>Number of deaths</th>
<th>Person-years</th>
<th>Rate (per 100 per year)</th>
<th>Rate ratio (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No GID during follow-up</td>
<td>640</td>
<td>125</td>
<td>561.0</td>
<td>22.3</td>
<td>Reference</td>
</tr>
<tr>
<td>GID during follow-up</td>
<td>640</td>
<td>99</td>
<td>581.3</td>
<td>17.0</td>
<td>0.78 (0.61-0.99)</td>
</tr>
</tbody>
</table>

Correctly classified approach

<table>
<thead>
<tr>
<th></th>
<th>Number of subjects</th>
<th>Number of deaths</th>
<th>Person-years</th>
<th>Rate (per 100 per year)</th>
<th>Rate ratio (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unexposed to GID</td>
<td>1280</td>
<td>125</td>
<td>692.5</td>
<td>18.1</td>
<td>Reference</td>
</tr>
<tr>
<td>No GID during follow-up</td>
<td>640</td>
<td>125</td>
<td>561.0</td>
<td>18.1</td>
<td>Reference</td>
</tr>
<tr>
<td>Exposed after GID prescription</td>
<td>640</td>
<td>99</td>
<td>581.3</td>
<td>17.0</td>
<td>0.94 (0.73-1.20)</td>
</tr>
</tbody>
</table>

Suissa-S. Pharmacoepidemiology and Drug Safety 2007; 16: 241-9
Evaluation of bias

- Definition of exposure(s) and outcome(s)
- Study design and sample size
- Time sequence
- Selection of study population
  - representative of population in study base?
  - comparison group?
- Ascertainment of exposure and outcome
  - instrument
  - methods of assessment similar for each study group?
  - knowledge of hypothesis and the other study axis (exposure/outcome)?
  - study subject/observer
- Recording and computation of results
  - same methods for each study group?
  - allocation of person-time appropriate?
  - varying results with severity of disease?
  - Theoretical vs. empirical definition?
  - Precision?
  - Selection bias?
  - Information bias?

Bias “approach” in cohort studies

**Design**

- Selection of study population independent of outcome of interest and follow-up (historical cohort study)
- Consider the possibility of confounding by indication and take precautions against this in the selection of control groups
Bias “approach” in cohort studies (2)

Data collection

- Structured and standardized methods for disease (and exposure) ascertainment
- Precise outcome criteria
- “Blinding” of observer with regard to hypothesis and/or exposure status
- Use registers (if feasible)
- Evaluate level of details in diagnosis of outcome according to exposure status

Bias “approach” in cohort studies (3)

Analysis

- Stratify results according to severity of outcome
- Calculate risk estimates for outcomes known to be unrelated to the exposure(s) of interest
- Calculate risk estimates for different exposure time windows
- Sensitivity analyses
  - Loss to follow-up, misclassification
Bias “approach” in case-control studies

**Design**
- Identify patients at primary level (if feasible)
- Objective and strict diagnostic criteria
- If feasible, select only patients whose disease would have come to medical attention regardless of exposure status
- Incident cases
- Physician assessing the case diagnosis should be unaware of exposure status
- Use registers (if feasible)
- Representative control group (from study base)

Bias “approach” in case-control studies (2)

**Data collection**
- Structured and standardized instrument for exposure assessment
- Validation of instrument
- Detailed exposure information
- If feasible, obtain exposure information from records completed before the occurrence of outcome
- “Blinding”
  - cases with regard to hypothesis
  - observer with regard to hypothesis/disease status
  - if feasible, obtain exposure information from individuals under diagnostic evaluation for the disease of interest
- Establish appropriate time sequence; relevant exposure prior to first signs of disease
Bias “approach” in case-control studies (3)

**Analysis**

- Calculate risk estimates for various degrees of disease
- Calculate risk estimates for exposure variables known to be unrelated to the outcome of interest
- Calculate risk estimates for different exposure time windows (if data are available)
- Sensitivity analyses
  - non-response, misclassification

Bias in epidemiologic studies

*Important aspects*

- Be careful with the first study
  - *Difficult to disprove hypotheses*

- Main principles
  - Comparability
  - Validity
  - Completeness