Stat 13, Intro. to Statistical Methods for the Life and Health Sciences.

1. Optional book problems.
2. Experiments and aspirin example.
3. Random sampling, random assignment, and blocking.
4. Blinding.
5. Portacaval shunt example.

Read chapter 4.

HW2 is due Wed, Feb12, 1159pm. 2.3.15, 3.3.18, and 4.1.23.

Midterm is Mon Feb24 in class.

The course website is http://www.stat.ucla.edu/~frederic/13/W25 .

1. Some good optional hw problems from the book, that you might want to look at on your own.

1.2.18, 1.2.19, 1.2.20, 1.3.17, 1.5.18, 2.1.38, 2.2.6, 2.2.24, 2.3.3, 2.3.25, 3.2.11, 3.2.12, 3.3.8, 3.3.19, 3.3.22, 3.5.23, 4.1.14, 4.1.18, 5.2.2, 5.2.10, 5.2.24, 5.3.11, 5.3.21, 5.3.24, 6.2.23, 6.3.1, 6.3.12, 6.3.22, 6.3.23.

2. Experiments and aspirin example.

Physicians' Health Study I (study aspirin's affect on reducing heart attacks.

- Started in 1982 with 22,071 male physicians.
- The physicians were **randomly assigned** into one of two groups.
  - Half took a 325mg aspirin every other day and half took a placebo.

Results

- Intended to go until 1995, the aspirin study was stopped in 1988 after finding significant results.
- 189 (1.7%) heart attacks occurred in the placebo group and 104 (0.9%) in the aspirin group. This is a 45% reduction in heart attacks for the aspirin group.
- What about confounding variables? Could the aspirin group be different than the placebo group in some other ways?
  - Did they have a better diet?
  - Did they exercise more?
  - Were they genetically less likely to have heart attacks?
  - Were they younger?

The Big Idea

- Confounding variables are often circumvented in experiments due to the **random assignment** of subjects to treatment groups.
- Randomly assigning people to groups tends to balance out all other variables between the groups.
- So confounding variables, including ones the researchers didn't anticipate, should be roughly equalized between the two groups and therefore should not be confounding.
- **Thus, cause and effect conclusions are sometimes possible in experiments through random assignment.** It must be a well run experiment though.

3. Random sampling and random assignment.

- With observational studies, **random sampling** is often done. This possibly allows us to make inferences from the sample to the population where the sample was drawn.
- With experiments, **random assignment** is done. This might allows us to conclude causation.

- The Physician's Health Study used random assignment. Did it also use random sampling?
- No, hardly any experiments use random sampling. Most get their subjects in other ways.
- The Physician's Health Study sent out invitation letters and questionnaires to all 261,248 male physicians between 40 and 84 years of age who lived in the United States.
- Of the 59,285 who were willing to participate in the trial, 26,062 were told they could not because of some medical condition or current medical treatment.

- So to what group can we generalize the results that taking aspirin can reduce heart attacks?
  - Just physicians in the study?
  - All male physicians between 40-84 years old?
  - All males physicians?
  - All males between 40-84 years olds?
  - All males?
  - Everyone between 40-84 years old?
  - Everyone?

Article Baseline Demographics After Random Assignment

Parameter	Placebo (n=129)	Uceris (n=128)
Mean age, years (range)	39.9 (12–68)	37.6 (13–66)
Men	77 (59.7)	70 (54.7)
Women	52 (40.3)	58 (45.3)
Mean disease duration (yrs)	6.3	5.5
Duration ≤1 year, n (%)	23 (17.8)	28 (21.9)
Duration >5 years, n (%)	51 (39.5)	44 (34.4)
Proctosigmoiditis	64 (49.6)	58 (45.3)
Left-sided colitis	44 (34.1)	37 (28.9)
Mean baseline UCDAI score	6.2	6.5
Mean baseline EI score	6.6	6.5
Prior mesalazine use	75 (58.1)	66 (51.6)
Prior sulfasalazine use	28 (21.7)	33 (25.8)

Sandborn WJ, Travis S, Moro L, Jones R, Gautille T, Bagin R, Huang M, Yeung P, Ballard ED 2nd Once-daily budesonide MMX® extended-release tablets induce remission in patients with mild to moderate ulcerative colitis: results from the CORE I study. *Gastroenterology* 2012 Nov;143(5):1218-26

Blocking and Random Assignment

- The goal in random assignment is to make the two groups as similar as possible in all ways other than the treatment.
- Sometime there are known confounders and you can block on (control for) these variables.
- For example, if our subjects consist of 60% females and 40% males, we can force each group to be 60% female and 40% male, using a matched pair design.
- Blocking makes sense when there are known confounders you want to control for. But randomly assigning subjects to groups makes them as similar as possible in terms of unknown confounders.

4. Blinding.

Even in experiments, the treatment and control groups can be different in ways other than the explanatory variable. This is especially true when the response variable is somewhat subjective.

Pain is an example. One study found that 1/4 of patients suffering from post-operative pain, when given a placebo (just a pill of sugar and water) claimed they experienced "significant prompt pain relief".

Blinding.

People might not be able to judge their own levels of pain very well, and may be influenced by the belief that they have taken an effective treatment.

Thus in an experiment with such a response variable, researchers should ensure the subject does not know whether he or she received the treatment or the control. This is called blinding.

In a *double-blind* experiment, neither the subject nor the researcher recording the response variable knows the level of the explanatory variable for each subject, i.e. treatment or control.

5. Portacaval shunt example.

The following example shows the importance of doing a randomized controlled experiment.

The portacaval shunt is a medical procedure aimed at curbing bleeding to death in patients with cirrhosis of the liver.

The following table summarizes 51 studies on the portacaval shunt. The poorly designed studies were very enthusiastic about the surgery, while the carefully designed studies prove that the surgery is largely ineffective.

	Degree of enthusiasm		
Design	High	Moderate	None
No controls	24	7	1
Controls, but not randomized	10	3	2
Randomized controlled	0	1	3

Portacaval shunt example.

Why did the poorly designed studies come to the wrong conclusion?

A likely explanation is that in the studies where patients were not randomly assigned to the treatment or control group, by and large the healthier patients were given the surgery.

This alone could explain why the treatment group outlived the control group in these studies.

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6. Coverage, adherer bias and Clofibrate example.

Surveys are observational.

- Coverage is a common issue. Coverage is the extent to which the people you sampled from represent the overall population. A survey at a fancy research hospital in a wealthy neighborhood may yield patients with higher incomes, higher education, etc.
- Non-response bias is another common problem. Poor coverage means the people getting the survey do not represent the general population. Non-response bias means that out of the people you gave the survey to, the people actually filling it out and submitting it are different from the people who did not.
- Same exact issues in web surveys.

Coverage, adherer bias, and Clofibrate example.

Non-response bias is similar to adherer bias, in experiments.
A drug called clofibrate was tested on 3,892 middle-aged men with heart trouble. It was supposed to prevent heart attacks.

1,103 assigned at random to take clofibrate,

2,789 to placebo (lactose) group.

Subjects were followed for 5 years.

Is this an experiment or an observational study?

Clofibrate	patients who died during followup
adherers	15%
non-adherers	25%
total	20%

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It is an experiment. Does Clofibrate work?

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Placebo	
adherers	15%
nonadherers	28%
total	21%

Those who took clofibrate did much better than those who didn't keep taking clofibrate. Does this mean clofibrate works?

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non-adherers	25%
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Placebo	
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nonadherers	**28%**
total	21%

Those who adhered to placebo also did much better than those who stopped adhering.

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adherers	15%
non-adherers	25%
total	**20%**

Placebo	
adherers	15%
nonadherers	28%
total	**21%**

All in all there was little difference between the two groups.

Clofibrate	patients who died during followup
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non-adherers	25%
total	**20%**

Placebo	
adherers	15%
nonadherers	28%
total	**21%**

Adherers did better than non-adherers, not because of clofibrate, but because they were healthier in general. Why?

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Adherers did better than non-adherers, not because of clofibrate, but because they were healthier in general. Why?

- adherers are the type to engage in healthier behavior.
- sick patients are less likely to adhere.