SCIENTIFIC MEDICAL RESEARCH

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LECTURE: 10+11+12

Chapter 12: Experimental Studies

12.1 Overview:

A useful video

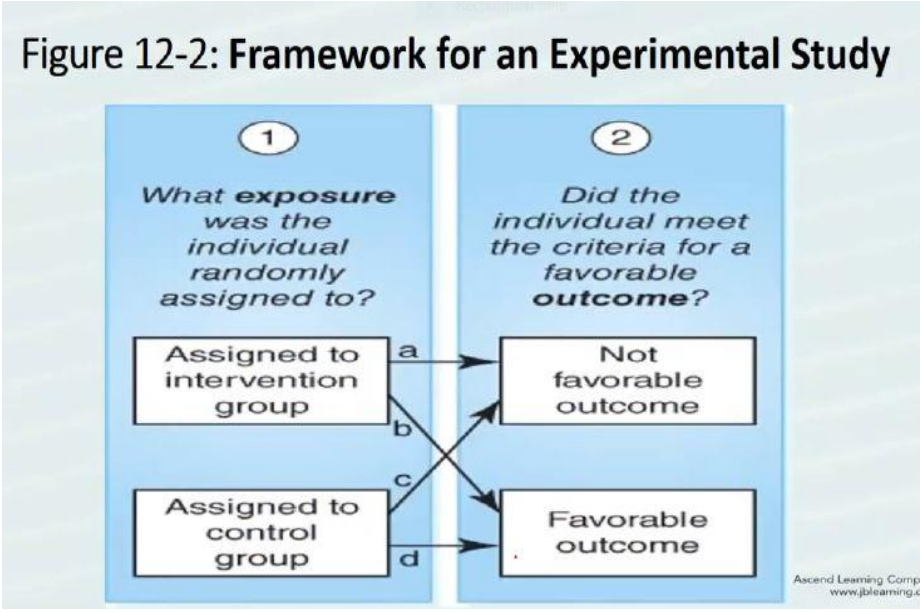
Experimental studies (intervention studies): Assigns participants to intervention and control groups in order to best whether an intervention causes an intended outcome

- **Assign participants to receive a particular exposure**
- Experimental studies like Randomized controlled trials (RCTs) are the gold standard for **assessing causality**
- in **random sampling** (used in the observational studies) we select randomly the participants from the whole population ,but in **randomization**(used in experimental studies) we know exactly who are the participants we will select(corona patients ,COPD patients ,,,) but the randomization is in the selecting of control group and intervention group.
- Randomization ensures that the two study groups (control &intervention) are **comparable**(the variables are equally distributed between the two groups)

FIGURE 12-1 Key Characteristics of Experimental Studies

Objective	Compare outcomes in participants assigned to an intervention or control group
Primary study question	Does the exposure cause the outcome?
Population	Similar participants are randomly assigned to an intervention or control group.
When to use this approach	Assessing causality
Requirement	The experiment is ethically justifiable.
First steps	1. Decide on the intervention and eligibility criteria. 2. Define what will constitute a favorable outcome. 3. Decide what control is an appropriate comparison for the intervention. 4. Decide whether blinding will be used to prevent participants and/or the researchers who will assess outcomes from knowing whether a participant has been assigned to the intervention or the control group. 5. Select the method for randomizing participants to an intervention or control group.
What to watch out for	Noncompliance
Key statistical measure	Efficacy

Figure 12-2: **Framework for an Experimental Study**



12.2 Describing the intervention:

- What will the intervention be ?
- What are the eligibility criteria for participants ?
- Where and how will participants receive the intervention?
- When, how often ,and for what duration will participants receive the intervention ?

12.3 Defining Outcomes:

- **Superiority trials** aim to demonstrate that a new intervention is better than some type of control
- Researchers must carefully define what constitutes a favorable outcome for an individual participant and for the experimental study as a whole

FIGURE 12-3 Types of Success

Goal	Success
Superiority trial	The intervention is better than the control.
Noninferiority trial	The intervention is not worse than the control.
Equivalence trial	The intervention is equal to the control.

FIGURE 12-4 Examples of Favorable Outcomes

Intervention	Intended Outcome	Favorable Outcome for an Individual	Unfavorable Outcome for an Individual	Favorable Outcome for the Study Population
New diet- and exercise-based weight-loss Program	Significant weight loss	The loss of ≥10% body weight and maintenance of lower weight for ≥ 6 months	The loss of <10% body weight or failure to maintain weight loss of ≥10% or more for ≥ 6 months	The proportion of those who lose at least 10% of their body weight and maintain that loss for at least 6 months is higher in the intervention group than in the control group.
New drug therapy	Improvement of the quality of life for those with a particular disease condition	Improvement in quality of life	Failure to demonstrate improvement in quality of life	The rate of improvement in the drug therapy (intervention) group is higher than the improvement rate in the placebo (control) group, according to a carefully defined and validated set of criteria for what constitutes improvement.
New preventive vaccine	The prevention of infection	Incident infection does not occur	Incident infection occurs	The incidence of infection in the vaccinated (intervention) group is lower than the incidence of infection in the unvaccinated (control) group, as confirmed by laboratory testing.

12.4 Selecting Controls:

one commonly used type of Control is a placebo

- ***Placebo***: an inactive comparison that is similar to the therapy being test
- Some studies may compare the new therapy to some existing ***standard of care(***. we can call it metaphorically a placebo)
- ***Various*** combinations of doses and durations of an intervention can be compared using a ***factorial design***
- Participants may serve as there own controls in a ***crossover design***

FIGURE 12-5 Examples of Types of Controls

Type of Control	Active Intervention	Comparison
Placebo/inactive comparison	Active pill	Inactive pill
	Injection of an active substance	Injection of saline solution
	Acupuncture needles inserted at acupuncture points	Acupuncture needles inserted at locations in the body that are not acupuncture points (sham acupuncture)
	Some other active ingredient	An inactive substance that is indistinguishable from the active intervention in terms of appearance, odor, taste, texture, and delivery mechanism
Active comparison/ standard of care	New therapy	Current best therapy for the condition being studied
	New therapy	Current standard therapy
	New therapy	Some other existing therapy
	Current therapy plus new therapy	Current therapy alone
Dose-response	Some dose of a medication	Alternate doses of the medication
	Some duration of a therapy	Alternate durations of the therapy
No intervention	New intervention	Participants assigned to the control group are asked to maintain their usual routines.
Self	New intervention	Each participant's status before the intervention is compared to his or her own status after the intervention.
	New intervention	Each participant receives the new intervention for some duration and the comparison for some duration, preferably in a random order.

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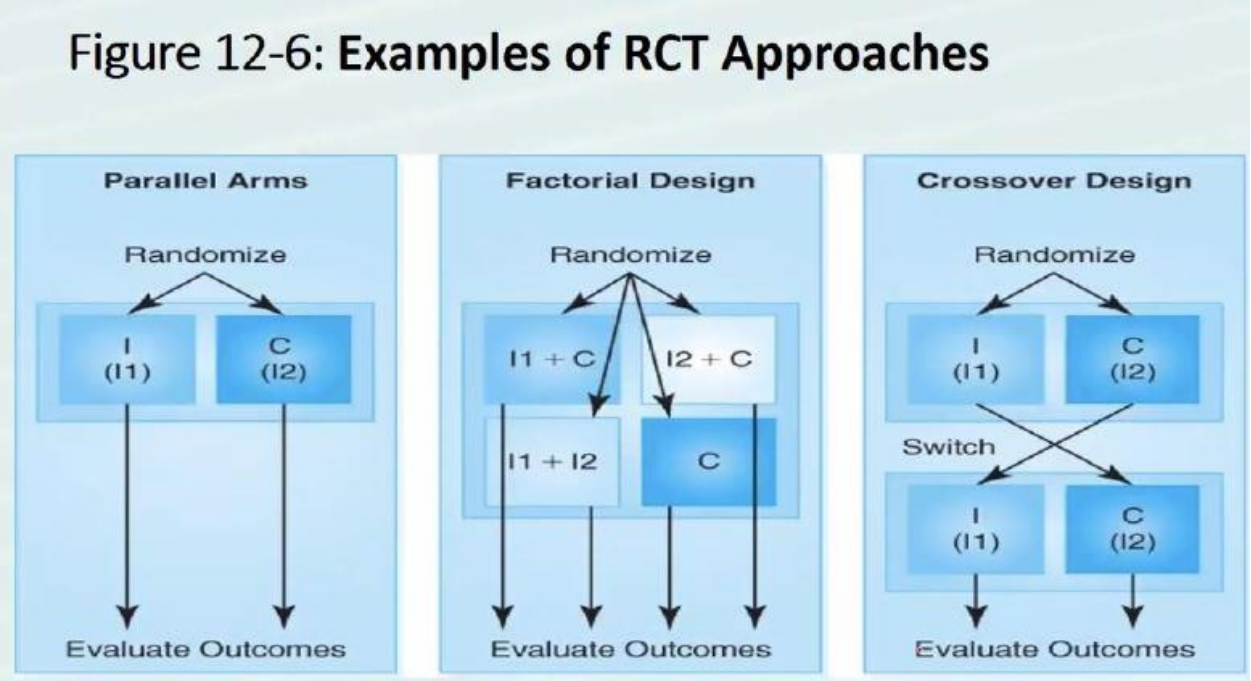
Examples of RCT approaches :

1-**Crossover Design** :every participant has the same probability to be selected in control group or intervention group

2-**Factorial Design** : we have more than one control group, or more than one intervention group, so we compare different interventions in various combinations (Ex. We give a certain drug to 3 different groups ,each of them with a different dose)



****_Hawthrone effect_** :Participants in both the active and comparison groups may change there behavior to better because they know they are being tested

12.5 blinding (masking):

**Is an experimental design element that keeps participants (and sometimes some members of the research team) from knowing whether a participant is in the active intervention group or the control group.

- we have 2 types of blinding :

  1-**A single-blind experimental study**, participants do not know whether they are in an active

  group or a control group.

  2- **A double-blind experimental study**, neither the participants nor the researchers

  assessing the participants' health status know which participants are in an active or control group.

- Blinding is intended to minimize **information bias**….. (bias) in an epidemiological study that arises due to systematic measurement error.
- There are many **types** of information bias:

  1-**Reporting bias** occurs when members of one study group systematically underreport or overreport an osure or outcome.

  2-**Detection bias**, also called surveillance bias, occurs when a population group that is routinely screened for adverse health conditions incorrectly appears to have a higher-than-typical rate of disease because more frequent testing enables a higher case detection rate in that population than in the general population.

  3-**Observer bias** occurs when an observer (a researcher) intentionally or unintentionally evaluates participants differently based on their group membership, such as systematically evaluating cases and controls in a case–control study differently.

- Blinding prevents participants and assessors from being able to evaluate outcomes differently based on the results they expect for an exposure.
- Blinding ensures that participants in the active intervention group will not report more favorable results simply because they expect a positive outcome.
- It also keeps assessors from intentionally or unconsciously recording more favorable results for participants in the active intervention group.
- Blinding is usually possible only when all participants are assigned to similar exposures.(e.g : If participants in both the active intervention group and the control group are taking pills (of the same color, shape, size, and taste) or if both are getting injections, a blinded study may be possible. In contrast, if the active intervention is a special diet and the controls eat their usual diets, if the active group will participate in exercise classes and the controls will be on their own, or if the active intervention will include both diet and exercise components and the control only a diet plan, then a blinded study may not be possible.
- To minimize the risk of bias in studies that are not blinded, it is helpful to identify **objective** outcome measures such as laboratory tests rather than relying on **subjective** outcome measures such as participants' self-reported feelings.

12.6 Randomization:

Randomization is the assignment of participants to an exposure group in an experimental study using a chance- based method that minimizes several types of possible bias.

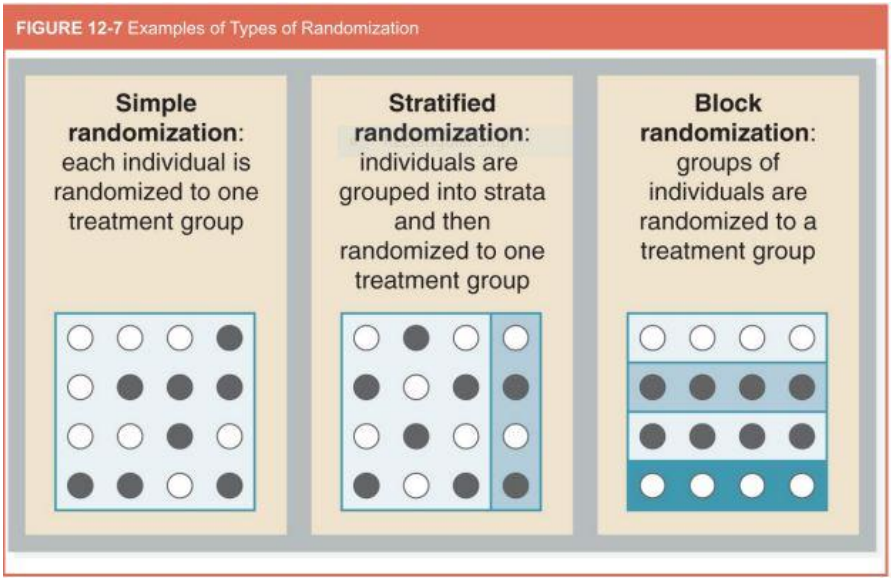
Randomization mitigates the allocation bias that might occur as a result of non-random assignment of participants to experimental study groups, such as when people with different exposure histories are not equally distributed across treatment arms.

There are many types of randomization:

1-Simple randomization is the use of a coin toss, a random number generator, or some other simple mechanism to randomly assign each individual in an experimental study to one of the exposure groups.

2-Stratified randomization is the division of a population into subgroups prior to randomly but systematically assigning each individual within each subgroup to one of the exposure groups in an experimental study.

- Stratified randomization is used when **it is important for members of certain subpopulations to be distributed evenly across the treatment arms of a trial**. For example, suppose that 75% of the volunteers for a study are female and only 25% are male. Stratified randomization can ensure that enough males are assigned to the intervention group. The list of female volunteers can be sorted into alphabetical order by last name, and then every other individual in the ordered list can be assigned to the active group. This same process can be repeated with the male volunteers. This stratified process will ensure that half of the females and half of the males are assigned to the intervention group.
  3-Block randomization is an allocation method that randomly assigns groups of people to an intervention group and other groups of people to a control group. In this method, randomization occurs at the group rather than individual level. For example, if there were 10 elementary schools in a county, schools could be randomly assigned to be intervention or control schools. All of the students in the 5 schools randomly assigned to the intervention group would receive the intervention. All of the students in the other 5 schools would be assigned to the comparison.



- Some experimental studies use nonrandomized approaches because randomization is unethical or is not feasible. A quasi-experimental design is an experimental study that assigns participants to an intervention or control group using a nonrandom method. Other than using a nonrandom method to assign participants to exposure groups, most quasi-experimental studies use methods similar to those of randomized studies. Most quasi-experimental studies use both pre- and post-intervention tests to compare the two arms of a controlled study. However, some quasi-experimental studies have no control group, and some use only a post-intervention
assessment (with or without a control group).
A natural experiment is a research study in which the independent variable is not
manipulated by the researcher but instead changes due to external forces. For example, a researcher may seek to understand the impact of a devastating tornado on the health of residents of the affected community by comparing residents in the damaged areas to residents of neighboring areas who were not directly harmed by the twister. Or suppose that a hospital announces that it will implement a new infection control policy.
group. These are not true
experimental studies because the "interventions"—a natural disaster and a policy change—are not ones that can be manipulated by a researcher, but they can be evaluated using analytic methods similar to those used for true experiments.

12.7 Ethical Considerations:

Number of issues, such as the following, must be considered before initiating an experimental study :

- The principle of equipoise states that experimental research should be conducted only when there is genuine uncertainty about which treatment will work better.
- The principle of distributive justice necessitates that the source population be an appropriate one and that the research study not exploit individuals from populations that are unlikely to have continued access to the therapy if it is found to be successful.
- The principle of respect for persons requires that all participants volunteer for a study without being unduly influenced by the prospect of being compensated for their participation. Respect also requires that all participants understand what it means to be a research subject, including the possibility of being assigned to a control group instead of the new intervention.
- The principles of beneficence and nonmaleficence require that researchers balance the likely benefits and risks of the study.
- Researchers must make careful decisions about when to use a placebo or another type of control, must put in place a system for monitoring adverse reactions, and must identify the conditions under which an experiment would be discontinued early either because the exposure proves to be risky or because the new intervention appears to be so beneficial that keeping it from the control group would be unethical

- An adverse event is a negative outcome that may be the direct result of a study-related exposure or may be a coincidental occurrence that is not directly related to the study but happens after an individual receives a study-related exposure..

FIGURE 12-8 Examples of Ethical Issues in Experimental Studies

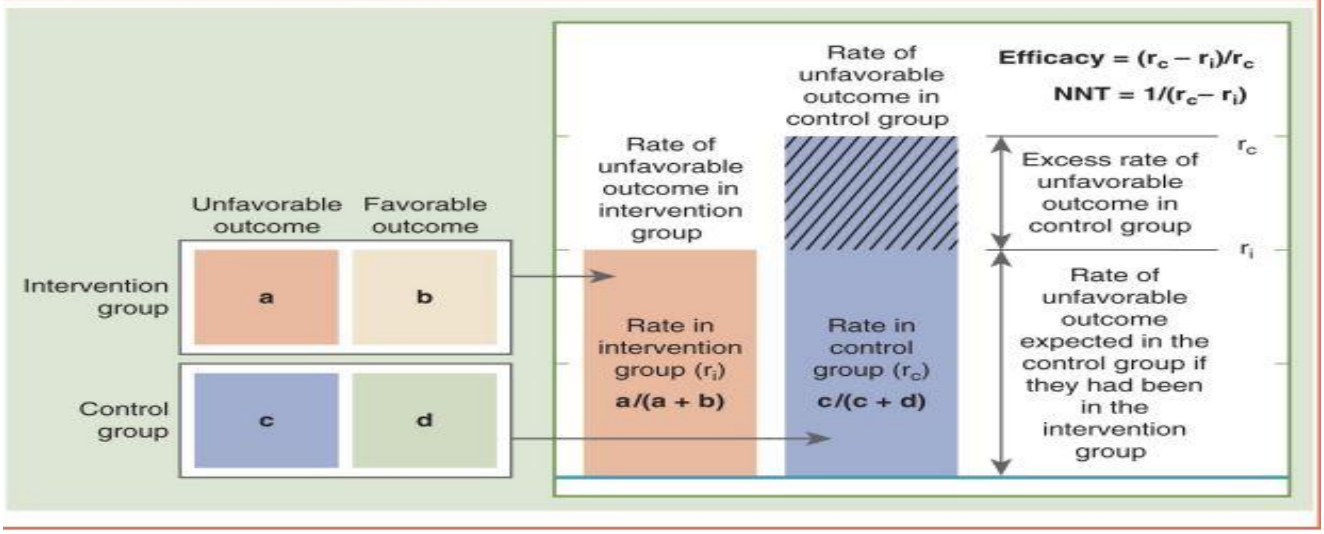
Study Stage	Examples of Questions to Ask
Study topic selection	▪ Is the study really necessary (equipoise)? ▪ Is an experimental design truly necessary?
Recruitment	▪ Is the source population an appropriate and justifiable one? ▪ Is the inducement to participate appropriate and not coercive?
Randomization	▪ Do participants truly understand that they might not receive the active intervention? ▪ Is it appropriate to use a placebo? Is it appropriate to use some other control?
Data collection	▪ How will adverse outcomes be monitored and addressed? ▪ When might an experiment need to be discontinued early?
Follow-up	▪ What happens if a participant experiences study-related harm after the conclusion of the study? ▪ Will participants have continuing access to the therapy if it is shown to be successful?

12.8 Efficacy:

Experimental studies use the statistics to quantify the impact of assigned exposure on the likelihood of having a favorable of an unfavorable outcome

Efficacy is a measure of the success of an intervention that is calculated as the proportion of individuals in the control group who experienced an unfavorable outcome but could have expected to have a favorable outcome if they had been assigned to the active group instead of the control group. A high efficacy is an indication that an intervention is successful. Efficacy typically refers to results under ideal circumstances,

FIGURE 12-9 Efficacy and Number Needed to Treat



- **The number needed to treat (NNT**) is the expected number of people who would have to receive a treatment to prevent an unfavourable outcome in one of those people (or, alternately stated, to achieve a favourable outcome in one person). A small NNT indicates a more effective intervention. If a drug intended to prevent stroke has an NNT of 5, then 5 people have to take the drug for 1 year (or some other specified time period) to prevent 1 of the 5 from having a stroke. If the drug has an NNT of 102, then 102 people have to take the drug to prevent 1 of the 102 from having a stroke.
- **The number needed to harm (NNH**) is the number of people who would need to receive a particular treatment in order to expect that one of those people would have a particular adverse outcome. A large NNH indicates a safer intervention. NNT and NNH are often used for cost-effectiveness analysis.

- **Effectiveness** is calculated with the same equation as efficacy but refers to results obtained under real-world, less-than-ideal conditions. For example, in a real-world setting, some participants might skip some doses of an

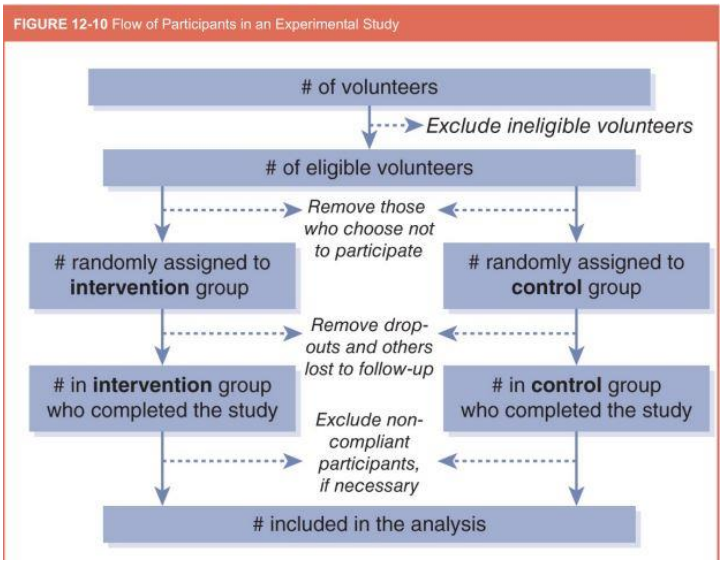
experimental drug, or they might not take the doses at the exact specified times, or they might not store the pills at the ideal temperature.

- **Efficiency** is an evaluation of the cost-effectiveness of an intervention that is based on both its effectiveness and resource considerations.

- Analysis for experimental studies typically uses either a **treatment-received approach** or **a treatment-assigned approach**.

  A treatment-received analysis of experimental data includes only the participants who were fully compliant with their assigned intervention or comparison protocol. Treatment-received analysis allows for the calculation of efficacy

  A treatment-assigned analysis (or intention-to-treat analysis) includes all participants, even if they were not fully compliant with their assigned protocol. Treatment-assigned analysis is better at measuring real-world (rather than ideal-world) effectiveness.



12.9 Screening and Diagnostic Test:

The goal of some studies of screening or diagnostic tests is to compare two assessment that are supposed to measure the same thing

A useful video

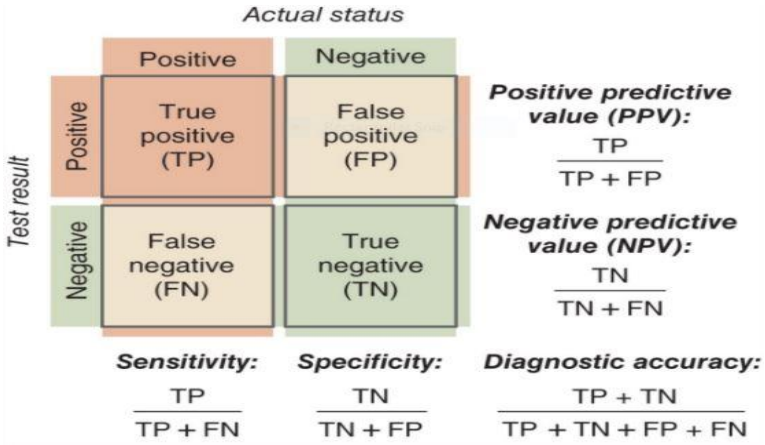
- A good test will have a value near 100% for the following **four** calculations :

1-**The sensitivity**, or true positive rate, is the proportion of people who actually have a disease (according to the reference standard) who test positive using the new test.

2-**The specificity**, or true negative rate, is the proportion of people who do not have the disease who test negative with the new test.

3-**The positive predictive value (PPV)** is the proportion of people who test positive with the new test who actually have the disease (according to the reference standard).

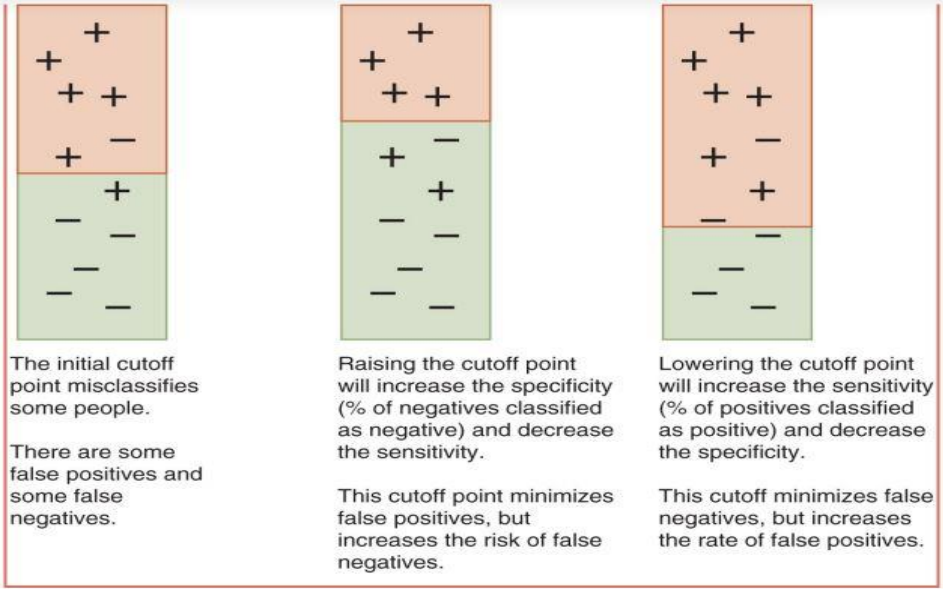
4-**The negative predictive value (NPV)** is the proportion of people who test negative who actually do not have the disease



For tests with a flexible cutoff point for defining positive and negative test results, there is always a trade-off between sensitivity and specificity (Figure 12-12). Increasing the sensitivity decreases the specificity. Increasing the specificity decreases the sensitivity. Consider the use of systolic blood pressure as a sign of hypertension

.Suppose that the cutoff for being classified as having clinically high blood pressure is reduced from 160 mm Hg to 140 mm Hg. The sensitivity of the test will increase, because a higher percentage of people with hypertension will be classified as hypertensive. The specificity will decrease, because a lower percentage of people without hypertension will be correctly classified as not being hypertensive

Three other measures are also commonly used for screening tests:
1- diagnostic accuracy → is the percentage of the participants who where either turn positive or true negative
2- positive likelihood ratio → examine whether anew test is good at predicting the presence of disease
3- negative likelihood ratio → examine whether a new test is good at predicting the absence of disease



The initial cutoff point misclassifies some people.

There are some false positives and some false negatives.

Raising the cutoff point will increase the specificity (% of negatives classified as negative) and decrease the sensitivity.

This cutoff point minimizes false positives, but increases the risk of false negatives.

Lowering the cutoff point will increase the sensitivity (% of positives classified as positive) and decrease the specificity.

This cutoff minimizes false negatives, but increases the rate of false positives.

*Chapter 13 is NOT included in the course

Chapter 14: Correlational Studies

14.1 Overview:

Useful videos : 1

2

- A ***correlational study/ecological study/aggregate study*** uses population-level data to look for associations between two or more group characteristics.
- No individual-level data are used.

Ex: we have 1000 participants , 200 of them have a stroke ,and the rest are not(we do not have control/case groups ,the same group is already divided) .So we look at the characteristics of each of the two groups.

FIGURE 14-1 Key Characteristics of Correlational (Ecological) Studies

Objective	Compare average levels of exposure and disease in several populations
Primary study question	Do populations with a higher rate of exposure have a higher rate of disease?
Population	Existing population-level data are used; there are no individual participants.
When to use this approach	The aim is to explore possible associations between an exposure and a disease using population-level data.
Requirement	The topic has not been previously explored using individual-level data.
First steps	1. Select the sources of data that will be used. 2. Decide on the variables to include in the analysis.
What to watch out for	The ecological fallacy Limited publication venues
Key statistical measure	Correlation

14.2 Aggregate Data:

- At least two population-level indicators must be available for each population (defined by place or time).
- These "exposures" and "outcomes" must be measured similarly in all populations being compared.

FIGURE 14-2 Sample Data Table

Population	Exposure 1	Outcome 1
A	48.2	14.1
B	65.1	17.0
C	37.8	14.9

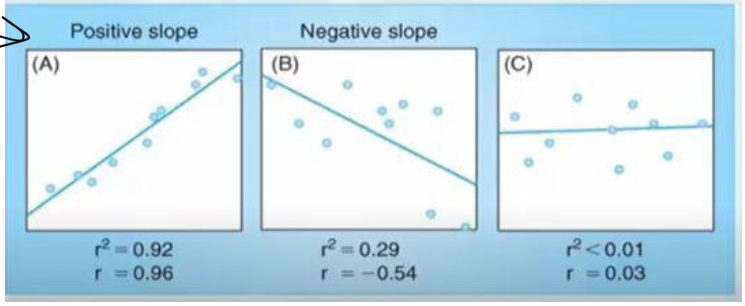
14.3 Correlation:

*the type of equation we use to represent the correlation depends on the level of the measurements of the variables (continuous, categorical ….)

* r^2 represent the significance

a- A positive slope → shows that higher levels of exposure are associated with higher rate of disease
b- A negative slope → snows that higher level of exposure are associated with lower rate of disease

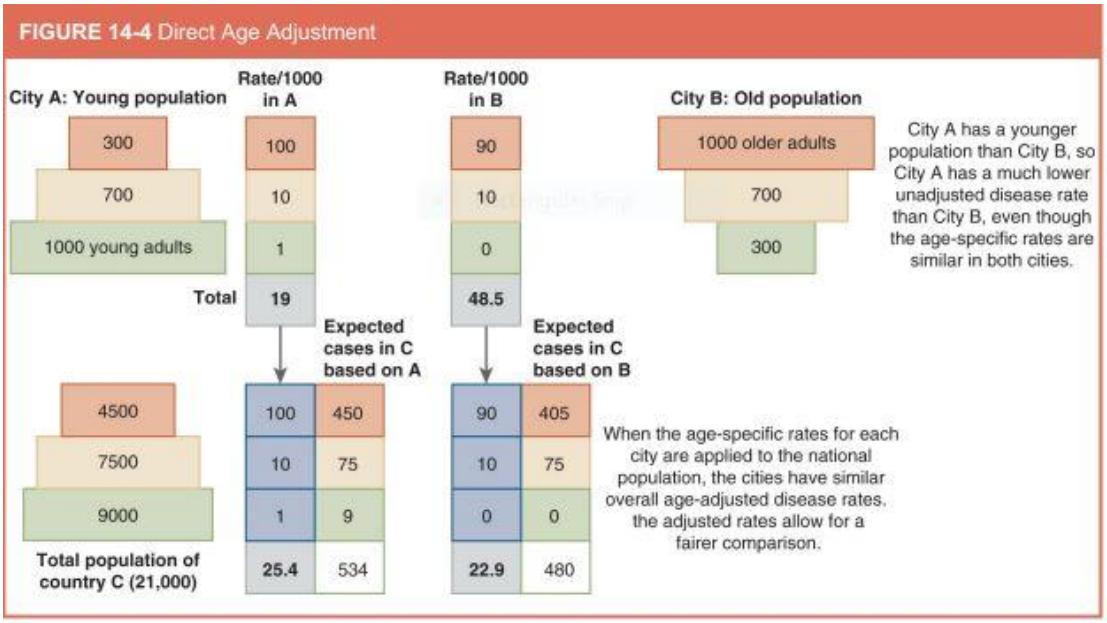
- For a two-variable analysis, plot each population on a scatterplot with the "exposure" on the *x*-axis and the "outcome" on the *y*-axis.
- A best-fit line defines the correlation (*r*) between the two variables.
- Use linear regression to fit more complex models of



14.4 Age adjustment:

- Use age-adjustment to more fairly compare two populations with very different age distributions.
- ***Direct age adjustment*** requires knowing age-specific rates of exposure and/or disease as well as the age distributions of the populations being compared.
- ***Indirect age adjustment*** does not require age-specific rates.

- The ***ecological fallacy*** is the incorrect attribution of population-level associations to individuals.



كان ابن مسعود ‹رضي الله عنه› يقول:

‹إني لأكره أن أرى الرجل فارغا، لا في عمل آخرة ولا في عمل دنيا›