Experimental Design

Controlled Experiments and Observational Studies

Does a “treatment” have an “effect?”

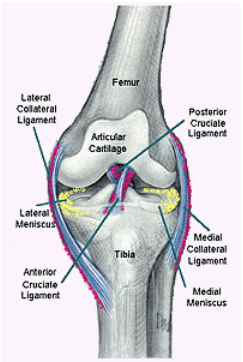
- Does vitamin C help to prevent colds?
- Does the use of cell phones while driving increase the probability of an accident?
- Does coffee consumption increase the risk of coronary disease?
- Does second-hand smoke cause cancer?
- Is moderate alcohol consumption beneficial?
- Does decreased dietary cholesterol lead to higher suicide rates?
- Are breast-fed babies smarter?

Is arthroscopy of the knee effective?

About 650,000 procedures per year at a cost of roughly $5000 each.

Study in New England Journal of Medicine

VA suggests halting surgery



How do we find out?

The basic idea is to compare two groups:

- An unexposed "control" group
- An exposed "treatment" group

How is the composition of these two groups to be determined?

- In a *controlled* experiment, membership is determined by the investigator.
- In an *observational study* the subjects select their own memberships

A controlled experiment has very substantial advantages.

Observational Studies and the Problem of Confounding

Is the use of cell phones while driving dangerous?

San Francisco Chronicle, March 19, 1996

People with cellular phones in their cars run a 34 percent higher risk of having accidents, researchers said yesterday.

And, according to the study, the danger mounts when drivers use the phone a lot or while doing something else, such as lighting a cigarette or drinking coffee.

Most often, it seems, motorists engrossed in a phone conversation run red lights and get into collisions at busy intersections. But even on the open highway, a car-phone can take people's minds off their driving.

``They kind of forget about the rest of the world," said John Violanti, a criminal justice Professor at the Rochester Institute of Technology who helped conduct the study. ``They're not intentionally cutting somebody off, (they're) just not seeing them."

The study, believed to be the first of its kind appears in the March issue of Accident Analysis and Prevention, a British journal.

The Cellular Telecommunications Industry Association in Washington, D.C., dismissed the study as limited and flawed.``It has glaring research shortcomings," said spokeswoman Pam Small.

The researchers, who plan a larger survey, countered that their findings, even though preliminary, should not be ignored at a time when cellular-phone sales are booming.

Violanti and James Marshal, a professor of social and preventitive medicine at the State University of New York at Buffalo, randomly selected 100 New York motorists who had been in an accident and 100 who had not. Of those in accidents, 13.7 percent owned cellular phones, and 10.6 percent of the accident free drivers had a phone in the car.

Through surveys and phone records, the researchers determined that the motorists who used car phones more often than average--50 minutes per month--were five times more likely to have accidents than those who either talked less or did not own a car phone.

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Comparison groups

Greater than average use while driving	*vs*	Less than average use while driving

Outcome: greater than average use group 5 times more likely to have an accident

This is an *observational study*--the subjects determined which groups they belonged to.

Are these two groups comparable?

In what ways that affect the outcome might the groups differ?

Confounding

These are examples of *confounding:* a difference between the treatment and control groups which affects the responses being studied.

Confounders:

- The amount a person drives
- Where that person drives
- When a person drives

What could be done about this?

There is always a possibility of confounding in observational studies.

Confounding

A confounder is associated with both group membership and outcome. It provides a possible alternative explanation for an outcome that differs between the two groups.

Not everything that can go wrong is confounding.

Not confounding:

- Inaccurate accident records
- Inaccurate phone records

Sex and Death

Study Suggests Sex May Help Men Live Longer. But researchers, critics agree more data needed

New York Times, December 1988

Men who have more sex seem to live longer, a statistical study of Welsh villagers in The British Medical Journal has found.

It is one of the rare studies of sex and death, and the authors lightheartedly suggested in the Journal article that the findings might result in new kinds of promotional campaigns for healthy living.

But before then, further studies of both sexes are needed to confirm their findings, the authors said. Two other scientists commenting in the same issue cautioned that because of its design, the study might not have identified factors that could have inadvertently influenced the findings —that ill people may be less likely to have sex, for example.

Having regular sex reduces the risk of death by about half, according to the analysis, part of a longterm study of chronic disease in the Welsh town of Caerphilly.

"Sexual activity seems to have a protective effect on men's health," Dr. George Davey-Smith's team concluded after analyzing death rates of nearly 1,000 men from ages 45 to 59 in Caerphilly.

Davey-Smith's team assessed the existence of heart disease in the men when they entered the study from 1979 to 1983. They asked the men about the frequency of sexual activity, and answers were put into categories ranging from "never" to "daily."

The authors said they tried to adjust the study to account for a factor that might explain the findings—that healthier men with healthier lifestyles engaged in more sex. Even so, they could not explain the differences in risk. Hormonal effects on the body resulting from frequent sex could be one possible explanation, Davey-Smith said.

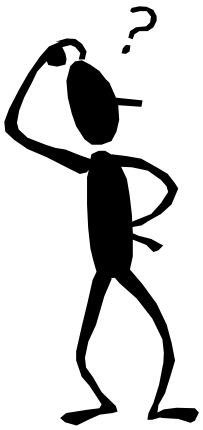
The Design

(for more details see the web site)

918 men aged 45-59 in Caerphilly interviewed (25% declined to answer question)

- Grouped into low, medium, and high frequency of orgasm
- Attempted to “statistically adjust” for age, height, body mass, blood pressure, cholesterol, social class, existing coronary disease, smoking
- 150 dead after 10 years
- (Adjusted) death rate for high frequency guys less than half that of low frequency guys

Confounders?
Other Problems?



Controlled Experiments

In a controlled experiment, membership is assigned by the experimenter.

Example: an experiment to determine the effectiveness of mammary artery ligation.

> To force more blood to flow into the heart of people with coronary artery disease, the mammary arteries were ligated. Popularized in a 1957 *Reader's Digest* article.

Patient entered surgery

⇩

Preliminary incision made

⇩

Random decision whether to tie off artery

⇩

Later examination by physician

Randomized, Double Blind Study

- Treatment was assigned at *random*
- *Neither* the patient nor the physician knew whether surgery was actually performed.

Study showed no essentially no difference between treatment and control, with some suggestion that control fared better.

Randomization:

- Eliminates possible human bias in assignment to treatment or control.
- Laws of chance guarantee that with enough subjects, the treatment and control groups will resemble each other with respect to other important variables.

Double Blind

- Acts as a *placebo* for the patient.
- Prevents unconscious bias in measuring the outcome.

Scientifically, these are the most effective designs, but they are often practically or *ethically* impossible.

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HIV Placebo Study Poses Ethical Dilemma for U.S

The United States is paying for experiments in poor countries in which many babies may die of AIDS because their HIV-infected mothers are given placebos instead of a protective drug, the patient advocacy group Public Citizen said yesterday.

The government says the studies are ethical because they are the only way to find new HIV protections that poor countries can afford. Pregnant women in developing countries today do not get the AZT therapy that American AIDS patients use to protect their unborn children.

But in a letter signed by prominent bioethicists and Dr. Wilbert Jordan, head of the Black Los Angeles AIDS Consortium, Public Citizen compared the U.S.-funded foreign research to the infamous "Tuskegee experiment" in Alabama, in which the government withheld syphilis treatment from poor African American patients.

Also, federal law forbids U.S. doctors from conducting experiments abroad that would not be tolerated in the United States, a letter from the critics to Health and Human Services Secretary Donna Shalala said. The letter urged a federal investigation.

Shalala did not immediately respond, but the National Institutes of Health and Centers for Disease Control and Prevenffon vigorously defended the studies.

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"In the absence of identifying some regimen that is affordable, hundreds of thousands of kids are going to die," said the CDC's Dr. Phillip Nieburg.

Studies have indicated that taking the drug AZT during pregnancy and labor and giving it to infants for six weeks after birth cuts by two-thirds babies' chances of contracting HIV from mothers.

But that treatment costs about $800 per person, too expensive for mothers in developing countries, so doctors are studying potential alternatives such as shorter courses of AZT or giving malnourished pregnant women vitamin A.

Nine U.S.-funded studies in Africa, Thailand and the Dominican Republic compare the possible new therapies with dummy pills, instead of giving the comparison women the U.S style AZT treatment. The government says a placebo comparison is the only way to prove potential new therapies are better than no treatment.

Even Short HIV Therapy Protects Kids

Risk of infection from mothers cut by 50% in study

(San Francisco Chronicle, February 19, 1998)

An AIDS prevention experiment has proved so remarkably effective that it could end the threat of death for millions of infants born worldwide to mothers infected with HIV, health officials in the United States and Thailand announced yesterday.

The experiment -- extremely controversial when it began -- involved giving a short, oral course of the anti-viral drug AZT to pregnant women already infected by HIV, the AIDS virus.

When similar preventive therapy began in a U.S. study four years ago, HIV-positive pregnant women took injections of AZT five times a day for up to four months of pregnancy and throughout labor. Their newborns were given AZT four times a day for six weeks. The infection rate among the infants dropped by 70 percent, and the routine became standard in the United States and most other industrialized countries.

The procedure, however, is extremely expensive and far beyond the reach of many women in Third World countries, where the cost of a single AIDS drug regimen can easily outstrip a developing nation's entire public health budget.

Because of the expense -- plus the difficulty in providing sterile injection needles and the limited numbers of AIDS physicians in the developing world -- scientists at the U.S. Centers for Disease Control and Prevention in Atlanta teamed with the Ministry of Public Health in Thailand and with similar officials in Abidjan, the capital of the Ivory Coast in Africa, for a far shorter and simpler AZT trial.

In the Thailand study, women were given AZT orally only twice a day starting in their 36th week of pregnancy and then again during labor. Their newborns received no drug at all.

The results, according to Thai and U.S. officials, showed that the risk of transmitting the disease from mother to newborn was cut by 51 percent. And although that result was not as good as the more elaborate American method, the short-course regimen is more applicable and more feasible for many countries in the developing world, officials said.

While the Thailand treatment cost about $50 to $80 per woman; the prolonged course costs about $800.

``By using a much shorter course during pregnancy, an oral dose rather than an intravenous dose during delivery, and no infant dose, we evaluated a regimen that could be realistically implemented in developing nations,'' said Dr. Helene Gayle, the CDC's leading AIDS prevention specialist.

``Now that the regimen has been proven safe and effective in Thailand,'' said Gayle, ``these findings offer hope of extending perinatal prevention to HIV-infected women throughout the developing world.''

During the Thailand AZT study, the HIV-infected women were randomly assigned to take either the drug or a placebo, with no AZT, in order to compare results. The use of placebos was sharply attacked by many AIDS specialists as an unethical experiment on Third World women who were being denied known medical help while possibly not understanding their rights as study participants. The controversy raged in AIDS circles for three years.

Thai and Ivory Coast AIDS experts, however, together with their American colleagues, insisted that only placebo controls could validate the results unequivocally.

With 90 percent of the data now reviewed and the experiment declared a success, a joint statement from the three government agencies yesterday said that the placebo trials have been halted and women who had been taking placebos are being given AZT instead. In addition, officials from the CDC, the U.N. AIDS program and the National Institutes of Health said they will recommend that placebo use be stopped in all mother-to-child transmission studies, about a half dozen of which are currently under way worldwide.

How *could* you do a study to learn if cell phones lead to increased risk of accidents?

Another Study of Cell Phones and Accidents

First proof: driving while talking on phone is a hazard.

The New York Times, Feb. 13 1997, p. A-30

Gina Kolata

The good news is that cellular phones do not cause brain cancer. The bad news? They are unfortunately a cause of car accidents. In fact, according to research by Drs. Donald A. Redelmeier and Robert J. Tibshirani, driving with the use of a cell phone can be likened to driving with a blood alcohol level of about 0.10 per cent. The chances of getting into an car accident while using a cellular phone is nearly equal to the chances of having an accident while slightly drunk.

Another factor in the chance of having an accident is the topic and content of conversation: A person who is not talking on the phone cannot become distracted by a shouting match with a boss or a significant other. Thus, the risk gets even greater if the person is discussing something important or especially is in the middle of an argument.

The researchers, a professor of medicine at the University of Toronto and a statistician at the same school, ran a study of 699 drivers who had cellular phones and who had also been involved in an accident. They analyzed 26,798 phone calls on cellular phones and determined that the risk of having an accident quadrupled when drivers spoke on the phone. With heated discussions, this rate is even higher.

The Design

Screened accidents for those involving drivers who owned cell phones. Determined from phone records that

- 25% were talking at time of accident
- 5% were talking on the phone at the same time on the previous day

This is the basic idea, but the details are more complicated. See Redelmeier and Tibshirani, *Chance*, vol 10, no. 2 1997: "Is using a car phone like driving drunk?"

Some details:

		Day before collision		
		On phone	Not on phone	Total
Day of collision	On phone	13	157	170
	Not phone	24	505	529
	Total	37	662	699

Key Concepts

- The difference between observational and controlled studies
- Confounder: a variable associated with both group membership and outcome
- The importance of randomization
- The placebo effect

A study was conducted to see whether fish oil is effective in reducing triglyceride levels in the blood. (It is good for one's heart to have low levels of triglycerides.) According to the article by Reuters on Dec. 10, 1996:

In the study, published in the International Journal of Cardiology this month, 40 patients, ages 18 to 70 years, were randomly selected to receive either 12 fish oil capsules a day (3.6 grams of omega 3), or 12 similar appearing soya oil capsules per day for two months. Prior to taking the capsules, all study participants avoided eating any fish for one month.

After 8 weeks, triglycerides increased 19.9% among people taking soya oil and decreased 27.8% in the fish oil group. Total cholesterol levels were not affected significantly.

Answer True or False and briefly explain why:

[T F] This was an observational study.

[T F] There was a placebo.

[T F] Confounding due to age differences in the two groups is likely to be a problem in this study.

Contrary to popular belief, people who sleep six to seven hours a night live longer, and those who sleep eight hours or more die younger, according to a California study, the largest ever conducted on the subject.

The controversial study, which tracked the sleeping habits of 1.1 million Americans for six years, undermines the advice of many sleep doctors who have long recommended that people get eight or nine hours of sleep every night. "There's an old idea that people should sleep eight hours a night, which has no more scientific basis than the gold at the end of the rainbow," said Daniel Kripke, a professor of psychiatry at the University of California at San Diego who led the study, published in today's Archives of General Psychiatry.

The study used data from a monumental survey conducted by the American Cancer Society between 1982 and 1988. Women sleeping eight, nine and 10 hours a night had 13 percent, 23 percent and 41 percent higher risk of dying, respectively, than those who slept seven hours, the study found. Men sleeping eight, nine and 10 hours a night had 12 percent, 17 percent and 34 percent greater risk of dying within the period.

[T F] The difference between long and short sleepers might be explained by the placebo effect.

[T F] A possible confounding factor is that the participants might not have reported the amount they slept accurately.

[T F] This is a controlled experiment

[**T F**] If older people sleep more, age would be a possible confounding factor.

[**T F]** If overweight people tend to sleep more, weight would be a possible confounding factor.

[**T F]** The study shows that if you sleep 10 hours per night, you can reduce your chance of dying by cutting back to 7 hours per night.