2

Observational Studies

That's not an experiment you have there, that's an experience.
—SIR R. A. FISHER (ENGLAND, 1890–1962)

1. INTRODUCTION

Controlled experiments are different from *observational studies*. In a controlled experiment, the investigators decide who will be in the treatment group and who will be in the control group. By contrast, in an observational study it is the subjects who assign themselves to the different groups: the investigators just watch what happens.

The jargon is a little confusing, because the word *control* has two senses.

- A *control* is a subject who did not get the treatment.
- A *controlled experiment* is a study where the investigators decide who will be in the treatment group and who will not.

Studies on the effects of smoking, for instance, are necessarily observational: nobody is going to smoke for ten years just to please a statistician. However, the treatment-control idea is still used. The investigators compare smokers (the treatment or "exposed" group) with non-smokers (the control group) to determine the effect of smoking.

The smokers come off badly in this comparison. Heart attacks, lung cancer, and many other diseases are more common among smokers than non-smokers. So there is a strong *association* between smoking and disease. If cigarettes cause

disease, that explains the association: death rates are higher for smokers because cigarettes kill. Thus, association is circumstantial evidence for causation. However, the proof is incomplete. There may be some hidden confounding factor which makes people smoke and also makes them get sick. If so, there is no point in quitting; that will not change the hidden factor. Association is not the same as causation.

Statisticians like Joseph Berkson and Sir R. A. Fisher did not believe the evidence against cigarettes, and suggested possible confounding variables. Epidemiologists (including Sir Richard Doll in England, and E. C. Hammond, D. Horn, H. A. Kahn in the United States) ran careful observational studies to show these alternative explanations were not plausible. Taken together, the studies make a powerful case that smoking causes heart attacks, lung cancer, and other diseases. If you give up smoking, you will live longer.[1]

Observational studies are a powerful tool, as the smoking example shows. But they can also be quite misleading. To see if confounding is a problem, it may help to find out how the controls were selected. The main issue: was the control group really similar to the treatment group—apart from the exposure of interest? If there is confounding, something has to be done about it, although perfection cannot be expected. Statisticians talk about *controlling for* confounding factors in an observational study. This is a third use of the word *control*.

One technique is to make comparisons separately for smaller and more homogeneous groups. For example, a crude comparison of death rates among smokers and non-smokers could be misleading, because smokers are disproportionately male and men are more likely than women to have heart disease anyway. The difference between smokers and non-smokers might be due to the sex difference. To eliminate that possibility, epidemiologists compare male smokers to male non-smokers, and females to females.

Age is another confounding variable. Older people have different smoking habits, and are more at risk for lung cancer. So the comparison between smokers and non-smokers is done separately by age as well as by sex. For example, male smokers age 55–59 are compared to male non-smokers age 55–59. This controls for age and sex. Good observational studies control for confounding variables. In the end, however, most observational studies are less successful than the ones on smoking. The studies may be designed by experts, but experts make mistakes too. Finding the weak points is more an art than a science, and often depends on information outside the study.

2. THE CLOFIBRATE TRIAL

The Coronary Drug Project was a randomized, controlled double-blind experiment, whose objective was to evaluate five drugs for the prevention of heart attacks. The subjects were middle-aged men with heart trouble. Of the 8,341 subjects, 5,552 were assigned at random to the drug groups and 2,789 to the control group. The drugs and the placebo (lactose) were administered in identical capsules. The patients were followed for 5 years.

One of the drugs on test was clofibrate, which reduces the levels of cholesterol in the blood. Unfortunately, this treatment did not save any lives. About 20% of the clofibrate group died over the period of followup, compared to 21% of the control group. A possible reason for this failure was suggested—many subjects in the clofibrate group did not take their medicine.

Subjects who took more than 80% of their prescribed medicine (or placebo) were called "adherers" to the protocol. For the clofibrate group, the 5-year mortality rate among the adherers was only 15%, compared to 25% among the non-adherers (table 1). This looks like strong evidence for the effectiveness of the drug. However, caution is in order. This particular comparison is observational not experimental—even though the data were collected while an experiment was going on. After all, the investigators did not decide who would adhere to protocol and who would not. The subjects decided.

Table 1. The clofibrate trial. Numbers of subjects, and percentages who died during 5 years of followup. Adherers take 80% or more of prescription.

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

Note: Data on adherence missing for 38 subjects in the clofibrate group and 94 in the placebo group. Deaths from all causes.
Source: The Coronary Drug Project Research Group, "Influence of adherence to treatment and response of cholesterol on mortality in the Coronary Drug Project," *New England Journal of Medicine* vol. 303 (1980) pp. 1038–41.

Maybe adherers were different from non-adherers in other ways, besides the amount of the drug they took. To find out, the investigators compared adherers and non-adherers in the control group. Remember, the experiment was double-blind. The controls did not know whether they were taking an active drug or the placebo; neither did the subjects in the clofibrate group. The psychological basis for adherence was the same in both groups.

In the control group too, the adherers did better. Only 15% of them died during the 5-year period, compared to 28% among the non-adherers. The conclusions:

(i) Clofibrate does not have an effect.
(ii) Adherers are different from non-adherers.

Probably, adherers are more concerned with their health and take better care of themselves in general. That would explain why they took their capsules and why they lived longer. Observational comparisons can be quite misleading. The investigators in the clofibrate trial were unusually careful, and they found out what was wrong with comparing adherers to non-adherers.[2]