Potential Errors in clinical studies

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outline

- What is Clinical Epidemiology about?
- Good science is good ethics.
- Error & bias
- How to minimize the bias

What is epidemiology?

- **Epidemiology** is the science of the study of the patterns, causes, and effects of health and disease conditions in defined populations.
- Epidemiologists help with study design, collection and statistical analysis of data, and interpretation and dissemination of results.

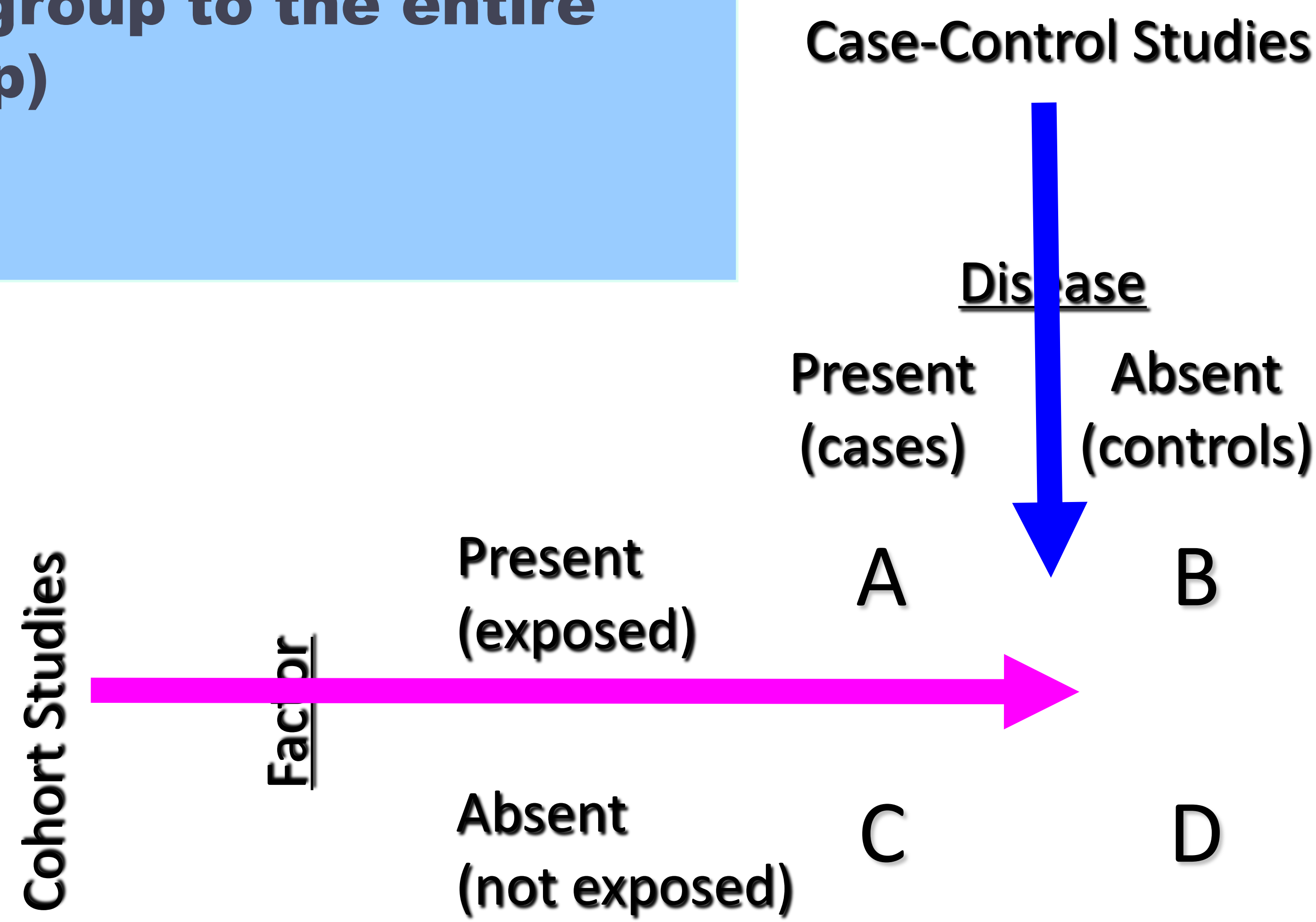
Clinical Epidemiology

- Epidemiology has helped develop methodology used in clinical research.
- Clinical Epidemiology extends the principles of epidemiology to the critical evaluation of diagnostic and therapeutic modalities in clinical practice.

Types of studies

- Analytic Studies
  - Experimental Study
  - Prospective Cohort Study-Clinical trial(RCT)
  - Retrospective Cohort Study
  - Case-Control Study
- Descriptive Studies
  - Analyses of Secular Trends
  - Case Series
  - Case Reports
- Systematic review

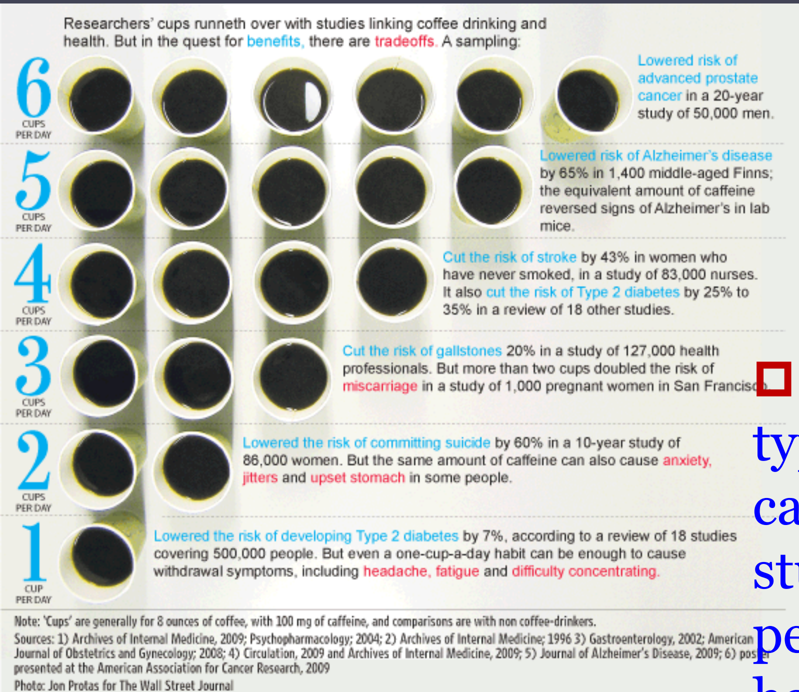
Sample to population (subgroup to the entire group)



Good Science is Good Ethics

"If a research study is so methodologically flawed that little or no reliable information will result, it is unethical to put subjects at risk or even to inconvenience them through participation in such a study. … Clearly, if it is not good science, it is not ethical."

- U.S. Dept. of Health and Human Services, *Policy for Protection of Human Subjects* (45 CFR 46, 1/1/92 ed.)



Coffee & Health

- Coffee consumption may protect against type2 2 diabetes, Parkinson's disease, liver cancer, and liver cirrhosis. And our latest study on coffee and mortality found that people who regularly drank coffee actually had a somewhat lower risk of death from cardiovascular disease than those who rarely drank coffee.
- This result needs to be confirmed in further studies, however. Harvard public Health school, Nurses' Health Study and the Health Professionals Follow-Up Study.

Quality control

- Scientific means close to true value

Error

Error is common in science, contrary to popular view.

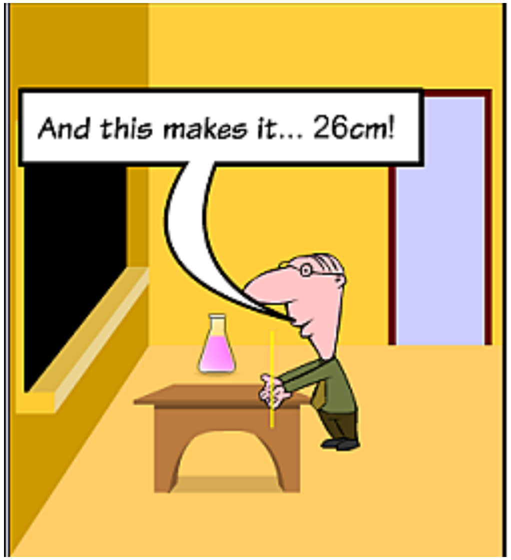
Errors can be differential (systematic) or non-differential (random)

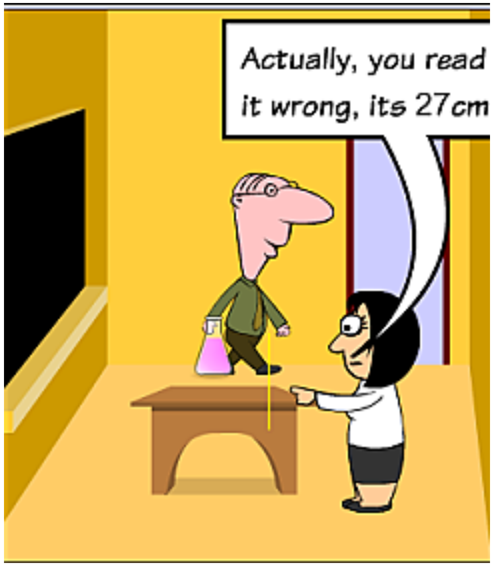
Random error: use of invalid outcome measure that equally misclassifies cases and controls

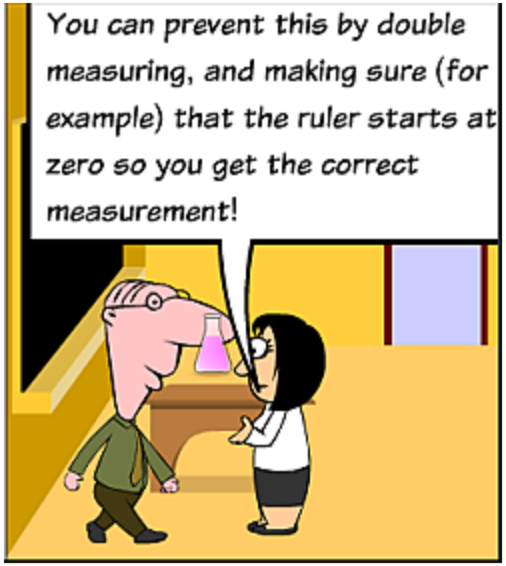
Differential error: use of an invalid measures that misclassifies cases in one direction and misclassifies controls in another

Term '*bias*' should be reserved for differential or systematic error

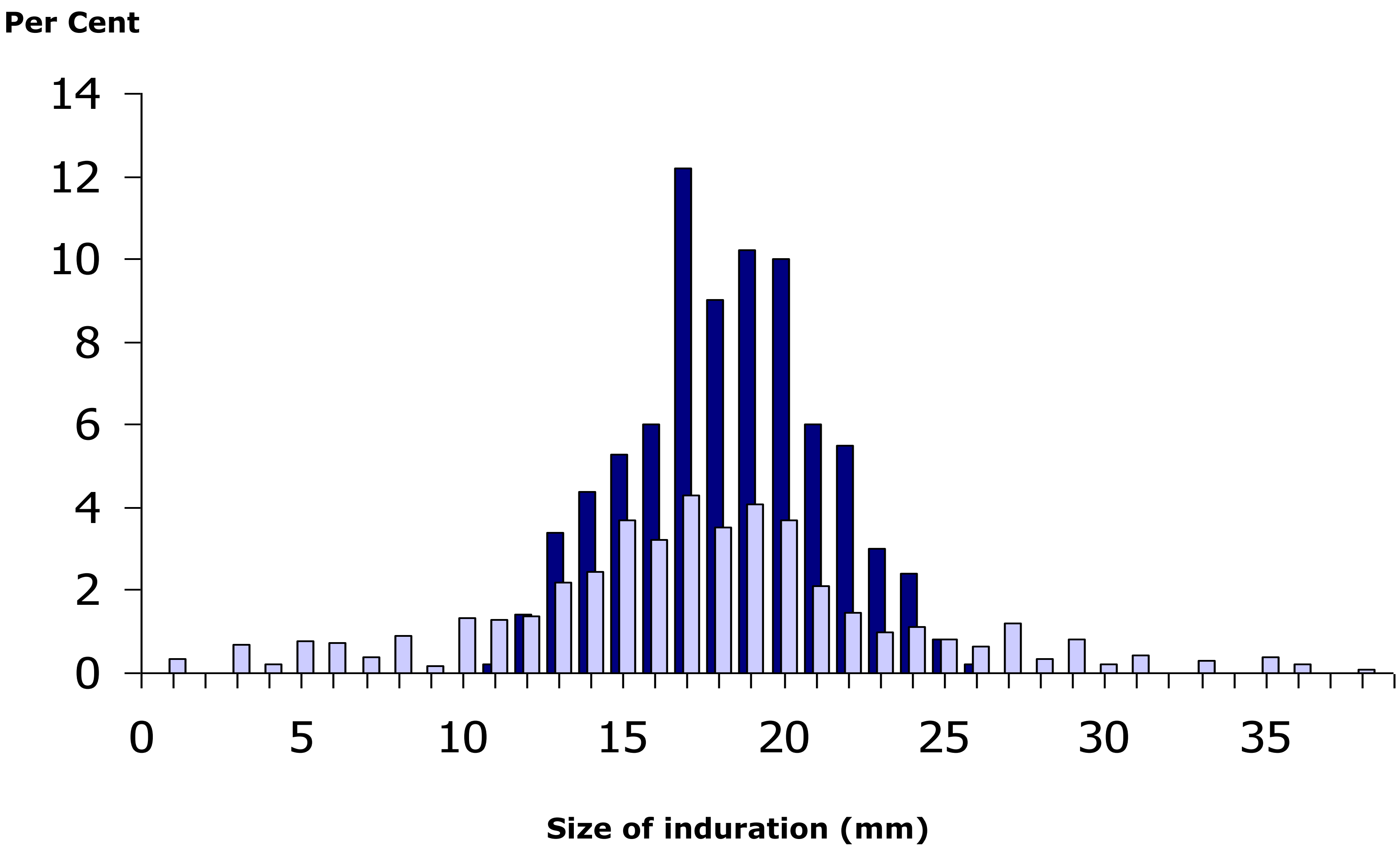
Random or systematic Error





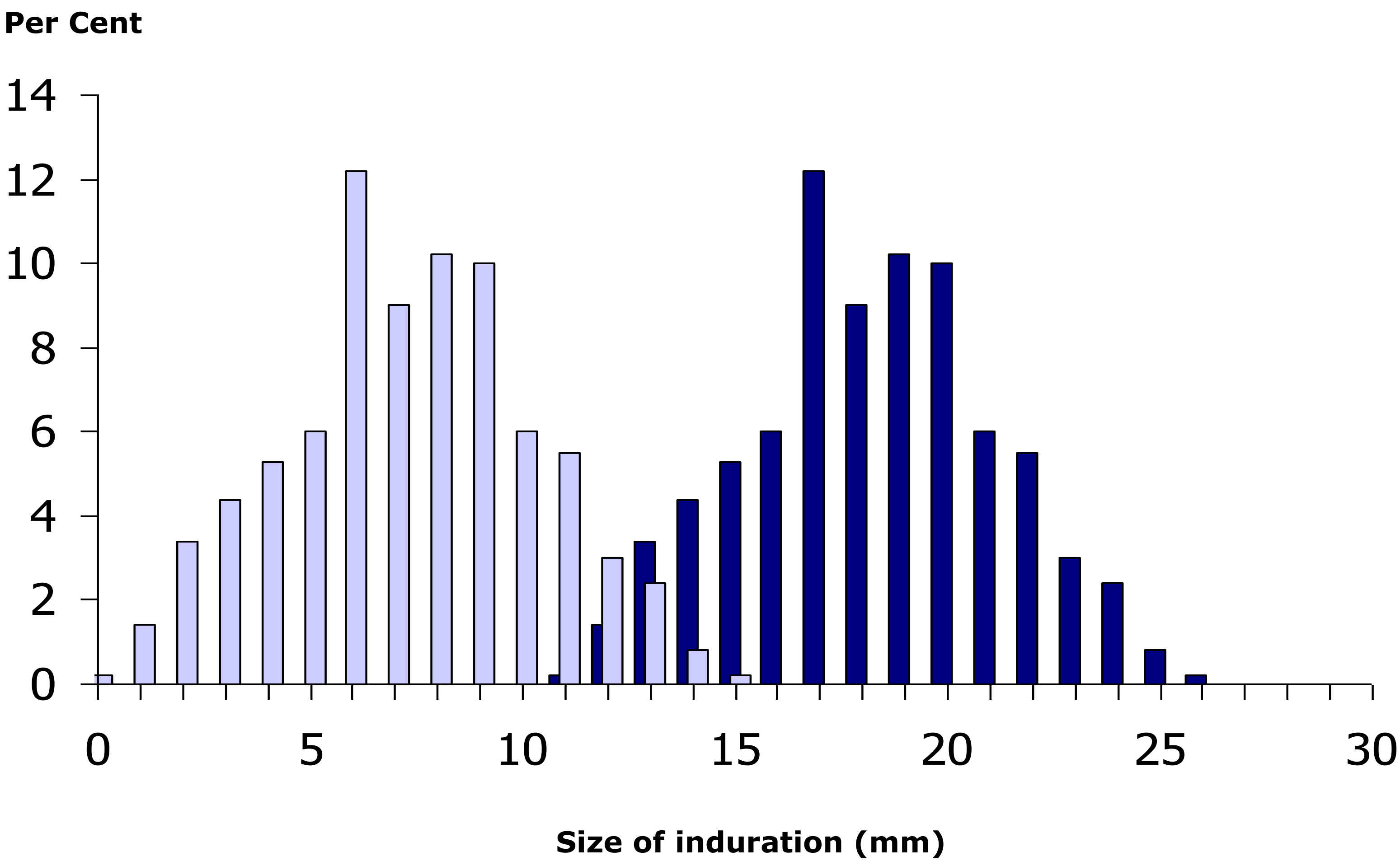


Random Error



WHO (www)

Systematic Error



WHO (www)

Errors in research

- ***Random error / chance***
  - ***Removable by increasing sample size***
- ***Bias***

What is Bias?

- **Definition: <u>Bias</u>** is a systematic error in estimation which is not reduced by increasing the study sample size (as opposed to random variation).

Bias is an error caused by systematically favoring some outcome over others.(a student said bias is kind of that you want some result instead of other)

Any trend in the collection, analysis, interpretation, publication or review of data that can lead to conclusions that are systematically different from the truth (Last, 2001)

A process at any state of inference tending to produce results that depart systematically from the true values (Fletcher et al, 1988)

Types of Bias

Selection bias
Unrepresentative nature of sample

Information (misclassification) bias
Errors in measurement of exposure of disease

Confounding bias
Distortion of exposure - disease relation by some other factor

This classification is by Miettinen OS in 1970s
See for example Miettinen & Cook, 1981 (www)

Selection Bias

- **Selective differences between comparison groups that impacts on relationship between exposure and outcome**

- **Usually results from comparative groups *not* coming from the same study base and *not* being representative of the populations they come from**

Selection Bias Examples

Self-selection Bias = publicity bias

- People referring themselves to the investigators following publicity about the study
- Self-referral of subjects is considered a threat to validity, since the reasons for self-referral may be associated with the outcome under study
- Example: study of leukaemia among troops present at the Smoky Atomic Test in Nevada, 82% of the participants were traced by the investigators but 18% contacted the investigators after publicity and leukaemia may have been over-represented in these people (had an axe to grind)

(www)

Selection Bias Examples

Self-selection Bias – healthy worker effect

- This can also occur before the subjects are identified for study e.g. the "healthy worker effect"
- Relatively healthy people become or remain workers, whereas those who remain unemployed, retired, disabled, or otherwise out of the active worker population are as a group less healthy
- May be less likely to get people in employment being able to put themselves forward as study subjects

(www)

Selection Bias Examples

Diagnostic Bias

- This is another type of selection bias that occurs before the subjects are identified for study
- Example: In a case-control study looking at the relationship between DVT and oral contraceptives. The GPs knew about the possible link between OC and DVT so women with suggestive symptoms and known use of OC were more likely to be referred to the hospital with "DVT"
- This could lead to an over-estimation of the effect of OC on DVT

'deep vein thrombosis` and OC

This is also referred to as "Hospital admission bias" or "Berkson's bias / fallacy"

Selection Bias Examples

Loss to follow-up = withdrawal bias

- Also known as follow-up bias
- When there is a differential loss to follow-up that is related to the exposure status
- Design and implementation of the study should try to minimise this and we should aim to ensure that all groups are followed as completely as possible and with equal rigour
- Single or double blinding should be used to ensure equal follow-up of all subjects

EpiCentre, Massey University, Palmerston North

Massey University

(www)

Selection Bias Examples

Case-control study:

Controls have less potential for exposure than cases

Outcome = brain tumour;

exposure = overhead high voltage power lines

Cases chosen from province wide cancer registry

Controls chosen from rural areas

Systematic differences between cases and controls

Selection Bias Examples

<u>Cohort study</u>:

Subjects in follow-up study of multiple sclerosis may differentially drop out due to disease se'verity

Differential attrition → selection bias

Selection Bias Examples

Self-selection bias:

- You want to determine the prevalence of HIV infection and You ask for volunteers for testing;- You find no HIV

- Is it correct to conclude that there is no HIV in this location?

Information / Measurement / Misclassification Bias

Method of gathering information is inappropriate and yields systematic errors in measurement of exposures or outcomes

If misclassification of exposure (or disease) is unrelated to disease (or exposure) then the misclassification is *non-differential*

If misclassification of exposure (or disease) is related to disease (or exposure) then the misclassification is *differential*

Distorts the true strength of association

Information / Measurement / Misclassification Bias

- Sources of information bias:
  - Subject variation
  - Observer variation
  - Deficiency of tools
  - Technical errors in measurement

Information / Measurement / Misclassification Bias

Recall bias:
Those exposed have a greater sensitivity for recalling exposure (reduced specificity)

- specifically important in case-control studies
- when exposure history is obtained retrospectively
-cases may more closely scrutinize their past history looking for ways to explain their illness
- controls, not feeling a burden of disease, may less closely examine their past history

Those who develop a cold are more likely to identify the exposure than those who do not – differential misclassification
- Case: Yes, I was sneezed on
- Control: No, can't remember any sneezing

Information / Measurement / Misclassification Bias

Reporting bias:
Individuals with severe disease tends to have complete records therefore more complete information about exposures and greater association found

Individuals who are aware of being participants of a study behave differently (Hawthorne effect)

Physician tends to record info from case group instead of control

Measurement & classification of exposure

- Environmental factor: drug, diet, chemical ,physical hazards;
- Genetic attributes: gene loci, SNP
- Physical characteristics: height, eye color
- Life habits: hot drink; smoking, sleeping late; get up earlier
- Mental states: anxiety, stress, depression.
- Social environment: war, gender discrimination, race discrimination, occupation discrimination

Controlling for Information Bias

- Blinding /masking
prevents investigators and interviewers from knowing case/control or exposed/non-exposed status of a given participant

- Form of survey
mail may impose less "white coat tension" than a phone or face-to-face interview

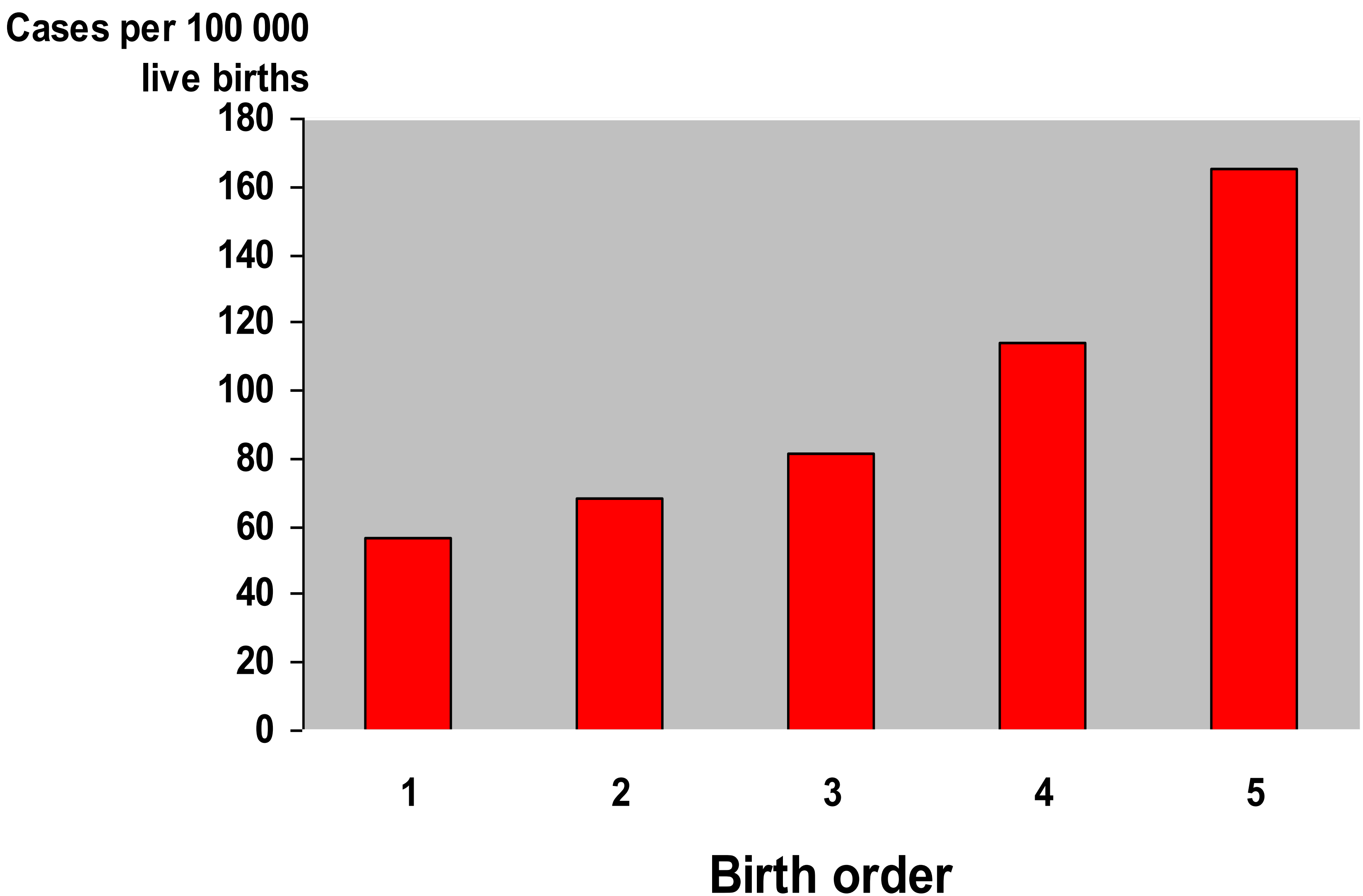
- Questionnaire
use multiple questions that ask same information acts as a built in double-check

- Accuracy
multiple checks in medical records
gathering diagnosis data from multiple sources

Confounding

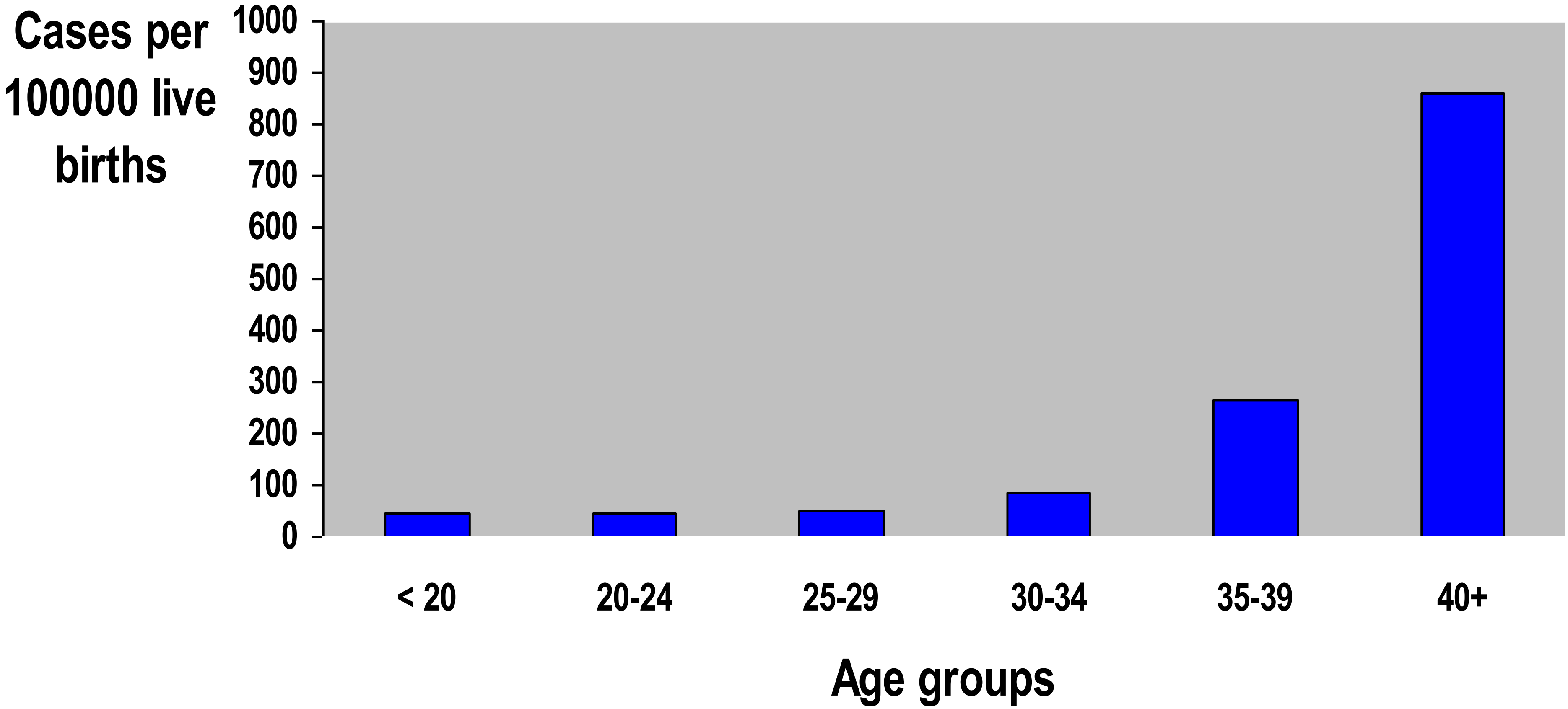
- "A confusion of effects"
- The apparent effect of the exposure of interest is distorted because the effect of an extraneous factor is mistaken for or mixed with the actual exposure effect
- The distortion can be large and lead to overestimation or underestimation of an effect, it can even change the apparent direction of an effect

Cases of Down Syndrome by Birth Order



EPIET (www)

Cases of Down Syndrome by Age Groups



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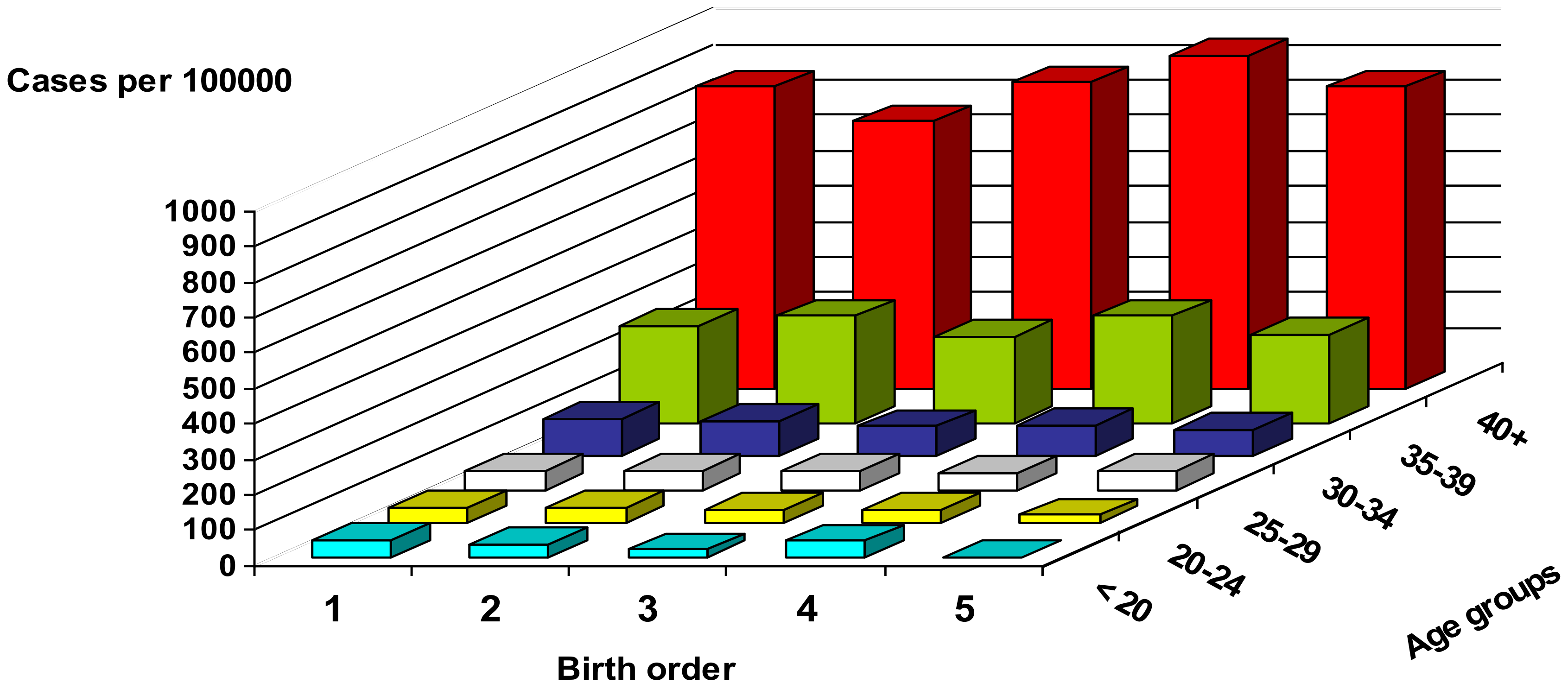
Cases of Down Syndrome by Birth Order and Maternal Age



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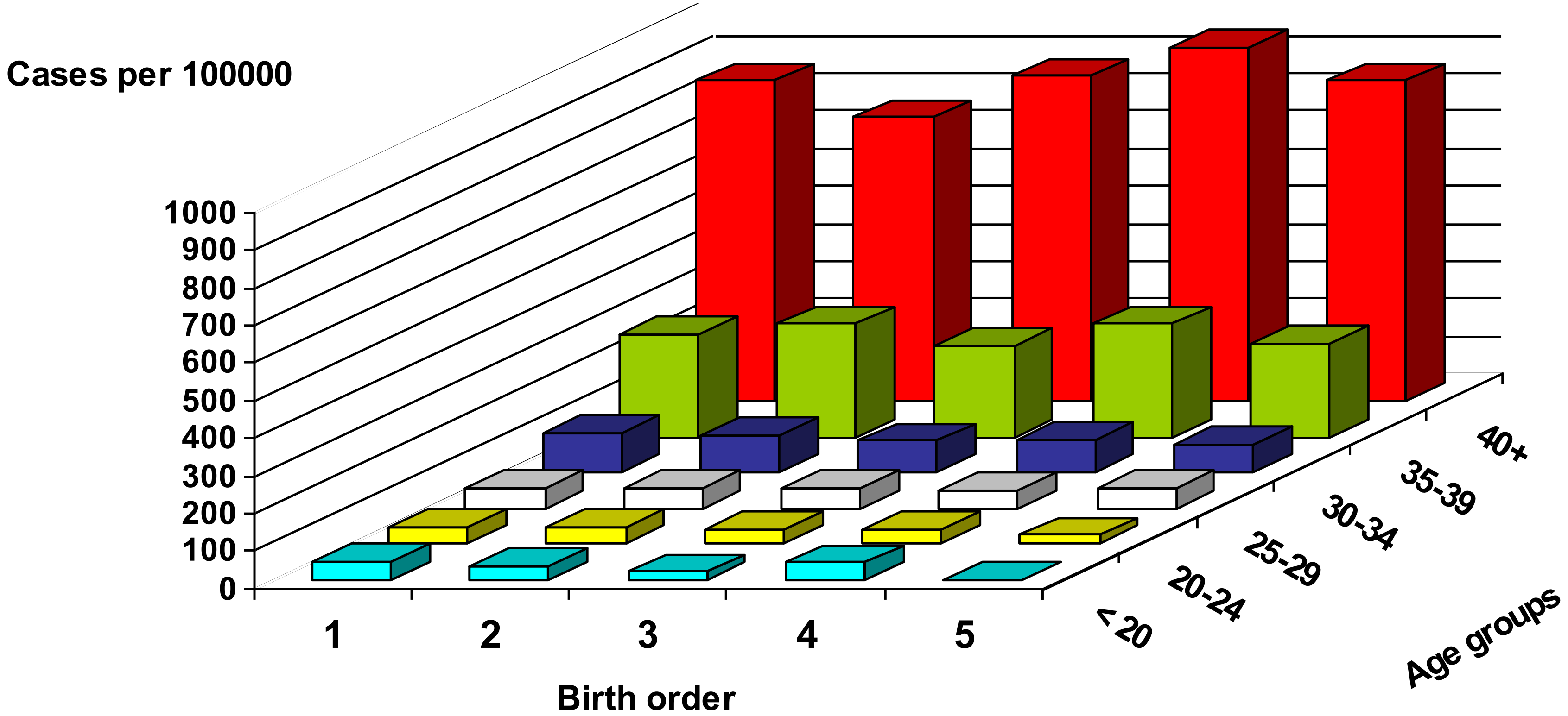
Cases of Down Syndrome by Birth Order and Maternal Age



If each case is matched with a same-age control, there will be no association. If analysis is repeated after stratification by age, there will be no association with birth order.

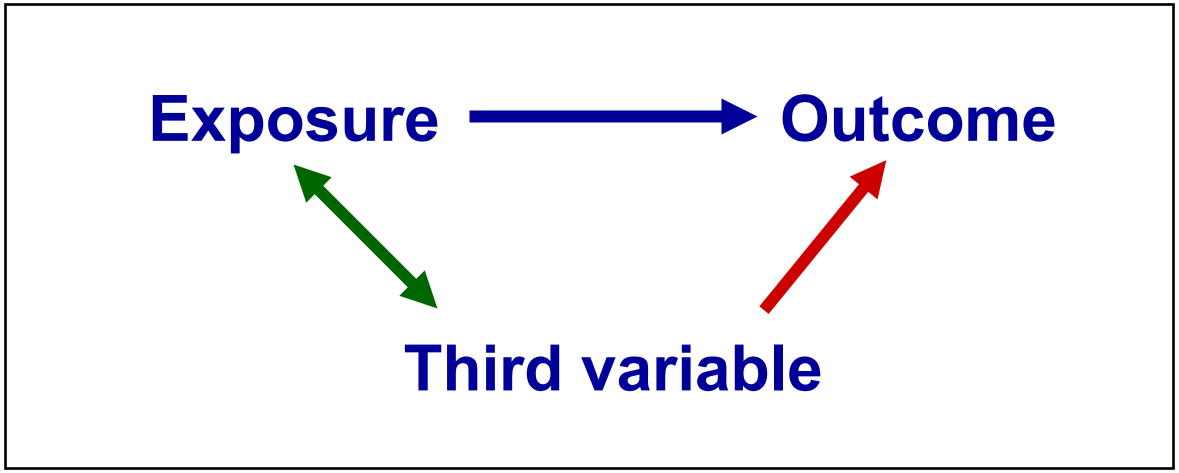
EPIET (www)

Confounding

- **A third factor which is related to <u>both</u> exposure and outcome, <u>and</u> which accounts for some/all of the observed relationship between one factor and outcome.**
- **Confounding occurs when the effects of two factors have not been separated and the analysis concludes that the effect is due to one factor rather than the other.**
- **Confounder <u>not</u> a result of the exposure**
  - **e.g., association between child's birth rank (exposure) and Down syndrome (outcome); mother's age a confounder?**
  - **e.g., association between mother's age (exposure) and Down syndrome (outcome); birth rank a confounder?**

Confounding

To be a confounding factor, two conditions must be met:



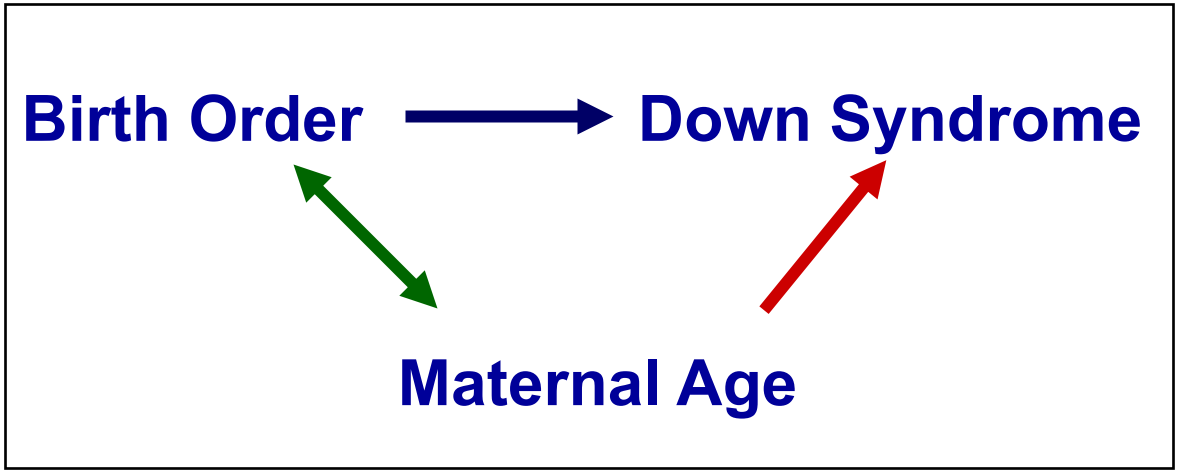
Be associated with exposure

- without being the consequence of exposure

Be associated with outcome

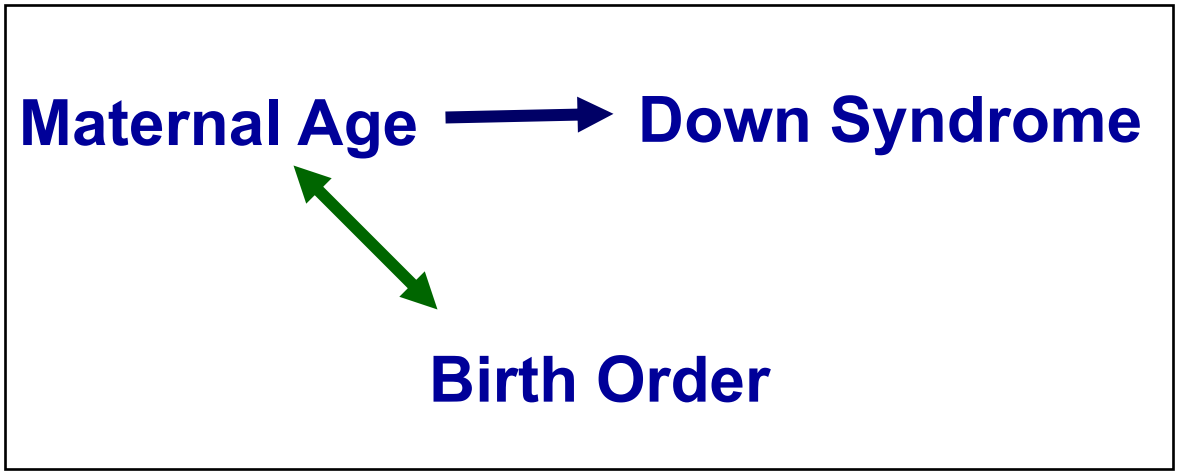
- independently of exposure (not an intermediary)

Confounding



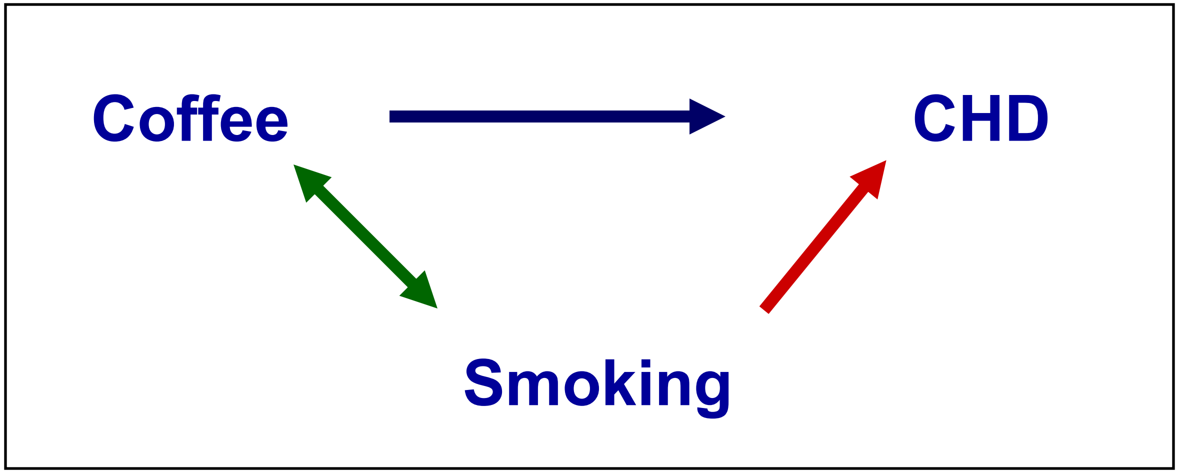
Maternal age is correlated with birth order and a risk factor even if birth order is low

Confounding ?



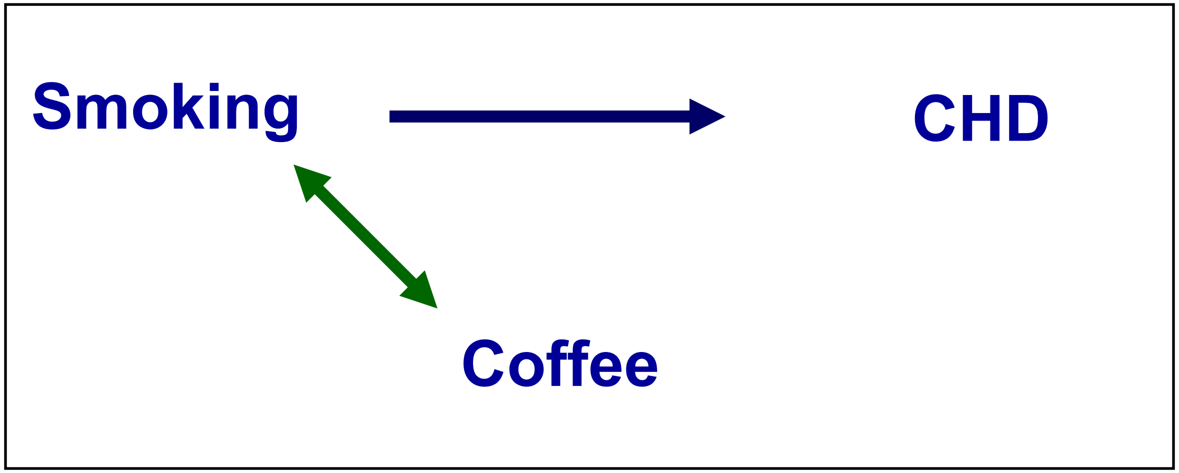
Birth order is correlatrisk factor in ed with maternal age but not a younger mothers

Confounding



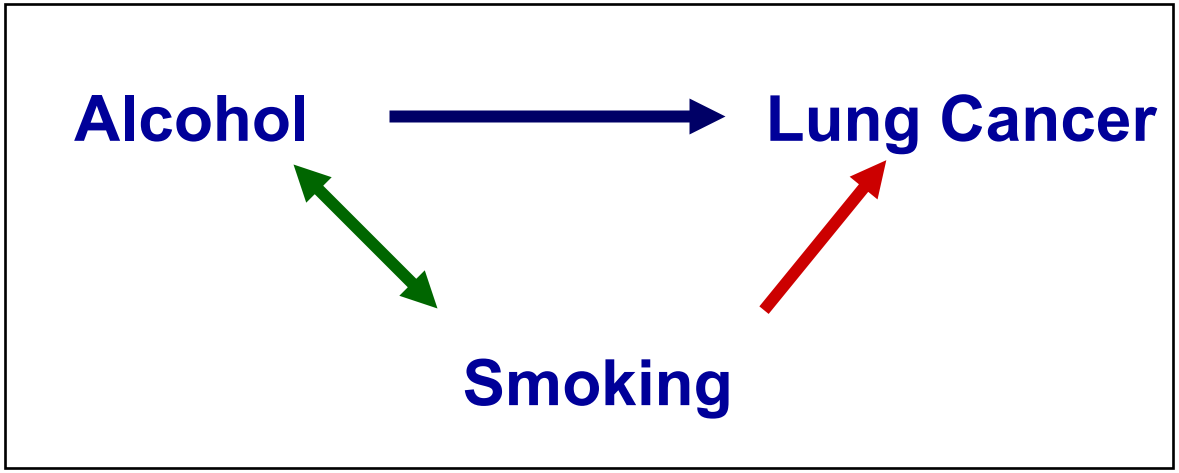
Smoking is correlated with coffee drinking and a risk factor even for those who do not drink coffee

Confounding ?



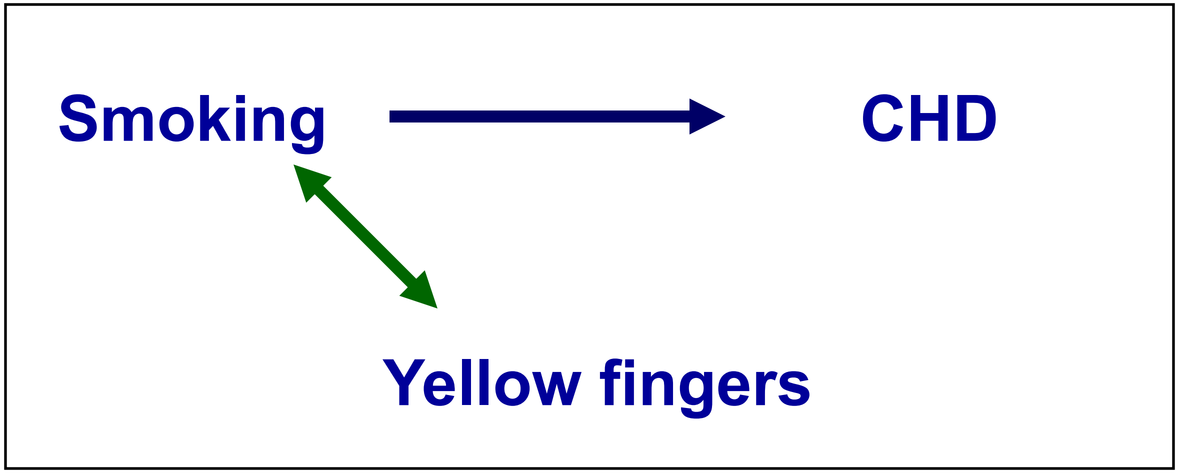
Coffee drinking may be correlated with smoking but is not a risk factor in non-smokers

Confounding



Smoking is correlated with alcohol consumption and a risk factor even for those who do not drink alcohol

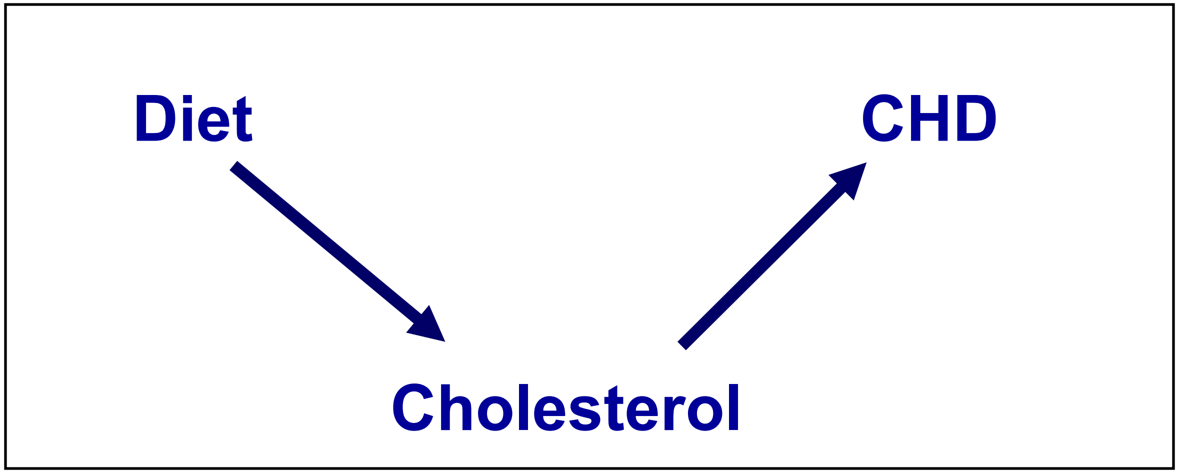
Confounding ?



Not related to the outcome

Not an independent risk factor

Confounding ?



On the causal pathway

P


PEANUTS
featuring
"Good ol' CharlieBrown"
by SCHULZ
I THINK I'VE DISCOVERED SOMETHING
WHEN YOU WAKE UP AT NIGHT, AND YOUR HEAD HURTS AND YOUR STOMACH FEELS FUNNY...
THE FIRST THING YOU DO IS PUT ON YOUR BATHROBE
THEN YOU DRINK A GLASS OF WATER AND TAKE SOME PILLS, AND YOU SIT BY YOURSELF IN THE DARK FOR AWHILE UNTIL YOU'RE READY TO GO BACK TO BED...
BUT IT'S NOT THE PILLS THAT MADE YOU FEEL BETTER..
IT'S THE BATHROBE!
SCHULZ

Solution to Confounding

For confounding to occur, the confounders should be differentially represented in the comparison groups.

Randomisation is an attempt to evenly distribute potential (unknown) confounders in study groups. It does not guarantee control of confounding.

Matching is another way of achieving the same. It ensures equal representation of subjects with known confounders in study groups. It has to be coupled with matched analysis.

Restriction for potential confounders in design also prevents confounding but causes loss of statistical power (instead stratified analysis may be tried).

HOW TO CONTROL FOR CONFOUNDERS?

- IN STUDY DESIGN…
  - RESTRICTION of subjects according to potential confounders (i.e. simply don’t include confounder in study)
  - RANDOM ALLOCATION of subjects to study groups to attempt to even out unknown confounders
  - MATCHING subjects on potential confounder thus assuring even distribution among study groups

HOW TO CONTROL FOR CONFOUNDERS?

- IN DATA ANALYSIS…
  - STRATIFIED ANALYSIS using the Mantel Haenszel method to adjust for confounders
  - MODEL FITTING using regression techniques

Cause-&-Effect Relationship

Panel 1: What to look for in observational studies

Is selection bias present?
In a cohort study, are participants in the exposed and unexposed groups similar in all important respects except for the exposure?

In a case-control study, are cases and controls similar in all important respects except for the disease in question?

Is information bias present?
In a cohort study, is information about outcome obtained in the same way for those exposed and unexposed?

In a case-control study, is information about exposure gathered in the same way for cases and controls?

Is confounding present?
Could the results be accounted for by the presence of a factor—eg, age, smoking, sexual behaviour, diet—associated with both the exposure and the outcome but not directly involved in the causal pathway?

If the results cannot be explained by these three biases, could they be the result of chance?
What are the relative risk or odds ratio and 95% CI?[11,12]

Is the difference statistically significant, and, if not, did the study have adequate power to find a clinically important difference?[13,14]

If the results still cannot be explained away, then (and only then) might the findings be real and worthy of note.

- Thank you for your attention!