بسم الله الرحمن الرحيم

Epidemiological and Research Studies

X

18-11-2024

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Analytical studies

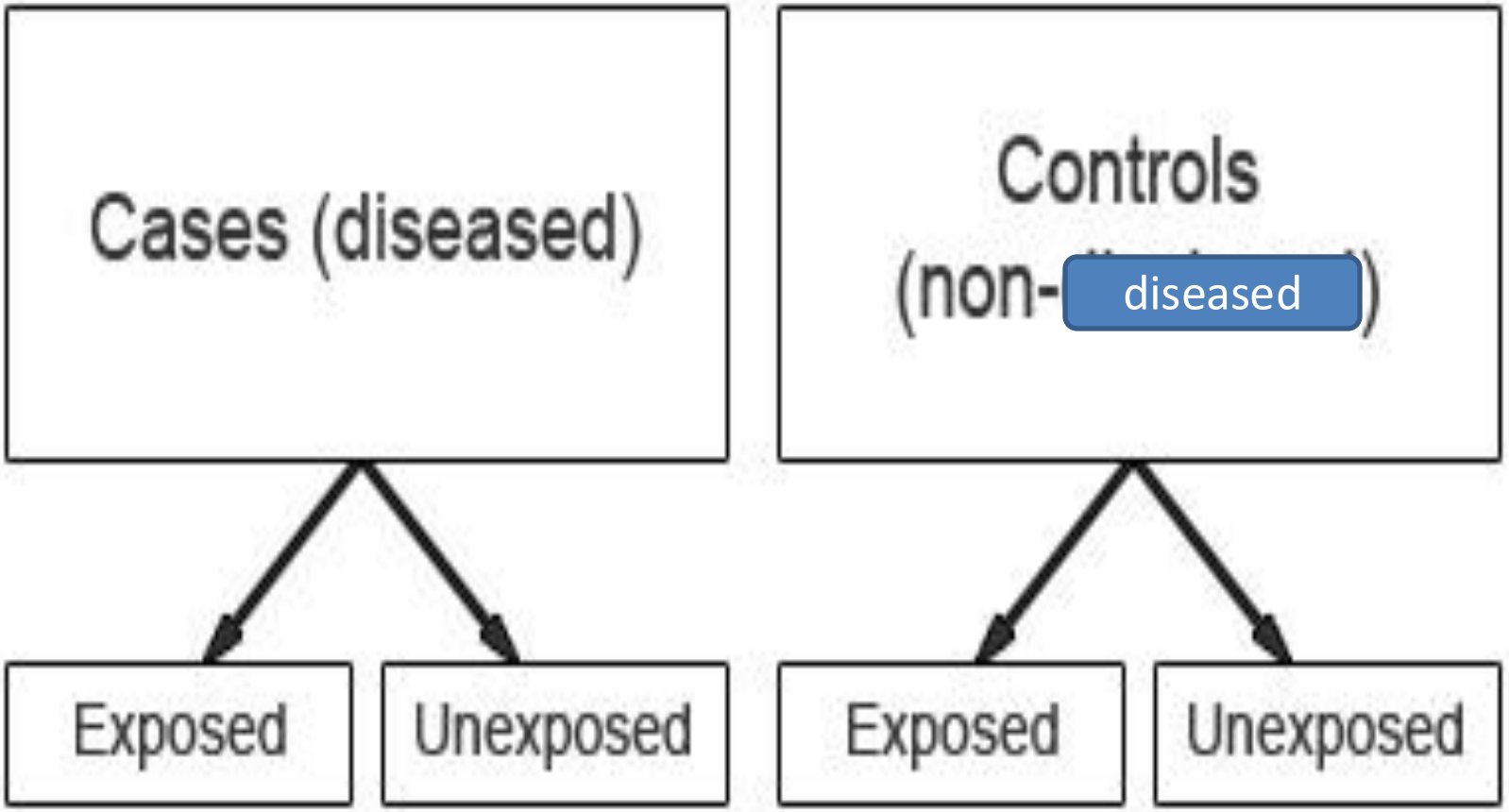
1. Cross-sectional
2. Case-control
3. Cohort

Case control Study

Issues in the design of case-control studies

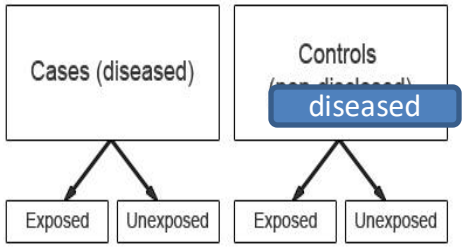
- Formulation of a clearly defined hypothesis
- Selection of cases
- Selection of controls
- Measuring exposure status

basic concepts,
application and
strengths of CCS
Issues in the design CCS
Common sources of bias in a CCS
Analysis of CCS
Strengths and weaknesses of CCS



case-control studies

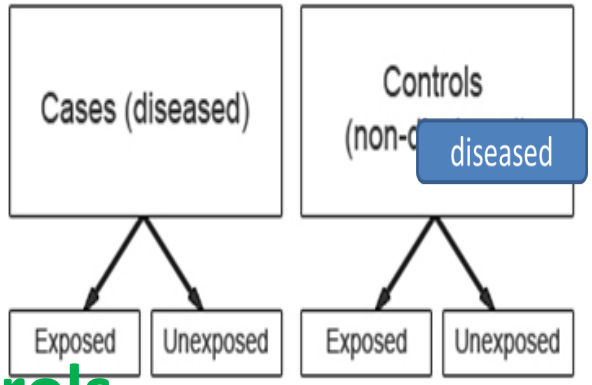
- **Case-control studies** are one of the frequently used study designs **due to the relative ease of its** application in **comparison with other** study designs



- **case-control studies (CCS)**
- **start with the identification of**
  - **a group of cases** (individuals with a particular health outcome) in a **given population**
  - **a group of controls** (individuals **without** the health outcome) to be included in the study.
  - **Then for each case and control it is determined whether they have been exposed to the factor understudy or not.**

Cont. ..CCS).

- In CCS the **prevalence of exposure** to a potential risk factor(s) is
  - **compared between cases and controls.**



- **If the prevalence of exposure** is
  - ✓ **more** common among **cases** than **controls,**
  - ✓ it **may be a risk factor for the outcome** under investigation.
- **A major characteristic of CCS is:**
  - **that data on potential risk factors are**
  - **collected retrospectively** and
  - ✓ as a result **may give rise to bias**
  - **This is a particular** problem associated with **case-control** studies and
    - **therefore needs to be carefully considered** during the **design and conduct of the study**

- CCSs are **longitudinal**, in contrast to cross-sectional studies.

- **CCSs** have been called **retrospective** studies **since the investigator is**
  - ✓ **looking backward from the disease to a possible cause.**

- ❖ The investigators collect **data on disease** occurrence **at**
- ❖ **one point in time**
- ❖ and **exposures** at a **previous point** in time.

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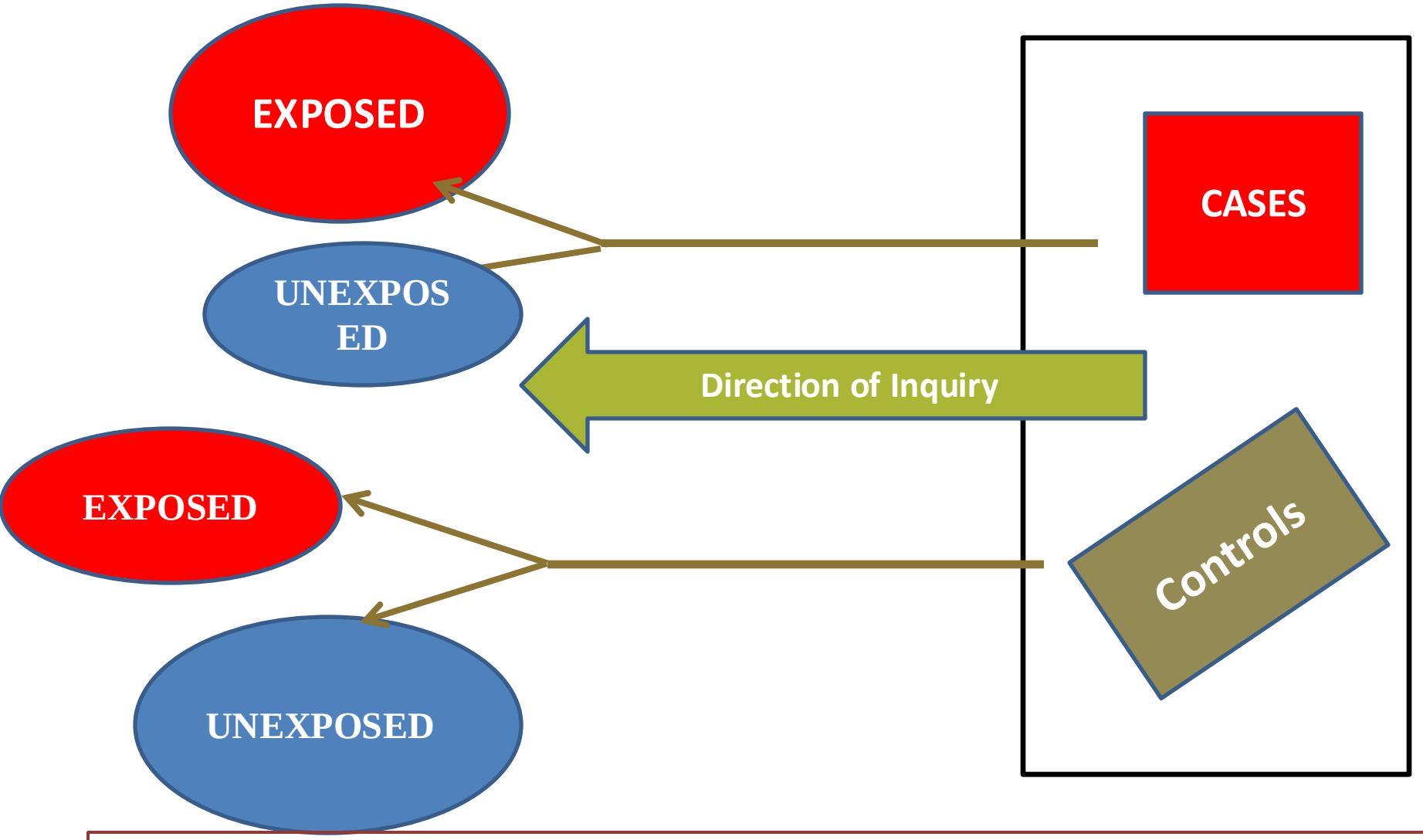
- ❖ Case-control studies provide a **relatively simple way to**
- ➢ **investigate causes of diseases**, especially **rare** diseases

Design of a Case-Control study



collect **data on disease** occurrence **at one point in time** and **exposures** at a **previous point** in time(**retrospectively**

Issues in the design of case-control studies

Formulation of a clearly defined hypothesis

- The **beginning** of a CCS should begin with the
- formulation of **a clearly defined hypothesis.**
- **Case definition** It is essential that the **case definition is clearly defined** at
- the outset of the investigation **to ensure that all cases included in the study are based on the same diagnostic criteria**

Source of cases

- The **source of** cases needs to be **clearly defined.**
- **Cases may be recruited from a number of sources**;
  - ✓ they may be recruited from a **hospital, clinic**, or may be **population bases**.
  - ✓ Population based case control studies are generally **more expensive and difficult to conduct**

Hepatitis C Virus Prevalence and Genotyping among Hepatocellular Carcinoma Patients in Baghdad

Waqar Abd Al Qahar Al-Kubaisy,Kadhim Jawad Obaid,Nor Aini Mohd Noor,Nik Shamsidah Binti Nik Ibrahim,Ahmed Albu-Kareem Al-Azawi

Hepatocellular carcinoma (HCC) is the third most common cause for cancer death in the world, now being especially linked to chronic hepatitis C virus (HCV) infection. This **case-control study consisting of 65 HCC patients and 82 patients with other malignant tumours as controls** was **conducted to determine the association of HCV markers with HCC**. Serum of each participant was obtained for detection of HCV Ab and RNA by DNA enzyme immunoassay (DEIA). Twenty six per cent (26.0%) of HCC patients had positive anti-HCV which was significantly greater than the control group (p=0.001). **HCC patients significantly have a risk** of **exposure to HCV infection almost 3 times** than the control group (**OR=2.87, 95**% C.I=1.1-7). Anti-HCV seropositive rate was significantly (p=0.03) higher among old age HCC patients and increases with age. Males with HCC significantly showed to have more than 9 times risk of exposure to HCV infection (OR=9.375, 95 % CI=1.299-67.647) than females. HCV-RNA seropositive rate was (70.8%) significantly higher among HCC patients compared to (22.2%) the control group (p=0.019). The most prevalent genotype (as a single or mixed pattern of infection) was HCV1b. This study detected a significantly higher HCV seropositive rate of antibodies and RNA in HCC patients.

The case group consisted of 65 patients, **histologically confirmed with HCC** and **a serum level of alpha-fetoprotein exceeding 400ng/ ml**, **while 82 patients with other malignant tumours (not related to gastro intestinal system)** were considered **as a control group**. **Four hospitals** namely Baghdad Teaching Hospital-Baghdad Medical City, Al Kadhmiya Teaching Hospital, Radiology and Nuclear Medicine Institute and Al Yarmuk General Teaching Hospital **were chosen for** data collection. **Only respondents with informed consent were interviewed** using a structured questionnaire and serum samples were taken for HCV markers analysis. **Patients with positive serum HBV were excluded** from this study. Serum sample of each participant was dispensed

Cont. **Selection of cases**

- CCS may use **incident** or **prevalent** cases.
  - **Incident cases** comprise **cases newly diagnosed during a defined time period**.
  - The **incident** cases is considered **as favored**,
  - as the **recall of past exposure(s) may be more accurate** among newly diagnosed cases. **In addition,**
  - **the temporal (time-based) sequence of exposure and disease is easier to assess among incident cases.**

- **Prevalent cases**
- comprise **individuals who have had the outcome**
- under investigation **for some time.**
- It may **give rise to recall bias as** prevalent cases may **be less likely to accurately** report past exposures(s).

Selection of controls

- A particular problem inherent in CCS is the selection of a comparable control group.
- **Controls are used to estimate the prevalence of exposure** in the population which gave rise to the cases.

➢ Therefore, **to minimize bias**, **the ideal control** group
➢ would comprise a random sample from the
➢ general population that gave rise to the cases.

❑ However, this is not always possible in practice.

- **The goal is to select individuals** in whom the distribution of exposure status would be the same as that of the cases in **the absence of an exposure** disease association.

Cont. …Selection of controls

- **The source of controls is dependent on the source of cases.**
- In **CCS where cases are hospital based**, it is common to recruit controls from **the hospital population**.
- However, the choice of controls from a hospital setting
- **should not include individuals with an outcome related to the exposure(s) being studied.**

For example, in a case-control study of the association between smoking and lung cancer the inclusion of controls being treated for a condition related to smoking (e.g. chronic bronchitis) may result in an underestimate of the strength of the association between exposure (smoking) and outcome.

- **Recruiting more than one control per case may improve the statistical** power of the study,
- though including **more than 4** controls per case is generally considered to be **no more efficient**.
- **Also**, the exposures of controls should be **measurable with similar accuracy** to those of the cases

Cont. .. Selection of controls

❑ Measuring exposure status

- ❖ Exposure status is measured **to assess** the
- ❖ **presence** or **level of exposure** for each individual **for**
- ➢ **the period of time prior to the onset of the disease** or condition under investigation when the exposure would
- ➢ have **acted as a causal factor**.
- ❖ Note **that in CCS** the **measurement** of **exposure is established after the development of disease** and as a result **is prone to both recall and observer bias.**

- ➢ **The procedures used for the collection of exposure**
- ➢ **Data should be the same for cases and controls.**

2. Common sources of bias in CCS

- Due to the **retrospective nature** of CCS, they **are**
- **particularly susceptible to the effects of bias,**
- **which may be introduced as a result of;**
  - **a poor study design** or
  - **during the collection of exposure and outcome data.**
- Because **the disease and exposure have already** occurred at the outset of a **CCS**, **there may be differential reporting of exposure information between cases and controls** based on their disease status. For example,
  - **cases and controls may recall past exposure differently (recall bias).** .
  - Similarly, **the recording of exposure information may vary depending on the investigator's knowledge** of an individual's disease status (**interviewer/observer bias**).

Therefore, the **design and conduct of the study** must be **carefully considered,** as there are limited options for the control of bias during the analysis

- **Selection bias in CCS Selection bias is** a particular problem inherent in case-control studies, where it gives **rise to non-comparability** between cases and controls.

Selection bias in CCS may occur when: ‘

- **cases (or controls**) are **included in (or excluded from**) a study because of **some characteristic they exhibit which is related to exposure to the risk factor under** evaluation'

.

- ✓ for **selection bias may be minimized** by selecting controls from **more than one source**

3. Analysis of case-control studies

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- The odds ratio (OR) is used in CCS
- to **estimate the strength of the association between exposure and outcome**.

*it is **not possible to estimate the incidence** of disease from a CCS*

The **OR is a measure of the odds of disease in the exposed compared to the odds of disease in the unexposed (controls)** and is **calculated as**:

$$OR = \frac{a/c}{b/d} = \frac{ad}{bc}$$

which is the ratio of the odds of exposure among the cases to the odds of exposure among the controls.

Results of a CCS can be presented in a 2x2 table

	Cases	Controls	Total
Exposed	a	b	a+b
Unexposed	c	d	c+d
Total	a+c	b+d	a+b+c+d

3. Analysis of case-control studies

RISK ESTIMATES(Odds ratio)

Odds ratio (OR)

- **Used in cross sectional, case-control**

Results of a case-control study can be presented in a **2x2 table** as follow

	Case (diseases)	control	Total
Exposed	a	b	a+b
Unexposed	c	d	c+d
Total	a+c	b+d	N

- **OR= a/(a+c) ÷ b/(b+d)= a/c ÷ b/d =ad/bc**

c/(a+c) d/(b+d)

which is the ratio of the odds of exposure among the cases to the odds of exposure among the controls.

3. Analysis of case-control studies

Example:

A case-control study was conducted to test the association between smoking and cancer of the pancreas of the 100 cases 60 of them were smokers , while of the 400 controls, 100 were smokers. Calculation of the OR from

Table 1. Hypothetical CCS of smoking and ca pancreas

Exposure	Cases	Control	Total
Smokers	60 (a)	100 (b)	160
Non Smokers	40 (c)	300 (d)	340
Total	100	400	500

$$OR = \frac{a/c}{b/d} = \frac{ad}{bc}$$

$$OR = \frac{60 \times 300}{100 \times 40}$$

$$OR = 4.5$$

The OR estimates that **cancer of the pancreas occurrence is 4.5 times more among smokers than non-smokers.**

NB: The odds ratio of smoking and cancer of the pancreas has been performed without **adjusting for potential confounders.**

4. Strengths and weaknesses of CCS

Strengths

- ✓ **Cost effective** relative to other analytical studies such as cohort studies.
- ✓ CCS are retrospective, and cases are identified at the beginning of the study; therefore **there is no long follow up** period (as compared to cohort studies)
- ▪ **Efficient** for the study of **diseases with long latency periods.**
- ✓ **Efficient** for the study of **rare diseases**
- ✓ Good for examining **multiple exposures.**

Weaknesses

- ➢ Particularly **prone to bias;** especially **selection**, **recall** and **observer bias**.
- ➢ CCS limited to **examining one outcome.**
- ➢ **Unable to estimate incidence rates** of disease
- ➢ **Poor** choice for the study of **rare exposures.**
- ➢ **The temporal sequence** between exposure and disease may be **difficult**
- ➢ **to determine.**

Thank you for attention

year 3 medical students

Epidemiological and Research Studies

Cohort Study

Cohort Study

begins with group of people free of disease & classified into subgroups
a group of individuals **exposed to a risk factor**
a group who are **unexposed to the risk** factor
are followed over time (often years)

Issues in the design of cohort studies understand the differences from a CCS,
*Potential bias in cohort studies
*Analysis of cohort studies
*calculate the basic measures (RR,AR
*appreciate its strengths and weaknesses.

Cohort Study

Also called: follow up study, or incidence studies,

Definition: Study in which persons,

- **based on their exposure to a determinant and**
- **free of the disease outcome at the start** of the study
- **are followed in time** to **assess the occurrence of the disease outcome**

- It begins with a group of people who **are free of disease**
- and who are **classified into subgroups according to exposure** to a **potential cause of disease or outcome**
- **Cases** are excluded at the beginning
- **Variables of interest are specified and measured** and the
- **whole cohort is followed up to see how the subsequent**
- **development of new cases of the disease** (or other outcome) **differs** between the groups
- **with** and **without exposure**

Cohort studies are a **form of longitudinal study** design that **flows from** the **exposure** **to** **outcome**.

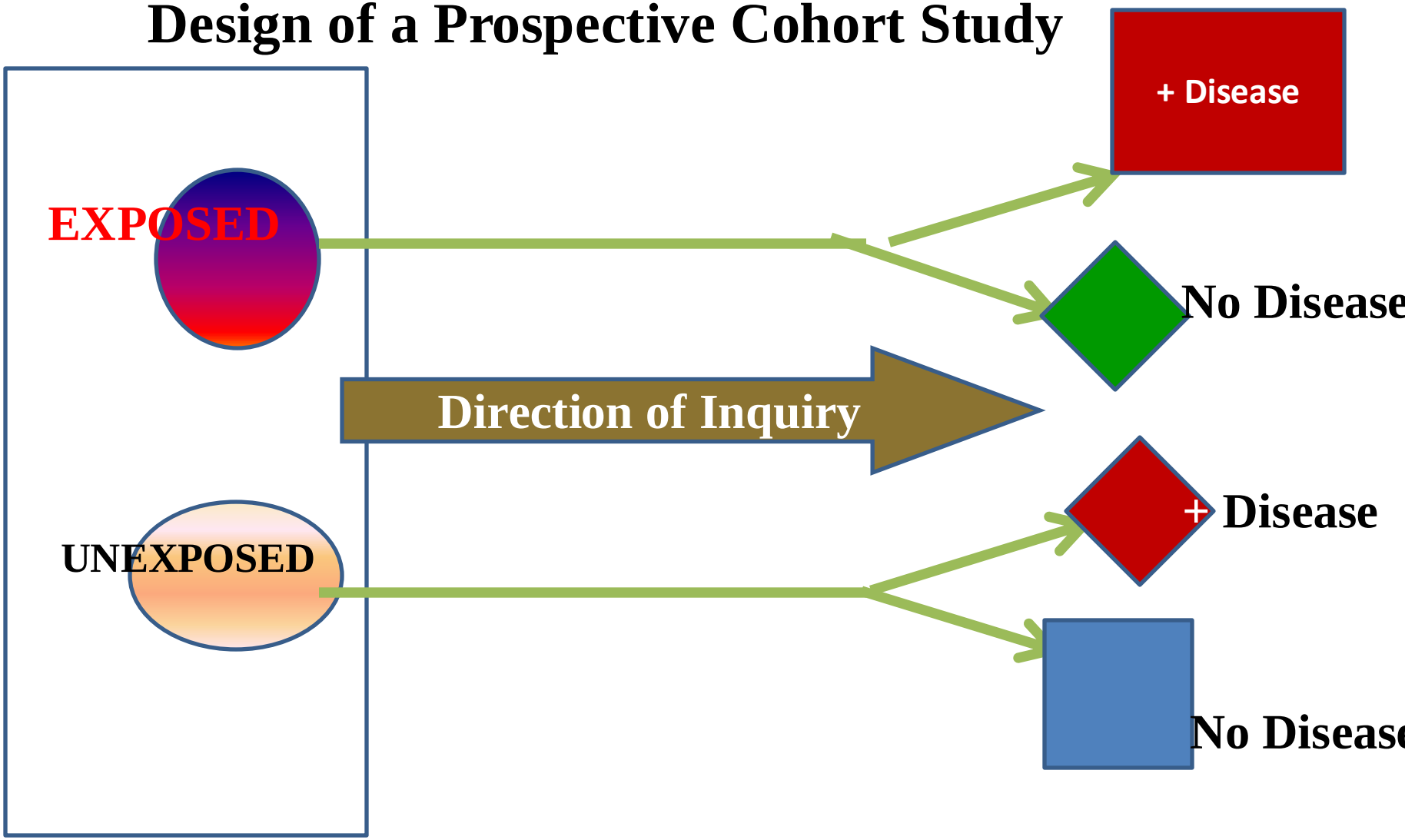
In a cohort study,

- **Group** of individuals **exposed to a putative risk factor**
- **Group** who are **unexposed to the risk** factor **are**

- **followed over time** (often years)
- **to determine the occurrence of disease**.
- The **incidence of disease**
- in the **exposed group** is **compared with** the
- **incidence** of disease in the **unexposed group**.

- Therefore **Relative risk (incidence risk or incidence rate)** is used **to assess whether the exposure and disease are causally linked**.
- **Cohort studies** be **prospective**

Design of a Prospective Cohort Study



It begins with group of people **free of disease** and **classified into subgroups**

a group of individuals **exposed to a risk factor**

a group who are **unexposed to the risk** factor

are followed over time (often years)

- **Cohort studies** be **prospective**
- **A prospective cohort** study is also called a
- **concurrent cohort study**,

where the **subjects have been followed up for a period and the outcomes of interest are recorded**

1. Issues in the design of cohort studies:

- **Selection of study groups**
- **Measuring exposure**
- **Measuring outcome**
- **Methods of follow-up**

*Issues in the design of cohort studies understand the differences from a CCS,
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- **Selection of study groups**

❖ The aim of a cohort study is to **select study participants who are identical with the exception**

❖ **of their exposure status**.

❖ **All study participants must be**

- **All study participants must be**
- **Free of the outcome under investigation and**
- **have the potential to develop the outcome** under investigation.

Measuring exposure

- **Levels of exposure** (e.g. packs of cigarettes smoked per year)are
  - **measured for each individual at baseline**
  - **at the beginning of** the study **and**
  - **Assessed at intervals during the period of follow-up.**
- **When several** exposures are being considered simultaneously, the **non-exposed group** should comprise all those with none of the risk factors under investigation.
- **A particular problem** occurring in cohort studies is **whether individuals in the control group are truly unexposed.**

For example, study participants may start smoking or they may fail to correctly recall past exposure.

❖ **Similarly**, those in the **exposed group** **may change** their **behavior in relation to** the exposure such as diet, smoking or alcohol consumption.

❑ **Exposure data may be obtained** from a number of sources including:

❑ **Medical** or **Employment records**, **standardized** questionnaires, interviews and by **physical examination**

❑Measuring outcome

❑ **Outcome measures may be obtained from various sources, including**

- **Directly from the participant**
- **Routine surveillance of cancer** registry data,
- **Death Certificates**, **Medical records**

❖ **Method used to ascertain outcome**

❖ **must be identical for both exposed and unexposed groups**

Issues in the design of cohort Selection of study groups
Measuring exposure
Measuring outcome
Methods of follow-up

❑ Methods of follow-up

❖ **The follow-up of study participants in a cohort study is a major challenge.**

- **A great deal of cost and time is required to ensure follow-up** of cohort members
- and to **update measures of exposures and confounders**,
- in addition to **monitoring participants' health outcomes**

The failure to collect outcome data for all members of the cohort will affect the validity of study results

- . .

1 Issues in the design of cohort studies understand the differences from a CCS,
2 Potential bias in cohort studies
3 Analysis of cohort studies
4 calculate the basic measures (relative risk, attributable risk etc
5 appreciate its strengths and weaknesses.

2- Potential sources of bias

A major source of potential bias in cohort studies is due to:

- **losses to follow-up.**
- **Cohort members may; die, Migrate, Change jobs or**
- **Refuse to continue to participate** in the study.

In addition, losses to follow-up **may be related to the**

- **exposure, outcome or both**. For example, individuals who develop the outcome may be less likely to continue to participate in the study.
- **The degree to which losses** to follow-up are correlated with exposure and outcome will **lead to serious bias** in the **measures of effect of exposure and outcome**

- **A major source of potential bias in cohort studies arises from**

- **The degree of accuracy with**

- **The degree of accuracy with which subjects have been classified with respect to their exposure or disease status.**
- **Differential misclassification can lead to an over or underestimate of the effect between exposure and outcome**

Analysis of cohort studies

- **Analysis of a cohort study uses either**
- **the risk or the rate ratio of disease in the exposed cohort**
- **compared with the rate or risk in the unexposed cohort.**

- **Risk estimates:**

To estimate risk of event to occur when exposed to a risk factor.

Relative risk (RR)

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

Exposure	+Ve Out com	no outcome	Total
positive	a	b	
Negative	c	d	
Total			

RR Used in cohort study

- **The risk is the relative incidence in the exposed and non exposed group**

Risk estimates

$$RR = \frac{\text{proportion of disease in exposed group}}{\text{proportion of disease in unexposed group}}$$

Example: A cohort study of smoking and cancer of the pancreas was conducted for 90,049 individuals and followed for 1 year. Consist of 27,042 smokers of them 42 were developed CA pancreas, while only 7 developed the CA pancreas among non smokers group . Is smoking is a risk factor for CA pancreas

Exposure	CA pancreas	no CA pancreas	Total
positive	a 42	b	27,042
Negative	C 7	d	
Total			90,049

	Cancer of the pancreas	No disease	Total	Incidence rate
Smokers	42	27,000	27,042	1.5/1000/yr
Non-smokers	7	63,000	63,007	0.1/1000/yr
Total	49	90,000	90,049	

the data, taken from a **cohort** study **to investigate the association between smoking and cancer of the pancreas,** the **relative and attributable risk** can be calculated as follows:

	Cancer of the pancreas	No disease	Total	Incidence rate
Smokers	42	27,000	27,042	1.5/1000/yr
Non-smokers	7	63,000	63,007	0.1/1000/yr
Total	49	90,000	90,049	

Rate Ratio = $\frac{\text{Incidence rate in exposed group (r1)}}{\text{Incidence rate in unexposed group (r0)}}$

RR = 1.5/0.1 = 15

The RR of 15 indicates that
the risk of cancer of the pancreas is 15 times higher among smokers than non-smokers.

4. Strengths and weaknesses of cohort studies

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understand the differences from a CCS,
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Strengths

- ✓ **Multiple outcomes** can be measured for any one exposure.
- ✓ **Can look at multiple exposures**.
- ✓ **Exposure is measured before the onset of disease**
- ✓ **Good for measuring rare exposures,** for example among different occupations.
- ✓ **Demonstrate direction of causality.**
- ✓ **Can measure incidence**

4. Strengths and weaknesses of cohort studies

Weaknesses

- Costly and time consuming.
- Prone to bias due to loss to follow-up.
- Prone to confounding.
- Participants may move between one exposure category
- Knowledge of exposure status may bias classification of the outcome.
- Being in the study may alter participant's behaviour.
- Poor choice for the study of a rare disease.
- **Classification of individuals (exposure or outcome status) can be affected by changes in diagnostic procedures.**

Thank you for attention

Qs ????