Epidemiological studies are either observational or experimental. We just reviewed two key observational studies, the case-control and cohort studies. These observational studies are considered “natural” experiments. Experimental studies are considered true experiments in which the investigator is in control of assigning the exposure.

The key feature of experimental study design is that the investigator assigns the exposure. In this way they mimic the laboratory experiments we are familiar with. Experiments are considered to be the gold standard of epidemiological research but just because a treatment can be effective in the ideal situation in which people are carefully selected and motivated to comply with the study does not mean that this result is truly applicable in a real world setting.

First a researcher determines the hypothesis formed. First researchers identify a study population. Study subjects recruited based on specific criteria (like if it is a treatment trial, they all have a certain disease) and their informed consent is sought. They subjects are randomly assigned into groups. Random assignment is often done by a computer. Researchers enter the study subjects ID numbers into the computer and program the computer to separate the subjects into the groups. These groups will include the treatment group and the non-treatment group.

These pictures show a program available on the internet that will do this for you. It is a free program. Click on the “randomize now” button and you can see what you need to put into the program to randomize subjects.
Eligible and willing subjects randomly allocated to receive one of the two or more interventions being compared

- Study groups are monitored for outcome under study (recurrence of disease, first occurrence of disease, getting better, side effects)
- Rates of the outcome in the various groups are compared

This is a sample of a flow diagram for an experimental study using aspirin to prevent cardiovascular disease in women. This study had a multi-stage design which ended up with 6 different groups. The women were originally randomized to receive a daily aspirin or placebo. We are going to discuss placebos shortly. The aspirin group was subdivided into groups given beta-carotene or a placebo. Then these groups were divided into groups given vitamin E or a placebo. As you can see this study ends up with eight groups:

(See slide)

So you can see that one study can actually look at a number of different factors as well as various combinations of these. Take some time to figure all of these out.

I thought you might enjoy this comic.
There are three common characteristics of experimental studies. In fact, experimental studies conducted within a clinical setting are often called Randomized Clinical Trials, showing the importance of randomization. Click on each one to obtain more information. First I want to make an important distinction between being randomly assigned into a study group. Many times when we are talking about obtaining a random sample of the population, we mean that we have a larger source population and people are randomly selected to get into the study. Everyone has an equal chance of being selected. In a clinical trial, people are often invited into the study because they have a certain disease and they are patients where the study is taking place. The random allocation or random assignment we refer to is that after the subjects are enrolled in the study, they are randomly assigned to receive the treatment or something else. The something else can be nothing, usual treatment, or a placebo. The reason this is done is to make the groups as equal as possible in terms of other characteristics. Each person has an equal chance of being assigned to the treatment group as any other person in the study. If we let physicians select who got the new treatment, they would very likely pick their sicker patients figuring they had less to lose than those who were doing well. Thus treatments that work may not appear to work.

The main reason we randomize our subjects into treatment and non-treatment groups is to make the two groups as comparable as possible at baseline on factors that might effect outcome.

We want the groups to only differ in terms of the treatment, so if there is a difference in the outcome we can reasonably say it is due to the treatment.

People vary and different characteristics of the people may impact on the treatment effect. Any group of individuals will vary in response to a "treatment" based upon their sex, age, overall health, severity of illness - in short, any factor that is relevant to response to the treatment. The investigator knows some of these (like severity of illness), but there are many unknown factors that are also relevant. Click return to go back to the main slide.
Random allocation works best with large numbers. If you have a sample of 10, and you randomly assign 5 to one group and 5 to another, you have a greater chance, for example that one group may have more women than the other. If you randomly assign 1000 people into two groups, the groups will be much more even distributed.

**Placebo:** A placebo is anything that seems to be a "real" medical treatment -- but isn't. It could be a pill, a shot, or some other type of "fake" treatment. What all placebos have in common is that they do not contain an active substance meant to affect health. The effect is tied to expectations. If an individual expected the placebo it decrease pain, it would likely do so. If they expected it to increase stress, their heart rate would go up and they might feel anxious. The fact that the placebo effect is tied to expectations doesn't make it imaginary or fake. Some studies show that there are actual physical changes that occur with the placebo effect. For instance, some studies have documented an increase in the body's production of endorphins, one of the body's natural pain relievers.

We use placebos because it is difficult to differentiate from the impact of a treatment and the placebo effect. Without placebos, we would incorrectly state that a treatment worked when in reality it did not. It is not always feasible to use a placebo. If one is testing a medication that causes severe side effects, it may not be ethical to give a placebo that mimics these side effects and as patients talk, they can quickly figure out who has the placebo. The vertebroplasty video was interesting as they did provide a sham surgery but it was clearly very important that they did so as both the treatment and placebo group improved following the surgery. Without a placebo, it would be impossible to know that the surgery was not effective. However, it may be that people who found relief from the procedure would not happy to know the study results.

The other concern with placebos are the ethical issues. People are uncomfortable with not being told what treatment they are getting. This is why the consent form needs to clearly indicate that
participants have a chance of not getting the actual medicine. Language uses terms like, It is like flipping a coin or rolling dice, It is not clear how well that actually works though because study participants who were interviewed after signing the consent would say things like, “I am sure I got the medication. My doctor would not give me a placebo.” The other concern with a placebo is in withholding a treatment that works. Or taking away treatment and giving a placebo, thus actually causing harm to the patient. Thus, ethically, placebos can only be given when the researcher does not really know how effective a treatment is. Also, if there is a standard treatment for a condition then the study participants may be randomized to receive the new treatment or the usual treatment. You cannot, for example, stop treating half of the diabetic patients to see the effect of a new dose of insulin. In addition, many randomized trial have set points at which the data will be examined to see if there is a statistical evidence of a clear advantage to the treatment, and people in the study who were receiving the placebo will now get the new drug. Click on the placebo to return to the previous slide. You can see how well it works.

**Blinding:** When we use the term blinding, we refer to the fact that researchers do not know which arm of the study they are in: treatment or non-treatment. Blinding is single when only the subject does not know his or her group. It is called double blinding when the researcher also does not know the group the subject is in. This is done so that the researcher does not indicate in some way to the subject if he or she is getting the real treatment. Blinding helps prevent bias in identifying the effect of the treatment and a placebo is an integral part of blinding. Blinding is not always possible, and one can still conduct a clinical trial without blinding or the use of placebos but people need to be aware of the potential for bias. Click return to go back to the main slide.
Experimental studies can be conducted in large populations groups or more commonly, as part of a drug treatment study. A central feature in these studies is that the investigator administers the treatment and generally participants are randomized into groups: those with and without the treatment. One famous large community study called Mr Fit, an acronym for The Multiple Risk Factor Intervention trial studies the impact on cardiovascular disease, focusing largely on dietary and lifestyle changes. Since it was actually much harder to get people to change these patterns than the researchers expected, for the most part this trial was a failure. Other community based intervention studies include the fluoridation of water in different communities and a comparison of rates of dental caries across populations. These studies tended to rely on community-level data and not follow individuals subjects, rather like the ecological studies we learned about previously. There have also been trials of exercise programs within elementary schools that have been conducted. And the women’s Health Study in which the trials on aspirin, vit E and Betacarotene described previously were conducted have had a strong impact on our understanding of women’s health.

We more often think of experimental studies are being used within the context of drug studies. A group of people with a certain medical condition may be given a drug to decrease the rate of side effects from their condition, e.g., evaluation of cholesterol lowering medication among people with high cholesterol or trials may be used to determine the effect of different cancer treatments, medication, radiation, etc. These trials are known as RCT (Randomized Clinical Trials) and they have a number of important characteristics, such as randomization, placebo, and blinding.
A) Study requires active participation and cooperation of participants but deviations from the protocol will occur related to side effects, illness, level of interest, and length of follow-up

B) Noncompliance makes the compared groups more alike, which reduces the ability of the investigator to detect a difference between the groups (diminishes study power)

C) Strategies to enhance compliance exist at the design phase (pick an interested group and design a simple protocol) and during the study itself (frequent contact with subjects, incentives to continue, such as free check-ups)

It is important to consider the difference between efficacy and effectiveness. Efficacy refers to how well a treatment works under ideal circumstances. During a clinical trial people are followed closely, given incentives to come to appointments, often provided with a lot of support.

Effectiveness refers to how well something works in a real setting. I had a sociology professor who once said the key question to ask is “Can YOAA do it?” YOAA refers to your ordinary American agency. Things that worked in an ideal situation may not work in the real world setting. People who complied with taking their medication during a clinical trial with constant reminders may be more likely to forget meds at home.

Intent to Treat refers to the fact that if you randomize someone to be in the intervention group and that person ends up not taking the treatment, you still evaluate the results based on the group to which the person was assigned. You do not only consider the impact on those who complied with the treatment.
For analysis, you can compute the relative risk like you had done in the cohort study. Again, we have the familiar 2 by 2 table. There is another type of analysis which is done when we are looking at time to death in some of the treatment studies, and that is called survival analysis. This method is beyond the scope of this class but I wanted you to know it exists.

Quiz Question

A research study enrolls children with leukemia and their healthy classmates to determine if living in new housing as a young child was associated with increased rates of disease. What type of study is this?

- Cross-sectional
- Ecological
- Case-control
- Prospective cohort
- Retrospective cohort
- Ambi-directional cohort
- Experimental study
A research study compares alcohol-related motor vehicle fatalities across states with different alcohol regulations to see if regulations are associated with fatality rates. What type of study is this?

- Cross-sectional
- Ecological
- Case-control
- Prospective cohort
- Retrospective cohort
- Ambi-directional cohort
- Experimental study

A research study enrolls subjects with diabetes to determine...

- Cross-sectional
- Ecological
- Case-control
- Prospective cohort
- Retrospective cohort
- Ambi-directional cohort
- Experimental study

A research study randomly assigns people with hepatitis C infection due to intra-venous drug use to receive a new medication "Drug C" to see if it can improve survival rates. What type of study is this?

- Cross-sectional
- Ecological
- Case-control
- Prospective cohort
- Retrospective cohort
- Ambi-directional cohort
- Experimental study
A researcher compares mortality rates among employees in the copper mines with people employed in sulfur mines during the 1920s using 1950-1970 death certificate data. What type of study is this?

- Cross sectional
- Ecological
- Case-control
- Prospective cohort
- Retrospective cohort
- Ambi-directional cohort
- Experimental study

You need to identify the cause of a new disease. So far this disease has infected 70 individuals in a remote fishing village in Peru. What type of study might you conduct?

- Cross sectional
- Ecological
- Case-control
- Prospective cohort
- Retrospective cohort
- Ambi-directional cohort
- Experimental study

People are concerned that computer use among young children (ages 2 and under) might lead to visual problems, poor socialization skills, and difficulty sleeping when they start kindergarten. What type of study might you conduct?

- Cross sectional
- Ecological
- Case-control
- Cohort
- Experimental study
You need to determine if the prevalence of binge drinking among USF students is more common among men or women. You hope to develop an intervention but you need to know how many staff to hire. What type of study might you conduct?

- Cross sectional
- Ecological
- Case-control
- Cohort
- Experimental study

What type of study is this?

- Cross sectional
- Ecological
- Case-control
- Prospective cohort
- Retrospective cohort
- Ambi-directional cohort
- Experimental study

What type of study is this?

- Cross sectional
- Ecological
- Case-control
- Prospective cohort
- Retrospective cohort
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- Experimental study
Match the study design with the correct measure of risk.

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Measure of Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case-control</td>
<td>Odds ratio</td>
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<tr>
<td>Cohort study</td>
<td>Relative Risk</td>
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<tr>
<td>Cross-sectional study</td>
<td>Prevalence Ratio</td>
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<tr>
<td>Experimental study</td>
<td>Survival Analysis</td>
</tr>
</tbody>
</table>

Certificate of Achievement

This certificate is proudly presented for honorable achievement to [Your Name Here]

For understanding research study designs and obtaining general epidemiological knowledge.