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Cohort and case-control studies

Dr Petra Wark, MSc PhD

Department of Epidemiology and Biostatistics
School of Public Health
p.wark@imperial.ac.uk

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Examples of day-to-day-life in the clinic

What may cause vitamin D deficiency?

Should I prescribe this drug to this patient? Is it likely to improve his situation? How often do site effects occur?

Doctor, is it safe to use statins? I heard they cause cancer

I got the [seasonal] flu. When will I feel better?

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Why do we conduct epidemiological studies to

- To describe health status of populations

- To understand the natural history, outcome and prognosis of a disease
- To evaluate the effectiveness and impact of a certain intervention
- To determine risk factors for a given disease, and evaluate the strengths of the associations

→ Two common types of studies that address the last set of questions are cohort and case-control studies.

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Hierarchy of study designs (recap)

- Systematic reviews and meta-analysis
- Randomised controlled trials
- **Cohort studies**
- **Case-control studies**
- Descriptive/cross-sectional studies
- Ecological studies
- Case reports/series

Learning outcomes

By the end of this lecture, you should be able to:

- Describe where cohort and case-control studies fit in the hierarchy of epidemiological studies
- Distinguish and describe the design of case-control and cohort studies by their core defining features
- List the strengths and weaknesses of cohort studies and case-control studies

- To be able to calculate crude odds ratios and relative risks from a two-by-two table
- To be able to interpret odds ratios and relative risks

Session Outline

- Cohort studies
  - Design features
  - Calculating risk ratios
  - Interpreting risk ratios
  - 2 min quiz
- Case-control studies
  - Design features
  - Calculating odds ratios
  - Interpreting odds ratios
- Contrasting characteristics of case-control and cohort studies (quiz)

What is a cohort?

- A “cohort” is a group of people who have something in common.
  - All students attending this class
  - Everybody who has received the swine flu vaccine
  - People with a vitamin D deficiency
  - All people who underwent a kidney transplantation
- A cohort can represent the disease-free population from which cases with the disease eventually arise

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Cohort study: study design

Compare risks/rates of disease

Individuals without the disease of interest

select → **Exposed** → *subdivide* → **Disease**

subdivide → **Disease-free**

select → **Unexposed** → *subdivide* → **Disease**

subdivide → **Disease-free**

Completeness of a cohort

- It is important to ensure that the cohort sample is representative of the total reference population.
- If the study population does *not* include all the people eligible according to the identification criteria, it is possible that the people overlooked or omitted would differ with regard to exposure characteristics and/or vital status.

Follow-up

- Once information on exposure has been obtained for each member of the cohort, the occurrence of the disease(s) of interest, vital status and causes of death have to be ascertained.
- Each person has to be followed up, and the disease endpoint, cause of death or his being alive assessed.
  - Failure to ascertain disease incidence or vital status for any appreciable segment of a study group may lead to erroneous or misleading conclusions
  - People lost to follow-up may be atypical, either because of vital status or of previous exposure, or factors (such as age) associated either with exposure or outcome

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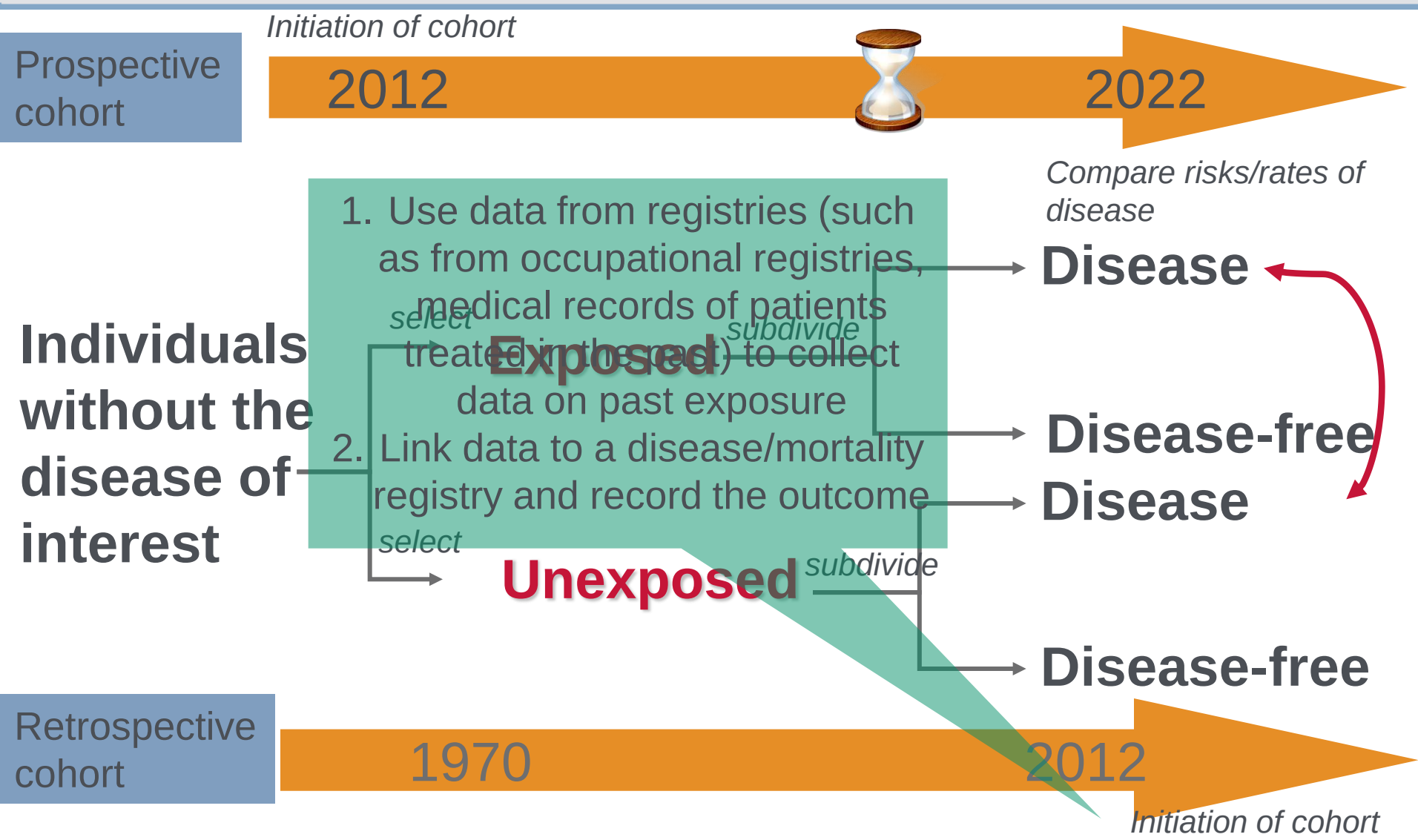
Prospective and retrospective cohorts



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Procedure for carrying out a cohort study

Procedure	Example
1 Select people who are exposed and people who are unexposed	Exposed: women who received fertility drugs Unexposed: women who did not receive such drugs
2 Follow the cohorts over time and determine how many people got disease after a certain time	Examine how many ovarian cancers occurred in both groups separately (and ideally when)
3 Compare risk of disease in the exposed and unexposed cohorts women the drugs	Compare risk of disease for women who got fertility drugs with risk of disease in who did not get

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Have the disease

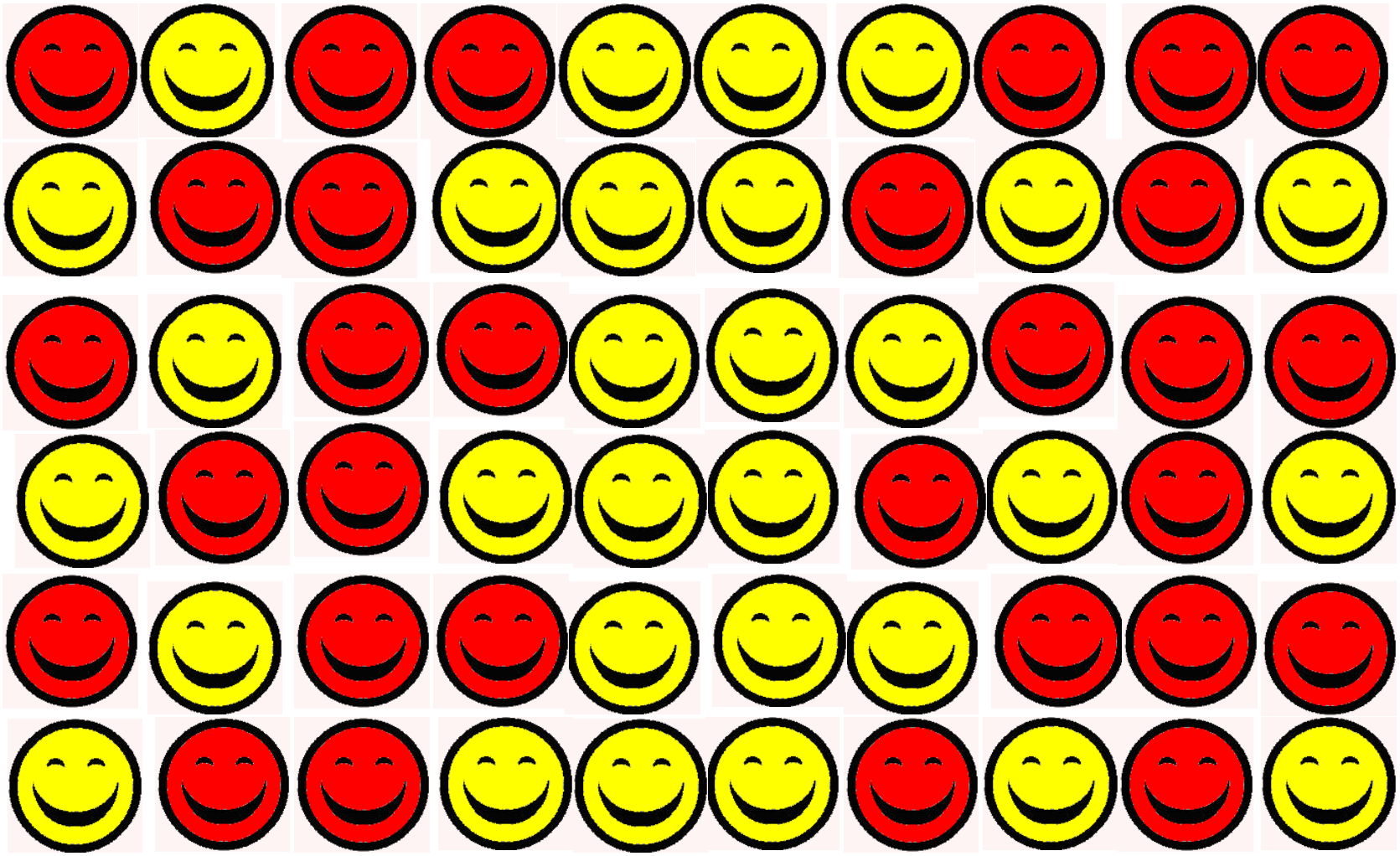
Disease free

exposed

unexposed

Cohort study: baseline

Imagine that we follow these people for 10 years



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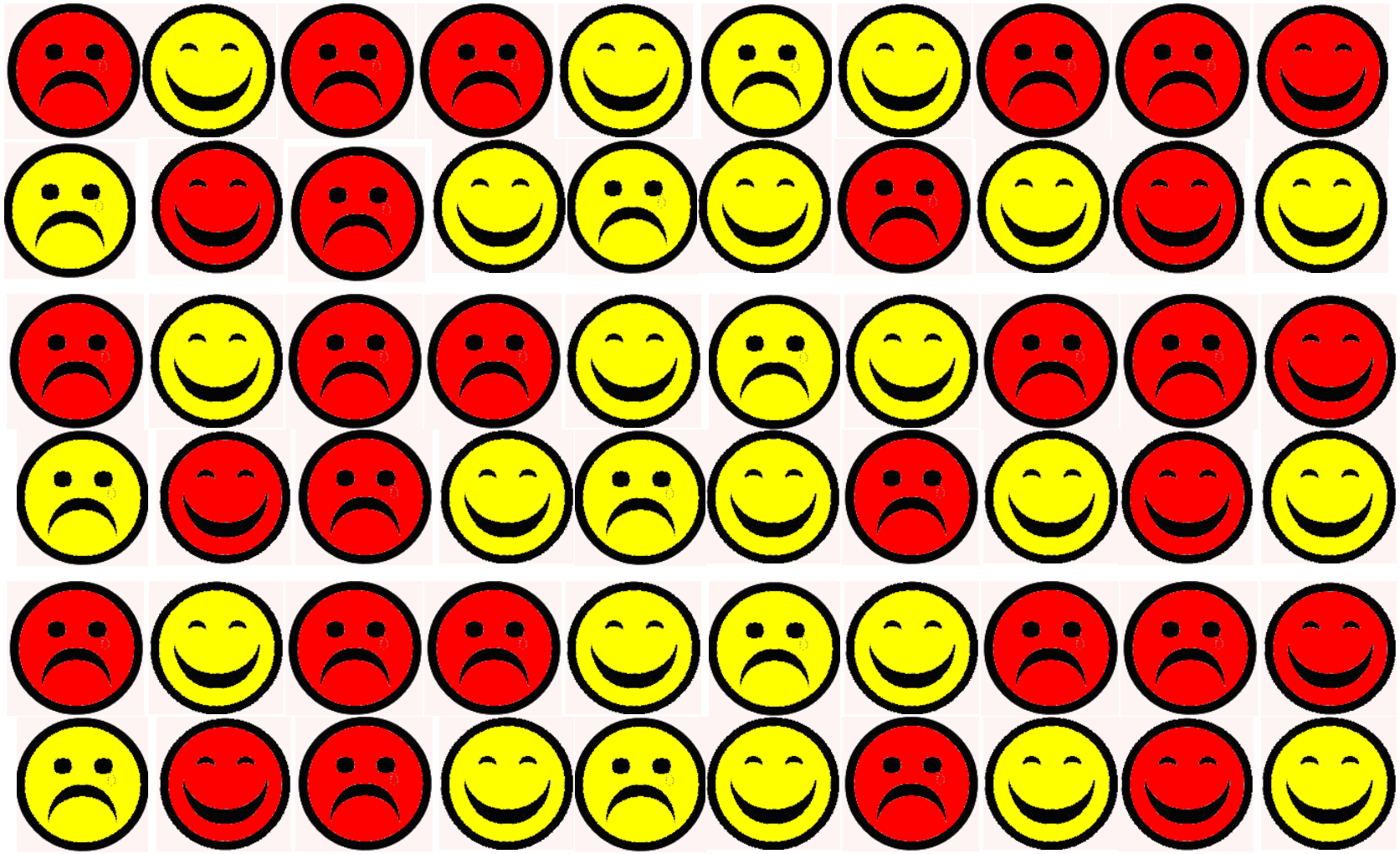
Have the disease

Disease free

exposed

unexposed

Cohort study: after 10 years



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Develop the disease

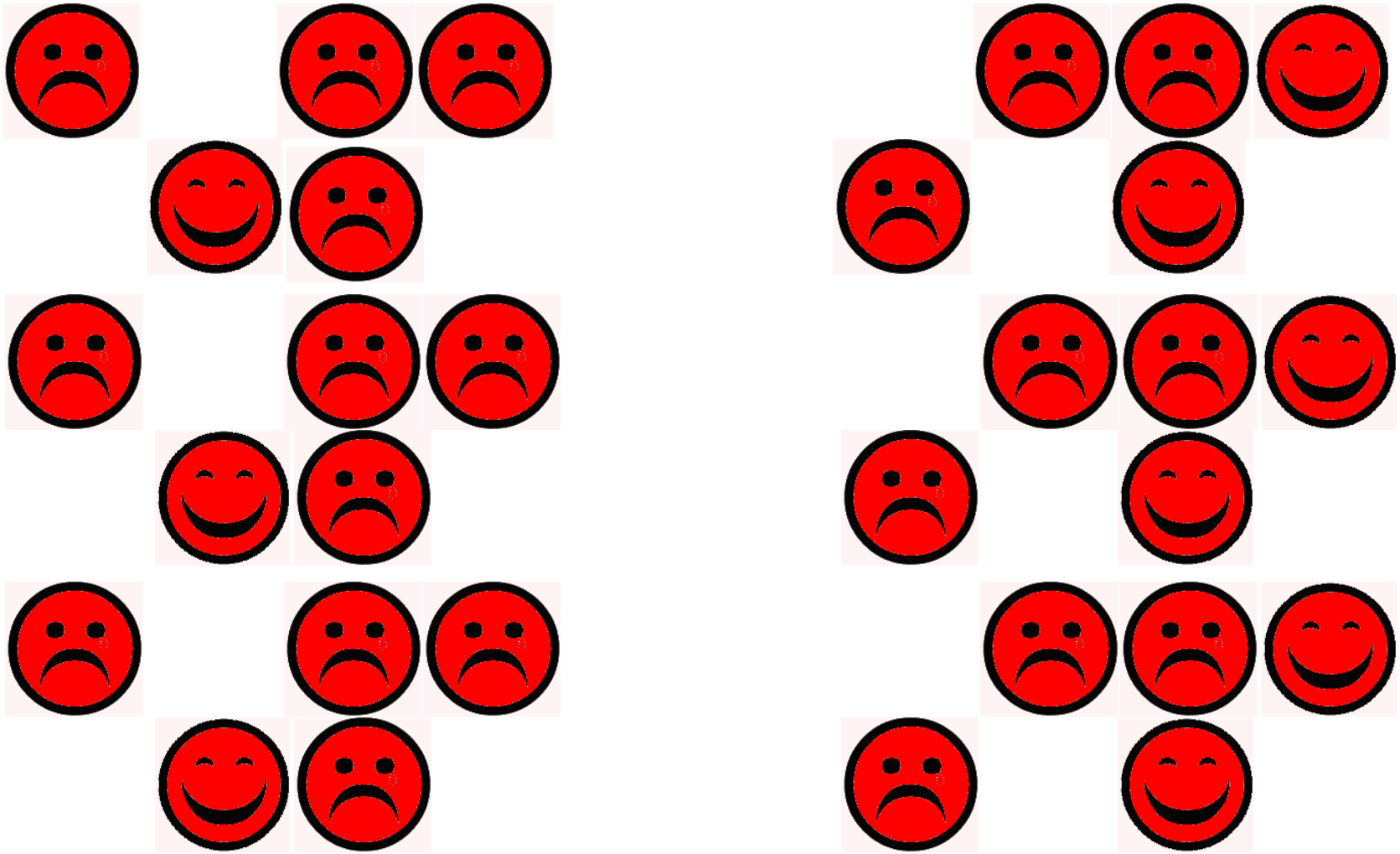
Remain disease free

exposed

unexposed

Group of exposed people

Risk of disease=21/30



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Develop the disease

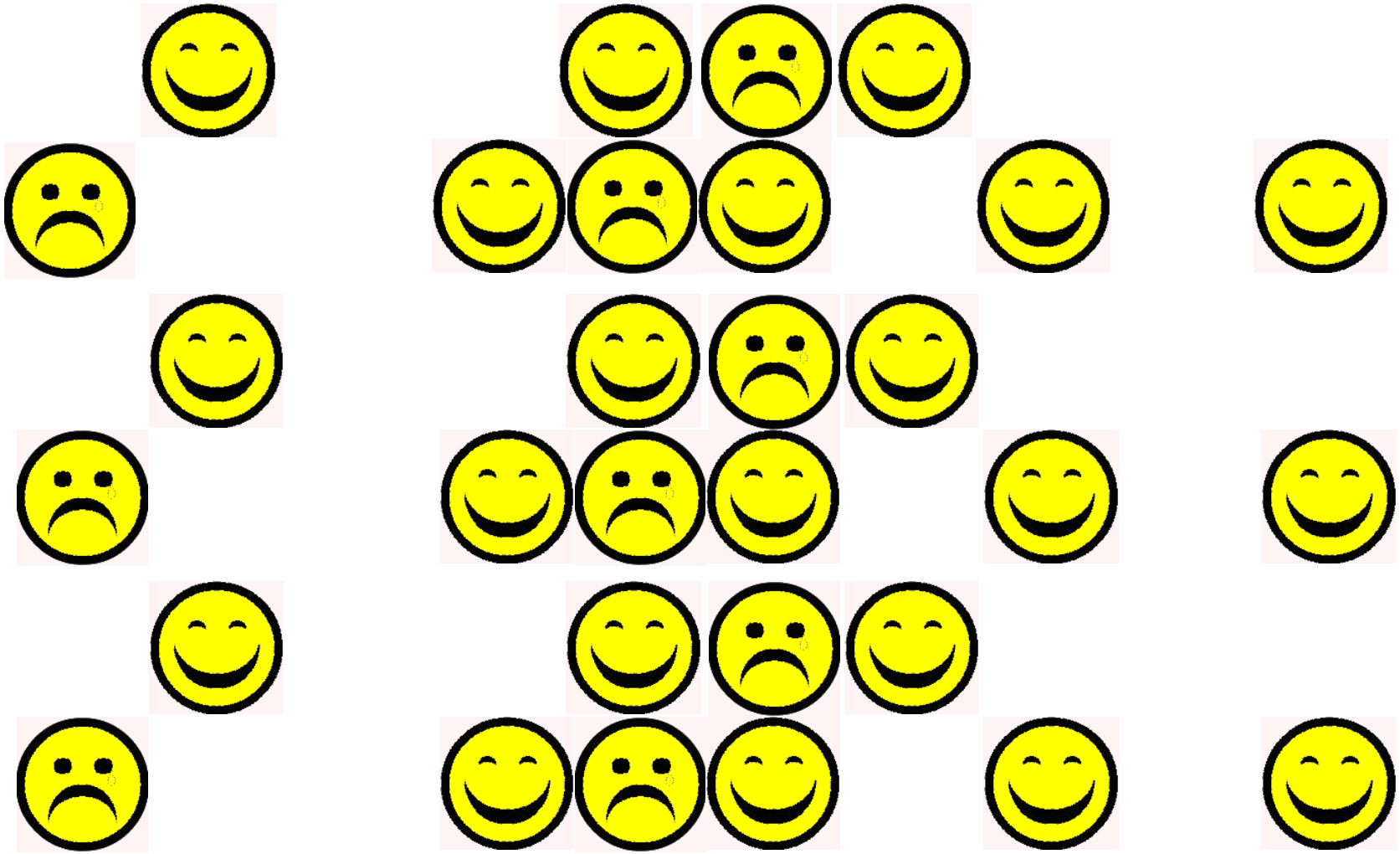
Remain disease free

exposed

unexposed

Group of unexposed people

Risk of disease= 9/30



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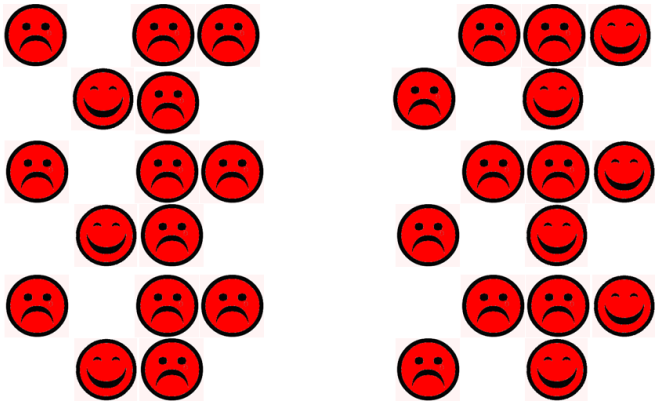
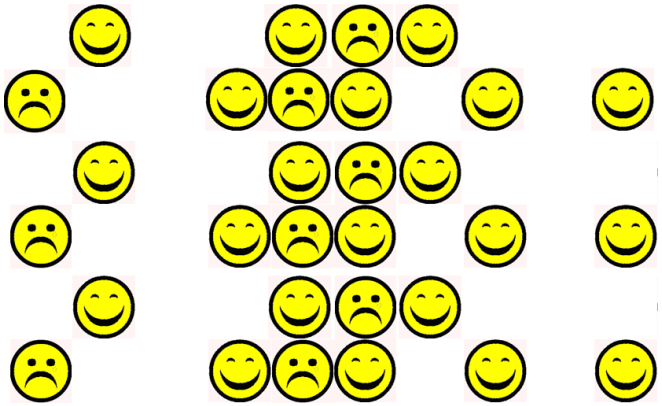
Comparing risk of disease in exposed and non-exposed

Exposed



Risk of disease=21/30

Unexposed



Risk of disease=9/30

Risk ratio = $\frac{21/30}{9/30} = 2.33$

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Calculating the risk ratio

	Disease	Disease-free	
Exposed	a	b	(a+b)
Unexposed	c	d	(c+d)

Risk ratio (RR)= $\frac{a/(a+b)}{c/(c+d)}$

Note: Follow-up time ("person-years") is often measured precisely in a cohort study; If so, you calculate a rate ratio or hazard ratio

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Interpretation of risk ratios

	RR<1	RR =1	RR>1
Interpretation	Risk of disease among exposed is smaller than the risk of disease among the unexposed	Risk of disease is equal among the exposed and unexposed	Risk of disease among the exposed is greater than the of the risk of the disease among the unexposed
In other words..	The exposure is associated with a decreased risk of the disease	The exposure is not associated with the disease	The exposure is associated with an increased risk

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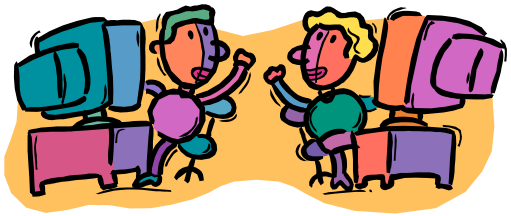
2 min exercise

- 200/1,000 of male current smokers will eventually develop lung cancer
- Only 20/1,000 males who never smoked will eventually develop lung cancer

The risk of lung cancer in current smokers is 10 times higher than in never smokers (i.e. 90% higher)

Or… risk in *never* smokers is 0.10 times the risk in *current* smokers

$$RR = \frac{200/1000}{20/1000} = 10$$



Compare the risk of lung cancer in smokers with risk in non-smokers

use a risk ratio & interpret

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Advantages and disadvantages of cohort studies

Advantages

- Able to look at multiple outcomes
- Able to follow through the natural history of disease
- Good design to look at risks related to rare exposures
- Incidence can be calculated
- Can minimise bias in estimating exposure if prospective

Disadvantages

- Inefficient for studying rare diseases
- Expensive and time consuming (if prospective)
- Loss to follow-up may introduce bias
- Healthy worker effect may cause bias in occupational cohorts

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Session Outline

- Cohort studies
  - Design features
  - Calculating risk ratios
  - Interpreting risk ratios
- Case-control studies
  - Design features
  - Calculating odds ratios
  - Interpreting odds ratios
- Contrasting characteristics of case-control and cohort studies (quiz)

Case-control studies

- Case-control studies are commonly used in epidemiology
- They are relatively cheap and quick to conduct
- Suitable for studying rare diseases
- Best suited to study diseases for which medical care is sought

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Case-control study: study design

Direction of enquiry

PAST → PRESENT

Compare odds of exposure

Exposed

Unexposed

subdivide

Cases (With disease)

select

Source population

Exposed

Unexposed

subdivide

Controls (Without disease)

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Daily Mail, 27 September 2008

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Why your mobile should carry a health warning

By **Barry Wigmore**

MOBILE phones should carry a health warning like those on cigarette packets, scientists warned yesterday.

The authorities must not make the same mistakes over possible links between mobile phones and brain cancer as they did with cigarettes and lung cancer, experts warned a powerful U.S. congressional committee.

It took 50 years to get the tobacco industry to acknowledge the risks, and 70 years to remove lead from paint and petrol, they said.

'Society must not repeat the situation we had with smoking and lung cancer, where we waited until every "i" was dotted and "t" was crossed before warnings were issued,' said Professor David Carpenter, director of the institute of health and environment at the University of Albany.

'Precaution is warranted even in the absence of absolutely final evidence concerning the magnitude of the risk – especially for children.'

Dr Ronald Herberman, director of the University of Pittsburgh Cancer Institute – one of the top U.S. cancer research centres – agreed and said: 'We must learn from our past to do a better job of interpreting evidence of potential risk.'

He said that in countries such as Britain and the U.S., 'every child is using cell phones all of the time'.

The committee heard that scientists are split over how dangerous mobile phones are to users.

But Dr Herberman said that most studies claiming there is no link between mobile phones and brain tumours are outdated because many defined regular mobile phone use as once a week.

He added that most do not include enough long-term users because a brain tumour can take many years to develop.

Both experts told the committee the brain cancer risk from mobile phone use is far greater for children than for adults. Dr Herberman produced a model showing how radiation from a mobile phone penetrates far deeper into the brain of a five-year-old than that of an adult.

The committee was shown a research paper published this month by the Royal Society in London which found that teenagers who start using mobile phones before the age of 20 are five times more likely to develop brain cancer at the age of 29 than those who did not use a mobile phone.

Another this year by a Swedish cancer specialist found that frequent cell phone users are twice as likely to develop a malignant tumour on the nerves of the 'handset ear' than on the other ear.

Dr Herberman said: 'I cannot tell you cell phones are definitely dangerous. But, I certainly cannot tell you that they are safe. Like the messages that warn of health risks on cigarette packs, cell phones need a precautionary message.'

CASE STUDY

MOTHER-of-three Ellen Marks yesterday blamed her husband's malignant brain tumour on his mobile phone use.

Mrs Marks told the U.S. congressional hearing that her husband Alan, 56, found out he had a brain tumour on his right frontal lobe in May.

The tumour is on the same side of his head where he held his mobile, which he used about 30 hours a month. He had used one for around 20 years.

Mrs Marks, from California, said that for many years before his tumour was diagnosed, his behaviour changed dramatically, alienating his family.

He had had to take bi-polar medications and anti-depressants during those years.

He has been given a prognosis of around five years.

'I often threatened to throw the mobile phone into the garbage and how I wish I had,' she said. 'This horror could have been avoided with a simple warning.'

Cancer risk: Mobile phones

Disease

Exposure

Is there an association between frequent use of mobile phones and risk of brain cancer?

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Selection of cases

Histologically confirmed malignant, primary brain tumour (ICD-10: C71)

After having established a clear definition and strict diagnostic criteria of the disease

- Disease registries (e.g. for cancer)
- Records of physicians (e.g. GPs)
- Hospital admission or discharge records
- Pathology department log books
- Screening units (e.g. for breast cancer)

Selection of controls

- Selection of an appropriate comparison group is the most difficult and critical issue in the design of case-control studies

- Controls are subjects free of the disease (or outcome of interest) during the same period of time in which the cases were identified.
  - They should come from the population of individuals who would have been identified and included as cases had they also developed the disease.
  - They should be representative of that population

Sources of controls

- General population
- Neighbourhood
- Friends/relatives
- Hospital or clinic-based
- (Random digit dialling)

Variation in amount of recall bias, response rates, selection bias, costs and feasibility

Measurement of exposure

Often self-reported:

- Interviews
- Questionnaires

Recall bias

More objective measures:

- Hospital records, employer registries
- Blood, urine tests, etc

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Procedure for carrying out a case-control study

Procedure	Example
1 Select cases with disease controls without disease	Cases: brain tumours Controls: from population without cancer
2 Obtain information on past exposures and other factors	Examine mobile phone use to classify people into exposure categories
3 Compare proportions of people exposed in cases and controls	Compare proportion of frequent mobile phone users in cases and controls

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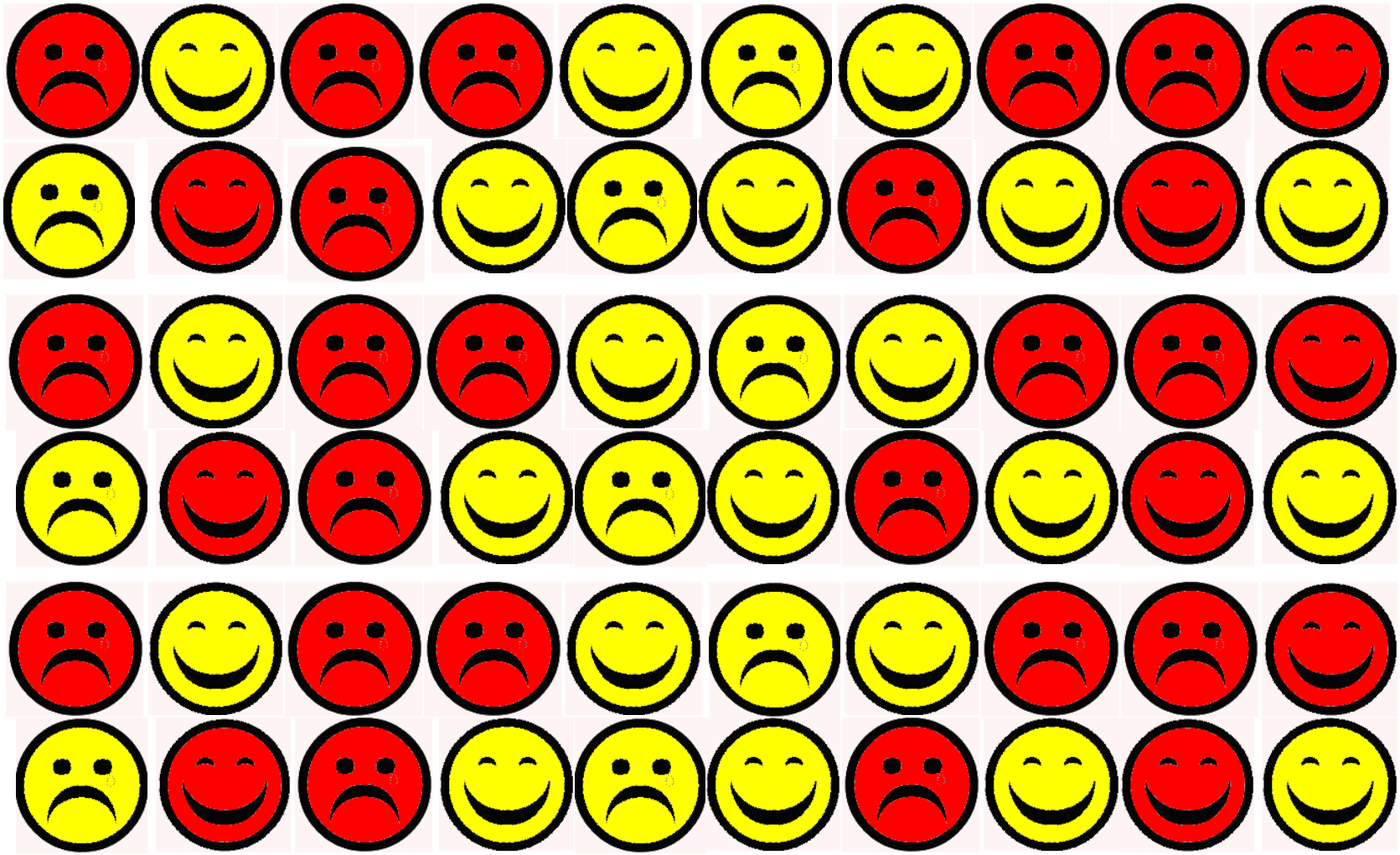
Cases (have the disease)

Controls (do not have the disease)

exposed

unexposed

Case-control study



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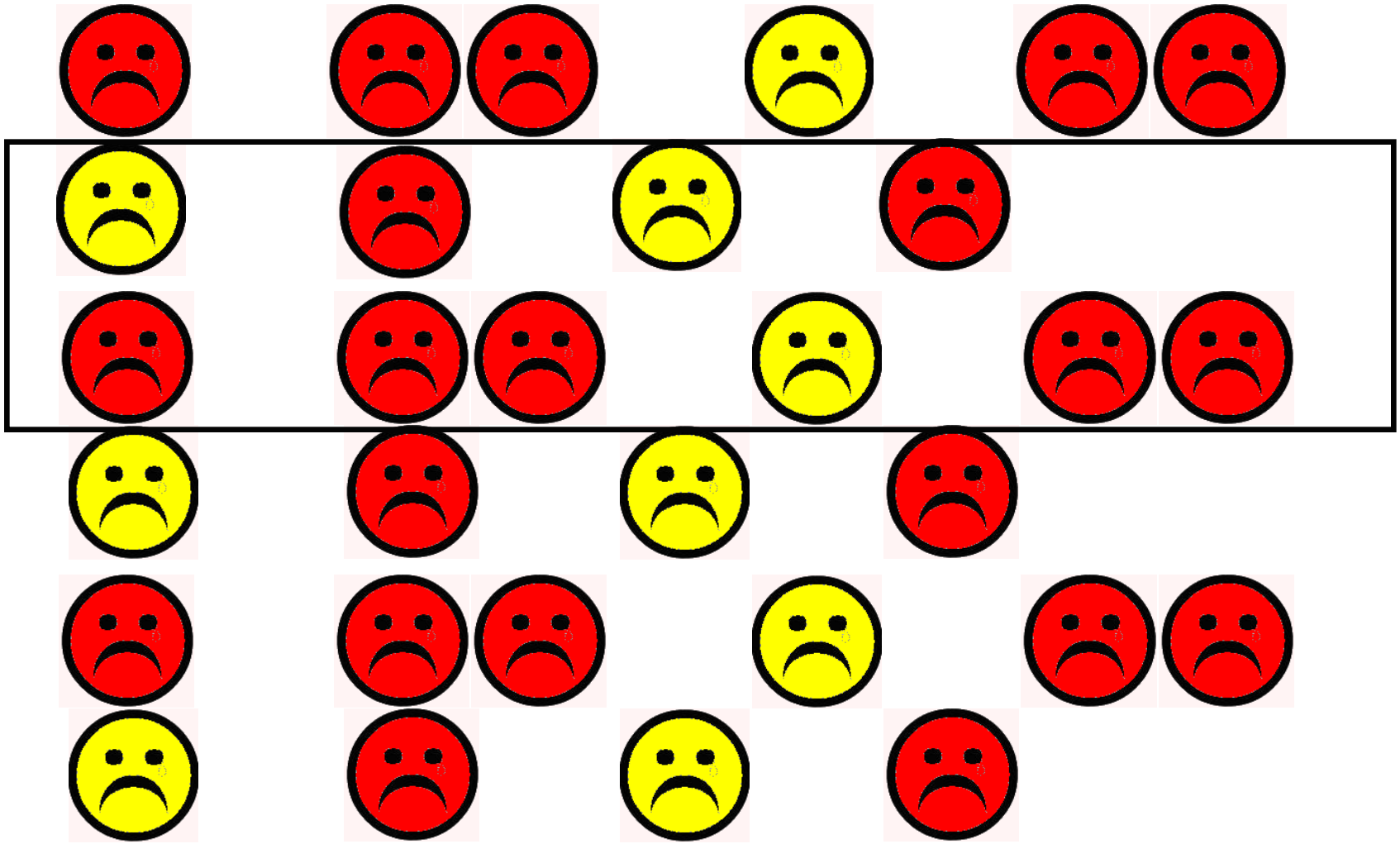
Cases (have the disease)

Controls (do not have the disease)

exposed

unexposed

Take a representative sample of the cases



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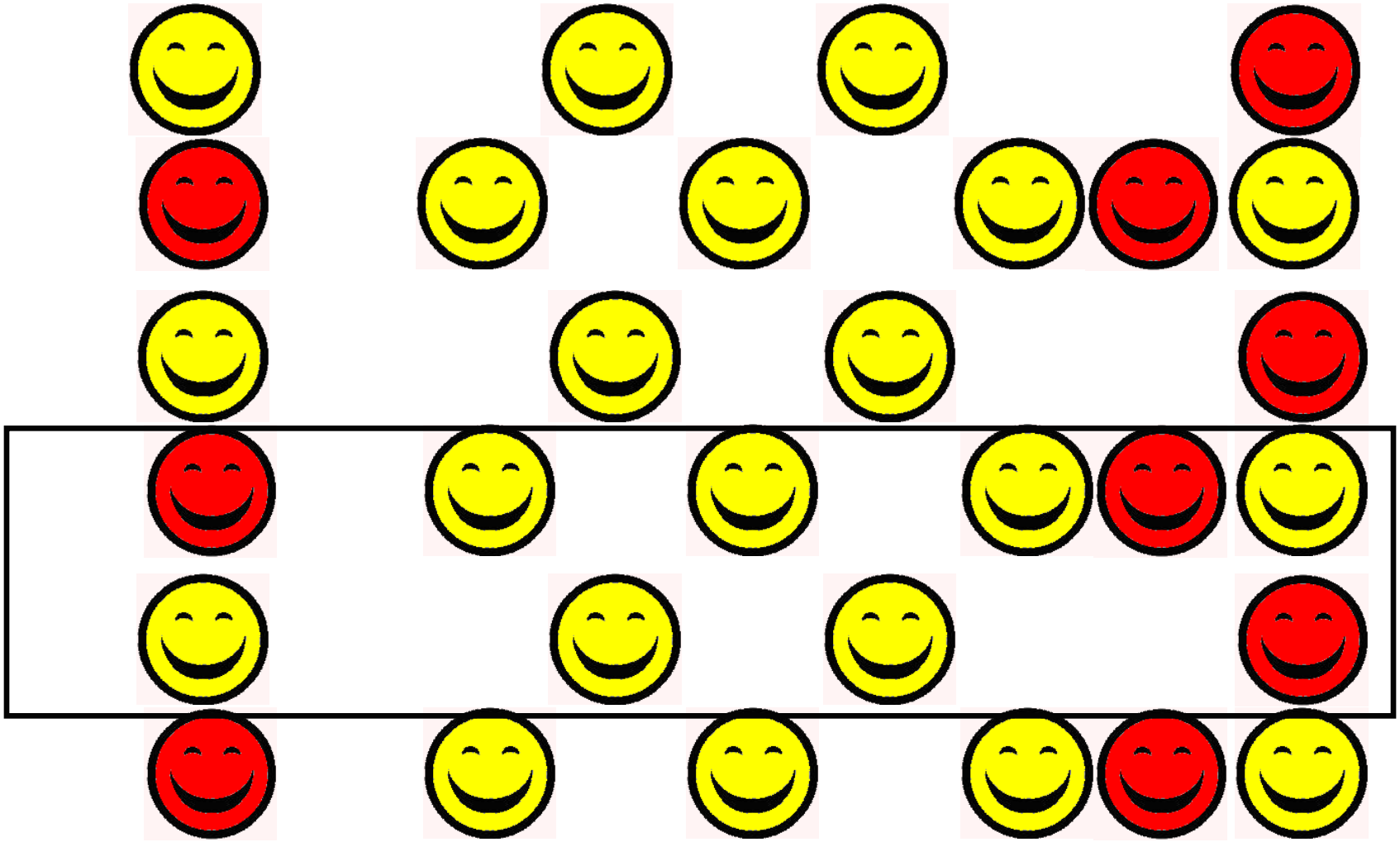
Cases (have the disease) — exposed

Controls (do not have the disease) — unexposed

Select a suitable control group



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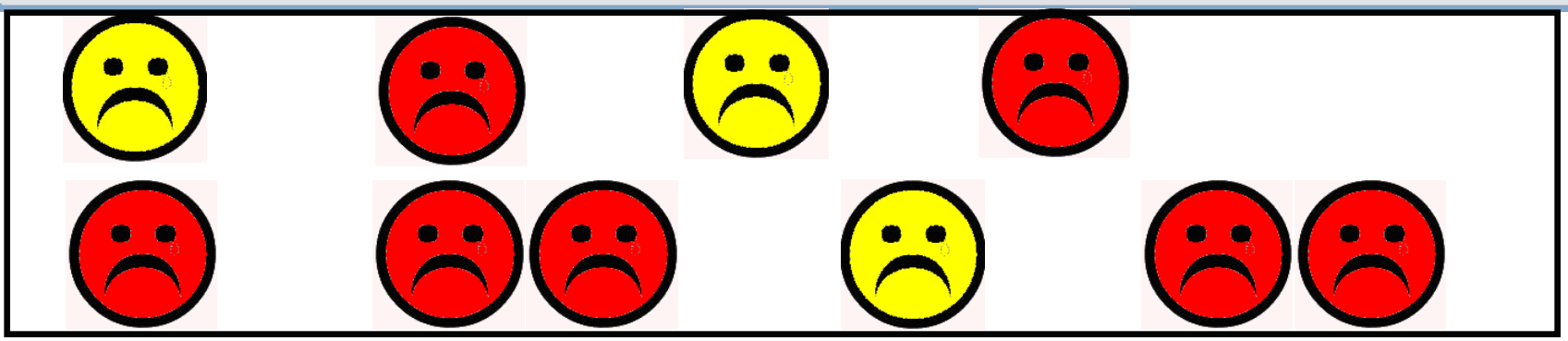
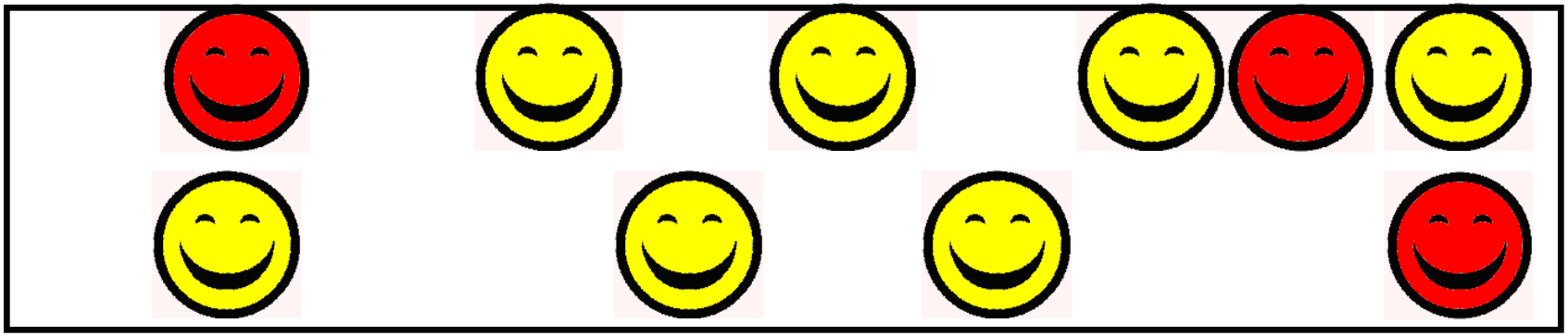
exposed

unexposed

Compare the odds of being exposed among cases and controls



a. Odds of being exposed (cases)= 7/3



b. Odds of being exposed (controls) = 3/7

c. Odds ratio = (7/3) / (3/7) = 5.44

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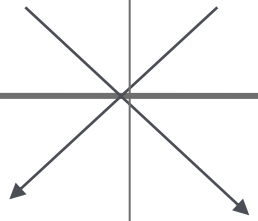
Alternative method for calculation of the odds ratio

	Exposed	Unexposed
Cases	a	b
Controls	c	d
	(a+c)	(b+d)



Odds ratio (OR)= (ad)/(cd)

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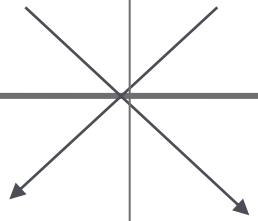
Alternative method for calculation of the odds ratio

	Exposed	Unexposed
Cases	7	3
Controls	3	7
	(a+c)	(b+d)



Odds ratio (OR)= (ad)/(cd)=(7*7)/(3*3)=5.44

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Interpretation of odds ratios

	OR<1	OR =1	OR>1
In terms of odds	Odds of exposure for cases are smaller than the odds of exposure for controls	Odds of exposure are equal among cases and controls	Odds of exposure for cases are greater than the odds of exposure for controls
In terms of disease risk	The exposure is associated with a decreased risk of the disease	The exposure is not associated with the disease	The exposure is associated with an increased risk

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Advantages and disadvantages of case-control studies

Advantages	Disadvantages
Good for rare diseases	Problems of selection of controls (Selection bias)
Quick and cost-efficient	Subject to recall bias
Can investigate many exposures simultaneously	Uncertainty of exposure-disease time relationship
	Poor for rare exposures
	Cannot calculate incidence rates directly

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Quiz :  if chacteristic of a case-control study

1. Suitable for studying rare diseases Case-control
2. Able to follow through the natural history of disease Cohort
3. Good design to look at risks related to rare exposures Cohort
4. Recall bias could be an issue Case-control
5. Incidence can be calculated Cohort
6. Well-suited to the evaluation of diseases with very long latency period Case-control

Recap: Learning outcomes

By the end of this lecture, you should be able to:

- Describe where cohort and case control studies fit in the hierarchy of epidemiological studies
- Distinguish and describe the design of case control and cohort studies by their core defining features
- List the strengths and weaknesses of cohort studies and case control studies

- To be able to calculate crude odds ratios and relative risks from a two-by-two table
- To be able to interpret odds ratios and relative risks

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Strenghts of case-control and cohort studies

Case-control study

- Quick, inexpensive
- Suitable for studying rare diseases
- Multiple risk factors for a disease can be studied
- Well-suited to the evaluation of diseases with very long latency period

Cohort study

- Able to look at multiple outcomes
- Able to follow through the natural history of disease
- Good design to look at risks related to rare exposures
- Incidence can be calculated
- Can minimise bias in estimating exposure if prospective

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Limitations of case-control and cohort studies

Case-control study

- Not suitable for studying rare exposures
- Incidence rates cannot be directly estimated
- Selection bias and recall bias

- *Note: associations expressed in terms of odds ratio, because incidence/rates/risks cannot be calculated*

Cohort study

- Inefficient for studying rare diseases
- Expensive and time consuming (if prospective)
- Loss to follow-up may introduce bias
- Healthy worker effect may cause bias in occupational cohorts

Confounding (mixing of effects between exposure, the disease and a third factor) may occur in both type of studies.

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Thank you!