Amsterdam UMC

Bias and confounding

how they affect study results and what you can do about them

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Errors in clinical research

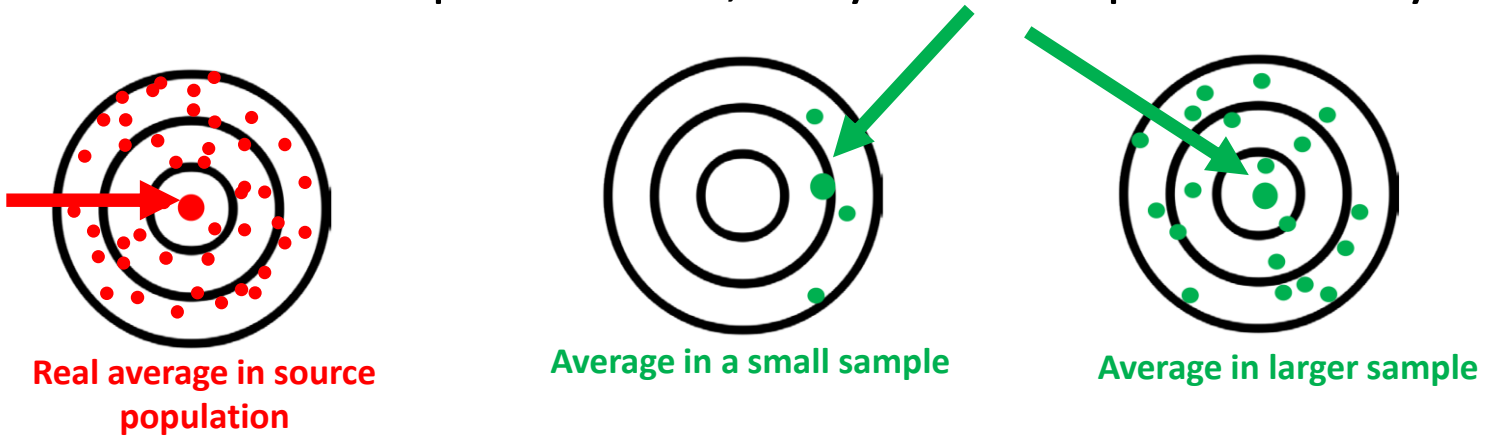
- Random error
- Systematic error

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

In **interpreting** study results 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

- Variability in the data
- Differences due to imprecision of measurements or because subjects in a group may have really different values
- As random errors are unpredictable, they affect reproducibility

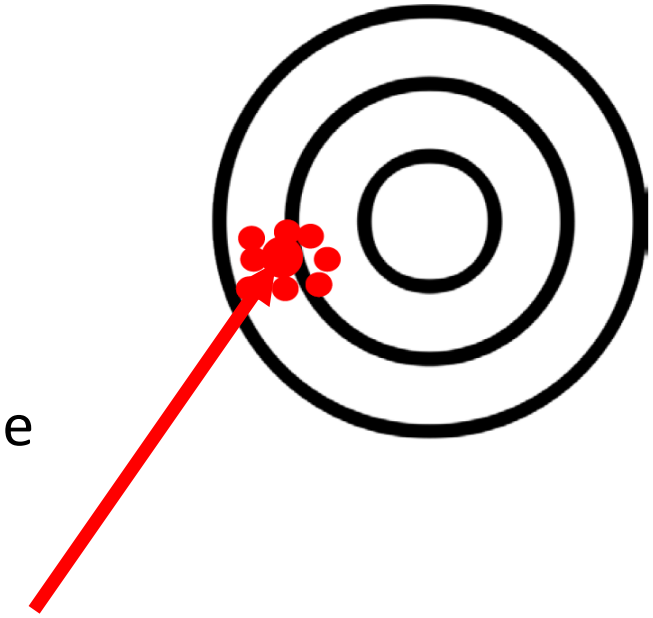


Solutions to reduce random error and find the correct average for the source population

- Increase sample size
- Measure exposures and outcomes more accurately

Systematic error

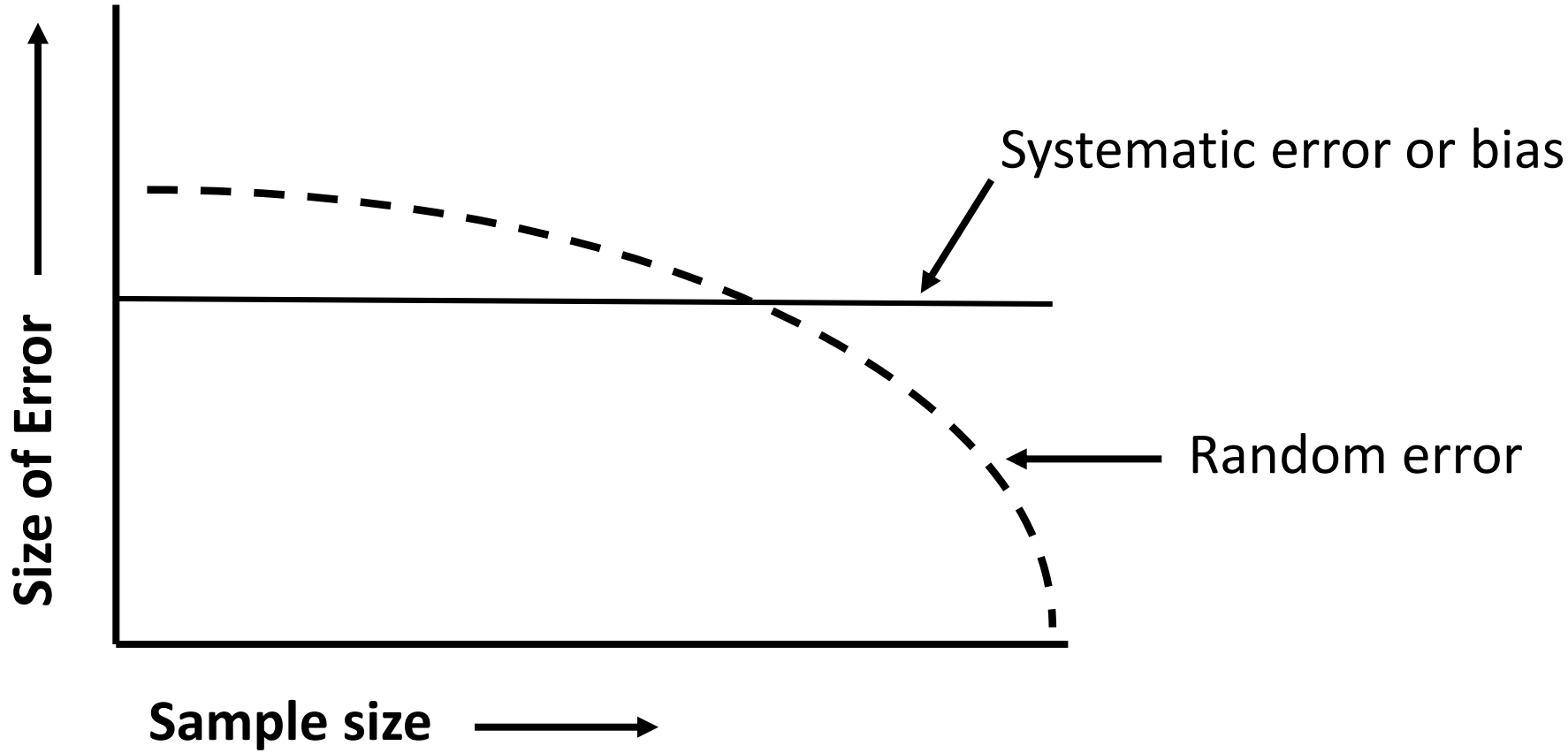
- Systematic error = **BIAS**
- Measurement is <u>systematically</u> wrong
- No decrease of bias with larger sample size



Average with systematic error

Random versus systematic error

the effect of sample size



Three main types of bias

A study may be biased depending on

- How the study subjects were **selected** — **Selection bias**
- How the study variables were **measured** — **Information bias**
- How the **association** between an exposure and an outcome was determined — **Confounding**

Exposure → **Outcome**

1. Selection Bias

Bias in how the study subjects were selected

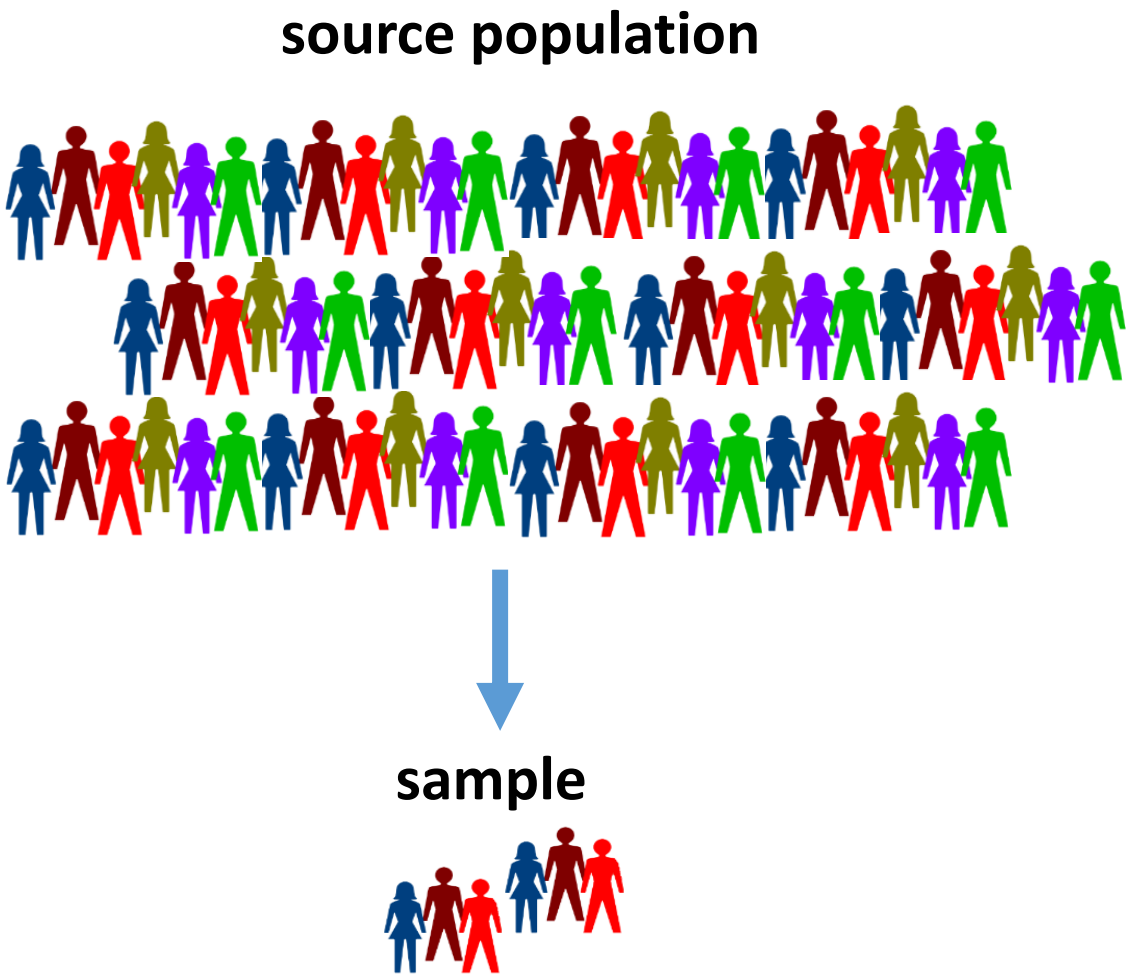
Selection bias

Stems from errors in the **selection procedure** of study participants, and from factors affecting **study participation**

Relationship between exposure and outcome may differ in those who participate in a study and those who don't

- Sampling bias
- Confounding by indication
- Incidence-prevalence bias
- Attrition bias
- Publication bias

Sampling bias



- A sample needs to be **representative**
- Where possible sample should be based on available information on potential respondents

Example

In estimates of CKD prevalence, census data or electoral rolls are suitable sampling frames to obtain random samples reflecting the age and sex distribution in the general population

- Often sampling methods are not reported ☹
- Even if a sample has been taken at random, there is still the possibility of response bias due to **non-response** of those included in the sample

Sampling bias

Typically found in

- All study designs (cross-sectional studies and cohort studies) using non-representative samples
- Especially studies with low response rates (e.g. surveys)

Consequences

- Over- or underestimation of frequencies or of effects/associations

Prevention

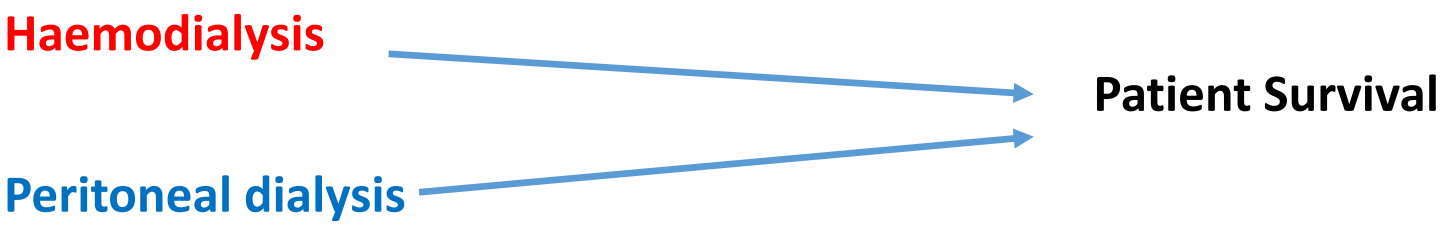
- Use of state-of-the-art techniques to obtain random samples
- Try to reduce non-response as much as possible

Confounding by indication

Selection bias in observational studies that is **induced by physicians** and due to unmeasured confounders

- Caused by the presence of an **indication** for at least one of the treatments

Example



- Best way to prevent away the effect of confounding by this indication is **randomization**
- Randomization increases the chance that both known and unknown confounders will be balanced across treatment groups - any remaining **differences are due to chance**
- **Better than adjustment** in statistical analysis. Adjustment can only correct for known confounders and not for unknown confounders

Confounding by indication

Typically found in

Non-randomized intervention studies

- cohort studies, case-control studies, cross-sectional studies

Consequences

- The comparison of outcomes between the two interventions / treatments will be unfair due to selection by prognosis and cannot be used for medical decision-making

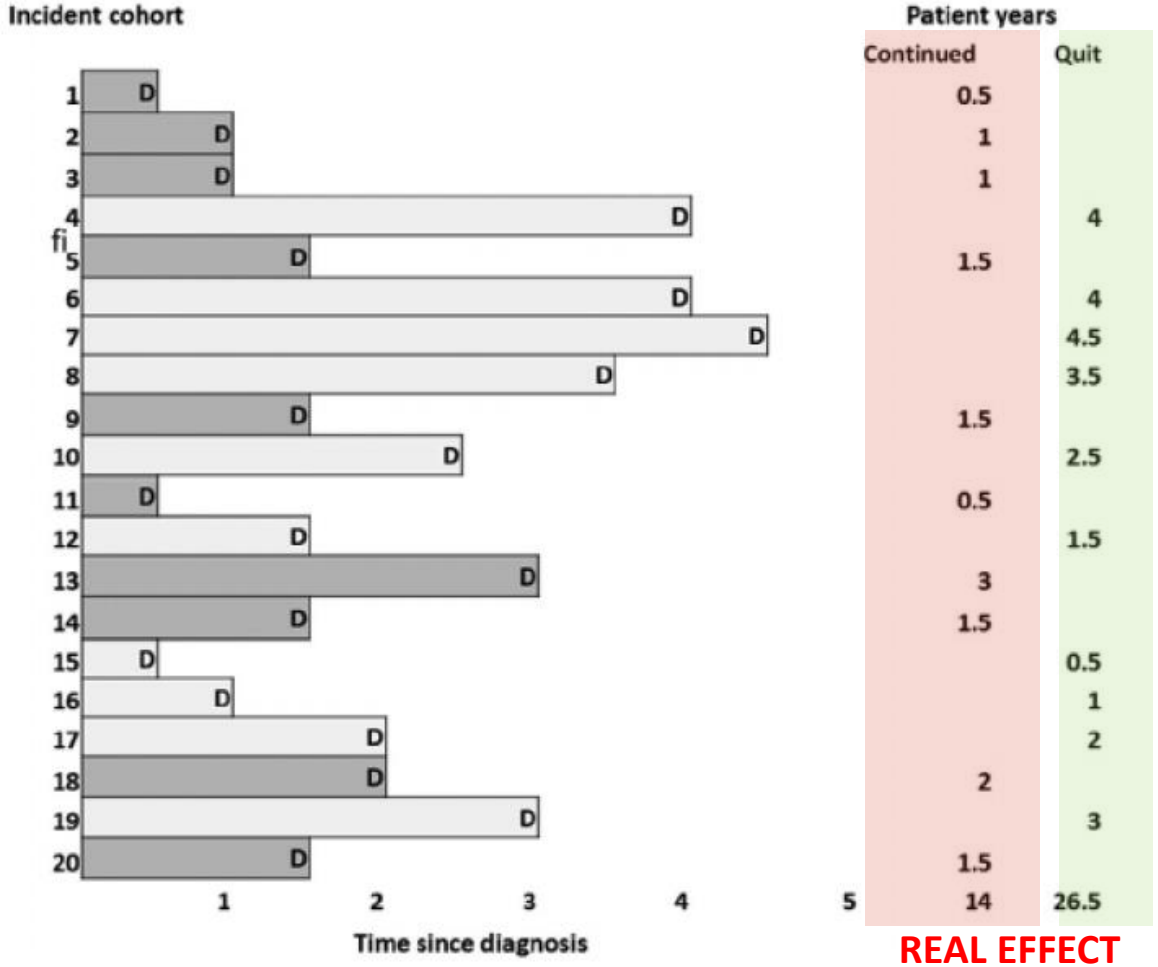
Prevention

- Randomization

Incidence-Prevalence bias

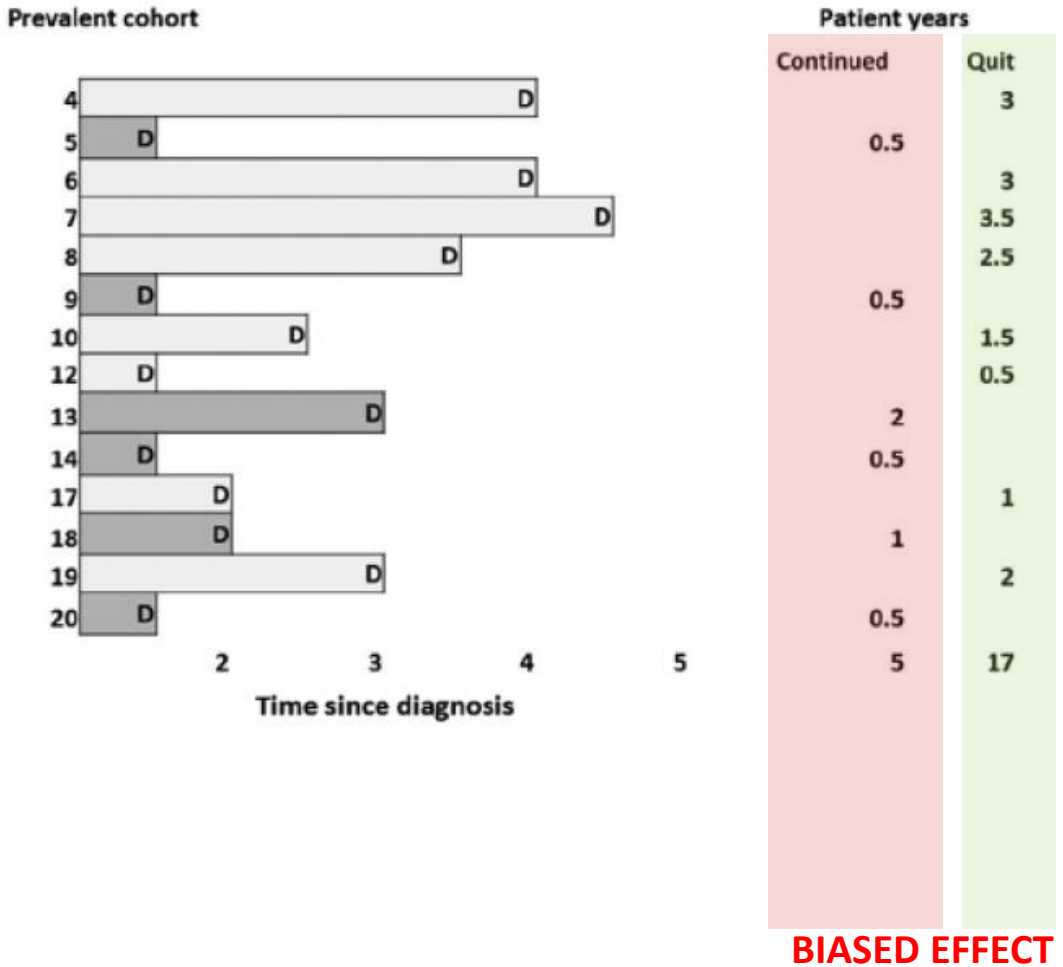
(synonym: Survivor bias)

Example: Patients diagnosed with severe emphysema who continued (pink) or quitted (green) smoking



REAL EFFECT

10 deaths in 14 patyrs vs 10 deaths in 26.5 patyrs -- mortality rate ratio = 1.89



BIASED EFFECT

6 deaths in 5 patyrs vs 8 deaths in 17 patyrs -- mortality rate ratio = 2.55

Incidence-Prevalence bias

(synonym: Survivor bias)

Typically found in

Study designs using prevalent patients

- cross-sectional studies, cohort studies not using incident patients, case-control studies

Consequences

- Over- or underestimation of effect estimates – the direction of the bias can go both ways

Attrition bias

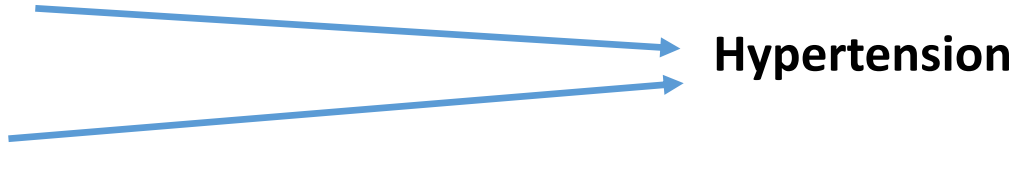
Attrition means the **loss of participants** during a study due to withdrawals, dropouts, or protocol deviations

- Problem: people leaving a study may be **systematically different** from those who continue

Example

Prescription of Healthy diet

Standard care



- In the group with the healthy diet, those who have problems with compliance may drop out, **leaving behind the more health-conscious patients in the study**

- May lead to a **potential overestimation of the effect of healthy diet** on hypertension

Attrition bias

Typically found in

Longitudinal studies

- RCTs, prospective cohort studies

Consequences

- Over- or underestimation of effects

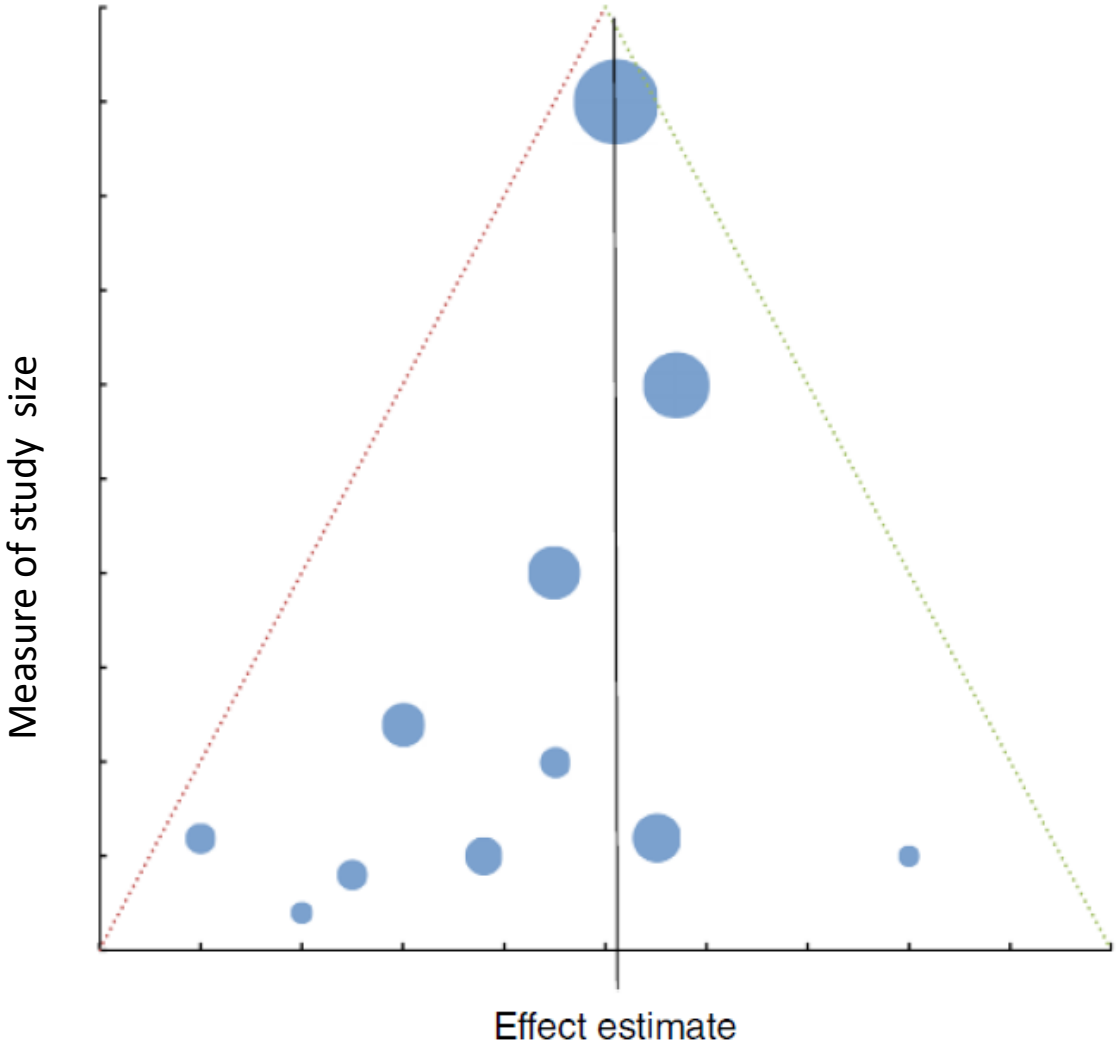
Publication bias

- Not the consequence of flaws in the study design or study conduct! Instead it stems from **behavior of authors and editors**
- *'Any tendency on the parts of investigators or editors to fail to publish results based on the direction or strength of the study findings'*
- Published papers may not be a representative sample of all studies performed; **overrepresentation of 'positive' studies**
- Originates during the entire study process

  From generating study results → choosing which of them to include in a manuscript

  → whether or not to submit the manuscript → whether or not to accept for publication
- Not all relevant studies using sound research methodology are accepted for publication
- Consequently, meta-analyses may overestimate treatment effects and risk factor associations → inappropriate clinical decision making / health policy decision making

Publication bias



- Unlike other types of bias, it can sometimes be detected by a funnel plot
- Effect plotted against measure of study size
- Vertical line to detect symmetry or asymmetry
- Larger dots represent larger studies
- Without publication bias these plots are shaped like a funnel
- Asymmetric - right lower side seems emptier – small studies are missing – pointing to publication bias
- Publication bias may affect <u>all study designs</u>

2. Information Bias

Bias in how the study variables were measured

Information bias

- Caused by errors in the measurement, collection, or interpretation of
  - exposure variable
  - disease/outcome variable
  - both
- In studies using categories for exposure and outcome, individuals may be placed in the incorrect category (= misclassification)
- This misclassification can be non-differential or differential
- Exposure misclassification is non-differential, if it is unrelated to the presence or occurrence of disease

Information bias

Intake of high-caloric beverages → **Cerebrovascular accident (CVA)**

Correct classification	CVA cases	Controls	Odds ratio	
High intake	250	100	5.0	→ True effect
Low intake	450	900	Reference	
Non-differential misclassification (in cases and controls: 20% was considered to have high intake instead of low intake and 20% was considered to have low intake instead of high intake)[a]	**CVA cases**	**Controls**	**Odds ratio**	
High intake	290	260	2.0	→ Biased effect
Low intake	410	740	Reference	

- Non-differential misclassification will always dilute a true effect

Information bias

- Recall bias
- Interviewer bias
- Observer bias
- Lead-time bias

Recall bias

Recall bias is caused by **differences in accuracy or completeness of recall to memory** of past events or experiences only after people know about outcomes. This self-reporting may lead to misclassification of exposure.

CASE STUDY – BIRTH DEFECTS

It turns out my baby has a birth defect ……..

I am thinking and thinking all over again what may have caused this defect …..

Other mothers with healthy babies will not do this … their memory will be less complete

This may lead to misclassification of exposure and ‘bias’ the relationship between a particular exposure and a birth defect …..

→ **Maternal recall bias**

Recall bias

Nephrology examples

- Glomerulonephritis patients may be asked about possible toxic exposures and may remember better than those without glomerulonephritis

- Women with acute pyelonephritis may be asked about frequent urinary tract infections in their mother, because the researcher considers genetic factors. Those with pyelonephritis may have discussed such infections with their mother and therefore know better if their mother suffered from such frequent infections

Recall bias

Typically found in

Study designs that use self-reporting

- case-control studies and retrospective cohort studies

Prevention

- Check individuals' recall using hospital records
- Use of controls suffering from another disease who may have searched their memory in a similarly thorough way

Interviewer bias

Systematic error due to **interviewer's (sub)conscious gathering of selective data, or their influence on subject response**

- Interviewers' expectations/opinions - asking leading questions
- Respondents may answer what they think the interviewer might like to hear - social desirability bias
- Physicians / investigators may increase recall bias by more intensive questioning of cases with the disease on factors known to be associated with disease (exposure suspicion bias)

Interviewer bias

Typically found in

All studies that make use of interviews

Reduced by

- Standardization of the interview
- Blinding the interviewer to the outcome/disease status of the respondent

Observer bias

Systematic difference between a true value and the observed value, due to observer variation

- Subjective judgements have greater chance of variability between observers
  - blood pressure readings using analogue sphygmomanometers were notorious for observer variability
  - doctors tended to round down blood pressure readings in patients they knew were on antihypertensive medication and to round them up in patients who were not
- If such differences in judgement are systematic, they may induce bias
- May play a role in the reporting, evaluation and processing of data as well as in the statistical analysis

Observer bias

Typically found in

RCTs and observational studies

Consequences

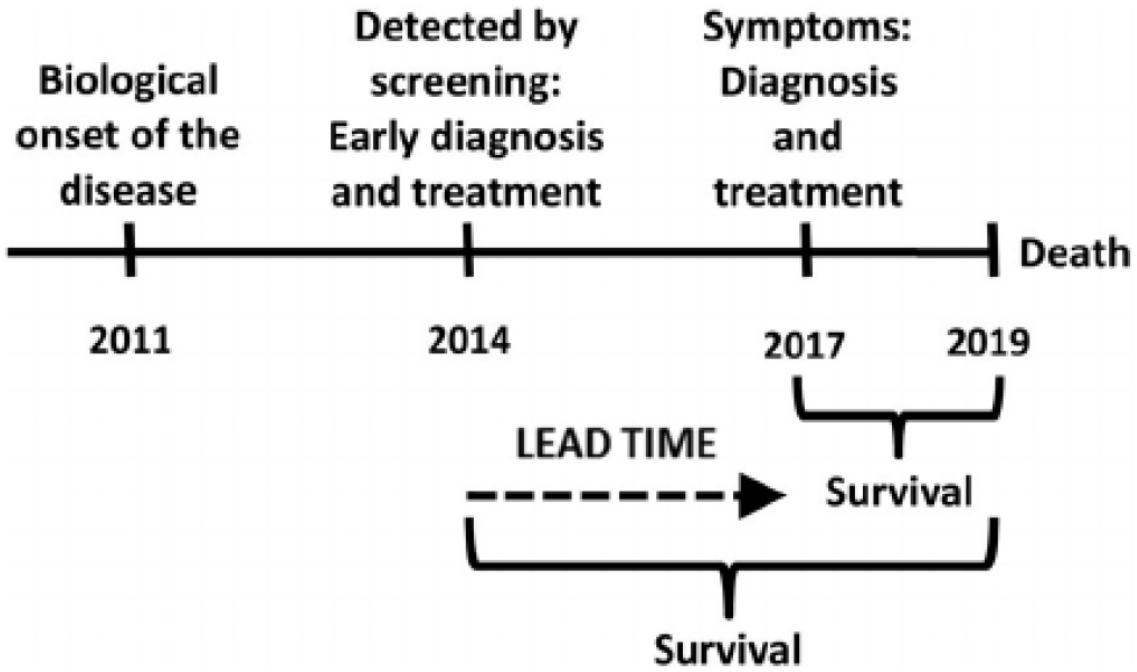
- Over- or underestimation of treatment effects

Prevention

- Clinicians, patients and statisticians should preferably be blinded to the treatment

Lead-time bias

- An apparent increase in survival resulting from **disease detection at an earlier stage**
- In reality there may not be an actual effect on survival, **just a longer period with the diagnosis**



Example – survival comparisons between regions with and without screening programmes

Lead-time bias

Nephrology example

- Cohort studies comparing policies of early and late start of dialysis
- When patients start dialysis at a higher eGFR without severe uraemic signs and symptoms, and their survival is compared to those starting dialysis at a lower eGFR with severe uraemic signs and symptoms, then this comparison may suffer from lead-time bias favouring those with an early start

Typically found in

- Cohort studies comparing survival times between screened subjects and those diagnosed based on symptoms
- Studies comparing survival between patients in different stages of disease

3. Confounding Bias

Bias in how the association between an exposure and an outcome was determined

Confounding bias

Exposure → **Outcome**

- Confounding is relevant in studies in which one would like to show an **effect** of an exposure on an outcome
- Is about how the **association** between an exposure and an outcome was determined
- Confounding causes a ‘mixing’ or ‘blurring’ of effects

When we <u>think</u> we are measuring the effect of an exposure on an outcome

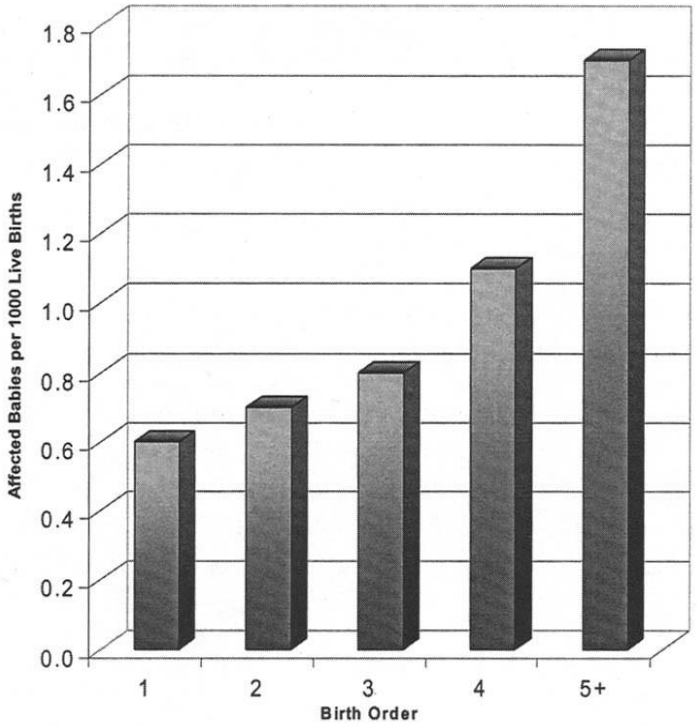
BUT

… we <u>actually</u> measure the effect of another (confounding!) factor

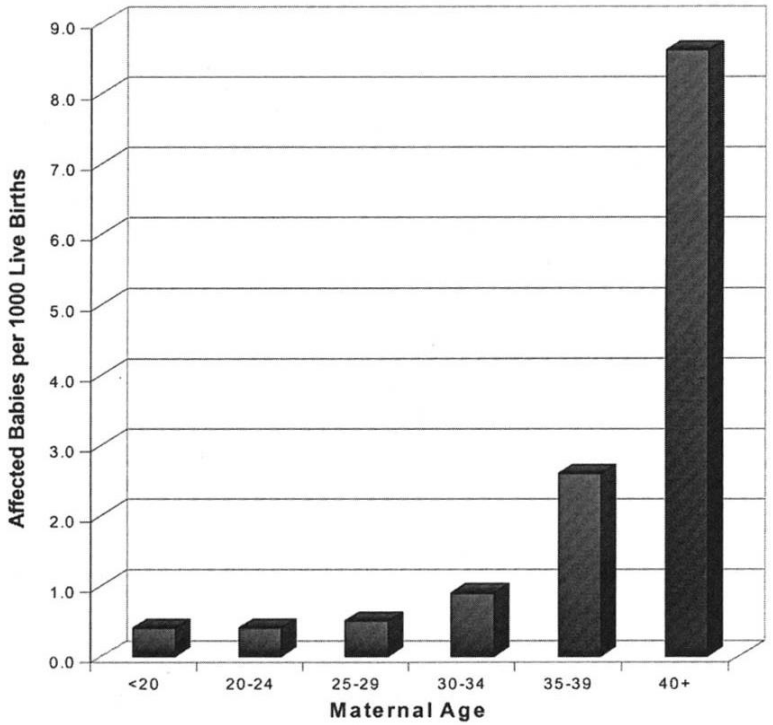
- Confounding obscures the ‘real’ effect of an exposure

Confounding = Blurring of effects

Birth order → **Prevalence of Down syndrome**



Prevalence of Down syndrome at birth by birth order (data of Stark and Mantel[2]).



Prevalence of Down syndrome at birth by mother's age.

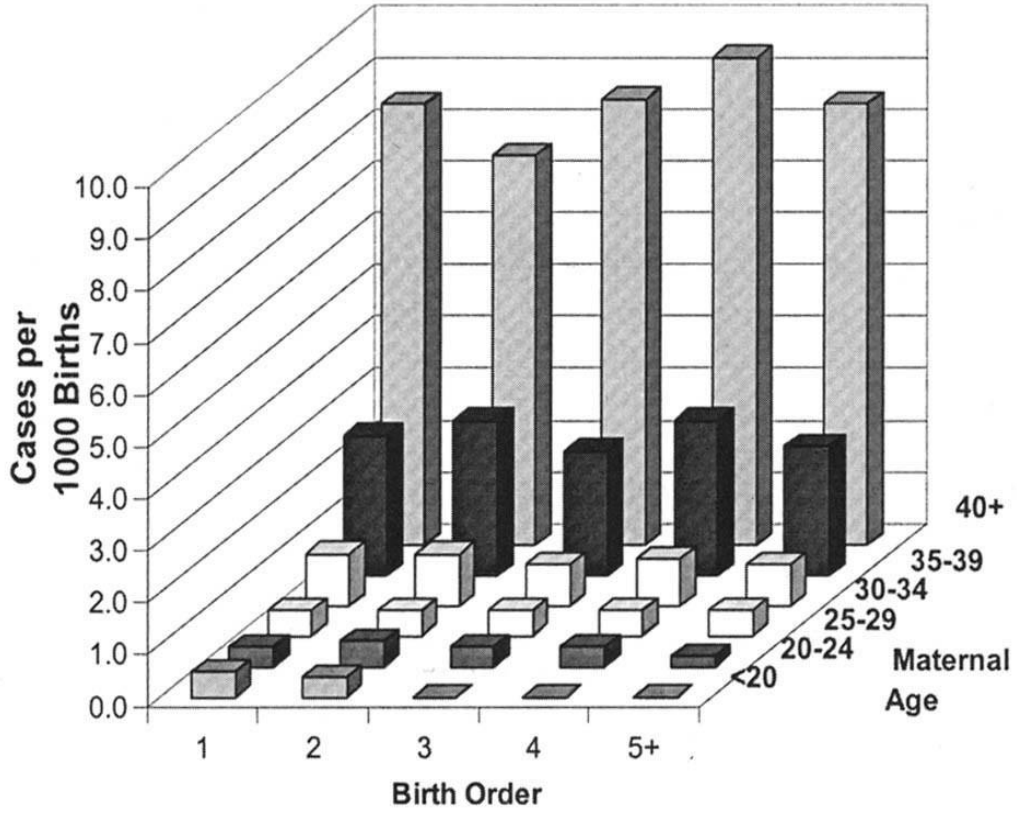
Would the effect of birth order be confounded by maternal age?

OR

Would the effect of maternal age be confounded by birth order?

Confounding = Blurring of effects

Birth order → **Prevalence of Down syndrome**

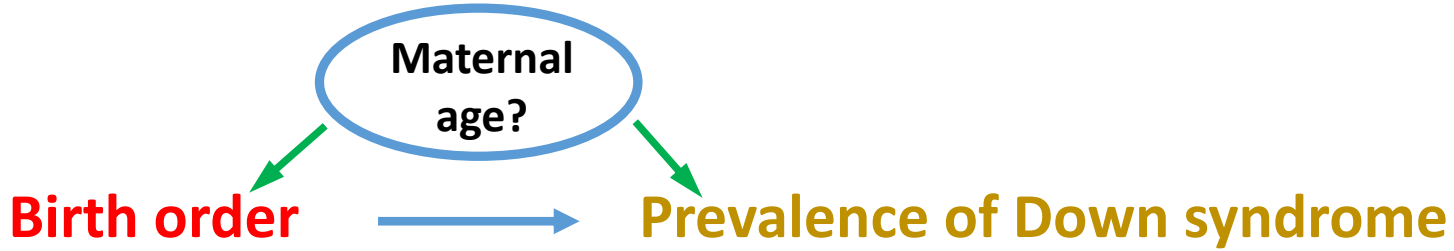


Prevalence of Down syndrome at birth by birth order and mother's age.

Thus the effect of birth order was confounded by the effect of maternal age

Variables need to satisfy certain criteria before you can qualify them as confounders!

Always the 1st step: Define exactly which exposure/outcome relationship you are studying!



Criteria for confounding

- Must be associated with the outcome/disease

and

- Must be associated with the exposure (= be unequally distributed between exposure groups)

and

- Must not be an effect of the exposure (=not be in causal pathway between exposure and outcome/disease)

Maternal age was a confounder indeed!

How to prevent or control for confounding?

√ **Prevention during study design**

- Randomization

- Restriction

- Matching

√ **Controlling during data analysis**

- Stratification
- Multivariable analysis

Summary

- Biases were discussed in relation to study designs where they frequently occur
- With exception of confounding bias, **bias cannot be repaired**
- Researchers should try very hard to **prevent bias in the study design, the study conduct/analysis and in the reporting of the study results**
- But …. no study is completely free from bias
- Any source of potentially important bias **should be mentioned in the discussion**
- Reviewers and readers must **look for biases** to see if the **study findings might be due to the way the study was designed or carried out** – in this way they can judge if the presented findings really reflect the truth or are 'biased'

Most figures and tables in this presentation were derived from Jager KJ et al. Nephrology (Carlton). 2020 Jun;25(6):435-441

THANK YOU FOR YOUR ATTENTION