

This works out to 39%. Similarly, the weighted average admission rate for the women is

$$\frac{.82 \times 933 + .68 \times 585 + .34 \times 918 + .35 \times 792 + .24 \times 584 + .07 \times 714}{4,526}$$

This works out to 43%. In these formulas, the weights are the same for the men and women; they are the totals from table 3. The admission rates are different for men and women; they are the rates from table 2. The final comparison: the weighted average admission rate for men is 39%, while the weighted average admission rate for women is 43%. The weighted averages control for the confounding factor—choice of major. These averages suggest that if anything, the admissions process is biased against the men.

5. CONFOUNDING

Hidden confounders are a major problem in observational studies. As discussed in section 1, epidemiologists found an association between exposure (smoking) and disease (lung cancer): heavy smokers get lung cancer at higher rates than light smokers; light smokers get the disease at higher rates than non-smokers. According to the epidemiologists, the association comes about because smoking causes lung cancer. However, some statisticians—including Sir R. A. Fisher—thought the association could be explained by confounding.

Confounders have to be associated with (i) the disease and (ii) the exposure. For example, suppose there is a gene which increases the risk of lung cancer. Now, if the gene also gets people to smoke, it meets both the tests for a confounder. This gene would create an association between smoking and lung cancer. The idea is a bit subtle: a gene that causes cancer but is unrelated to smoking is not a confounder and is sideways to the argument, because it does not account for the facts—the association between smoking and cancer.⁹ Fisher's "constitutional hypothesis" explained the association on the basis of genetic confounding; nowadays, there is evidence from twin studies to refute this hypothesis (review exercise 11, chapter 15).

Confounding means a difference between the treatment and control groups—other than the treatment—which affects the responses being studied. A confounder is a third variable, associated with exposure and with disease.

Exercise Set A

1. In the U.S. in 2000, there were 2.4 million deaths from all causes, compared to 1.9 million in 1970—a 25% increase.¹⁰ True or false, and explain: the data show that the public's health got worse over the period 1970–2000.

2. Data from the Salk vaccine field trial suggest that in 1954, the school districts in the NFIP trial and in the randomized controlled experiment had similar exposures to the polio virus.
 - (a) The data also show that children in the two vaccine groups (for the randomized controlled experiment and the NFIP design) came from families with similar incomes and educational backgrounds. Which two numbers in table 1 (p. 6) confirm this finding?
 - (b) The data show that children in the two no-consent groups had similar family backgrounds. Which pair of numbers in the table confirm this finding?
 - (c) The data show that children in the two control groups had different family backgrounds. Which pair of numbers in the table confirm this finding?
 - (d) In the NFIP study, neither the control group nor the no-consent group got the vaccine. Yet the no-consent group had a lower rate of polio. Why?
 - (e) To show that the vaccine works, someone wants to compare the 44/100,000 in the NFIP study with the 25/100,000 in the vaccine group. What's wrong with this idea?
3. Polio is an infectious disease; for example, it seemed to spread when children went swimming together. The NFIP study was not done blind: could that bias the results? Discuss briefly.
4. The Salk vaccine field trials were conducted only in certain experimental areas (school districts), selected by the Public Health Service in consultation with local officials.¹¹ In these areas, there were about 3 million children in grades 1, 2, or 3; and there were about 11 million children in those grades in the United States. In the experimental areas, the incidence of polio was about 25% higher than in the rest of the country. Did the Salk vaccine field trials cause children to get polio instead of preventing it? Answer yes or no, and explain briefly.
5. Linus Pauling thought that vitamin C prevents colds, and cures them too. Thomas Chalmers and associates did a randomized controlled double-blind experiment to find out.¹² The subjects were 311 volunteers at the National Institutes of Health. These subjects were assigned at random to 1 of 4 groups:

<i>Group</i>	<i>Prevention</i>	<i>Therapy</i>
1	placebo	placebo
2	vitamin C	placebo
3	placebo	vitamin C
4	vitamin C	vitamin C

All subjects were given six capsules a day for prevention, and an additional six capsules a day for therapy if they came down with a cold. However, in group 1 both sets of capsules just contained the placebo (lactose). In group 2, the prevention capsules had vitamin C while the therapy capsules were filled with the placebo. Group 3 was the reverse. In group 4, all the capsules were filled with vitamin C.

There was quite a high dropout rate during the trial. And this rate was significantly higher in the first 3 groups than in the 4th. The investigators noticed this, and found the reason. As it turned out, many of the subjects broke the blind. (That

is quite easy to do; you just open a capsule and taste the contents; vitamin C—ascorbic acid—is sour, lactose is not.) Subjects who were getting the placebo were more likely to drop out.

The investigators analyzed the data for the subjects who remained blinded, and vitamin C had no effect. Among those who broke the blind, groups 2 and 4 had the fewest colds; groups 3 and 4 had the shortest colds. How do you interpret these results?

6. (Hypothetical.) One of the other drugs in the Coronary Drug Project (section 2) was nicotinic acid.¹³ Suppose the results on nicotinic acid were as reported below. Something looks wrong. What, and why?

	<i>Nicotinic acid</i>		<i>Placebo</i>	
	<i>Number</i>	<i>Deaths</i>	<i>Number</i>	<i>Deaths</i>
Adherers	558	13%	1,813	15%
Non-adherers	487	26%	882	28%
Total group	1,045	19%	2,695	19%

7. (Hypothetical.) In a clinical trial, data collection usually starts at “baseline,” when the subjects are recruited into the trial but before they are assigned to treatment or control. Data collection continues until the end of followup. Two clinical trials on prevention of heart attacks report baseline data on smoking, shown below. In one of these trials, the randomization did not work. Which one, and why?

		<i>Number of persons</i>	<i>Percent who smoked</i>
(i)	Treatment	1,012	49.3%
	Control	997	69.0%
(ii)	Treatment	995	59.3%
	Control	1,017	59.0%

8. Some studies find an association between liver cancer and smoking. However, alcohol consumption is a confounding variable. This means—
- Alcohol causes liver cancer.
 - Drinking is associated with smoking, and alcohol causes liver cancer.
- Choose one option, and explain briefly.

9. Breast cancer is one of the most common malignancies among women in the U.S. If it is detected early enough—before the cancer spreads—chances of successful treatment are much better. Do screening programs speed up detection by enough to matter?

The first large-scale trial was run by the Health Insurance Plan of Greater New York, starting in 1963. The subjects (all members of the plan) were 62,000 women age 40 to 64. These women were divided at random into two equal groups. In the treatment group, women were encouraged to come in for annual screening, including examination by a doctor and X-rays. About 20,200 women in the treatment group did come in for the screening; but 10,800 refused. The control group was offered usual health care. All the women were followed for many years.

Results for the first 5 years are shown in the table below.¹⁴ ("HIP" is the usual abbreviation for the Health Insurance Plan.)

Deaths in the first five years of the HIP screening trial, by cause. Rates per 1,000 women.

		Cause of Death			
		Breast cancer		All other	
		Number	Rate	Number	Rate
Treatment group					
Examined	20,200	23	1.1	428	21
Refused	10,800	16	1.5	409	38
Total	31,000	39	1.3	837	27
Control group	31,000	63	2.0	879	28

Epidemiologists who worked on the study found that (i) screening had little impact on diseases other than breast cancer; (ii) poorer women were less likely to accept screening than richer ones; and (iii) most diseases fall more heavily on the poor than the rich.

- (a) Does screening save lives? Which numbers in the table prove your point?
 - (b) Why is the death rate from all other causes in the whole treatment group ("examined" and "refused" combined) about the same as the rate in the control group?
 - (c) Breast cancer (like polio, but unlike most other diseases) affects the rich more than the poor. Which numbers in the table confirm this association between breast cancer and income?
 - (d) The death rate (from all causes) among women who accepted screening is about half the death rate among women who refused. Did screening cut the death rate in half? If not, what explains the difference in death rates?
10. (This continues exercise 9.)
- (a) To show that screening reduces the risk from breast cancer, someone wants to compare 1.1 and 1.5. Is this a good comparison? Is it biased against screening? For screening?
 - (b) Someone claims that encouraging women to come in for breast cancer screening increases their health consciousness, so these women take better care of themselves and live longer for that reason. Is the table consistent or inconsistent with the claim?
 - (c) In the first year of the HIP trial, 67 breast cancers were detected in the "examined" group, 12 in the "refused" group, and 58 in the control group. True or false, and explain briefly: screening causes breast cancer.
11. Cervical cancer is more common among women who have been exposed to the herpes virus, according to many observational studies.¹⁵ Is it fair to conclude that the virus causes cervical cancer?
12. Physical exercise is considered to increase the risk of spontaneous abortion. Furthermore, women who have had a spontaneous abortion are more likely to have another. One observational study finds that women who exercise regularly have fewer spontaneous abortions than other women.¹⁶ Can you explain the findings of this study?