5

Scientific Medical Research

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NOTE: All the details in the tables are required.

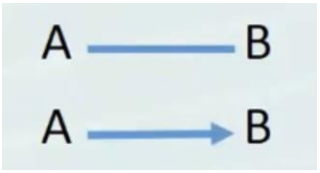
Today's lecture is about the last 2 study approaches: -

12.1 Experimental studies: (intervention studies), these studies assign participants to receive a particular exposure (Certain drug, diet program…. etc.)

The primary distinction is that observational designs (such as cross-sectional, case-control, and cohort studies) do not "do" anything to participants; they simply ask for a report on participants' experience while experimental studies do intervene.

Example: an observational study may ask whether participants eat or do not eat an apple a day, run or do not run on a treadmill. In contrast, an experimental study may assign some or all study participants to eat one red delicious apple daily, run on treadmill every other day, take a pill every 12 hours, or read a health brochure.

Experimental studies are the gold standard for assessing causality especially RCT.



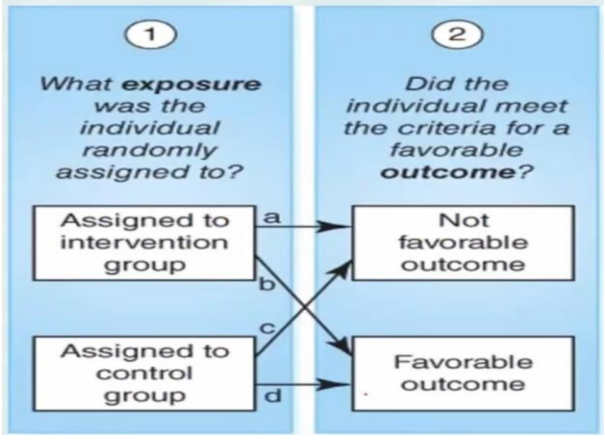
When we say that there is a **relationship** between A and B, this does not mean that A will necessarily lead to B.

But in experimental studies like RCT we can conclude for sure that A ***leads*** to B and that's what we mean by Assessing ***Causality***

They are used for clinical trials of new therapies, field trials of individual-level preventive interventions like vaccinations, and community trials (often cluster randomized trials) of public health and environmental interventions. Because the researcher assigns participants to receive a particular exposure; the exact dose, duration, and frequency of the exposure are known. The researcher knows when the exposure occurred, so the health status of each participant before and after the exposure may have caused a particular outcome.

A typical experimental study design in health science is a randomized controlled trial (RCT):

- Some participants are randomly assigned to an active intervention group.
- The remaining participants are assigned to a control group.
- Participants from both groups are followed forward in time to see who has a favorable outcome and who does not.



12.2 Describing the Intervention

The first step in an experimental study is to carefully define the intervention that participants assigned to and to decide on the person, place, and time (PPT) criteria for the study.

The description should state exactly: very strict requirements.

1-What the intervention will be.
2-The eligibility criteria for participants (inclusion and exclusion).
3-Where and how participants will receive the intervention.
4-When, how often, and for what duration participants will receive the intervention**.**

**The purpose of this description is that all participants in the intervention group should receive the same intervention (regarding when, how often, duration)

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

12.3 Defining Outcomes

Researcher must carefully define what constitutes a favorable outcome for an individual participant and for the experimental study as a whole. **These measures of success must be stipulated prior to the initiation of the study.**

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.

Because the term “better/improving quality of life” can be defined in so many ways, the researcher must carefully define what constitutes a favorable outcome.
1- Intervention is more effective than a current therapy at curing existing disease
2- New intervention is more effective than a placebo at preventing new disease fromoccurring.
3- Less expensive intervention and is therefore economically more favorable.
The measures of individual success can be translated as study success, if favorable result in intervention group is significantly greater than in control group.

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

Experimental studies usually assign some participants to the active intervention and the remainder to a control group.

One commonly used type of control is a placebo, an inactive comparison that is similar to the therapy being tested. **Examples of placebos** are a sugar pill used as a control for a pill with an active medication, a saline injection used as a control for an injection of an active substance , and a sham procedure that is designed to look and feel like a real clinical procedure= as a control for the active one.

The mere act of taking a pill or receiving some other form of therapy, even if it is inactive, is often enough to make recipients feel better. Placebo-controlled studies allow the effect of the active therapy to be examined separately from the boost in health status that people may experience simply by participating in a clinical trial or other intervention.
Some studies compare the new drug with standard of care to check if it's better and other times the new one may be given in addition to the existing one.

Types of control:

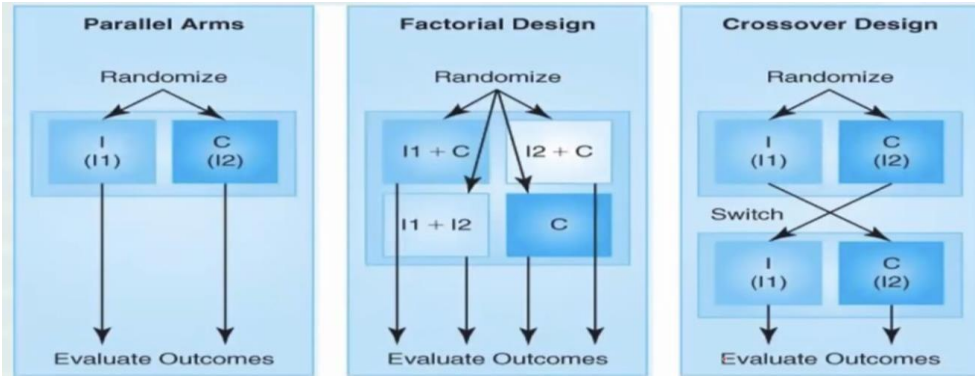
Type of Control	Active Intervention	Comparison
Placebo/inactive comparison	Active pill	Inactive pill
	Injection of an active substance	Injection of saline solution
	Acupuncture needles inserted at acupuncture points	Acupuncture needles inserted at locations in the body that are not acupuncture points (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.

Example on RCT approach:

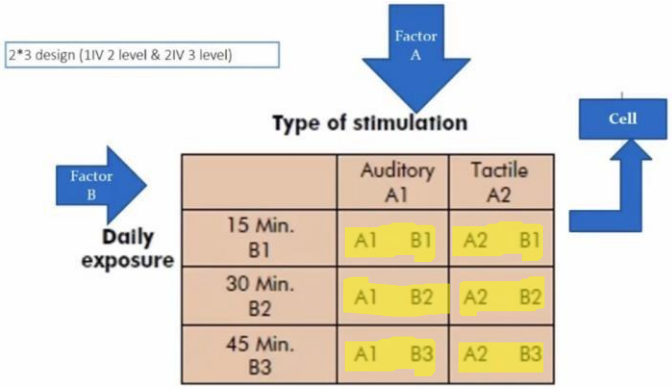
-Parallel arms (general): in this design, subjects are randomized to one or more study arms and each study arm will be allocated a different intervention, then we evaluate outcomes.

-Factorial design: different interventions are compared in various combinations (Intervention 1 + Control (placebo...etc.), Intervention 2 + Control (Placebo…etc.), Intervention 1 + Intervention 2, Control (Placebo…etc.)) within one randomized controlled trial, and then we evaluate the outcomes.

-Crossover Design: In which the researcher assigns some participants first to the active intervention and then the control and assigns other participants first to control and then to the active intervention, and then we evaluate the outcomes.



This is **an example on the factorial design**, we can see that we have Factor A which is the type of stimulation (Auditory A1, Tactile A2) and we have Factor B which is the daily exposure of this stimulation (15 Min B1, 30 Min B2, 45Min B3); so we will have 6 choices to analyze (highlighted above), in the conclusion we will have decided that this certain stimulation must be applied for this certain period of time .



Although experimental studies sometimes include a control group of participants who are randomly assigned to maintain their usual routines, this method is usually not preferred. The approach raises ethical concerns about discouraging the adoption of healthier lifestyles during the course of the study. It also raises concerns about the **Hawthorne effect (bias) that can occur when participants in a study change their behavior for the better because they know they are being observed.

> **For Example**, suppose a researcher is initiating a study of a new weight-loss program and plans to randomly assign participants either to the new therapy or to a usual routine group. In this situation, simply informing the controls that they will be weighed at the start and end of the study period will be enough to spur a sizable proportion of the control group to initiate an exercise program, start eating a healthier diet, or take other steps to lose weight. These changes may interfere with the accurate measurement of the impact of the new intervention.

12.5 Blinding (masking)

When participants in an experimental study and perhaps some research team members don't know whether a participant is in intervention or control group.

Single-blind study: participants are unaware of their exposure status.

Double-blind study: neither participants nor the person assessing the participants know.

Triple-blinded: even who distributes participants doesn't know

1- **Blinding minimizes the information bias** that can occur if participants or assessors are able to evaluate outcomes differently based on the results they expect for an exposure.

For example, blinding prevents participants in the active intervention group from reporting more favorable results because they expect a positive outcome.

2- **Blinding also prevents assessors from recording more favorable results**, either intentionally or unconsciously, for participants in the active intervention group, which would be a type of Observer bias.

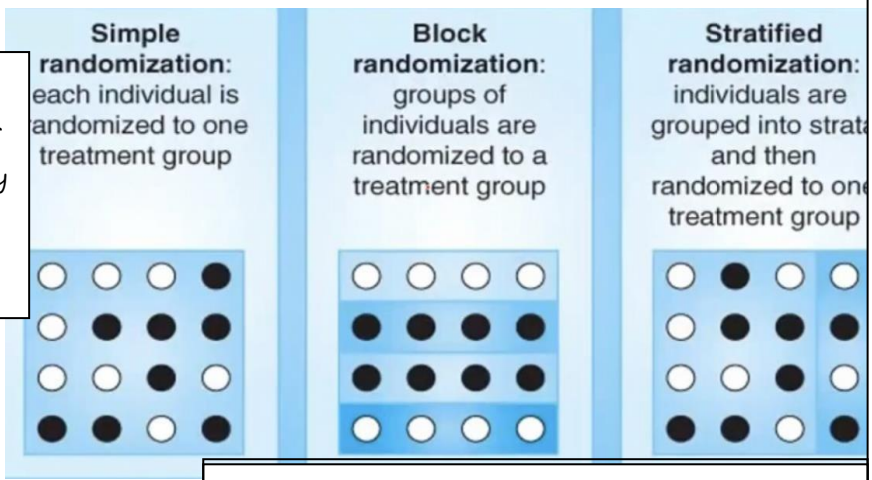
Blinding is possible when all participants are assigned to similar exposures. If participants in both the active intervention group and the control group are taking pills (of the same color, shape, size, and taste) or if both are getting injection.

In contrast, if the active group will participate in exercise classes and the controls will be on their own then a blinded study may not be possible. To minimize the likelihood of bias in studies that are not blinded, it is helpful to identify objective outcome measures (such as laboratory tests) rather than subjective outcome measures (such as participants' self-reported feelings).

12.6 Randomization

Assigning participants to an exposure group in an experimental study reduces several types of bias such as **allocation bias** (when people with different backgrounds not distributed across treatment arms) also the self-selection problems, but not the **selection bias** (people who volunteer are not representative of source population.

Uses coin toss, random number generator or any uncomplicated process



If we have 10 schools, all students from 5 of those schools randomly assigned to intervention and students from the other 5 schools into control

Stratified randomization randomly assigns individuals within certain subgroups to a particular exposure. Useful when simple randomization may not result in enough members of certain subgroups being randomized to each of the exposure groups.

For example, suppose that 75% of the volunteers for a study are F and only 25% are M. To ensure that enough males are assigned to the intervention group, two separate randomization processes one for females and one for males. This would ensure that 50% of the females are assigned to the intervention group along with 50% of the males.

BOOK STUFF: Non-randomize approaches may be needed when randomization is unethical or not feasible such as Quasi-experimental designs (most of them use pre- and post-intervention tests to compare to the 2 arms of a controlled study. Some have no control group and some only use the post-intervention with or without control group.

Natural experiment: when the researcher has no control over the intervention like in natural disaster or policy change. (Not true experimental studies)

12.6 Ethical consideration

All research with human participants or their identifiable personal data raises ethical concerns that researchers must address, but experimental studies involve a particularly high level of ethical risks, because the researcher assigns participants to exposures that the participants do not choose and may have been unlikely to encounter what they had not volunteered to participate in a research project.

**most important ethical consideration the principle equipoise which states that experimental research should be conducted only when there is genuine uncertainty about which treatment will work better.

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?

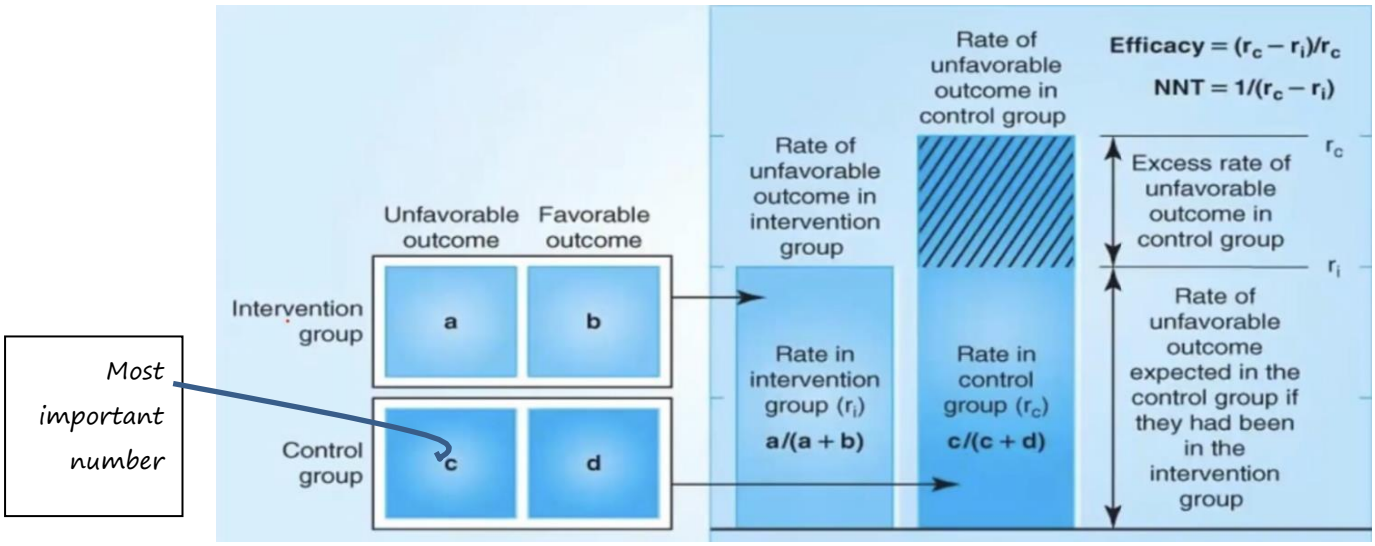
All these issues and Qs should be part of the research plan before you start.

18.8 Analysis

Experimental studies use many of the same measures of association that cohort studies do, including: rate ratios, attributable risk (excess risk or risk reduction), attributable risk percentages, measures of survival, and various types of regression models. Cohort studies use these measures to examine the impact of an unassigned exposure on the incidence of

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

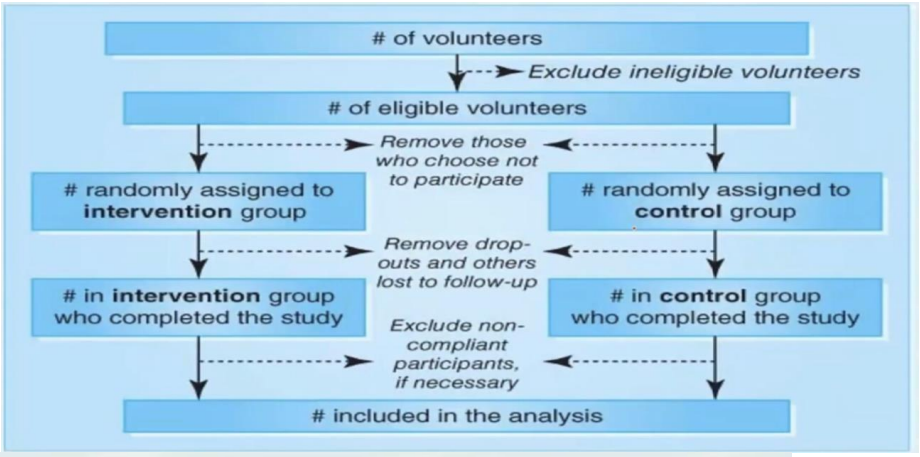
- **Efficacy** is the proportion of individuals in the control group who experience an unfavorable outcome who could have been expected to have a better outcome if they had been assigned to the active group instead of the control group.
  A high efficacy is an indicator that an intervention is successful. More precisely, efficacy refers to results under ideal circumstances, such as when an experiment is conducted in a controlled laboratory setting and all participants are fully compliant with the protocol.
- **Effectiveness** is calculated with the same equation as efficacy but refers to results obtained under less than ideal circumstances.
  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 time, or they might not store the pills at the ideal temperature.
  Number needed to treat (NNT): the expected number of people who would have to receive a treatment to prevent an unfavorable outcome in one person.
  A small NNT indicates a more effective intervention. Ex if it =102 for a drug that prevent stroke it means that 102 people have to take the drug to prevent only one from having a stroke.
  Book: **number needed to harm (NNH):** people who would need to receive treatment to expect one of them would have a particular adverse outcome.



Ex: if we're testing for a drug that lowers BP the unfavorable outcome is BP higher than 140 so assume 15 participants got a high BP in control and 10 in intervention, we can't say that the lower BP in the rest is due to the drug, we say that the drug could prevent the unfavorable outcome.

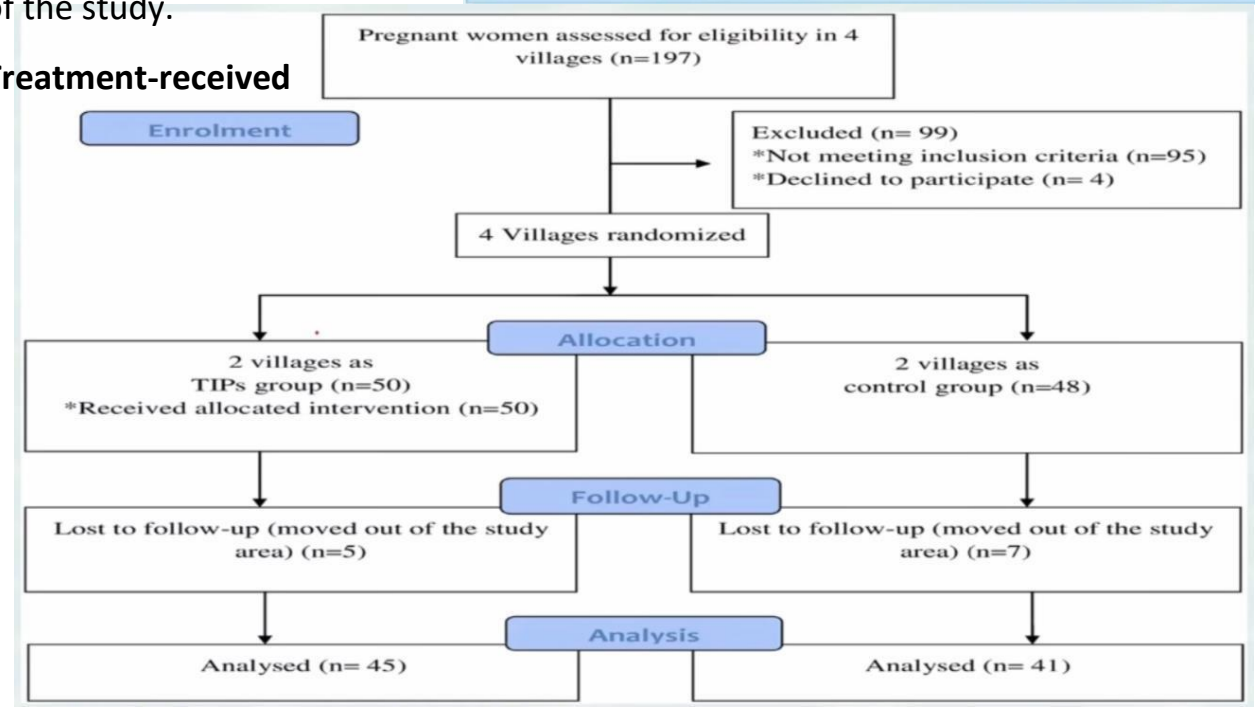
So efficacy = (15-10)/15=33% NNT= 1/ (15-10) =20%

-Flow of participant in experimental studies (this is needed for magazines usually) to check your commitment to the ethical consideration. Go back to video min 33:50



Included in reports for finding of the study.

Treatment-received

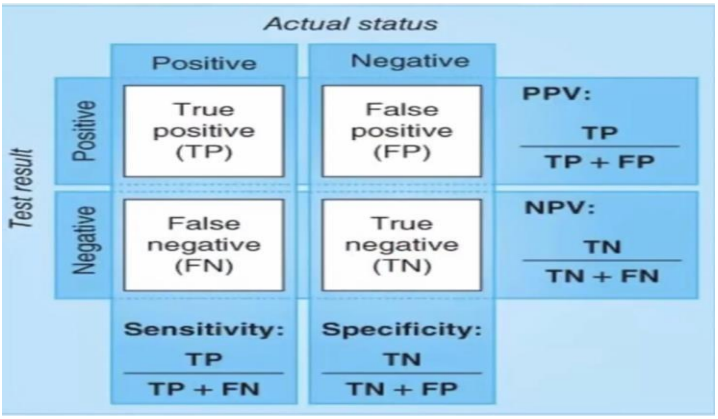


Approach: limits analysis to the participants who were fully compliant with their assigned intervention. We can calculate efficacy

Treatment-assigned approach (intention-to-treatment): includes all participants even if they were not fully compliant with their assigned intervention. Measure the real world not ideal world.

12.9 Screening and Diagnostic tests

Ex: a new blood antigen test for type of cancer compared to biopsy (gold /reference standard) an eligibility criteria is needed, patient that have the disease and participants free from the disease and the examiner should be blinded.



The Sensitivity: it is the proportion of people who actually have a disease (according to the reference standard) who test positive using the new test.

The Specificity: it is the proportion of people who don't have the disease who test negative with the new test.

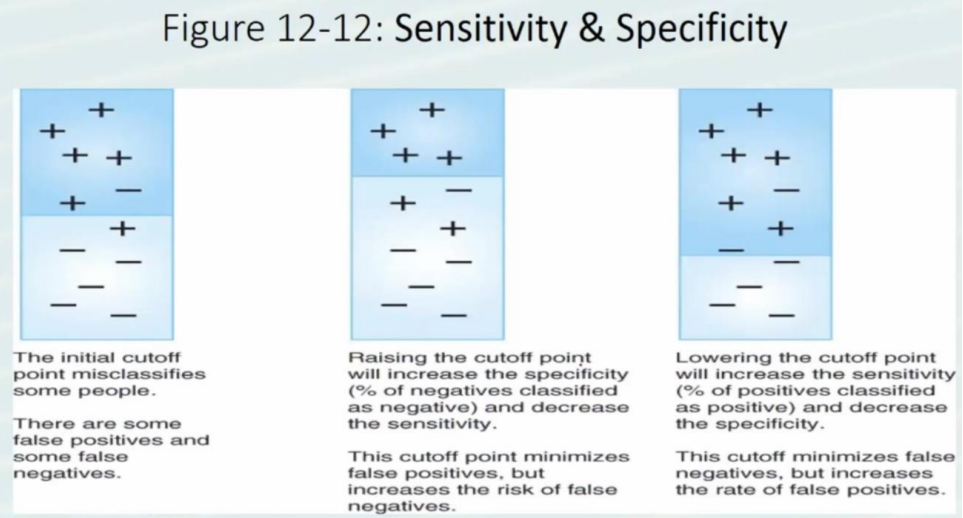
The Positive Predictive Value (PPV): it is the proportion of those who test positive with the new test who actually have the disease (according to reference standard).

The Negative Predictive Value (NPV): it is the proportion of those who test negative who actually do not have the disease.

**A Good screening or diagnostic test will have higher values for each of these measures- ideally 100% for all four calculations.

Qs by the Dr: TP= 50 / FP= 50 / FN=60 / TN=100

Cutoff point starts as 0.5mg/dl then rose to 0.6 then decreased to (0.3). So a tradeoff between specificity and sensitivity.



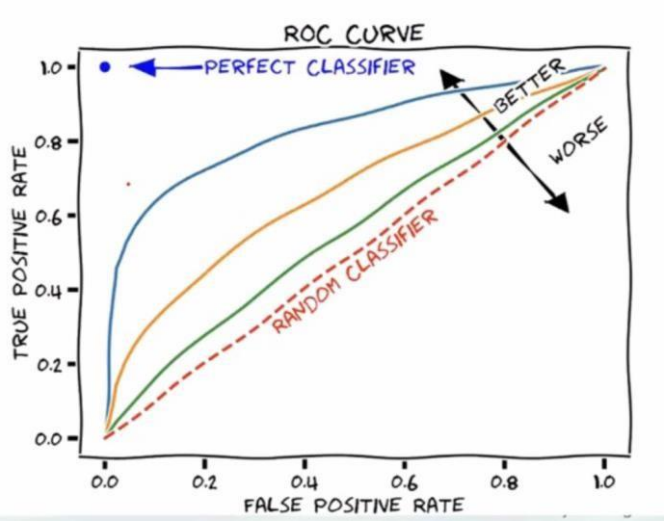
Receiver operating characteristic (ROC) curve.

Used to graphically examine the accuracy of a diagnostic test.

Sensitivity (y axis) and 1-Specificity (x axis)

The cutoff point (blue line) gives the best results, will be adopted in the study.

Three other measures are also commonly used for screening tests (their calculations are not included in the exam)



-**The diagnostic accuracy:** is the percentage of the participants who were either true positives or true negatives (the percentage for which both the reference test and the new test yield the same result). An ideal test will have 100% diagnostic accuracy.

-**The positive likelihood ratio (LR+)** test examines whether a new test is good at predicting the presence of disease. calculated as the probability that an individual with the disease has a positive test divided by the probability that an individual without the disease has a positive test. A larger one indicates good results. $$LR+=\frac{sensitivity}{1-specificity}$$

The negative likelihood ratio (LR-): examines if the new test is good at predicting the absence of disease. Calculated as the probability that an individual with the disease has a negative test divided by the probability that an individual without the disease has a negative test. A smaller one indicates good results. $$LR-=\frac{1-sensitivity}{specificity}$$

14.1 Correlational studies (ecological/aggregate).

We use the sample population to measure exposure and outcome at the same time without knowing who has the exposure or following up (without following up) who get the outcome.
Use population-level data to look for associations between 2 or more group characteristics. Without the use of individual-level data that's why it's called aggregate.
And ecological when exploring environmental exposures like air pollution.
Almost all them are secondary analyses so existing data source is used.

Ex: does the prevalence of DM increase in obese people?

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 2 populations -level indicators must be available for each population (defined place or time).
These "exposures"& "outcomes" must be measured similarly in all populations being compared.
We don't care about the relation between exposure and outcome, we calculate the exposure mean and outcome mean

FIGURE 14-2 Sample Data Table

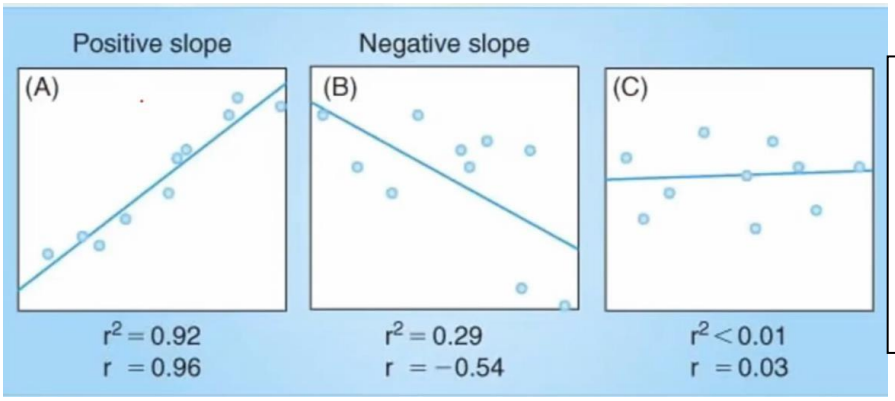
Population	Exposure 1	Outcome 1
A	48.2	14.1
B	65.1	17.0
C	37.8	14.9

14.3 Analysis: correlation

- For a two-variable analysis, plot each population on a scatterplot with the "exposure" independent on the x-axis & “outcome" dependent variable on the y-axis.
- A best-fit line defines the correlation (r) between the 2 variables.
- Use linear regression to fit more complex models of correlation.

When all the points fall near a sloped line, the correlation is strong (A)
When the points not exactly linear but line for trend can be drawn through them it’s mild or moderate correlation. (B)
When the points appear to be randomly placed and no obvious line can be drew through them, or the best line is horizontal then the correlation is weak or nonexistent.

a-Higher levels of exposure are associated with higher rates of disease



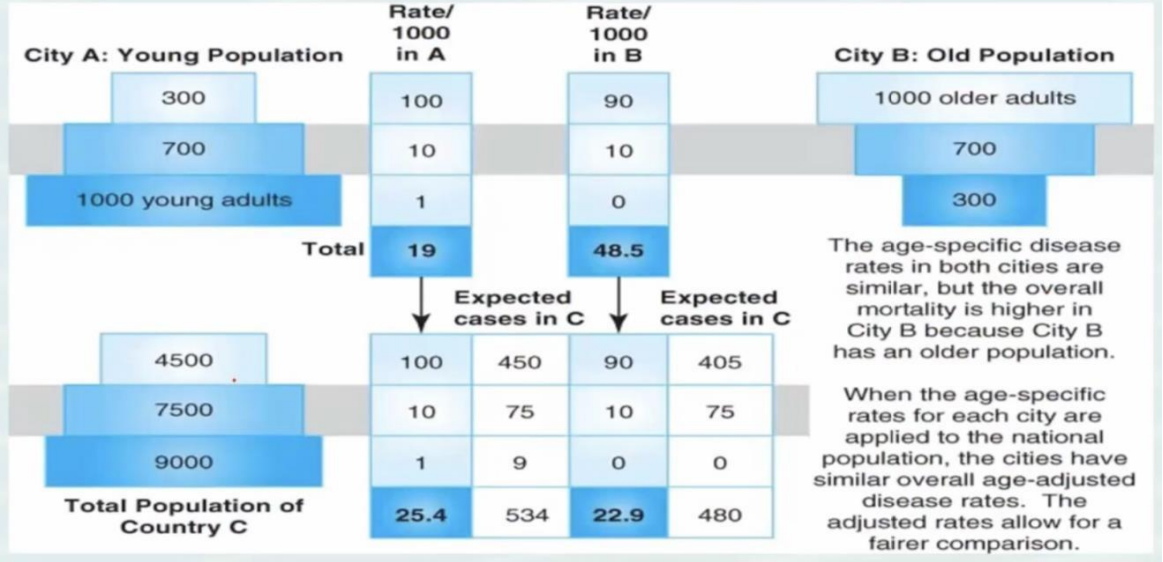
b-Higher levels of exposure are associated with lower rates of disease

14.4 Age adjustment

Use age-adjustment to more fairly compare two populations with very different age distributions, because populations might be considerably younger or older

Direct age adjustment requires knowing age-specific rates of exposure and/or disease as well as the age distributions of the populations begins compared.
Indirect age adjustment doesn't require age-specific rates but population age distribution.

Figure 14-4: Direct Age Adjustment



14.5 Avoiding the ecology fallacy

The ecology fallacy: the incorrect attribution of population- level associations to individual (the incorrect assumption that individuals follow the trends observed in population-level data).

Ex: we have a relation between the body mass index and DM, if we had a patient with a normal body mass index with DM, you shouldn't feel this is so strange only because the study says there is arelation between them, because remember the correlation doesn't = 100% between them.

Extra from the book:

on randomization

When there are ethical concerns about the appropriateness of not assigning all participants to a potentially life-saving intervention, it may be possible for participants to serve as their own controls. A **before-and-after study** is a non-randomized experimental study that measures the same individuals before and after an intervention. Some experimental studies use a **crossover design** in which the researcher assigns some participants first to the active intervention and then the control and assigns other participants first to the control and then to the active intervention. (Both groups may take a break, called a **washout period**, between the two arms of the experiment in order to reduce the **carryover effects** of the first treatment biasing the apparent results of the second treatment.) Each participant's status before the intervention is compared to his or her own status after the intervention. However, the results of crossover experimental designs may not be as clear-cut as placebo studies because time alone can lead to significant improvements or declines in health status, especially among those who are severely ill.

On ethical consideration

- The principle of distributive justice implies that the source population must be an appropriate one and that the research must 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. For example, researchers must make a careful decision about when to use placebo or another type of control, must put in place a monitoring system for 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 reaction to an intervention or another bad outcome related to a study.

Good Luck