

Study Designs in Pharmacoepidemiology

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Overview of Scientific Methods

- The whole point of science is to uncover the truth.
- Two tools to peruse scientific inquiry:
 - Our senses - through which we experience the world and make observations
 - Our ability to reason - which enables us to make logical inferences

Scientific method Contd.

- In science we impose logic on observations
- There are two kinds of logic we impose: **deductive and inductive inferences**
- **Deductive inferences**: from the general (theory) to the specific, the observations
- **Inductive inferences**: we go from specific to the general. We make many observations, discern a pattern, make generalizations, and infer an explanation

Scientific method contd..

- The scientific methods from the perspective of inductive approach is a three-stage process:
 - In the first stage one studies a sample of study participants
 - Second, one generalizes the information obtained from this sample of study participants drawing a conclusion about a population in general
→ an association
 - Third, one establishes causation, making inferences

Cont'd

- There are four types of associations that may be observed in a study:
 - no association
 - artifactual association (false association due to either chance or bias)
 - indirect or confounded association
 - true, casual associations

Observed Association

- If an association is observed, the first question asked must always be ...

“Is it real?”

Cont'd

- Establishing associations requires hypothesis testing
- There are two types of hypothesis in the scientific investigation:
 1. null hypothesis $/H_0/$ and
 2. alternative hypothesis $/H_A/$
- The hypothesis we test statistically is called the null hypothesis

Cont'd

Example: suppose we are testing the efficacy of a new drug on patients with myocardial infarction.

1. We divide the patients in to two groups:
 drug and no drug
2. Measure mortality in the two groups
3. We say our hypothesis that the drug makes no difference and what we hope to do is to reject the 'no difference' hypothesis, based on evidence from our sample patients

Cont'd

4. We specify our test hypothesis as follows:

- H_0 (null hypothesis): death rate in group treated with Drug A = death rate in group treated with Drug B
- That is equivalent to say: H_0 : death rate in group A - death rate in group B = 0
- We test this against an alternate hypothesis known as H_A , the difference in death rate between the two groups does not equal to 0

Cont'd

- If the observed difference is sufficiently greater than zero difference, we reject the null hypothesis.
- If we reject the null hypothesis of no difference, we accept the alternate hypothesis
- We can never be certain that we are right in either accepting or rejecting a hypothesis

Guidelines for establishing causation

- The best known criteria for assessing causation were proposed in 1965 by Sir Austin Bradford Hill :
- Hill's criteria or more appropriately termed as guidelines.

1. Consistency

- Repeated observation of an association in studies conducted on different populations under different circumstances
- If studies conducted by....
 - different researchers
 - at different times
 - in different settings
 - on different populations
 - using different study designs.....all produce consistent results, this strengthens the argument for causation
- *e.g.* The association between cigarette smoking and lung cancer has been consistently demonstrated in a number of different types of epidemiological study (ecological, case-control, cohort)

2. Strength of the association

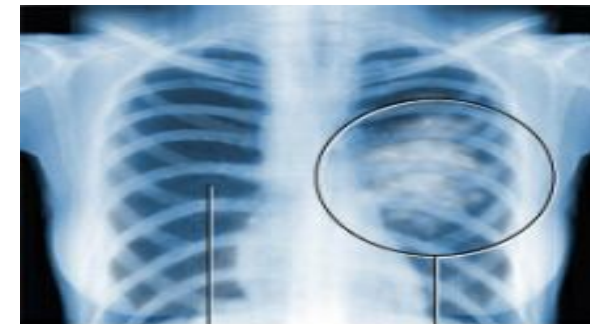
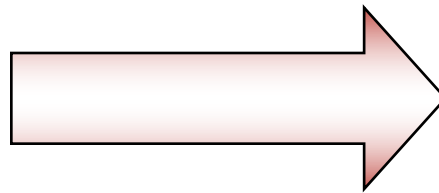
- "Measures of association"
 - used to quantify the strength of the association between an exposure and outcome
 - *e.g.* Relative risk, odds ratio
- Strong associations are more likely to be causal than weak associations
 - The larger the relative risk (RR) or odds ratio (OR), the greater the likelihood that the relationship is causal
- Weak associations are more likely to be explained by undetected biases or confounders

Strength of the association

- How large must a relative risk or odds ratio be to be considered 'strong':
 - 2 ? 4 ? 20 ??
- No universal agreement regarding what constitutes a 'strong' or 'weak' association
 - An OR or RR > 2.0 is 'moderately strong'
 - An OR or RR > 5.0 is 'strong'
- The relationship between smoking and lung cancer is an excellent example of a 'strong association'
 - odds ratios and relative risks in different studies are in the 4 to 20 range

3. Temporality

- This refers to the necessity for the exposure to precede the outcome (effect) in time
- Any claim of causation must involve the cause preceding in time the presumed effect
- Easier to establish in certain study designs
 - Prospective cohort study



Exposure

TIME

Normal
lung

Cancer

Outcome



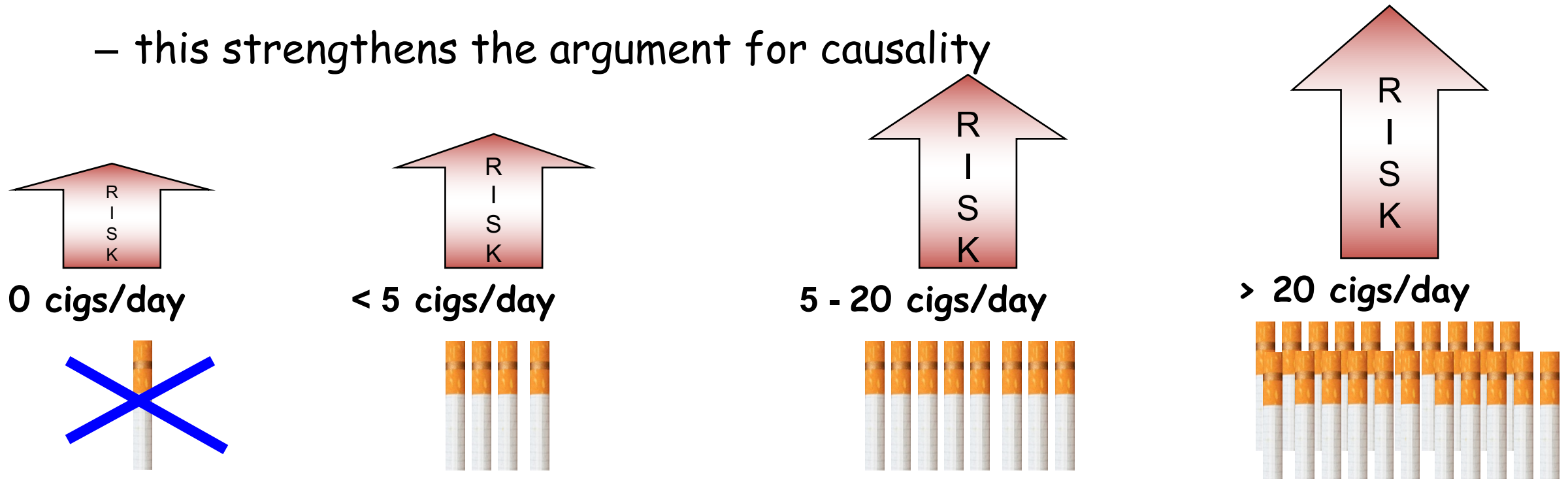
Temporality

- This refers to the necessity for the exposure to precede the outcome (effect) in time
- Any claim of causation must involve the cause preceding in time the presumed effect
- Easier to establish in certain study designs
 - Prospective cohort study
- Lack of temporality rules out causality

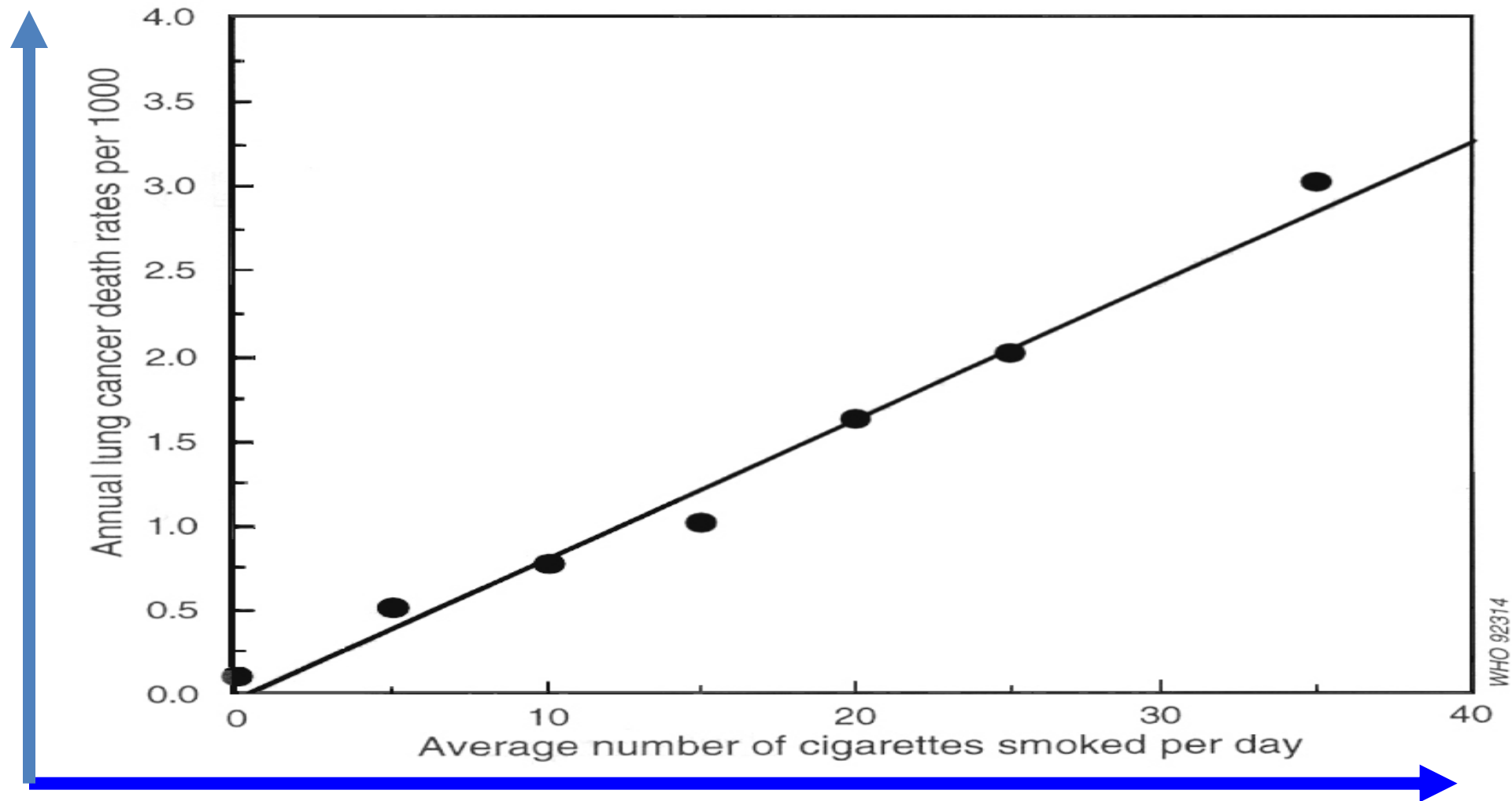


4. Dose-response relationship

- Dose-response ('biological gradient')
 - the relationship between the amount of exposure (dose) to a substance and the resulting changes in outcome (response)
- If an increase in the level of exposure increases the risk of the outcome
 - this strengthens the argument for causality



Death rates from lung cancer (per 1000) by number of cigarettes smoked, British doctors, 1951–1961



5. Biological Plausibility

- Plausibility refers to the biological plausibility of the hypothesized causal relationship between the exposure and the outcome
 - *Is there a logical and plausible biological mechanism to explain the relationship?*
- Biological plausibility is not a particularly useful viewpoint for assessing a causal relationship

6. STUDY DESIGN

Relative ability of different types of study to 'prove' causation

NB: Assuming study well-designed & conducted & bias etc. minimised

| Type of Study | Ability to 'prove' causation |
|--------------------------------|------------------------------|
| 1) Randomised Controlled Trial | STRONG |
| 2) Cohort Study | Moderate |
| 3) Case-control study | Moderate |
| 4) Cross-sectional study | WEAK |
| 5) Ecological study | WEAK |

Cont'd

7. Reversibility:

- Does the removal of a possible cause lead to reduction of disease risk?

8. Specificity of association:

- Certain exposure should be associated with single exposure
- Weakest of all criteria
- Considered as an additional support if others hold true.

Is this association causal?

Does consumption of French fries by preschool children cause breast cancer?

Strength

Consistency

Temporality

Dose response

Biological plausibility

Study design

Children who eat fries raise breast cancer risk

Frequent servings at ages 3-5 increased later chance of disease in study

REUTERS

Updated: 6:25 p.m. ET Aug. 18, 2005

WASHINGTON - Very young children who eat French fries frequently have a much higher risk of breast cancer as adults, U.S. researchers reported.

A study of American nurses found that one additional serving of fries per week at ages three to five increased breast cancer risk by 27 percent.

"Researchers are finding more evidence that diet early in life could play a role in the development of



Is this association causal?

Does consumption of French fries by preschool children cause breast cancer?

Strength

Weak: OR = 1.27

Consistency

No

Temporality

Yes

Dose response

No

Biological plausibility

Yes

Study design

Case Control

Is this association causal?

Is this association causal?

| | |
|--|-----------------|
| Does consumption of French fries by pregnant women increase the risk of childhood breast cancer? | |
| Strength | Weak: OR = 1.27 |
| Consistency | No |
| Temporality | Yes |
| Dose response | No |
| Biological plausibility | Yes |
| Study design | Case Control |

Is this association causal?

Is this association causal?

Does cigarette smoking cause lung cancer?

Strength

Strong: OR, RR = 4 - 20

Consistency

Yes

Temporality

Yes

Dose response

Yes

Biological plausibility

Yes

Study design

Ecological, C/S, CC, Cohort

Is this association causal?

Is this association causal?

Does cigarette smoking cause lung cancer?

Strength

Strong: RR = 20

Consistency

Yes

Temporality

Yes

Dose response

Yes

Biological plausibility

Yes

Study design

Ecological, C/S, CC, Cohort

yes

Is this association causal?

When using them, don't forget Hill's advice:

- None of these nine viewpoints can bring indisputable evidence for or against a cause and effect hypothesis What they can do, with greater or less strength, is to help answer the fundamental question—is there any other way of explaining the set of facts before us, is there any other answer equally, or more, likely than cause and effect?" (Cited in Doll, 1991).

Error in Pharmacoepidemiology

- ✓ An epidemiologic study is properly viewed as an exercise in measurement with accuracy as the goal.
- ✓ Accuracy is the absence of both systematic and random error.
- ✓ The great challenge of pharmacoepidemiology is to obtain an accurate estimate of the relationship between drug exposure and health status.

Types of Bias

- Selection bias
- Information bias
- Confounding

Selection bias

- A method of participant selection that distorts the exposure - outcome relationships from that present in the target population.
- Occur when the selection of participants in one group results in a different outcome than the selection from the other

Examples of Selection Bias

- Select volunteers as exposed group and non-volunteers as non-exposed group in a study of screening effectiveness
 - Volunteers could be more health conscious than non-volunteers, thus resulting in less disease
 - Volunteers could also be at higher risk, such as having a family history of illness, thus resulting in more disease
- Study health of workers in a workplace exposed to some occupational exposures comparing to health of general population
 - Working individuals are likely to be healthier than general population that includes unemployed people (Healthy Worker Effect)
- Use prevalent cases instead of incidence cases

Controlling Selection Bias

- Define criteria of selection of diseased and non-diseased participants independent of exposures in a case-control study
- Define criteria of selection of exposed and non-exposed participants independent of disease outcomes in a cohort study
- Use randomized clinical trials

Information Bias

- **Information bias** occurs when information is collected differently between two groups, leading to an error in the conclusion of the association
- When information is incorrect, there is misclassification
 - **Differential misclassification** occurs when the level of misclassification differs between the two groups
 - **Non-differential misclassification** occurs when the level of misclassification does not differ between the two groups

Sources of Information Bias

- Subject variation
- Observer variation
- Deficiency of Tools
- Technical Errors in Measurement

Examples of Information Bias

- **Interviewer** knows the status of the subjects before the interview process
 - Interviewer may probe differently about exposures in the past if he or she knows the subjects as cases
- Subjects may **recall** past exposure better or in more detail if he or she has the disease (recall bias)
- **Surrogates**, such as relatives, provide exposure information for dead cases, but **living controls** provide exposure information themselves

Controlling Information Bias

- Have a standardized protocol for data collection
- Make sure sources and methods of data collection are similar for all study groups
- Make sure interviewers and study personnel are unaware of exposure/disease status
- Adapt a strategy to assess potential information bias

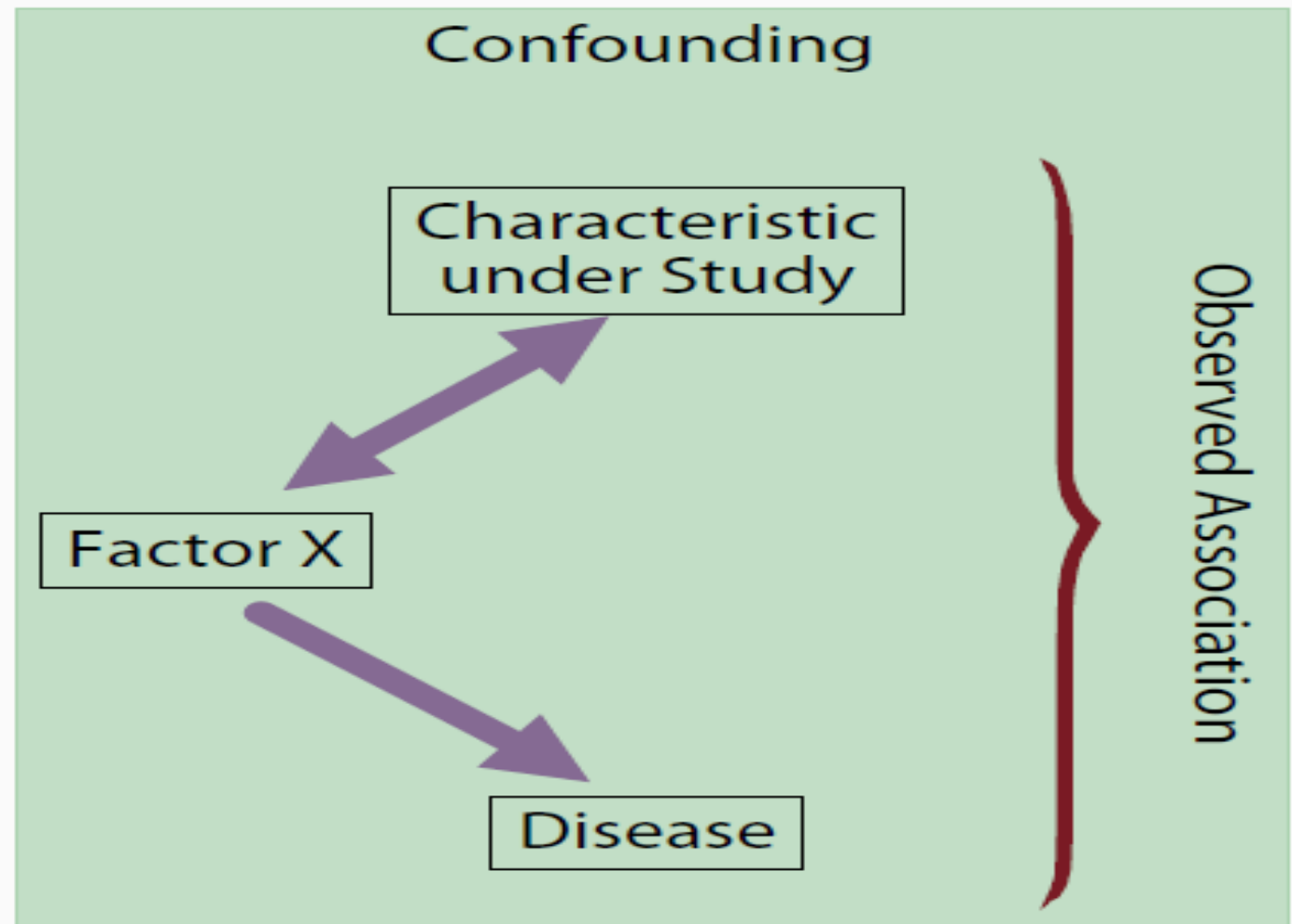
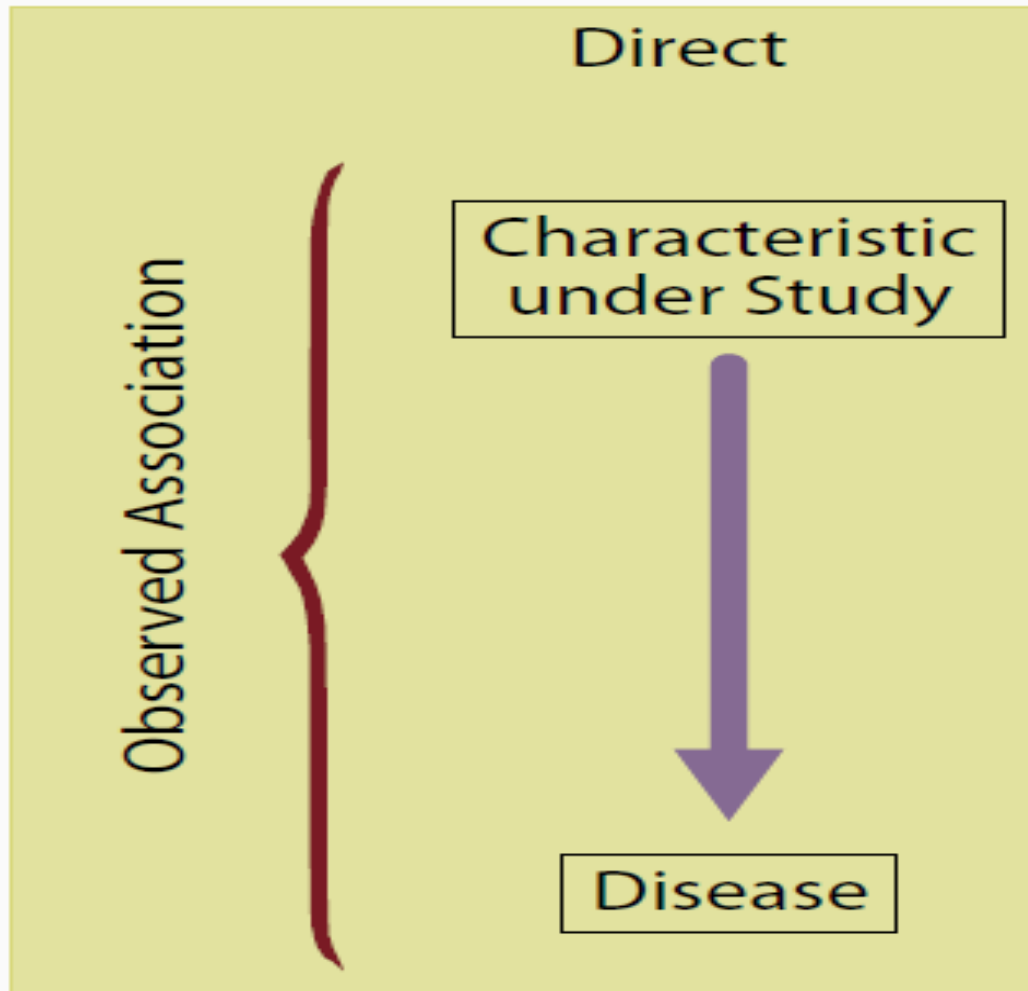
Confounding

- **Confounding** occurs when the observed result between exposure and disease differs from the truth because of the influence of the third variable
- For example, crude mortality rate (crude effect) of City A differs from the rate of City B—**but** after adjusting for age, the adjusted rates do not differ
 - Age distribution differs between the two cities
 - ▶ Age confounds the association

Bias and Confounding

- **Bias** is a systematic error in a study and cannot be fixed
- Confounding may lead to errors in the conclusion of a study, but, when confounding variables are known, the effect may be fixed

Types of Statistical Associations



Confounding

- Effect of a factor of interest is mingled with (confounded with) that of another factor
- Confounding is a situation in which a measure of the effect of an exposure is distorted because of the association of exposure with other factor(s) that influence the outcome under study
- Confounding occurs where an apparent association between a presumed exposure and an outcome is in fact accounted for by a third variable not in the postulated causal pathway; such a variable must be itself associated with both presumed exposure and outcome

Confounding

- In a study of whether Factor A is a risk factor for Disease B, X is a **confounder** if:
 1. It is a risk factor for Disease B
 2. It is associated with Factor A (but is not a result of exposure to factor A)

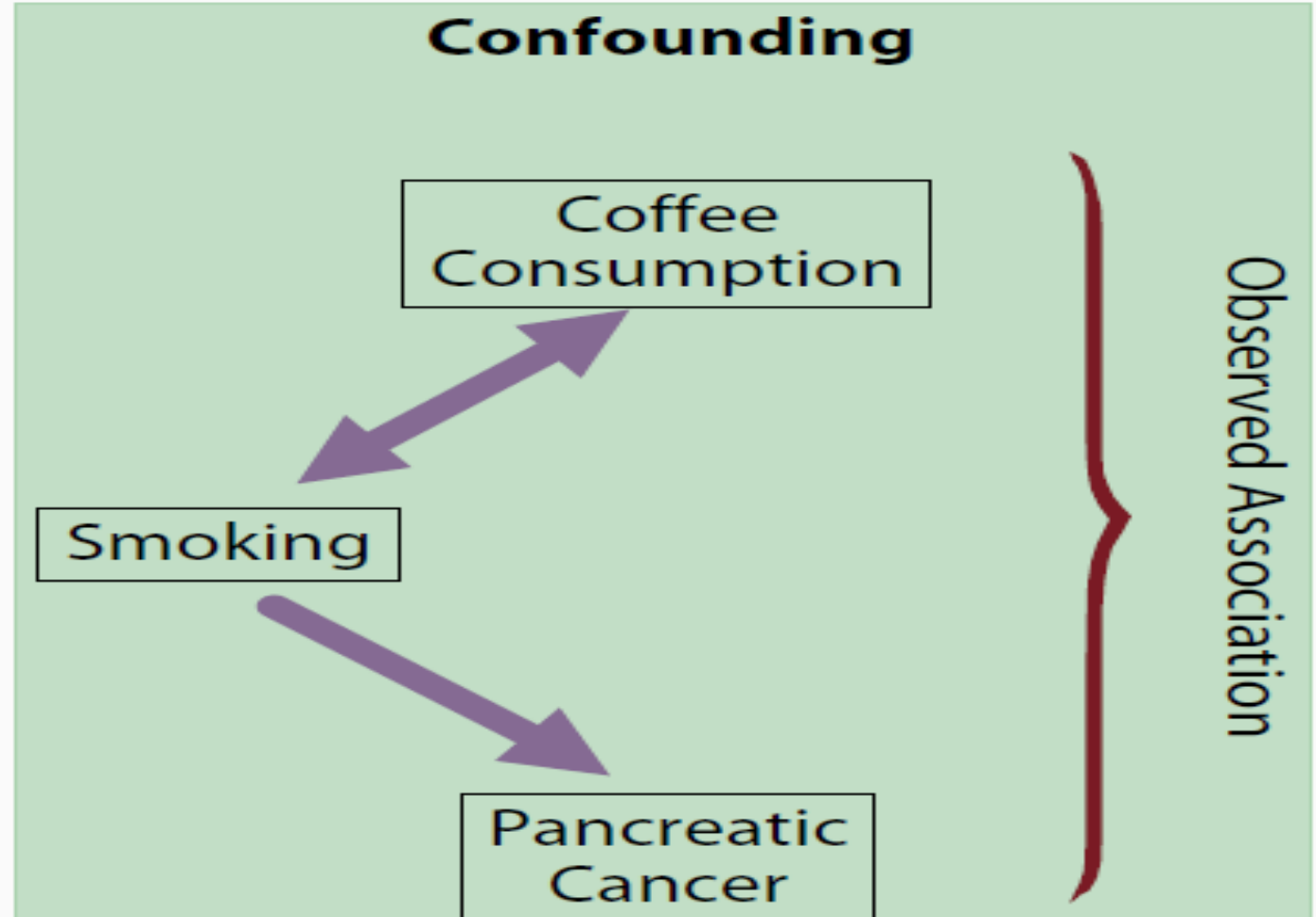
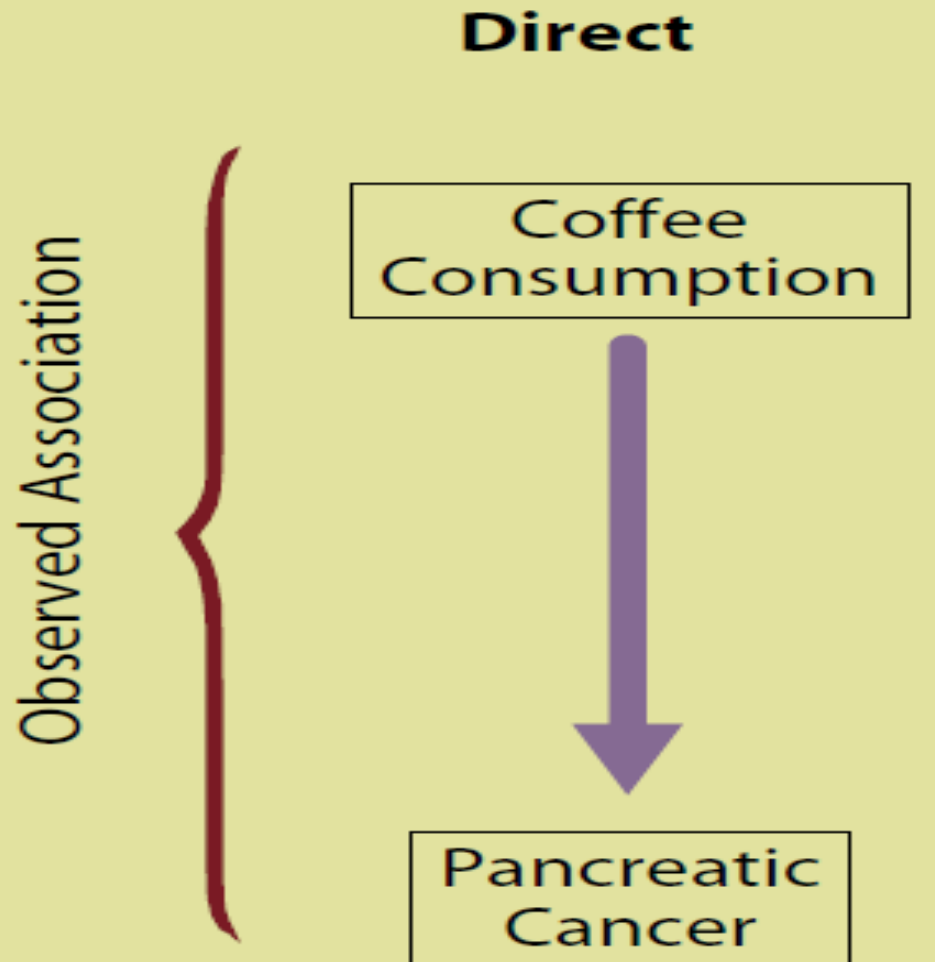
Example of Confounding: Pancreatic Cancer Study

- In the study of whether coffee consumption is a risk factor for pancreatic cancer, smoking is a **confounder** if:
 1. It is a known risk factor for pancreatic cancer
 2. It is associated with coffee drinking but is not a result of coffee drinking

Examples ... confounding



Types of Statistical Associations: Coffee Consumption and Pancreatic Cancer



Methods used to control for confounding

✓ In the design stage:

- ❖ **Randomization** - applicable only to experimental studies
- ❖ **Restriction** - can limit the study to people who have particular characteristics
- ❖ **Matching**
 - ❖ *Group matching*: selecting controls in such a manner that the proportion of controls with a certain characteristics is identical to the proportion of cases with the same characteristics
 - ❖ *Individual matching*: for each case selected , control is selected who is similar to the case in terms of the specific variable of concern

Cont'd

- We control confounding at the analysis stage by:
 - **Stratification:** which involves the measurement of strength of associations in well defined and homogenous categories (strata) of the confounding variable.
 - **Statistical modeling (regression):** multivariate model controls a number of confounding variables simultaneously.

Consequences of Making Errors

CAUTION

Type I Errors vs. Type II Errors

Type I Error (false positive): Concluding there is a difference between the groups being studied when, in fact, there is no difference.

Type II Error (false negative): Concluding there is no difference between the groups being studied when, in fact, there is a difference.

Type I and Type II errors can be illustrated using the following table:

| Researcher's Conclusion | Actual Results | |
|-------------------------|------------------|------------------|
| | Difference | No Difference |
| Difference | Correct decision | Type I error |
| No difference | Type II error | Correct decision |

Cont'd

Actions to be taken based on decisions:

1. If we believe the null hypothesis (i.e., fail to reject it) we will not use the drug

→ **Consequence of wrong decision:** type II error. Since in reality the drug is beneficial, by withholding it, we will allow patients to die who might otherwise have survived.

Cont'd

2. If we reject null hypothesis in favor of the alternative hypothesis we will use the drug

→ **Consequence of wrong decision:** type I error. We will use the drug but the patient don't benefit. Presuming the drug is not harmful in itself, we don not directly hurt the patients but since we think that we have found the cure, we may no longer test other drugs

Study Designs

- A careful examination of a phenomenon; implies sound methods of scientific investigation

Study Designs

- The rules that govern the process of collecting and arranging the data for analysis.
- It is a formal approach to scientific or scholarly investigation.

Study Designs

- Generation of hypothesis may come from anecdotal observations;
- while testing of those hypothesis must be done by making controlled observations, free of systematic bias
- Statistical techniques to be valid must be applied to data obtained from well-designed studies

- two general types of study designs:

1. Observational studies:

- nature determines who is exposed to the factor of interest and who is not exposed.
- These studies demonstrate association

2. Experimental studies

- the investigator determines who is exposed
- These may prove causation

Observational studies

- Most common approach in pharmacoepidemiology for testing hypothesis
- The investigator can only observe the occurrence of disease in people who already segregated in to groups on the basis of some exposure
- Are of two types: **descriptive and analytical**

Descriptive studies:

- not aimed specifically to test hypothesis
- allows the generation of hypothesis, which can be tested by analytical or experimental design
- Characterize the occurrence and distribution of problems by time, place and person

Types of descriptive studies:

➤ 5 types

a. Case report:

Case reports are reports of events observed in single patients.

- Example: a published case report about a young woman who was taking oral contraceptives and who suffered a pulmonary embolism.

b. Case series:

- Case series are collections of patients, all of whom have a single exposure, whose clinical outcomes are then evaluated and described.
- Alternatively case series can be collections of patients with a single outcome, looking at their antecedent exposures.

- ✓ Used to generate hypothesis

Example: In 1940's Alton Ochsner, USA, observed that virtually all of the patients of whom he was operating for lung cancer gave history of cigarette smoking.

- ✓ Based on his case series observations, he hypothesized that cigarette smoking is linked with lung cancer

c. Ecological descriptive studies

- the unit of measurement is an aggregate (e.g., family, clan, or school) or an ecological unit (a village, town or country)
- Do not provide individual data

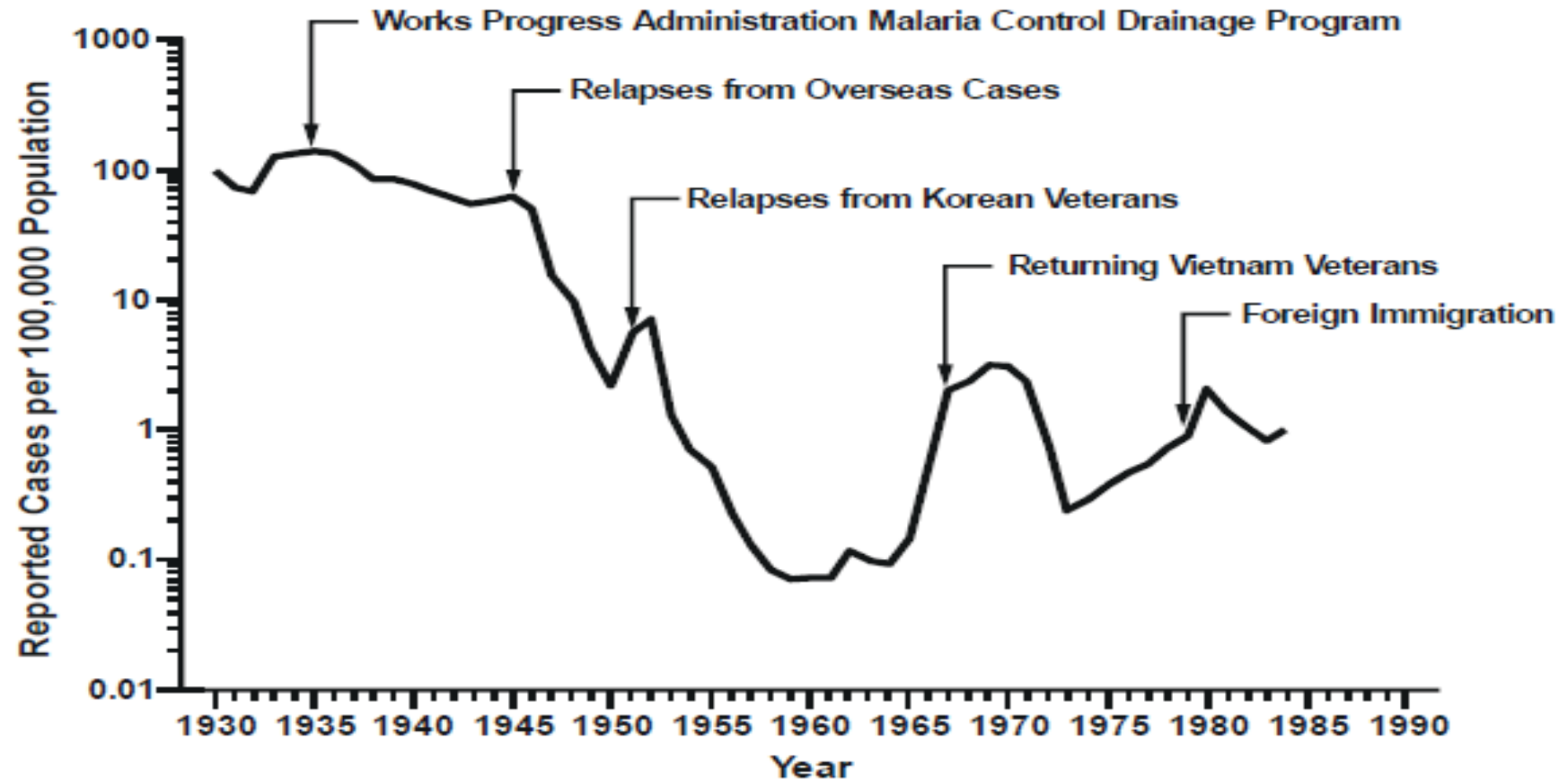
Examples:

1. Hypertension rates and average per capita salt consumption compared between two communities.
2. Mortality from CHD in relation to per capita cigarette sales among the regions of Ethiopia.

Ecological studies

- Cross-sectional ecological studies
- Longitudinal ecological studies
 - On going surveillance or frequent cross-sectional studies to measure trends in disease rates over many years in a defined population.
 - By comparing the trends in disease rates with other changes in the society. E.g. war, immigration, introduction of vaccines etc.

Figure 5.3
Malaria by year of report, United States, 1930-1990



Original article

International comparisons of prostate cancer mortality rates with dietary practices and sunlight levels

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Abstract

Prostate cancer mortality rates vary widely across the world. The purpose of this study is to identify environmental factors associated with prostate cancer mortality risk. Prostate cancer mortality rates in 71 countries were compared to per capita food intake rates using age-adjusted cancer rates (year 2000) from the International Agency for Research on Cancer, and food consumption data (1990–1992) provided by the Food and Agricultural Organization of the United Nations. Simple regression models were applied to prostate cancer mortality rates and consumption rates for 38 foods (or food categories), and sunlight levels (latitude from the equator and ultraviolet indexes). The analysis found a correlation between increased prostate cancer mortality rates and the consumption of total animal calories, total animal fat calories, meat, animal fat, milk, sugar, alcoholic beverages, and stimulants. The consumption of cereal grains and rice, in particular, correlated strongly with decreasing prostate cancer mortality. The analysis found that increased sunlight levels and consumption of oilseeds, soybeans, and onions also correlate with decreased prostate cancer mortality risk. Stepwise multiple regression analysis was used to build a regression model with minimum colinearity between the variables. Cereals, total animal fat calories, sugar, and onions are the foods that resulted in a model with the best fit. Cereals, ultraviolet index, sugar, and onions were the variables found to provide the best fit in a model when ambient sunlight exposure was included as a factor. © 2006 Elsevier Inc. All rights reserved.

Keywords: Prostate cancer; Epidemiology; Cancer prevention; Diet; Sunlight; International

Ecological fallacy

- Relate the frequency with which some characteristic (e.g., smoking) and some outcome (e.g., lung cancer) occur in the same geographic area.
- There is no information as to whether the people who smoked are the same people who developed lung cancer

d. Cross-sectional studies or community /population surveys

- Entail the collection of data on a cross-section of the population
- Most cross-sectional studies do not aim at testing a hypothesis about an association and are thus descriptive

- They provide a prevalence rate at a particular point in time (point prevalence) or over a period of time (period prevalence)
- This design may also be used in health systems research to describe 'prevalence' by certain characteristics- patterns of health service utilization and compliance or in opinion surveys

Advantages and disadvantages of cross-sectional studies

Advantages

They are relatively quick and inexpensive

Often a good step for cohort study

Provide prevalence information

Can study several factors or outcomes at one time?

Often provide early clues for hypothesis generation

Disadvantages

Does not allow the true temporal sequence of exposure and outcome

Potential bias - Neyman (late look) in surveys and Length bias in screening programs

Potential sampling bias

Not feasible for rare conditions

Cont'd

Prevalence per 1,000 =

$$\frac{\text{No. of cases of a disease present in the population at a specified time}}{\text{No. of persons in the population at that specified time}} \times 1,000$$

Incidence rate per 1,000 =

$$\frac{\text{Number of NEW cases of a disease occurring in a population during a specified period of time}}{\text{Total person-time (The sum of the time periods of observation of each person who has been observed for all or part of the entire time period)}} \times 1,000$$

Example 1

- The population of the city of Atlantis on March 30, 2012 was 183,000
- Number of new active cases of TB occurring between January 1 and June 30, 2012 = 26
- Number of active TB cases according to the city register on June 30, 2012 = 264
- Calculate incidence and prevalence of TB?
- Incidence 14 per 100,000 population
- prevalence 144 per 100,000 population

Example 2

- Questionnaires were mailed to every 10th person listed in the city telephone directory. Each person was asked to provide his or her age, sex and smoking habits and presence of any respiratory symptoms during the preceding seven days: this is an example what type of study design?
- **Descriptive cross sectional**

e. Trend studies:

- Data may be collected at different points in time and changes in the pattern are analyzed
- Though different study participants are studied at each time, each sample can represent the same type of population

- Often involves a long period of data collection
- In most cases, one researcher does not personally collect that data used in trend study
- but instead conduct a secondary analysis of data collected overtime by several others or routinely collected data

Analytical studies

- Observational studies, where the primary goal of a study is establishing a relationship (association) between a risk factor and an outcome
- Always require a comparison group
- Are of two types: **case control and cohort studies**

Case control studies

- are studies that compare cases /with a disease/ to controls /without the disease/, looking for differences in antecedent exposures.
- Obtain their information on exposures retrospectively by taking a history and/or from records
- Most commonly used analytical strategy in epidemiology
- More appropriate in clinical setting
- It is relatively simple except that it is backward looking

Cont'd

- Efficient for rare diseases, because all cases that fit the study criteria in a particular setting within a specific period are usually included

Example: Oral contraceptive for venous thromboembolism...

basic design concepts:

- The first step in case control study is to detect a number of people with the disease under study: **the cases**
- Then select the number of people who are free of the disease: **the controls**
- The cases and controls are then investigated to see which risk factors differ between them
- A higher frequency of risk factor among cases than among controls is indicative of its association that may be of etiological significance

Selection of cases

- Cases identified for case-control studies are often those from
 - hospital setting,
 - physicians' private practices or
 - disease registries


Cont'd

Selection of controls

- Four general principles :
 - Controls should be drawn from amongst those who are free of the disease being studied
 - Usually we would exempt anyone who, although disease - free now has had the disease in the past

Cont'd

- Controls should be drawn from the same general population that gave rise to the cases.

 to protect against the possible distorting effects of unknown, or unmeasured, confounders and effect modifiers

- Controls should have some potential for the disease. ??
- Controls are drawn from the same source (such as the same hospital) as were the cases or from the community served by the same medical services

Cont'd

Hospital controls

- Are convenient and cheap sources of controls, especially in situations where a clinical procedure such as blood sample is required to measure the risk factor
 - Their medical data are likely to be of comparable quality to those from cases and may have been collected prior to classification as controls
- remove the possibility of observer bias

Cont'd

- There is good chance that their quality of recall will also be similar to that of the cases, since they are in the same environment
- As with the cases, they are likely to be thinking about the antecedents of their disease and they are likely to be cooperative, especially as they have time to spare

Sources of Control

| | | |
|---|--|--|
| Hospital | <ul style="list-style-type: none"> • Easily identified, sufficient number, low cost • Quality of recall • More likely to cooperate thereby minimizing potential bias from nonresponse | <ul style="list-style-type: none"> • Differ from the general population such that they do not accurately represent the exposure distribution in a population where cases were obtained. |
| General Population | <ul style="list-style-type: none"> • Represent the population from which cases were selected | <ul style="list-style-type: none"> • Costly and time consuming • Sampling may be difficult • Poor recall • Less motivated • Less cooperative |
| Special groups (family, relatives, friends) | <ul style="list-style-type: none"> • Healthier than hospital controls • More likely cooperative • Provide more control over possible confounding factors | <ul style="list-style-type: none"> • If exposure is similar to the one experienced by cases, an underestimation of the true association would result |

Cont'd

- One disadvantage with hospital controls is that the risk factor for the study disease may also be a risk factor for the condition that a particular control has, this condition being the cause of his/her hospitalization.
- This may result in the following scenario:
the probability of the risk among control is greater than the probability of the risk among un diseased ($P_{\text{control}} > P_{\text{un diseased}}$) or the reverse

Cont'd

- **Example:** in studying the role of Aspirin in MI, if our controls are with large numbers of those who suffer from arthritis then would expect many of them to take Aspirin to alleviate pain.
- Hence when we consider lack of Aspirin as the risk factor for MI, $P_{\text{control}} < P_{\text{un diseased}}$ (we have bias in the direction contrary to the risk factor)

Cont'd

Community controls

- Controls drawn from the community have the great advantage of being drawn directly from the true population of without the disease
- Assuming they are drawn randomly, they provide a valid for the estimation of attributable risk when the disease is rare
- The disadvantage with random community control is they are inconvenient to capture and their data are inferior in quality
- Random sampling requires a sampling frame, which may be difficult to obtain
- Locating and visiting selected controls at home may be expensive and time consuming

Cont'd

Other sources

- These include medical system other than hospitals and special group in the community who have some relation to cases such as friends, neighbors and relatives
- Special community controls have the advantage of not requiring a sampling frame, although neighborhood controls may be difficult to obtain due to non-response within a limited population
- Friends and relatives are unlikely to refuse to cooperate and so are easy and cheap to identify and to obtain

Cont'd

- How many controls do we need?
 - Increase in number of controls will definitely increase precision in estimates and tests
 - Economic and time consideration is very important
 - Extra precision will be subject to the law of diminishing returns
 - Rarely will it be worth having a case: control ratio of above 1:4

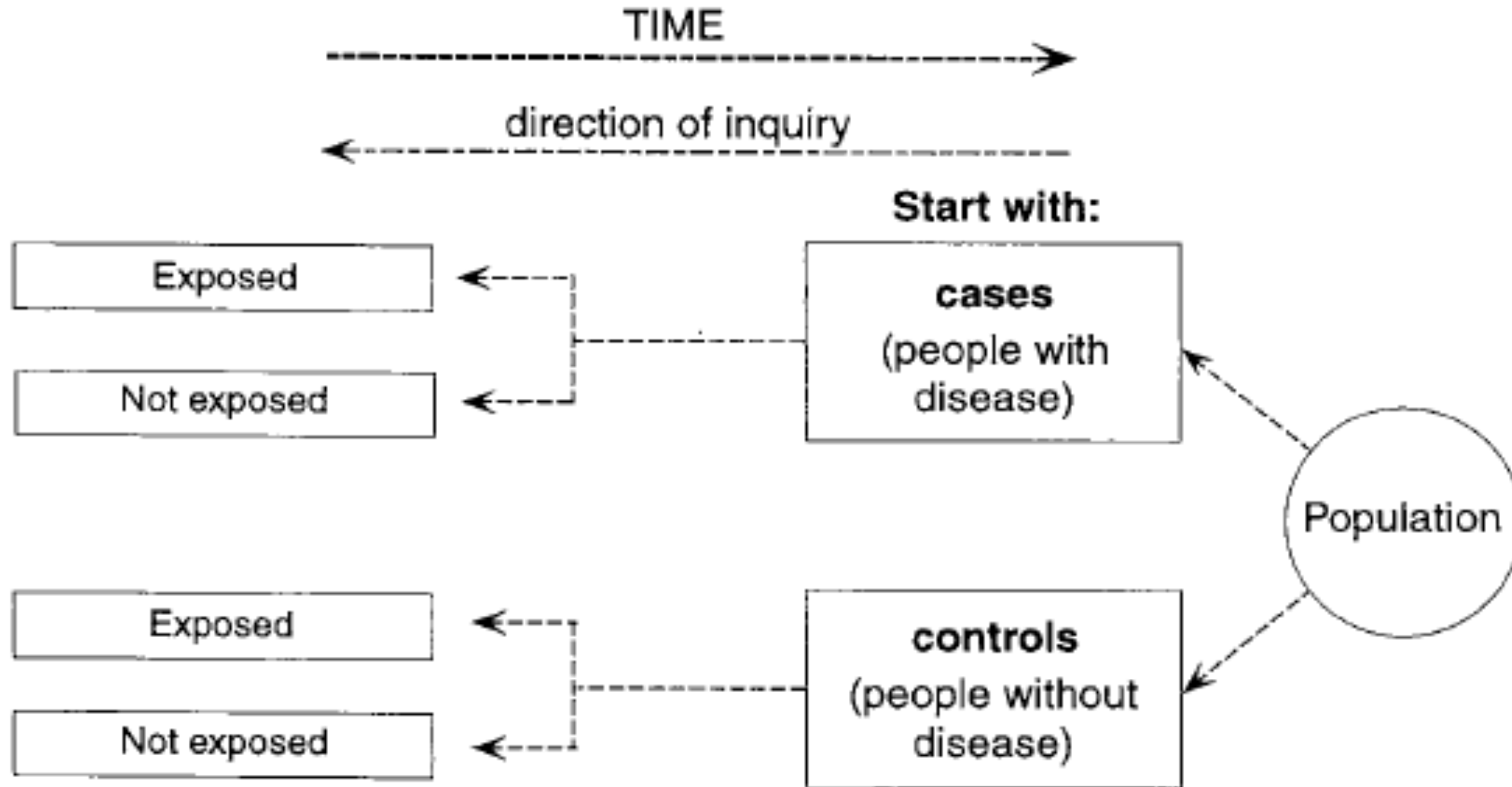
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- To deal with the problem (confounding) in the design and conduct of case control study, matching cases and controls is essential
- The objective of matching is to make the two compared groups similar with regard to the distribution of selected, known extraneous factors.

Cont'd

- Matching may be of two types: group matching and individual matching
- Group matching consists of selecting controls in such a manner that the proportion of controls with certain characteristic is identical to the proportion of cases with the same characteristic
- In individual matching, for each case selected for the study, a control is selected who is similar to the case in terms of the specific variables of concern

Design of a Case-Control Study



Design of a Case-Control Studies

| | | |
|-------------|-----------------|------------------------|
| | Develop Disease | Do Not Develop Disease |
| Exposed | a | b |
| Not Exposed | c | d |

$$\text{OR} = \frac{\text{odds that an exposed person develops disease}}{\text{odds that a non-exposed person develops disease}}$$

$$= \frac{a/b}{c/d}$$

$$= \frac{ad}{bc}$$

| | | |
|------------------------|----------------------|----------------------------|
| | CASES (with disease) | CONTROLS (without disease) |
| History of exposure | a | b |
| No history of exposure | c | d |

$$\text{OR} = \frac{\text{odds that a case was exposed}}{\text{odds that a control was exposed}}$$

$$= \frac{a/c}{b/d}$$

$$= \frac{ad}{bc}$$

Cont'd

| | | |
|-------------|---------|------------|
| | Disease | No Disease |
| Exposed | a | b |
| Not Exposed | c | d |

An odds ratio of

| | | |
|--------------------------------|--|--|
| 1.0 or (≈ 1.0) | <ul style="list-style-type: none"> Means that the odds of exposure among cases is the same as the odds of exposure among controls | <ul style="list-style-type: none"> The exposure is <u>not associated</u> with the disease. |
| > 1.0 | <ul style="list-style-type: none"> Means that the odds of exposure among cases is greater than the odds of exposure among controls. | <ul style="list-style-type: none"> The exposure may be a <u>risk factor</u> for the disease |
| < 1.0 | <ul style="list-style-type: none"> Means that the odds of exposure among cases is lower than the odds of exposure among controls | <ul style="list-style-type: none"> The exposure may be <u>protective</u> against the disease. |

Example 1

TABLE 10-2. A Hypothetical Example of a Case-Control Study of Coronary Heart Disease and Cigarette Smoking

| | CHD Cases | Controls |
|-------------------------|------------------|-----------------|
| Smoke cigarettes | 112 | 176 |
| Do not smoke cigarettes | 88 | 224 |
| Totals | 200 | 400 |
| % Smoking cigarettes | 56 | 44 |

TABLE 10-3. History of Use of Artificial Sweeteners in Bladder Cancer Cases and Controls

| Artificial Sweetener Use | Cases | Controls |
|---------------------------------|--------------|-----------------|
| Ever | 1,293 | 2,455 |
| Never | 1,707 | 3,321 |
| Total | 3,000 | 5,776 |

From Hoover RN, Strasser PH: Artificial sweeteners and human bladder cancer: Preliminary results. Lancet 1:837-840, 1980.

Example 2

- Suppose that a case control study was conducted among men in Ethiopia in order to find out whether a mother's khat chewing during pregnancy influenced her son's birth weight. Investigators selected 500 low birth weight children and 1000 controls. The study found out that 90 cases' mothers and 50 controls' mothers had used khat during pregnancy. Calculate and interpret the odds ratio.
- $$\text{OR} = \frac{\text{Odd that a case was exposed}}{\text{Odd that a control was exposed}} = \frac{90 \times 950}{410 \times 50} = 4.2$$

Example 2

- Smoking histories are obtained from all patients entering a hospital who have lip cancer and are compared with smoking histories of patients with cold sores who enter the same hospital, this is an example what type of study design and why?
- **Case control study**

Advantages and disadvantages of case - control studies

Advantages

Quicker and cheaper than follow up studies because there is no waiting time involved. This makes it suitable for diseases with long latency

Well suited to investigations of risk factors for rare diseases, otherwise there may be problems in generating a sufficient number of diseased people to produce accurate results

Disadvantages

The absence of epidemiological denominators (population at risk) makes the calculation of incidence rates, and hence of attributable risks, impossible

Particularly prone to bias compared with other analytic designs, in particular selection and recall bias

Many risk factors can be studied simultaneously. For example, cases and controls may be asked a series of questions on aspects of their life style

Temporality is a serious problem in many case-control studies where it is not possible to determine whether the attribute led to the disease/condition, or vice versa

Relatively efficient, requiring a smaller sample than a cohort study

Little problem with attrition

Sometimes they are the earliest practical observational strategy for determining an association

Is inefficient for the evaluation of rare exposures

Being a case might reflect survival rather than morbidity. For instance, suppose that heavy smokers who have a heart attack tend to die immediately before reach the hospital. Hence, a case-control study of heavy smokers and myocardial infraction, which selects both cases and controls from hospital, will then find that there are rather fewer heavy smokers amongst the cases than the controls. This may even appear to suggest that heavy smoking is protective against MI

WHAT IS COHORT?

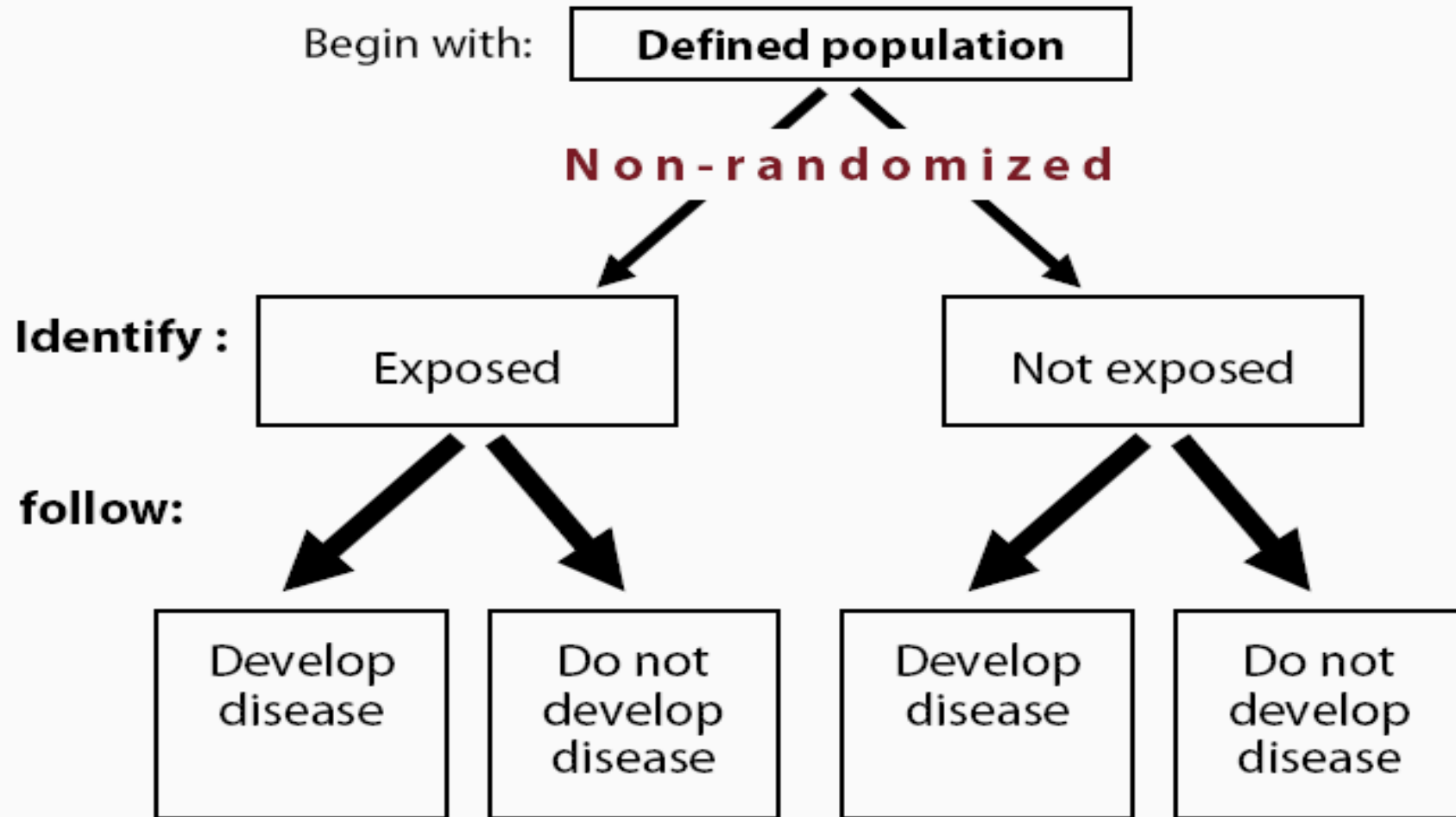
- Ancient Roman military unit, A band of warriors.
- Persons banded together.
- Group of persons with a common statistical characteristic. [Latin]
- E.g. age, birth date,



Cohort study design

- Begins with a group of people (a cohort) free of disease,
 - are classified into subgroups to exposure to a potential cause of disease outcome
- Provide the best information about causation of diseases and the most direct measurement of the risk of developing disease

Design of a Cohort Study



Types of Cohort Study

- Prospective cohort study
- Retrospective (historical) cohort study
- Combination of Retrospective and Prospective Cohort study.

Cont'd

Retrospective cohort

- The starting point, i.e., the point of initial exposure occurred sometime in the past and the experience of the population is followed up to present

Cont'd

■ **Retrospective cohort study**

- Investigator
 - ▶ Uses existing data collected in the past to identify the population and the exposure status (exposed/not exposed groups)
 - ▶ Determines at present the (development) status of disease
- Investigator spends a relatively short time to:
 - ▶ Assemble study population (and the exposed/not exposed groups) from past data
 - ▶ Determine disease status at the present time (no future follow-up)

Cont'd

- Depends upon the availability of data or records that allow reconstruction of the exposure or cohorts to a suspected risk factor and follow up of their mortality or morbidity overtime
- Advantages:
- Suffer less from the disadvantage of time and expense

Cont'd

- Disadvantages:
 - All relevant variables may not be available in the original records
 - It may be difficult to ascertain that the study population was free from condition at the start of the comparison
 - Attrition problems may be serious due to loss of records, incomplete records or difficulties in tracing or locating all of the original population for further study

RESEARCH ARTICLE

Open Access



Effectiveness of isoniazid preventative therapy in reducing incidence of active tuberculosis among people living with HIV/AIDS in public health facilities of Addis Ababa, Ethiopia: a historical cohort study

Mahlet Semu¹, Teferi Gedif Fenta^{2*}, Girmay Medhin³ and Dawit Assefa⁴

Abstract

Background: Human Immunodeficiency Virus (HIV) pandemic has exacerbated tuberculosis disease especially in Sub-Saharan African countries. The World Health Organization (WHO) and Joint United Nations Program on HIV/AIDS (UNAIDS) have recommended Isoniazid Preventive Therapy (IPT) for HIV infected patients to reduce the burden of tuberculosis (TB). Ethiopia has been implementing IPT since 2007. However, effectiveness of IPT in averting occurrence of active tuberculosis among HIV infected patients has not been assessed.

Methods: Retrospective cohort study was employed using secondary data from public health institutions of Addis Ababa. Descriptive statistics and Generalized Linear Model based on Poisson regression was used for data analysis.

Results: From 2524 HIV infected patients who were followed for 4106 Person-Years, a total of 277 incident Tuberculosis (TB) cases occurred. TB Incidence Rate was 0.21/100 Person-Year, 0.86/100 Person-Year & 7.18/100 Person-Year among IPT completed, in-completed and non-exposed patients, respectively. The adjusted Incidence Rate Ratio (aIRR) among IPT completed vs. non-exposed patients was 0.037 (95% CI, 0.016-0.072). Gender, residence area, employment status, baseline WHO stage of the disease (AIDS) and level of CD4 counts were identified as risk factors for TB incidence. The aIRR among patients who took Highly Active Anti-Retroviral Therapy (HAART) with IPT compared to those who took HAART alone was 0.063 (95% CI 0.035-0.104). IPT significantly reduced occurrence of active TB for 3 years.

Conclusions: IPT significantly reduced tuberculosis incidence by 96.3% compared to IPT non-exposed patients. Moreover concomitant use of HAART with IPT has shown a significant reduction in tuberculosis incidence by 93.7% than the use of HAART alone. Since IPT significantly protected occurrence of active TB for 3 years, its implementation should be further strengthened in the country.

Keywords: IPT, Incidence of active TB, TB/HIV co-infection, Ethiopia

Table 5 Incidence rate, univariate and multivariate analysis among IPT completed, in-completed and non-exposed patients in public health facilities of Addis Ababa, during 2007-June 2012

| Patient profile | Event/P/Y | IR/100P-Y | Crude IRR (95% CI) | Adjusted IRR(95% CI) |
|------------------|-----------|-----------|--------------------|----------------------|
| Over all | 277/4106 | 6.7 | | |
| IPT completed | 7/33.3 | 0.21 | 0.03(0.01–0.06) | 0.04(0.05–0.07) |
| IPT in-completed | 8/7.8 | 0.86 | 0.84(0.36–1.33) | 0.89(0.49–1.76) |
| IPT non-exposed | 262/36.49 | 7.18 | 1 | 1 |

Cont'd

Prospective cohort study

- The starting point of observation is now and the population is followed into the future

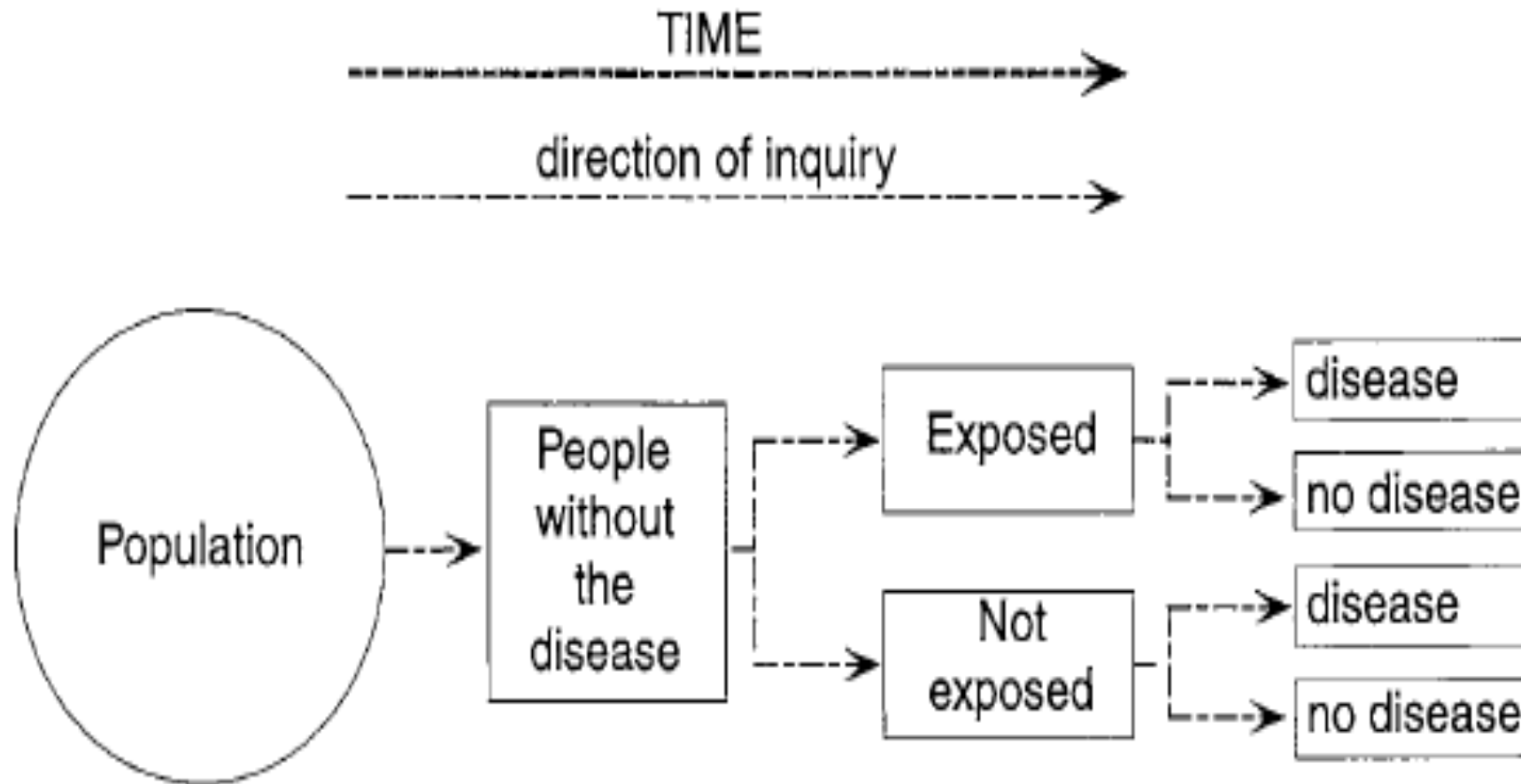
Cont'd

■ **Prospective cohort study**

— Investigator

- ▶ Starts the study (from the beginning) with the identification of the population and the exposure status (exposed/not exposed groups)
- ▶ Follows them (over time) for the development of disease
- ▶ Takes a relatively long time to complete the study (as long as the length of the study)

Design of a Cohort Study



Cont'd

TABLE 11-5. Risk Calculations in a Cohort Study

| | | Then Follow to See Whether | | Totals | Incidence Rates of Disease |
|---------------|-------------|--|-----------------------------|---|-------------------------------|
| | | Disease Develops | Disease Does Not Develop | | |
| First, Select | Exposed | <i>a</i> | <i>b</i> | <i>a + b</i> | $\frac{a}{a+b}$ |
| | Not exposed | <i>c</i> | <i>d</i> | <i>c + d</i> | $\frac{c}{c+d}$ |
| | | $\frac{a}{a+b}$ = Incidence in exposed | | $\frac{c}{c+d}$ = Incidence in nonexposed | |

TABLE 11-4. Interpreting Relative Risk (RR) of a Disease

| | |
|-----------|--|
| If RR = 1 | Risk in exposed equal to risk in nonexposed (no association) |
| If RR > 1 | Risk in exposed greater than risk in nonexposed (positive association; possibly causal) |
| If RR < 1 | Risk in exposed less than risk in nonexposed (negative association; possibly protective) |

$$\text{Relative risk} = \frac{\text{Incidence in exposed}}{\text{Incidence in nonexposed}} = \frac{\left(\frac{a}{a+b}\right)}{\left(\frac{c}{c+d}\right)}$$

Example 1

TABLE 11-6. Smoking and Coronary Heart Disease (CHD): A Hypothetical Cohort Study of 3,000 Cigarette Smokers and 5,000 Nonsmokers

| | CHD Develops | CHD Does Not Develop | Totals | Incidence per 1,000 per Year |
|-------------------------|--------------|----------------------|--------|------------------------------|
| Smoke cigarettes | 84 | 2,916 | 3,000 | 28.0 |
| Do not smoke cigarettes | 87 | 4,913 | 5,000 | 17.4 |

- Calculate and interpreted RR?
- $RR = \frac{\text{Risk among exposed}}{\text{Risk among non exposed}} = \frac{84 \cdot 5000}{87 \cdot 3000} = 1.6$

Example 2

- Explain type of study design and why?
- Occurrence of cancer was identified between April 1991 and July 2002 for 50,000 troops who served in the first Gulf War (ended April 1991) and 50,000 troops who served elsewhere during the same period.
- **Retrospective Cohort**
- The physical examination records of the incoming first year class of 1961 at the School of Pharmacy are examined in 1988 to see whether the freshmen's recorded height and weight at the time of admission to the School were related to their chance of developing coronary heart disease:
- **Retrospective cohort**

Cont'd

TABLE 12-3. Summary of Attributable Risk Calculations

| | In Exposed Group | In Total Population |
|--|--|--|
| Incidence attributable to exposure | $\left(\text{Incidence in exposed group} \right) - \left(\text{Incidence in nonexposed group} \right)$ | $\left(\text{Incidence in total population} \right) - \left(\text{Incidence in nonexposed group} \right)$ |
| Proportion of incidence attributable to exposure | $\frac{\left(\text{Incidence in exposed group} \right) - \left(\text{Incidence in nonexposed group} \right)}{\text{Incidence in exposed group}}$ | $\frac{\left(\text{Incidence in total population} \right) - \left(\text{Incidence in nonexposed group} \right)}{\text{Incidence in total population}}$ |

Example 2

- Calculate and interpreted AR, and PAR?

| TABLE 12-1. Smoking and Coronary Heart Disease (CHD): A Hypothetical Cohort Study of 3,000 Cigarette Smokers and 5,000 Nonsmokers | | | | |
|---|--------------|----------------------|-------|------------------------------|
| | CHD Develops | CHD Does Not Develop | Total | Incidence per 1,000 per Year |
| Smoke cigarettes | 84 | 2,916 | 3,000 | 28.0 |
| Do not smoke cigarettes | 87 | 4,913 | 5,000 | 17.4 |

✓ Attributable Risk Calculation for the Exposed Group

$$\begin{aligned}
 & \left(\text{Incidence in} \right) - \left(\text{Incidence in} \right) \\
 & \left(\text{exposed group} \right) - \left(\text{nonexposed group} \right) \\
 & = \frac{28.0 - 17.4}{1,000} = \frac{10.6}{1,000}
 \end{aligned}$$

- What does this mean?
- It means that 10.6 of the 28/1000 incident cases in smokers are attributable to the fact that these people smoke.

Cont'd

- The proportion of the total incidence in the exposed group that is attributable to the exposure

$$\frac{\left(\text{Incidence in exposed group} \right) - \left(\text{Incidence in nonexposed group} \right)}{\text{Incidence in exposed group}} = \frac{28.0 - 17.4}{28.0} = \frac{10.6}{28.0} = 0.379 = 37.9\%$$

- 37.9% of the morbidity from CHD among smokers may be attributable to smoking and could presumably be prevented by eliminating smoking.
- The incidence in the total population with 44% of smokers.

$$\left(\frac{\text{Incidence in smokers}}{1,000} \right) \left(\frac{\% \text{ Smokers}}{100} \right) + \left(\frac{\text{Incidence in nonsmokers}}{1,000} \right) \left(\frac{\% \text{ Nonsmokers}}{100} \right) = \frac{22.1}{1,000}$$
$$\left(\frac{28.0}{1,000} \right) (0.44) + \left(\frac{17.4}{1,000} \right) (0.56) = \frac{22.1}{1,000}$$

Cont'd

- The attributable risk in the total population:

$$\left(\frac{\text{Incidence in total population}}{1,000} \right) - \left(\frac{\text{Incidence in nonexposed group}}{1,000} \right) = \frac{22.1}{1,000} - \frac{17.4}{1,000} = \frac{4.7}{1,000}$$

- The *proportion* of the incidence in the *total population* that is attributable to the exposure

$$\frac{\left(\frac{\text{Incidence in total population}}{1,000} \right) - \left(\frac{\text{Incidence in nonexposed group}}{1,000} \right)}{\frac{\text{Incidence in total population}}{1,000}} = \frac{22.1 - 17.4}{22.1} = 21.3\%$$

- What does this tell us?
- 21.3% (4.7) of the incidence of CHD in the total population can be attributed to smoking, and if an effective prevention program eliminated smoking, the best that we could hope to achieve would be a reduction of 21.3% (4.7) in the incidence of CHD in the total population (which includes both smokers and nonsmokers).

Advantages and disadvantages of cohort studies

| Advantages | Disadvantages |
|---|--|
| <p>Relative risk can be calculated</p> <p>Allows concluding a cause-effect relationship</p> <p>No chance of bias being introduced due to awareness of being sick as in encountered in case-control studies</p> <p>Less chance for the problem of selective survival or selective recall</p> | <p>Cohort studies are long-term and are thus not always feasible; they are relatively inefficient for studying rare conditions</p> <p>Costly in time, personnel, space and patient follow-up</p> <p>Sample sizes required are large, especially for infrequent conditions</p> <p>Attritions or loss of people from the sample or control during the study is the major problem. The higher the proportion lost (say beyond 10 - 15%) the more serious the potential bias</p> |

Cohort studies are capable of identifying other diseases that may be related to the same risk factor

Allows estimating attributable risks, thus indicating the absolute magnitude of disease attributable to the risk factor

If a probability sample is taken from the reference population, it is possible to generalize from the sample to the reference population with a known degree of precision

There may be also be attrition among investigators

Over a long period, many changes may occur in the environment, among individuals or in the type of intervention , and these may confuse the issue of association and attributable risk

Over a long period, study procedures may influence the behaviour of the persons investigated in such a way that the development of the disease may be influenced accordingly (Hawthorne effect)

A serious ethical problem may arise when it becomes apparent that the exposed population is manifesting significant disease excess before the follow-up period is completed

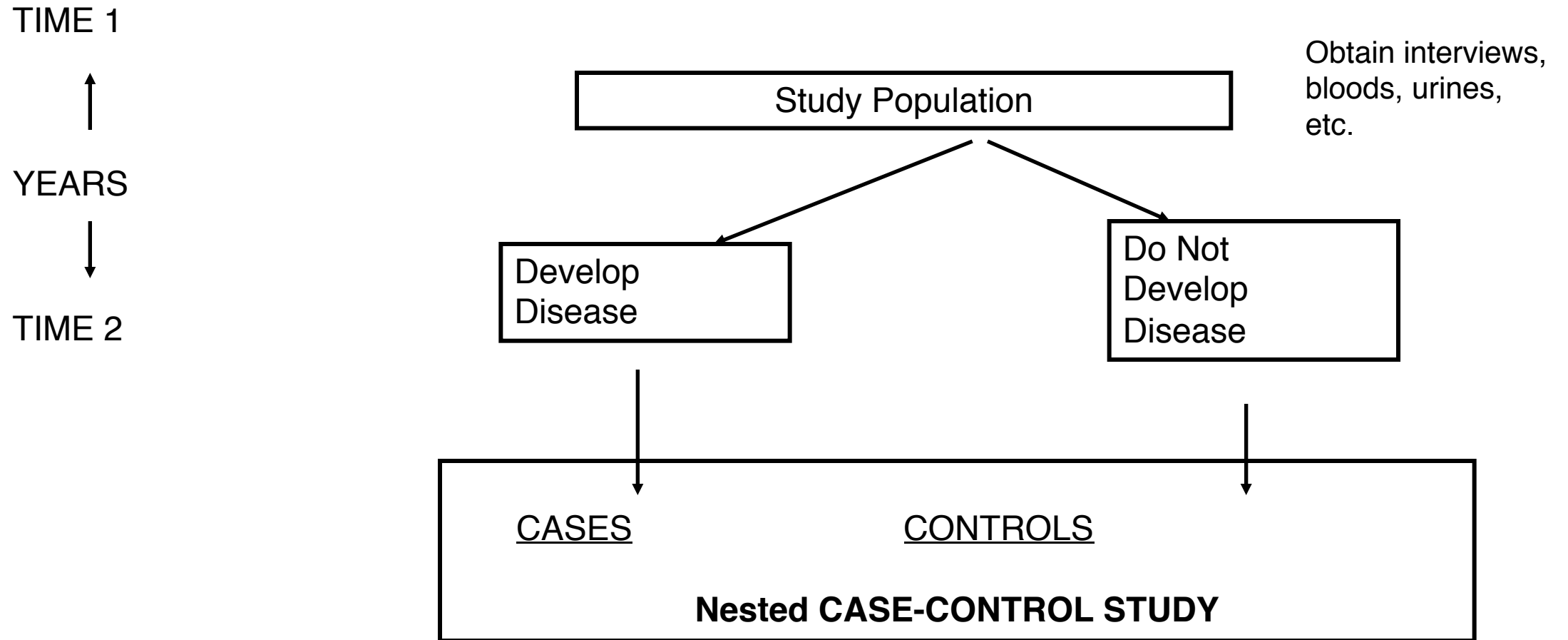
Nested - case control study design

- Hybrid design in which a case control study is nested in a cohort
- At the time the population is identified, baseline obtained from interviews, blood or urine samples taken
- The population is then followed over time
- A case control is carried out using persons in whom the disease developed (cases) and sample of those in whom the disease did not develop as controls

Advantages

- Problem of possible recall bias is eliminated as interviews are performed at the beginning of the study
- Temporal relationship is easily ascertained unlike traditional case control study
- More economical to conduct as compared to cohort study in which lab analysis of all specimens obtained would have to be carried out often at a great cost to define exposed and non-exposed groups; while in nested case control study, the specimens collected are frozen and it is after the disease development in some subjects that a case control study begun

Nested Case-Control Studies



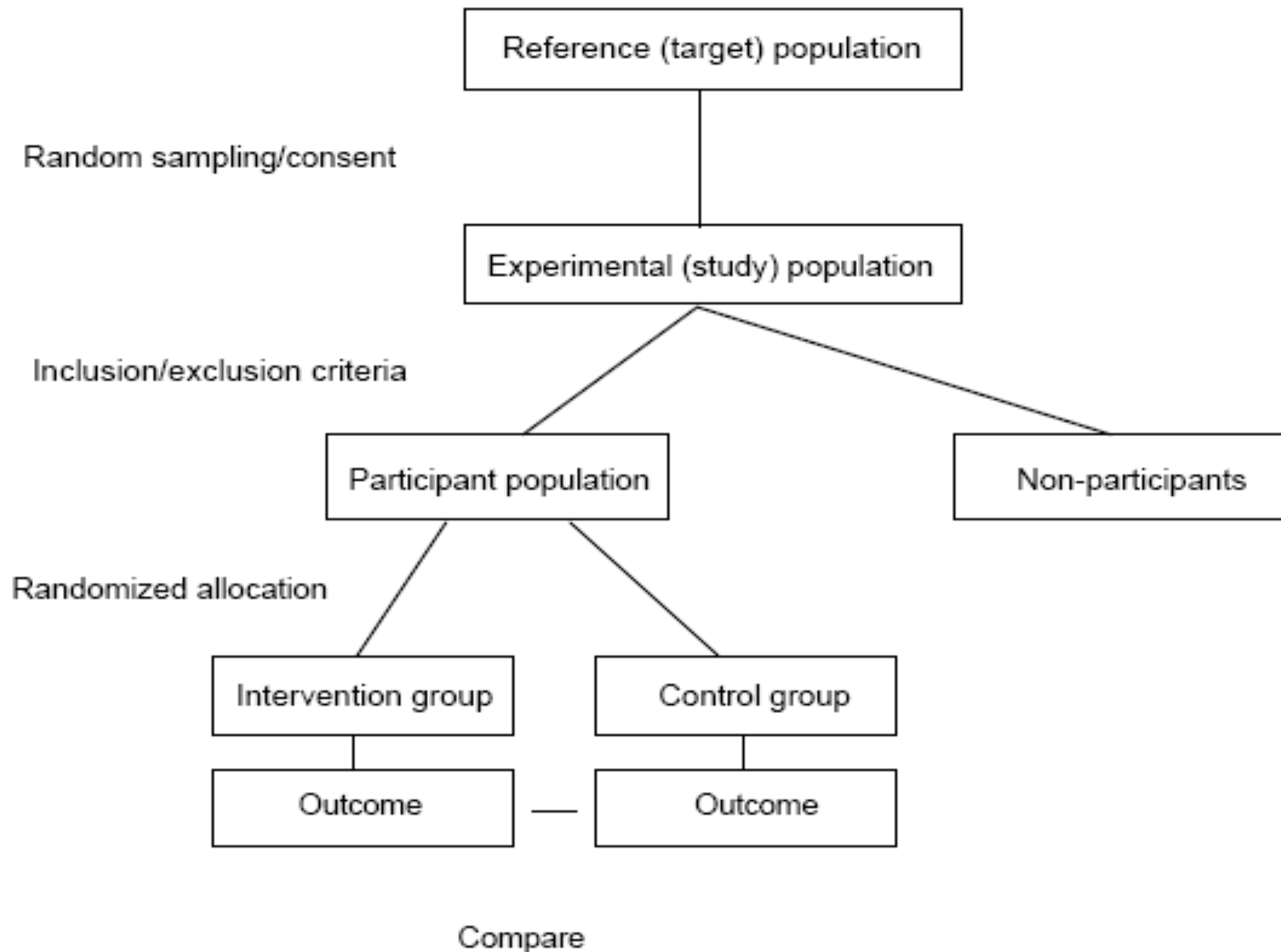
Experimental studies/ clinical trial

- Provide data of high quality
- As in a cohort study, individuals are enrolled on the basis of their exposure status
- The distinguishing characteristic of experimental study design is that the investigators themselves allocate the exposure
- The best epidemiological study design to prove causation

Cont'd

- The experimenter (investigator) has control of the subjects, the intervention, outcome measurements, and sets the conditions under which the experiment is conducted
- The investigator determines who will be exposed to the intervention and who will not.
- Are of two types :
 - the randomized clinical trial (RCT) and
 - the community intervention trial (CIT)

Flow Chart of an Experiment



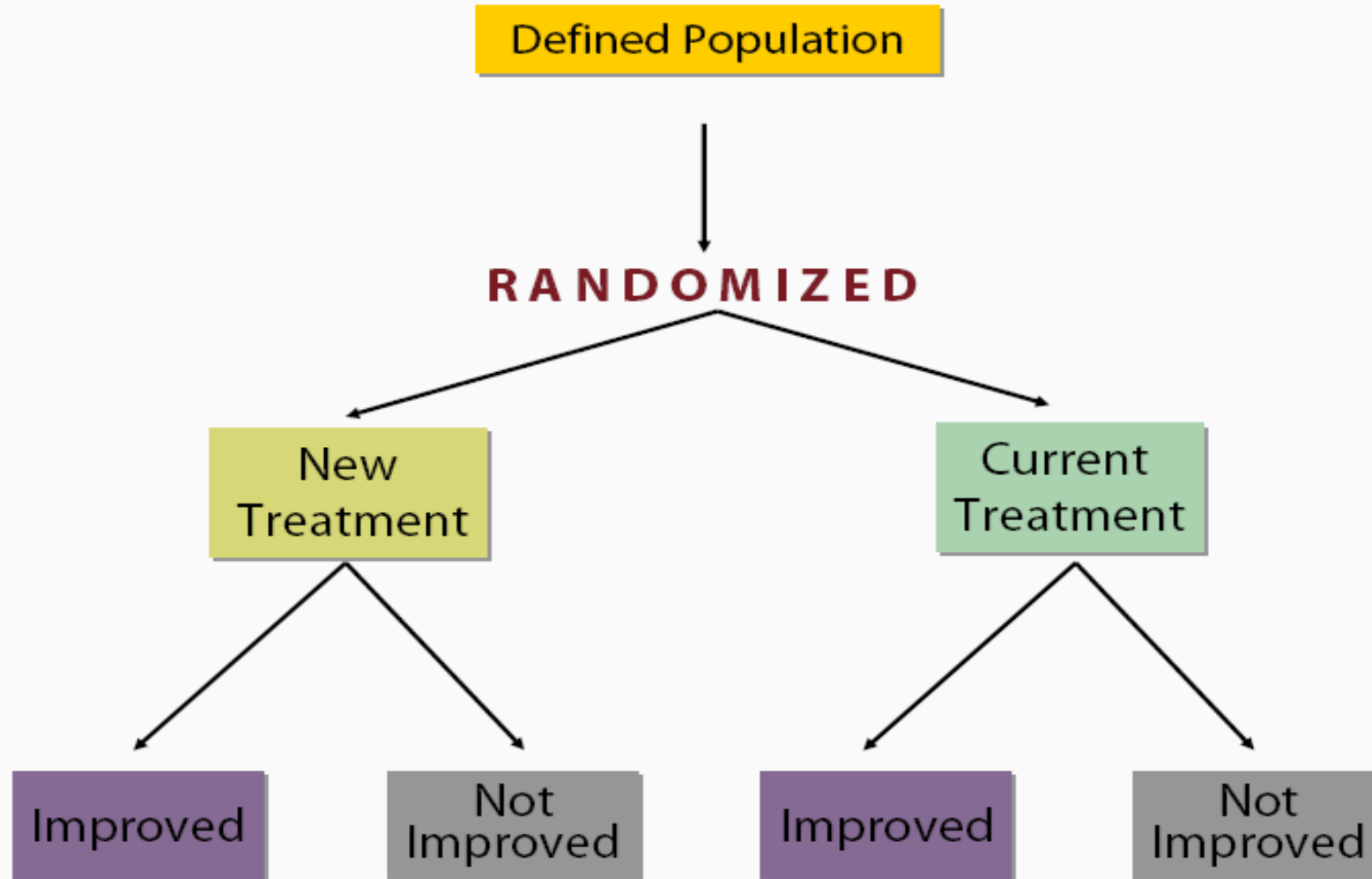
The randomized clinical trial (RCT)

- It is the research strategy by which evidence of effectiveness is measured
- It is the randomized, controlled, double blind clinical trial, commonly known as an RCT
- Based on their purpose, clinical trials are categorized as follows:

Cont'd

- a. Prophylactic trials,
 - e.g., immunization, contraception
- b. Therapeutic trials,
 - e.g., drug treatment, surgical procedure
- c. Safety trials: e.g., side effects of oral contraceptives and injectables
- d. Risk-trials, e.g., providing the etiology of a disease by inducing it with the putative agent in animals, or withdrawing the agent

Design of a Randomized Clinical Trial



When can a Randomized Trial be used?

- A randomized trial to be feasible and justifiable the following requirements should generally be met:
 - ✓ the exposure should potentially be modifiable (factors like genotype, family history, and demographic characteristics cannot be altered so their impacts on disease occurrence must be studied with observational designs)
 - ✓ The exposure should be potentially modifiable by the investigator (exposure such as occupation, marital status, and smoking habits can in principle be changed but often impossible or impractical to assign people at random among the possible categories for research purpose).

When is RCT be used?

- ✓ There is a genuine uncertainty about which intervention strategy is superior
- ❖ Example: It has often be observed that motorcyclists who wear a helmet are much less likely to die of head injury in a motor cycle crash than are unhelmeted motorcyclists. There is little doubt the mechanical protection provided by the helmet is largely responsible for this difference. It would almost certainly deemed unethical to withhold helmets at random for some motorcyclists in order to get further evidence that helmets actually do protect against fatal head injury.

When is RCT be used?

- ✓ The primary outcomes are relatively common and occur relatively soon
- ✓ RCT can be expensive, especially when a large number of participants is required, the period of follow up is lengthy and identification of outcome is costly
- ✓ If we administer the drug and the patient improves, can we attribute the improvement to administration of the drug?

Cont'd

Prof. Hugo Muensch of Harvard said, *'results can always be improved by omitting controls'*

- ✓ *A sea captain was given samples of anti-nausea pills to test during journey. The need for controls was carefully explained to him. Upon return of the ship, the captain reported the results enthusiastically. 'Practically every one of the controls was ill and not one of subjects had any trouble. Really wonderful stuff'. A skeptic asked how he had chosen the controls and the subjects. 'oh, I gave the stuff to my seamen and used the passenger as controls'*

Community intervention trials (CITs)

- The major difference between RCTs and CITs is that the randomization is done on communities rather than individuals
- Examples:
 - Testing a vaccine: Some communities will be randomly assigned to receive the vaccine, while other communities will either not be vaccinated, or will be vaccinated with placebo
 - A test of whether the introduction of iron-fortified salt in the community would reduce the incidence of anemia in the community

Cont'd

- Very often, blinding is not possible in these types of studies, and contamination and co-interventions become serious problems
- Contamination occurs when individuals from one of the experimental groups receive the intervention from the other experimental group.
- For example, in the study of iron-fortified salt, some of the members of the community receiving non-fortified salt might hear about the fortified salt, and may acquire it from the other community (the reverse is also possible)
 - This is particularly so if the communities are geographically close

Control selection

Historical controls

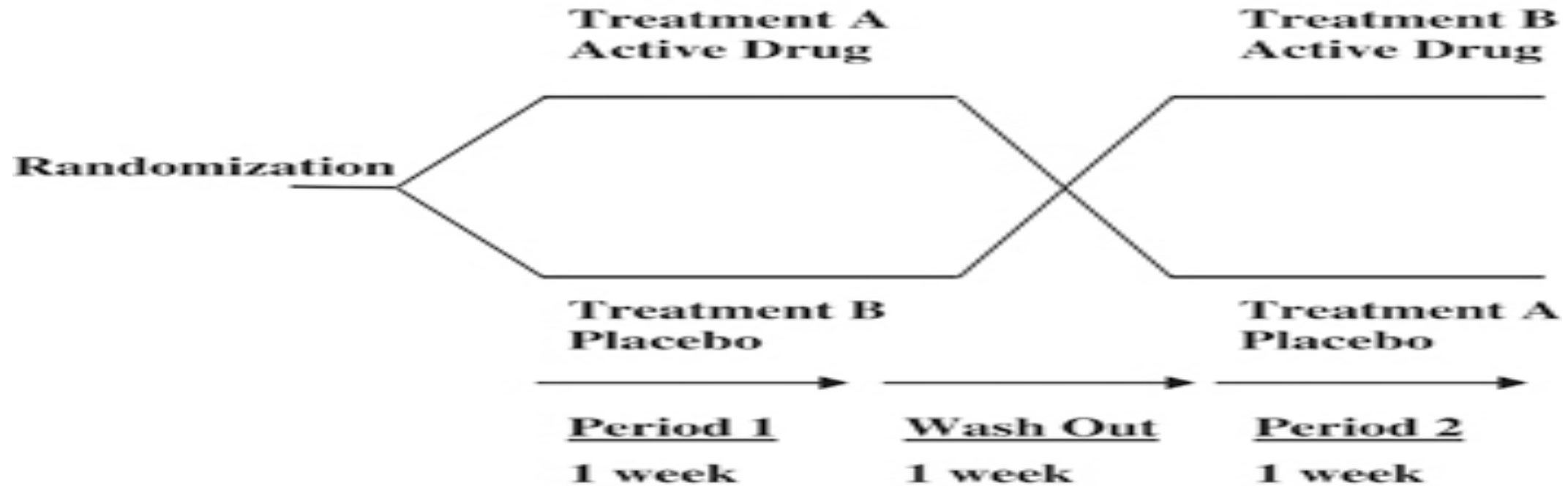
- Go back to records of patients with the same disease who were treated before the new test therapy become available
- Simple and attractive
- When the disease is uniformly fatal initially and a new drug becomes available, a significant decline in case fatality rate would support the conclusion that new drug is having an effect

- Problems of using historical controls
 - Difference in the quality of data collection existed now because of the study and in the past for services only(quality and kind of data)
 - Many things other than the therapy may change over calendar time (nutrition, lifestyles, living conditions, etc)

Designs used in experimental studies

- There are two approaches used in allocating treatment and control regimes: **either parallel or crossover.**
 - **A parallel design** is where subjects receive **only one treatment and the change in outcome response** in one group of subjects (receiving treatment of interest) is compared with that in another group of subjects receiving a different (or control) treatment.
 - **In a crossover design** each subject **receives both (all) treatments** in a randomized order with suitable gaps between treatments (wash-out) and outcomes/ response is compared within subjects.

Cross-over Study Design



Design of experimental studies

➤ An advantage of the crossover design over the parallel design

1. Subject characteristics are approximately constant for both treatment groups (exposure categories).
2. A crossover design is that, as all subjects receive the treatment under investigation,
3. The statistical power of the study is greater than in a parallel study of equivalent size, where only a proportion of the subjects receive the treatment under investigation.
4. A crossover design may be suitable for , but may not be suitable where the treatment is given continuously throughout the treatment period.

Commonly used design options

One group Pre-test, Post-test

| | Time | | | |
|-------|------|---------|---|---------|
| | | 1 (pre) | | 2(post) |
| Exp G | | Q | X | Q |

- ✓ Single selected group under observation, with a careful measurement being done before applying the experimental treatment and then measuring after.
- ✓ This design has minimal internal validity
- ✓ No external validity

Design options contd.

Two groups, Nonrandom Selection, Pre-test, Post-test

| | Time | | | |
|-----------|------|---------|---|---------|
| | | 1 (pre) | | 2(post) |
| Exp G | | Q1 | X | Q3 |
| Control G | | Q2 | | Q4 |

- ✓ In the absence of randomization, the possibility always exists that some critical difference, not reflected in the pretest, is operating to contaminate the posttest data.
- ✓ For example, if the experimental group consists of volunteers, they may be more highly motivated, or if they happen to have a different experience background that affects how they interact with the experimental treatment - such factors rather than X by itself, may account for the differences.

Design options cont'd.

Two groups, Random Selection, Pre-test, Post-test

| | | Time | | |
|-----------|---|---------|---|---------|
| | | 1 (pre) | | 2(post) |
| Exp G | R | Q1 | X | Q3 |
| Control G | R | Q2 | | Q4 |

- ✓The advantage here is the randomization, so that any differences that appear in the posttest should be the result of the experimental variable rather than possible difference between the two groups to start with.
- ✓Has good internal validity
- ✓But external validity or generalizability of the study is limited by the possible effect of pre-testing.

Design options contd.

The Solomon Four-Group

| | Time | | | |
|------------|------|---------|---|---------|
| | | 1 (pre) | | 2(post) |
| Exp G1 | R | Q1 | X | Q3 |
| Control G1 | R | Q2 | | Q4 |
| Exp G2 | R | | X | Q5 |
| Control G2 | R | | | Q6 |

- ✓ there are two experimental and two control groups
- ✓ assesses the plausibility of pre-test sensitization effects

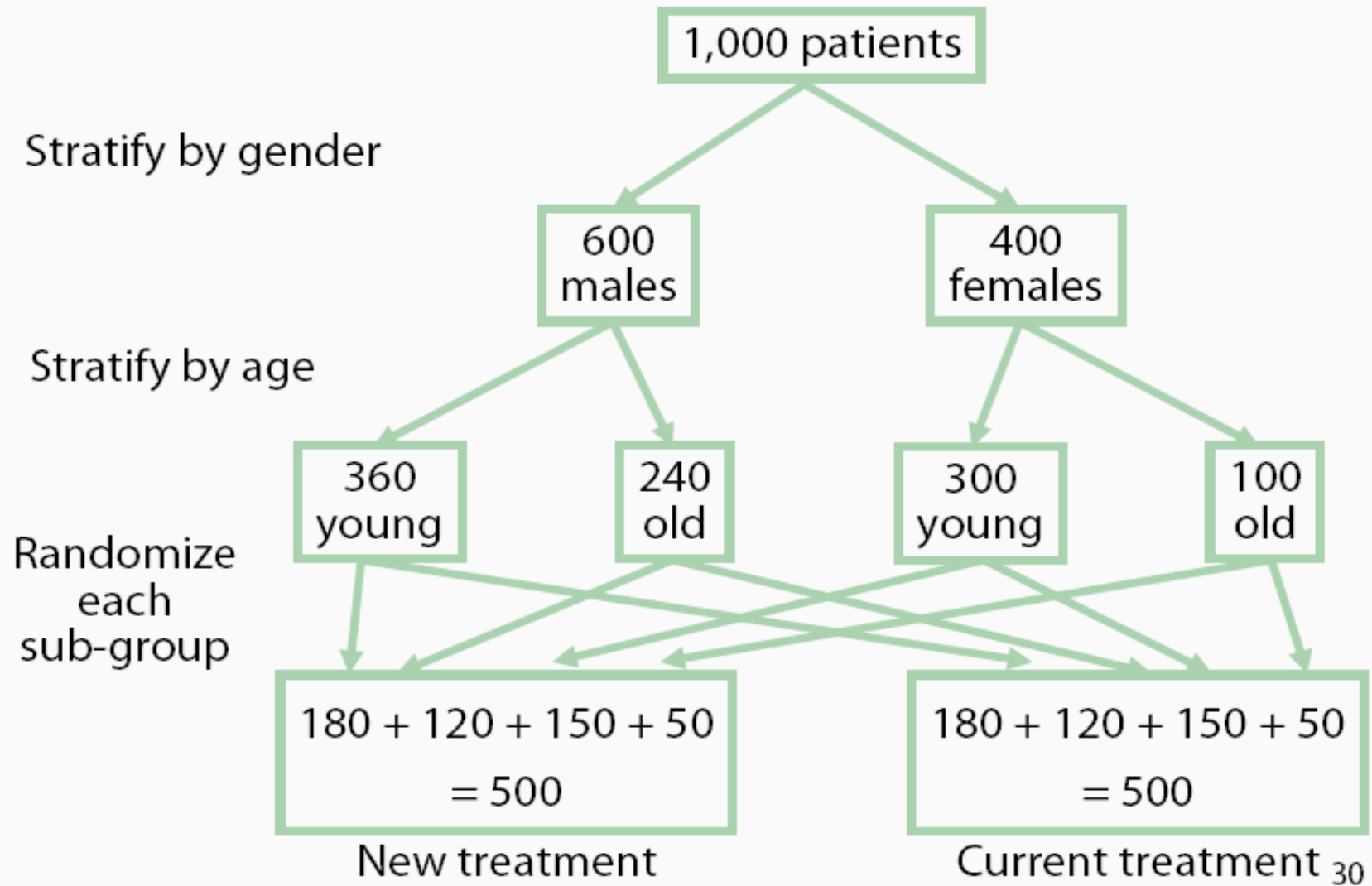
Techniques used to control errors in experimental studies

- Randomization
- Stratified randomization
- Blinding (Masking)

Cont'd

- Randomization is used to equalize the distributions of confounding factors, whether they are known or unknown.
- Then, the assigned treatment is the most likely explanation for any observed difference between treatment groups in the clinical outcomes (improvement in the illness or the occurrence of adverse clinical events).
- Stratified randomization is used to ensure the equal distribution of uncommon confounders among study groups.

Diagram of Stratified Randomization



- Blinding is used to minimize detection bias, and is particularly important where the outcome is subjective.
- Reporting of subjective symptoms by study participants and the detection of even objectively defined outcome events may be influenced by knowledge of the medications used.
- Thus, follow-up data collection will only be unbiased if both parties (patient and investigator) are unaware of the treatment assigned.

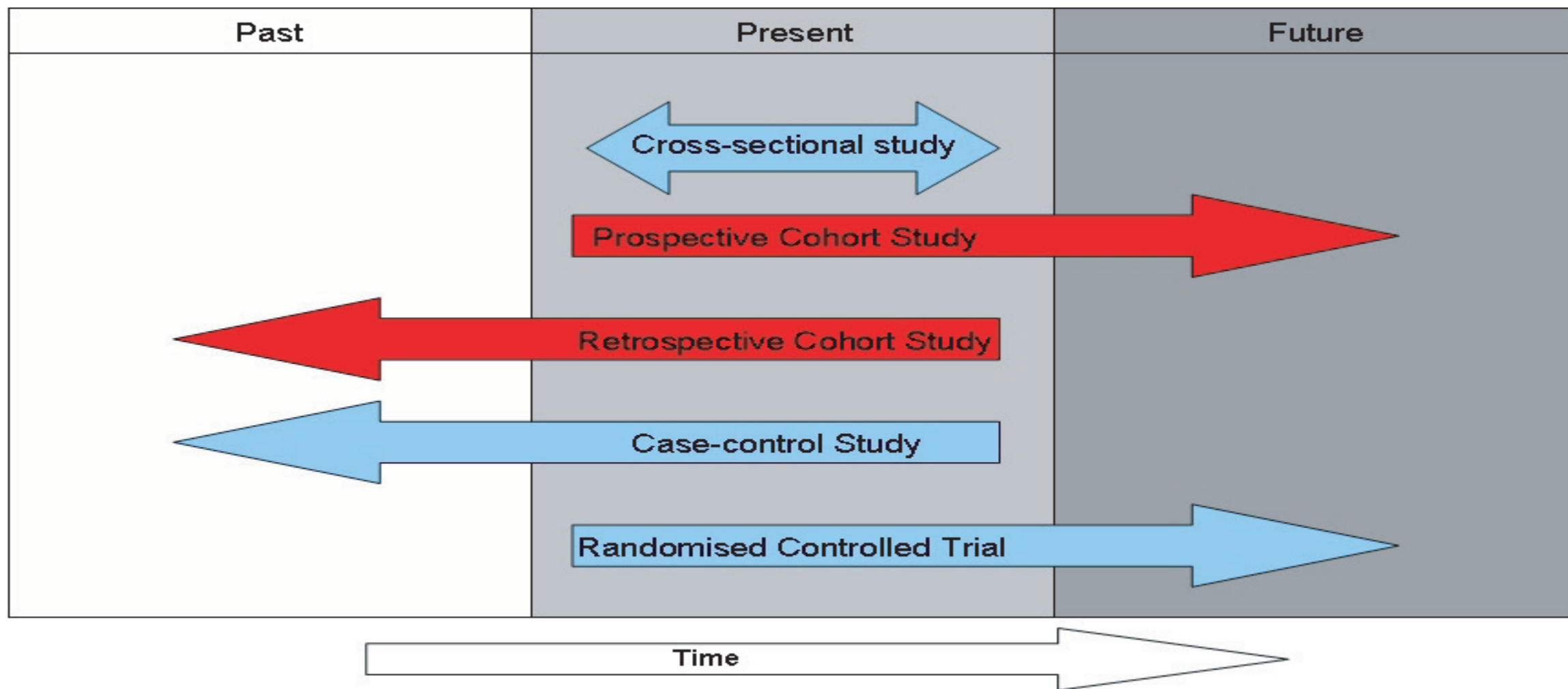
Example

- Subjects were children enrolled in a health maintenance organization. At 2 months, each child was randomly given one of two types of a new vaccine against rotavirus infection. Parents were called by a nurse two weeks later and asked whether the children had experienced any of a list of side-effects. This is an example of what type of study design and why?

Advantages and disadvantages of experimental approach

| Advantages | Disadvantages |
|--|--|
| The ability to manipulate or assign the exposure | Lack of reality. In most human situations, it is impossible to randomize all risk factors except those under examination |
| The ability to randomize subjects to experimental and control groups | Difficulties in extrapolation |
| The ability to control confounding and eliminate sources of spurious association | Ethical problems. In human experimentation, people are either deliberately exposed to risk factors (in etiological studies) or treatment is deliberately withheld from cases (intervention trials) |

| | |
|-----------------------------------|--|
| The ability to ensure temporality | Non-representativeness of samples. Many experiments are carried out on captive populations or volunteers, who are not necessarily representative of the population at large |
| The ability to replicate findings | Experiments in hospitals (where the experimental approach is most feasible and is frequently used) suffer from several resources of selection bias |



Cont'd

Selection of study design

The type of study design chosen depends on:

- The type of problem
- The knowledge already available about the problem and
- Resources available for the study

| Research questions and study design | | |
|---|--|---|
| State of knowledge of the problem | Types of research questions | Types of study design |
| Knowing that the problem exists but little about its characteristics or possible causes | <p>What is the nature/magnitude of the problem:</p> <ul style="list-style-type: none"> • Who is affected? When and where? • How do the affected people behave? • What do they know, believe, and think about the problem? | <p>Exploratory or descriptive studies:</p> <p>Descriptive</p> <p>Case studies</p> <p>Cross-sectional surveys</p> <p>Qualitative methods</p> |

| | | |
|---|--|---|
| Suspecting that certain factor contribute to the problem | Are certain factors associated with the problem? (e.g. is lack of school sex education related to high incidence of STD?) | Analytical (comparative studies): Cross-sectional Comparative Case control studies Cohort studies |
| Having established that certain factors are associated with the problem, desiring to establish the extent to which a particular factor causes or contributes to the problem | What is the cause of the problem? Will removal of a particular factor prevent or reduce the problem(e.g. stopping Khat, stopping smoking, providing safe water) | Experimental or quasi-experimental study design |
| Having sufficient knowledge about cause and to develop and asses an intervention which would prevent, control or solve the problem | What is the effect of a particular interventions/strategy? (e.g, new drug, special educational programme) | Experimental or quasi-experimental study designs |

Data collection in Pharmacoepidemiology

- Data collection techniques allow us to systematically collect information about our subjects of study and about the settings in which they occur
- If data are collected haphazardly, it will be difficult to answer research questions in conclusive way

Data collection techniques:

- Using available information (record review)
- Observing
- Interviewing
- Administering written questionnaires
- Focus group discussions

Observing

- Observation is a technique, which involves systematically selecting, watching and recording behaviors and characteristics of living beings, objects or phenomena
- Observation of human behaviors is a much used data collection technique. It can be undertaken in two different ways:
 - Participant observation: the observer takes part in the situation he or she observes
 - Non-participant observation: the observer watches the situation, openly or concealed, but does not participate

- Observations are usually complementary to other data collection techniques
- They can give additional, more accurate information on the behaviour of people than interview or questionnaires: questionnaire may be incomplete because we forget to ask certain questions and informants may forget or be unwilling to mention certain things
- Observations can therefore check on information collected (especially on sensitive topics such as alcohol or drug use, or stigmatization of leprosy, TB, epilepsy or AIDS patients)
- Observations can also be a primary source of information

Interviewing

- An interview is a data collection technique that involves oral questioning of respondents, either individually or as group
- Answers to the question posed during an interview can be recorded by writing them down
- Interviews can be conducted with varying degrees of flexibility

a. High degree of flexibility

- A structured or loosely structured method of asking questions can be used for interviewing individuals as well as groups of key informants
- A flexible method of interviewing is useful if a researcher has yet little understanding of the problem or situation under investigation
- It is frequently applied in exploratory studies and also used during case studies

- **Example:** interviews using an interview schedule, to ensure that all issues are discussed, but allowing flexibility in timing and the order in which the questions are asked
- The interviewer may ask additional questions on the spot in order to gain as much useful information as possible
- Questions are open ended: the respondent is unrestricted in what and how he answers

b. Low degree of flexibility

- Are useful when the researcher is relatively knowledgeable about expected answers or
- When the number of respondents being interviewed is relatively large
- **Example:** interviews using a questionnaire with a fixed list of questions in a standard sequence, which have mainly fixed or pre-categorized answers

Self administering written questionnaires

- A self-administered questionnaire: is a data collection tool in which written questions are presented that are to be answered by the respondents in written form
- A self-administered questionnaire can be administered in different ways, for example:
 - through mailing to respondents who should mail their responses back

- Gathering all or part of the respondents in one place at one time, giving oral or written instructions, and letting the respondents fill out the questionnaires; or
- Hand - delivering questionnaires to respondents and collecting them latter
- The questions can be either open ended or closed (with pre-categorized answers)

Focus group discussions

- Used to collect information from a group through guided discussions of the study topic

| Advantages and disadvantages of various data collection techniques | | |
|--|---|---|
| Technique | Advantages | Disadvantage |
| Using available information | <p>Is inexpensive, because data is already there</p> <p>Permits examination of trends over the past</p> | <p>Data is not always easily accessible</p> <p>Ethical issues concerning confidentiality may arise</p> <p>Information may be imprecise or incomplete</p> <p>Data collection may not be standardized</p> |

| | | |
|------------------|---|--|
| <p>Observing</p> | <p>Gives more detailed and context related information</p> <p>Permits collection of information on facts not mentioned in the questionnaire</p> | <p>Ethical issues concerning confidentiality or privacy may arise</p> <p>Observer bias may occur(observer may only notice what interest him or her)</p> <p>The presence of the data collector can influence the situation observed</p> <p>Thorough training of research assistants is required</p> |
|------------------|---|--|

| | | |
|--------------------------------|--|--|
| Interviewing | <p>Is suitable for use with illiterates</p> <p>Permits clarification of questions</p> <p>Has high response rate than written questionnaires</p> <p>Permits collection of in depth information and exploration spontaneous remarks by respondents</p> | <p>The presence of the interviewer can influence response</p> <p>Reports of events may be less complete than information gained through observations</p> <p>The interviewer may inadvertently influence the respondents</p> <p>Open ended data is difficult to analyze</p> |
| Small scale flexible interview | | |

| | | |
|-------------------------------------|---|--|
| Large scale fixed interview | Is easy to analyze | Important information may be missed because spontaneous remarks by respondent are usually not recorded or explored |
| Administering written questionnaire | Less expensive, permits anonymity and may result in more honest responses, does not require research assistants, eliminates bias due to phrasing questions differently with different respondents | <p>Cannot be used with illiterate respondents</p> <p>There is often a low rate of response</p> <p>Questions may be misunderstood</p> |

- Bias in information collection and its possible causes
 - ✓ Bias in information collection is a distortion, which results in the information not being representative of the true situation
 - ✓ Bias in information collection can occur as a result of:
 - Defective instruments such as:
 - Questionnaires with

- Fixed or closed questions on topics about which too little is known
- Open ended questions without guidelines on how to ask (or to answer) them
- Vaguely phrased questions; or
- Questions placed in an illogical order
- Weighing scales, which are not standardized

This sources of bias can be prevented by carefully planning the data collection process and by pre-testing the data collection tools

Observer Bias

- Observer bias can easily occur when conducting observation or utilizing loosely structured group or individual interviews
- There is a risk that the data collector will only see or hear things in which he or she is interested or will miss information that is critical to the research
- Observations protocols and guidelines for conducting loosely structured interviews should be prepared, and training and practice should be provided to data collectors in using both these tools

Selection bias

- If a large proportion of the population under study refuses to cooperate (non-response) or if the sampling procedure used in the study is not adequate, this results in selection bias
- This type of the bias affects the representativeness of the study

Information bias

- Information bias may occur while abstraction information from records or statistics

- Many times, medical records are incomplete or incomprehensible. This poses some problems if you want to use these records in your research
- Another example of information bias is called recall (or memory) bias. This form of bias is related to the inconsistencies in the memory of informants

Effect of the interview (er) on the informant

- The informant may mistrust the intention of the interview and move away certain questions or give misleading answers

- Such bias can be reduced by adequately introducing the purpose of the study to informants, by taking sufficient time for the interview, and by assuring informants that the data collected will be confidential
- It is also important to be careful in the selection of interviewers
- In a study soliciting the reasons for the low utilization of local health service, for example, one should not ask health workers of the health center concerned to interview the population. Their use as interviewers would certainly influences the results of the study

There are several ways by which you could make the data to be collected more reliable

- **Training:** train all the members of your health team/data collectors to collect accurate data, to avoid bias and to record carefully and you would check the accuracy of their work
- **Use of different sources:** take the information from a number of different sources. If you then compared the data from the different sources you might well be able to identify inconsistencies and thus inaccuracies

- **Pre testing:** pre-testing is a try out of the questionnaire. Pre-testing is carried out on a small number of respondents who are comparable with sample of correspondents but are part of it
- **Supervision:** regular supervision during the data collection process

Summary points on data collection

- The following are the methods of data collection
 - Using available information (records)
 - Observing
 - Interviewing
 - Administering written questionnaire
 - Focus group discussions

- Bias in information collection is a distortion, which results in the information not being representative of the true situation
- Possible sources of bias during data collection:
 - Defective instruments
 - Observer bias
 - Selection bias
 - Information bias
 - Effect of the interview on the informant

- Data collection can be improved by:
 - Training of data collectors
 - Pre-testing the questionnaire
 - Supervision
 - Use of different sources for comparison

Design and evaluation of survey questions

What is a good questions?

- It produces answers that provide meaningful information about what we are trying to describe
- When applied repeatedly produces consistent results
 - All people answering it should understand it in consistent way and in a way consistent with what the researchers expected to mean
 - A good question must be able to be administered in a consistent way

- It consistently communicates to all respondents the kind of answers that are wanted and acceptable
 - Example: when did you move to AA?
 - Possible answers: in 1982; when I was 18; after I left high school, etc
 - The question does not provide a clue about what kind of answer to give
 - A good question: in what year did you move to AA?

- There are five basic characteristics of question and answers that are fundamental to a good measurement process:
 - Qs need to be consistently understood
 - Qs need to be consistently administered
 - What constitutes an adequate answer should be consistently communicated
 - Unless measuring knowledge is a goal of the question, all respondents should have access to the information needed to answer the question accurately
 - Respondents must be willing to provide the answers called for in the question

Question evaluation

- Analysis of resulting data to evaluate the strength of predictive relationships among answers and with other characteristics of respondents
- Comparisons of data from alternatively worded questions asked of comparable samples
- Comparison of answers against records
- Measuring the consistency of answers of the same respondents at two points in time

- **Thank you**