Epidemiology in a palatable way – the problem of bias

Hong Kong Society of Nephrology

Annual Scientific Meeting 2018

Kitty J. Jager MD PhD
Errors in clinical research

- Random error

- Systematic error

When performing a study a researcher must attempt to reduce both sources of error.

In interpreting a study a reader must be aware of both sources of error and find out if and how the researchers have tried to address them.
Random error

- Due to variability in the data
- The average of measurements in a group may vary due to chance
- Affects reproducibility (as random errors are unpredictable)
- Decreases when sample size increases

Solutions
- Increase sample size
- Measure outcomes more accurately

Hong Kong, 29th September 2018
• Systematically wrong

• No decrease with larger sample size

• Systematic error = BIAS
Random versus systematic error

Effect of sample size

Error

Sample size

Systematic error or bias

Random error
Three main types of bias

Selection bias
- physician-level
- researcher-level
- patient-level

Information bias

Confounding
Selection bias

- Errors in
  - Selection of study subjects
  - Their study participation

- Systematic differences in characteristics between those selected and participating and those who are not
  
  *Study sample is not representative of the source population*

- Selection bias may occur at
  - Physician level
  - Researcher level
  - Patient level
When reading a study always ask yourself:

“Has the current clinical practice of the physicians participating in the study influenced the selection of patients?”
Example: Is diabetes a risk factor for the incidence of advanced CKD?

General population sample
n=17,757

Advanced CKD
n=842

Non-advanced CKD
n=16,915
## Diabetes as risk factor for advanced CKD?

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Diabetic subjects</th>
<th>Non-diabetic subjects</th>
<th>Incidence Rate Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Person years</td>
<td>52,759</td>
<td>1,250</td>
<td>51,509</td>
<td></td>
</tr>
<tr>
<td>Advanced CKD</td>
<td>842</td>
<td>75</td>
<td>767</td>
<td></td>
</tr>
<tr>
<td>Incidence rate (per 1000 py)</td>
<td>(842/52,759) *1000= 16</td>
<td>(75/1,250) *1000= 60</td>
<td>(767/51,509) *1000= 15</td>
<td>60/15= 4.00</td>
</tr>
</tbody>
</table>

Selection bias – physician level

- (75/1250) *1000 = 60
- (767/51509) *1000 = 15

60/15 = 4.00
Is this correct?
   In principle yes ..... 
   But ... possibly the effect of diabetes is overestimated
   • Diabetes is a known risk factor for advanced CKD
   • Diabetic patients’ renal function is usually better monitored
   • Earlier detection of advanced CKD

What would have been better?
   • Determine disease (advanced CKD) and exposure (DM)
     • Objectively and
     • In an equally frequent manner
   • Think about current medical practice potentially affecting the results
Selection bias – researcher level

Researcher level bias, when reading a study always ask yourself:

“Are the outcomes of the exposed group compared to those of the right control group?”
Do living kidney donors have an increased risk of ESRD?

3,698 living kidney donors

1,000,000 controls from the general population matched on age/sex/ethnicity

### Risk of ESRD after kidney donation

<table>
<thead>
<tr>
<th></th>
<th>Kidney Donors</th>
<th>General population</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persons</td>
<td>3,698</td>
<td>1,000,000</td>
<td></td>
</tr>
<tr>
<td>ESRD</td>
<td>11</td>
<td>268</td>
<td></td>
</tr>
<tr>
<td>Incidence rate per year (pmp)</td>
<td>180</td>
<td>268</td>
<td>0.67</td>
</tr>
</tbody>
</table>

Donating a kidney is protective against developing ESRD!

Selection bias – researcher level

• Numbers are correct, but is living donation truly protective?

• Kidney donors are screened on being healthy
  • Less hypertension
  • Less diabetes
  • Better health prospects

Solution: find a better control group
  • With similar baseline characteristics (and therefore similar baseline risk)
  • Siblings who were suitable for donation, but did not donate?
Selection bias – patient level

Should we screen the general population for chronic kidney disease?

Invite all adults in the general population to order a free dipstick test via internet.
Selection bias – patient level

Who will respond?

*Hopefully a representative sample of the general population*

But in reality....

- Those with family history of kidney disease
  - These people are more likely to have an increased risk of kidney disease
    → Result in overestimation of the risk of CKD in the general population

- Those interested in their health
  - Have a low risk (healthy lifestyle)
    → Result in underestimation of the risk of CKD in the general population

- Net effect on your results? Unknown ......
Three main types of bias

- **Selection bias**
  - Patient-level
  - Researcher-level
  - Physician-level

- **Information bias**

- **Confounding**
Information bias

- Often this takes the form of recall bias
- Recall bias = bias in the information received from study participants
- Problem occurs in case control studies
- Is due to participants providing information on the exposure after the disease has (or has not) occurred
Recall bias

Cases
- Will have searched their memory thoroughly
- May provide a precise report of potential risk factors experienced in the past

Controls
- Will not have searched their memories (or made any enquiries with other people)
- May provide more ‘socially accepted’ answers while reporting potential risk factors
Risk factors associated with acute pyelonephritis in healthy women

**Setting:** Case-control study

**Cases:** women with pyelonephritis who were identified from computerized databases.

**Controls:** randomly selected women of similar age without pyelonephritis diagnosis in the previous 5 years.

**Measurements:** computer-assisted telephone interview
Example: Recall bias

Questions
UTI history in the participant's mother?

Cases are more likely to have talked about this with their mothers than the controls did. Effect of UTI in mothers may therefore be overestimated.

Solution:
- Use standardized questionnaires
- Use new incident cases and ask about recent past
- Use information from patient records instead of relying on people’s memory
Other common types of bias

Bias
- Confounding by indication
- Incidence-prevalence
- Observer
- Spectrum
- Channeling
- Confounding
- Healthy worker
- Immortal time
- Misclassification of exposure or outcome
- Recall
- Information
- Citation
- Selection
- Referral
- Lead time
- Chronology
- Non-response
- Loss to follow-up
- Healthy volunteer
- Self-selection
- Reporting
- Collider
- Confounder
- Publication
- Confirmation
- Interviewer
Rudy Giuliani (former mayor of New York):

“I had prostate cancer, 5-6 years ago.
My chance of surviving prostate cancer – and thank God, I was cured of it – in the United States was 82%.
My chance of surviving prostate cancer in the United Kingdom? Only 44% under socialized medicine.”

- Prostate cancer survival in the United States is better than in the United Kingdom!

Is this true?
Lead time bias

- US: screening program → earlier diagnosis

- Early diagnosis leads to a longer survival from the point of diagnosis
- In reality there is likely no difference in survival between US and UK

Hong Kong, 29th September 2018
Publication bias

Due to the fact that studies showing no effect, negative or undesirable results are often not published.

Can be investigated using funnel plots

Plotting the effect size against a measure of uncertainty, eg the SE: gives a clue as to the size of the study

Effect of intravenous magnesium on mortality after myocardial infarction – Sterne et al. BMJ 2011
Publication bias

Systematic review of effect of magnesium on mortality after myocardial infarction

In small studies only strong and beneficial effects!
There are virtually no smaller studies with a harmful effect.

This suggest that only those with a large effect size or a small standard error were published!!

Caused by:
• Editors / reviewers

Effect of intravenous magnesium on mortality after myocardial infarction – Sterne et al. BMJ 2011
Take home messages

• Bias = systematic error

Main types:
  • Selection bias
  • Information bias
  • Confounding
    But many subtypes and many different names/synonyms used

• May occur at all stages of your research and be introduced by for example medical practice, study design and study volunteers

Hong Kong, 29th September 2018