Observational studies

Controlled experiment:

The investigator chooses who receives the treatment.

Observational study:

The subjects themselves choose whether they receive the treatment.

Key issues:

- Correlation (association) is not causation.
- Confounding
- Simpson's paradox

The clofibrate trial

Coronary drug project:

A randomized, controlled, double-blind experiment to evaluate 5 drugs (including clofibrate) for the prevention of heart disease.

Subjects: Middle-aged men with heart trouble.

- 5,552 assigned at random to the drug groups
- 2,789 assigned at random to the control group (placebo=lactose)
- Patients followed 5 years.

Note: most examples taken from Freedman, Psiani, Purves (1998) *Statistics*, 3rd ed, Ch 2

Clofibrate

- Reduces the level of cholesterol in the blood
- Didn't save any lives in the trial:
  - 20% dead in clofibrate group
  - 21% dead in control group
- Possible cause: adherence

  (Many subjects didn't take their medicine.)
- In clofibrate group: [Adherer: took >80% of medicine.]
  - Adherers: 15% mortality rate
  - Non-adherers: 25% mortality rate

Adherence in the clofibrate trial

	Clofibrate		Placebo	
	Number	Deaths	Number	Deaths
Adherers	708	15%	1,813	15%
Non-adherers	357	25%	882	28%
Overall	1,103	20%	2,789	21%

Adherers and non-adherers differ in ways other than whether they took their medicine!

Conclusion: Clofibrate has no effect (on the death rate).

Causes of association

Suppose A is associated with B.

This may be because:

- A causes B
- B causes A
- X is associated with both A and B.

Confounding

In the association of A and B, X is a confounder if it is associated with both A and B.

X need not be a cause of either A or B.

For example, in the consideration of smoking and lung cancer, a gene which

- causes smoking but is not associated with lung cancer is not a confounder.
- causes lung cancer but is not associated with smoking is not a confounder.
- causes lung cancer and is associated with smoking is a confounder.

Disease P——

- First observed in Europe in 18th century; important cause of ill-health, disability and premature death among the very poor. Spread across Europe by the beginning of the 19th century.
- It seemed to hit some villages more than others; many households were spared, but some had disease cases year after year.
- Sanitary conditions in diseased households were primitive. Flies were everywhere.
- One blood-sucking fly (*Simulium*) had the same geographical range as the disease, at least in Europe, and was most active in the spring, when most of the cases developed.

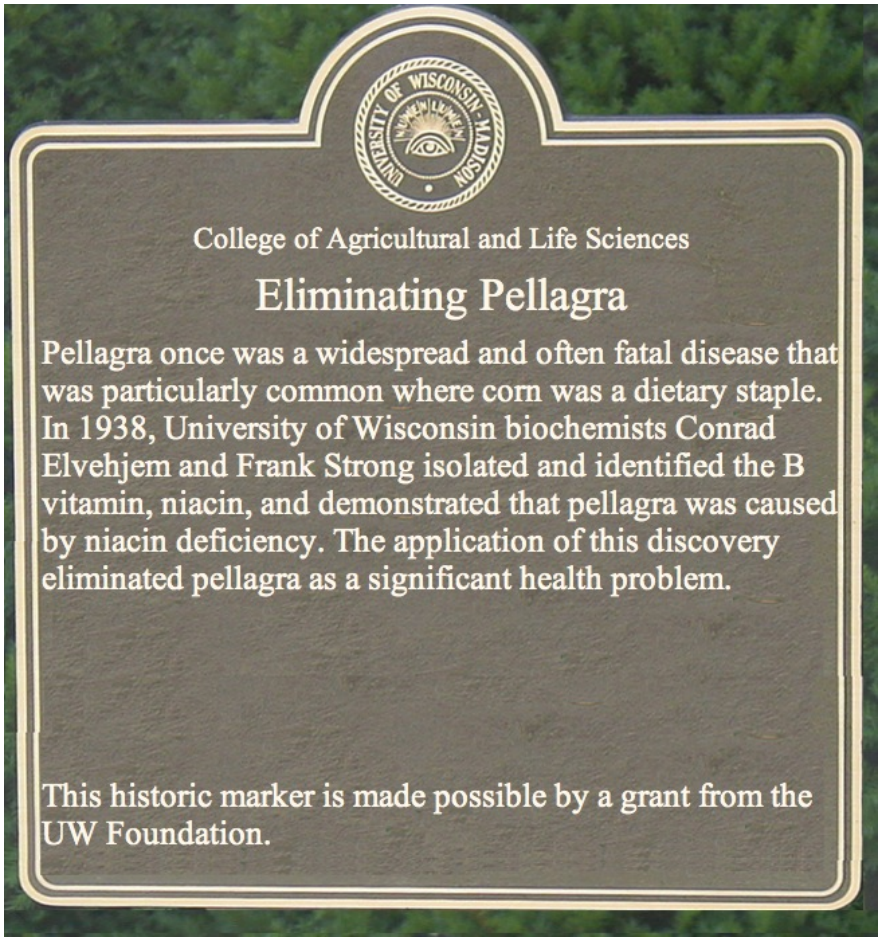
Many epidemiologists concluded the disease was infectious and—like malaria, yellow fever, or typhus—was transmitted from one person to another by insects.

Was this conclusion justified?

Discussion

- The disease is pellagra; a series of observational studies and experiments showed that pellagra is caused by a bad diet, and is not infectious.
- The disease can be prevented or cured by foods rich in what was called the P-P (pellagra-preventive) factor, now called niacin.
- Niacin occurs naturally in meat, milk, eggs, some vegetables, and certain grains. Corn, however, contains relatively little niacin.
- In the pellagra areas, the poor ate corn and not much else.
- The flies were a marker of poverty, not a cause of pellagra.

Correlation is not causation!



Cervical cancer and circumcision

- Cervical cancer was for many years one of the most common cancers among women.
- Cervical cancer was quite rare among Jews and Moslems.
- In the 1950's, several investigators concluded that circumcision of the males was the protective factor.

Was this conclusion justified?

Discussion

- It turns out that cervical cancer is a sexually transmitted disease, spread by contact.
- Current research suggests that certain strains of HPV (human papilloma virus) are the causal agents.
- Some women are more sexually active than others, and have more partners, and are thus more likely to be exposed to the disease.
- Early studies did not pay attention to this confounding variable.

Correlation is not causation!

Ultrasound and low birthweight

- Several experiments on lab animals have shown that ultrasound examinations can cause low birthweight. Is this also true for humans?
- Investigators ran an observational study to find out.
- The investigators found a number of confounding variables and adjusted for them. Even so, there was an association: Babies exposed to ultrasound in the womb had lower birthweight, on average, than babies who were not exposed.

Is this evidence that ultrasound causes lower birthweight?

Discussion

The investigators concluded that the ultrasound and low birthweights had a common cause—problem pregnancies.

Later, a randomized controlled experiment was done to get more definite evidence. If anything, ultrasound was protective.

Correlation is not causation!

Marriage status and child abuse

- A newspaper article reported on an organization who had studied the relationship between abuse of a child and the marriage status of the child's parents.
- It was found that children of single parents were more often abused.
- The investigators concluded (quite strongly) that encouraging marriage would reduce the rate of child abuse.

Is this conclusion justified?

Discussion

No attempt had been made to take account of differences in income/poverty.

That child abuse is more frequent in single parents is not sufficient evidence for the conclusion that being single causes one to abuse children.

Correlation is not causation!

Gene expression

- Schadt *et al.*, Nature Genetics, 422:297–302 (2003) reported on genome-wide gene expression in liver tissue and obesity in mice who had been on a high-fat, atherogenic diet for 4 months.
- They identified a set of genes that showed quite strong differences in expression in mice with high subcutaneous fat-pad-mass (FPM) versus those with low FPM.
- One might conclude that the gene expression differences contributed to the obesity differences.

Would such a conclusion be justified?

Discussion

No. It is impossible to tell whether the gene expression differences are part of the etiology of obesity or of the pathology of obesity.

Correlation is not causation!

Controlling for a confounder

The problem with observational studies is that subjects differ among themselves in crucial ways besides the treatment.

We deal with this by controlling for the confounding variable(s)—we compare smaller, more homogeneous subgroups.

- Anticipate, measure, and control for possible confounders.
- Think about other possible confounders that were not considered.
- Never draw very strong conclusions from a single observational study.

Sex bias in graduate admissions

Observational study on sex bias in graduate admissions at the University of California, Berkeley.

During the study period:

- 44% (of 8,442) men were admitted
- 35% (of 4,321) women were admitted

Does this indicate a sex bias?

Sex bias in graduate admissions

For the six largest majors:

	Men		Women	
Major	Number of applicants	Percent admitted	Number of applicants	Percent admitted
A	825	62	108	82
B	560	63	25	68
C	325	37	593	34
D	417	33	375	35
E	191	28	393	24
F	373	6	341	7

Simpson's paradox:

Relationships between variables within subgroups can be reversed when the subgroups are combined.

Summary

- In controlled experiments, we can ensure (by randomization) that the treatment and control groups are the same, except for the treatment.
- In observational studies, the treatment and control groups may differ in crucial ways aside from the treatment.
- We try to identify and control for such confounding factors.
- We must always consider the possibility that there are additional, unidentified confounders.
- Correlation is not causation.