MEDICAL UNIVERSITY – PLEVEN
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Lecture № 5

EPIDEMIOLOGY – PART 3

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EXPERIMENTAL STUDIES

These studies involve **an active attempt to change** a disease determinant, such as an exposure or a behaviour, or the progress of the disease

RANDOMIZED CONTROLLED TRIALS

RANDOMIZED CONTROLLED TRIALS

A study in which people are allocated at random to receive one of several interventions.

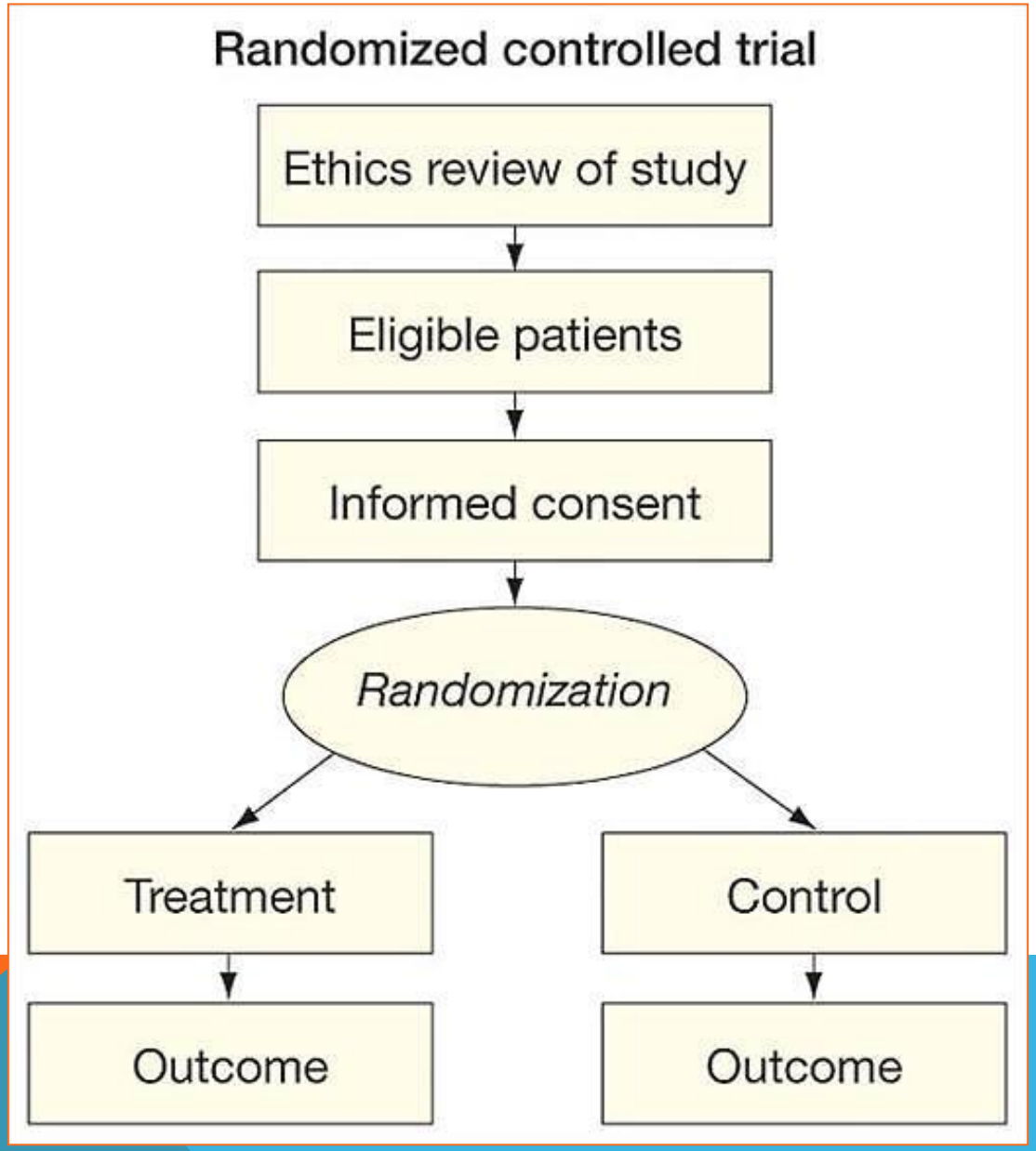
- Experiments to study a new preventive or therapeutic regimen;
- Subjects in a population are randomly allocated to groups, usually called treatment and control groups;
- All participants have equal chance of being allocated to each intervention group;
- The results are assessed by comparing the outcome in the two or more groups.

Randomisation is used to combat selection bias.

Be careful! The "random" refers to **random allocation to either experimental or control group**; it does not refer to random *selection or sampling* of the patients to include in the trial.

Random allocation means **allocating them by chance** (e.g., the toss of a coin). As long as you have relatively large groups (50 or more people in each), This means that **the two study groups will end up equivalent (comparable)** in terms of factors such as age, sex, and even other things that you do not even know about (such as their reaction to the medication).

Important examination point: **Do not confuse *random allocation* to experimental and control groups with *random selection* of a sample**. Random selection of a sample ensures that the sample is representative of the broad population; it is typically used in a survey (i.e., an observational study). Random allocation ensures the experimental and control groups are equivalent, but does not ensure they are representative of the broad population. Indeed, they are most likely not, as they all have the disease being studied.


Randomized controlled trial
Ethics review of study
Eligible patients
Informed consent
Randomization
Treatment
Control
Outcome
Outcome

Experimental Group

- receive new intervention
- (also called treatment group or intervention group interchangeably)

Control Group

- can be
  - conventional practice
  - no intervention (this may be conventional practice)
  - placebo

Exclusion and inclusion criteria should be applied identically to both groups in the study.

SPECIAL CONSIDERATIONS

Placebo effect is an effect attributed to the expectation that a therapy will have an effect or side effect. Placebo effect is due to the power of suggestion.

Blinding is the process used in which the participants, investigators and/or assessors remain ignorant concerning the treatments which participants are receiving. The aim is to minimize observer bias, in which the assessor, the person making a measurement, have a prior interest or belief that one treatment is better than another, and therefore scores one better than another just because of that.

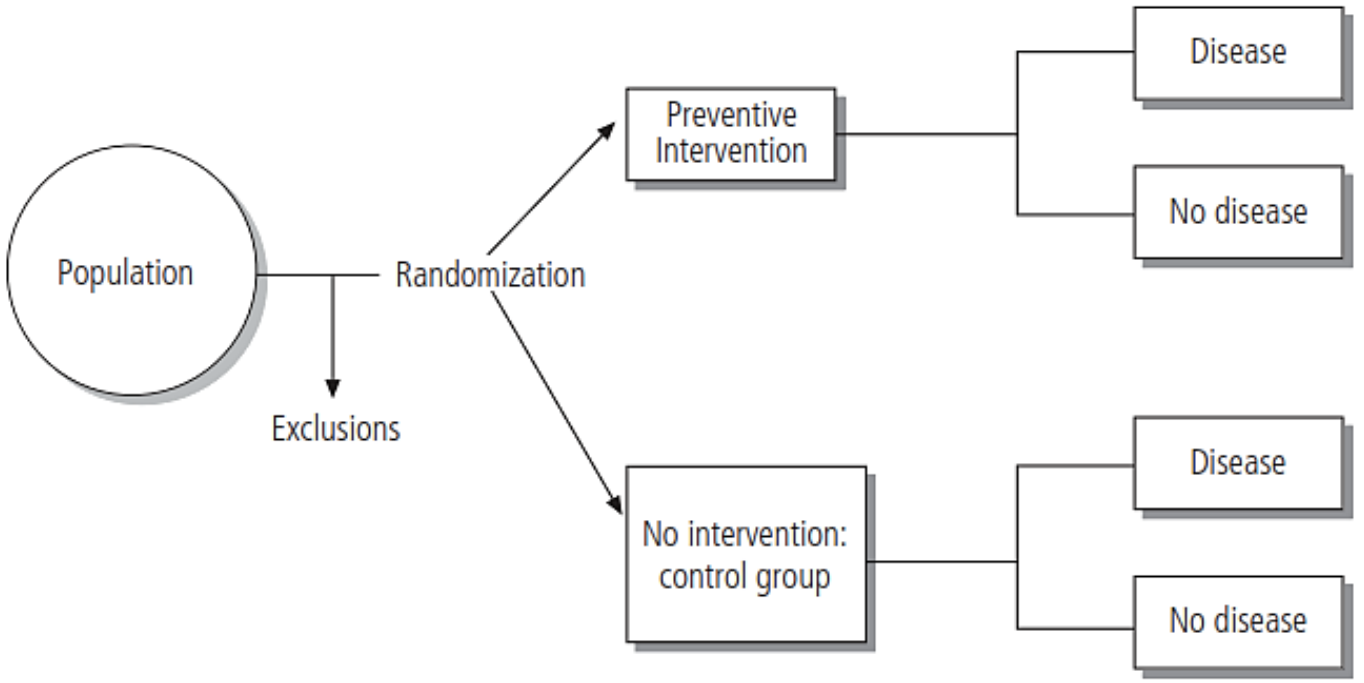
Example 7.2. *A randomized trial was carried out among Whitehall (English) civil servants to measure in middle-aged men the health effects of stopping smoking. A total of 1445 male cigarette smokers aged 40–59 years who were at a high risk of developing cardiorespiratory diseases were randomly allocated to intervention (714 men) or normal care (731 men). Those in the intervention group received individual advice on the relation of smoking to health. Most then expressed their wish to stop smoking and received further support over the next 12 months. The two groups were then followed up for twenty years (Rose & Colwell, 1992).*

FIELD TRIALS

CHARACTERISTICS

- Involve people who are healthy but presumed to be at risk;
- Data collection takes place “in the field” – usually among non-institutionalized people in the general population;
- Can be used to evaluate interventions – Salk vaccine for prevention of poliomyelitis.

Figure 3.8. Design of a field trial



Example 7.3. *The Community Intervention Trial for Smoking Cessation (COMMIT) was a multicentre project designed to evaluate a community-wide smoking cessation programme in the USA. This trial began in 1989 in 11 matched pairs of communities. One community of each pair was randomly assigned to receive the smoking cessation programme with the other acting as a control. The intervention was designed to promote smoking cessation by using a wide range of community resources to affect attitudes and policies towards smoking (COMMIT Research Group, 1991).*

COMMUNITY TRIALS

CHARACTERISTICS

- Treatment groups are communities rather than individuals;
- Appropriate for diseases that are influenced by social conditions and for which prevention efforts target group behaviour;
- Targetting everyone may prevent more cases of disease than targetting just high-risk individuals;
- Environmental modifications may be easier to accomplish than large-scale voluntary behaviour change;
- Community interventions reach people in their “native habitat”;
- Community interventions can be logistically simpler and less costly since they avoid the step of sorting the population into risk groups typical for “high-risk” strategies.

LIMITATIONS

- Random allocation of communities is not pactical.
- Only a small number of communities can be included.
- It is difficult to isolate communities where intervention is taking place from general social changes.
- Definitive conclusions about the overall effectiveness of the community wide efforts are not always possible.

Box 3.6. Stanford Five-City Community Intervention Trial

The Stanford Five-City Project started in 1978 as one of several community intervention studies designed to lower population risk of cardiovascular disease. Researchers believed that the community approach was the best way to address the large compounded risk of mild elevations of multiple risk factors and the interrelation of several health behaviours. Although some components of the intervention proved effective when evaluated individually (for example, efficiency of the mass media and other community-wide programs), large, favourable changes in risk factor also occurred in the control sites. Part of the problem was related to design limitations. Internal validity was compromised by the fact that only a few intervention units could be studied in sufficient detail. Researchers also noted the need to improve educational interventions and expand the environmental and health policy components of health promotion.[19]

ADVANTAGES AND DISADVANTAGES OF INTERVENTION TRIALS

- The main advantages of this type of study are:

1. *Random allocation* of subjects ensures that allocation of subjects to the different study groups is unaffected by selection bias.
2. *Random allocation* ensures that the groups are well balanced in relation to known and, more importantly, unknown factors that may affect the outcome(s) of the study (provided the study is sufficiently large).
3. If the allocation is *double-blind*, measurement bias is also minimized.
4. *Multiple outcomes* can be studied for any one intervention.
5. Incidence of disease can be measured in the various study groups.

- The main disadvantages of this type of study are:

1. Intervention trials, particularly field trials, are large enterprises. They are very expensive and time-consuming.
2. They may raise important ethical problems.
3. It may be difficult to ensure compliance and avoid contamination throughout the trial, particularly in trials of long duration.

BIASES

Table 3.4. Advantages and disadvantages of different observational study designs

	Ecological	Cross-sectional	Case-control	Cohort
Probability of:				
selection bias	NA	medium	high	low
recall bias	NA	high	high	low
loss to follow-up	NA	NA	low	high
confounding	High	medium	medium	medium
time required	Low	medium	medium	high
cost	Low	medium	medium	high

NA: not applicable.

BIASES MENTIONED TILL NOW

- Ecollogical fallacy
- Selection bias: *Any aspect of the way subjects are assembled in the study that creates a systematic difference between the compared populations that is not due to the association under study.*
- Information bias: *Any aspect of the way information is collected in the study that creates a systematic difference between the compared populations that is not due to the association under study.*
- Responder bias /recall bias/
- Loss to follow-up
- The effects of non-participation
- Healthy worker effect

SOMETHING MORE ABOUT CONFOUNDING

AN EXAMPLE: WHO CAN RUN FASTER, MEN OR WOMEN?

Exposure = gender Outcome = speed

Null Hypothesis: average speed of men = average speed of women

All men and women in one town invited to participate in a road race. On race day, both men and women come and race. The average running time for the men is faster than the women.

CONCLUSION: Men run faster than women because of their gender.

AN EXAMPLE: WHO CAN RUN FASTER, MEN OR WOMEN?

But Wait! Someone notices that women with young children did not race. In fact, women who ran the race were, on average, older than men who ran. For example, the average age of women was 50 years while the average age of men was 25 years.

CONCLUSION: Perhaps men were faster not because of their gender, but because they were younger.

AN EXAMPLE: WHO CAN RUN FASTER, MEN OR WOMEN?

So another race is held, this time making sure ages in the two compared groups (men and women) are comparable. That is, the men and women have same distribution of ages.

Race result: Once again, men are faster.

CONCLUSION: Controlling for age, men are still faster than women.

AN EXAMPLE: WHO CAN RUN FASTER, MEN OR WOMEN?

BUT WAIT! Someone points out that the men are, on average, taller than the women.

CONCLUSION: Perhaps men were faster not due to their gender, but because their legs are longer.

So another race is held, this time making sure heights and ages in the two groups (men and women) are comparable.

Race result: Once again, men are faster.

AN EXAMPLE: WHO CAN RUN FASTER, MEN OR WOMEN?

BUT WAIT! Someone points out that 50% of the women had hair longer than their shoulders, and only 5% of the men did!

CONCLUSION??? Long hair made the women run slower.

Is this a reasonable conclusion?

LESSONS FROM THE ROAD RACE: CRITERIA FOR A CHARACTERISTIC TO BE A CONFOUNDER

In general, for a characteristic to be a potential confounder, it **must be associated with both the disease (outcome) and the exposure under study.** (Why are age and height competing explanations, but not hair length?)

The confounder must be associated with the disease independently of the exposure.

Age and height are associated with speed regardless of gender. Taller people (both men and women) have greater speed. Younger people (both men and women) have greater speed.

CONTROLLING FOR CONFOUNDING IN THE DESIGN PHASE

Randomization - with sufficient sample size, randomization is **likely to control** for both known and **unknown confounders**.

Restriction - restrict admissibility criteria for study subjects and limit entrance to individuals who fall within a specified category of the confounder (**known confounder**).

Example: In the road race, you can restrict the race to people in a certain age range (say, 25-30) or to people in given height range.

CONTROLLING FOR CONFOUNDING IN THE DESIGN PHASE

Matching - select study subjects so that the potential confounders are distributed in an identical manner among the exposed and unexposed groups (cohort study) or among the cases and controls (case control study)

Example: matching in cohort study of exercise and heart attack.

Two groups: exercisers and non-exercisers

Confounders to be matched: age, sex, smoking

Exposed subject is a 45 year old female who doesn't smoke

Thus, you need to find an unexposed subject who is a 45 year old female who doesn't smoke. (Can loosen the age match to 45 + or – a couple of years)

CAUSATION IN EPIDEMIOLOGY

DEFINITION OF CAUSALITY

- Causality can be defined as cause effect relationship
- In epidemiology cause is the exposure and effect is disease or death
- Causal relation is a complex phenomenon

HOW TO ESTABLISH CAUSAL INFERENCE

For infectious disease → Koch's postulate

For chronic disease → Hill's criteria

HENLE-KOCH POSTULATE (1884)

- The parasite must be present in all who have the disease.
- The parasite can never occur in healthy persons.
- The parasite can be isolated, cultured and capable of passing the disease to healthy experimental animal.
- The organism must be isolated from the experimentally infected animal.

LIMITATIONS OF KOCH POSTULATE

- Disease production may require co-factors.
- Viruses cannot be cultured like bacteria because viruses need living cells in which to grow.
- Pathogenic viruses can be present without clinical disease (sub-clinical infections, carrier states).

The Bradford-Hill criteria (J Roy Soc Med 1965:58:295-300)

1. Strength of the association.

According to Hill, the stronger the association between a risk factor and outcome, the more likely the relationship is to be causal.

2. Consistency of findings.

Have the same findings must be observed among different populations, in different study designs and different times?

3. Specificity of the association.

There must be a one to one relationship between cause and outcome.

4. Temporal sequence of association.

Exposure must precede outcome.

5. Biological gradient.

Change in disease rates should follow from corresponding changes in exposure (dose-response).

6. Biological plausibility.

Presence of a potential biological mechanism. Does the association make sense biologically?

7. Coherence.

Does the relationship agree with the current knowledge of the natural history/biology of the disease?

8. Experiment.

Does the removal of the exposure alter the frequency of the outcome?

9. Analogy.

Have there been similar situations in the past?

Strength of Association

- How strong is strong (rule of thumb)

Relative risk	"Meaning"
1.1-1.3	Weak
1.4-1.7	Modest
1.8-3.0	Moderate
3-8	Strong
8-16	Very strong
16-40	Dramatic
40+	Overwhelming

Specificity

- This means a cause lead to a single effect, not multiple effect
- However, a single cause often leads to multiple effect. Smoking is a perfect example

Table 5.3. Relative ability of different types of study to "prove" causation

Type of study	Ability to "prove" causation
Randomized controlled trials	Strong
Cohort studies	Moderate
Case-control studies	Moderate
Cross-sectional studies	Weak
Ecological studies	Weak