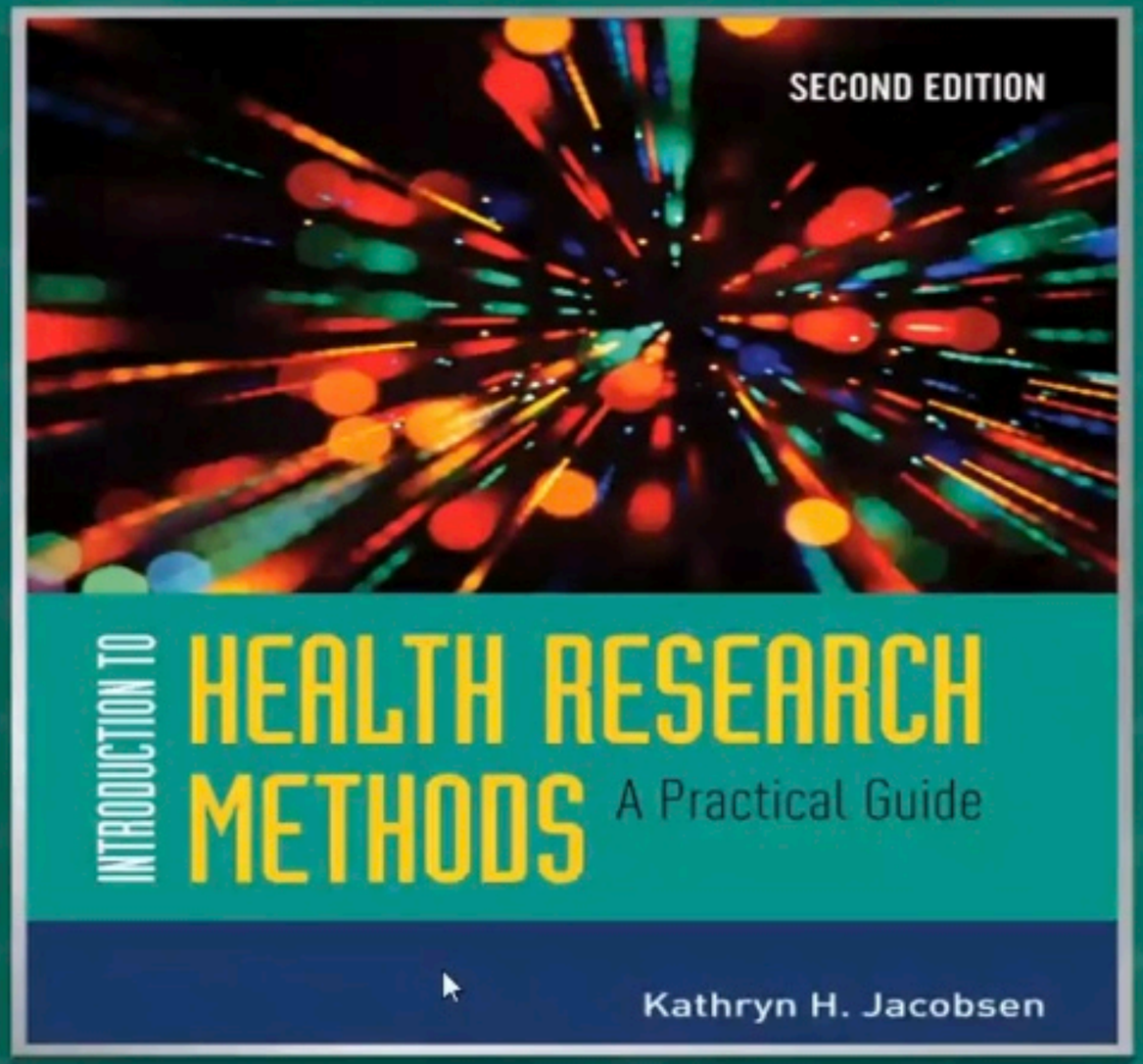
SCIENTIFIC MEDICAL RESEARCH

Week 5

Experimental Studies

Chapter 12



12.1 Overview

- *Experimental studies* (*intervention studies*) assign participants to receive a particular exposure.
- Experimental studies like ***randomized controlled trials (RCTs)*** are the gold standard for assessing causality.

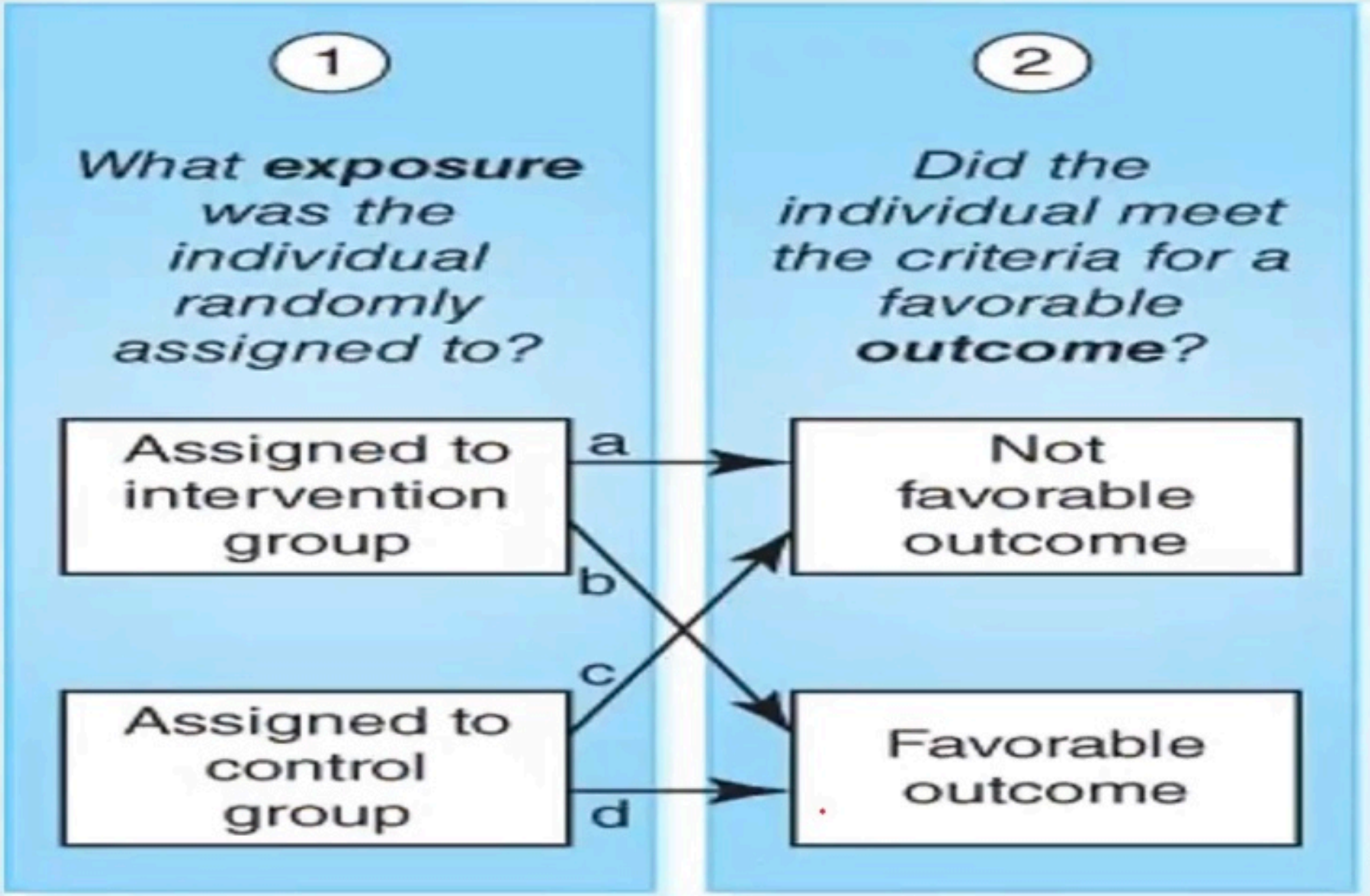
A —— B

A ⟶ B

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

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

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.

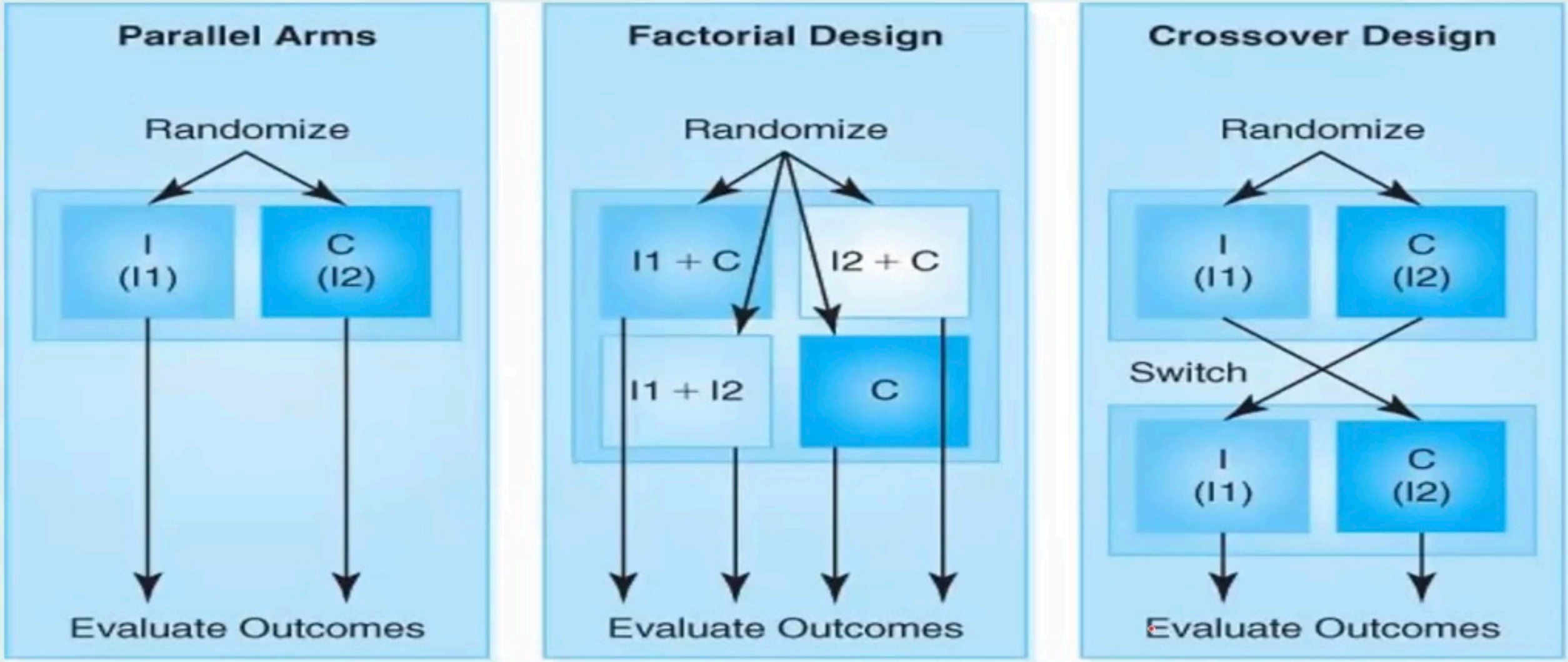
12.4 Selecting Controls (1 of 2)

- ***Placebo***: an inactive comparison that is similar to the therapy being tested
- Some studies may compare the new therapy to some existing ***standard of care***.
- Various combinations of doses and durations of an intervention can be compared using a ***factorial design***.
- Participants may serve as their 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.

Figure 12-6: **Examples of RCT Approaches**



2*3 design (1IV 2 level & 2IV 3 level)

Factor A

Type of stimulation

Cell

Factor B

Daily exposure

	Auditory A1	Tactile A2
15 Min. B1	A1 B1	A2 B1
30 Min. B2	A1 B2	A2 B2
45 Min. B3	A1 B3	A2 B3

FIGURE 8.2 Example of a factorial design.

12.4 Selecting Controls (2 of 2)

- Watch out for the ***Hawthorne effect***: Participants in both the active & comparison groups may change their behavior for the better because they know they are being observed.

12.5 Blinding

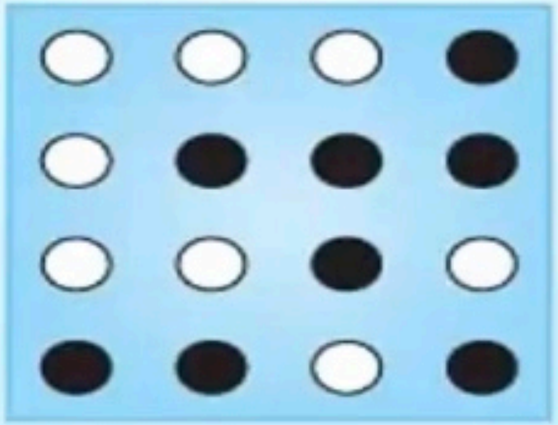
- ***Blinding* (*masking*):** hiding information about whether a participant is in the active intervention group or the control group
  - *Single-blind study*: Participants are unaware of their exposure status.
  - *Double-blind study*: Neither the participants nor the persons assessing the participants' health status know which participants are in the active and control groups.
- Blinding minimizes *information bias.*

12.6 Randomization

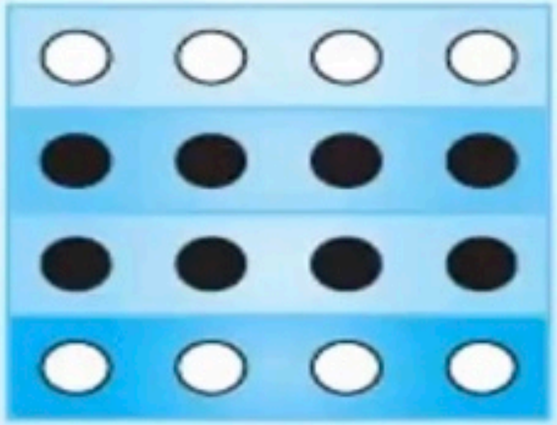
- Randomization minimizes the bias that would occur if participants were able to choose the intervention or control group they preferred.

Figure 12-7: Types of Randomization

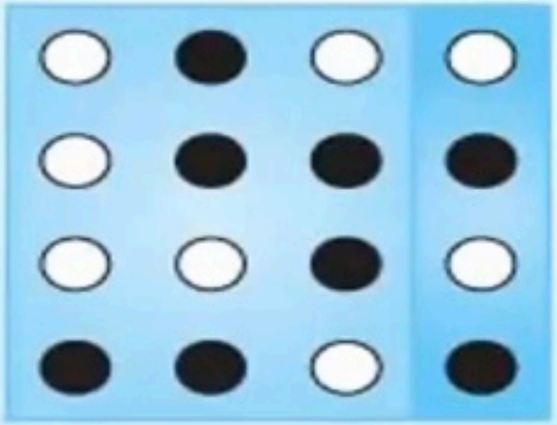
Simple randomization: each individual is randomized to one treatment group



Block randomization: groups of individuals are randomized to a treatment group



Stratified randomization: individuals are grouped into strata and then randomized to one treatment group



12.7 Ethical Considerations

- Intervention studies raise special ethical concerns because the researcher is assigning participants to exposures.
- ***Equipoise***: An experiment should only be conducted when there is genuine uncertainty about the outcome.

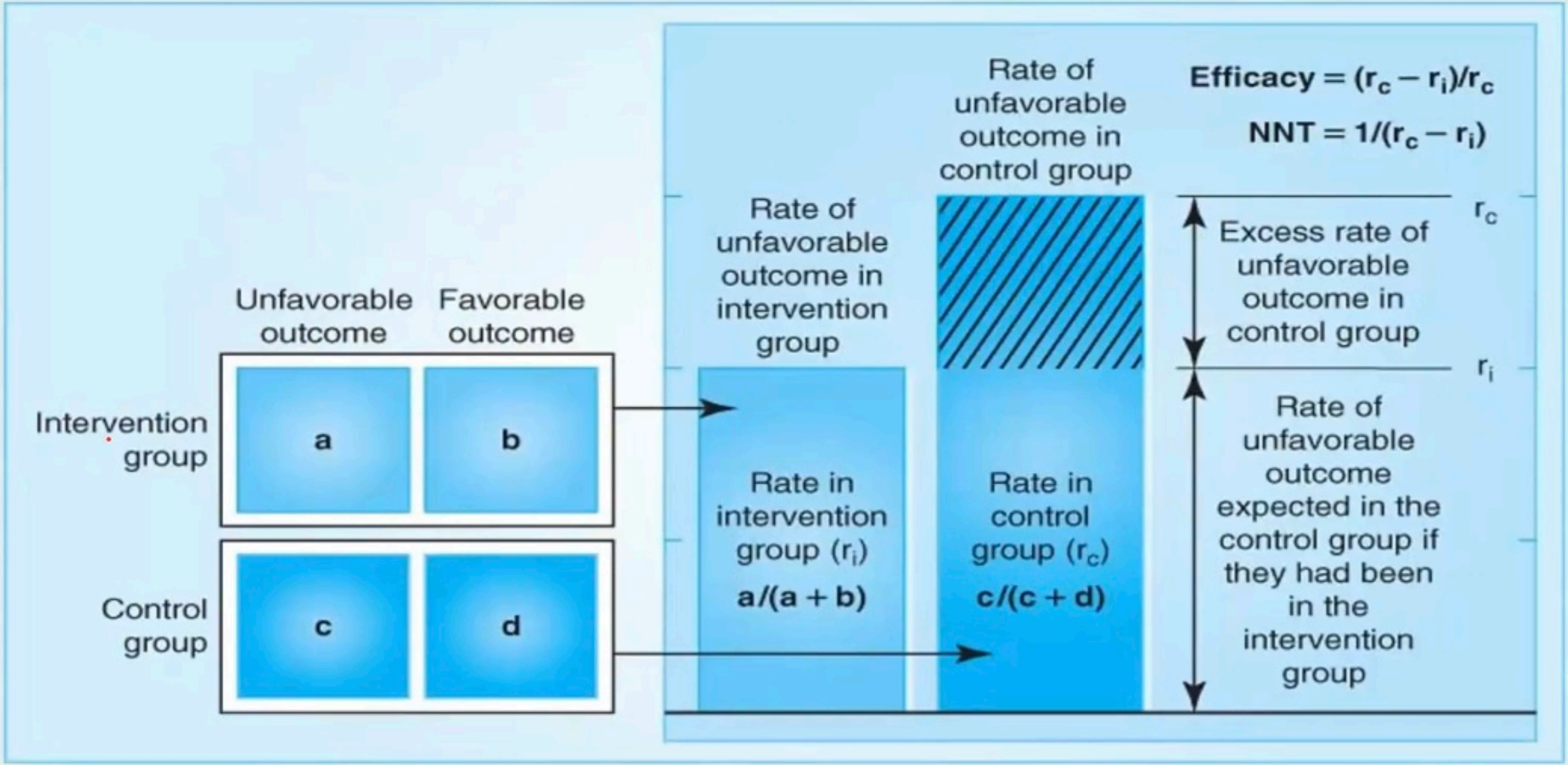
FIGURE 12-8 Examples of Ethical Issues in Experimental Studies

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 Analysis (1 of 2)

- ***Efficacy:*** the proportion of individuals in the control group who experience an unfavorable outcome when they could have been expected to have a favorable outcome if they had been assigned to the active group instead of the control.
- ***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.

Figure 12-9: Efficacy & NNT



12.8 Analysis (1 of 2)

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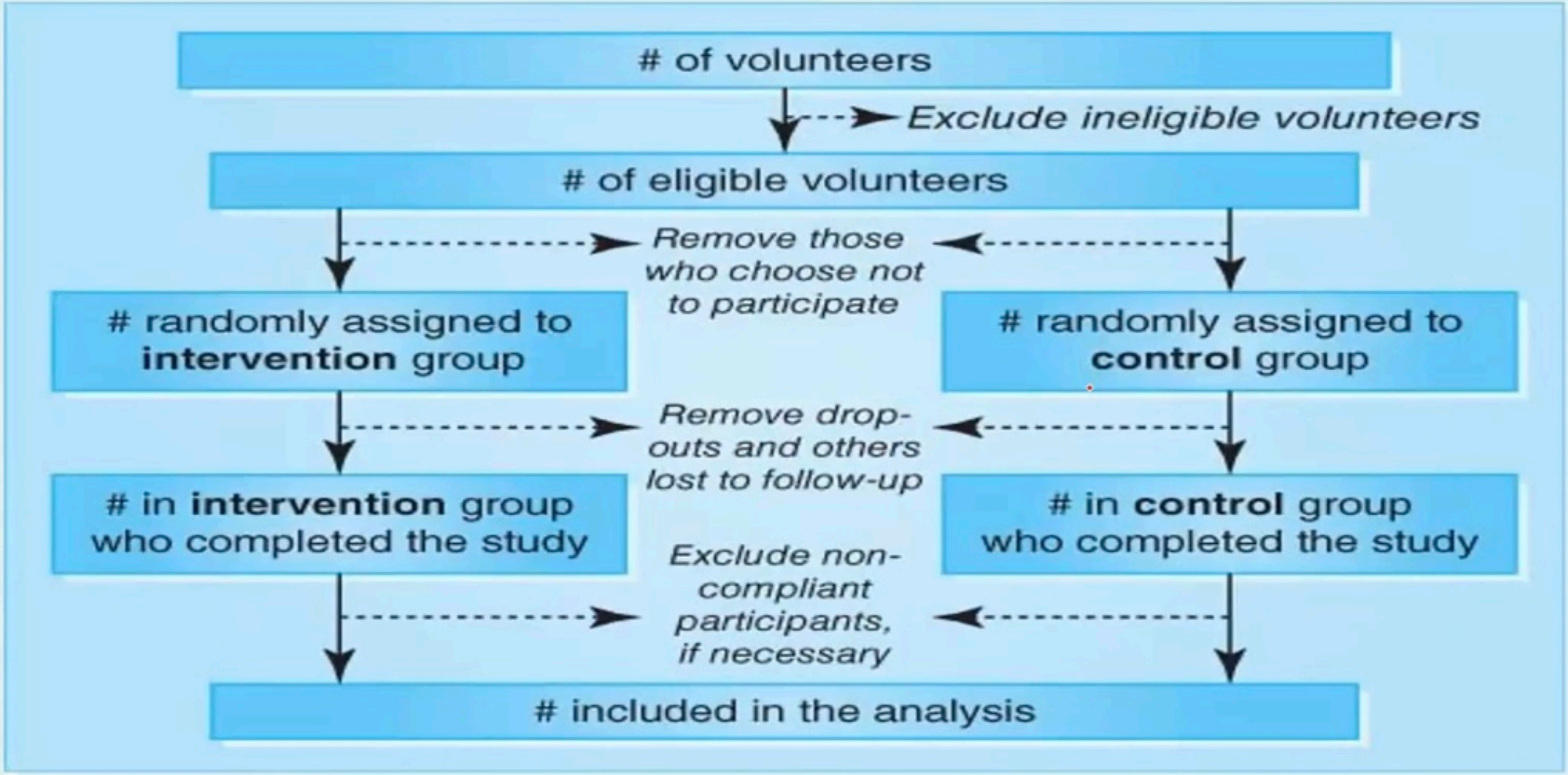
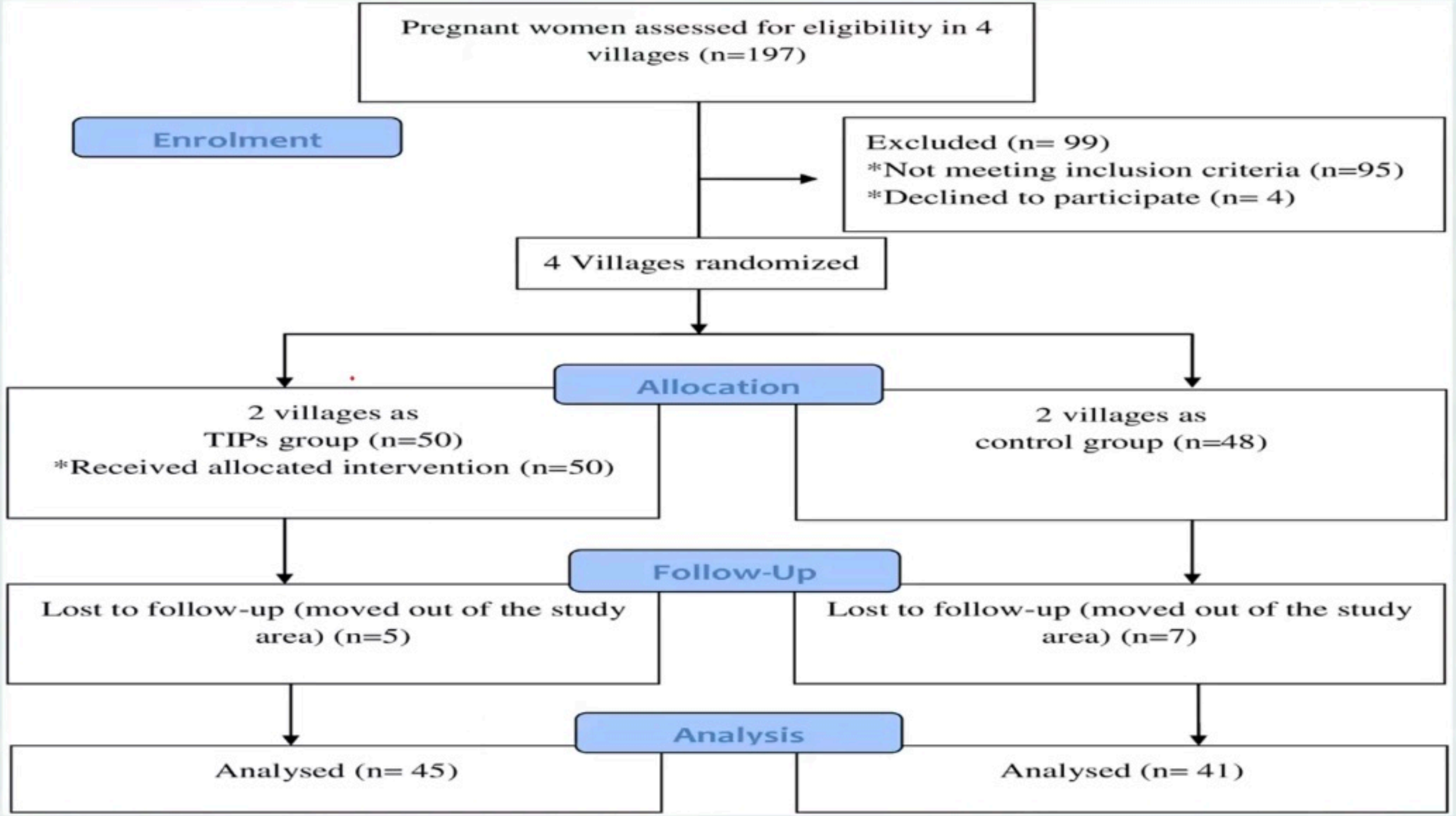
Figure 12-10: **Flow of Participants in an Experimental Study**




Pregnant women assessed for eligibility in 4 villages (n=197)
Enrolment
Excluded (n= 99)
*Not meeting inclusion criteria (n=95)
*Declined to participate (n= 4)
4 Villages randomized
Allocation
2 villages as
TIPs group (n=50)
*Received allocated intervention (n=50)
2 villages as
control group (n=48)
Follow-Up
Lost to follow-up (moved out of the study area) (n=5)
Lost to follow-up (moved out of the study area) (n=7)
Analysis
Analysed (n= 45)
Analysed (n= 41)

12.8 Analysis (2 of 2)

- ***Treatment-received approach***: limits analysis to the participants who were fully compliant with their assigned intervention
- ***Treatment-assigned approach*** (or ***intention-to-treat approach***): includes all participants even if they were not fully compliant with their assigned intervention

12.9 Screening & Diagnostic Tests

A good test will have a value near 100% for these four calculations:

- ***Sensitivity*:** the proportion of people who actually have a disease (according to the reference standard) who test positive using the new test
- ***Specificity*:** the proportion of people who do not have the disease who test negative with the new test
- ***Positive predictive value (PPV)*:** the proportion of those who test positive with the new test who actually have the disease (according to the reference standard)
- ***Negative predictive value (NPV)*:** the proportion of those who test negative who actually do not have the disease

Figure 12-11: Screening & Diagnostic Test Results

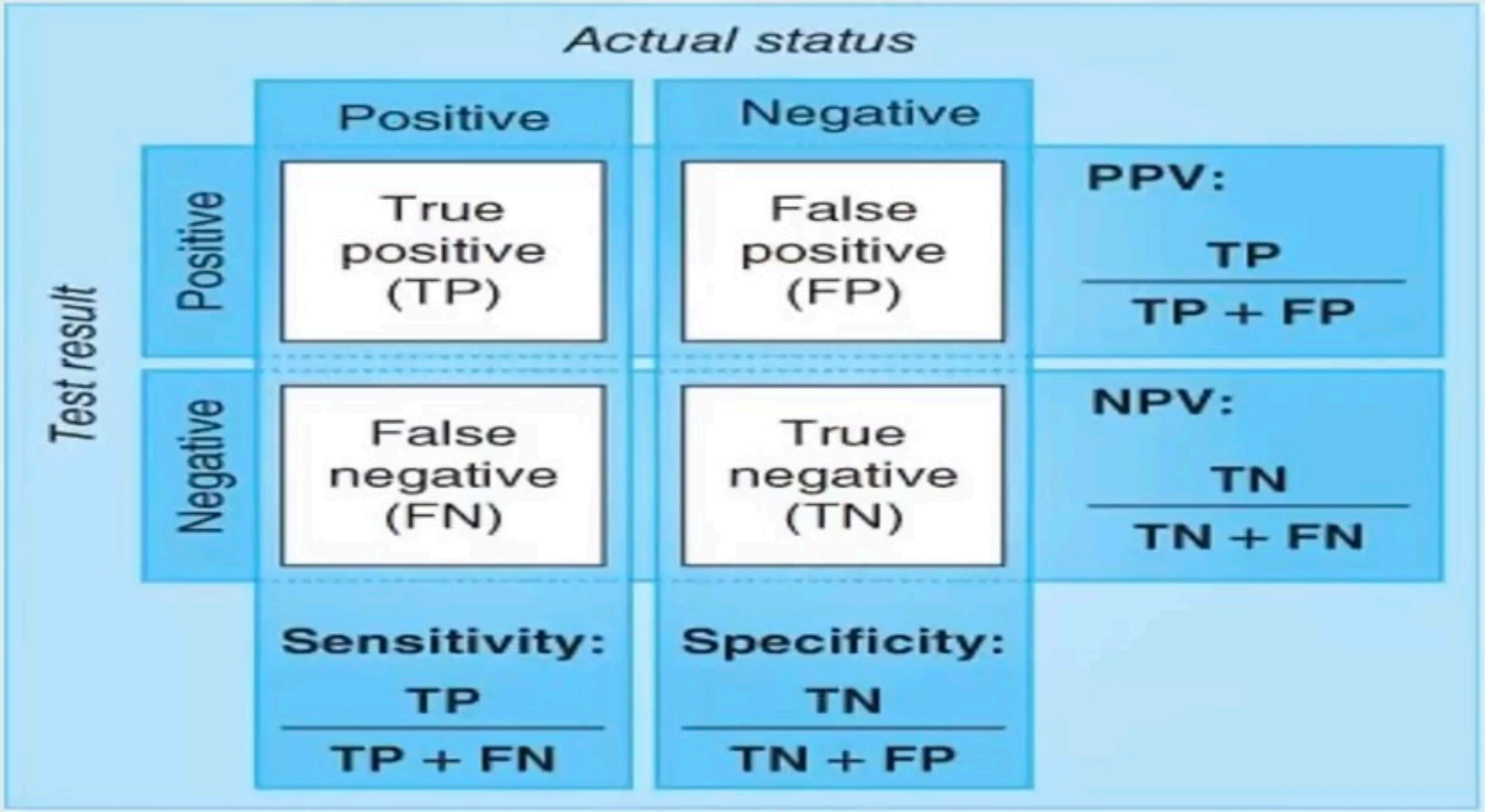
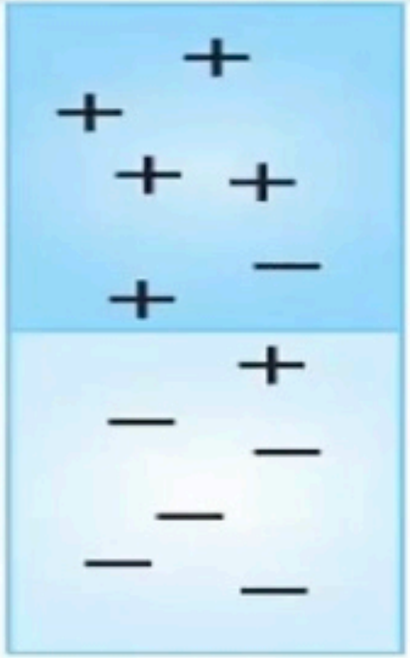
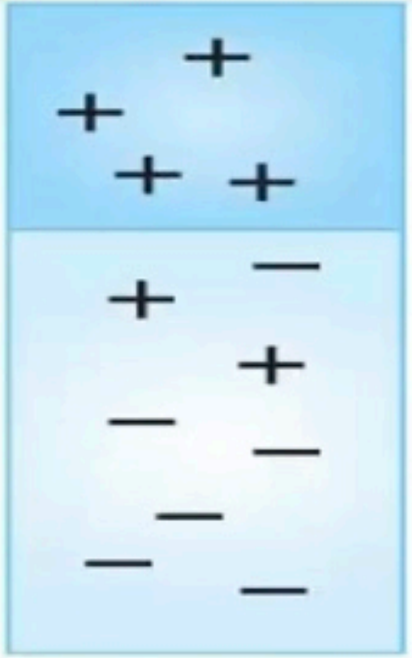


Figure 12-12: Sensitivity & Specificity



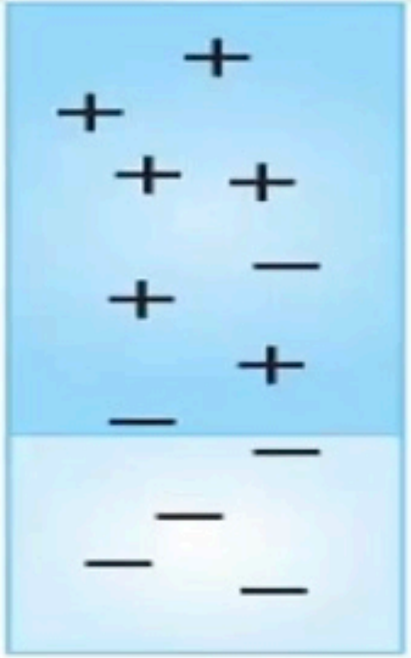
The initial cutoff point misclassifies some people.

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.

Receiver Operating Characteristic (ROC) Curve

- Used to graphically examine the accuracy of a diagnostic test
- Sensitivity (Y axis) and 1-Specificity (on X axis)
- See area under the curve (AUC)

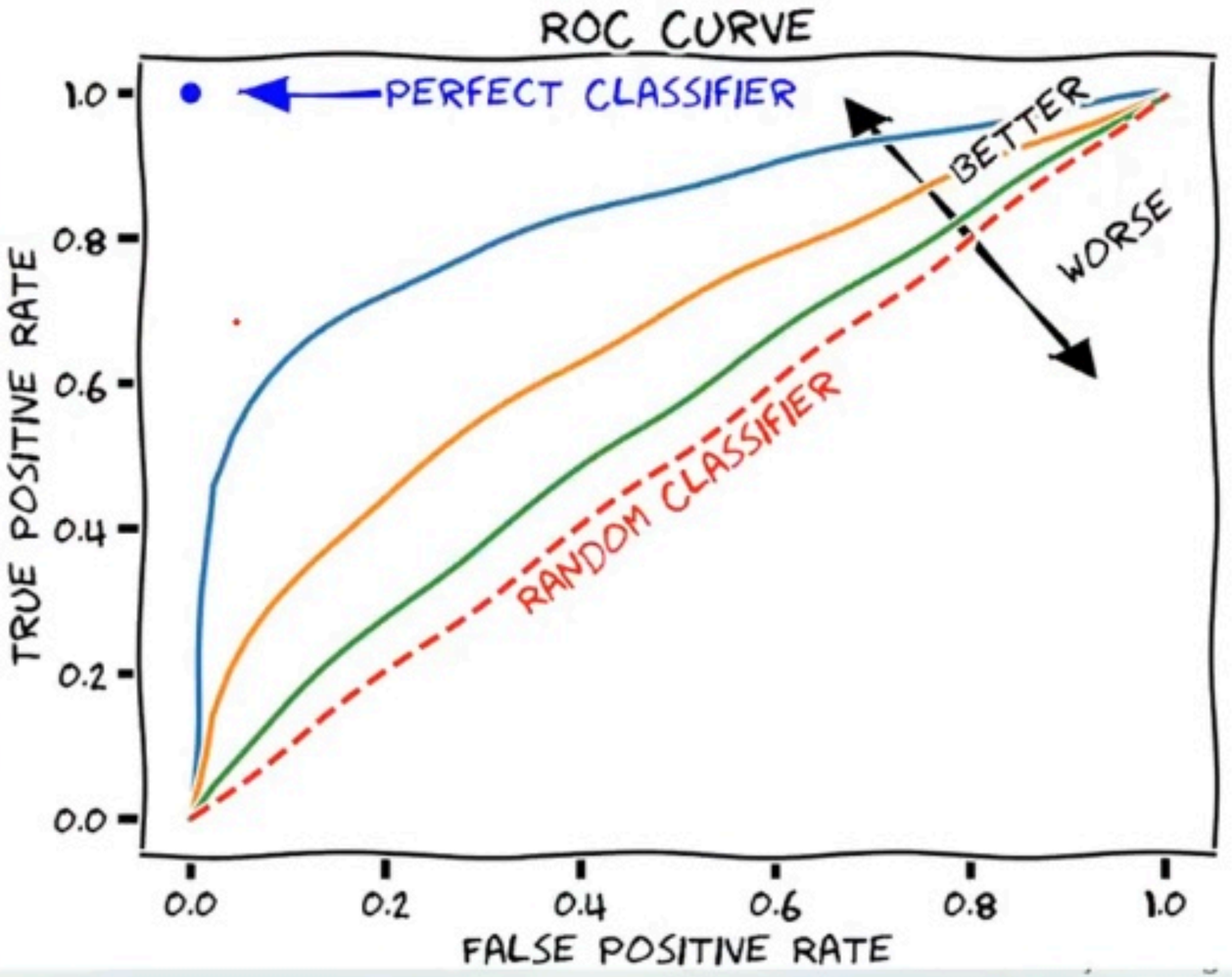
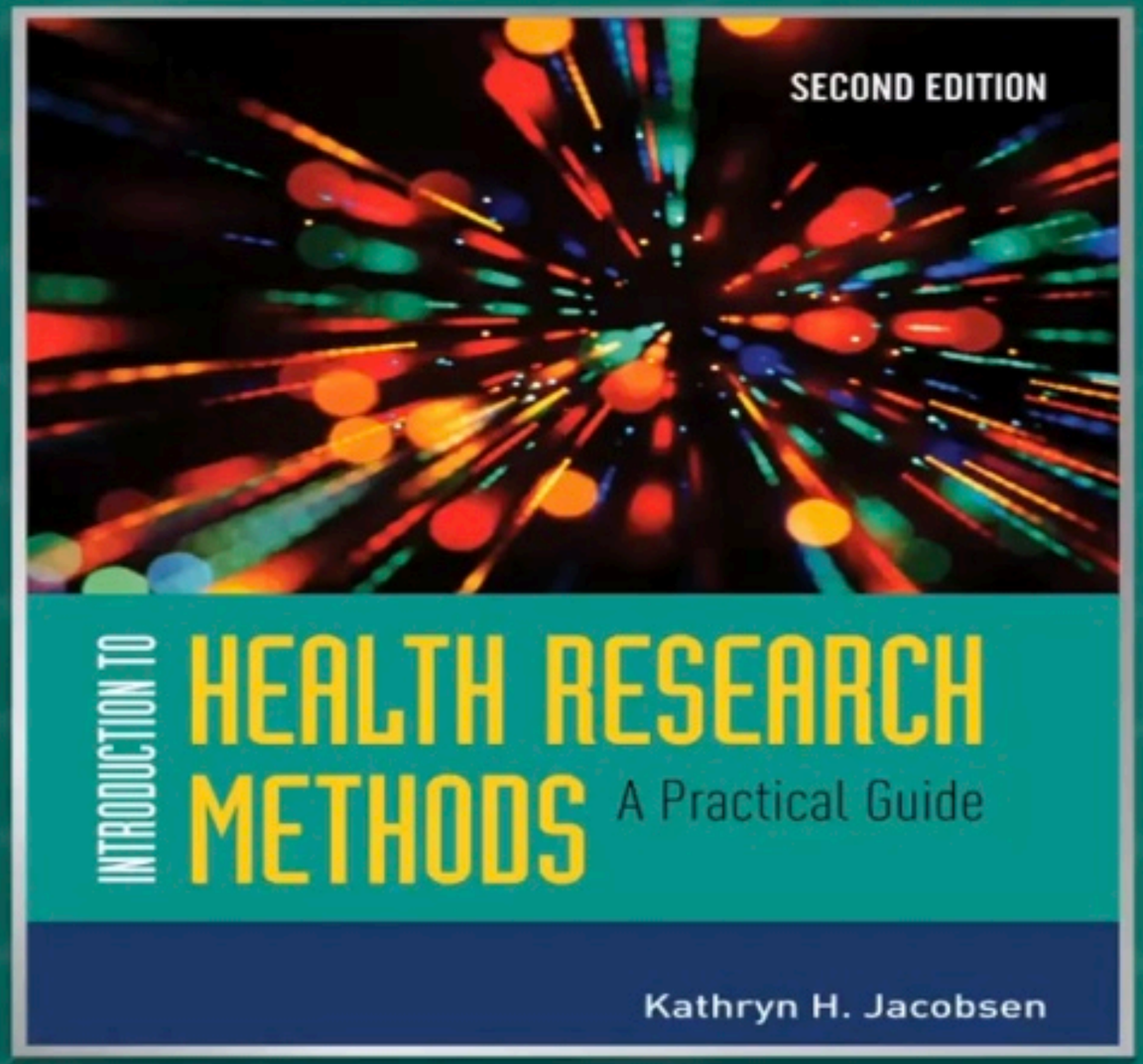


Figure 12-12: Sensitivity & Specificity

- Positive Likelihood ratio (LR+)= Sensitivity/ 1-Specificity
- Negative Likelihood ratio (LR-)= 1- Sensitivity/ Specificity

Correlational Studies

Chapter 14



14.1 Overview

- 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.

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” & “outcomes” must be measured similarly in all populations being compared.

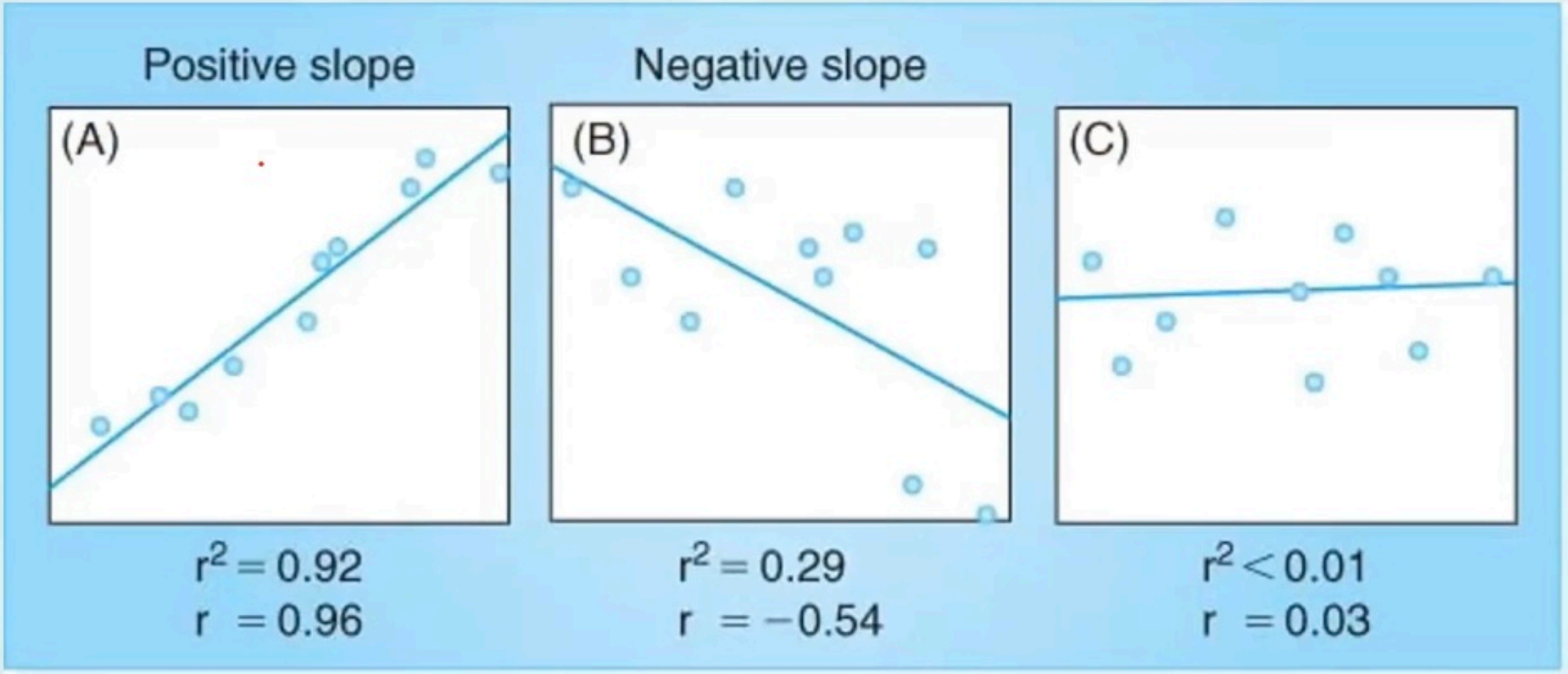
FIGURE 14-2 Sample Data Table

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

14.3 Analysis: Correlation

- For a two-variable analysis, plot each population on a scatterplot with the "exposure" on the *x*-axis & 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 correlation.

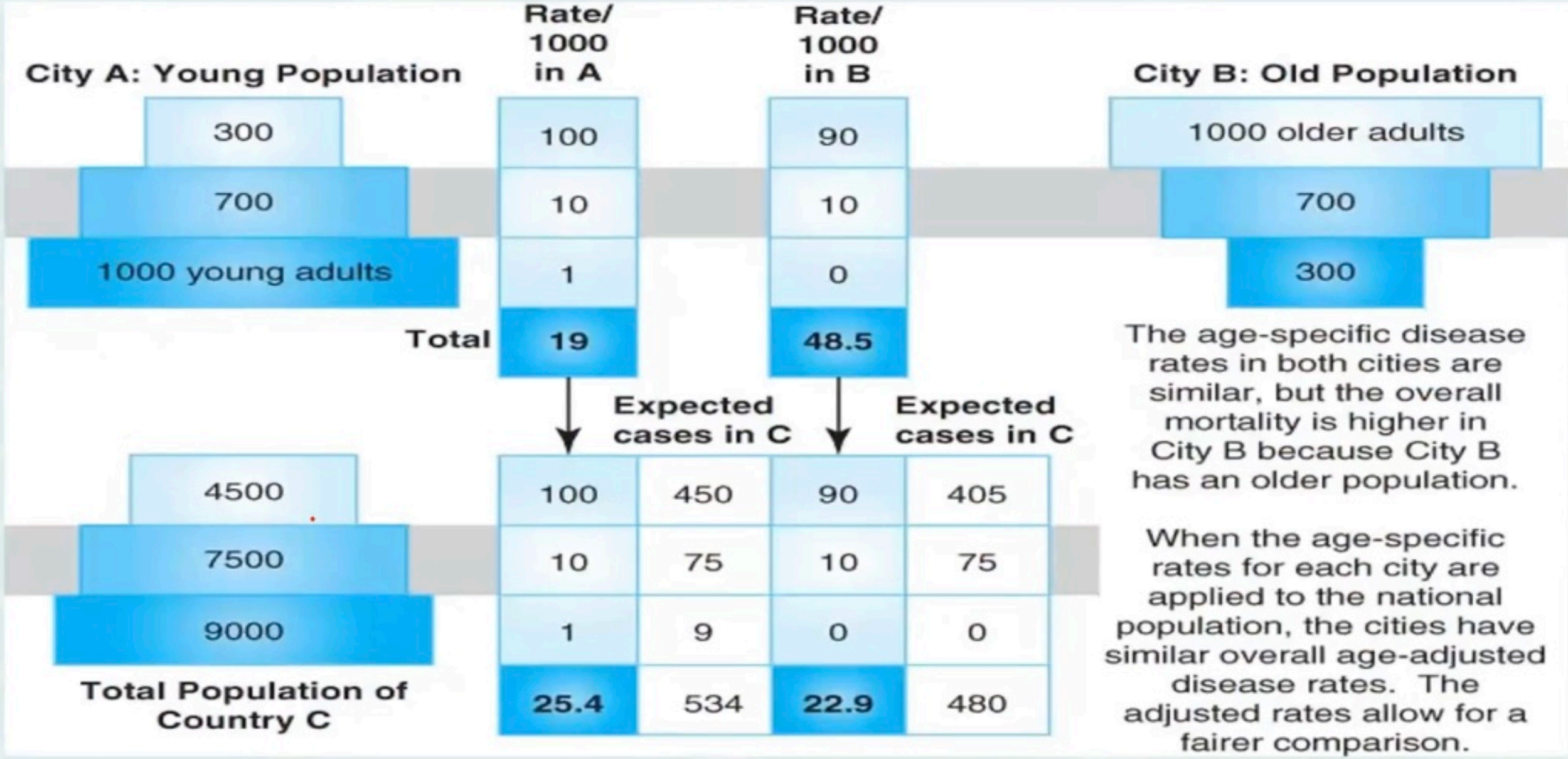
Figure 14-3: Types of Correlational Sloes



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.

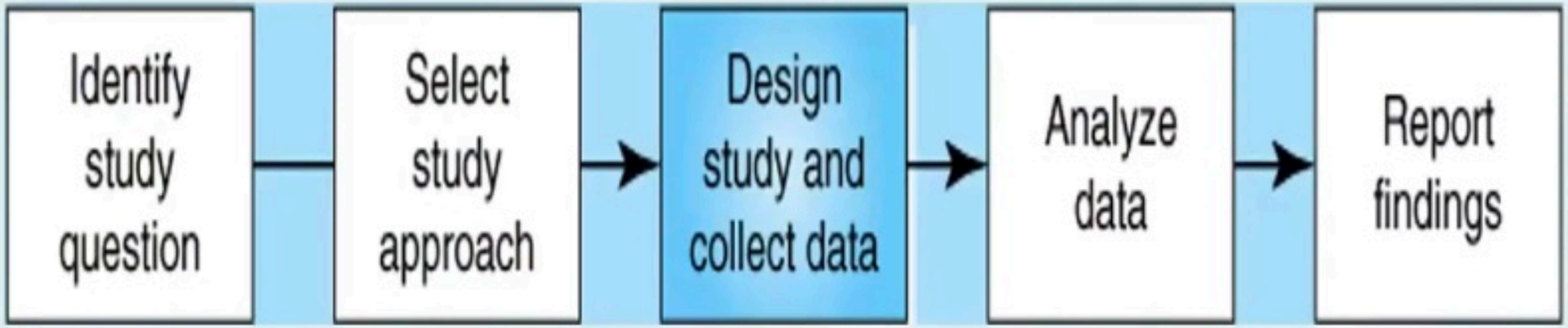
Figure 14-4: Direct Age Adjustment



14.5 Avoiding the Ecological Fallacy

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

STEP 3



The End
Good Luck