Study Design and Bias

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Review

Two main topics today:

1. Study Design
    1. Observational Studies
    2. Randomized Clinical Trials
2. Bias

Study Design

Conducting a study is the general method by which we seek to answer scientific questions (null hypothesis)

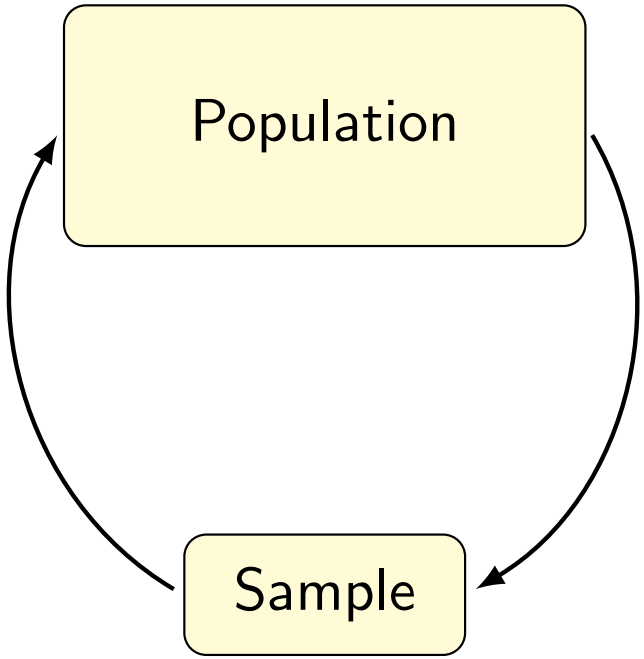
The most types of studies are observational studies, a heading under which a number of various study paradigms fall

The more well-known and rigorous types of studies are clinical trials, and specifically, randomized clinical trials

Ideal Study Design

Ideally, for a given population we can:

- Obtain a list of everyone in the population
- Select from this list completely at random
- Each person is equally difficult/costly to sample
- Everybody selected responds to the survey



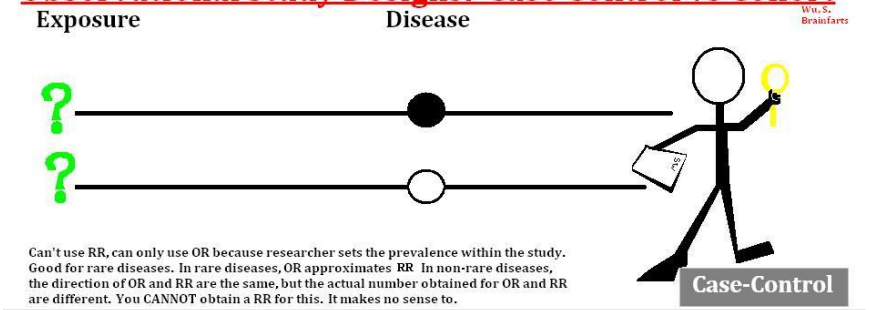
Observational Studies

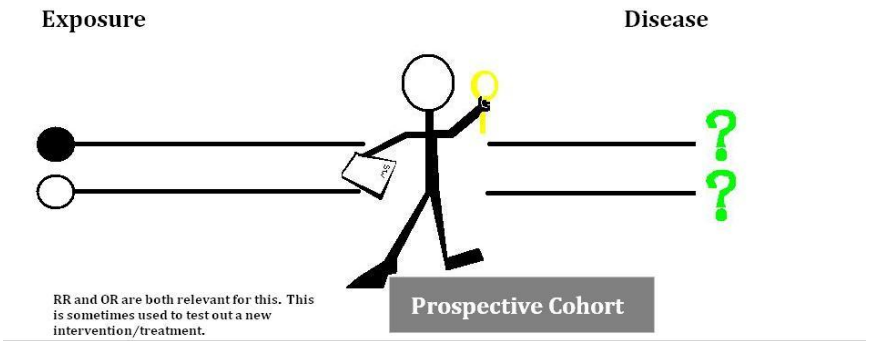
The most common observational studies, and the ones we will discuss today include

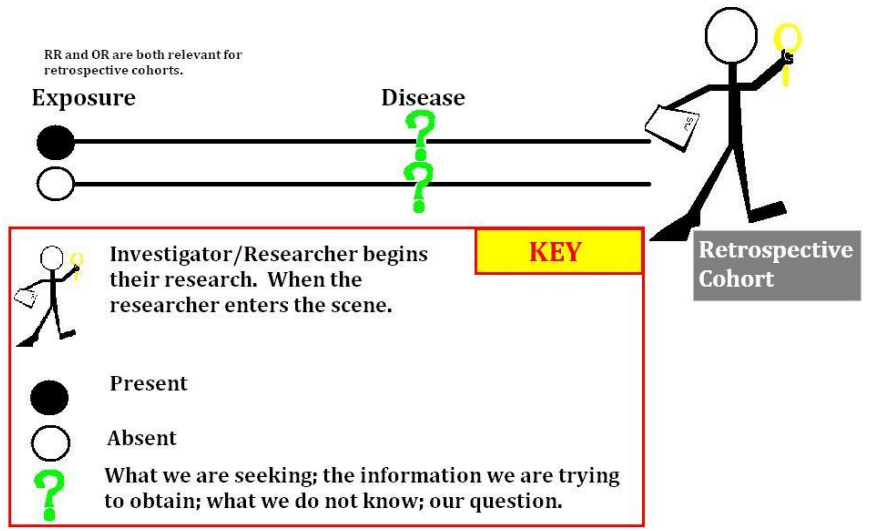
1. Case-control
2. Longitudinal
3. Retrospective

The defining characteristic of each of these is the lack of intervention on the part of the researcher. Study participants are found in the wild and information is gathered – the primary difference between each of these is the time at which the researcher "asks the question."

Observational Study Designs: Case Control vs Cohort







Types of Observational Studies

Case-control: Two existing groups are collected based on outcome and compared on the basis of a supposed causal attribute. Basically a snapshot in time. For example, collecting 750 individuals with and without lung cancer and asking smoking status

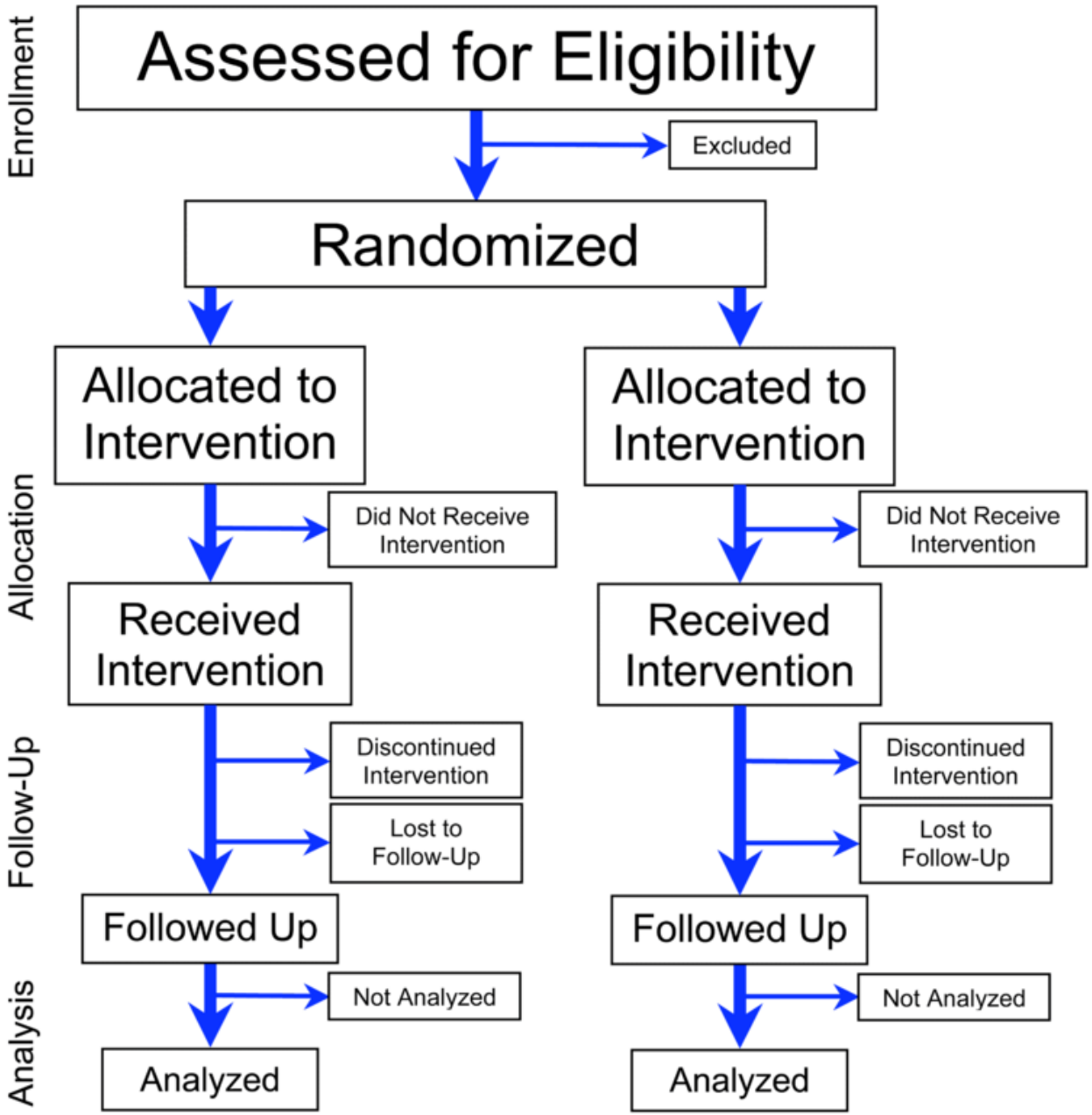
Longitudinal: Also called prospective. Here, participants are collected based on some exposure and then followed for a period of time, prior to outcomes being known. For example, the ABCD study is collecting brain scans and diagnostics on 10,000 US children. We can partition groups based on pre-term birth status and evaluate outcomes over time

Retrospective: Similar to a longitudinal, but is done following the outcome in question. This is most common in cases with rare outcomes. To study exposures related to Parkinson's, for example, a very large prospective study would be needed to ensure enough positive outcomes would be collected

Randomized Clinical Trial (RCT)

The "gold standard" of study design is a double-blind randomized and controlled clinical trial

- Subjects are assigned to treatment or control groups *at random*
- Randomized groups should be as similar as possible
- Neither investigator nor subjects known which group they are in with use of placebo
- Intent to Treat (ITT) analyzes results based on treatment assigned rather than treatment received


Enrollment
Assessed for Eligibility
Excluded
Randomized
Allocation
Allocated to Intervention
Did Not Receive Intervention
Received Intervention
Allocated to Intervention
Did Not Receive Intervention
Received Intervention
Follow-Up
Discontinued Intervention
Lost to Follow-Up
Followed Up
Discontinued Intervention
Lost to Follow-Up
Followed Up
Analysis
Not Analyzed
Analyzed
Not Analyzed
Analyzed

Intent to Treat

The Coronary Drug Project Research Group published an article in the *New England Journal of Medicine* (1980) describing a randomized controlled double-blind experiment involving the drug clofibrate, which reduces the level of cholesterol in the blood

	Clofibrate	
	Number	Deaths
Adherers	708	15%
Nonadherers	357	25%
Total	1,103	20%

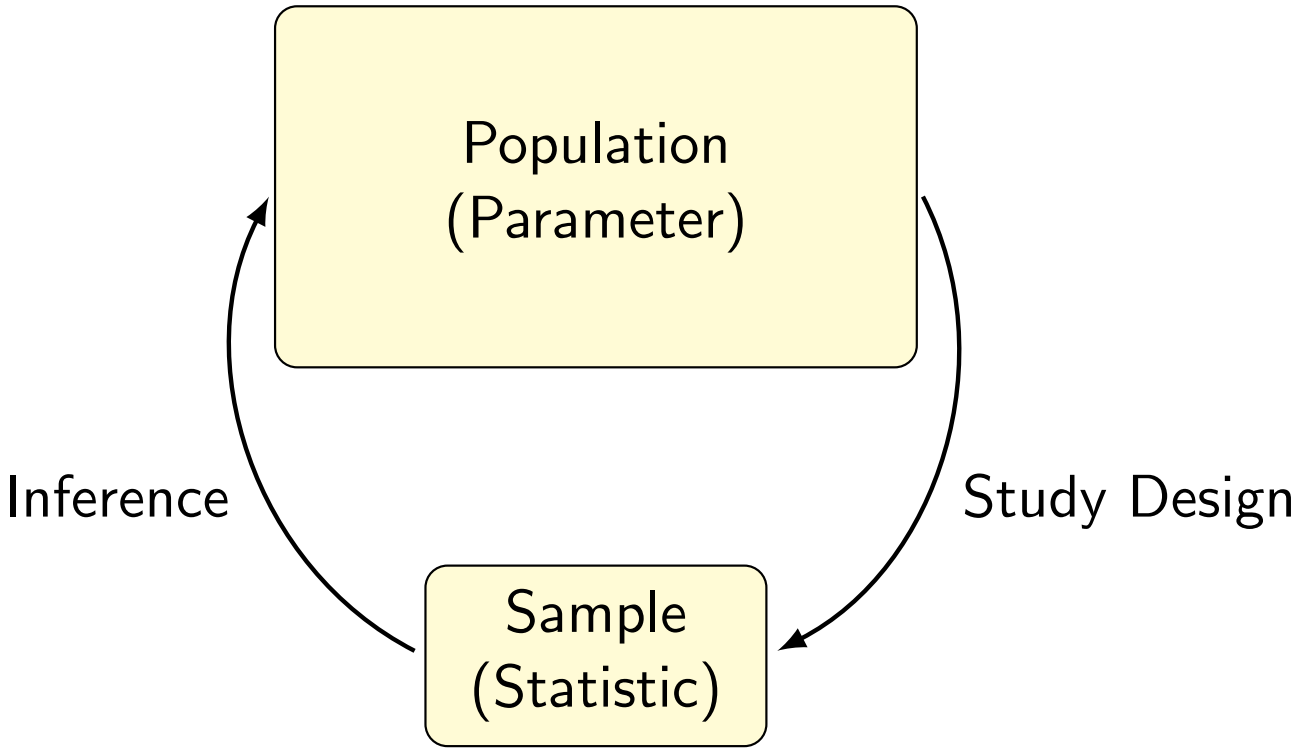
Subjects who took more than 80% of their prescribed medicine were called "adherers"

Clofibrate and Placebo Results

	Clofibrate		Placebo	
	Number	Deaths	Number	Deaths
Adherers	708	15%	1,813	15%
Nonadherers	357	25%	882	28%
Total	1,103	20%	2,789	21%

- Taking into account the placebo results as well, clofibrate no longer looks effective
- One possibility is that adherers are more concerned with their health, and take better care of themselves in general
- Take-home message: comparing subjects *as they were randomized* is the only completely valid way of carrying out a controlled experiment; all other comparisons are subject to confounding and bias

Statistical Process

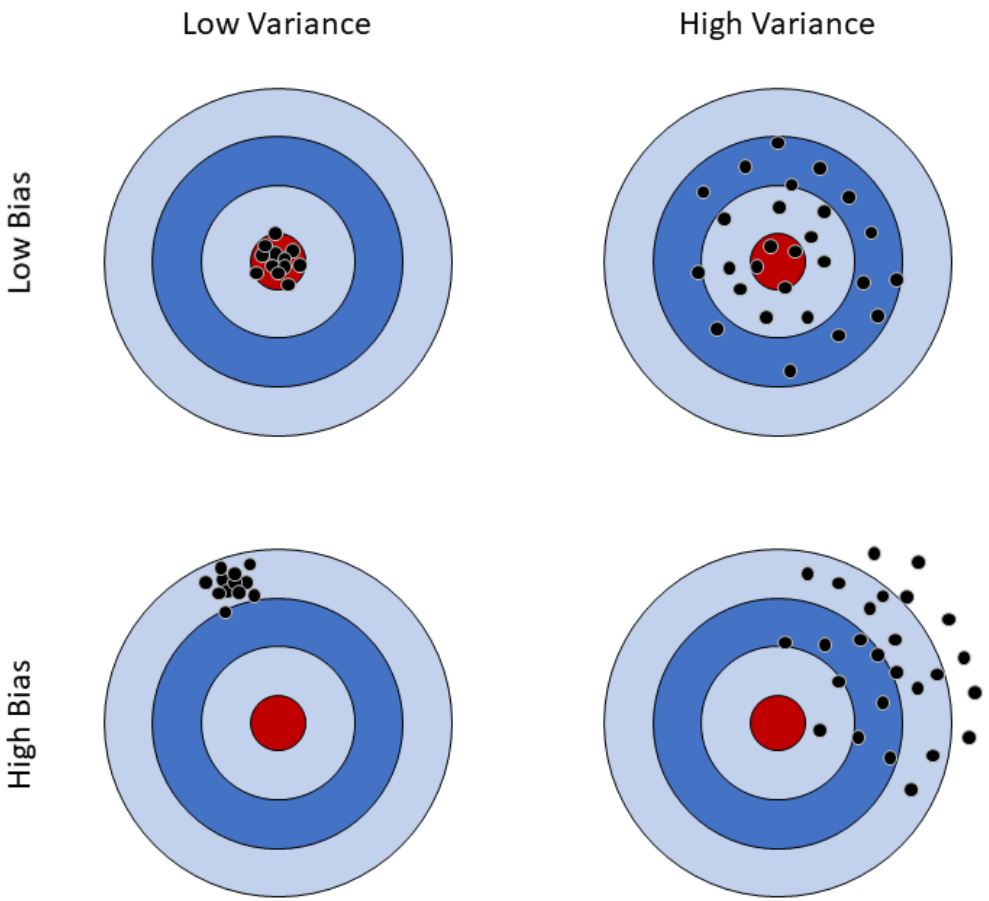


Variance and Bias

Suppose a population has a true mean value of μ which we hope to estimate by taking a sample and determining the sample mean $\overline{X}$. He, we are referring to the variance and bias of the statistic rather than the population.

- The *variance* is a measure of dispersion. If variance is high, the range of values $\overline{X}$ may fall in tends to be large, though we are just as likely to overestimate the value as we are to underestimate it. At any rate, the expected value is $E(\overline{X}) = \mu$
- The *bias*, on the other hand, is a systematic departure from the true value. If our statistic is biased, regardless of sample size, we have $E(\overline{X}) = \mu + \text{Bias}$

Variance and Bias



Sample Bias

- The 1936 US Presidential election between incumbent FDR and Republican Alfred Landon, six years into the Great Depression.
- The *Literary Digest* magazine, which had correctly predicted each election since 1916, mailed 10 million questionaires to addresses gather from telephone books and club membership lists, with 2.4 million responses returned
- The *Digest* predicted a landslide victory for Landon: 57% to 43%
- In the actual election, Roosevelt won 62% to 38%

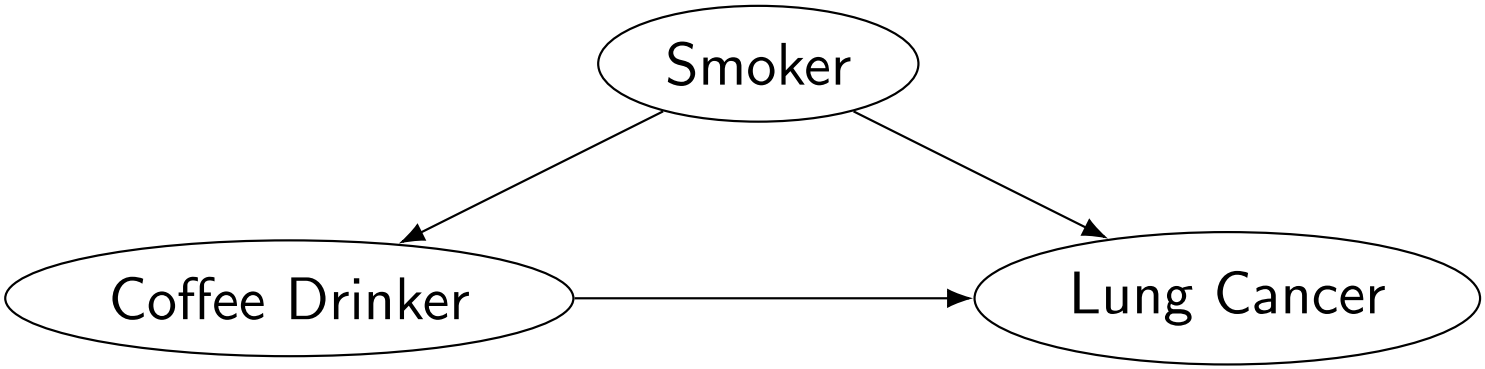
Extrapolation Bias

For practical, ethical, and economic reasons clinical trials of new treatments usually only involve adults, with only about 25% of drugs subject to pediatric studies.

Propofol is a sedative that has consistently been shown to be safe in adults. In 1992, the British government recommended against using it on patients under 16 after a number of children receiving propofol died in the ICU. A 2001 controlled trial found that 9.5% of children died after receiving propofol, compared with 3.8% on a different sedative

Confounding

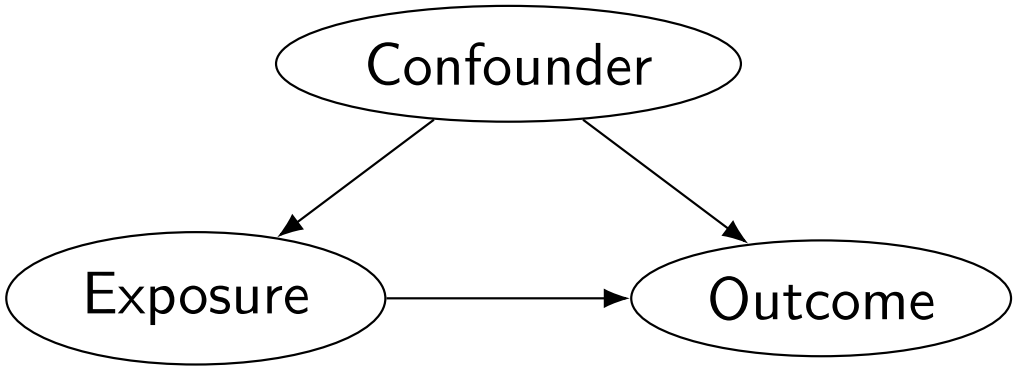
- Many epidemiologic studies have shown that coffee drinkers have an increased risk of lung cancer
- However, what researchers also noticed is that smokers are more likely to drink coffee



- Once researchers controlled for smoking status, they no longer found a change in lung cancer risk due to drinking coffee (article)

Confounding

- A confounder (lurking variable) is a third variable, which is related to both exposure and outcome
- Because of this, confounders distort the relationship between exposure and outcome



Summary

- Observational studies and randomized clinical trials
- Samples should be representative of population in question
- Bias occurs when a (little s) statistic systematically differs from the population parameter
    i. Sample and selection bias
    ii. Non-response bias
    iii. Extrapolation bias
    iv. Confounding
- Well designed studies are conducted in such a way as to minimize the potential for bias

Sources

Wikipedia

School of hard knocks