Causal Inference

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August 26, 2018

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Part I

Causal inference without models

Chapter 1
A DEFINITION OF CAUSAL EFFECT

By reading this book you are expressing an interest in learning about causal inference. But, as a human being, you have already mastered the fundamental concepts of causal inference. You certainly know what a causal effect is; you clearly understand the difference between association and causation; and you have used this knowledge constantly throughout your life. In fact, had you not understood these causal concepts, you would have not survived long enough to read this chapter—or even to learn to read. As a toddler you would have jumped right into the swimming pool after observing that those who did so were later able to reach the jam jar. As a teenager, you would have skied down the most dangerous slopes after observing that those who did so were more likely to win the next ski race. As a parent, you would have refused to give antibiotics to your sick child after observing that those children who took their medicines were less likely to be playing in the park the next day.

Since you already understand the definition of causal effect and the difference between association and causation, do not expect to gain deep conceptual insights from this chapter. Rather, the purpose of this chapter is to introduce mathematical notation that formalizes the causal intuition that you already possess. Make sure that you can match your causal intuition with the mathematical notation introduced here. This notation is necessary to precisely define causal concepts, and we will use it throughout the book.

1.1 Individual causal effects

Zeus is a patient waiting for a heart transplant. On January 1, he receives a new heart. Five days later, he dies. Imagine that we can somehow know, perhaps by divine revelation, that had Zeus not received a heart transplant on January 1, he would have been alive five days later. Equipped with this information most would agree that the transplant caused Zeus's death. The heart transplant intervention had a causal effect on Zeus's five-day survival.

Another patient, Hera, also received a heart transplant on January 1. Five days later she was alive. Imagine we can somehow know that, had Hera not received the heart on January 1, she would still have been alive five days later. Hence the transplant did not have a causal effect on Hera's five-day survival.

These two vignettes illustrate how humans reason about causal effects: We compare (usually only mentally) the outcome when an action A is taken with the outcome when the action A is withheld. If the two outcomes differ, we say that the action A has a causal effect, causative or preventive, on the outcome. Otherwise, we say that the action A has no causal effect on the outcome. Epidemiologists, statisticians, economists, and other social scientists often refer to the action A as an intervention, an exposure, or a treatment.

Capital letters represent random variables. Lower case letters denote particular values of a random variable.

To make our causal intuition amenable to mathematical and statistical analysis we will introduce some notation. Consider a dichotomous treatment variable A (1: treated, 0: untreated) and a dichotomous outcome variable Y (1: death, 0: survival). In this book we refer to variables such as A and Y that may have different values for different individuals as *random variables*. Let $Y^{a=1}$ (read Y under treatment $a = 1$) be the outcome variable that would have been observed under the treatment value $a = 1$, and $Y^{a=0}$ (read Y under treatment $a = 0$) the outcome variable that would have been observed under

the treatment value $a = 0$. $Y^{a=1}$ and $Y^{a=0}$ are also random variables. Zeus has $Y^{a=1} = 1$ and $Y^{a=0} = 0$ because he died when treated but would have survived if untreated, while Hera has $Y^{a=1} = 0$ and $Y^{a=0} = 0$ because she survived when treated and would also have survived if untreated.

We can now provide a formal definition of a *causal effect for an individual*: the treatment A has a causal effect on an individual's outcome Y if $Y^{a=1} \neq Y^{a=0}$ for the individual. Thus the treatment has a causal effect on Zeus's outcome because $Y^{a=1} = 1 \neq 0 = Y^{a=0}$, but not on Hera's outcome because $Y^{a=1} = 0 = Y^{a=0}$. The variables $Y^{a=1}$ and $Y^{a=0}$ are referred to as *potential outcomes* or as *counterfactual outcomes*. Some authors prefer the term "potential outcomes" to emphasize that, depending on the treatment that is received, either of these two outcomes can be potentially observed. Other authors prefer the term "counterfactual outcomes" to emphasize that these outcomes represent situations that may not actually occur (that is, counter to the fact situations).

Sometimes we abbreviate the expression "individual i has outcome $Y^a = 1$" by writing $Y_i^a = 1$. Technically, when i refers to a specific individual, such as Zeus, Y_i^a is not a random variable as we are assuming that individual counterfactual outcomes are deterministic (see Fine Point 1.2).

Causal effect for individual i:
$Y_i^{a=1} \neq Y_i^{a=0}$

For each individual, one of the counterfactual outcomes—the one that corresponds to the treatment value that the individual actually received—is actually factual. For example, because Zeus was actually treated ($A = 1$), his counterfactual outcome under treatment $Y^{a=1} = 1$ is equal to his observed (actual) outcome $Y = 1$. That is, an individual with observed treatment A equal to a, has observed outcome Y equal to his counterfactual outcome Y^a. This equality can be succinctly expressed as $Y = Y^A$ where Y^A denotes the counterfactual Y^a evaluated at the value a corresponding to the individual's observed treatment A. The equality $Y = Y^A$ is referred to as *consistency*.

Consistency:
if $A_i = a$, then $Y_i^a = Y^{A_i} = Y_i$

Individual causal effects are defined as a contrast of the values of counterfactual outcomes, but only one of those outcomes is observed for each individual—the one corresponding to the treatment value actually experienced by the individual. All other counterfactual outcomes remain unobserved. The unhappy conclusion is that, in general, individual causal effects cannot be identified—tthat is, cannot be expressed as function of the observed data—because of missing data. (See Fine Point 2.1 for a possible exception.)

1.2 Average causal effects

We needed three pieces of information to define an individual causal effect: an outcome of interest, the actions $a = 1$ and $a = 0$ to be compared, and the individual whose counterfactual outcomes $Y^{a=0}$ and $Y^{a=1}$ are to be compared. However, because identifying individual causal effects is generally not possible, we now turn our attention to an aggregated causal effect: the average causal effect in a population of individuals. To define it, we need three pieces of information: an outcome of interest, the actions $a = 1$ and $a = 0$ to be compared, and a well-defined population of individuals whose outcomes $Y^{a=0}$ and $Y^{a=1}$ are to be compared.

Take Zeus's extended family as our population of interest. Table 1.1 shows the counterfactual outcomes under both treatment ($a = 1$) and no treatment ($a = 0$) for all 20 members of our population. Let us first focus our attention on the last column: the outcome $Y^{a=1}$ that would have been observed for each individual if they had received the treatment (a heart transplant). Half of the members of the population (10 out of 20) would have died if they had received a heart transplant. That is, the proportion of individuals that would have developed the outcome had all population individuals received $a = 1$ is

Fine Point 1.1

Interference. An implicit assumption in our definition of counterfactual outcome is that an individual's counterfactual outcome under treatment value a does not depend on other individuals' treatment values. For example, we implicitly assumed that Zeus would die if he received a heart transplant, regardless of whether Hera also received a heart transplant. That is, Hera's treatment value did not interfere with Zeus's outcome. On the other hand, suppose that Hera's getting a new heart upsets Zeus to the extent that he would not survive his own heart transplant, even though he would have survived had Hera not been transplanted. In this scenario, Hera's treatment interferes with Zeus's outcome. Interference between individuals is common in studies that deal with contagious agents or educational programs, in which an individual's outcome is influenced by their social interaction with other population members.

In the presence of interference, the counterfactual Y_i^a for an individual i is not well defined because an individual's outcome depends also on other individuals' treatment values. As a consequence "the causal effect of heart transplant on Zeus's outcome" is not well defined when there is interference. Rather, one needs to refer to "the causal effect of heart transplant on Zeus's outcome when Hera does not get a new heart" or "the causal effect of heart transplant on Zeus's outcome when Hera does get a new heart." If other relatives and friends' treatment also interfere with Zeus's outcome, then one may need to refer to the causal effect of heart transplant on Zeus's outcome when "no relative or friend gets a new heart," "when only Hera gets a new heart," etc. because the causal effect of treatment on Zeus's outcome may differ for each particular allocation of hearts. The assumption of no interference was labeled "no interaction between units" by Cox (1958), and is included in the "stable-unit-treatment-value assumption (SUTVA)" described by Rubin (1980). See Halloran and Struchiner (1995), Sobel (2006), Rosenbaum (2007), and Hudgens and Halloran (2009) for a more detailed discussion of the role of interference in the definition of causal effects. Unless otherwise specified, we will assume no interference throughout this book.

Table 1.1

	$Y^{a=0}$	$Y^{a=1}$
Rheia	0	1
Kronos	1	0
Demeter	0	0
Hades	0	0
Hestia	0	0
Poseidon	1	0
Hera	0	0
Zeus	0	1
Artemis	1	1
Apollo	1	0
Leto	0	1
Ares	1	1
Athena	1	1
Hephaestus	0	1
Aphrodite	0	1
Cyclope	0	1
Persephone	1	1
Hermes	1	0
Hebe	1	0
Dionysus	1	0

$\Pr[Y^{a=1} = 1] = 10/20 = 0.5$. Similarly, from the other column of Table 1.1, we can conclude that half of the members of the population (10 out of 20) would have died if they had not received a heart transplant. That is, the proportion of individuals that would have developed the outcome had all population individuals received $a = 0$ is $\Pr[Y^{a=0} = 1] = 10/20 = 0.5$. Note that we have computed the counterfactual risk under treatment to be 0.5 by counting the number of deaths (10) and dividing them by the total number of individuals (20), which is the same as computing the average of the counterfactual outcome across all individuals in the population (to see the equivalence between risk and average for a dichotomous outcome, use the data in Table 1.1 to compute the average of $Y^{a=1}$).

We are now ready to provide a formal definition of the *average causal effect* in the population: an average causal effect of treatment A on outcome Y is present if $\Pr[Y^{a=1} = 1] \neq \Pr[Y^{a=0} = 1]$ in the population of interest. Under this definition, treatment A does not have an average causal effect on outcome Y in our population because both the risk of death under treatment $\Pr[Y^{a=1} = 1]$ and the risk of death under no treatment $\Pr[Y^{a=0} = 1]$ are 0.5. That is, it does not matter whether all or none of the individuals receive a heart transplant: half of them would die in either case. When, like here, the average causal effect in the population is null, we say that the *null hypothesis of no average causal effect* is true. Because the risk equals the average and because the letter E is usually employed to represent the population average or mean (also referred to as 'E'xpectation), we can rewrite the definition of a non-null average causal effect in the population as $\mathrm{E}[Y^{a=1}] \neq \mathrm{E}[Y^{a=0}]$ so that the definition applies to both dichotomous and nondichotomous outcomes.

The presence of an "average causal effect of heart transplant A" is defined by a contrast that involves the two actions "receiving a heart transplant ($a =$

Fine Point 1.2

Multiple versions of treatment. Another implicit assumption in our definition of a individual's counterfactual outcome under treatment value a is that there is only one version of treatment value $A = a$. For example, we said that Zeus would die if he received a heart transplant. This statement implicitly assumes that all heart transplants are performed by the same surgeon using the same procedure and equipment. That is, that there is only one version of the treatment "heart transplant." If there were multiple versions of treatment (e.g., surgeons with different skills), then it is possible that Zeus would survive if his transplant were performed by Asclepios, and would die if his transplant were performed by Hygieia. In the presence of multiple versions of treatment, the counterfactual Y_i^a for an individual i is not well defined because an individual's outcome depends on the version of treatment a. As a consequence "the causal effect of heart transplant on Zeus's outcome" is not well defined when there are multiple versions of treatment. Rather, one needs to refer to "the causal effect of heart transplant on Zeus's outcome when Asclepios performs the surgery" or "the causal effect of heart transplant on Zeus's outcome when Hygieia performs the surgery." If other components of treatment (e.g., procedure, place) are also relevant to the outcome, then one may need to refer to "the causal effect of heart transplant on Zeus's outcome when Asclepios performs the surgery using his rod at the temple of Kos" because the causal effect of treatment on Zeus's outcome may differ for each particular version of treatment.

Like the assumption of no interference (see Fine Point 1.1), the assumption of no multiple versions of treatment is included in the "stable-unit-treatment-value assumption (SUTVA)" described by Rubin (1980). Robins and Greenland (2000) made the point that if the versions of a particular treatment (e.g., heart transplant) had the same causal effect on the outcome (survival), then the counterfactual $Y^{a=1}$ would be well-defined. VanderWeele (2009) formalized this point as the assumption of "treatment variation irrelevance," i.e., the assumption that multiple versions of treatment $A = a$ may exist but they all result in the same outcome Y_i^a. We return to this issue in Chapter 3 but, unless otherwise specified, we will assume treatment variation irrelevance throughout this book.

Average causal effect in population: $\mathrm{E}[Y^{a=1}] \neq \mathrm{E}[Y^{a=0}]$

1)" and "not receiving a heart transplant ($a = 0$)." When more than two actions are possible (i.e., the treatment is not dichotomous), the particular contrast of interest needs to be specified. For example, "the causal effect of aspirin" is meaningless unless we specify that the contrast of interest is, say, "taking, while alive, 150 mg of aspirin by mouth (or nasogastric tube if need be) daily for 5 years" versus "not taking aspirin." Note that this causal effect is well defined even if counterfactual outcomes under other interventions are not well defined or even do not exist (e.g., "taking, while alive, 500 mg of aspirin by absorption through the skin daily for 5 years").

Absence of an average causal effect does not imply absence of individual effects. Table 1.1 shows that treatment has an individual causal effect on 12 members (including Zeus) of the population because, for each of these 12 individuals, the value of their counterfactual outcomes $Y^{a=1}$ and $Y^{a=0}$ differ. Of the 12 , 6 were harmed by treatment, including Zeus $\left(Y^{a=1} - Y^{a=0} = 1\right)$, and 6 were helped $\left(Y^{a=1} - Y^{a=0} = -1\right)$. This equality is not an accident: the average causal effect $\mathrm{E}[Y^{a=1}] - \mathrm{E}[Y^{a=0}]$ is always equal to the average $\mathrm{E}[Y^{a=1} - Y^{a=0}]$ of the individual causal effects $Y^{a=1} - Y^{a=0}$, as a difference of averages is equal to the average of the differences. When there is no causal effect for any individual in the population, i.e., $Y^{a=1} = Y^{a=0}$ for all individuals, we say that the *sharp causal null hypothesis* is true. The sharp causal null hypothesis implies the null hypothesis of no average effect.

As discussed in the next chapters, average causal effects *can* sometimes be identified from data, even if individual causal effects cannot. Hereafter we refer to 'average causal effects' simply as 'causal effects' and the null hypothesis of no average effect as the causal null hypothesis. We next describe different measures of the magnitude of a causal effect.

Technical Point 1.1

Causal effects in the population. Let $\mathrm{E}[Y^a]$ be the mean counterfactual outcome had all individuals in the population received treatment level a. For discrete outcomes, the mean or expected value $\mathrm{E}[Y^a]$ is defined as the weighted sum $\sum_y y\, p_{Y^a}(y)$ over all possible values y of the random variable Y^a, where $p_{Y^a}(\cdot)$ is the probability mass function of Y^a, i.e., $p_{Y^a}(y) = \Pr[Y^a = y]$. For dichotomous outcomes, $\mathrm{E}[Y^a] = \Pr[Y^a = 1]$. For continuous outcomes, the expected value $\mathrm{E}[Y^a]$ is defined as the integral $\int y f_{Y^a}(y)\, dy$ over all possible values y of the random variable Y^a, where $f_{Y^a}(\cdot)$ is the probability density function of Y^a. A common representation of the expected value that applies to both discrete and continuous outcomes is $\mathrm{E}[Y^a] = \int y dF_{Y^a}(y)$, where $F_{Y^a}(\cdot)$ is the cumulative distribution function (CDF) of the random variable Y^a. We say that there is a non-null average causal effect in the population if $\mathrm{E}[Y^a] \neq \mathrm{E}[Y^{a'}]$ for any two values a and a'.

The average causal effect, defined by a contrast of means of counterfactual outcomes, is the most commonly used population causal effect. However, a population causal effect may also be defined as a contrast of, say, medians, variances, hazards, or CDFs of counterfactual outcomes. In general, a causal effect can be defined as a contrast of any functional of the distributions of counterfactual outcomes under different actions or treatment values. The causal null hypothesis refers to the particular contrast of functionals (mean, median, variance, hazard, CDF, ...) used to define the causal effect.

1.3 Measures of causal effect

We have seen that the treatment 'heart transplant' A does not have a causal effect on the outcome 'death' Y in our population of 20 family members of Zeus. The causal null hypothesis holds because the two counterfactual risks $\Pr[Y^{a=1} = 1]$ and $\Pr[Y^{a=0} = 1]$ are equal to 0.5. There are equivalent ways of representing the causal null. For example, we could say that the risk $\Pr[Y^{a=1} = 1]$ minus the risk $\Pr\left[Y^{a=0} = 1\right]$ is zero $(0.5 - 0.5 = 0)$ or that the risk $\Pr[Y^{a=1} = 1]$ divided by the risk $\Pr\left[Y^{a=0} = 1\right]$ is one $(0.5/0.5 = 1)$. That is, we can represent the causal null by

(i) $\Pr[Y^{a=1} = 1] - \Pr[Y^{a=0} = 1] = 0$

(ii) $\dfrac{\Pr[Y^{a=1} = 1]}{\Pr[Y^{a=0} = 1]} = 1$

(iii) $\dfrac{\Pr[Y^{a=1} = 1]/\Pr[Y^{a=1} = 0]}{\Pr[Y^{a=0} = 1]/\Pr[Y^{a=0} = 0]} = 1$

where the left-hand side of the equalities (i), (ii), and (iii) is the causal risk difference, risk ratio, and odds ratio, respectively.

The causal risk difference in the population is the average of the individual causal effects $Y^{a=1} - Y^{a=0}$ on the difference scale, i.e., it is a measure of the average individual causal effect. By contrast, the causal risk ratio in the population is not the average of the individual causal effects $Y^{a=1}/Y^{a=0}$ on the ratio scale, i.e., it is a measure of causal effect in the population but is not the average of any individual causal effects.

Suppose now that another treatment A, cigarette smoking, has a causal effect on another outcome Y, lung cancer, in our population. The causal null hypothesis does not hold: $\Pr[Y^{a=1} = 1]$ and $\Pr[Y^{a=0} = 1]$ are not equal. In this setting, the causal risk difference, risk ratio, and odds ratio are not 0, 1, and 1, respectively. Rather, these causal parameters quantify the strength of the same causal effect on different scales. Because the causal risk difference, risk ratio, and odds ratio (and other summaries) measure the causal effect, we refer to them as *effect measures*.

Each effect measure may be used for different purposes. For example, imagine a large population in which 3 in a million individuals would develop the outcome if treated, and 1 in a million individuals would develop the outcome if untreated. The causal risk ratio is 3, and the causal risk difference is 0.000002. The causal risk ratio (multiplicative scale) is used to compute how many times

Fine Point 1.3

Number needed to treat. Consider a population of 100 million patients in which 20 million would die within five years if treated ($a = 1$), and 30 million would die within five years if untreated ($a = 0$). This information can be summarized in several equivalent ways:

- the causal risk difference is $\Pr[Y^{a=1} = 1] - \Pr[Y^{a=0} = 1] = 0.2 - 0.3 = -0.1$
- if one treats the 100 million patients, there will be 10 million fewer deaths than if one does not treat those 100 million patients.
- one needs to treat 100 million patients to save 10 million lives
- on average, one needs to treat 10 patients to save 1 life

We refer to the average number of individuals that need to receive treatment $a = 1$ to reduce the number of cases $Y = 1$ by one as the number needed to treat (NNT). In our example the NNT is equal to 10. For treatments that reduce the average number of cases (i.e., the causal risk difference is negative), the NNT is equal to the reciprocal of the absolute value of the causal risk difference:

$$NNT = \frac{-1}{\Pr[Y^{a=1} = 1] - \Pr[Y^{a=0} = 1]}$$

Like the causal risk difference, the NNT applies to the population and time interval on which it is based. For treatments that increase the average number of cases (i.e., the causal risk difference is positive), one can symmetrically define the *number needed to harm*. The NNT was introduced by Laupacis, Sackett, and Roberts (1988). For a discussion of the relative advantages and disadvantages of the NNT as an effect measure, see Grieve (2003).

treatment, relative to no treatment, increases the disease risk. The causal risk difference (additive scale) is used to compute the absolute number of cases of the disease attributable to the treatment. The use of either the multiplicative or additive scale will depend on the goal of the inference.

1.4 Random variability

At this point you could complain that our procedure to compute effect measures is somewhat implausible. Not only did we ignore the well known fact that the immortal Zeus cannot die, but—more to the point—our population in Table 1.1 had only 20 individuals. The populations of interest are typically much larger.

In our tiny population, we collected information from all the individuals. In practice, investigators only collect information on a sample of the population of interest. Even if the counterfactual outcomes of all study individuals were known, working with samples prevents one from obtaining the exact proportion of individuals in the population who had the outcome under treatment value a, e.g., the probability of death under no treatment $\Pr[Y^{a=0} = 1]$ cannot be directly computed. One can only estimate this probability.

1st source of random error: Sampling variability

Consider the individuals in Table 1.1. We have previously viewed them as forming a twenty-person population. Suppose we view them as a random sample from a much larger, near-infinite super-population (e.g., all immortals). We denote the proportion of individuals in the sample who would have

died if unexposed as $\widehat{\Pr}[Y^{a=0} = 1] = 10/20 = 0.50$. The sample proportion $\widehat{\Pr}[Y^{a=0} = 1]$ does not have to be exactly equal to the proportion of individuals who would have died if the entire super-population had been unexposed, $\Pr[Y^{a=0} = 1]$. For example, suppose $\Pr[Y^{a=0} = 1] = 0.57$ in the population but, because of random error due to sampling variability, $\widehat{\Pr}[Y^{a=0} = 1] = 0.5$ in our particular sample. We use the sample proportion $\widehat{\Pr}[Y^a = 1]$ to estimate the super-population probability $\Pr[Y^a = 1]$ under treatment value a. The "hat" over Pr indicates that the sample proportion $\widehat{\Pr}[Y^a = 1]$ is an estimator of the corresponding population quantity $\Pr[Y^a = 1]$. We say that $\widehat{\Pr}[Y^a = 1]$ is a *consistent estimator* of $\Pr[Y^a = 1]$ because the larger the number of individuals in the sample, the smaller the difference between $\widehat{\Pr}[Y^a = 1]$ and $\Pr[Y^a = 1]$ is expected to be. This occurs because the error due to sampling variability is random and thus obeys the law of large numbers.

An estimator $\hat{\theta}$ of θ is consistent if, with probability approaching 1, the difference $\hat{\theta} - \theta$ approaches zero as the sample size increases towards infinity.

Caution: the term 'consistency' when applied to estimators has a different meaning from that which it has when applied to counterfactual outcomes.

Because the super-population probabilities $\Pr[Y^a = 1]$ cannot be computed, only consistently estimated by the sample proportions $\widehat{\Pr}[Y^a = 1]$, one cannot conclude with certainty that there is, or there is not, a causal effect. Rather, a statistical procedure must be used to test the causal null hypothesis $\Pr[Y^{a=1} = 1] = \Pr[Y^{a=0} = 1]$; the procedure quantifies the chance that the difference between $\widehat{\Pr}[Y^{a=1} = 1]$ and $\widehat{\Pr}[Y^{a=0} = 1]$ is wholly due to sampling variability.

So far we have only considered sampling variability as a source of random error. But there may be another source of random variability: perhaps the values of an individual's counterfactual outcomes are not fixed in advance. We have defined the counterfactual outcome Y^a as the individual's outcome had he received treatment value a. For example, in our first vignette, Zeus would have died if treated and would have survived if untreated. As defined, the values of the counterfactual outcomes are fixed or deterministic for each individual, e.g., $Y^{a=1} = 1$ and $Y^{a=0} = 0$ for Zeus. In other words, Zeus has a 100% chance of dying if treated and a 0% chance of dying if untreated. However, we could imagine another scenario in which Zeus has a 90% chance of dying if treated, and a 10% chance of dying if untreated. In this scenario, the counterfactual outcomes are stochastic or nondeterministic because Zeus's probabilities of dying under treatment (0.9) and under no treatment (0.1) are neither zero or one. The values of $Y^{a=1}$ and $Y^{a=0}$ shown in Table 1.1 would be possible realizations of "random flips of mortality coins" with these probabilities. Further, one would expect that these probabilities vary across individuals because not all individuals are equally susceptible to develop the outcome. Quantum mechanics, in contrast to classical mechanics, holds that outcomes are inherently nondeterministic. That is, if the quantum mechanical probability of Zeus dying is 90%, the theory holds that no matter how much data we collect about Zeus, the uncertainty about whether Zeus will actually develop the outcome if treated is irreducible.

2^{nd} source of random error: Nondeterministic counterfactuals

Table 1.2

	A	Y
Rheia	0	0
Kronos	0	1
Demeter	0	0
Hades	0	0
Hestia	1	0
Poseidon	1	0
Hera	1	0
Zeus	1	1
Artemis	0	1
Apollo	0	1
Leto	0	0
Ares	1	1
Athena	1	1
Hephaestus	1	1
Aphrodite	1	1
Cyclope	1	1
Persephone	1	1
Hermes	1	0
Hebe	1	0
Dionysus	1	0

Thus, in causal inference, random error derives from sampling variability, nondeterministic counterfactuals, or both. However, for pedagogic reasons, we will continue to largely ignore random error until Chapter 10. Specifically, we will assume that counterfactual outcomes are deterministic and that we have recorded data on every individual in a very large (perhaps hypothetical) super-population. This is equivalent to viewing our population of 20 individuals as a population of 20 billion individuals in which 1 billion individuals are identical to Zeus, 1 billion individuals are identical to Hera, and so on. Hence, until Chapter 10, we will carry out our computations with Olympian certainty.

Then, in Chapter 10, we will describe how our statistical estimates and confidence intervals for causal effects in the super-population are identical ir-

Technical Point 1.2

Nondeterministic counterfactuals. For nondeterministic counterfactual outcomes, the mean outcome under treatment value a, $\mathrm{E}[Y^a]$, equals the weighted sum $\sum_y y\, p_{Y^a}(y)$ over all possible values y of the random variable Y^a, where the probability mass function $p_{Y^a}(\cdot) = \mathrm{E}\left[Q_{Y^a}(\cdot)\right]$, and $Q_{Y^a}(y)$ is a random probability of having outcome $Y = y$ under treatment level a. In the example described in the text, $Q_{Y^{a=1}}(1) = 0.9$ for Zeus. (For continuous outcomes, the weighted sum is replaced by an integral.)

More generally, a nondeterministic definition of counterfactual outcome does not attach some particular value of the random variable Y^a to each individual, but rather a statistical distribution $\Theta_{Y^a}(\cdot)$ of Y^a. The nondeterministic definition of causal effect is a generalization of the deterministic definition in which $\Theta_{Y^a}(\cdot)$ is a random CDF that may take values between 0 and 1. The average counterfactual outcome in the population $\mathrm{E}[Y^a]$ equals $\mathrm{E}\left\{\mathrm{E}\left[Y^a \mid \Theta_{Y^a}(\cdot)\right]\right\}$. Therefore, $\mathrm{E}[Y^a] = \mathrm{E}\left[\int y\, d\Theta_{Y^a}(y)\right] = \int y\, d\mathrm{E}[\Theta_{Y^a}(y)] = \int y\, dF_{Y^a}(y)$, because we define $F_{Y^a}(\cdot) = \mathrm{E}\left[\Theta_{Y_i^a}(\cdot)\right]$. Although the possibility of nondeterministic counterfactual outcomes implies no changes in our definitions of population causal effect and of effect measures, nondeterministic counterfactual outcomes introduce random variability.

Note that, if the counterfactual outcomes are binary and nondeterministic, the causal risk ratio in the population $\frac{\mathrm{E}[Q_{Y^{a=1}}(1)]}{\mathrm{E}[Q_{Y^{a=0}}(1)]}$ is equal to the weighted average $\mathrm{E}\left[W\left\{Q_{Y^{a=1}}(1)/Q_{Y^{a=0}}(1)\right\}\right]$ of the individual causal effects $Q_{Y^{a=1}}(1)/Q_{Y^{a=0}}(1)$ on the ratio scale, with weights $W = \frac{Q_{Y^{a=0}}(1)}{\mathrm{E}[Q_{Y^{a=0}}(1)]}$.

respective of whether the world is stochastic (quantum) or deterministic (classical) at the level of individuals. In contrast, confidence intervals for the average causal effect in the actual study sample will differ depending on whether counterfactuals are deterministic versus stochastic. Fortunately, super-population effects are in most cases the causal effects of substantive interest.

1.5 Causation versus association

Obviously, the data available from actual studies look different from those shown in Table 1.1. For example, we would not usually expect to learn Zeus's outcome if treated $Y^{a=1}$ *and* also Zeus's outcome if untreated $Y^{a=0}$. In the real world, we only get to observe one of those outcomes because Zeus is either treated or untreated. We referred to the observed outcome as Y. Thus, for each individual, we know the observed treatment level A and the outcome Y as in Table 1.2.

The data in Table 1.2 can be used to compute the proportion of individuals that developed the outcome Y among those individuals in the population that happened to receive treatment value a. For example, in Table 1.2, 7 individuals died ($Y = 1$) among the 13 individuals that were treated ($A = 1$). Thus the risk of death in the treated, $\Pr[Y = 1|A = 1]$, was 7/13. More generally, the conditional probability $\Pr[Y = 1|A = a]$ is defined as the proportion of individuals that developed the outcome Y among those individuals in the population of interest that happened to receive treatment value a.

When the proportion of individuals who develop the outcome in the treated $\Pr[Y = 1|A = 1]$ equals the proportion of individuals who develop the outcome in the untreated $\Pr[Y = 1|A = 0]$, we say that treatment A and outcome Y are independent, that A is not associated with Y, or that A does not predict Y. *Independence* is represented by $Y \perp\!\!\!\perp A$—or, equivalently, $A \perp\!\!\!\perp Y$— which is read as Y and A are independent. Some equivalent definitions of independence

Dawid (1979) introduced the symbol $\perp\!\!\!\perp$ to denote independence

are

(i) $\Pr[Y=1|A=1] - \Pr[Y=1|A=0] = 0$

(ii) $\dfrac{\Pr[Y=1|A=1]}{\Pr[Y=1|A=0]} = 1$

(iii) $\dfrac{\Pr[Y=1|A=1]/\Pr[Y=0|A=1]}{\Pr[Y=1|A=0]/\Pr[Y=0|A=0]} = 1$

where the left-hand side of the inequalities (i), (ii), and (iii) is the associational risk difference, risk ratio, and odds ratio, respectively.

For a continuous outcome Y we define *mean independence* between treatment and outcome as: $\mathrm{E}[Y|A=1] = \mathrm{E}[Y|A=0]$. Independence and mean independence are the same concept for dichotomous outcomes.

We say that treatment A and outcome Y are dependent or associated when $\Pr[Y=1|A=1] \neq \Pr[Y=1|A=0]$. In our population, treatment and outcome are indeed associated because $\Pr[Y=1|A=1] = 7/13$ and $\Pr[Y=1|A=0] = 3/7$. The associational risk difference, risk ratio, and odds ratio (and other measures) quantify the strength of the association when it exists. They measure the association on different scales, and we refer to them as *association measures*. These measures are also affected by random variability. However, until Chapter 10, we will disregard statistical issues by assuming that the population in Table 1.2 is extremely large.

For dichotomous outcomes, the risk equals the average in the population, and we can therefore rewrite the definition of association in the population as $\mathrm{E}[Y|A=1] \neq \mathrm{E}[Y|A=0]$. For continuous outcomes Y, we can also define association as $\mathrm{E}[Y|A=1] \neq \mathrm{E}[Y|A=0]$. For binary A, Y and A are not associated if and only if they are not statistically correlated.

In our population of 20 individuals, we found (i) no causal effect after comparing the risk of death if all 20 individuals had been treated with the risk of death if all 20 individuals had been untreated, and (ii) an association after comparing the risk of death in the 13 individuals who happened to be treated with the risk of death in the 7 individuals who happened to be untreated. Figure 1.1 depicts the causation-association difference. The population (represented by a diamond) is divided into a white area (the treated) and a smaller grey area (the untreated).

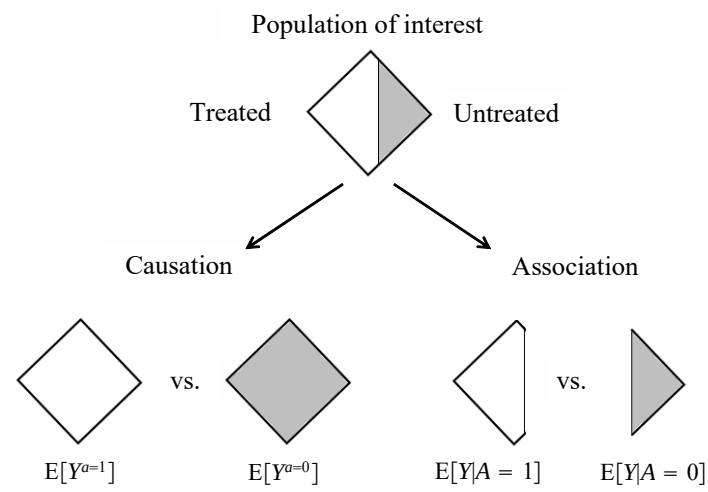


Figure 1.1

The definition of causation implies a contrast between the whole white diamond (all individuals treated) and the whole grey diamond (all individuals untreated), whereas association implies a contrast between the white (the treated) and the grey (the untreated) areas of the original diamond.

We can use the notation we have developed thus far to formalize the distinction between causation and association. The risk $\Pr[Y = 1|A = a]$ is a conditional probability: the risk of Y in the subset of the population that meet the condition 'having actually received treatment value a' (i.e., $A = a$). In contrast the risk $\Pr[Y^a = 1]$ is an unconditional—also known as marginal—probability, the risk of Y^a in the entire population. Therefore, *association* is defined by a different risk in two disjoint subsets of the population determined by the individuals' actual treatment value ($A = 1$ or $A = 0$), whereas *causation* is defined by a different risk in the same population under two different treatment values ($a = 1$ or $a = 0$). Throughout this book we often use the redundant expression 'causal effect' to avoid confusions with a common use of 'effect' meaning simply association.

The difference between association and causation is critical. Suppose the causal risk ratio of 5-year mortality is 0.5 for aspirin vs. no aspirin, and the corresponding associational risk ratio is 1.5 because individuals at high risk of cardiovascular death are preferentially prescribed aspirin. After a physician learns these results, she decides to withhold aspirin from her patients because those treated with aspirin have a greater risk of dying compared with the untreated. The doctor will be sued for malpractice.

These radically different definitions explain the well-known adage "association is not causation." In our population, there was association because the mortality risk in the treated (7/13) was greater than that in the untreated (3/7). However, there was no causation because the risk if everybody had been treated (10/20) was the same as the risk if everybody had been untreated. This discrepancy between causation and association would not be surprising if those who received heart transplants were, on average, sicker than those who did not receive a transplant. In Chapter 7 we refer to this discrepancy as *confounding*.

Causal inference requires data like the hypothetical data in Table 1.1, but all we can ever expect to have is real world data like those in Table 1.2. The question is then under which conditions real world data can be used for causal inference. The next chapter provides one answer: conduct a randomized experiment.

Chapter 2
RANDOMIZED EXPERIMENTS

Does your looking up at the sky make other pedestrians look up too? This question has the main components of any causal question: we want to know whether certain action (your looking up) affects certain outcome (other people's looking up) in certain population (say, residents of Madrid in 2017). Suppose we challenge you to design a scientific study to answer this question. "Not much of a challenge," you say after some thought, "I can stand on the sidewalk and flip a coin whenever someone approaches. If heads, I'll look up; if tails, I'll look straight ahead. I'll repeat the experiment a few thousand times. If the proportion of pedestrians who looked up within 10 seconds after I did is greater than the proportion of pedestrians who looked up when I didn't, I will conclude that my looking up has a causal effect on other people's looking up. By the way, I may hire an assistant to record what people do while I'm looking up." After conducting this study, you found that 55% of pedestrians looked up when you looked up but only 1% looked up when you looked straight ahead.

Your solution to our challenge was to conduct a randomized experiment. It was an experiment because the investigator (you) carried out the action of interest (looking up), and it was randomized because the decision to act on any study subject (pedestrian) was made by a random device (coin flipping). Not all experiments are randomized. For example, you could have looked up when a man approached and looked straight ahead when a woman did. Then the assignment of the action would have followed a deterministic rule (up for man, straight for woman) rather than a random mechanism. However, your findings would not have been nearly as convincing if you had conducted a non randomized experiment. If your action had been determined by the pedestrian's sex, critics could argue that the "looking up" behavior of men and women differs (women may look up less often than do men after you look up) and thus your study compared essentially "noncomparable" groups of people. This chapter describes why randomization results in convincing causal inferences.

2.1 Randomization

Neyman (1923) applied counterfactual theory to the estimation of causal effects via randomized experiments

In a real world study we will not know both of Zeus's potential outcomes $Y^{a=1}$ under treatment and $Y^{a=0}$ under no treatment. Rather, we can only know his observed outcome Y under the treatment value A that he happened to receive. Table 2.1 summarizes the available information for our population of 20 individuals. Only one of the two counterfactual outcomes is known for each individual: the one corresponding to the treatment level that he actually received. The data are missing for the other counterfactual outcomes. As we discussed in the previous chapter, this missing data creates a problem because it appears that we need the value of both counterfactual outcomes to compute effect measures. The data in Table 2.1 are only good to compute association measures.

Randomized experiments, like any other real world study, generate data with missing values of the counterfactual outcomes as shown in Table 2.1. However, randomization ensures that those missing values occurred by chance. As a result, effect measures can be computed —or, more rigorously, consistently estimated—in randomized experiments despite the missing data. Let us be more precise.

Suppose that the population represented by a diamond in Figure 1.1 was near-infinite, and that we flipped a coin for each individual in such population.

Table 2.1

	A	Y	Y^0	Y^1
Rheia	0	0	0	?
Kronos	0	1	1	?
Demeter	0	0	0	?
Hades	0	0	0	?
Hestia	1	0	?	0
Poseidon	1	0	?	0
Hera	1	0	?	0
Zeus	1	1	?	1
Artemis	0	1	1	?
Apollo	0	1	1	?
Leto	0	0	0	?
Ares	1	1	?	1
Athena	1	1	?	1
Hephaestus	1	1	?	1
Aphrodite	1	1	?	1
Cyclope	1	1	?	1
Persephone	1	1	?	1
Hermes	1	0	?	0
Hebe	1	0	?	0
Dionysus	1	0	?	0

We assigned the individual to the white group if the coin turned tails, and to the grey group if it turned heads. Note this was not a fair coin because the probability of heads was less than 50%—fewer people ended up in the grey group than in the white group. Next we asked our research assistants to administer the treatment of interest ($A = 1$), to individuals in the white group and a placebo ($A = 0$) to those in the grey group. Five days later, at the end of the study, we computed the mortality risks in each group, $\Pr[Y = 1|A = 1] = 0.3$ and $\Pr[Y = 1|A = 0] = 0.6$. The associational risk ratio was $0.3/0.6 = 0.5$ and the associational risk difference was $0.3 - 0.6 = -0.3$. We will assume that this was an *ideal randomized experiment* in all other respects: no loss to follow-up, full adherence to the assigned treatment over the duration of the study, a single version of treatment, and double blind assignment (see Chapter 9). Ideal randomized experiments are unrealistic but useful to introduce some key concepts for causal inference. Later in this book we consider more realistic randomized experiments.

Now imagine what would have happened if the research assistants had misinterpreted our instructions and had treated the grey group rather than the white group. Say we learned of the misunderstanding after the study finished. How does this reversal of treatment status affect our conclusions? Not at all. We would still find that the risk in the treated (now the grey group) $\Pr[Y = 1|A = 1]$ is 0.3 and the risk in the untreated (now the white group) $\Pr[Y = 1|A = 0]$ is 0.6. The association measure would not change. Because individuals were randomly assigned to white and grey groups, the proportion of deaths among the exposed, $\Pr[Y = 1|A = 1]$ is expected to be the same whether individuals in the white group received the treatment and individuals in the grey group received placebo, or vice versa. When group membership is randomized, which particular group received the treatment is irrelevant for the value of $\Pr[Y = 1|A = 1]$. The same reasoning applies to $\Pr[Y = 1|A = 0]$, of course. Formally, we say that groups are exchangeable.

Exchangeability means that the risk of death in the white group would have been the same as the risk of death in the grey group had individuals in the white group received the treatment given to those in the grey group. That is, the risk under the potential treatment value a among the treated, $\Pr[Y^a = 1|A = 1]$, equals the risk under the potential treatment value a among the untreated, $\Pr[Y^a = 1|A = 0]$, for both $a = 0$ and $a = 1$. An obvious consequence of these (conditional) risks being equal in all subsets defined by treatment status in the population is that they must be equal to the (marginal) risk under treatment value a in the whole population: $\Pr[Y^a = 1|A = 1] = \Pr[Y^a = 1|A = 0] = \Pr[Y^a = 1]$. Because the counterfactual risk under treatment value a is the same in both groups $A = 1$ and $A = 0$, we say that the actual treatment A does not predict the counterfactual outcome Y^a. Equivalently, exchangeability means that the counterfactual outcome and the actual treatment are independent, or $Y^a \perp\!\!\!\perp A$, for all values a. Randomization is so highly valued because it is expected to produce exchangeability. When the treated and the untreated are exchangeable, we sometimes say that treatment is exogenous, and thus *exogeneity* is commonly used as a synonym for exchangeability.

Exchangeability: $Y^a \perp\!\!\!\perp A$ for all a

The previous paragraph argues that, in the presence of exchangeability, the counterfactual risk under treatment in the white part of the population would equal the counterfactual risk under treatment in the entire population. But the risk under treatment in the white group is not counterfactual at all because the white group was actually treated! Therefore our ideal randomized experiment allows us to compute the counterfactual risk under treatment in the population $\Pr[Y^{a=1} = 1]$ because it is equal to the risk in the treated $\Pr[Y = 1|A = 1] =$

Technical Point 2.1

Full exchangeability and mean exchangeability. Randomization makes the Y^a jointly independent of A which implies, but is not implied by, exchangeability $Y^a \perp\!\!\!\perp A$ for each a. Formally, let $\mathcal{A} = \{a, a', a'', ...\}$ denote the set of all treatment values present in the population, and $Y^{\mathcal{A}} = \left\{Y^a, Y^{a'}, Y^{a''}, ...\right\}$ the set of all counterfactual outcomes. Randomization makes $Y^{\mathcal{A}} \perp\!\!\!\perp A$. We refer to this joint independence as *full exchangeability*. For a dichotomous treatment, $\mathcal{A} = \{0, 1\}$ and full exchangeability is $\left(Y^{a=1}, Y^{a=0}\right) \perp\!\!\!\perp A$.

For a dichotomous outcome and treatment, exchangeability $Y^a \perp\!\!\!\perp A$ can also be written as $\Pr[Y^a = 1|A = 1] = \Pr[Y^a = 1|A = 0]$ or, equivalently, as $\mathrm{E}[Y^a|A = 1] = \mathrm{E}[Y^a|A = 0]$ for all a. We refer to the last equality as *mean exchangeability*. For a continuous outcome, exchangeability $Y^a \perp\!\!\!\perp A$ implies mean exchangeability $\mathrm{E}[Y^a|A = a'] = \mathrm{E}[Y^a]$, but mean exchangeability does not imply exchangeability because distributional parameters other than the mean (e.g., variance) may not be independent of treatment.

Neither full exchangeability $Y^{\mathcal{A}} \perp\!\!\!\perp A$ nor exchangeability $Y^a \perp\!\!\!\perp A$ are required to prove that $\mathrm{E}[Y^a] = \mathrm{E}[Y|A = a]$. Mean exchangeability is sufficient. As sketched in the main text, the proof has two steps. First, $\mathrm{E}[Y|A = a] = \mathrm{E}[Y^a|A = a]$ by consistency. Second, $\mathrm{E}[Y^a|A = a] = \mathrm{E}[Y^a]$ by mean exchangeability. Because exchangeability and mean exchangeability are identical concepts for the dichotomous outcomes used in this chapter, we use the shorter term "exchangeability" throughout.

0.3. That is, the risk in the treated (the white part of the diamond) is the same as the risk if everybody had been treated (and thus the diamond had been entirely white). Of course, the same rationale applies to the untreated: the counterfactual risk under no treatment in the population $\Pr[Y^{a=0} = 1]$ equals the risk in the untreated $\Pr[Y = 1|A = 0] = 0.6$. The causal risk ratio is 0.5 and the causal risk difference is -0.3. In ideal randomized experiments, association *is* causation.

Here is another explanation for exchangeability $Y^a \perp\!\!\!\perp A$ in a randomized experiment. The counterfactual outcome Y^a, like one's genetic make-up, can be thought of as a fixed characteristic of a person existing before the treatment A was randomly assigned. This is because Y^a encodes what would have been one's outcome if assigned to treament a and thus does not depend on the treatment you later receive. Because treatment A was randomized, it is independent of both your genes and Y^a. The difference between Y^a and your genetic make-up is that, even conceptually, you can only learn the value of Y^a after treatment is given and then only if one's treatment A is equal to a.

Caution:
$Y^a \perp\!\!\!\perp A$ is different from $Y \perp\!\!\!\perp A$

Before proceeding, please make sure you understand the difference between $Y^a \perp\!\!\!\perp A$ and $Y \perp\!\!\!\perp A$. Exchangeability $Y^a \perp\!\!\!\perp A$ is defined as independence between the counterfactual outcome and the observed treatment. Again, this means that the treated and the untreated would have experienced the same risk of death if they had received the same treatment level (either $a = 0$ or $a = 1$). But independence between the counterfactual outcome and the observed treatment $Y^a \perp\!\!\!\perp A$ does not imply independence between the observed outcome and the observed treatment $Y \perp\!\!\!\perp A$. For example, in a randomized experiment in which exchangeability $Y^a \perp\!\!\!\perp A$ holds and the treatment has a causal effect on the outcome, then $Y \perp\!\!\!\perp A$ does not hold because the treatment is associated with the observed outcome.

Suppose there is a causal effect on some individuals so that $Y^{a=1} \neq Y^{a=0}$. Since $Y = Y^A$, then Y^a with a evaluated at the observed treatment A is the observed Y^A, which depends on A and thus will not be independent of A.

Does exchangeability hold in our heart transplant study of Table 2.1? To answer this question we would need to check whether $Y^a \perp\!\!\!\perp A$ holds for $a = 0$ and for $a = 1$. Take $a = 0$ first. Suppose the counterfactual data in Table 1.1 are available to us. We can then compute the risk of death under no treatment $\Pr[Y^{a=0} = 1|A = 1] = 7/13$ in the 13 treated individuals and the risk of death

Fine Point 2.1

Crossover randomized experiments. Individual (also known as subject-specific) causal effects can sometimes be identified via randomized experiments. For example, suppose we want to estimate the causal effect of lightning bolt use A on Zeus's blood pressure Y. We define the counterfactual outcomes $Y^{a=1}$ and $Y^{a=0}$ to be 1 if Zeus's blood pressure is temporarily elevated after calling or not calling a lightning strike, respectively. Suppose we convinced Zeus to use his lightning bolt only when suggested by us. Yesterday morning we flipped coin and obtained heads. We then asked Zeus to call a lightning strike ($a = 1$). His blood pressure was elevated after doing so. This morning we flipped a coin and obtained tails. We then asked Zeus to refrain from using his lightning bolt ($a = 0$). His blood pressure did not increase. We have conducted a *crossover randomized experiment* in which an individual's outcome is sequentially observed under two treatment values. One might argue that, because we have observed both of Zeus's counterfactual outcomes $Y^{a=1} = 1$ and $Y^{a=0} = 0$, using a lightning bolt has a causal effect on Zeus's blood pressure.

In crossover randomized experiments, an individual is observed during two or more periods. The individual receives a different treatment value in each period and the order of treatment values is randomly assigned. The main purported advantage of the crossover design is that, unlike in non-crossover designs, for each treated individual there is a perfectly exchangeable untreated subject—him or herself. A direct contrast of an individual's outcomes under different treatment values allows the identification of individual effects under the following conditions: 1) treatment is of short duration and its effects do not carry-over to the next period, and 2) the outcome is a condition of abrupt onset that completely resolves by the next period. Therefore crossover randomized experiments cannot be used to study the effect of heart transplant, an irreversible action, on death, an irreversible outcome.

Often treatment is randomized at many different periods. If the individual causal effect changes with time, we obtain the average of the individual time-specific causal effects.

under no treatment $\Pr[Y^{a=0} = 1|A = 0] = 3/7$ in the 7 untreated individuals. Since the risk of death under no treatment is greater in the treated than in the untreated individuals, i.e., $7/13 > 3/7$, we conclude that the treated have a worse prognosis than the untreated, that is, that the treated and the untreated are not exchangeable. Mathematically, we have proven that exchangeability $Y^a \perp\!\!\!\perp A$ does not hold for $a = 0$. (You can check that it does not hold for $a = 1$ either.) Thus the answer to the question that opened this paragraph is 'No'.

But only the observed data in Table 2.1, not the counterfactual data in Table 1.1, are available in the real world. Since Table 2.1 is insufficient to compute counterfactual risks like the risk under no treatment in the treated $\Pr[Y^{a=0} = 1|A = 1]$, we are generally unable to determine whether exchangeability holds in our study. However, suppose for a moment, that we actually had access to Table 1.1 and determined that exchangeability does not hold in our heart transplant study. Can we then conclude that our study is not a randomized experiment? No, for two reasons. First, as you are probably already thinking, a twenty-person study is too small to reach definite conclusions. Random fluctuations arising from sampling variability could explain almost anything. We will discuss random variability in Chapter 10. Until then, let us assume that each individual in our population represents 1 billion individuals that are identical to him or her. Second, it is still possible that a study is a randomized experiment even if exchangeability does not hold in infinite samples. However, unlike the type of randomized experiment described in this section, it would need to be a randomized experiment in which investigators use more than one coin to randomly assign treatment. The next section describes randomized experiments with more than one coin.

2.2 Conditional randomization

Table 2.2

	L	A	Y
Rheia	0	0	0
Kronos	0	0	1
Demeter	0	0	0
Hades	0	0	0
Hestia	0	1	0
Poseidon	0	1	0
Hera	0	1	0
Zeus	0	1	1
Artemis	1	0	1
Apollo	1	0	1
Leto	1	0	0
Ares	1	1	1
Athena	1	1	1
Hephaestus	1	1	1
Aphrodite	1	1	1
Cyclope	1	1	1
Persephone	1	1	1
Hermes	1	1	0
Hebe	1	1	0
Dionysus	1	1	0

Table 2.2 shows the data from our heart transplant randomized study. Besides data on treatment A (1 if the individual received a transplant, 0 otherwise) and outcome Y (1 if the individual died, 0 otherwise), Table 2.2 also contains data on the prognostic factor L (1 if the individual was in critical condition, 0 otherwise), which we measured before treatment was assigned. We now consider two mutually exclusive study designs and discuss whether the data in Table 2.2 could have arisen from either of them.

In design 1 we would have randomly selected 65% of the individuals in the population and transplanted a new heart to each of the selected individuals. That would explain why 13 out of 20 individuals were treated. In design 2 we would have classified all individuals as being in either critical ($L = 1$) or noncritical ($L = 0$) condition. Then we would have randomly selected 75% of the individuals in critical condition and 50% of those in noncritical condition, and transplanted a new heart to each of the selected individuals. That would explain why 9 out of 12 individuals in critical condition, and 4 out of 8 individuals in non critical condition, were treated.

Both designs are randomized experiments. Design 1 is precisely the type of randomized experiment described in Section 2.1. Under this design, we would use a single coin to assign treatment to all individuals (e.g., treated if tails, untreated if heads): a loaded coin with probability 0.65 of turning tails, thus resulting in 65% of the individuals receiving treatment. Under design 2 we would not use a single coin for all individuals. Rather, we would use a coin with a 0.75 chance of turning tails for individuals in critical condition, and another coin with a 0.50 chance of turning tails for individuals in non critical condition. We refer to design 2 experiments as *conditionally randomized experiments* because we use several randomization probabilities that depend (are conditional) on the values of the variable L. We refer to design 1 experiments as *marginally randomized experiments* because we use a single unconditional (marginal) randomization probability that is common to all individuals.

As discussed in the previous section, a marginally randomized experiment is expected to result in exchangeability of the treated and the untreated:

$$\Pr[Y^a = 1|A = 1] = \Pr[Y^a = 1|A = 0] \quad \text{or} \quad Y^a \perp\!\!\!\perp A \quad \text{for all } a.$$

In contrast, a conditionally randomized experiment will not generally result in exchangeability of the treated and the untreated because, by design, each group may have a different proportion of individuals with bad prognosis.

Thus the data in Table 2.2 could not have arisen from a marginally randomized experiment because 69% treated versus 43% untreated individuals were in critical condition. This imbalance indicates that the risk of death in the treated, had they remained untreated, would have been higher than the risk of death in the untreated. That is, treatment A predicts the counterfactual risk of death under no treatment, and exchangeability $Y^a \perp\!\!\!\perp A$ does not hold. Since our study was a randomized experiment, you can safely conclude that the study was a randomized experiment with randomization conditional on L.

Our conditionally randomized experiment is simply the combination of two separate marginally randomized experiments: one conducted in the subset of individuals in critical condition ($L = 1$), the other in the subset of individuals in non critical condition ($L = 0$). Consider first the randomized experiment being conducted in the subset of individuals in critical condition. In this subset, the treated and the untreated are exchangeable. Formally, the counterfactual mortality risk under each treatment value a is the same among the treated

and the untreated given that they all were in critical condition at the time of treatment assignment. That is,

$$\Pr[Y^a = 1|A = 1, L = 1] = \Pr[Y^a = 1|A = 0, L = 1] \text{ or } Y^a \perp\!\!\!\perp A|L = 1 \text{ for all } a,$$

where $Y^a \perp\!\!\!\perp A|L = 1$ means Y^a and A are independent given $L = 1$. Similarly, randomization also ensures that the treated and the untreated are exchangeable in the subset of individuals that were in noncritical condition, that is, $Y^a \perp\!\!\!\perp A|L = 0$. When $Y^a \perp\!\!\!\perp A|L = l$ holds for all values l we simply write $Y^a \perp\!\!\!\perp A|L$. Thus, although conditional randomization does not guarantee unconditional (or marginal) exchangeability $Y^a \perp\!\!\!\perp A$, it guarantees *conditional exchangeability* $Y^a \perp\!\!\!\perp A|L$ within levels of the variable L. In summary, randomization produces either marginal exchangeability (design 1) or conditional exchangeability (design 2).

Conditional exchangeability: $Y^a \perp\!\!\!\perp A|L$ for all a

We know how to compute effect measures under marginal exchangeability. In marginally randomized experiments the causal risk ratio $\Pr[Y^{a=1} = 1]/\Pr[Y^{a=0} = 1]$ equals the associational risk ratio $\Pr[Y = 1|A = 1]/\Pr[Y = 1|A = 0]$ because exchangeability ensures that the counterfactual risk under treatment level a, $\Pr[Y^a = 1]$, equals the observed risk among those who received treatment level a, $\Pr[Y = 1|A = a]$. Thus, if the data in Table 2.2 had been collected during a marginally randomized experiment, the causal risk ratio would be readily calculated from the data on A and Y as $\dfrac{7/13}{3/7} = 1.26$. The question is how to compute the causal risk ratio in a conditionally randomized experiment. Remember that a conditionally randomized experiment is simply the combination of two (or more) separate marginally randomized experiments conducted in different subsets of the population, e.g., $L = 1$ and $L = 0$. Thus we have two options.

In a marginally randomized experiment, the values of the counterfactual outcomes are missing completely at random (MCAR). In a conditionally randomized experiment, the values of the counterfactual outcomes are not MCAR, but they are missing at random (MAR) conditional on the covariate L. The terms MCAR, MAR, and NMAR (not missing at random) were introduced by Rubin (1976).

First, we can compute the average causal effect in each of these subsets of strata of the population. Because association is causation within each subset, the stratum-specific causal risk ratio $\Pr[Y^{a=1} = 1|L = 1]/\Pr[Y^{a=0} = 1|L = 1]$ among people in critical condition is equal to the stratum-specific associational risk ratio $\Pr[Y = 1|L = 1, A = 1]/\Pr[Y = 1|L = 1, A = 0]$ among people in critical condition. And analogously for $L = 0$. We refer to this method to compute stratum-specific causal effects as *stratification*. Note that the stratum-specific causal risk ratio in the subset $L = 1$ may differ from the causal risk ratio in $L = 0$. In that case, we say that the effect of treatment is modified by L, or that there is *effect modification* by L.

Stratification and effect modification are discussed in more detail in Chapter 4.

Second, we can compute the average causal effect $\Pr[Y^{a=1} = 1]/\Pr[Y^{a=0} = 1]$ in the entire population, as we have been doing so far. Whether our principal interest lies in the stratum-specific average causal effects versus the average causal effect in the entire population depends on practical and theoretical considerations discussed in detail in Chapter 4 and in Part III. As one example, you may be interested in the average causal effect in the entire population, rather than in the stratum-specific average causal effects, if you do not expect to have information on L for future individuals (e.g., the variable L is expensive to measure) and thus your decision to treat cannot depend on the value of L. Until Chapter 4, we will restrict our attention to the average causal effect in the entire population. The next two sections describe how to use data from conditionally randomized trials to compute the average causal effect in the entire population.

2.3 Standardization

Our heart transplant study is a conditionally randomized experiment: the investigators used a random procedure to assign hearts ($A = 1$) with probability 50% to the 8 individuals in noncritical condition ($L = 0$), and with probability 75% to the 12 individuals in critical condition ($L = 1$). First, let us focus on the 8 individuals—remember, they are really the average representatives of 8 billion individuals—in noncritical condition. In this group, the risk of death among the treated is $\Pr[Y = 1|L = 0, A = 1] = \frac{1}{4}$, and the risk of death among the untreated is $\Pr[Y = 1|L = 0, A = 0] = \frac{1}{4}$. Because treatment was randomly assigned to individuals in the group $L = 0$, i.e., $Y^a \perp\!\!\!\perp A|L = 0$, the observed risks are equal to the counterfactual risks. That is, in the group $L = 0$, the risk in the treated equals the risk if everybody had been treated, $\Pr[Y = 1|L = 0, A = 1] = \Pr[Y^{a=1} = 1|L = 0]$, and the risk in the untreated equals the risk if everybody had been untreated, $\Pr[Y = 1|L = 0, A = 0] = \Pr[Y^{a=0} = 1|L = 0]$. Following an analogous reasoning, we can conclude that the observed risks equal the counterfactual risks in the group of 12 individuals in critical condition, i.e., $\Pr[Y = 1|L = 1, A = 1] = \Pr[Y^{a=1} = 1|L = 1] = \frac{2}{3}$, and $\Pr[Y = 1|L = 1, A = 0] = \Pr[Y^{a=0} = 1|L = 1] = \frac{2}{3}$.

Suppose now our goal is to compute the causal risk ratio $\Pr[Y^{a=1} = 1]/\Pr[Y^{a=0} = 1]$. The numerator of the causal risk ratio is the risk if all 20 individuals in the population had been treated. From the previous paragraph, we know that the risk if all individuals had been treated is $\frac{1}{4}$ in the 8 individuals with $L = 0$ and $\frac{2}{3}$ in the 12 individuals with $L = 1$. Therefore the risk if all 20 individuals in the population had been treated will be a weighted average of $\frac{1}{4}$ and $\frac{2}{3}$ in which each group receives a weight proportional to its size. Since 40% of the individuals (8) are in group $L = 0$ and 60% of the individuals (12) are in group $L = 1$, the weighted average is $\frac{1}{4} \times 0.4 + \frac{2}{3} \times 0.6 = 0.5$. Thus the risk if everybody had been treated $\Pr[Y^{a=1} = 1]$ is equal to 0.5. By following the same reasoning we can calculate that the risk if nobody had been treated $\Pr[Y^{a=0} = 1]$ is also equal to 0.5. The causal risk ratio is then $0.5/0.5 = 1$.

More formally, the marginal counterfactual risk $\Pr[Y^a = 1]$ is the weighted average of the stratum-specific risks $\Pr[Y^a = 1|L = 0]$ and $\Pr[Y^a = 1|L = 1]$ with weights equal to the proportion of individuals in the population with $L = 0$ and $L = 1$, respectively. That is, $\Pr[Y^a = 1] = \Pr[Y^a = 1|L = 0] \Pr[L = 0] + \Pr[Y^a = 1|L = 1] \Pr[L = 1]$. Or, using a more compact notation, $\Pr[Y^a = 1] = \sum_l \Pr[Y^a = 1|L = l] \Pr[L = l]$, where $\sum_l$ means sum over all values l that occur in the population. By conditional exchangeability, we can replace the counterfactual risk $\Pr[Y^a = 1|L = l]$ by the observed risk $\Pr[Y = 1|L = l, A = a]$ in the expression above. That is, $\Pr[Y^a = 1] = \sum_l \Pr[Y = 1|L = l, A = a] \Pr[L = l]$. The left-hand side of this equality is an unobserved counterfactual risk whereas the right-hand side includes observed quantities only, which can be computed using data on L, A, and Y. When, as here, a counterfactual quantity can be expressed as function of the distribution (i.e., probabilities) of the observed data, we say that the counterfactual quantity is identified or identifiable; otherwise, we say it is unidentified or not identifiable.

Standardized mean
$\sum_l \mathrm{E}[Y|L = l, A = a]$
$\times \Pr[L = l]$

The method described above is known in epidemiology, demography, and other disciplines as *standardization*. For example, the numerator $\sum_l \Pr[Y = 1|L = l, A = 1] \Pr[L = l]$ of the causal risk ratio is the standardized risk in the treated using the population as the standard. In the presence of conditional exchangeability, this standardized risk can be interpreted as the (counterfactual) risk that would have been observed had all the individuals in the population

been treated.

The standardized risks in the treated and the untreated are equal to the counterfactual risks under treatment and no treatment, respectively. Therefore, the causal risk ratio $\frac{\Pr[Y^{a=1}=1]}{\Pr[Y^{a=0}=1]}$ can be computed by standardization as $\frac{\sum_l \Pr[Y=1|L=l,A=1]\Pr[L=l]}{\sum_l \Pr[Y=1|L=l,A=0]\Pr[L=l]}$.

2.4 Inverse probability weighting

In the previous section we computed the causal risk ratio in a conditionally randomized experiment via standardization. In this section we compute this causal risk ratio via inverse probability weighting. The data in Table 2.2 can be displayed as a tree in which all 20 individuals start at the left and progress over time towards the right, as in Figure 2.1. The leftmost circle of the tree contains its first branching: 8 individuals were in non critical condition ($L=0$) and 12 in critical condition ($L=1$). The numbers in parentheses are the probabilities of being in noncritical, $\Pr[L=0]=8/20=0.4$, or critical, $\Pr[L=1]=12/20=0.6$, condition. Let us follow, for example, the branch $L=0$. Of the 8 individuals in this branch, 4 were untreated ($A=0$) and 4 were treated ($A=1$). The conditional probability of being untreated is $\Pr[A=0|L=0]=4/8=0.5$, as shown in parentheses. The conditional probability of being treated $\Pr[A=1|L=0]$ is 0.5 too. The upper right circle represents that, of the 4 individuals in the branch ($L=0, A=0$), 3 survived ($Y=0$) and 1 died ($Y=1$). That is, $\Pr[Y=0|L=0,A=0]=3/4$ and $\Pr[Y=1|L=0,A=0]=1/4$. The other branches of the tree are interpreted analogously. The circles contain the bifurcations defined by non treatment variables. We now use this tree to compute the causal risk ratio.

Figure 2.1 is an example of a finest fully randomized causally interpreted structured tree graph or FFRCISTG (Robins 1986, 1987). Did we win the prize for the worst acronym ever?

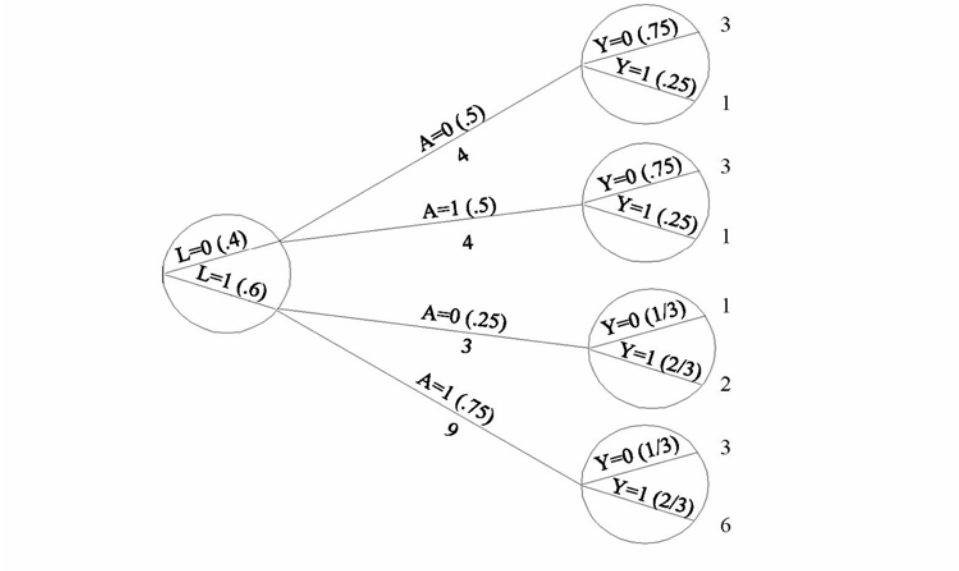


Figure 2.1

Fine Point 2.2

Risk periods. We have defined a risk as the proportion of individuals who develop the outcome of interest during a particular period. For example, the 5-day mortality risk in the treated $\Pr[Y = 1|A = 0]$ is the proportion of treated individuals who died during the first five days of follow-up. Throughout the book we often specify the period when the risk is first defined (e.g., 5 days) and, for conciseness, omit it later. That is, we may just say "the mortality risk" rather than "the five-day mortality risk."

The following example highlights the importance of specifying the risk period. Suppose a randomized experiment was conducted to quantify the causal effect of antibiotic therapy on mortality among elderly humans infected with the plague bacteria. An investigator analyzes the data and concludes that the causal risk ratio is 0.05, i.e., on average antibiotics decrease mortality by 95%. A second investigator also analyzes the data but concludes that the causal risk ratio is 1, i.e., antibiotics have a null average causal effect on mortality. Both investigators are correct. The first investigator computed the ratio of 1-year risks, whereas the second investigator computed the ratio of 100-year risks. The 100-year risk was of course 1 regardless of whether individuals received the treatment. When we say that a treatment has a causal effect on mortality, we mean that death is delayed, not prevented, by the treatment.

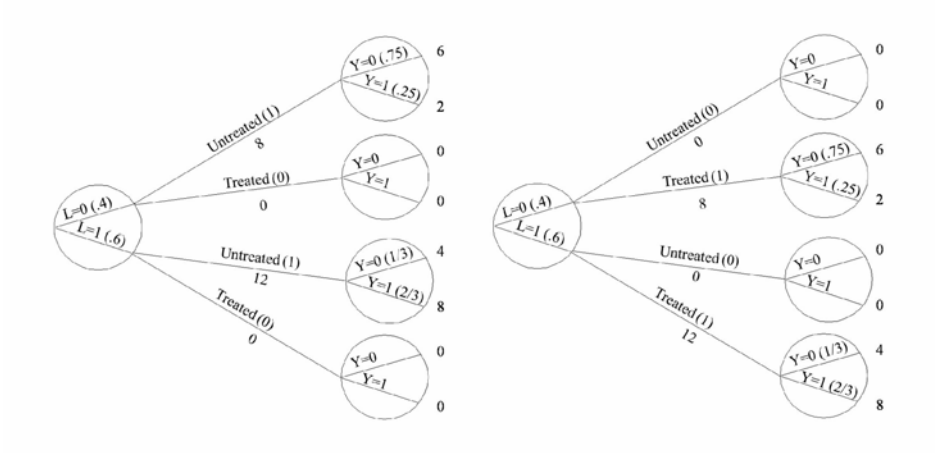


Figure 2.2

The denominator of the causal risk ratio, $\Pr[Y^{a=0} = 1]$, is the counterfactual risk of death had everybody in the population remained untreated. Let us calculate this risk. In Figure 2.1, 4 out of 8 individuals with $L = 0$ were untreated, and 1 of them died. How many deaths would have occurred had the 8 individuals with $L = 0$ remained untreated? Two deaths, because if 8 individuals rather than 4 individuals had remained untreated, then 2 deaths rather than 1 death would have been observed. If the number of individuals is multiplied times 2, then the number of deaths is also doubled. In Figure 2.1, 3 out of 12 individuals with $L = 1$ were untreated, and 2 of them died. How many deaths would have occurred had the 12 individuals with $L = 1$ remained untreated? Eight deaths, or 2 deaths times 4, because 12 is 3×4. That is, if all $8 + 12 = 20$ individuals in the population had been untreated, then $2 + 8 = 10$ would have died. The denominator of the causal risk ratio, $\Pr[Y^{a=0} = 1]$, is $10/20 = 0.5$. The first tree in Figure 2.2 shows the population had everybody remained untreated. Of course, these calculations rely on the condition that treated individuals with $L = 0$, had they remained untreated, would have had the same probability of death as those who actually remained untreated. This condition is precisely exchangeability given $L = 0$.

The numerator of the causal risk ratio $\Pr[Y^{a=1} = 1]$ is the counterfactual risk of death had everybody in the population been treated. Reasoning as in the previous paragraph, this risk is calculated to be also $10/20 = 0.5$, under exchangeability given $L = 1$. The second tree in Figure 2.2 shows the population had everybody been treated. Combining the results from this and the previous paragraph, the causal risk ratio $\Pr[Y^{a=1} = 1]/\Pr[Y^{a=0} = 1]$ is equal to $0.5/0.5 = 1$. We are done.

Let us examine how this method works. The two trees in Figure 2.2 are a simulation of what would have happened had all individuals in the population been untreated and treated, respectively. These simulations are correct under conditional exchangeability. Both simulations can be pooled to create a hypothetical population in which every individual appears as a treated and as an untreated individual. This hypothetical population, twice as large as the original population, is known as the *pseudo-population*. Figure 2.3 shows the entire pseudo-population. Under conditional exchangeability $Y^a \perp\!\!\!\perp A|L$ in the original population, the treated and the untreated are (unconditionally) exchangeable in the pseudo-population because the L is independent of A. That is, the associational risk ratio in the pseudo-population is equal to the causal risk ratio in both the pseudo-population and the original population.

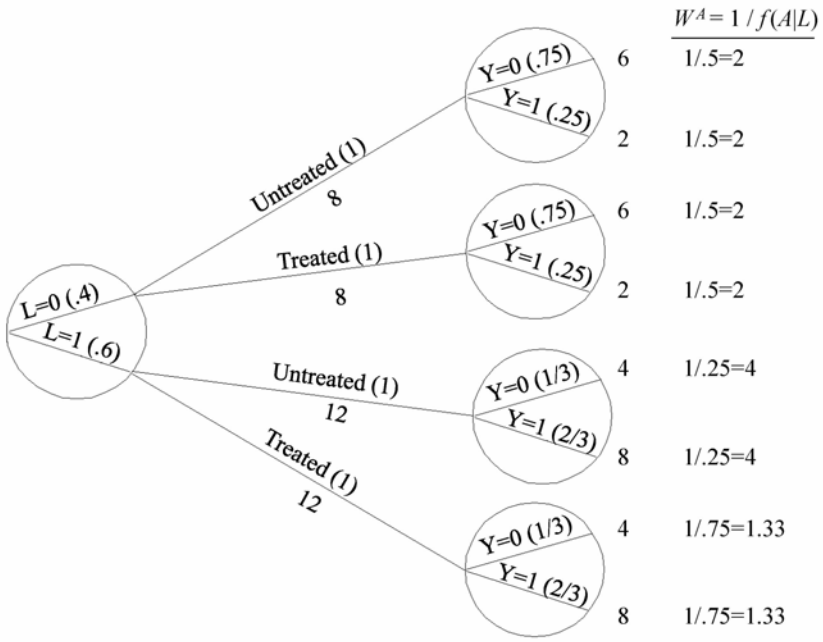


Figure 2.3

IP weighted estimators were proposed by Horvitz and Thompson (1952) for surveys in which subjects are sampled with unequal probabilities

This method is known as *inverse probability (IP) weighting*. To see why, let us look at, say, the 4 untreated individuals with $L = 0$ in the population of Figure 2.1. These individuals are used to create 8 members of the pseudo-population of Figure 2.3. That is, each of them receives a weight of 2, which is equal to $1/0.5$. Figure 2.1 shows that 0.5 is the conditional probability of staying untreated given $L = 0$. Similarly, the 9 treated individuals with $L = 1$ in Figure 2.1 are used to create 12 members of the pseudo-population. That is, each of them receives a weight of $1.33 = 1/0.75$. Figure 2.1 shows that 0.75 is the conditional probability of being treated given $L = 1$. Informally, the pseudo-population is created by weighting each individual in the population

Technical Point 2.2

Formal definition of IP weights. An individual's IP weight depends on her values of treatment A and covariate L. For example, a treated individual with $L = l$ receives the weight $1/\Pr[A = 1|L = l]$, whereas an untreated individual with $L = l'$ receives the weight $1/\Pr[A = 0|L = l']$. We can express these weights using a single expression for all individuals—regardless of their individual treatment and covariate values—by using the probability density function (PDF) of A rather than the probability of A. The conditional PDF of A given L evaluated at the values a and l is represented by $f_{A|L}[a|l]$, or simply as $f[a|l]$. For discrete variables A and L, $f[a|l]$ is the conditional probability $\Pr[A = a|L = l]$. In a conditionally randomized experiment, $f[a|l]$ is positive for all l such that $\Pr[L = l]$ is nonzero.

Since the denominator of the weight for each individual is the conditional density evaluated at the individual's own values of A and L, it can be expressed as the conditional density evaluated at the random arguments A and L (as opposed to the fixed arguments a and l), that is, as $f[A|L]$. This notation, which appeared in Figure 2.3, is used to define the IP weights $W^A = 1/f[A|L]$. It is needed to have a unified notation for the weights because $\Pr[A = A|L = L]$ is not considered proper notation.

IP weight: $W^A = 1/f[A|L]$

by the inverse of the conditional probability of receiving the treatment level that she indeed received. These IP weights are shown in Figure 2.3.

IP weighting yielded the same result as standardization—causal risk ratio equal to 1— in our example above. This is no coincidence: standardization and IP weighting are mathematically equivalent (see Technical Point 2.3). In fact, both standardization and IP weighting can be viewed as procedures to build a new tree in which all individuals receive treatment a. Each method uses a different set of the probabilities to build the counterfactual tree: IP weighting uses the conditional probability of treatment A given the covariate L (as shown in Figure 2.1), standardization uses the probability of the covariate L and the conditional probability of outcome Y given A and L.

Because both standardization and IP weighting simulate what would have been observed if the variable (or variables in the vector) L had not been used to decide the probability of treatment, we often say that these methods *adjust for* L. In a slight abuse of language we sometimes say that these methods *control for* L, but this "analytic control" is quite different from the "physical control" in a randomized experiment. Standardization and IP weighting can be generalized to conditionally randomized studies with continuous outcomes (see Technical Point 2.3).

Why not finish this book here? We have a study design (an ideal randomized experiment) that, when combined with the appropriate analytic method (standardization or IP weighting), allows us to compute average causal effects. Unfortunately, randomized experiments are often unethical, impractical, or untimely. For example, it is questionable that an ethical committee would have approved our heart transplant study. Hearts are in short supply and society favors assigning them to individuals who are more likely to benefit from the transplant, rather than assigning them randomly among potential recipients. Also one could question the feasibility of the study even if ethical issues were ignored: double-blind assignment is impossible, individuals assigned to medical treatment may not resign themselves to forego a transplant, and there may not be compatible hearts for those assigned to transplant. Even if the study were feasible, it would still take several years to complete it, and decisions must be made in the interim. Frequently, conducting an observational study is the least bad option.

Technical Point 2.3

Equivalence of IP weighting and standardization. Assume that $f[a|l]$ is positive for all l such that $\Pr[L=l]$ is nonzero. This positivity condition is guaranteed to hold in conditionally randomized experiments. Under positivity, the standardized mean for treatment level a is defined as $\sum_l \mathrm{E}[Y|A=a,L=l]\ \Pr[L=l]$ and the IP weighted mean of Y for treatment level a is defined as $\mathrm{E}\left[\frac{I(A=a)Y}{f[A|L]}\right]$ i.e., the mean of Y, reweighted by the IP weight $W^A = 1/f[A|L]$, in individuals with treatment value $A=a$. The indicator function $I(A=a)$ is the function that takes value 1 for individuals with $A=a$, and 0 for the others.

We now prove the equality of the IP weighted mean and the standardized mean under positivity. By definition of an expectation, $\mathrm{E}\left[\frac{I(A=a)Y}{f[A|L]}\right] = \sum_l \frac{1}{f[a|l]}\ \{\mathrm{E}[Y|A=a,L=l]\ f[a|l]\Pr[L=l]\}$

$= \sum_l \{\mathrm{E}[Y|A=a,L=l]\ \Pr[L=l]\}$ where in the final step we cancelled $f[a|l]$ from the numerator and denominator, and in the first step we did not need to sum over the possible values of A because because for any $a\prime$ other than a the quantity $I(a\prime=a)$ is zero. The proof treats A and L as discrete but not necessarily dichotomous. For continuous L simply replace the sum over L with an integral.

The proof makes no reference to counterfactuals or to causality. However if we further assume conditional exchangeability then both the IP weighted and the standardized means are equal to the counterfactual mean $\mathrm{E}[Y^a]$. Here we provide two different proofs of this last statement. First, we prove equality of $\mathrm{E}[Y^a]$ and the standardized mean as in the text

$\mathrm{E}[Y^a] = \sum_l \mathrm{E}[Y^a|L=l]\Pr[L=l] = \sum_l \mathrm{E}[Y^a|A=a,L=l]\Pr[L=l] = \sum_l \mathrm{E}[Y|A=a,L=l]\Pr[L=l]$

where the second equality is by conditional exchangeability and positivity, and the third by consistency. Second, we prove equality of $\mathrm{E}[Y^a]$ and the IP weighted mean as follows:

$\mathrm{E}\left[\frac{I(A=a)}{f[A|L]}Y\right]$ is equal to $\mathrm{E}\left[\frac{I(A=a)}{f[A|L]}Y^a\right]$ by consistency. Next, because positivity implies $f[a|L]$ is never 0, we have

$\mathrm{E}\left[\frac{I(A=a)}{f[A|L]}Y^a\right] = \mathrm{E}\left\{\mathrm{E}\left[\frac{I(A=a)}{f[a|L]}Y^a \middle| L\right]\right\} = \mathrm{E}\left\{\mathrm{E}\left[\frac{I(A=a)}{f[a|L]} \middle| L\right]\mathrm{E}[Y^a|L]\right\}$ (by conditional exchangeability).

$= \mathrm{E}\{\mathrm{E}[Y^a|L]\}$ (because $\mathrm{E}\left[\frac{I(A=a)}{f[a|L]} \middle| L\right] = 1$)

$= \mathrm{E}[Y^a]$

The extension to polytomous treatments (i.e., a can take more than two values) is straightforward. When treatment is continuous, which is unlikely in conditionally randomized experiments, effect estimates based on the IP weights $W^A = 1/f[A|L]$ have infinite variance and thus cannot be used. Chapter 12 describes generalized weights. In Technical Point 3.1, we discuss that the results above do not longer hold in the absence of positivity.

Chapter 3
OBSERVATIONAL STUDIES

Consider again the causal question "does one's looking up at the sky make other pedestrians look up too?" After considering a randomized experiment as in the previous chapter, you concluded that looking up so many times was too time-consuming and unhealthy for your neck bones. Hence you decided to conduct the following study: Find a nearby pedestrian who is standing in a corner and not looking up. Then find a second pedestrian who is walking towards the first one and not looking up either. Observe and record their behavior during the next 10 seconds. Repeat this process a few thousand times. You could now compare the proportion of second pedestrians who looked up after the first pedestrian did, and compare it with the proportion of second pedestrians who looked up before the first pedestrian did. Such a scientific study in which the investigator observes and records the relevant data is referred to as an observational study.

If you had conducted the observational study described above, critics could argue that two pedestrians may both look up not because the first pedestrian's looking up causes the other's looking up, but because they both heard a thunderous noise above or some rain drops started to fall, and thus your study findings are inconclusive as to whether one's looking up makes others look up. These criticisms do not apply to randomized experiments, which is one of the reasons why randomized experiments are central to the theory of causal inference. However, in practice, the importance of randomized experiments for the estimation of causal effects is more limited. Many scientific studies are not experiments. Much human knowledge is derived from observational studies. Think of evolution, tectonic plates, global warming, or astrophysics. Think of how humans learned that hot coffee may cause burns. This chapter reviews some conditions under which observational studies lead to valid causal inferences.

3.1 Identifiability conditions

For simplicity, this chapter considers only randomized experiments in which all participants remain under follow-up and adhere to their assigned treatment throughout the entire study. Chapters 8 and 9 discuss alternative scenarios.

Ideal randomized experiments can be used to identify and quantify average causal effects because the randomized assignment of treatment leads to exchangeability. Take a marginally randomized experiment of heart transplant and mortality as an example: if those who received a transplant had not received it, they would have been expected to have the same death risk as those who did not actually receive the heart transplant. As a consequence, an associational risk ratio of 0.7 from the randomized experiment is expected to equal the causal risk ratio.

Observational studies, on the other hand, may be much less convincing (for an example, see the introduction to this chapter). A key reason for our hesitation to endow observational associations with a causal interpretation is the lack of randomized treatment assignment. As an example, take an observational study of heart transplant and mortality in which those who received the heart transplant were more likely to have a severe heart condition. Then, if those who received a transplant had not received it, they would have been expected to have a greater death risk than those who did not actually receive the heart transplant. As a consequence, an associational risk ratio of 1.1 from the observational study would be a compromise between the truly beneficial effect of transplant on mortality (which pushes the associational risk ratio to be under 1) and the underlying greater mortality risk in those who received transplant (which pushes the associational risk ratio to be over 1). The best explanation

for an association between treatment and outcome in an observational study is not necessarily a causal effect of the treatment on the outcome.

While recognizing that randomized experiments have intrinsic advantages for causal inference, sometimes we are stuck with observational studies to answer causal questions. What do we do? We analyze our data as if treatment had been randomly assigned conditional on the measured covariates—though we know this is at best an approximation. Causal inference from observational data then revolves around the hope that the observational study can be viewed as a conditionally randomized experiment.

An observational study can be conceptualized as a conditionally randomized experiment under the following three conditions:

1. the values of treatment under comparison correspond to well-defined interventions that, in turn, correspond to the versions of treatment in the data

2. the conditional probability of receiving every value of treatment, though not decided by the investigators, depends only on the measured covariates

3. the conditional probability of receiving every value of treatment is greater than zero, i.e., positive

In this chapter we describe these three conditions in the context of observational studies. Condition 1 was referred to as consistency in Chapter 1, condition 2 was referred to as exchangeability in the previous chapters, and condition 3 was referred to as positivity in Technical Point 2.3.

We will see that these conditions are often heroic, which explains why causal inferences from observational studies are viewed with suspicion. However, if the analogy between observational study and conditionally randomized experiment happens to be correct in our data, then we can use the methods described in the previous chapter—IP weighting or standardization—to compute causal effects from observational studies. For example, in the previous chapter, we computed a causal risk ratio equal to 1 using the data in Table 2.2, which arose from a conditionally randomized experiment. If the same data, now shown in Table 3.1, had arisen from an observational study and the three conditions above held true, we would also compute a causal risk ratio equal to 1.

Table 3.1

	L	A	Y
Rheia	0	0	0
Kronos	0	0	1
Demeter	0	0	0
Hades	0	0	0
Hestia	0	1	0
Poseidon	0	1	0
Hera	0	1	0
Zeus	0	1	1
Artemis	1	0	1
Apollo	1	0	1
Leto	1	0	0
Ares	1	1	1
Athena	1	1	1
Hephaestus	1	1	1
Aphrodite	1	1	1
Cyclope	1	1	1
Persephone	1	1	1
Hermes	1	1	0
Hebe	1	1	0
Dionysus	1	1	0

Importantly, in ideal randomized experiments the data contain sufficient information to identify causal effects. That is, for a conditionally randomized trial, we would only need the data in Table 3.1 to compute the causal risk ratio of 1. In contrast, the information contained in observational data is insufficient to identify causal effects. To identify the causal risk ratio from an observational study, we would need to supplement the data in Table 3.1 with the conditions of consistency, exchangeability, and positivity. We therefore refer to these conditions as *identifiability* conditions. Causal inference from observational data requires two elements: data and identifiability conditions. See Fine Point 3.1 for a more precise definition of identifiability.

When any of the identifiability conditions does not hold, the analogy between observational study and conditionally randomized experiment breaks down. In that situation, there are other possible approaches to causal inference from observational data, which require a different set of identifiability conditions. One of these approaches is hoping that a predictor of treatment, referred to as an *instrumental variable*, behaves as if it had been randomly assigned conditional on the measured covariates. We discuss instrumental variable methods in Chapter 16.

Rubin (1974, 1978) extended Neyman's theory for randomized experiments to observational studies. Rosenbaum and Rubin (1983) referred to the combination of exchangeability and positivity as *weak ignorability,* and to the combination of full exchangeability (see Technical Point 2.1) and positivity as *strong ignorability*.

Fine Point 3.1

Identifiability of causal effects. We say that an average causal effect is (non parametrically) identifiable when the distribution of the observed data is compatible with a single value of the effect measure. Conversely, we say that an average causal effect is nonidentifiable when the distribution of the observed data is compatible with several values of the effect measure. For example, if the study in Table 3.1 had arisen from a conditionally randomized experiment in which the probability of receiving treatment depended on the value of L (and hence conditional exchangeability $Y^a \perp\!\!\!\perp A|L$ holds by design) then we showed in the previous chapter that the causal effect is identifiable: the causal risk ratio equals 1, without requiring any further assumptions. However, if the data in Table 3.1 had arisen from an observational study, then the causal risk ratio equals 1 only if we supplement the data with the assumption of conditional exchangeability $Y^a \perp\!\!\!\perp A|L$. To identify the causal effect in observational studies, we need an assumption external to the data, an identifying assumption. In fact, if we decide not to supplement the data with the identifying assumption, then the data in Table 3.1 are consistent with a causal risk ratio

- lower than 1, if risk factors other than L are more frequent among the treated.
- greater than 1, if risk factors other than L are more frequent among the untreated.
- equal to 1, if all risk factors except L are equally distributed between the treated and the untreated or, equivalently, if $Y^a \perp\!\!\!\perp A|L$.

This chapter discusses the assumptions required for nonparametric identification of average causal effects, that is, for identification that does not require any modeling assumptions when the size of the study population is quasi-infinite. Part II will discuss the use of models to estimate average causal effects.

Not surprisingly, observational methods based on the analogy with a conditionally randomized experiment have been traditionally privileged in disciplines in which this analogy is often reasonable (e.g., epidemiology), whereas instrumental variable methods have been traditionally privileged in disciplines in which observational studies cannot often be conceptualized as conditionally randomized experiments given the measured covariates (e.g., economics). Until Chapter 16, we will focus on causal inference approaches that rely on the ability of the observational study to emulate a conditionally randomized experiment. We now describe in more detail each of the three identifiability conditions.

3.2 Exchangeability

We have already said much about exchangeability $Y^a \perp\!\!\!\perp A$. In marginally (i.e., unconditionally) randomized experiments, the treated and the untreated are exchangeable because the treated, had they remained untreated, would have experienced the same average outcome as the untreated did, and vice versa. This is so because randomization ensures that the independent predictors of the outcome are equally distributed between the treated and the untreated groups.

An independent predictor of the outcome is a covariate associated with the outcome Y within levels of treatment. For dichotomous outcomes, independent predictors of the outcome are often referred to as *risk factors* for the outcome.

For example, take the study summarized in Table 3.1. We said in the previous chapter that exchangeability clearly does not hold in this study because 69% treated versus 43% untreated individuals were in critical condition $L = 1$ at baseline. This imbalance in the distribution of an independent outcome

predictor is not expected to occur in a marginally randomized experiment (actually, such imbalance might occur by chance but let us keep working under the illusion that our study is large enough to prevent chance findings).

On the other hand, an imbalance in the distribution of independent outcome predictors L between the treated and the untreated is expected by design in conditionally randomized experiments in which the probability of receiving treatment depends on L. The study in Table 3.1 is such a conditionally randomized experiment: the treated and the untreated are not exchangeable—because the treated had, on average, a worse prognosis at the start of the study—but the treated and the untreated are conditionally exchangeable within levels of the variable L. In the subset $L = 1$ (critical condition), the treated and the untreated are exchangeable because the treated, had they remained untreated, would have experienced the same average outcome as the untreated did, and vice versa. And similarly for the subset $L = 0$. An equivalent statement: conditional exchangeability $Y^a \perp\!\!\!\perp A|L$ holds in conditionally randomized experiments because, within levels of L, all other predictors of the outcome are equally distributed between the treated and the untreated groups.

Back to observational studies. When treatment is not randomly assigned by the investigators, the reasons for receiving treatment are likely to be associated with some outcome predictors. That is, like in a conditionally randomized experiment, the distribution of outcome predictors will generally vary between the treated and untreated groups in an observational study. For example, the data in Table 3.1 could have arisen from an observational study in which doctors tend to direct the scarce heart transplants to those who need them most, i.e., individuals in critical condition $L = 1$. In fact, if the only outcome predictor that is unequally distributed between the treated and the untreated is L, then one can refer to the study in Table 3.1 as either (i) an observational study in which the probability of treatment $A = 1$ is 0.75 among those with $L = 1$ and 0.50 among those with $L = 0$, or (ii) a (non blinded) conditionally randomized experiment in which investigators randomly assigned treatment $A = 1$ with probability 0.75 to those with $L = 1$ and 0.50 to those with $L = 0$. Both characterizations of the study are logically equivalent. Under either characterization, conditional exchangeability $Y^a \perp\!\!\!\perp A|L$ holds and standardization or IP weighting can be used to identify the causal effect.

Fine Point 3.2 introduces the relation between lack of exchangeability and *confounding*.

Of course, the crucial question for the observational study is whether L is the only outcome predictor that is unequally distributed between the treated and the untreated. Sadly, the question must remain unanswered. For example, suppose the investigators of our observational study strongly believe that the treated and the untreated are exchangeable within levels of L. Their reasoning goes as follows: "Heart transplants are assigned to individuals with low probability of rejecting the transplant, that is, a heart with certain human leukocyte antigen (HLA) genes will be assigned to an individual who happen to have compatible genes. Because HLA genes are not predictors of mortality, it turns out that treatment assignment is essentially random within levels of L." Thus our investigators are willing to work under the *assumption* that conditional exchangeability $Y^a \perp\!\!\!\perp A|L$ holds.

The key word is "assumption." No matter how convincing the investigators' story may be, in the absence of randomization, there is no guarantee that conditional exchangeability holds. For example, suppose that, unknown to the investigators, doctors prefer to transplant hearts into nonsmokers. If two individual with $L = 1$ have similar HLA genes, but one of them is a smoker ($U = 1$) and the other one is a nonsmoker ($U = 0$), the one with $U = 1$ has a lower probability of receiving treatment $A = 1$. When the distribution of smoking,

Fine Point 3.2

Exchangeability and confounding. We now relate the concepts of exchangeability and confounding in a setting in which the two other identifying assumptions—positivity and consistency—hold. In the absence of selection bias (see Chapter 8), the assumption of conditional exchangeability given L is often known as the assumption of no unmeasured confounding given L (see Chapter 7).

In a marginally randomized experiment, exchangeability $Y^a \perp\!\!\!\perp A$ ensures that effect measures can be computed when complete data on treatment A and outcome Y are available. For example, the causal risk ratio equals the associational risk ratio. There is no confounding or, equivalently, the causal effect is identifiable given data on A and Y.

In an ideal conditionally randomized experiment, conditional exchangeability $Y^a \perp\!\!\!\perp A|L$ ensures that effect measures can be computed when complete data on treatment A, outcome Y, and variable L are available. For example, the causal risk ratio equals the ratio of standardized risks. There is no unmeasured confounding given the measured variable L or, equivalently, the causal effect is identifiable given data on L, A and Y.

In an observational study, there is no guarantee that the treated and the untreated are conditionally exchangeable given L only. Thus the effect measures may not be computed even if complete data on L, A, and Y are available because of unmeasured confounding (i.e., other variables besides L must be measured and conditioned on to achieve exchangeability). Equivalently, the causal effect is not identifiable given the measured data.

We use U to denote unmeasured variables. Because unmeasured variables cannot be used for standardization or IP weighting, the causal effect cannot be identified when the measured variables L are insufficient to achieve conditional exchangeability.

an important predictor of the outcome, differs between the treated (with lower proportion of smokers $U = 1$) and the untreated (with higher proportion of smokers $U = 1$) with $L = 1$, conditional exchangeability given L does not hold. Importantly, collecting data on smoking would not prevent the possibility that other imbalanced outcome predictors, unknown to the investigators, remain unmeasured.

Thus exchangeability $Y^a \perp\!\!\!\perp A|L$ may not hold in observational studies. Specifically, conditional exchangeability $Y^a \perp\!\!\!\perp A|L$ will not hold if there exist unmeasured independent predictors U of the outcome such that the probability of receiving treatment A depends on U within strata of L. Worse yet, even if conditional exchangeability $Y^a \perp\!\!\!\perp A|L$ held, the investigators cannot empirically verify that is actually the case. How can they check that the distribution of smoking is equal in the treated and the untreated if they have not collected data on smoking? What about all the other unmeasured outcome predictors U that may also be differentially distributed between the treated and the untreated? When we analyze an observational study under the assumption of conditional exchangeability, we must hope that our expert knowledge guides us correctly to collect enough data so that the assumption is at least approximately true.

To verify conditional exchangeability, one needs to confirm that $\Pr[Y^a = 1|A = a, L = l] = \Pr[Y^a = 1|A \neq a, L = l]$. But this is logically impossible because, for individuals who do not receive treatment a ($A \neq a$) the value of Y^a is unknown and so the right hand side cannot be empirically evaluated.

Because investigators can use their expert knowledge to enhance the plausibility of the conditional exchangeability assumption. They can measure many relevant variables L (e.g., determinants of the treatment that are also independent outcome predictors), rather than only one variable as in Table 3.1, and then assume that conditional exchangeability is approximately true within the strata defined by the combination of all those variables L. Unfortunately, no matter how many variables are included in L, there is no way to test that the assumption is correct, which makes causal inference from observational data a risky task. The validity of causal inferences requires that the investigators' expert knowledge is correct. This knowledge, encoded as the assumption of exchangeability conditional on the measured covariates, supplements the data in an attempt to identify the causal effect of interest.

3.3 Positivity

Some investigators plan to conduct an experiment to compute the average effect of heart transplant A on 5-year mortality Y. It goes without saying that the investigators will assign some individuals to receive treatment level $A = 1$ and others to receive treatment level $A = 0$. Consider the alternative: the investigators assign all individuals to either $A = 1$ or $A = 0$. That would be silly. With all the individuals receiving the same treatment level, computing the average causal effect would be impossible. Instead we must assign treatment so that, with near certainty, some individuals will be assigned to each of the treatment groups. In other words, we must ensure that there is a probability greater than zero—a positive probability—of being assigned to each of the treatment levels. This is the *positivity* condition.

The positive condition is sometimes referred to as the *experimental treatment assumption*.

We did not emphasize positivity when describing experiments because positivity is taken for granted in those studies. In marginally randomized experiments, the probabilities $\Pr[A = 1]$ and $\Pr[A = 0]$ are both positive by design. In conditionally randomized experiments, the conditional probabilities $\Pr[A = 1|L = l]$ and $\Pr[A = 0|L = l]$ are also positive by design for all levels of the variable L that are eligible for the study. For example, if the data in Table 3.1 had arisen from a conditionally randomized experiment, the conditional probabilities of assignment to heart transplant would have been $\Pr[A = 1|L = 1] = 0.75$ for those in critical condition and $\Pr[A = 1|L = 0] = 0.50$ for the others. Positivity holds, conditional on L, because neither of these probabilities is 0 (nor 1, which would imply that the probability of no heart transplant $A = 0$ would be 0). Thus we say that there is positivity if $\Pr[A = a|L = l] > 0$ for all a involved in the causal contrast. Actually, this definition of positivity is incomplete because, if our study population were restricted to the group $L = 1$, then there would be no need to require positivity in the group $L = 0$. Positivity is only needed for the values l that are present in the population of interest.

Positivity: $\Pr[A = a|L = l] > 0$ for all values l with $\Pr[L = l] \neq 0$ in the population of interest.

In addition, positivity is only required for the variables L that are required for exchangeability. For example, in the conditionally randomized experiment of Table 3.1, we do not ask ourselves whether the probability of receiving treatment is greater than 0 in individuals with blue eyes because the variable "having blue eyes" is not necessary to achieve exchangeability between the treated and the untreated. (The variable "having blue eyes" is not an independent predictor of the outcome Y conditional on L and A, and was not even used to assign treatment.) That is, the standardized risk and the IP weighted risk are equal to the counterfactual risk after adjusting for L only; positivity does not apply to variables that, like "having blue eyes", do not need to be adjusted for.

In observational studies, neither positivity nor exchangeability are guaranteed. For example, positivity would not hold if doctors always transplant a heart to individuals in critical condition $L = 1$, i.e., if $\Pr[A = 0|L = 1] = 0$, as shown in Figure 3.1. A difference between the conditions of exchangeability and positivity is that positivity can sometimes be empirically verified (see Chapter 12). For example, if Table 3.1 corresponded to data from an observational study, we would conclude that positivity holds for L because there are people at all levels of treatment (i.e., $A = 0$ and $A = 1$) in every level of L (i.e., $L = 0$ and $L = 1$).Our discussion of standardization and IP weighting in the previous chapter was explicit about the exchangeability condition, but only implicitly assumed the positivity condition (explicitly in Technical Point 2.3). Our previous definitions of standardized risk and IP weighted risk are

actually only meaningful when positivity holds. To intuitively understand why the standardized and IP weighted risk are not well-defined when the positivity condition fails, consider Figure 3.1. If there were no untreated individuals ($A = 0$) with $L = 1$, the data would contain no information to simulate what would have happened had all treated individuals been untreated because there would be no untreated individuals with $L = 1$ that could be considered exchangeable with the treated individuals with $L = 1$. See Technical Point 3.1 for details.

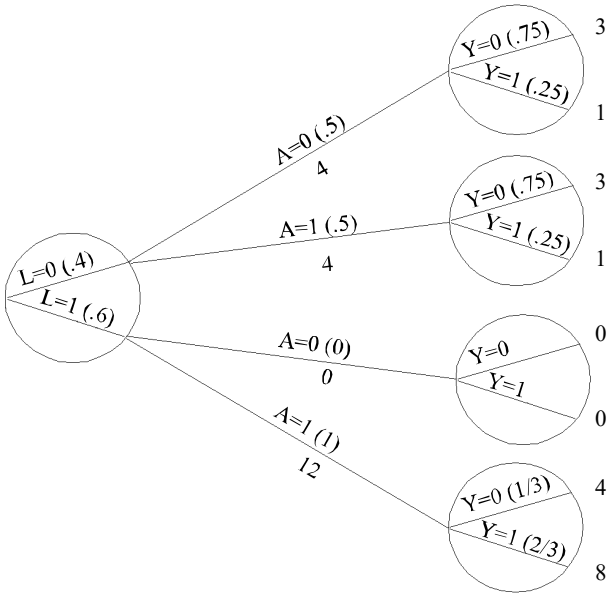


Figure 3.1

3.4 Consistency: First, define the counterfactual outcome

Consistency means that the observed outcome for every treated individual equals her outcome if she had received treatment, and that the observed outcome for every untreated individual equals her outcome if she had remained untreated, that is, $Y^a = Y$ for every individual with $A = a$. This statement seems so obviously true that some readers may be wondering whether there are any situations in which consistency does not hold. After all, if I take aspirin $A = 1$ and I die ($Y = 1$), isn't it always the case that my outcome $Y^{a=1}$ under aspirin also equals 1? The apparent simplicity of the consistency condition is deceptive. Let us unpack consistency by explicitly describing its two main components: (1) a precise specification of the counterfactual outcomes Y^a via a detailed specification of the superscript a, and (2) the linkage of the counterfactual outcomes to the observed outcomes. This section deals with the first component of consistency.

Robins and Greenland (2000) argued that well-defined counterfactuals, or mathematically equivalent concepts, are necessary for meaningful causal inference. If the counterfactuals are ill-defined, the inference is also ill-defined.

Consider again a randomized experiment to compute the average effect of heart transplant A on 5-year mortality Y. Before enrolling patients in the study, the investigators wrote a protocol in which the two interventions of interest—heart transplant $A = 1$ and medical therapy $A = 0$—were described in detail. For example, the investigators specified that individuals assigned to heart transplant $A = 1$ were to receive certain pre-operative procedures,

Technical Point 3.1

Positivity for standardization and IP weighting. We have defined the standardized mean for treatment level a as $\sum_l \mathrm{E}[Y|A=a,L=l]\Pr[L=l]$. However, this expression can only be computed if the conditional quantity $\mathrm{E}[Y|A=a,L=l]$ is well defined, which will be the case when the conditional probability $\Pr[A=a|L=l]$ is greater than zero for all values l that occur in the population. That is, when positivity holds. (Note the statement $\Pr[A=a|L=l]>0$ for all l with $\Pr[L=l]\neq 0$ is effectively equivalent to $f[a|L]>0$ with probability 1.) Therefore, the standardized mean is defined as

$$\sum_l \mathrm{E}[Y|A=a,L=l]\Pr[L=l] \quad \text{if } \Pr[A=a|L=l]>0 \text{ for all } l \text{ with } \Pr[L=l]\neq 0,$$

and is undefined otherwise. The standardized mean can be computed only if, for each value of the covariate L in the population, there are some individuals that received the treatment level a.

The IP weighted mean $\mathrm{E}\left[\frac{I(A=a)Y}{f[A|L]}\right]$ is no longer equal to $\mathrm{E}\left[\frac{I(A=a)Y}{f[a|L]}\right]$ when positivity does not hold. Specifically, $\mathrm{E}\left[\frac{I(A=a)Y}{f[a|L]}\right]$ is undefined because the undefined ratio $\frac{0}{0}$ occurs in computing the expectation. On the other hand, the IP weighted mean $\mathrm{E}\left[\frac{I(A=a)Y}{f[A|L]}\right]$ is *always* well defined since its denominator $f[A|L]$ can never be zero. However, it is now a biased estimate of the counterfactual mean even under exchangeability. In particular, when positivity fails to hold, $\mathrm{E}\left[\frac{I(A=a)Y}{f[A|L]}\right]$ is equal to $\Pr[L\in Q(a)]\sum_l \mathrm{E}[Y|A=a,L=l,L\in Q(a)]\Pr[L=l|L\in Q(a)]$ where $Q(a)=\{l;\Pr(A=a|L=l)>0\}$ is the set of values l for which $A=a$ may be observed with positive probability. Therefore, under exchangeability, $\mathrm{E}\left[\frac{I(A=a)Y}{f[A|L]}\right]$ equals $\mathrm{E}[Y^a|L\in Q(a)]\Pr[L\in Q(a)]$.

From the definition of $Q(a)$, $Q(0)$ cannot equal $Q(1)$ when A is binary and positivity does not hold. In this case the contrast $\mathrm{E}\left[\frac{I(A=1)Y}{f[A|L]}\right]-\mathrm{E}\left[\frac{I(A=0)Y}{f[A|L]}\right]$ has no causal interpretation, even under exchangeability, because it is a contrast between two different groups. Under positivity, $Q(1)=Q(0)$ and the contrast is the average causal effect if exchangeability holds.

Fine Point 1.2 introduced the concept of multiple versions of treatment. We refer to a treatment with multiple versions as a *compound treatment*. For more on compound treatments, see Section 6.4 and VanderWeele and Hernán (2013).

anesthesia, surgical technique, post-operative intensive care, and immunosuppressive therapy. Had the protocol not specified these details, it is possible that each doctor had conducted the heart transplant in a different way, perhaps using her preferred surgical technique or immunosuppressive therapy. That is, different versions of the treatment "heart transplant" might have been applied to each patient in the study.

The presence of multiple versions of treatment is problematic when the causal effect varies across versions because then the magnitude of the average causal effect of treatment depends on the proportion of individuals who received each version. For example, the average causal effect of "heart transplant" in a study in which most doctors used a traditional surgical technique may differ from that in a study in which most doctors used a novel surgical technique. The treatment "heart transplant" is not a unique treatment but rather a collection of versions of treatment, each of them with a different effect on the outcome. Therefore, it is not clear what we mean when we say "the causal effect of heart transplant."

In the presence of multiple versions of treatment, the values a are not well defined, which means that the counterfactual outcomes Y^a are not well de-

fined, which in turn means that the causal effect is not well defined. To handle the problem of multiple versions of treatment, randomized experiments have protocols that clearly specify the interventions a under study, so that the counterfactual outcomes Y^a are well defined. For the same reason, when making causal inferences from observational data, we need to specify the values a under study as unambiguously as possible. While this task is relatively straightforward for medical interventions, like heart transplant, it is much harder for treatments that do not correspond to actual interventions in the real world, like obesity.

Suppose we conduct an observational study to quantify the "causal effect of obesity" A at age 40 on the risk of mortality Y by age 50. The causal effect is defined by a contrast of the risks if all individuals had been obese $\Pr[Y^{a=1} = 1]$ and nonobese $\Pr[Y^{a=0} = 1]$ at age 40. But what exactly is meant by "the risks if all individuals had been obese"? The answer is not straightforward because there are many different ways in which an individual could have become obese. That is, there are multiple versions of the treatment $A = 1$.

For simplicity, we consider the usual definition of obesity (body mass index$\geq$30), More precise definitions of adiposity would not fundamentally alter our exposition.

Take Kronos, who is obese. Suppose Kronos was obese because his genes predisposed him to large amounts of fat tissue in both his waist and his coronary arteries. He had a fatal myocardial infarction at age 49 despite exercising moderately, keeping a healthy diet, and having a favorable intestinal microbiota. However, if he had been obese not because of his genes but because of lack of exercise, too many calories in the diet, or an unfavorable intestinal microbiota, then he would not have died by age 50. Because it is unclear which version of the treatment "obesity" $A = 1$ we are considering, the counterfactual outcome $Y^{a=1}$ under "obesity" $a = 1$ is ill-defined.

Hernán and Taubman (2008) discuss the tribulations of two world leaders—a despotic king and a clueless president—who tried to estimate the effect of obesity in their own countries.

The counterfactual outcome $Y^{a=0}$ if Kronos had been nonobese is also ill-defined. If Kronos had not been obese, he might have either died or not died by age 50, depending on how he managed to remain nonobese. For example, a nonobese Kronos might have died if he had been nonobese through a lifetime of exercise (a bicycle accident), cigarette smoking (lung cancer), or bariatric surgery (adverse reaction to anesthesia), and might have survived if he had been nonobese through a better diet (fewer calories from devouring his children), more favorable genes (less visceral fat tissue), or a different microbiota (less fat absorption). Because it is unclear which version of the treatment "no obesity" $A = 0$ we are considering, the counterfactual outcome $Y^{a=0}$ under "no obesity" $a = 0$ is ill-defined.

Ill-defined counterfactual outcomes $Y^{a=0}$ and $Y^{a=1}$ result in vague causal questions. The question "What is the causal effect of obesity on mortality?" is vague because the answer depends on the versions of the treatment "obesity" that we consider. We could replace our question about the effect of obesity by a question about the causal effect of varying lifetime exercise just enough to either prevent or guarantee obesity, but that is still a vague question. We would need to define the actual duration, intensity, and type of exercise (swimming, running, playing basketball...) and how the time devoted to exercise would otherwise be spent (playing with your children, rehearsing with your band, watching television...). The point is that the vagueness of causal questions can be reduced by a more detailed specification of the versions of treatment, but cannot be completely eliminated. The best we can do is to specify the versions of treatment with as much detail as we believe necessary. Some vagueness is inherent to all causal questions, though the degree of vagueness is especially high for causal questions involving biological (e.g., body weight, LDL-cholesterol) or social (e.g., socioeconomic status) "treatments."

Causal questions about obesity may be less vague in other settings. Consider the effect of obesity on job discrimination as measured by the proportion of job applicants called for a personal interview after the employer reviews the applicant's resume and photograph. Because the treatment here is really "obesity as perceived by the employer," the mechanisms that led to obesity are irrelevant.

Not being able to perfectly specify the versions of treatment is not as bad

as it sounds. Absolute precision in the definition of the treatment versions is not needed for useful causal inference; all that is required is that no meaningful vagueness remains. For example, scientists agree that the benefits of running clockwise around your neighborhood's park are the same as those of running counterclockwise. Therefore, when describing the treatment "varying lifetime exercise," the direction of the running need not be specified. This and other aspects of the versions of treatment are deemed to be irrelevant because varying them would not lead to different counterfactual outcomes. That is, we only need *sufficiently well-defined* treatment versions a for a meaningful interpretation of the counterfactual outcomes Y^a and the counterfactual contrasts that define the causal effect.

The phrase "no causation without manipulation" (Holland 1986) captures the idea that meaningful causal inference requires sufficiently well-defined interventions (versions of treatment). However, bear in mind that sufficiently well-defined interventions may not be humanly feasible, or practicable, interventions at a particular time in history. For example, the causal effect of genetic variants on human disease was sufficiently well defined even before the existence of technology for genetic modification (Hernán 2016).

Which begs the question of "How do we know that a version of treatment is sufficiently well-defined" or, equivalently, that no meaningful vagueness remains? The answer is "We don't." Declaring a version of treatment sufficiently well-defined is a matter of agreement among experts based on the available substantive knowledge. Today we agree that the direction of running is irrelevant, but future research might prove us wrong if it is demonstrated that, say, leaning the body to the right, but not to the left, while running is harmful. At any point in history, experts who write the protocols of randomized experiments make an attempt to eliminate as much vagueness as possible by employing the subject-matter knowledge at their disposal. Section 3.6 describes an analogous strategy for observational analyses.

The above discussion illustrates an intrinsic feature of causal inference: the articulation of causal questions is contingent on domain expertise and informal judgment. What we view as a scientifically meaningful causal question at present may turn out to be viewed as too vague in the future after learning that finer components of the treatment versions affect the outcome and therefore the magnitude of the causal effect. Years from now, scientists will probably refine our obesity question in terms of cellular modifications which we barely understand at this time. Again, the term sufficiently well-defined treatment relies on expert consensus, which by definition changes over time. Fine Point 3.3 describes an alternative, but logically equivalent way, to make causal questions more precise.

At this point, some readers may rightly note that the process of better specifying the treatment may alter the original question. We started by declaring our interest in the effect of obesity, but we ended up by discussing hypothetical interventions on exercise. The more we focus on providing a sufficiently well-defined causal interpretation to our analyses, the farther from the original question we seem to get. But that is a good thing. Forcing us to refine the causal question, until it is agreed that no meaningful vagueness remains, is a fundamental component of any causal inference exercise. Declaring our interest in "the effect of obesity" is just a starting point for a discussion with our colleagues. During that discussion, we will sharpen the causal question by refining the specification of the treatment versions until, hopefully, a consensus is reached. The more precisely we define the treatment versions, the fewer opportunities for miscommunication among scientists exist, especially when the numerical estimates of causal effect do not agree across studies.

So far we have only reviewed the first component of consistency: the specification of sufficiently well-defined treatments. But a relatively unambiguous interpretation of numerical estimates also requires the second component of consistency.

Fine Point 3.3

Possible worlds. Some philosophers of science define causal contrasts using the concept of "possible worlds." The actual world is the way things actually are. A possible world is a way things might be. Imagine a possible world a where everybody receives treatment value a, and a possible world a' where everybody receives treatment value a'. The mean of the outcome is $\mathrm{E}[Y^a]$ in the first possible world and $\mathrm{E}[Y^{a'}]$ in the second one. These philosophers say that there is an average causal effect if $\mathrm{E}[Y^a] \neq \mathrm{E}[Y^{a'}]$ and the worlds a and a' are the two worlds closest to the actual world where all individuals receive treatment value a and a', respectively.

We introduced an individual's counterfactual outcome Y^a as her outcome under a sufficiently well-defined intervention that assigned treatment value a to her. These philosophers prefer to think of the counterfactual Y^a as the outcome in the possible world that is closest to our world and where the individual was treated with a. Both definitions are equivalent when the only difference between the closest possible world and the actual world is that the intervention of interest took place. The possible worlds formulation of counterfactuals replaces the sometimes difficult problem of specifying the intervention of interest by the equally difficult problem of describing the closest possible world that is minimally different from the actual world. Stalnaker (1968) and Lewis (1973) proposed counterfactual theories based on possible worlds.

3.5 Consistency: Second, link to the data

For an expanded dicussion of the issues described in Sections 3.4 and 3.5, see the text and references in Hernán (2016), and in Robins and Weissman (2016).

Suppose we agree that all versions of treatment a are sufficiently well-defined and, therefore, that no meaningful vagueness remains in the specification of the causal effect. For example, say that we decided to clarify our causal question about obesity by specifying some form of lifetime exercise modification, $a = 1$, as the version of the treatment "obesity" we are interested in. Now the counterfactual outcomes Y^a are sufficiently well defined and we can shift our attention to the equal sign in the consistency condition $Y^a = Y$.

Take again Kronos, who was obese because of interactions between his genes and gut bacteria and did not die, but would have died if he had been obese because of physical inactivity. That is, his counterfactual outcome $Y^{a=1}$ equals 0 under our version of obesity $a = 1$, but his observed outcome Y equals 1 even though he was obese. The equality of the consistency condition $Y^a = Y$ appears to break down.

The implication is that, if we want to quantify the causal effect of versions of treatment $a = 1$ and $a = 0$ using observational data, we need to have data in which individuals receive the versions of treatment $a = 1$ and $a = 0$. For example, suppose we want to quantify the effect of obesity due to a lifetime of physical inactivity on mortality between ages 40 and 50, and that we have observational data from a large cohort of humans, some of them obese by age 40. These individuals became obese for reasons such as bad genetic luck, poor diet, insufficient exercise, unfavorable gut bacteria, lack of access to bariatric surgery, smoking cessation, and combinations of the above. Because these various mechanisms have different effects on mortality, we do not expect that the observed 10-year mortality risk in these individuals is equal to the 10-year risk of death in these same individuals if they had become obese through insufficient exercise. Therefore, it is unclear whether we can use our data to quantify the causal effect $\Pr[Y^{a=1} = 1] - \Pr[Y^{a=0} = 1]$ of interest.

To preserve the link between the counterfactual outcomes $Y^{a=0}$ and the observed outcomes Y, we can restrict the analysis data set to include only the treatment versions a of interest. The goal is to ensure that only individuals receiving the version(s) of interest $a = 1$ are considered as treated individuals

($A = 1$) in the analysis, and similarly for the untreated. If interested in the causal effect of exercise, we need to specify the version(s) of exercise we are interested in (e.g., duration, intensity, frequency, type) and then include in the group $A = 1$ only individuals whose observed data are consistent with the version(s) of interest. But restriction to the versions of interest is impossible when, as it happens often, we have no data on the version of treatment. In fact, we may not be able to even enumerate the versions of treatment.

See Technical Point 3.2 for additional discussion on the vagueness of causal inference when the versions of treatment are unknown.

One way out of this problem is to assume that the effects of all versions of treatment are identical—that is, if there is *treatment-variation irrelevance*—or at least all in the same direction. In some cases, this may be a reasonable assumption. For example, if interested in the average causal effect of high versus normal blood pressure on stroke, empirical evidence suggests that lowering blood pressure through different pharmacological mechanisms results in similar outcomes. We might then argue that a precise definition of the versions of the treatment "blood pressure", as well as a detailed characterization of the versions present in the data, is unnecessary to link the potential and observed outcomes. In other cases, however, the validity of the assumption is less clear. For example, if interested in the average causal effect of weight maintenance on death, empirical evidence suggests that some interventions would increase the risk (e.g., continuation of smoking), whereas others would decrease it (e.g., moderate exercise). In practice, many observational analyses implictily assume treatment-variation irrelevance when making causal inferences about treatments with multiple versions.

Treatment-variation irrelevance was defined in Fine Point 1.2. Formally, this conditions holds if, for any two versions $A(r)$ and $A'(r)$ of compound treatment $R = r$, $Y_i^{r,a(r)} = Y_i^{r,a'(r)}$ for all i and r , where $Y_i^{r,a(r)}$ is individual i's counterfactual outcome under version $A(r) = a(r)$ of compound treatment $R = r$.

In summary, ill-defined treatments like "obesity" complicate the interpretation of causal effect estimates (previous section), but so do sufficiently well-defined treatments in the absence of matching data (this section). Detecting a mismatch between the treatments versions of interest and the data at hand requires a careful characterization of the versions of treatment that operate in the population. Such characterization is simple in experiments (i.e., whatever intervention investigators use to assign treatment) and relatively straightforward in some observational analyses (e.g., those studying the effects of medical treatments), but difficult or impossible in many observational analyses that study the effects of biological and social factors.

Of course, the characterization of the treatment versions present in the data would be unnecessary if experts explicitly agreed that all versions have a similar causal effect. However, because experts are fallible, the best we can do is to make these discussions and our assumptions as transparent as possible, so that others can directly challenge our arguments. The next section describes a procedure to achieve that transparency.

3.6 The target trial

The target trial—or its logical equivalents—is central to the causal inference framework. Dorn (1953), Cochran (1972), Rubin (1974), Feinstein (1971), and Dawid (2000) used it. Robins (1986) generalized the concept to time-varying treatments.

For each causal effect, we can imagine a (hypothetical) randomized experiment that can quantify it. We refer to that experiment as the target experiment or the target trial, and we resort to causal analyses of observational data when the target trial is not feasible, ethical, or timely. That is, causal inference from observational data can be viewed as an attempt to emulate the target trial. If the emulation is successful, there is no difference between the numerical results that the observational data and the target trial would have yielded, had the latter been conducted. As we said in Section 3.1, if the analogy between observational study and a conditionally randomized experiment happens to

be correct in our data, then we can use the methods described in the previous chapter—IP weighting or standardization—to compute causal effects from observational studies. (Incidentally, see Fine Point 3.4 for how to use observational data to compute the proportion of cases attributable to treatment.)

Therefore "what randomized experiment are you trying to emulate?" is a key question for causal inference from observational data. For each causal question that we intend to answer using observational data, we can describe (i) the target trial that we would like to, but cannot, conduct, and (ii) how the observational data can be used to emulate that target trial.

Hernán and Robins (2016) reviewed the key components of the target trial that need to be specified—regardless of whether the causal inference is based on a randomized experiment or an observational study—and emulation procedures when using observational data.

Describing the target trial can be done by specifying the key components of its protocol: eligibility criteria, treatment strategies, outcome, follow-up, causal contrast, and statistical analysis. Throughout this book we will study each of these components. Here we focus on the treatment strategies or, in the language of this chapter, the versions of treatment that will be compared across groups. As discussed in the previous two sections, investigators will first specify the treatment versions of interest and then identify individuals who receive them in the data.

Consider again the causal effect of "obesity" on mortality. The first step for investigators is to make their causal question less vague. For example, they may agree that their goal is estimating the effect of losing 5% of body mass index every year, starting at age 40 and for as long as their body mass index stays over 25, under the assumption that it doesn't matter how the weight loss is achieved provided it is not the result of cigarette smoking. They can now transfer this treatment strategy to the protocol of a target trial which they will attempt to emulate with the data at their disposal.

This book's authors and their collaborators have followed a similar procedure to estimate the effect of weight loss using observational data (see, for example, Danaei et al, 2016). We tried to carefully define the timing of the treatment strategies under the assumption that the method used to lose weight was irrelevant.

An explicit emulation of the target trial prevents investigators from conducting an oversimplified analysis that compares the risk of death in obese versus nonobese individuals at age 40. That comparison corresponds implicitly to a target trial in which obese individuals are instantaneously modified to a body mass index of 25 at baseline (through a massive liposuction?). Such target trial cannot be emulated because very few people, if anyone, in the real world undergo such instantaneous change, and thus the counterfactual outcomes cannot be linked to the observed outcomes.

The conceptualization of causal inference from observational data as an attempt to emulate a target trial is not universally accepted. Some authors presuppose that "the average causal effect of A on Y" is a well-defined quantity, no matter what A and Y stand for. For example, when considering the effect of obesity, they claim that it is not necessary to carefully specify the treatment versions of the target trial. While we argue that specifying the treatment versions is necessary for a causal interpretation of numerical estimates of causal effect, some authors question the need for such quantitative interpretation. Their argument goes like this:

For some examples of this point of view, see Pearl (2009), Schwartz et al (2016), and Glymour and Spiegelman (2016).

> We may not precisely know which particular causal effect is being estimated in an observational study, but is that really so important if indeed some causal effect exists? A strong association between obesity and mortality may imply that there exists some intervention on body weight that reduces mortality. There is value in learning that many deaths could have been prevented if all obese people had been forced, somehow, to be of normal weight, even if the intervention (the version of treatment) required for achieving that transformation is unspecified.

This is an appealing, but risky, argument. Accepting it raises an important

Fine Point 3.4

Attributable fraction. We have described effect measures like the causal risk ratio $\Pr[Y^{a=1}=1]/\Pr[Y^{a=0}=1]$ and the causal risk difference $\Pr[Y^{a=1}=1]-\Pr[Y^{a=0}=1]$. Both the causal risk ratio and the causal risk difference are examples of effect measures that compare the counterfactual risk under treatment $a=1$ with the counterfactual risk under treatment $a=0$. However, one could also be interested in measures that compare the observed risk with the counterfactual risk under either treatment $a=1$ or $a=0$. This contrast between observed and counterfactual risks allows us to compute the proportion of cases that are attributable to treatment in an observational study, i.e., the proportion of cases that would not have occurred had treatment not occurred. For example, suppose that all 20 individuals in our population attended a dinner in which they were served either ambrosia $(A=1)$ or nectar $(A=0)$. The following day, 7 of the 10 individuals who received $A=1$, and 1 of the 10 individuals who received $A=0$, were sick. For simplicity, assume exchangeability of the treated and the untreated so that the causal risk ratio is $0.7/0.1=7$ and the causal risk difference is $0.7-0.1=0.6$. (In conditionally randomized experiments, one would compute these effect measures via standardization or IP weighting.) It was later discovered that the ambrosia had been contaminated by a flock of doves, which explains the increased risk summarized by both the causal risk ratio and the causal risk difference. We now address the question 'what fraction of the cases was attributable to consuming ambrosia?'

In this study we observed 8 cases, i.e., the observed risk was $\Pr[Y=1]=8/20=0.4$. The risk that would have been observed if everybody had received $a=0$ is $\Pr[Y^{a=0}=1]=0.1$. The difference between these two risks is $0.4-0.1=0.3$. That is, there is an excess 30% of the individuals who did fall ill but would not have fallen ill if everybody in the population had received $a=0$ rather than their treatment A. Because $0.3/0.4=0.75$, we say that 75% of the cases are attributable to treatment $a=1$: compared with the 8 observed cases, only 2 cases would have occurred if everybody had received $a=0$. This *excess fraction* or *attributable fraction* is defined as

$$\frac{\Pr[Y=1]-\Pr[Y^{a=0}=1]}{\Pr[Y=1]}$$

See Fine Point 5.4 for a discussion of the excess fraction in the context of the sufficient-component-cause framework.

Besides the excess fraction, other definitions of attributable fraction have been proposed. For example, the *etiologic fraction* is defined as the proportion of cases whose disease originated from a biologic (or other) process in which treatment had an effect. This is a mechanistic definition of attributable fraction that does not rely on the concept of excess cases and thus can only be computed in randomized experiments under strong assumptions.

problem: Ill-defined versions of treatment prevent a proper consideration of exchangeability and positivity in observational studies.

Let us talk about exchangeability first. To correctly emulate the target trial, investigators need to emulate randomization itself, which is tantamount to achieving exchangeability of the treated and the untreated, possibly conditional on covariates L. If we renounce to characterize the treatment version corresponding to our causal question about obesity, how can we even try to identify and measure the covariates L that make obese and nonobese individuals conditionally exchangeable, i.e., covariates L that are determinants of the versions of treatment (obesity) and also risk factors for the outcome (mortality)? When trying to estimate the effect of an unspecified treatment version, the usual uncertainty regarding conditional exchangeability is exacerbated.

The acceptance of unspecified versions of treatment also affects positivity. Suppose we decide to compute the effect of obesity on mortality by adjusting for covariates L that include diet and exercise. It is possible that, for some values of these variables, no individual will be obese; that is, positivity does not hold. If enough biologic knowledge is available, one could preserve positivity by restricting the analysis to the strata of L in which the population contains both obese and nonobese individuals, but these strata may be no

longer representative of the original population.

Positivity violations point to another potential problem: unspecified versions of treatment may correspond to a target trial that implements unreasonable interventions. The apparently straightforward comparison of obese and nonobese individuals in observational studies masks the true complexity of interventions such as 'make everybody in the population instantly nonobese.' Had these interventions been made explicit, investigators would have realized that these drastic changes are unlikely to be observed in the real world, and therefore they are irrelevant for anyone considering weight loss. A more reasonable, even if still ill-characterized, intervention may be to reduce body mass index by 5% annually as discussed above. Anchoring causal inferences to a target trial not only helps sharpen the specification of the causal question in observational analyses, but also makes the inferences more relevant for decision making.

Extreme interventions are more likely to go unrecognized when they are not explicitly specified.

The problems generated by unspecified treatment versions cannot be dealt with by applying sophisticated statistical methods. All analytic methods for causal inference from observational data described in this book yield effect estimates that are only as well defined as the treatment versions that are being compared. Although the exchangeability condition can be replaced by other unverifiable conditions (see Chapter 16) and the positivity condition can be waived if one is willing to make untestable extrapolations via modeling (Chapter 14), the requirement of sufficiently well-defined versions of treatment is so fundamental that it cannot be waived without simultaneously negating the possibility of describing the causal effect that is being estimated.

Is everything lost when the observational data cannot be used to emulate an interesting target trial? Not really. Observational data may still be quite useful by focusing on non-causal *prediction*, for which the concept of target trial does not apply. That obese individuals have a higher mortality risk than nonobese individuals means that obesity is a predictor of—is associated with—mortality. This is an important piece of information to identify individuals at high risk of mortality. Note, however, that by simply saying that obesity predicts—is associated with—mortality, we remain agnostic about the causal effects of obesity on mortality: obesity might predict mortality in the sense that carrying a lighter predicts lung cancer. Thus the association between obesity and mortality is an interesting hypothesis-generating exercise and a motivation for further research (why does obesity predict mortality anyway?), but not necessarily an appropriate justification to recommend a weight loss intervention targeted to the entire population.

By retreating into prediction from observational data, we avoid tackling questions that cannot be logically asked in randomized experiments, not even in principle. On the other hand, when causal inference is the ultimate goal, prediction may be unsatisfying.

Technical Point 3.2

Cheating consistency. For a compound treatment R with multiple, relevant versions of treatment, consistency requires that the versions of treatment—the interventions—are well-defined and are present in the data. Interestingly, even if the versions of treatment are not well defined, we may still articulate a consistency condition that is guaranteed to hold (Hernán and VanderWeele, 2011): For individuals with $R_i = r$ we let $A_i(r)$ denote the version of treatment $R_i = r$ actually received by individual i; for individuals with $R_i \neq r$ we define $A_i(r) = 0$ so that $A_i(r) \in \{0\} \cup \mathcal{A}(r)$. The consistency condition then requires for all i,

$$Y_i = Y_i^{r,a(r)} \text{ when } R_i = r \text{ and } A_i(r) = a(r).$$

That is, the outcome for every individual who received a particular version of treatment $R = r$ equals his outcome if he had received that particular version of treatment. This statement is true by definition of version of treatment if we in fact define the counterfactual $Y_i^{r,a(r)}$ for individual i with $R_i = r$ and $A_i(r) = a(r)$ as individual i's outcome that he actually had under actual treatment r and actual version $a(r)$. However, using this consistency condition is self-defeating because, as discussed in the main text, it prevents us from understanding what effect is being estimated and from being able to evaluate the other two identifiability conditions.

Similarly, consider the following hypothetical intervention: 'assign everybody to being nonobese by changing the determinants of body weight to reflect the distribution of those determinants in those who are nonobese in the study population.' This intervention would randomly assign a version of treatment to each individual in the study population so that the resulting distribution of versions of treatment exactly matches the distribution of versions of treatment in the study population. Analogously, we can propose another hypothetical, random intervention that assigns everybody to being obese.

This trick is implicitly used in the analysis of many observational studies that compare the risks $\Pr[Y = 1|A = 1]$ and $\Pr[Y = 1|A = 0]$ (often conditional on other variables) to endow the contrast with a causal interpretation. A problem with this trick is, of course, that the proposed random interventions may not match any realistic interventions we are interested in. Learning that intervening on 'the determinants of body weight to reflect the distribution of those determinants in those with nonobese weight' decreases mortality by, say, 30% does not imply that any real world intervention on obesity (e.g., by modifying caloric intake or exercise levels) will decrease mortality by 30% too. In fact, if intervening on 'determinants of body weight in the population' requires intervening on genetic factors, then a 30% reduction in mortality may be unattainable by interventions that can actually be implemented in the real world.

Chapter 4
EFFECT MODIFICATION

So far we have focused on the average causal effect in an entire population of interest. However, many causal questions are about subsets of the population. Consider again the causal question "does one's looking up at the sky make other pedestrians look up too?" You might be interested in computing the average causal effect of treatment—your looking up to the sky— in city dwellers and visitors separately, rather than the average effect in the entire population of pedestrians.

The decision whether to compute average effects in the entire population or in a subset depends on the inferential goals. In some cases, you may not care about the variations of the effect across different groups of individuals. For example, suppose you are a policy maker considering the possibility of implementing a nationwide water fluoridation program. Because this public health intervention will reach all households in the population, your primary interest is in the average causal effect in the entire population, rather than in particular subsets. You will be interested in characterizing how the causal effect varies across subsets of the population when the intervention can be targeted to different subsets, or when the findings of the study need to be applied to other populations.

This chapter emphasizes that there is not such a thing as *the* causal effect of treatment. Rather, the causal effect depends on the characteristics of the particular population under study.

4.1 Definition of effect modification

Table 4.1

	M	Y^0	Y^1
Rheia	1	0	1
Demeter	1	0	0
Hestia	1	0	0
Hera	1	0	0
Artemis	1	1	1
Leto	1	0	1
Athena	1	1	1
Aphrodite	1	0	1
Persephone	1	1	1
Hebe	1	1	0
Kronos	0	1	0
Hades	0	0	0
Poseidon	0	1	0
Zeus	0	0	1
Apollo	0	1	0
Ares	0	1	1
Hephaestus	0	0	1
Cyclope	0	0	1
Hermes	0	1	0
Dionysus	0	1	0

We started this book by computing the average causal effect of heart transplant A on death Y in a population of 20 members of Zeus's extended family. We used the data in Table 1.1, whose columns show the individual values of the (generally unobserved) counterfactual outcomes $Y^{a=0}$ and $Y^{a=1}$. After examining the data in Table 1.1, we concluded that the average causal effect was null. Half of the members of the population would have died if everybody had received a heart transplant, $\Pr[Y^{a=1} = 1] = 10/20 = 0.5$, and half of the members of the population would have died if nobody had received a heart transplant, $\Pr[Y^{a=0} = 1] = 10/20 = 0.5$. The causal risk ratio $\Pr[Y^{a=1} = 1]/\Pr[Y^{a=0} = 1]$ was $0.5/0.5 = 1$ and the causal risk difference $\Pr[Y^{a=1} = 1] - \Pr[Y^{a=0} = 1]$ was $0.5 - 0.5 = 0$.

We now consider two new causal questions: What is the average causal effect of A on Y in women? And in men? To answer these questions we will use Table 4.1, which contains the same information as Table 1.1 plus an additional column with an indicator M for sex: $M = 1$ for females (referred to as women in this book) and $M = 0$ for males (referred to as men). For convenience, we have rearranged the table so that women occupy the first 10 rows, and men the last 10 rows.

Let us first compute the average causal effect in women. To do so, we need to restrict the analysis to the first 10 rows of the table with $M = 1$. In this subset of the population, the risk of death under treatment is $\Pr[Y^{a=1} = 1|M = 1] = 6/10 = 0.6$ and the risk of death under no treatment is $\Pr[Y^{a=0} = 1|M = 1] = 4/10 = 0.4$. The causal risk ratio is $0.6/0.4 = 1.5$ and the causal risk difference is $0.6 - 0.4 = 0.2$. That is, on average, heart transplant A

increases the risk of death Y in women.

Let us next compute the average causal effect in men. To do so, we need to restrict the analysis to the last 10 rows of the table with $M = 0$. In this subset of the population, the risk of death under treatment is $\Pr[Y^{a=1} = 1|M = 0] = 4/10 = 0.4$ and the risk of death under no treatment is $\Pr[Y^{a=0} = 1|M = 0] = 6/10 = 0.6$. The causal risk ratio is $0.4/0.6 = 2/3$ and the causal risk difference is $0.4 - 0.6 = -0.2$. That is, on average, heart transplant A *decreases* the risk of death Y in men.

Our example shows that a null average causal effect in the population does not imply a null average causal effect in a particular subset of the population. In Table 4.1, the *null hypothesis of no average causal effect* is true for the entire population, but not for men or women when taken separately. It just happens that the average causal effects in men and in women are of equal magnitude but in opposite direction. Because the proportion of each sex is 50%, both effects cancel out exactly when considering the entire population. Although exact cancellation of effects is probably rare, heterogeneity of the individual causal effects of treatment is often expected because of variations in individual susceptibilities to treatment. An exception occurs when the *sharp null hypothesis of no causal effect* is true. Then no heterogeneity of effects exists because the effect is null for every individual and thus the average causal effect in any subset of the population is also null.

See Section 6.5 for a structural classification of effect modifiers.

Additive effect modification:
$\mathrm{E}[Y^{a=1} - Y^{a=0}|M = 1] \neq \mathrm{E}[Y^{a=1} - Y^{a=0}|M = 0]$

Multiplicative effect modification:
$\frac{\mathrm{E}[Y^{a=1}|M=1]}{\mathrm{E}[Y^{a=0}|M=1]} \neq \frac{\mathrm{E}[Y^{a=1}|M=0]}{\mathrm{E}[Y^{a=0}|M=0]}$

We are now ready to provide a definition of effect modifier. We say that M is a modifier of the effect of A on Y when the average causal effect of A on Y varies across levels of M. Since the average causal effect can be measured using different effect measures (e.g., risk difference, risk ratio), the presence of effect modification depends on the effect measure being used. For example, sex M is an effect modifier of the effect of heart transplant A on mortality Y on the *additive* scale because the causal risk difference varies across levels of M. Sex M is also an effect modifier of the effect of heart transplant A on mortality Y on the multiplicative scale because the causal risk ratio varies across levels of M. Note that we only consider variables M that are not affected by treatment A as effect modifiers. Variables affected by treatment may be *mediators* of the effect of treatment.

Note that we do not consider effect modification on the odds ratio scale because the odds ratio is rarely, if ever, the parameter of interest for causal inference.

In Table 4.1 the causal risk ratio is greater than 1 in women ($M = 1$) and less than 1 in men ($M = 0$). Similarly, the causal risk difference is greater than 0 in women ($M = 1$) and less than 0 in men ($M = 0$). That is, there is *qualitative effect modification* because the average causal effects in the subsets $M = 1$ and $M = 0$ are in the opposite direction. In the presence of qualitative effect modification, additive effect modification implies multiplicative effect modification, and vice versa. In the absence of qualitative effect modification, however, one can find effect modification on one scale (e.g., multiplicative) but not on the other (e.g., additive). To illustrate this point, suppose that, in a second study, we computed the quantities shown to the left of this line. In this study, there is no additive effect modification by M because the causal risk difference among individuals with $M = 1$ equals that among individuals with $M = 0$, i.e., $0.9 - 0.8 = 0.1 = 0.2 - 0.1$. However, in this study there is multiplicative effect modification by M because the causal risk ratio among individuals with $M = 1$ differs from that among individuals with $M = 0$, that is, $0.9/0.8 = 1.1 \neq 0.2/0.1 = 2$. Since one cannot generally state that there is, or there is not, effect modification without referring to the effect measure being used (e.g., risk difference, risk ratio), some authors use the term *effect-measure modification*, rather than effect modification, to emphasize the dependence of the concept on the choice of effect measure.

Multiplicative, but not additive, effect modification by M:
$\Pr[Y^{a=0} = 1|M = 1] = 0.8$
$\Pr[Y^{a=1} = 1|M = 1] = 0.9$
$\Pr[Y^{a=0} = 1|M = 0] = 0.1$
$\Pr[Y^{a=1} = 1|M = 0] = 0.2$

4.2 Stratification to identify effect modification

Stratification: the causal effect of A on Y is computed in each stratum of M. For dichotomous M, the stratified causal risk differences are:
$\Pr[Y^{a=1} = 1|M = 1] -$
$\Pr[Y^{a=0} = 1|M = 1]$
and
$\Pr[Y^{a=1} = 1|M = 0] -$
$\Pr[Y^{a=0} = 1|M = 0]$

A stratified analysis is the natural way to identify effect modification. To determine whether M modifies the causal effect of A on Y, one computes the causal effect of A on Y in each level (stratum) of the variable M. In the previous section, we used the data in Table 4.1 to compute the causal effect of transplant A on death Y in each of the two strata of sex M. Because the causal effect differed between the two strata (on both the additive and the multiplicative scale), we concluded that there was (additive and multiplicative) effect modification by M of the causal effect of A on Y.

But the data in Table 4.1 are not the typical data one encounters in real life. Instead of the two columns with each individual's counterfactual outcomes $Y^{a=1}$ and $Y^{a=0}$, one will find two columns with each individual's treatment level A and observed outcome Y. How does the unavailability of the counterfactual outcomes affect the use of stratification to detect effect modification? The answer depends on the study design.

Consider first an ideal marginally randomized experiment. In Chapter 2 we demonstrated that, leaving aside random variability, the average causal effect of treatment can be computed using the observed data. For example, the causal risk difference $\Pr[Y^{a=1} = 1] - \Pr[Y^{a=0} = 1]$ is equal to the observed associational risk difference $\Pr[Y = 1|A = 1] - \Pr[Y = 1|A = 0]$. The same reasoning can be extended to each stratum of the variable M because, if treatment assignment was random and unconditional, exchangeability is expected in every subset of the population. Thus the causal risk difference in women, $\Pr[Y^{a=1} = 1|M = 1] - \Pr[Y^{a=0} = 1|M = 1]$, is equal to the associational risk difference in women, $\Pr[Y = 1|A = 1, M = 1] - \Pr[Y = 1|A = 0, M = 1]$. And similarly for men.

Thus, to identify effect modification by M in an ideal experiment with unconditional randomization, one just needs to conduct a stratified analysis, that is, to compute the association measure in each level of the variable M.

Consider now an ideal randomized experiment with conditional randomization. In a population of 40 people, transplant A has been randomly assigned with probability 0.75 to those in severe condition ($L = 1$), and with probability 0.50 to the others ($L = 0$). The 40 individuals can be classified into two nationalities according to their passports: 20 are Greek ($M = 1$) and 20 are Roman ($M = 0$). The data on L, A, and death Y for the 20 Greeks are shown in Table 2.2 (same as Table 3.1). The data for the 20 Romans are shown in Table 4.2. The population risk under treatment, $\Pr[Y^{a=1} = 1]$, is 0.55, and the population risk under no treatment, $\Pr[Y^{a=0} = 1]$, is 0.40. (Both risks are readily calculated by using either standardization or IP weighting. We leave the details to the reader.) The average causal effect of transplant A on death Y is therefore $0.55 - 0.40 = 0.15$ on the risk difference scale, and $0.55/0.40 = 1.375$ on the risk ratio scale. In this population, heart transplant increases the mortality risk.

Table 4.2
Stratum $M = 0$

	L	A	Y
Cybele	0	0	0
Saturn	0	0	1
Ceres	0	0	0
Pluto	0	0	0
Vesta	0	1	0
Neptune	0	1	0
Juno	0	1	1
Jupiter	0	1	1
Diana	1	0	0
Phoebus	1	0	1
Latona	1	0	0
Mars	1	1	1
Minerva	1	1	1
Vulcan	1	1	1
Venus	1	1	1
Seneca	1	1	1
Proserpina	1	1	1
Mercury	1	1	0
Juventas	1	1	0
Bacchus	1	1	0

As discussed in the previous chapter, the calculation of the causal effect would have been the same if the data had arisen from an observational study in which we believe that conditional exchangeability $Y^a \perp\!\!\!\perp A|L$ holds.

We now discuss how to conduct a stratified analysis to investigate whether nationality M modifies the effect of A on Y. The goal is to compute the causal effect of A on Y in the Greeks, $\Pr[Y^{a=1} = 1|M = 1] - \Pr[Y^{a=0} = 1|M = 1]$, and in the Romans, $\Pr[Y^{a=1} = 1|M = 0] - \Pr[Y^{a=0} = 1|M = 0]$. If these two causal risk differences differ, we will say that there is additive effect modification by M. And similarly for the causal risk ratios if interested in multiplicative effect

Fine Point 4.1

Effect in the treated. This chapter is concerned with average causal effects in subsets of the population. One particular subset is the treated ($A = 1$). The *average causal effect in the treated* is not null if $\Pr[Y^{a=1} = 1|A = 1] \neq \Pr[Y^{a=0} = 1|A = 1]$ or, by consistency, if

$$\Pr[Y = 1|A = 1] \neq \Pr[Y^{a=0} = 1|A = 1].$$

That is, there is a causal effect in the treated if the observed risk among the treated individuals does not equal the counterfactual risk had the treated individuals been untreated. The causal risk difference in the treated is $\Pr[Y = 1|A = 1] - \Pr[Y^{a=0} = 1|A = 1]$. The causal risk ratio in the treated, also known as the standardized morbidity ratio (SMR), is $\Pr[Y = 1|A = 1]/\Pr[Y^{a=0} = 1|A = 1]$. The causal risk difference and risk ratio in the untreated are analogously defined by replacing $A = 1$ by $A = 0$. Figure 4.1 shows the groups that are compared when computing the effect in the treated and the effect in the untreated.

The average effect in the treated will differ from the average effect in the population if the distribution of individual causal effects varies between the treated and the untreated. That is, when computing the effect in the treated, treatment group $A = 1$ is used as a marker for the factors that are truly responsible for the modification of the effect between the treated and the untreated groups. However, even though one could say that there is effect modification by the pretreatment variable M even if M is only a surrogate (e.g., nationality) for the causal effect modifiers, one would not say that there is modification of the effect A by treatment A because it sounds confusing.

See Section 6.6 for a graphical representation of true and surrogate effect modifiers. The bulk of this book is focused on the causal effect in the population because the causal effect in the treated, or in the untreated, cannot be directly generalized to time-varying treatments (see Part III).

modification.

The procedure to compute the conditional risks $\Pr[Y^{a=1} = 1|M = m]$ and $\Pr[Y^{a=0} = 1|M = m]$ in each stratum m has two stages: 1) stratification by M, and 2) standardization by L (or, equivalently, IP weighting with weights depending on L). We computed the standardized risks in the Greek stratum ($M = 1$) in Chapter 2: the causal risk difference was 0 and the causal risk ratio was 1. Using the same procedure in the Roman stratum ($M = 0$), we can compute the risks $\Pr[Y^{a=1} = 1|M = 0] = 0.6$ and $\Pr[Y^{a=0} = 1|M = 0] = 0.3$. (Again, we leave the details to the reader.) Therefore, the causal risk difference is 0.3 and the causal risk ratio is 2 in the stratum $M = 0$. Because these effect measures differ from those in the stratum $M = 1$, we say that there is both additive and multiplicative effect modification by nationality M of the effect of transplant A on death Y. This effect modification is not qualitative because the effect is harmful or null in both strata $M = 0$ and $M = 1$.

Step 2 can be ignored when M is equal to the variables L that are needed for conditional exchangeability (see Section 4.4).

We have shown that, in our study population, nationality M modifies the effect of heart transplant A on the risk of death Y. However, we have made no claims about the mechanisms involved in such effect modification. In fact, it is possible that nationality is simply a marker for the factor that is truly responsible for the modification of the causal effect. For example, suppose that the quality of heart surgery is better in Greece than in Rome. One would then find effect modification by nationality even though, technically, passport-defined nationality does not modify the effect. For example, improving the quality of heart surgery in Rome, or moving Romans to Greece, would eliminate the modification of the causal effect by passport-defined nationality. Whenever we want to emphasize this distinction, we will refer to nationality as a *surrogate effect modifier*, and to quality of care as a *causal effect modifier*.

See Section 6.6 for a graphical representation of surrogate and causal effect modifiers.

Therefore, our use of the term effect modification by M does not necessarily imply that M plays a causal role in the modification of the effect. To avoid

potential confusions, some authors prefer to use the more neutral term "effect heterogeneity across strata of M" rather than "effect modification by M." The next chapter introduces "interaction," a concept related to effect modification, that does attribute a causal role to the variables involved.

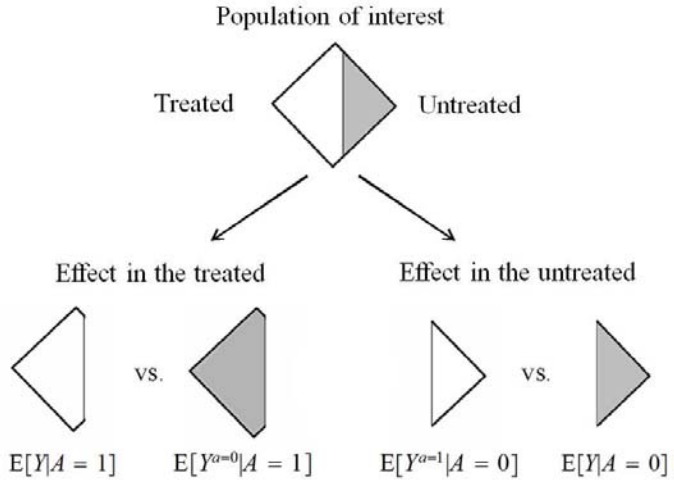


Figure 4.1

4.3 Why care about effect modification

There are several related reasons why investigators are interested in identifying effect modification, and why it is important to collect data on pre-treatment descriptors M even in randomized experiments.

First, if a factor M modifies the effect of treatment A on the outcome Y then the average causal effect will differ between populations with different prevalence of M. For example, the average causal effect in the population of Table 4.1 is harmful in women and beneficial in men. Because there are 50% of individuals of each sex and the sex-specific harmful and beneficial effects are equal but of opposite sign, the average causal effect in the entire population is null. However, had we conducted our study in a population with a greater proportion of women (e.g., graduating college students), the average causal effect in the entire population would have been harmful. Other examples: the effects of exposure to asbestos differ between smokers and nonsmokers, the effects of antiretroviral therapy differ between relatively healthy and severely ill HIV-infected individuals, the effects of universal health care differ between low-income and high-income families.

That is, the average causal effect in a population depends on the distribution of individual causal effects in the population. There is generally no such a thing as "*the* average causal effect of treatment A on outcome Y (period)", but "the average causal effect of treatment A on outcome Y in a population with a particular mix of causal effect modifiers."

Some refer to lack of transportability as lack of external validity.

The extrapolation of causal effects computed in one population to a second population is referred to as transportability of causal inferences across populations (see Fine Point 4.2). In our example, the causal effect of heart

Technical Point 4.1

Computing the effect in the treated. We computed the average causal effect in the population under conditional exchangeability $Y^a \perp\!\!\!\perp A|L$ for both $a = 0$ and $a = 1$. Computing the average causal effect in the treated only requires *partial exchangeability* $Y^{a=0} \perp\!\!\!\perp A|L$. In other words, it is irrelevant whether the risk in the untreated, had they been treated, equals the risk in those who were actually treated. The *average causal effect in the untreated* is computed under the partial exchangeability condition $Y^{a=1} \perp\!\!\!\perp A|L$.

We now describe how to compute the counterfactual risk $\Pr[Y^a = 1|A = a']$ via standardization, and a more general approach to compute the counterfactual mean $\mathrm{E}[Y^a|A = a']$ via IP weighting, under the above assumptions of partial exchangeability:

- Standardization: $\Pr[Y^a = 1|A = a']$ is equal to $\sum_l \Pr[Y = 1|A = a, L = l] \Pr[L = l|A = a']$. See Miettinen (1973) for a discussion of standardized risk ratios.
- IP weighting: $\mathrm{E}[Y^a|A = a']$ is equal to the IP weighted mean $\dfrac{\mathrm{E}\left[\dfrac{I(A=a)Y}{f(A|L)} \Pr[A = a'|L]\right]}{\mathrm{E}\left[\dfrac{I(A=a)}{f(A|L)} \Pr[A = a'|L]\right]}$ with weights $\dfrac{\Pr[A = a'|L]}{f(A|L)}$. For dichotomous A, this equality was derived by Sato and Matsuyama (2003). See Hernán and Robins (2006) for further details.

transplant A on risk of death Y differs between men and women, and between Romans and Greeks. Thus the average causal effect in this population may not be transportable to other populations with a different distribution of effect modifiers such as sex and nationality.

Note that conditional causal effects in the strata defined by the effect modifiers may be more transportable than the causal effect in the entire population, but there is no guarantee that the conditional effect measures in one population equal the conditional effect measures in another population. This is so because there could be other unmeasured, or unknown, causal effect modifiers whose conditional distributions vary between the two populations, or for other reasons that are described in Fine Point 4.2.

A setting in which transportability may not be an issue: Smith and Pell (2003) could not identify any major modifiers of the effect of parachute use on death after "gravitational challenge" (e.g., jumping from an airplane at high altitude). They concluded that conducting randomized trials of parachute use restricted to a particular group of people would not compromise the transportability of the findings to other groups.

Transportability of causal effects is an unverifiable assumption that relies heavily on subject-matter knowledge. For example, most experts would agree that the health effects (on either the additive or multiplicative scale) of increasing a household's annual income by $100 in Niger cannot be trasported to the Netherlands, but most experts would agree that the health effects of use of cholesterol-lowering drugs in Europeans can be transported to Canadians.

Second, evaluating the presence of effect modification is helpful to identify the groups of individuals that would benefit most from an intervention. In our example of Table 4.1, the average causal effect of treatment A on outcome Y was null. However, treatment A had a beneficial effect in men ($M = 0$), and a harmful effect in women ($M = 1$). If a physician knew that there is qualitative effect modification by sex then, in the absence of additional information, she would treat the next patient only if he happens to be a man. The situation is slightly more complicated when, as in our second example, there is multiplicative, but not additive, effect modification. Here treatment reduces the risk of the outcome by 10% in individuals with $M = 0$ and also by 10% in individuals

with $M = 1$, i.e., there is no additive effect modification by M because the causal risk difference is 0.1 in all levels of M. Thus, an intervention to treat all patients would be equally effective in reducing risk in both strata of M, despite the fact that there is multiplicative effect modification. In fact, if there is a nonzero causal effect in at least one stratum of M and the counterfactual risk $\Pr[Y^{a=0} = 1|M = m]$ varies with m, then effect modification is guaranteed on either the additive or the multiplicative scale.

Several authors (e.g., Blot and Day, 1979; Rothman et al., 1980; Saracci, 1980) have referred to additive effect modification as the one of interest for public health purposes.

Additive, but not multiplicative, effect modification is the appropriate scale to identify the groups that will benefit most from intervention. In the absence of additive effect modification, it is usually not very helpful to learn that there is multiplicative effect modification.

In our second example, the presence of multiplicative effect modification follows from the mathematical fact that, because the risk under no treatment in the stratum $M = 1$ equals 0.8, the maximum possible causal risk ratio in the $M = 1$ stratum is $1/0.8 = 1.25$. Thus the causal risk ratio in the stratum $M = 1$ is guaranteed to differ from the causal risk ratio of 2 in the $M = 0$ stratum. In these situations, the presence of multiplicative effect modification is simply the consequence of different risk under no treatment $\Pr[Y^{a=0} = 1|M = m]$ across levels of M. In the presence of different risks under no treatment, it is more informative to report the risk differences than the risk ratios. In fact, it is most informative to report the two counterfactual risks $\Pr[Y^{a=1} = 1|M = m]$ and $\Pr[Y^{a=0} = 1|M = m]$ in every level m of M.

Finally, the identification of effect modification may help understand the biological, social, or other mechanisms leading to the outcome. For example, a greater risk of HIV infection in uncircumcised compared with circumcised men may provide new clues to understand the disease. The identification of effect modification may be a first step towards characterizing the interactions between two treatments. Note that the terms "effect modification" and "interaction" are sometimes used as synonymous in the scientific literature. This chapter focused on "effect modification." The next chapter describes "interaction" as a causal concept that is related to, but different from, effect modification.

4.4 Stratification as a form of adjustment

Until this chapter, our only goal was to compute the average causal effect in the entire population. In the absence of marginal randomization, achieving this goal requires adjustment for the variables L that ensure conditional exchangeability of the treated and the untreated. For example, in Chapter 2 we determined that the average causal effect of heart transplant A on mortality Y was null, that is, the causal risk ratio $\Pr\left[Y^{a=1} = 1\right] / \Pr\left[Y^{a=0} = 1\right] = 1$. We used the data in Table 2.2 to adjust for the prognostic factor L via both standardization and IP weighting.

The present chapter adds another potential goal to the analysis: to identify effect modification by variables M. To achieve this goal, we need to stratify by M before adjusting for L. For example, in this chapter we stratified by nationality M before adjusting for the prognostic factor L to determine that the average causal effect of heart transplant A on mortality Y differed between Greeks and Romans. In summary, standardization (or IP weighting) is used to adjust for L and stratification is used to identify effect modification by M.

But stratification is not always used to identify effect modification by M.

Fine Point 4.2

Transportability. Causal effects estimated in one population are often intended to make decisions in another population, which we will refer to as the target population. Suppose we have correctly estimated the average causal effect of treatment in our study population under exchangeability, positivity, and consistency. Will the effect be the same in the target population? That is, can we "transport" the effect from the study population to the target population? The answer to this question depends on the characteristics of both populations. Specifically, transportability of effects from one population to another may be justified if the following characteristics are similar between the two populations:

- Effect modification: The causal effect of treatment may differ across individuals with different susceptibility to the outcome. For example, if women are more susceptible to the effects of treatment than men, we say that sex is an effect modifier. The distribution of effect modifiers in a population will generally affect the magnitude of the causal effect of treatment in that population. If the distribution of effect modifiers differ between the study population and the target population, then the magnitude of the causal effect of treatment will differ too.
- Interference: In many settings, treating one individual may indirectly affect the treatment level of other individuals in the population. For example, a socially active individual may convince his friends to join him while exercising, and thus an intervention on that individual's physical activity may be more effective than an intervention on a socially isolated individual. The distribution of contact patterns among individuals may affect the magnitude of the causal effect of treatment in a population. If the contact patterns differ between the study population and the target population, then the magnitude of the causal effect of treatment will differ too.
- Versions of treatment: The causal effect of treatment depends on the distribution of versions of treatment in the population. If this distribution differs between the study population and the target population, then the magnitude of the causal effect of treatment will differ too.

Note that the transportability of causal inferences across populations may sometimes be improved by restricting our attention to the average causal effects in the strata defined by the effect modifiers (rather than to the average effect), or by using the stratum-specific effects in the study population to reconstruct the average causal effect in the target population. For example, the four stratum-specific effect measures (Roman women, Greek women, Roman men, and Greek men) in our population can be combined in a weighted average to reconstruct the average causal effect in another population with a different mix of sex and nationality. The weight assigned to each stratum-specific measure is the proportion of individuals in that stratum in the second population. However, there is no guarantee that this reconstructed effect will coincide with the true effect in the target population because of possible between-population differences in the distribution of unmeasured effect modifiers, interference patterns, and distribution of versions of treatment.

In practice stratification is often used as an alternative to standardization (and IP weighting) to adjust for L. In fact, the use of stratification as a method to adjust for L is so widespread that many investigators consider the terms "stratification" and "adjustment" as synonymous. For example, suppose you ask an epidemiologist to adjust for the prognostic factor L to compute the effect of heart transplant A on mortality Y. Chances are that she will immediately split Table 2.2 into two subtables—one restricted to individuals with $L = 0$, the other to individuals with $L = 1$—and would provide the effect measure (say, the risk ratio) in each of them. That is, she would calculate the risk ratios $\Pr[Y = 1|A = 1, L = l] / \Pr[Y = 1|A = 0, L = l] = 1$ for both $l = 0$ and $l = 1$.

These two stratum-specific associational risk ratios can be endowed with a causal interpretation under conditional exchangeability given L: they measure the average causal effect in the subsets of the population defined by $L = 0$ and $L = 1$, respectively. They are *conditional effect measures*. In contrast

Under conditional exchangeability given L, the risk ratio in the subset $L = l$ measures the average causal effect in the subset $L = l$ because, if $Y^a \coprod A|L$, then $\Pr[Y = 1|A = a, L = 0] = \Pr[Y^a = 1|L = 0]$

the risk ratio of 1 that we computed in Chapter 2 was a marginal (unconditional) effect measure. In this particular example, all three risk ratios—the two conditional ones and the marginal one—happen to be equal because there is no effect modification by L. Stratification necessarily results in multiple stratum-specific effect measures (one per stratum defined by the variables L). Each of them quantifies the average causal effect in a nonoverlapping subset of the population but, in general, none of them quantifies the average causal effect in the entire population. Therefore, we did not consider stratification when describing methods to compute the average causal effect of treatment in the population in Chapter 2. Rather, we focused on standardization and IP weighting.

In addition, unlike standardization and IP weighting, adjustment via stratification requires computing the effect measures in subsets of the population defined by a combination of *all* variables L that are required for conditional exchangeability. For example, when using stratification to estimate the effect of heart transplant in the population of Tables 2.2 and 4.2, one must compute the effect in Romans with $L = 1$, in Greeks with $L = 1$, in Romans with $L = 0$, and in Greeks with $L = 0$; but one cannot compute the effect in Romans by simply computing the association in the stratum $M = 0$ because nationality M, by itself, is insufficient to guarantee conditional exchangeability.

Robins (1986, 1987) described the conditions under which stratum-specific effect measures for time-varying treatments will not have a causal interpretation even if in the presence of exchangeability, positivity, and well-defined interventions.

That is, the use of stratification forces one to evaluate effect modification by all variables L required to achieve conditional exchangeability, regardless of whether one is interested in such effect modification. In contrast, stratification by M followed by IP weighting or standardization to adjust for L allows one to deal with exchangeability and effect modification separately, as described above.

Other problems associated with the use of stratification are noncollapsibility of certain effect measures like the odds ratio (see Fine Point 4.3) and inappropriate adjustment that leads to bias when, in the case for time-varying treatments, it is necessary to adjust for time-varying variables L that are affected by prior treatment (see Part III).

Stratification requires positivity in addition to exchangeability: the causal effect cannot be computed in subsets $L = l$ in which there are only treated, or untreated, individuals.

Sometimes investigators compute the causal effect in only some of the strata defined by the variables L. That is, no stratum-specific effect measure is computed for some strata. This form of stratification is known as *restriction*. For causal inference, stratification is simply the application of restriction to several comprehensive and mutually exclusive subsets of the population, with exchangeability within each of these subsets. An important use of restriction is the preservation of positivity (see Chapter 3).

4.5 Matching as another form of adjustment

Matching is another adjustment method. The goal of matching is to construct a subset of the population in which the variables L have the same distribution in both the treated and the untreated. As an example, take our heart transplant example in Table 2.2 in which the variable L is sufficient to achieve conditional exchangeability. For each untreated individual in non critical condition ($A = 0, L = 0$) randomly select a treated individual in non critical condition ($A = 1, L = 0$), and for each untreated individual in critical condition ($A = 0, L = 1$) randomly select a treated individual in critical condition ($A = 1, L = 1$). We refer to each untreated individual and her corresponding treated individual as a matched pair, and to the variable L as the matching factor. Suppose we formed

the following 7 matched pairs: Rheia-Hestia, Kronos-Poseidon, Demeter-Hera, Hades-Zeus for $L = 0$, and Artemis-Ares, Apollo-Aphrodite, Leto-Hermes for $L = 1$. All the untreated, but only a sample of treated, in the population were selected. In this subset of the population comprised of matched pairs, the proportion of individuals in critical condition ($L = 1$) is the same, by design, in the treated and in the untreated (3/7).

Our discussion on matching applies to cohort studies only. In case-control designs (briefly discussed in Chapter 8), we often match cases and non-cases (i.e., controls) rather than the treated and the untreated. Even if the matching factors suffice for conditional exchangeability, matching in cases and controls does not achieve unconditional exchangeability of the treated and the untreated in the matched population. Adjustment for the matching factors using some form of stratification is required to estimate conditional (stratum-specific) effect measures.

To construct our matched population we replaced the treated in the population by a subset of the treated in which the matching factor L had the same distribution as that in the untreated. Under the assumption of conditional exchangeability given L, the result of this procedure is (unconditional) exchangeability of the treated and the untreated in the matched population. Because the treated and the untreated are exchangeable in the matched population, their average outcomes can be directly compared: the risk in the treated is 3/7, the risk in the untreated is 3/7, and hence the causal risk ratio is 1. Note that matching ensures *positivity* in the matched population because strata with only treated, or untreated, individuals are excluded from the analysis.

Often one chooses the group with fewer individuals (the untreated in our example) and uses the other group (the treated in our example) to find their matches. The chosen group defines the subpopulation on which the causal effect is being computed. In the previous paragraph we computed the *effect in the untreated*. In settings with fewer treated than untreated individuals across all strata of L, we generally compute the *effect in the treated*. Also, matching needs not be one-to-one (matching pairs), but it can be one-to-many (matching sets).

In many applications, L is a vector of several variables. Then, for each untreated individual in a given stratum defined by a combination of values of all the variables in L, we would have randomly selected one (or several) treated individual(s) from the same stratum.

As the number of matching factors increases, so does the probability that no exact matches exist for an individual. There is a vast literature, beyond the scope of this book, on how to find approximate matches in those settings.

Matching can be used to create a matched population with any chosen distribution of L, not just the distribution in the treated or the untreated. The distribution of interest can be achieved by individual matching, as described above, or by *frequency matching*. An example of the latter is a study in which one randomly selects treated individuals in such a way that 70% of them have $L = 1$, and then repeats the same procedure for the untreated.

Because the matched population is a subset of the original study population, the distribution of causal effect modifiers in the matched study population will generally differ from that in the original, unmatched study population, as discussed in the next section.

4.6 Effect modification and adjustment methods

Standardization, IP weighting, stratification/restriction, and matching are different approaches to estimate average causal effects, but they estimate different types of causal effects. These four approaches can be divided into two groups according to the type of effect they estimate: standardization and IP weighting can be used to compute either marginal or conditional effects, stratification/restriction and matching can only be used to compute conditional effects in certain subsets of the population. All four approaches require exchangeability, positivity, and consistency, but the subsets of the population in which these conditions need to hold depend on the causal effect of interest. For example, to compute the conditional effect among individuals with $L = l$, any

Technical Point 4.2

Pooling of stratum-specific effect measures. So far we have focused on the conceptual, non statistical, aspects of causal inference by assuming that we work with the entire population rather than with a sample from it. Thus we talk about computing causal effects rather than about (consistently) estimating them. In the real world, however, we can rarely compute causal effects in the population. We need to estimate them from samples, and thus obtaining reasonably narrow confidence intervals around our estimated effect measures is an important practical concern.

When dealing with stratum-specific effect measures, one commonly used strategy to reduce the variability of the estimates is to combine all stratum-specific effect measures into one pooled stratum-specific effect measure. The idea is that, *if the effect measure is the same in all strata* (i.e., if there is no effect-measure modification), then the pooled effect measure will be a more precise estimate of the common effect measure. Several methods (e.g., Woolf, Mantel-Haenszel, maximum likelihood) yield a pooled estimate, sometimes by computing a weighted average of the stratum-specific effect measures with weights chosen to reduce the variability of the pooled estimate. Greenland and Rothman (2008) review some commonly used methods for stratified analysis. Pooled effect measures can also be computed using regression models that include all possible product terms between all covariates L, but no product terms between treatment A and covariates L, i.e., models saturated (see Chapter 11) with respect to L.

The main goal of pooling is to obtain a narrower confidence interval around the common stratum-specific effect measure, but the pooled effect measure is still a conditional effect measure. In our heart transplant example, the pooled stratum-specific risk ratio (Mantel-Haenszel method) was 0.88 for the outcome Z. This result is only meaningful if the stratum-specific risk ratios 2 and 0.5 are indeed estimates of the same stratum-specific causal effect. For example, suppose that the causal risk ratio is 0.9 in both strata but, because of the small sample size, we obtained estimates of 0.5 and 2.0. In that case, pooling would be appropriate and the Mantel-Haenszel risk ratio would be closer to the truth than either of the stratum-specific risk ratios. Otherwise, if the causal stratum-specific risk ratios are truly 0.5 and 2.0, then pooling makes little sense and the Mantel-Haenszel risk ratio could not be easily interpreted. In practice, it is not always obvious to determine whether the heterogeneity of the effect measure across strata is due to sampling variability or to effect-measure modification. The finer the stratification, the greater the uncertainty introduced by random variability.

Table 4.3

	L	A	Z
Rheia	0	0	0
Kronos	0	0	1
Demeter	0	0	0
Hades	0	0	0
Hestia	0	1	0
Poseidon	0	1	0
Hera	0	1	1
Zeus	0	1	1
Artemis	1	0	1
Apollo	1	0	1
Leto	1	0	0
Ares	1	1	1
Athena	1	1	1
Hephaestus	1	1	1
Aphrodite	1	1	0
Cyclope	1	1	0
Persephone	1	1	0
Hermes	1	1	0
Hebe	1	1	0
Dionysus	1	1	0

of the above methods requires exchangeability in that subset only; to estimate the marginal effect in the entire population, IP weighting and standardization require exchangeability in all levels of L.

In the absence of effect modification, the effect measures computed via these four approaches will be equal. For example, we concluded that the average causal effect of heart transplant A on mortality Y was null both in the entire population of Table 2.2 (standardization and IP weighting), in the subsets of the population in critical condition $L = 1$ and non critical condition $L = 0$ (stratification), and in the untreated (matching). All methods resulted in a causal risk ratio equal to 1. However, the effect measures computed via these four approaches will not generally be equal. To illustrate how the effects may vary, let us compute the effect of heart transplant A on high blood pressure Z (1: yes, 0 otherwise) using the data in Table 4.3. We assume that exchangeability $Z^a \perp\!\!\!\perp A|L$ and positivity hold. We use the risk ratio scale for no particular reason.

Standardization and IP weighting yield the average causal effect in the entire population $\Pr[Z^{a=1} = 1]/\Pr[Z^{a=0} = 1] = 0.8$ (these and the following calculations are left to the reader). Stratification yields the conditional causal risk ratios $\Pr[Z^{a=1} = 1|L = 0]/\Pr[Z^{a=0} = 1|L = 0] = 2.0$ in the stratum $L = 0$, and $\Pr[Z^{a=1} = 1|L = 1]/\Pr[Z^{a=0} = 1|L = 1] = 0.5$ in the stratum $L = 1$. Matching, using the matched pairs selected in the previous section, yields the causal risk ratio in the untreated $\Pr[Z^{a=1} = 1|A = 0]/\Pr[Z = 1|A = 0] = 1.0$.

We have computed four causal risk ratios and have obtained four different

Table 4.4

	M	A	Y
Rheia	1	0	0
Demeter	1	0	0
Hestia	1	0	0
Hera	1	0	0
Artemis	1	0	1
Leto	1	1	0
Athena	1	1	1
Aphrodite	1	1	1
Persephone	1	1	0
Hebe	1	1	1
Kronos	0	0	0
Hades	0	0	0
Poseidon	0	0	1
Zeus	0	0	1
Apollo	0	0	0
Ares	0	1	1
Hephaestus	0	1	1
Cyclope	0	1	1
Hermes	0	1	0
Dionysus	0	1	1

Part II describes how standardization, IP weighting, and stratification can be used in combination with parametric or semiparametric models. For example, standard regression models are a form of stratification in which the association between treatment and outcome is estimated within levels of all the other covariates in the model.

numbers: $0.8, 2.0, 0.5$, and 1.0. All of them are correct. Leaving aside random variability (see Technical Point 4.2), the explanation of the differences is qualitative effect modification: Treatment doubles the risk among individuals in noncritical condition ($L = 0$, causal risk ratio 2.0) and halves the risk among individuals in critical condition ($L = 1$, causal risk ratio 0.5). The average causal effect in the population (causal risk ratio 0.8) is beneficial because there are more individuals in critical condition than in noncritical condition. The causal effect in the untreated is null (causal risk ratio 1.0), which reflects the larger proportion of individuals in noncritical condition in the untreated compared with the entire population. This example highlights the primary importance of specifying the population, or the subset of a population, to which the effect measure corresponds.

The previous chapter argued that a well-defined causal effect is a prerequisite for meaningful causal inference. This chapter argues that a well characterized target population is another such prerequisite. Both prerequisites are automatically present in experiments that compare two or more interventions in a population that meets certain a priori eligibility criteria. However, these prerequisites cannot be taken for granted in observational studies. Rather, investigators conducting observational studies need to explicitly define the causal effect of interest and the subset of the population in which the effect is being computed. Otherwise, misunderstandings might easily arise when effect measures obtained via different methods are different. In our example above, one investigator who used IP weighting (and computed the effect in the entire population) and another one who used matching (and computed the effect in the untreated) need not engage in a debate about the superiority of one analytic approach over the other. Their discrepant effect measures result from the different causal question asked by each investigator rather than from their choice of analytic approach. In fact, the second investigator could have used IP weighting to compute the effect in the untreated or in the treated (see Technical Point 4.1).

A final note. Stratification can be used to compute average causal effects in subsets of the population, but not individual (subject-specific) effects. We cannot generally compare the mortality outcome had Zeus been treated with the mortality outcome had he been untreated. Estimating subject-specific effects would require subject-specific exchangeability, e.g., for a treated individual we need a perfectly exchangeable untreated individual. Because the assumption of individual exchangeability is generally untenable, adjustment methods require only exchangeability between groups (i.e., the treated and the untreated). As a result, only average causal effects in groups—populations or subsets of populations—can be computed in general.

Fine Point 4.3

Collapsibility and the odds ratio. In the absence of multiplicative effect modification by M, the causal risk ratio in the entire population, $\Pr[Y^{a=1}=1]/\Pr[Y^{a=0}=1]$ is equal to the conditional causal risk ratios $\Pr[Y^{a=1}=1|M=m]/\Pr[Y^{a=0}=1|M=m]$ in every stratum m of M. More generally, the causal risk ratio is a weighted average of the stratum-specific risk ratios. For example, if the causal risk ratios in the strata $M=1$ and $M=0$ were equal to 2 and 3, respectively, then the causal risk ratio in the population would be greater than 2 and less than 3. That the value of the causal risk ratio (and the causal risk difference) in the population is always constrained by the range of values of the stratum-specific risk ratios is not only obvious but also a desirable characteristic of any effect measure.

Now consider a hypothetical effect measure (other than the risk ratio or the risk difference) such that the population effect measure were not a weighted average of the stratum-specific measures. That is, the population effect measure would not necessarily lie inside of the range of values of the stratum-specific effect measures. Such effect measure would be an odd one. The odds ratio (pun intended) is such an effect measure, as we now discuss.

Suppose the data in Table 4.4 were collected to compute the causal effect of altitude A on depression Y in a population of 20 individuals who were not depressed at baseline. The treatment A is 1 if the individual moved to a high altitude residence (on the top of Mount Olympus), 0 otherwise; the outcome Y is 1 if the individual subsequently developed depression, 0 otherwise; and M is 1 if the individual was female, 0 if male. The decision to move was random, i.e., those more prone to develop depression were as likely to move as the others; effectively $Y^a \perp\!\!\!\perp A$. Therefore the risk ratio $\Pr[Y=1|A=1]/\Pr[Y=1|A=0]=2.3$ is the causal risk ratio in the population, and the odds ratio $\dfrac{\Pr[Y=1|A=1]/\Pr[Y=0|A=1]}{\Pr[Y=1|A=0]/\Pr[Y=0|A=0]}=5.4$ is the causal odds ratio $\dfrac{\Pr[Y^{a=1}=1]/\Pr[Y^{a=1}=0]}{\Pr[Y^{a=0}=1]/\Pr[Y^{a=0}=0]}$ in the population. The risk ratio and the odds ratio measure the same causal effect on different scales.

Let us now compute the sex-specific causal effects on the risk ratio and odds ratio scales. The (conditional) causal risk ratio $\Pr[Y=1|M=m,A=1]/\Pr[Y=1|M=m,A=0]$ is 2 for men $(M=0)$ and 3 for women $(M=1)$. The (conditional) causal odds ratio $\dfrac{\Pr[Y=1|M=m,A=1]/\Pr[Y=0|M=m,A=1]}{\Pr[Y=1|M=m,A=0]/\Pr[Y=0|M=m,A=0]}$ is 6 for men $(M=0)$ and 6 for women $(M=1)$. The causal risk ratio in the population, 2.3, is in between the sex-specific causal risk ratios 2 and 3. In contrast, the causal odds ratio in the population, 5.4, is smaller (i.e., closer to the null value) than both sex-specific odds ratios, 6. The causal effect, when measured on the odds ratio scale, is bigger in each half of the population than in the entire population. The population causal odds ratio can be closer to the null value than the non-null stratum-specific causal odds ratio when M is an independent risk factor for Y and, as in our randomized experiment, A is independent of M (Miettinen and Cook, 1981).

We say that an effect measure is collapsible when the population effect measure can be expressed as a weighted average of the stratum-specific measures. In follow-up studies the risk ratio and the risk difference are collapsible effect measures, but the odds ratio—or the rarely used odds difference—is not (Greenland 1987). The noncollapsibility of the odds ratio, which is a special case of Jensen's inequality (Samuels 1981), may lead to counterintuitive findings like those described above. The odds ratio is collapsible under the sharp null hypothesis—both the conditional and unconditional effect measures are then equal to the null value—and it is approximately collapsible—and approximately equal to the risk ratio—when the outcome is rare (say, $<10\%$) in every stratum of a follow-up study.

One important consequence of the noncollapsibility of the odds ratio is the logical impossibility of equating "lack of exchangeability" and "change in the conditional odds ratio compared with the unconditional odds ratio." In our example, the change in odds ratio was about 10% $(1-6/5.4)$ even though the treated and the untreated were exchangeable. Greenland, Robins, and Pearl (1999) reviewed the relation between noncollapsibility and lack of exchangeability.

Chapter 5
INTERACTION

Consider again a randomized experiment to answer the causal question "does one's looking up at the sky make other pedestrians look up too?" We have so far restricted our interest to the causal effect of a single treatment (looking up) in either the entire population or a subset of it. However, many causal questions are actually about the effects of two or more simultaneous treatments. For example, suppose that, besides randomly assigning your looking up, we also randomly assign whether you stand in the street dressed or naked. We can now ask questions like: what is the causal effect of your looking up if you are dressed? And if you are naked? If these two causal effects differ we say that the two treatments under consideration (looking up and being dressed) interact in bringing about the outcome.

When joint interventions on two or more treatments are feasible, the identification of interaction allows one to implement the most effective interventions. Thus understanding the concept of interaction is key for causal inference. This chapter provides a formal definition of interaction between two treatments, both within our already familiar counterfactual framework and within the sufficient-component-cause framework.

5.1 Interaction requires a joint intervention

Suppose that in our heart transplant example, individuals were assigned to receiving either a multivitamin complex ($E = 1$) or no vitamins ($E = 0$) before being assigned to either heart transplant ($A = 1$) or no heart transplant ($A = 0$). We can now classify all individuals into 4 treatment groups: vitamins-transplant ($E = 1$, $A = 1$), vitamins-no transplant ($E = 1$, $A = 0$), no vitamins-transplant ($E = 0$, $A = 1$), and no vitamins-no transplant ($E = 0$, $A = 0$). For each individual, we can now imagine 4 potential or counterfactual outcomes, one under each of these 4 treatment combinations: $Y^{a=1,e=1}$, $Y^{a=1,e=0}$, $Y^{a=0,e=1}$, and $Y^{a=0,e=0}$. In general, an individual's counterfactual outcome $Y^{a,e}$ is the outcome that would have been observed if we had intervened to set the individual's values of A and E to a and e, respectively. We refer to interventions on two or more treatments as *joint interventions*.

The counterfactual Y^a corresponding to an intervention on A alone is the joint counterfactual $Y^{a,e}$ if the observed E takes the value e, i.e., $Y^a = Y^{a,E}$. In fact, consistency is a special case of this recursive substitution. Specifically, the observed $Y = Y^A = Y^{A,E}$, which is our definition of consistency.

We are now ready to provide a definition of interaction within the counterfactual framework. There is interaction between two treatments A and E if the causal effect of A on Y after a joint intervention that set E to 1 differs from the causal effect of A on Y after a joint intervention that set E to 0. For example, there would be an interaction between transplant A and vitamins E if the causal effect of transplant on survival had everybody taken vitamins were different from the causal effect of transplant on survival had nobody taken vitamins.

When the causal effect is measured on the risk difference scale, we say that there is *interaction between A and E on the additive scale* in the population if

$$\Pr\left[Y^{a=1,e=1} = 1\right] - \Pr\left[Y^{a=0,e=1} = 1\right] \neq \Pr\left[Y^{a=1,e=0} = 1\right] - \Pr\left[Y^{a=0,e=0} = 1\right].$$

For example, suppose the causal risk difference for transplant A when everybody receives vitamins, $\Pr\left[Y^{a=1,e=1} = 1\right] - \Pr\left[Y^{a=0,e=1} = 1\right]$, were 0.1, and

that the causal risk difference for transplant A when nobody receives vitamins, $\Pr\left[Y^{a=1,e=0}=1\right]-\Pr\left[Y^{a=0,e=0}=1\right]$, were 0.2. We say that there is interaction between A and E on the additive scale because the risk difference $\Pr\left[Y^{a=1,e=1}=1\right]-\Pr\left[Y^{a=0,e=1}=1\right]$ is less than the risk difference $\Pr\left[Y^{a=1,e=0}=1\right]-\Pr\left[Y^{a=0,e=0}=1\right]$. Using simple algebra, it can be easily shown that this inequality implies that the causal risk difference for vitamins E when everybody receives a transplant, $\Pr\left[Y^{a=1,e=1}=1\right]-\Pr\left[Y^{a=1,e=0}=1\right]$, is also less than the causal risk difference for vitamins E when nobody receives a transplant A, $\Pr\left[Y^{a=0,e=1}=1\right]-\Pr\left[Y^{a=0,e=0}=1\right]$. That is, we can equivalently define interaction between A and E on the additive scale as

$$\Pr\left[Y^{a=1,e=1}=1\right]-\Pr\left[Y^{a=1,e=0}=1\right]\neq\Pr\left[Y^{a=0,e=1}=1\right]-\Pr\left[Y^{a=0,e=0}=1\right].$$

The two inequalities displayed above show that treatments A and E have equal status in the definition of interaction.

Let us now review the difference between interaction and effect modification. As described in the previous chapter, a variable M is a modifier of the effect of A on Y when the average causal effect of A on Y varies across levels of M. Note the concept of effect modification refers to the causal effect of A, not to the causal effect of M. For example, sex was an effect modifier for the effect of heart transplant in Table 4.1, but we never discussed the effect of sex on death. Thus, when we say that M modifies the effect of A we are not considering M and A as variables of equal status, because only A is considered to be a variable on which we could hypothetically intervene. That is, the definition of effect modification involves the counterfactual outcomes Y^a, not the counterfactual outcomes $Y^{a,m}$. In contrast, the definition of interaction between A and E gives equal status to both treatments A and E, as reflected by the two equivalent definitions of interaction shown above. The concept of interaction refers to the joint causal effect of two treatments A and E, and thus involves the counterfactual outcomes $Y^{a,e}$ under a joint intervention.

5.2 Identifying interaction

In previous chapters we have described the conditions that are required to identify the average causal effect of a treatment A on an outcome Y, either in the entire population or in a subset of it. The three key identifying conditions were exchangeability, positivity, and consistency. Because interaction is concerned with the joint effect of two (or more) treatments A and E, identifying interaction requires exchangeability, positivity, and consistency for both treatments.

Suppose that vitamins E were randomly, and unconditionally, assigned by the investigators. Then positivity and consistency hold, and the treated $E=1$ and the untreated $E=0$ are expected to be exchangeable. That is, the risk that would have been observed if all individuals had been assigned to transplant $A=1$ and vitamins $E=1$ equals the risk that would have been observed if all individuals who received $E=1$ had been assigned to transplant $A=1$. Formally, the marginal risk $\Pr\left[Y^{a=1,e=1}=1\right]$ is equal to the conditional risk $\Pr\left[Y^{a=1}=1|E=1\right]$. As a result, we can rewrite the definition of interaction between A and E on the additive scale as

$$\begin{aligned}&\Pr\left[Y^{a=1}=1|E=1\right]-\Pr\left[Y^{a=0}=1|E=1\right]\\&\neq\Pr\left[Y^{a=1}=1|E=0\right]-\Pr\left[Y^{a=0}=1|E=0\right],\end{aligned}$$

Technical Point 5.1

Interaction on the additive and multiplicative scales. The equality of causal risk differences $\Pr\left[Y^{a=1,e=1}=1\right]-\Pr\left[Y^{a=0,e=1}=1\right]=\Pr\left[Y^{a=1,e=0}=1\right]-\Pr\left[Y^{a=0,e=0}=1\right]$ can be rewritten as

$$\Pr\left[Y^{a=1,e=1}=1\right]=\left\{\Pr\left[Y^{a=1,e=0}=1\right]-\Pr\left[Y^{a=0,e=0}=1\right]\right\}+\Pr\left[Y^{a=0,e=1}=1\right].$$

By subtracting $\Pr\left[Y^{a=0,e=0}=1\right]$ from both sides of the equation, we get $\Pr\left[Y^{a=1,e=1}=1\right]-\Pr\left[Y^{a=0,e=0}=1\right]=$

$$\left\{\Pr\left[Y^{a=1,e=0}=1\right]-\Pr\left[Y^{a=0,e=0}=1\right]\right\}+\left\{\Pr\left[Y^{a=0,e=1}=1\right]-\Pr\left[Y^{a=0,e=0}=1\right]\right\}.$$

This equality is another compact way to show that treatments A and E have equal status in the definition of interaction.

When the above equality holds, we say that there is no *interaction between A and E on the additive scale*, and we say that the causal risk difference $\Pr\left[Y^{a=1,e=1}=1\right]-\Pr\left[Y^{a=0,e=0}=1\right]$ is additive because it can be written as the sum of the causal risk differences that measure the effect of A in the absence of E and the effect of E in the absence of A. Conversely, there is interaction between A and E on the additive scale if $\Pr\left[Y^{a=1,e=1}=1\right]-\Pr\left[Y^{a=0,e=0}=1\right]\neq$

$$\left\{\Pr\left[Y^{a=1,e=0}=1\right]-\Pr\left[Y^{a=0,e=0}=1\right]\right\}+\left\{\Pr\left[Y^{a=0,e=1}=1\right]-\Pr\left[Y^{a=0,e=0}=1\right]\right\}.$$

The interaction is *superadditive* if the 'not equal to' ($\neq$) symbol can be replaced by a 'greater than' ($>$) symbol. The interaction is *subadditive* if the 'not equal to' ($\neq$) symbol can be replaced by a 'less than' ($<$) symbol.

Analogously, one can define interaction on the multiplicative scale when the effect measure is the causal risk ratio, rather than the causal risk difference. We say that there is *interaction between A and E on the multiplicative scale* if

$$\frac{\Pr\left[Y^{a=1,e=1}=1\right]}{\Pr\left[Y^{a=0,e=0}=1\right]}\neq\frac{\Pr\left[Y^{a=1,e=0}=1\right]}{\Pr\left[Y^{a=0,e=0}=1\right]}\times\frac{\Pr\left[Y^{a=0,e=1}=1\right]}{\Pr\left[Y^{a=0,e=0}=1\right]}.$$

The interaction is *supermultiplicative* if the 'not equal to' ($\neq$) symbol can be replaced by a 'greater than' ($>$) symbol. The interaction is *submultiplicative* if the 'not equal to' ($\neq$) symbol can be replaced by a 'less than' ($<$) symbol.

which is exactly the definition of modification of the effect of A by E on the additive scale. In other words, when treatment E is randomly assigned, then the concepts of interaction and effect modification coincide. The methods described in Chapter 4 to identify modification of the effect of A by M can now be applied to identify interaction of A and E by simply replacing the effect modifier M by the treatment E.

Now suppose treatment E was not assigned by investigators. To assess the presence of interaction between A and E, one still needs to compute the four marginal risks $\Pr\left[Y^{a,e}=1\right]$. In the absence of marginal randomization, these risks can be computed for both treatments A and E, under the usual identifying assumptions, by standardization or IP weighting conditional on the measured covariates. An equivalent way of conceptualizing this problem follows: rather than viewing A and E as two distinct treatments with two possible levels (1 or 0) each, one can view AE as a combined treatment with four possible levels (11, 01, 10, 00). Under this conceptualization the identification of interaction between two treatments is not different from the identification of the causal effect of one treatment that we have discussed in previous chapters. The same methods, under the same identifiability conditions, can be used. The only difference is that now there is a longer list of values that the treatment of interest can take, and therefore a greater number of counterfactual outcomes.

Sometimes one may be willing to assume (conditional) exchangeability for

treatment A but not for treatment E, e.g., when estimating the causal effect of A in subgroups defined by E in a randomized experiment. In that case, one cannot generally assess the presence of interaction between A and E, but can still assess the presence of effect modification by E. This is so because one does not need any identifying assumptions involving E to compute the effect of A in each of the strata defined by E. In the previous chapter we used the notation M (rather than E) for variables for which we are not willing to make assumptions about exchangeability, positivity, and consistency. For example, we concluded that the effect of transplant A was modified by nationality M, but we never required any identifying assumptions for the effect of M because we were not interested in using our data to compute the causal effect of M on Y. In Section 4.2 we argued on substantive grounds that M is a surrogate effect modifier; that is, M does not act on the outcome and therefore does not interact with A—no action, no interaction. But M is a modifier of the effect of A on Y because M is correlated with (e.g., it is a proxy for) an unidentified variable that actually has an effect on Y and interacts with A. Thus there can be modification of the effect of A by another variable without interaction between A and that variable.

Interaction between A and E without modification of the effect of A by E is also logically possible, though probably rare, because it requires dual effects of A and exact cancellations (VanderWeele 2009).

In the above paragraphs we have argued that a sufficient condition for identifying interaction between two treatments A and E is that exchangeability, positivity, and consistency are all satisfied for the joint treatment (A, E) with the four possible values $(0, 0)$, $(0, 1)$, $(1, 0)$, and $(1, 1)$. Then standardization or IP weighting can be used to estimate the joint effects of the two treatments and thus to evaluate interaction between them. In Part III, we show that this condition is not necessary when the two treatments occur at different times. For the remainder of Part I (except this chapter) and most of Part II, we will focus on the causal effect of a single treatment A.

In Chapter 1 we described deterministic and nondeterministic counterfactual outcomes. Up to here, we used deterministic counterfactuals for simplicity. However, none of the results we have discussed for population causal effects and interactions require deterministic counterfactual outcomes. In contrast, the following section of this chapter only applies in the case that counterfactuals are deterministic. Further, we also assume that treatments and outcomes are dichotomous.

5.3 Counterfactual response types and interaction

Individuals can be classified in terms of their deterministic counterfactual responses. For example, in Table 4.1 (same as Table 1.1), there are four types of people: the "doomed" who will develop the outcome regardless of what treatment they receive (Artemis, Athena, Persephone, Ares), the "immune" who will not develop the outcome regardless of what treatment they receive (Demeter, Hestia, Hera, Hades), the "helped" who will develop the outcome only if untreated (Hebe, Kronos, Poseidon, Apollo, Hermes, Dyonisus), and the "hurt" who will develop the outcome only if treated (Rheia, Leto, Aphrodite, Zeus, Hephaestus, Cyclope). Each combination of counterfactual responses is often referred to as a response pattern or a *response type*. Table 5.1 display the four possible response types.

Table 5.1

Type	$Y^{a=0}$	$Y^{a=1}$
Doomed	1	1
Helped	1	0
Hurt	0	1
Immune	0	0

When considering two dichotomous treatments A and E, there are 16 possible response types because each individual has four counterfactual outcomes, one under each of the four possible joint interventions on treatments A and

E: $(1,1)$, $(0,1)$, $(1,0)$, and $(0,0)$. Table 5.2 shows the 16 response types for two treatments. This section explores the relation between response types and the presence of interaction in the case of two dichotomous treatments A and E and a dichotomous outcome Y.

Table 5.2

	$Y^{a,e}$ for each a,e value			
Type	$1,1$	$0,1$	$1,0$	$0,0$
1	1	1	1	1
2	1	1	1	0
3	1	1	0	1
4	1	1	0	0
5	1	0	1	1
6	1	0	1	0
7	1	0	0	1
8	1	0	0	0
9	0	1	1	1
10	0	1	1	0
11	0	1	0	1
12	0	1	0	0
13	0	0	1	1
14	0	0	1	0
15	0	0	0	1
16	0	0	0	0

Miettinen (1982) described the 16 possible response types under two binary treatments and outcome.

The first type in Table 5.2 has the counterfactual outcome $Y^{a=1,e=1}$ equal to 1, which means that an individual of this type would die if treated with both transplant and vitamins. The other three counterfactual outcomes are also equal to 1, i.e., $Y^{a=1,e=1} = Y^{a=0,e=1} = Y^{a=1,e=0} = Y^{a=0,e=0} = 1$, which means that an individual of this type would also die if treated with (no transplant, vitamins), (transplant, no vitamins), or (no transplant, no vitamins). In other words, neither treatment A nor treatment E has any effect on the outcome of such individual. He would die no matter what joint treatment he is assigned to. Now consider type 16. All the counterfactual outcomes are 0, i.e., $Y^{a=1,e=1} = Y^{a=0,e=1} = Y^{a=1,e=0} = Y^{a=0,e=0} = 0$. Again, neither treatment A nor treatment E has any effect on the outcome of an individual of this type. She would survive no matter what joint treatment she is assigned to. If all individuals in the population were of types 1 and 16, we would say that neither A nor E has any causal effect on Y; the sharp causal null hypothesis would be true for the joint treatment (A, E). As a consequence, the causal effect of A is independent of E, and vice versa.

Let us now focus our attention on types 4, 6, 11, and 13. Individuals of type 4 would only die if treated with vitamins, whether they do or do not receive a transplant, i.e., $Y^{a=1,e=1} = Y^{a=0,e=1} = 1$ and $Y^{a=1,e=0} = Y^{a=0,e=0} = 0$. Individuals of type 13 would only die if not treated with vitamins, whether they do or do not receive a transplant, i.e., $Y^{a=1,e=1} = Y^{a=0,e=1} = 0$ and $Y^{a=1,e=0} = Y^{a=0,e=0} = 1$. Individuals of type 6 would only die if treated with transplant, whether they do or do not receive vitamins, i.e., $Y^{a=1,e=1} = Y^{a=1,e=0} = 1$ and $Y^{a=0,e=1} = Y^{a=0,e=0} = 0$. Individuals of type 11 would only die if not treated with transplant, whether they do or do not receive vitamins, i.e., $Y^{a=1,e=1} = Y^{a=1,e=0} = 0$ and $Y^{a=0,e=1} = Y^{a=0,e=0} = 1$. If all individuals in the population were of types 4, 6, 11, and 13, we would again say that the causal effect of A is independent of E, and vice versa.

Of the 16 possible response types in Table 5.2, we have identified 6 types (numbers $1, 4$, 6, 11,13, 16) with a common characteristic: for an individual with one of those response types, the causal effect of treatment A on the outcome Y is the same regardless of the value of treatment E, and the causal effect of treatment E on the outcome Y is the same regardless of the value of treatment A. In a population in which every individual has one of these 6 response types, the causal effect of treatment A in the presence of treatment E, as measured by the causal risk difference $\Pr\left[Y^{a=1,e=1} = 1\right] - \Pr\left[Y^{a=0,e=1} = 1\right]$, would equal the causal effect of treatment A in the absence of treatment E, as measured by the causal risk difference $\Pr\left[Y^{a=1,e=0} = 1\right] - \Pr\left[Y^{a=0,e=0} = 1\right]$. That is, if all individuals in the population have response types 1, 4, 6, 11, 13 and 16 then there will be no interaction between A and E on the additive scale.

Greenland and Poole (1988) noted that Miettinen's response types were not invariant to recoding of A and E (i.e., switching the labels "0" and "1"). They partitioned the 16 response types of Table 5.2 into these three equivalence classes that are invariant to recoding.

The presence of additive interaction between A and E implies that, for some individuals in the population, the value of their two counterfactual outcomes under $A = a$ cannot be determined without knowledge of the value of E, and vice versa. That is, there must be individuals in at least one of the following three classes:

1. those who would develop the outcome under only one of the four treatment combinations (types 8, 12, 14, and 15 in Table 5.2)

Technical Point 5.2

Monotonicity of causal effects. Consider a setting with a dichotomous treatment A and outcome Y. The value of the counterfactual outcome $Y^{a=0}$ is greater than that of $Y^{a=1}$ only among individuals of the "helped" type. For the other 3 types, $Y^{a=1} \geq Y^{a=0}$ or, equivalently, an individual's counterfactual outcomes are monotonically increasing (i.e., nondecreasing) in a. Thus, when the treatment cannot prevent any individual's outcome (i.e., in the absence of "helped" individuals), all individuals' counterfactual response types are monotonically increasing in a. We then simply say that the causal effect of A on Y is monotonic.

The concept of monotonicity can be generalized to two treatments A and E. The causal effects of A and E on Y are monotonic if every individual's counterfactual outcomes $Y^{a,e}$ are monotonically increasing in both a and e. That is, if there are no individuals with response types $\left(Y^{a=1,e=1}=0, Y^{a=0,e=1}=1\right)$, $\left(Y^{a=1,e=1}=0, Y^{a=1,e=0}=1\right)$, $\left(Y^{a=1,e=0}=0, Y^{a=0,e=0}=1\right)$, and $\left(Y^{a=0,e=1}=0, Y^{a=0,e=0}=1\right)$.

2. those who would develop the outcome under two treatment combinations, with the particularity that the effect of each treatment is exactly the opposite under each level of the other treatment (types 7 and 10)

3. those who would develop the outcome under three of the four treatment combinations (types 2, 3, 5, and 9)

On the other hand, the absence of additive interaction between A and E implies that either no individual in the population belongs to one of the three classes described above, or that there is a perfect cancellation of equal deviations from additivity of opposite sign. Such cancellation would occur, for example, if there were an equal proportion of individuals of types 7 and 10, or of types 8 and 12.

For more on cancellations that result in additivity even when interaction types are present, see Greenland, Lash, and Rothman (2008).

The meaning of the term "interaction" is clarified by the classification of individuals according to their counterfactual response types (see also Fine Point 5.1). We now introduce a tool to conceptualize the causal mechanisms involved in the interaction between two treatments.

5.4 Sufficient causes

The meaning of interaction is clarified by the classification of individuals according to their counterfactual response types. We now introduce a tool to represent the causal mechanisms involved in the interaction between two treatments. Consider again our heart transplant example with a single treatment A. As reviewed in the previous section, some individuals die when they are treated, others when they are not treated, others die no matter what, and others do not die no matter what. This variety of response types indicates that treatment A is not the only variable that determines whether or not the outcome Y occurs.

Take those individuals who were actually treated. Only some of them died, which implies that treatment alone is insufficient to always bring about the outcome. As an oversimplified example, suppose that heart transplant $A = 1$ only results in death in individuals allergic to anesthesia. We refer to the smallest set of background factors that, together with $A = 1$, are sufficient to inevitably produce the outcome as U_1. The simultaneous presence of treatment

Fine Point 5.1

More on counterfactual types and interaction. The classification of individuals by counterfactual response types makes it easier to consider specific forms of interaction. For example, we may be interested in learning whether some individuals will develop the outcome when receiving both treatments $E = 1$ and $A = 1$, but not when receiving only one of the two. That is, whether individuals with counterfactual responses $Y^{a=1,e=1} = 1$ and $Y^{a=0,e=1} = Y^{a=1,e=0} = 0$ (types 7 and 8) exist in the population. VanderWeele and Robins (2007a, 2008) developed a theory of sufficient cause interaction for 2 and 3 treatments, and derived the identifying conditions for synergism that are described here. The following inequality is a sufficient condition for these individuals to exist:

$$\Pr\left[Y^{a=1,e=1} = 1\right] - \left(\Pr\left[Y^{a=0,e=1} = 1\right] + \Pr\left[Y^{a=1,e=0} = 1\right]\right) > 0$$

$$\text{or, equivalently, } \Pr\left[Y^{a=1,e=1} = 1\right] - \Pr\left[Y^{a=0,e=1} = 1\right] > \Pr\left[Y^{a=1,e=0} = 1\right]$$

That is, in an experiment in which treatments A and E are randomly assigned, one can compute the three counterfactual risks in the above inequality, and empirically check that individuals of types 7 and 8 exist.

Because the above inequality is a sufficient but not a necessary condition, it may not hold even if types 7 and 8 exist. In fact this sufficient condition is so strong that it may miss most cases in which these types exist. A weaker sufficient condition for synergism can be used if one knows, or is willing to assume, that receiving treatments A and E cannot prevent any individual from developing the outcome, i.e., if the effects are monotonic (see Technical Point 5.2). In this case, the inequality

$$\Pr\left[Y^{a=1,e=1} = 1\right] - \Pr\left[Y^{a=0,e=1} = 1\right] > \Pr\left[Y^{a=1,e=0} = 1\right] - \Pr\left[Y^{a=0,e=0} = 1\right]$$

is a sufficient condition for the existence of types 7 and 8. In other words, when the effects of A and E are monotonic, the presence of superadditive interaction implies the presence of type 8 (monotonicity rules out type 7). This sufficient condition for synergism under monotonic effects was originally reported by Greenland and Rothman in a previous edition of their book. It is now reported in Greenland, Lash, and Rothman (2008).

In genetic research it is sometimes interesting to determine whether there are individuals of type 8, a form of interaction referred to as *compositional epistasis*. VanderWeele (2010) reviews empirical tests for compositional epistasis.

($A = 1$) and allergy to anesthesia ($U_1 = 1$) is a minimal *sufficient cause* of the outcome Y.

Now take those individuals who were not treated. Again only some of them died, which implies that lack of treatment alone is insufficient to bring about the outcome. As an oversimplified example, suppose that no heart transplant $A = 0$ only results in death if individuals have an ejection fraction less than 20%. We refer to the smallest set of background factors that, together with $A = 0$, are sufficient to produce the outcome as U_2. The simultaneous absence of treatment ($A = 0$) and presence of low ejection fraction ($U_2 = 1$) is another sufficient cause of the outcome Y.

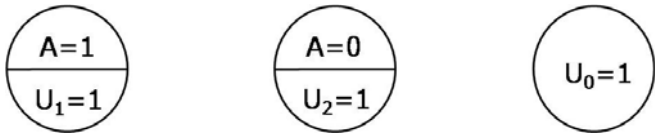
Finally, suppose there are some individuals who have neither U_1 nor U_2 and that would have developed the outcome whether they had been treated or untreated. The existence of these "doomed" individuals implies that there are some other background factors that are themselves sufficient to bring about the outcome. As an oversimplified example, suppose that all individuals with pancreatic cancer at the start of the study will die. We refer to the smallest set of background factors that are sufficient to produce the outcome regardless of treatment status as U_0. The presence of pancreatic cancer ($U_0 = 1$) is another sufficient cause of the outcome Y.

By definition of background factors, the dichotomous variables U cannot be intervened on, and cannot be affected by treatment A.

We described 3 sufficient causes for the outcome: treatment $A = 1$ in the presence of U_1, no treatment $A = 0$ in the presence of U_2, and presence

of U_0 regardless of treatment status. Each sufficient cause has one or more *components*, e.g., $A = 1$ and $U_1 = 1$ in the first sufficient cause. Figure 5.1 represents each sufficient cause by a circle and its components as sections of the circle. The term *sufficient-component causes* is often used to refer to the sufficient causes and their components.

Figure 5.1



The graphical representation of sufficient-component causes helps visualize a key consequence of effect modification: as discussed in Chapter 4, the magnitude of the causal effect of treatment A depends on the distribution of effect modifiers. Imagine two hypothetical scenarios. In the first one, the population includes only 1% of individuals with $U_1 = 1$ (i.e., allergy to anesthesia). In the second one, the population includes 10% of individuals with $U_1 = 1$. The distribution of U_2 and U_0 is identical between these two populations. Now, separately in each population, we conduct a randomized experiment of heart transplant A in which half of the population is assigned to treatment $A = 1$. The average causal effect of heart transplant A on death will be greater in the second population because there are more individuals susceptible to develop the outcome if treated. One of the 3 sufficient causes, $A = 1$ plus $U_1 = 1$, is 10 times more common in the second population than in the first one, whereas the other two sufficient causes are equally frequent in both populations.

The graphical representation of sufficient-component causes also helps visualize an alternative concept of interaction, which is described in the next section. First we need to describe the sufficient causes for two treatments A and E. Consider our vitamins and heart transplant example. We have already described 3 sufficient causes of death: presence/absence of A (or E) is irrelevant, presence of transplant A regardless of vitamins E, and absence of transplant A regardless of vitamins E. In the case of two treatments we need to add 2 more ways to die: presence of vitamins E regardless of transplant A, and absence of vitamins regardless of transplant A. We also need to add four more sufficient causes to accommodate those who would die only under certain combination of values of the treatments A and E. Thus, depending on which background factors are present, there are 9 possible ways to die:

Greenland and Poole (1988) first enumerated these 9 sufficient causes.

1. by treatment A (treatment E is irrelevant)
2. by the absence of treatment A (treatment E is irrelevant)
3. by treatment E (treatment A is irrelevant)
4. by the absence of treatment E (treatment A is irrelevant)
5. by both treatments A and E
6. by treatment A and the absence of E
7. by treatment E and the absence of A
8. by the absence of both A and E
9. by other mechanisms (both treatments A and E are irrelevant)

In other words, there are 9 possible sufficient causes with treatment components $A = 1$ only, $A = 0$ only, $E = 1$ only, $E = 0$ only, $A = 1$ and $E = 1$, $A = 1$ and $E = 0$, $A = 0$ and $E = 1$, $A = 0$ and $E = 0$, and neither A or E matter. Each of these sufficient causes includes a set of background factors from U_1,..., U_8 and U_0. Figure 5.2 represents the 9 sufficient-component causes for two treatments A and E.

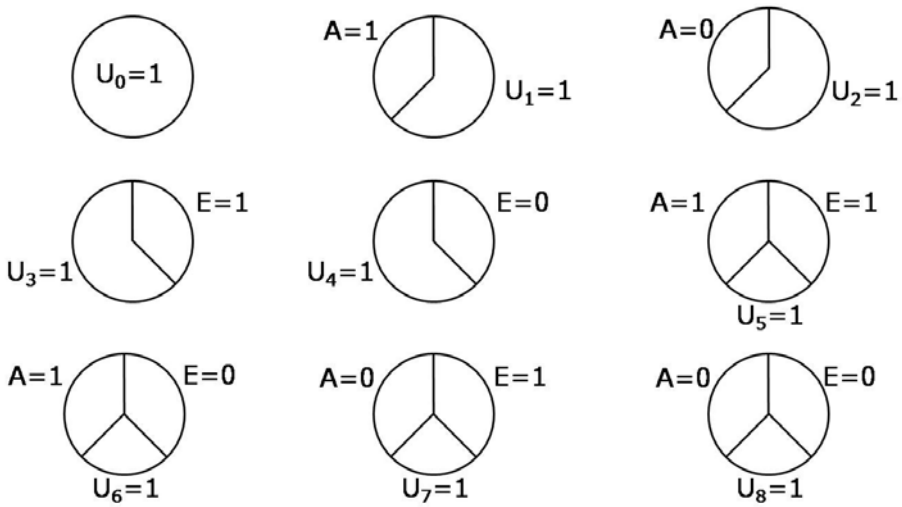


Figure 5.2

This graphical representation of sufficient-component causes is often referred to as "the causal pies."

Not all 9 sufficient-component causes for a dichotomous outcome and two treatments exist in all settings. For example, if receiving vitamins $E = 1$ does not kill any individual, regardless of her treatment A, then the 3 sufficient causes with the component $E = 1$ will not be present. The existence of those 3 sufficient causes would mean that some individuals (e.g., those with $U_3 = 1$) would be killed by receiving vitamins ($E = 1$), that is, their death would be prevented by not giving vitamins ($E = 0$) to them. Also note that some of the background factors U may be unnecessary. For example, if lack of vitamins and transplant were sufficient to bring about the outcome by themselves in some people, then the background factor U_8 in the last sufficient-component cause could be omitted.

5.5 Sufficient cause interaction

The colloquial use of the term "interaction between treatments A and E" evokes the existence of some causal mechanism by which the two treatments work together (i.e., "interact") to produce certain outcome. Interestingly, the definition of interaction within the counterfactual framework does not require any knowledge about those mechanisms nor even that the treatments work together (see Fine Point 5.3). In our example of vitamins E and heart transplant A, we said that there is an interaction between the treatments A and E if the causal effect of A when everybody receives E is different from the causal effect of A when nobody receives E. That is, interaction is defined by the contrast of counterfactual quantities, and can therefore be identified by conducting an ideal randomized experiment in which the conditions of exchangeability, positivity, and consistency hold for both treatments A and E.

Fine Point 5.2

From counterfactuals to sufficient-component causes, and vice versa. There is a correspondence between the counterfactual response types and the sufficient component causes. In the case of a dichotomous treatment and outcome, suppose an individual has none of the background factors U_0, U_1, U_2. She will have an "immune" response type because she lacks the components necessary to complete all of the sufficient causes, whether she is treated or not. The table below displays the mapping between response types and sufficient-component causes in the case of one treatment A.

Type	$Y^{a=0}$	$Y^{a=1}$	Component causes
Doomed	1	1	$U_0 = 1$ or $\{U_1 = 1$ and $U_2 = 1\}$
Helped	1	0	$U_0 = 0$ and $U_1 = 0$ and $U_2 = 1$
Hurt	0	1	$U_0 = 0$ and $U_1 = 1$ and $U_2 = 0$
Immune	0	0	$U_0 = 0$ and $U_1 = 0$ and $U_2 = 0$

A particular combination of component causes corresponds to one and only one counterfactual type. However, a particular response type may correspond to several combinations of component causes. For example, individuals of the "doomed" type may have any combination of component causes including $U_0 = 1$, no matter what the values of U_1 and U_2 are, or any combination including $\{U_1 = 1$ and $U_2 = 1\}$.

Sufficient-component causes can also be used to provide a mechanistic description of exchangeability $Y^a \coprod A$. For a dichotomous treatment and outcome, exchangeability means that the proportion of individuals who would have the outcome under treatment, and under no treatment, is the same in the treated $A = 1$ and the untreated $A = 0$. That is, $\Pr[Y^{a=1} = 1|A = 1] = \Pr[Y^{a=1} = 1|A = 0]$ and $\Pr[Y^{a=0} = 1|A = 1] = \Pr[Y^{a=0} = 1|A = 0]$.

Now the individuals who would develop the outcome if treated are the "doomed" and the "hurt", that is, those with $U_0 = 1$ or $U_1 = 1$. The individuals who would get the outcome if untreated are the "doomed" and the "helped", that is, those with $U_0 = 1$ or $U_2 = 1$. Therefore there will be exchangeability if the proportions of "doomed" + "hurt" and of "doomed" + "helped" are equal in the treated and the untreated. That is, exchangeability for a dichotomous treatment and outcome can be expressed in terms of sufficient-component causes as $\Pr[U_0 = 1$ or $U_1 = 1|A = 1] = \Pr[U_0 = 1$ or $U_1 = 1|A = 0]$ and $\Pr[U_0 = 1$ or $U_2 = 1|A = 1] = \Pr[U_0 = 1$ or $U_2 = 1|A = 0]$.

For additional details see Greenland and Brumback (2002), Flanders (2006), and VanderWeele and Hernán (2006). Some of the above results were generalized to the case of two or more dichotomous treatments by VanderWeele and Robins (2008).

There is no need to contemplate the causal mechanisms (physical, chemical, biologic, sociological...) that underlie the presence of interaction.

This section describes a second concept of interaction that perhaps brings us one step closer to the causal mechanisms by which treatments A and E bring about the outcome. This second concept of interaction is not based on counterfactual contrasts but rather on sufficient-component causes, and thus we refer to it as interaction within the sufficient-component-cause framework or, for brevity, *sufficient cause interaction*.

A sufficient cause interaction between A and E exists in the population if A and E occur together in a sufficient cause. For example, suppose individuals with background factors $U_5 = 1$ will develop the outcome when jointly receiving vitamins ($E = 1$) and heart transplant ($A = 1$), but not when receiving only one of the two treatments. Then a sufficient cause interaction between A and E exists if there exists an individual with $U_5 = 1$. It then follows that if there exists an individual with counterfactual responses $Y^{a=1,e=1} = 1$ and $Y^{a=0,e=1} = Y^{a=1,e=0} = 0$, a sufficient cause interaction between A and E is present.

Sufficient cause interactions can be synergistic or antagonistic. There is *synergism* between treatment A and treatment E when $A = 1$ and $E = 1$

Fine Point 5.3

Biologic interaction. In epidemiologic discussions, sufficient cause interaction is commonly referred to as biologic interaction (Rothman et al, 1980). This choice of terminology might seem to imply that, in biomedical applications, there exist biological mechanisms through which two treatments A and E act on each other in bringing about the outcome. However, this may not be necessarily the case as illustrated by the following example proposed by VanderWeele and Robins (2007a).

Suppose A and E are the two alleles of a gene that produces an essential protein. Individuals with a deleterious mutation in both alleles ($A = 1$ and $E = 1$) will lack the essential protein and die within a week after birth, whereas those with a mutation in none of the alleles (i.e., $A = 0$ and $E = 0$) or in only one of the alleles (i.e., $A = 0$ and $E = 1$, $A = 1$ and $E = 0$) will have normal levels of the protein and will survive. We would say that there is synergism between the alleles A and E because there exists a sufficient component cause of death that includes $A = 1$ and $E = 1$. That is, both alleles work together to produce the outcome. However, it might be argued that they do not physically act on each other and thus that they do not interact in any biological sense.

are present in the same sufficient cause, and *antagonism* between treatment A and treatment E when $A = 1$ and $E = 0$ (or $A = 0$ and $E = 1$) are present in the same sufficient cause. Alternatively, one can think of antagonism between treatment A and treatment E as synergism between treatment A and no treatment E (or between no treatment A and treatment E).

Unlike the counterfactual definition of interaction, sufficient cause interaction makes explicit reference to the causal mechanisms involving the treatments A and E. One could then think that identifying the presence of sufficient cause interaction requires detailed knowledge about these causal mechanisms. It turns out that this is not always the case: sometimes we can conclude that sufficient cause interaction exists even if we lack any knowledge whatsoever about the sufficient causes and their components. Specifically, if the inequalities in Fine Point 5.1 hold, then there exists synergism between A and E. That is, one can empirically check that synergism is present without ever giving any thought to the causal mechanisms by which A and E work together to bring about the outcome. This result is not that surprising because of the correspondence between counterfactual response types and sufficient causes (see Fine Point 5.2), and because the above inequality is a sufficient but not a necessary condition, i.e., the inequality may not hold even if synergism exists.

Rothman (1976) described the concepts of synergism and antagonism within the sufficient-component-cause framework.

5.6 Counterfactuals or sufficient-component causes?

The sufficient-component-cause framework and the counterfactual (potential outcomes) framework address different questions. The sufficient component cause model considers sets of actions, events, or states of nature which together inevitably bring about the outcome under consideration. The model gives an account of the causes of a particular effect. It addresses the question, "Given a particular effect, what are the various events which might have been its cause?" The potential outcomes or counterfactual model focuses on one particular cause or intervention and gives an account of the various effects of that cause. In contrast to the sufficient component cause framework, the potential outcomes framework addresses the question, "What would have occurred if a particular factor were intervened upon and thus set to a different level than it in fact

A counterfactual framework of causation was already hinted by Hume (1748).

Technical Point 5.3

Monotonicity of causal effects and sufficient causes. When treatment A and E have monotonic effects, then some sufficient causes are guaranteed not to exist. For example, suppose that cigarette smoking ($A = 1$) never prevents heart disease, and that physical inactivity ($E = 1$) never prevents heart disease. Then no sufficient causes including either $A = 0$ or $E = 0$ can be present. This is so because, if a sufficient cause including the component $A = 0$ existed, then some individuals (e.g., those with $U_2 = 1$) would develop the outcome if they were unexposed ($A = 0$) or, equivalently, the outcome could be prevented in those individuals by treating them ($A = 1$). The same rationale applies to $E = 0$. The sufficient component causes that cannot exist when the effects of A and E are monotonic are crossed out in Figure 5.3.

was?" Unlike the sufficient component cause framework, the counterfactual framework does not require a detailed knowledge of the mechanisms by which the factor affects the outcome.

The counterfactual approach addresses the question "what happens?" The sufficient-component-cause approach addresses the question "how does it happen?" For the contents of this book—conditions and methods to estimate the average causal effects of hypothetical interventions—the counterfactual framework is the natural one. The sufficient-component-cause framework is helpful to think about the causal mechanisms at work in bringing about a particular outcome. Sufficient-component causes have a rightful place in the teaching of causal inference because they help understand key concepts like the dependence of the magnitude of causal effects on the distribution of background factors (effect modifiers), and the relationship between effect modification, interaction, and synergism.

The sufficient-component-cause framework was developed in philosophy by Mackie (1965). He introduced the concept of *INUS* condition for Y: an *I*nsufficient but *N*ecessary part of a condition which is itself *U*nnecessary but exclusively *S*ufficient for Y.

Though the sufficient-component-cause framework is useful from a pedagogic standpoint, its relevance to actual data analysis is yet to be determined. In its classical form, the sufficient-component-cause framework is deterministic, its conclusions depend on the coding on the outcome, and is by definition limited to dichotomous treatments and outcomes (or to variables that can be recoded as dichotomous variables). This limitation practically rules out the consideration of any continuous factors, and restricts the applicability of the framework to contexts with a small number of dichotomous factors. However, recent extensions of the sufficient-component-cause framework to stochastic settings and to categorical and ordinal treatments may lead to an increased application of this approach to realistic data analysis. Finally, even allowing for recent extensions of the sufficient-component-cause framework, we may rarely have the large amount of data needed to study the fine distinctions it makes.

To estimate causal effects more generally, the counterfactual framework will likely continue to be the one most often employed. Some apparently alternative frameworks—causal diagrams, decision theory—are essentially equivalent to the counterfactual framework, as described in the next chapter.

Fine Point 5.4

More on the attributable fraction. Fine Point 3.1 defined the excess fraction for treatment A as the proportion of cases attributable to treatment A in a particular population, and described an example in which the excess fraction for A was 75%. That is, 75% of the cases would not have occurred if everybody had received treatment $a = 0$ rather than their observed treatment A. Now consider a second treatment E. Suppose that the excess fraction for E is 50%. Does this mean that a joint intervention on A and E could prevent 125% $(75\% + 50\%)$ of the cases? Of course not.

Clearly the excess fraction cannot exceed 100% for a single treatment (either A or E). Similarly, it should be clear that the excess fraction for any joint intervention on A and E cannot exceed 100%. That is, if we were allowed to intervene in any way we wish (by modifying A, E, or both) in a population, we could never prevent a fraction of disease greater than 100%. In other words, no more than 100% of the cases can be attributed to the lack of certain intervention, whether single or joint. But then why is the sum of excess fractions for two single treatments greater than 100%? The sufficient-component-cause framework helps answer this question.

As an example, suppose that Zeus had background factors $U_5 = 1$ (and none of the other background factors) and was treated with both $A = 1$ and $E = 1$. Zeus would not have been a case if either treatment A or treatment E had been withheld. Thus Zeus is counted as a case prevented by an intervention that sets $a = 0$, i.e., Zeus is part of the 75% of cases attributable to A. But Zeus is also counted as a case prevented by an intervention that sets $e = 0$, i.e., Zeus is part of the 50% of cases attributable to E. No wonder the sum of the excess fractions for A and E exceeds 100%: some individuals like Zeus are counted twice!

The sufficient-component-cause framework shows that it makes little sense to talk about the fraction of disease attributable to A and E separately when both may be components of the same sufficient cause. For example, the discussion about the fraction of disease attributable to either genes or environment is misleading. Consider the mental retardation caused by phenylketonuria, a condition that appears in genetically susceptible individuals who eat certain foods. The excess fraction for those foods is 100% because all cases can be prevented by removing the foods from the diet. The excess fraction for the genes is also 100% because all cases would be prevented if we could replace the susceptibility genes. Thus the causes of mental retardation can be seen as either 100% genetic or 100% environmental. See Rothman, Greenland, and Lash (2008) for further discussion.

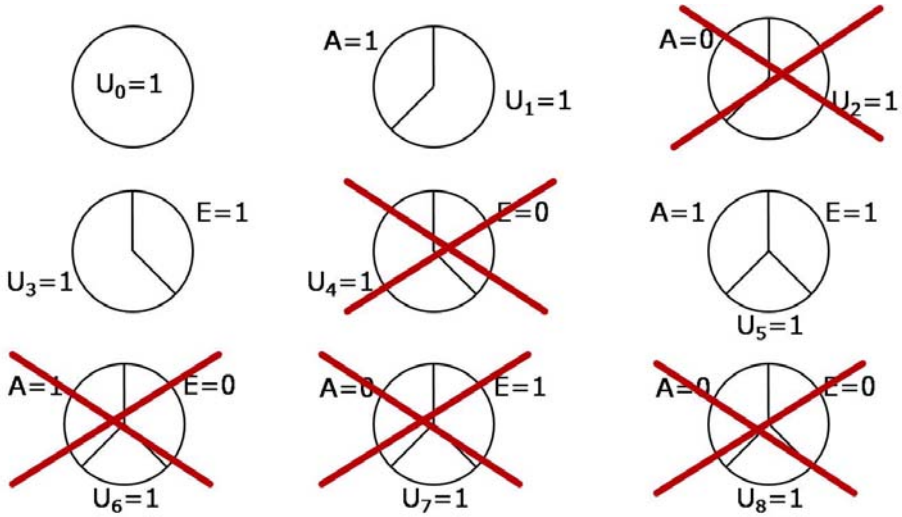


Figure 5.3

Chapter 6
GRAPHICAL REPRESENTATION OF CAUSAL EFFECTS

Causal inference generally requires expert knowledge and untestable assumptions about the causal network linking treatment, outcome, and other variables. Earlier chapters focused on the conditions and methods to compute causal effects in oversimplified scenarios (e.g., the causal effect of your looking up on other pedestrians' behavior, an idealized heart transplant study). The goal was to provide a gentle introduction to the ideas underlying the more sophisticated approaches that are required in realistic settings. Because the scenarios we considered were so simple, there was really no need to make the causal network explicit. As we start to turn our attention towards more complex situations, however, it will become crucial to be explicit about what we know and what we assume about the variables relevant to our particular causal inference problem.

This chapter introduces a graphical tool to represent our qualitative expert knowledge and a priori assumptions about the causal structure of interest. By summarizing knowledge and assumptions in an intuitive way, graphs help clarify conceptual problems and enhance communication among investigators. The use of graphs in causal inference problems makes it easier to follow a sensible advice: draw your assumptions before your conclusions.

6.1 Causal diagrams

Comprehensive books on this subject have been written by Pearl (2009) and Spirtes, Glymour and Scheines (2000).

This chapter describes graphs, which we will refer to as causal diagrams, to represent key causal concepts. The modern theory of diagrams for causal inference arose within the disciplines of computer science and artificial intelligence. This and the next three chapters are focused on problem conceptualization via causal diagrams.

Take a look at the graph in Figure 6.1. It comprises three nodes representing random variables (L, A, Y) and three edges (the arrows). We adopt the convention that time flows from left to right, and thus L is temporally prior to A and Y, and A is temporally prior to Y. As in previous chapters, L, A, and Y represent disease severity, heart transplant, and death, respectively.

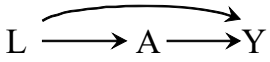


Figure 6.1

The presence of an arrow pointing from a particular variable V to another variable W indicates either that we know there is a direct causal effect (i.e., an effect not mediated through any other variables on the graph) for at least one individual, or that we are unwilling to assume such individual causal effects do not exist. Alternatively, the lack of an arrow means that we know, or are willing to assume, that V has no direct causal effect on W for any individual in the population. For example, in Figure 6.1, the arrow from L to A means that either we know that disease severity affects the probability of receiving a heart transplant or that we are not willing to assume otherwise. A standard causal diagram does not distinguish whether an arrow represents a harmful effect or a protective effect. Furthermore, if, as in figure 6.1, a variable (here, Y) has two causes, the diagram does not encode how the two causes interact.

Causal diagrams like the one in Figure 6.1 are known as *directed acyclic graphs*, which is commonly abbreviated as DAGs. "Directed" because the edges imply a direction: because the arrow from L to A is into A, L may cause A, but not the other way around. "Acyclic" because there are no cycles: a variable cannot cause itself, either directly or through another variable.

Technical Point 6.1

Causal directed acyclic graphs. We define a directed acyclic graph (DAG) G to be a graph whose nodes (vertices) are random variables $V = (V_1, \ldots, V_M)$ with directed edges (arrows) and no directed cycles. We use PA_m to denote the parents of V_m, i.e., the set of nodes from which there is a direct arrow into V_m. The variable V_m is a descendant of V_j (and V_j is an ancestor of V_m) if there is a sequence of nodes connected by edges between V_j and V_m such that, following the direction indicated by the arrows, one can reach V_m by starting at V_j. For example, consider the DAG in Figure 6.1. In this DAG, $M = 3$ and we can choose $V_1 = L$, $V_2 = A$, and $V_3 = Y$; the parents PA_3 of $V_3 = Y$ are (L, A). We will adopt the notational convention that if $m > j$, V_m is not an ancestor of V_j.

A causal DAG is a DAG in which 1) the lack of an arrow from node V_j to V_m can be interpreted as the absence of a direct causal effect of V_j on V_m (relative to the other variables on the graph), 2) all common causes, even if unmeasured, of any pair of variables on the graph are themselves on the graph, and 3) any variable is a cause of its descendants.

Causal DAGs are of no practical use unless we make an assumption linking the causal structure represented by the DAG to the data obtained in a study. This assumption, referred to as the causal Markov assumption, states that, conditional on its direct causes, a variable V_j is independent of any variable for which it is not a cause. That is, conditional on its parents, V_j is independent of its non-descendants. This latter statement is mathematically equivalent to the statement that the density $f(V)$ of the variables V in DAG G satisfies the Markov factorization

$$f(v) = \prod_{j=1}^{M} f(v_j \mid pa_j) \ .$$

Directed acyclic graphs have applications other than causal inference. Here we focus on *causal* directed acyclic graphs. Informally, a directed acyclic graph is causal if the common causes of any pair of variables in the graph are also in the graph. For a formal definition of causal directed acyclic graphs, see Technical Point 6.1.

For example, suppose in our study individuals are randomly assigned to heart transplant A with a probability that depends on the severity of their disease L. Then L is a common cause of A and Y, and needs to be included in the graph, as shown in the causal diagram in Figure 6.1. Now suppose in our study individuals are randomly assigned to heart transplant with the same probability regardless of their disease severity. Then L is not a common cause of A and Y and need not be included in the causal diagram. Figure 6.1 represents a conditionally randomized experiment, whereas Figure 6.2 represents a marginally randomized experiment.

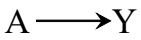


Figure 6.2

Figure 6.1 may also represent an observational study. Specifically, Figure 6.1 represents an observational study in which we are willing to assume that the assignment of heart transplant A depends on disease severity L *and on no other causes of* Y. Otherwise, those causes of Y, even if unmeasured, would need to be included in the diagram, as they would be common causes of A and Y. In the next chapter we will describe how the willingness to consider Figure 6.1 as the causal diagram for an observational study is the graphic translation of the assumption of conditional exchangeability given L, $Y^a \perp\!\!\!\perp A|L$ for all a.

Many people find the graphical approach to causal inference easier to use and more intuitive than the counterfactual approach. However, the two approaches are intimately linked. Specifically, associated with each graph is an underlying counterfactual model (see Technical Point 6.2). It is this model that provides the mathematical justification for the heuristic, intuitive graphical methods we now describe. However, conventional causal diagrams do not

Technical Point 6.2

Counterfactual models associated with a causal DAG. A causal DAG G represents an underlying counterfactual model. To provide a formal definition of the counterfactual model represented by a DAG G, we use the following notation. For any random variable W, let $\mathcal{W}$ denote the support (i.e., the set of possible values w) of W. For any set of ordered variables $W_1, \ldots, W_m$, define $\overline{w}_m = (w_1, \ldots, w_m)$. Let R denote any subset of variables in V and let r be a value of R. Then V_m^r denotes the counterfactual value of V_m when R is set to r.

A nonparametric structural equation model (NPSEM) represented by a DAG G with vertex set V assumes the existence of unobserved random variables (errors) ϵ_m and deterministic unknown functions $f_m(pa_m, \epsilon_m)$ such that $V_1 = f_1(\epsilon_1)$ and the one-step ahead counterfactual $V_m^{\overline{v}_{m-1}} \equiv V_m^{pa_m}$ is given by $f_m(pa_m, \epsilon_m)$. That is, only the parents of V_m have a direct effect on V_m relative to the other variables on G. Both the factual variable V_m and the counterfactuals V_m^r for any $R \subset V$ are obtained recursively from V_1 and $V_j^{\overline{v}_{j-1}}$, $m \geq j > 1$. For example, $V_3^{v_1} = V_3^{v_1, V_2^{v_1}}$, i.e., the counterfactual value $V_3^{v_1}$ of V_3 when V_1 is set to v_1 is the one-step ahead counterfactual $V_3^{v_1, v_2}$ with v_2 equal to the counterfactual value $V_2^{v_1}$ of V_2. Similarly, $V_3 = V_3^{V_1, V_2^{V_1}}$ and $V_3^{v_1, v_4} = V_3^{v_1}$ because V_4 is not a cause of V_3.

Robins (1986) called this NPSEM a finest causally interpreted structural tree graph (FCISTGs). Pearl (2000) showed how to represent this model with a DAG under the assumption that every variable on the graph is subject to intervention with well-defined causal effects. Robins (1986) also proposed more realistic CISTGs in which only a subset of the variables are subject to intervention. For expositional purposes, we will assume that every variable can be intervened on, even though the statistical methods considered here do not actually require this assumption.

A FCISTG model does not imply that the causal Markov assumption holds; additional statistical independence assumptions are needed. For example, Pearl (2000) assumed an NPSEM in which all error terms ϵ_m are mutually independent. We refer to Pearl's model with independent errors as an NPSEM-IE. In contrast, Robins (1986) only assumed that the one-step ahead counterfactuals $V_m^{\overline{v}_{m-1}} = f_m(pa_m, \epsilon_m)$ and $V_j^{\overline{v}_{j-1}} = f_j(pa_j, \epsilon_j)$, $j < m$, are jointly independent when $\overline{v}_{j-1}$ is a subvector of the $\overline{v}_{m-1}$, and referred to this as the finest fully randomized causally interpreted structured tree graph (FFRCISTG) model, which was introduced in Chapter 2. Robins (1986) showed this assumption implies that the causal Markov assumption holds. An NPSEM-IE is an FFRCISTGs but not vice-versa because an NPSEM-IE makes stronger assumptions than an FFRCISTG (Robins and Richardson 2010).

A DAG represents an NPSEM but we need to specify which type. For example, the DAG in Figure 6.2 may correspond to either an NPSEM-IE that implies full exchangeability $\left(Y^{a=0}, Y^{a=1}\right) \perp\!\!\!\perp A$, or to an FFRCISTG that only implies marginal exchangeability $Y^a \perp\!\!\!\perp A$ for both $a = 0$ and $a = 1$. In this book we assume that DAGs represent FFRCISTGs.

Richardson and Robins (2013) developed the Single World Intervention Graph (SWIG).

include the underlying counterfactual variables on the graph. Therefore the link between graphs and counterfactuals has remained traditionally hidden. An advanced type of causal directed acyclic graph—the Single World Intervention Graph (SWIG)—seamlessly unifies the counterfactual and graphical approaches to causal inference by explicitly including the counterfactual variables on the graph. We defer the introduction of SWIGs until Chapter 7 as the material covered in this chapter serves as a necessary prerequisite.

Causal diagrams are a simple way to encode our subject-matter knowledge, and our assumptions, about the qualitative causal structure of a problem. But, as described in the next sections, causal diagrams also encode information about potential associations between the variables in the causal network. It is precisely this simultaneous representation of association and causation that makes causal diagrams such an attractive tool. What follows is an informal introduction to graphic rules to infer associations from causal diagrams. Our emphasis is on conceptual insight rather than on formal rigor.

6.2 Causal diagrams and marginal independence

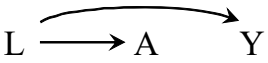


Figure 6.3

Consider the following two examples. First, suppose you know that aspirin use A has a preventive causal effect on the risk of heart disease Y, i.e., $\Pr[Y^{a=1} = 1] \neq \Pr[Y^{a=0} = 1]$. The causal diagram in Figure 6.2 is the graphical translation of this knowledge for an experiment in which aspirin A is randomly, and unconditionally, assigned. Second, suppose you know that carrying a lighter A has no causal effect (causative or preventive) on anyone's risk of lung cancer Y, i.e., $\Pr[Y^{a=1} = 1] = \Pr[Y^{a=0} = 1]$, and that cigarette smoking L has a causal effect on both carrying a lighter A and lung cancer Y. The causal diagram in Figure 6.3 is the graphical translation of this knowledge. The lack of an arrow between A and Y indicates that carrying a lighter does not have a causal effect on lung cancer; L is depicted as a common cause of A and Y.

To draw Figures 6.2 and 6.3 we only used your knowledge about the causal relations among the variables in the diagram but, interestingly, these causal diagrams also encode information about the expected associations (or, more exactly, the lack of them) among the variables in the diagram. We now argue heuristically that, in general, the variables A and Y will be associated in both Figure 6.2 and 6.3, and describe key related results from causal graphs theory.

Take first the randomized experiment represented in Figure 6.2. Intuitively one would expect that two variables A and Y linked only by a causal arrow would be associated. And that is exactly what causal graphs theory shows: when one knows that A has a causal effect on Y, as in Figure 6.2, then one should also generally expect A and Y to be associated. This is of course consistent with the fact that, in an ideal randomized experiment with unconditional exchangeability, causation $\Pr[Y^{a=1} = 1] \neq \Pr[Y^{a=0} = 1]$ implies association $\Pr[Y = 1|A = 1] \neq \Pr[Y = 1|A = 0]$, and vice versa. A heuristic that captures the causation-association correspondence in causal diagrams is the visualization of the paths between two variables as pipes or wires through which association flows. Association, unlike causation, is a symmetric relationship between two variables; thus, when present, association flows between two variables regardless of the direction of the causal arrows. In Figure 6.2 one could equivalently say that the association flows from A to Y or from Y to A.

A path between two variables R and S in a DAG is a route that connects R and S by following a sequence of (nonintersecting) edges. A path is causal if it consists entirely of edges with their arrows pointing in the same direction. Otherwise it is noncausal.

Now let us consider the observational study represented in Figure 6.3. We know that carrying a lighter A has no causal effect on lung cancer Y. The question now is whether carrying a lighter A is associated with lung cancer Y. That is, we know that $\Pr[Y^{a=1} = 1] = \Pr[Y^{a=0} = 1]$ but is it also true that $\Pr[Y = 1|A = 1] = \Pr[Y = 1|A = 0]$? To answer this question, imagine that a naive investigator decides to study the effect of carrying a lighter A on the risk of lung cancer Y (we do know that there is no effect but this is unknown to the investigator). He asks a large number of people whether they are carrying lighters and then records whether they are diagnosed with lung cancer during the next 5 years. Hera is one of the study participants. We learn that Hera is carrying a lighter. But if Hera is carrying a lighter ($A = 1$), then it is more likely that she is a smoker ($L = 1$), and therefore she has a greater than average risk of developing lung cancer ($Y = 1$). We then intuitively conclude that A and Y are expected to be associated because the cancer risk in those carrying a lighter ($A = 1$) is different from the cancer risk in those not carrying a lighter ($A = 0$), or $\Pr[Y = 1|A = 1] \neq \Pr[Y = 1|A = 0]$. In other words, having information about the treatment A improves our ability to predict the outcome Y, even though A does not have a causal effect on Y. The investigator will make a mistake if he concludes that A has a causal effect on Y just because A and Y are associated. Causal graphs theory again confirms our intuition. In

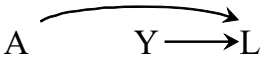


Figure 6.4

graphic terms, A and Y are associated because there is a flow of association from A to Y (or, equivalently, from Y to A) through the common cause L.

Let us now consider a third example. Suppose you know that certain genetic haplotype A has no causal effect on anyone's risk of becoming a cigarette smoker Y, i.e., $\Pr[Y^{a=1} = 1] = \Pr[Y^{a=0} = 1]$, and that both the haplotype A and cigarette smoking Y have a causal effect on the risk of heart disease L. The causal diagram in Figure 6.4 is the graphical translation of this knowledge. The lack of an arrow between A and Y indicates that the haplotype does not have a causal effect on cigarette smoking, and L is depicted as a common effect of A and Y. The common effect L is referred to as a *collider* on the path $A - L - Y$ because two arrowheads collide on this node.

Again the question is whether A and Y are associated. To answer this question, imagine that another investigator decides to study the effect of haplotype A on the risk of becoming a cigarette smoker Y (we do know that there is no effect but this is unknown to the investigator). He makes genetic determinations on a large number of children, and then records whether they end up becoming smokers. Apollo is one of the study participants. We learn that Apollo does not have the haplotype ($A = 0$). Is he more or less likely to become a cigarette smoker ($Y = 1$) than the average person? Learning about the haplotype A does not improve our ability to predict the outcome Y because the risk in those with ($A = 1$) and without ($A = 0$) the haplotype is the same, or $\Pr[Y = 1|A = 1] = \Pr[Y = 1|A = 0]$. In other words, we would intuitively conclude that A and Y are not associated, i.e., A and Y are independent or $A \perp\!\!\!\perp Y$. The knowledge that both A and Y cause heart disease L is irrelevant when considering the association between A and Y. Causal graphs theory again confirms our intuition because it says that colliders, unlike other variables, block the flow of association along the path on which they lie. Thus A and Y are independent because the only path between them, $A \rightarrow L \leftarrow Y$, is blocked by the collider L.

In summary, two variables are (marginally) associated if one causes the other, or if they share common causes. Otherwise they will be (marginally) independent. The next section explores the conditions under which two variables A and Y may be independent conditionally on a third variable L.

6.3 Causal diagrams and conditional independence

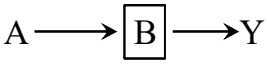


Figure 6.5

We now revisit the settings depicted in Figures 6.2, 6.3, and 6.4 to discuss the concept of conditional independence in causal diagrams.

According to Figure 6.2, we expect aspirin A and heart disease Y to be associated because aspirin has a causal effect on heart disease. Now suppose we obtain an additional piece of information: aspirin A affects the risk of heart disease Y because it reduces platelet aggregation B. This new knowledge is translated into the causal diagram of Figure 6.5 that shows platelet aggregation B (1: high, 0: low) as a mediator of the effect of A on Y.

Once a third variable is introduced in the causal diagram we can ask a new question: is there an association between A and Y within levels of (conditional on) B? Or, equivalently: when we already have information on B, does information about A improve our ability to predict Y? To answer this question, suppose data were collected on A, B, and Y in a large number of individuals, and that we restrict the analysis to the subset of individuals with low platelet aggregation ($B = 0$). The square box placed around the node B in Figure 6.5

represents this restriction. (We would also draw a box around B if the analysis were restricted to the subset of individuals with $B = 1$.)

Because no conditional independences are expected in complete causal diagrams (those in which all possible arrows are present), it is often said that information about associations is in the missing arrows.

Individuals with low platelet aggregation ($B = 0$) have a lower than average risk of heart disease. Now take one of these individuals. Regardless of whether the individual was treated ($A = 1$) or untreated ($A = 0$), we already knew that he has a lower than average risk because of his low platelet aggregation. In fact, because aspirin use affects heart disease risk *only* through platelet aggregation, learning an individual's treatment status does not contribute any additional information to predict his risk of heart disease. Thus, in the subset of individuals with $B = 0$, treatment A and outcome Y are not associated. (The same informal argument can be made for individuals in the group with $B = 1$.) Even though A and Y are marginally associated, A and Y are conditionally independent (unassociated) given B because the risk of heart disease is the same in the treated and the untreated within levels of B: $\Pr[Y = 1|A = 1, B = b] = \Pr[Y = 1|A = 0, B = b]$ for all b. That is, $A \perp\!\!\!\perp Y|B$. Graphically, we say that a box placed around variable B blocks the flow of association through the path $A \rightarrow B \rightarrow Y$.

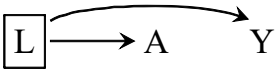


Figure 6.6

Let us now return to Figure 6.3. We concluded in the previous section that carrying a lighter A was associated with the risk of lung cancer Y because the path $A \leftarrow L \rightarrow Y$ was open to the flow of association from A to Y. The question we ask now is whether A is associated with Y conditional on L. This new question is represented by the box around L in Figure 6.6. Suppose the investigator restricts the study to nonsmokers ($L = 1$). In that case, learning that an individual carries a lighter ($A = 1$) does not help predict his risk of lung cancer ($Y = 1$) because the entire argument for better prediction relied on the fact that people carrying lighters are more likely to be smokers. This argument is irrelevant when the study is restricted to nonsmokers or, more generally, to people who smoke with a particular intensity. Even though A and Y are marginally associated, A and Y are conditionally independent given L because the risk of lung cancer is the same in the treated and the untreated within levels of L: $\Pr[Y = 1|A = 1, L = l] = \Pr[Y = 1|A = 0, L = l]$ for all l. That is, $A \perp\!\!\!\perp Y|L$. Graphically, we say that the flow of association between A and Y is interrupted because the path $A \leftarrow L \rightarrow Y$ is blocked by the box around L.

Blocking the flow of association between treatment and outcome through the common cause is the graph-based justification to use stratification as a method to achieve exchangeability.

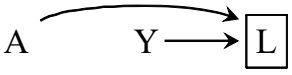


Figure 6.7

Finally, consider Figure 6.4 again. We concluded in the previous section that having the haplotype A was independent of being a cigarette smoker Y because the path between A and Y, $A \rightarrow L \leftarrow Y$, was blocked by the collider L. We now argue heuristically that, in general, A and Y will be conditionally associated within levels of their common effect L. Suppose that the investigators, who are interested in estimating the effect of haplotype A on smoking status Y, restricted the study population to individuals with heart disease ($L = 1$). The square around L in Figure 6.7 indicates that they are conditioning on a particular value of L. Knowing that an individual with heart disease lacks haplotype A provides some information about her smoking status because, in the absence of A, it is more likely that another cause of L such as Y is present. That is, among people with heart disease, the proportion of smokers is increased among those without the haplotype A. Therefore, A and Y are inversely associated conditionally on $L = 1$. The investigator will make a mistake if he concludes that A has a causal effect on Y just because A and Y are associated within levels of L. In the extreme, if A and Y were the only causes of L, then among people with heart disease the absence of one of them would perfectly predict the presence of the other. Causal graphs theory shows that indeed conditioning on a collider like L opens the path $A \rightarrow L \leftarrow Y$, which

See Chapter 8 for more on associations due to conditioning on common effects.

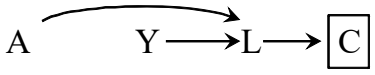


Figure 6.8

was blocked when the collider was not conditioned on. Intuitively, whether two variables (the causes) are associated cannot be influenced by an event in the future (their effect), but two causes of a given effect generally become associated once we stratify on the common effect.

As another example, the causal diagram in Figure 6.8 adds to that in Figure 6.7 a diuretic medication C whose use is a consequence of a diagnosis of heart disease. A and Y are also associated within levels of C because C is a common effect of A and Y. Causal graphs theory shows that conditioning on a variable C affected by a collider L also opens the path $A \rightarrow L \leftarrow Y$. This path is blocked in the absence of conditioning on either the collider L or its consequence C.

This and the previous section review three structural reasons why two variables may be associated: one causes the other, they share common causes, or they share a common effect and the analysis is restricted to certain level of that common effect. Along the way we introduced a number of graphical rules that can be applied to any causal diagram to determine whether two variables are (conditionally) independent. The arguments we used to support these graphical rules were heuristic and relied on our causal intuitions. These arguments, however, have been formalized and mathematically proven. See Fine Point 6.1 for a systematic summary of the graphical rules, and Fine Point 6.2 for an introduction to the concept of faithfulness.

The mathematical theory underlying the graphical rules is known as "d-separation" (Pearl 1995).

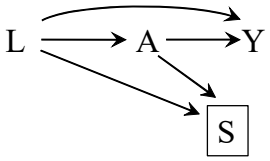


Figure 6.9

There is another possible source of association between two variables that we have not discussed yet: chance or random variability. Unlike the structural reasons for an association between two variables—causal effect of one on the other, shared common causes, conditioning on common effects—random variability results in chance associations that become smaller when the size of the study population increases.

To focus our discussion on structural associations rather than chance associations, we continue to assume until Chapter 10 that we have recorded data on every individual in a very large (perhaps hypothetical) population of interest.

6.4 Positivity and well-defined interventions in causal diagrams

Because causal diagrams encode our qualitative expert knowledge about the causal structure, they can be used as a visual aid to help conceptualize causal problems and guide data analyses. In fact, the formulas that we described in Chapter 2 to quantify treatment effects—standardization and IP weighting—can also be derived using causal graphs theory, as part of what is sometimes referred to as the do-calculus. Therefore, our choice of counterfactual theory in Chapters 1-5 did not really privilege one particular approach but only one particular notation.

Pearl (2009) reviews quantitative methods for causal inference that are derived from graph theory.

Regardless of the notation used (counterfactuals or graphs), exchangeability, positivity, and consistency are conditions required for causal inference via standardization or IP weighting. If any of these conditions does not hold, the numbers arising from the data analysis may not be appropriately interpreted as measures of causal effect. In Chapters 7 and 8 we discuss how the exchangeability condition is translated into graph language. Here we focus on positivity and consistency.

Positivity is roughly translated into graph language as the condition that the arrows from the nodes L to the treatment node A are not deterministic. The first component of consistency—well-defined interventions—means that the arrow from treatment A to outcome Y corresponds to a possibly hypothet-

A more precise discussion of positivity in causal graphs is given by Richardson and Robins (2013).

Fine Point 6.1

D-separation. To define d-separation ('d-' stands for directional), we first define the terms "path" and "blocked path." A path is a sequence of edges connecting two variables on the graph (with each edge occurring only once). We define a path to be either blocked or open according to the following graphical rules.

1. If there are no variables being conditioned on, a path is blocked if and only if two arrowheads on the path collide at some variable on the path. For example, in Figure 6.1, the path $L \rightarrow A \rightarrow Y$ is open, whereas the path $A \rightarrow Y \leftarrow L$ is blocked because two arrowheads on the path collide at Y. We call Y a collider on the path $A \rightarrow Y \leftarrow L$.

2. Any path that contains a noncollider that has been conditioned on is blocked. For example, in Figure 6.5, the path between A and Y is blocked after conditioning on B. We use a square box around a variable to indicate that we are conditioning on it.

3. A collider that has been conditioned on does not block a path. For example, in Figure 6.7, the path between A and Y is open after conditioning on L.

4. A collider that has a descendant that has been conditioned on does not block a path. For example, in Figure 6.8, the path between A and Y is open after conditioning on C, a descendant of the collider L.

Rules 1–4 can be summarized as follows. A path is blocked if and only if it contains a noncollider that has been conditioned on, or it contains a collider that has not been conditioned on and has no descendants that have been conditioned on. Equivalently, given a DAG and a distribution over its nodes, if each variable is independent of its non-descendants conditional on its parents, then if the two sets of variables are d-separated given a third set, the two sets are conditionally independent given the third (i.e., independent within every joint stratum of the third variables).

Two variables are said to be d-separated if all paths between them are blocked (otherwise they are d-connected). Two sets of variables are said to be d-separated if each variable in the first set is d-separated from every variable in the second set. Thus, A and L are not marginally independent (d-connected) in Figure 6.1 because there is one open path between them ($L \rightarrow A$), despite the other path ($A \rightarrow Y \leftarrow L$)'s being blocked by the collider Y. In Figure 6.4, however, A and Y are marginally independent (d-separated) because the only path between them is blocked by the collider L. In Figure 6.5, we conclude that A is conditionally independent of Y, given B. From Figure 6.7 we infer that A is not conditionally independent of Y, given L, and from Figure 6.8 we infer that A is not conditionally independent of Y, given C.

The d-separation rules to infer associational statements from causal diagrams were formalized by Pearl (1995). A mathematically equivalent set of graphical rules, known as "moralization", was developed by Lauritzen et al. (1990).

ical but relatively unambiguous intervention. In the causal diagrams discussed in this book, positivity is implicit unless otherwise specified, and consistency is embedded in the notation because we only consider treatment nodes with relatively well-defined interventions. Note that positivity is concerned with arrows into the treatment nodes, and well-defined interventions are only concerned with arrows leaving the treatment nodes.

Influence diagrams are causal diagrams augmented with decision nodes to represent the interventions of interest (Dawid 2000, 2002).

Thus, the treatment nodes are implicitly given a different status compared with all other nodes. Some authors make this difference explicit by including *decision nodes* in causal diagrams. Though this decision-theoretic approach largely leads to the same methods described here, we do not include decision nodes in the causal diagrams presented in this chapter. Because we are always explicit about the potential interventions on the variable A, the additional nodes (to represent the potential interventions) would be somewhat redundant.

The different status of treatment nodes compared with other nodes was also graphically explicit in the causal trees introduced in Chapter 2, in which

Fine Point 6.2

Faithfulness. In a causal DAG the absence of an arrow from A to Y indicates that the sharp null hypothesis of no causal effect of A on any individual's Y holds, and an arrow from A to Y (as in Figure 6.2) indicates that A has a causal effect on the outcome Y of at least one individual in the population. We would generally expect that in a setting represented by Figure 6.2 there is both an average causal effect of A on Y, $\Pr[Y^{a=1} = 1] \neq \Pr[Y^{a=0} = 1]$, and an association between A and Y, $\Pr[Y = 1|A = 1] \neq \Pr[Y = 1|A = 0]$. However, that is not necessarily true: a setting represented by Figure 6.2 may be one in which there is neither an average causal effect nor an association.

For an example, remember the data in Table 4.1. Heart transplant A increases the risk of death Y in women (half of the population) and decreases the risk of death in men (the other half). Because the beneficial and harmful effects of A perfectly cancel out, the average causal effect is null, $\Pr[Y^{a=1} = 1] = \Pr[Y^{a=0} = 1]$. Yet Figure 6.2 is the correct causal diagram because treatment A affects the outcome Y of some individuals—in fact, of all individuals—in the population.

When, as in our example, the causal diagram makes us expect a non-null association that does not actually exist in the data, we say that the joint distribution of the data is not faithful to the causal DAG. In our example the unfaithfulness was the result of effect modification (by sex) with opposite effects of exactly equal magnitude in each half of the population. Such perfect cancellation of effects is rare, and thus we will assume faithfulness throughout this book. Because unfaithful distributions are rare, in practice lack of d-separation (See Fine Point 6.1) can be equated to non-zero association.

There are, however, instances in which faithfulness is violated by design. For example, consider the prospective study in Section 4.5. The average causal effect of A on Y was computed after matching on L. In the matched population, L and A are not associated because the distribution of L is the same in the treated and the untreated. That is, individuals are selected into the matched population because they have a particular combination of values of L and A. The causal diagram in Figure 6.9 represents the setting of a matched study in which selection S (1: yes, 0: no) is determined by both A and L. The box around S indicates that the analysis is restricted to those selected into the matched cohort ($S = 1$). According to d-separation rules, there are two open paths between A and L when conditioning on S: $L \rightarrow A$ and $L \rightarrow S \leftarrow A$. Thus one would expect L and A to be associated conditionally on S. However, matching ensures that L and A are not associated (see Chapter 4). Why the discrepancy? Matching creates an association via the path $L \rightarrow S \leftarrow A$ that is of equal magnitude, but opposite direction, as the association via the path $L \rightarrow A$. The net result is a perfect cancellation of the associations. Matching leads to unfaithfulness.

Finally, faithfulness may be violated when there exist deterministic relations between variables on the graph. Specifically, when two variables are linked by paths that include deterministic arrows, then the two variables are independent if all paths between them are blocked, but might also be independent even if some paths were open. In this book we will assume faithfulness unless we say otherwise.

non-treatment branches corresponding to nontreatment variables L and Y were enclosed in circles, and in the "pies" representing sufficient causes in Chapter 5, which distinguish between potential treatments A and E and background factors U. Also, our discussion on well-defined versions of treatment in Chapter 3 emphasizes the requirements imposed on the treatment variables A that do not apply to other variables.

In contrast, the causal diagrams in this chapter apparently assign the same status to all variables in the diagram—this is indeed the case when causal diagrams are considered as representations of nonparametric structural equations models (see Technical Point 6.2). The apparently equal status of all variables in causal diagrams may be misleading, especially when some of those variables are ill-defined. It may be okay to draw a causal diagram that includes a node for "obesity" as the outcome Y or even as a covariate L. However, for the reasons discussed in Chapter 3, it is generally not okay to draw a causal diagram that includes a node for "obesity" as a treatment A. In causal diagrams, nodes

Fine Point 6.3

Discovery of causal structure. In this book we use causal diagrams as a way to represent our expert knowledge—or assumptions—about the causal structure of the problem at hand. That is, the causal diagram guides the data analysis. How about going in the opposite direction? Can we learn the causal structure by conducting data analyses without making assumptions about the causal structure? The process of learning components of the causal structure through data analysis is referred to as discovery.

Discovery is often impossible. For example, suppose that we find a strong association between two variables B and C in our data. We cannot learn much about the causal structure involving B and C because their association is consistent with at least 4 causal diagrams: B causes C ($B \to C$), C causes B, ($C \to B$), B and C share a cause U ($B \longleftarrow U \to C$), and B and C have a common effect that is conditioned on. If we knew the time sequence of B and C, we could only rule out one of these causal diagrams, either $B \to C$ (if C predates B) or $C \to B$ (if B predates C).

There are, however, some settings in which learning causal structure from data is theoretically possible. Suppose we have an infinite amount of data on 3 variables Z, A , Y and we know that their time sequence is Z first, A second, and Y last. Our data analysis concludes that all 3 variables are marginally associated with each other, and that the only conditional independence that holds is $Z \perp\!\!\!\perp Y|A$. Then, if we are willing to assume that faithfulness holds, the only possible causal diagram consistent with our data analysis is $Z \to A \to Y$ with perhaps a common cause U of Z and A in addition to (or in place of) the arrow from Z to A. That is, we have learned that that there is definitely an arrow from A to Y.

The problem is, of course, that we do not have an infinite sample size, so using this result is difficult in practice. With large enough data, we will never be able to demonstrate perfect conditional independence.

for treatment variables with multiple relevant versions need to be sufficiently well-defined.

For example, suppose that we are interested in the causal effect of the compound treatment R, where $R = 1$ is defined as "exercising at least 30 minutes daily," and $R = 0$ is defined as "exercising less than 30 minutes daily." Individuals who exercise longer than 30 minutes will be classified as $R = 1$, and thus each of the possible durations $30, 31, 32...$ minutes can be viewed as a different version of the treatment $R = 1$. For each individual with $R = 1$ in the study, the versions of treatment $A(r = 1)$ can take values $30, 31, 32, ...$ indicating all possible durations of exercise greater or equal than 30 minutes. For each individual with $R = 0$ in the study $A(r = 0)$ can take values $0, 1, 2..., 29$ including all durations of less than 30 minutes. That is, per the definition of compound treatment, multiple values $a(r)$ can be mapped onto a single value $R = r$.

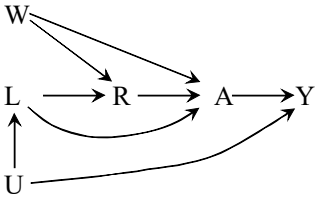


Figure 6.10

Figure 6.10 shows how a causal diagram can appropriately depict a compound treatment R. The causal diagram also include nodes for the treatment versions A—a vector including all the variables $A(r)$—, two sets of common causes L and W, and unmeasured variables U. Unlike other causal diagrams described in this chapter, the one in Figure 6.10 incudes nodes (R and A) that are deterministically related. The multiple versions A are sufficiently specified when, as in Figure 6.10, there are no direct arrows from R to Y.

Being explicit about the compound treatment R of interest and its versions $A(r)$ is an important step towards having a well-defined causal effect, identifying relevant data, and choosing adjustment variables. Also, it is the basis of research efforts aimed at discovering the causal structure based on data analyses that assume faithfulness (see Fine Point 6.3).

6.5 A structural classification of bias

The word "bias" is frequently used by investigators making causal inferences. There are several related, but technically different, uses of the term "bias" (see Chapter 10). We say that there is *systematic bias* when the data are insufficient to identify—compute—the causal effect even with an infinite sample size. As a result, no estimator can be consistent (review Chapter 1 for a definition of consistent estimator).

For the average causal effects within levels of L, there is conditional bias whenever $\Pr[Y^{a=1}|L = l] - \Pr[Y^{a=0}|L = l]$ differs from $\Pr[Y|L = l, A = 1] - \Pr[Y|L = l, A = 0]$ for at least one stratum l. That is, there is bias whenever the effect measure (e.g., causal risk ratio or difference) and the corresponding association measure (e.g., associational risk ratio or difference) are not equal. As discussed in Section 2.3, conditional exchangeability $Y^a \perp\!\!\!\perp A|L$ implies the absence of conditional bias. The converse is also true: absence of conditional bias implies conditional exchangeability.

For the average causal effect in the entire population, there is (unconditional) bias when $\Pr[Y^{a=1} = 1] - \Pr[Y^{a=0} = 1] \neq \Pr[Y = 1|A = 1] - \Pr[Y = 1|A = 0]$. Absence of conditional bias implies that we can obtain an unbiased estimate of the average causal effect in the entire population by, say, standardization.

Under faithfulness, the presence of conditional bias implies the presence of unconditional bias since without faithfulness positive bias in one stratum of L might exactly cancel the negative bias in another.

Informally, we often refer to systematic bias as any structural association between treatment and outcome that does not arise from the causal effect of treatment on outcome in the population of interest. Because causal diagrams are helpful to represent different sources of association, we use causal diagrams to classify systematic bias according to its source, and thus to sharpen discussions about bias.

When the null hypothesis of no causal effect of treatment on the outcome holds, but treatment and outcome are associated in the data, we say that there is *bias under the null*. In the observational study summarized in Table 3.1, there was bias under the null because the causal risk ratio was 1 whereas the associational risk ratio was 1.26. Any causal structure that results in bias under the null will also cause bias under the alternative (i.e.,when treatment does have a non-null effect on the outcome). However, the converse is not true.

For example, conditioning on some variables may cause bias under the alternative but not under the null, as decribed by Greenland (1977) and Hernán (2017). Read Chapter 8 before reading these papers.

Bias under the null can result from two different causal structures:

1. Common causes: When the treatment and outcome share a common cause, the association measure generally differs from the effect measure. Epidemiologists use the term *confounding* to refer to this bias.

2. Conditioning on common effects: This structure is the source of bias that epidemiologists refer to as *selection bias*.

There is another possible source of bias under the null: measurement error. So far we have assumed that all variables—treatment A , outcome Y, and covariates L— are perfectly measured. In practice, however, some degree of measurement error is expected. The bias due to measurement error is referred to as *measurement bias* or information bias.

Another form of bias may also result from (nonstructural) random variability. See Chapter 10.

The three types of systematic bias—confounding, selection, measurement—may arise in observational studies, but also in randomized experiments. This may not be obvious from previous chapters, in which we conceptualized observational studies as some sort of imperfect randomized experiments, whereas our discussion of randomized experiments was restricted to ideal studies in which no participants are lost during the follow-up, all participants adhere to

the assigned treatment, and the assigned treatment remains unknown to both study participants and investigators. We might as well have told you a fairy tale or a mythological story. Real randomized experiments rarely look like that. The remaining chapters of Part I will elaborate on the sometimes fuzzy boundary between experimenting and observing.

Specifically, in the next three chapters we turn our attention to the use of causal diagrams to represent three classes of biases: confounding bias due to the presence of common causes (Chapter 7), selection bias due to the selection of individuals (Chapter 8), and measurement bias due to the measurement of variables (Chapter 9). Before that, we take a brief detour to describe causal diagrams in the presence of effect modification.

6.6 The structure of effect modification

Identifying potential sources of bias is a key use of causal diagrams: we can use our causal expert knowledge to draw graphs and then search for sources of association between treatment and outcome. Causal diagrams are less helpful to illustrate the concept of effect modification that we discussed in Chapter 4.

Figure 6.11

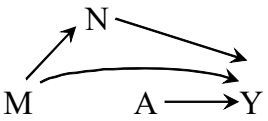


Figure 6.12

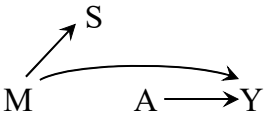


Figure 6.13

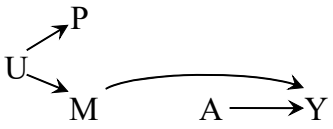


Figure 6.14

Suppose heart transplant A was randomly assigned in an experiment to identify the average causal effect of A on death Y. For simplicity, let us assume that there is no bias, and thus Figure 6.2 adequately represents this study. Computing the effect of A on the risk of Y presents no challenge. Because association is causation, the associational risk difference $\Pr[Y = 1|A = 1] - \Pr[Y = 1|A = 0]$ can be interpreted as the causal risk difference $\Pr[Y^{a=1} = 1] - \Pr[Y^{a=0} = 1]$. The investigators, however, want to go further because they suspect that the causal effect of heart transplant varies by the quality of medical care offered in each hospital participating in the study. Thus, the investigators classify all individuals as receiving high ($M = 1$) or normal ($M = 0$) quality of care, compute the stratified risk differences in each level of M as described in Chapter 4, and indeed confirm that there is effect modification by M on the additive scale. The causal diagram in Figure 6.11 includes the effect modifier M with an arrow into the outcome Y but no arrow into treatment A (which is randomly assigned and thus independent of M). Two important caveats.

First, the causal diagram in Figure 6.11 would still be a valid causal diagram if it did not include M because M is not a common cause of A and Y. It is only because the causal question makes reference to M (i.e., what is the average causal effect of A on Y *within levels of* M?), that M needs to be included in the causal diagram. Other variables measured along the path between "quality of care" M and the outcome Y could also qualify as effect modifiers. For example, Figure 6.12 shows the effect modifier "therapy complications" N, which partly mediates the effect of M on Y.

Second, the causal diagram in Figure 6.11 does not necessarily indicate the presence of effect modification by M. The causal diagram implies that both A and M affect death Y, but it does not distinguish among the following three qualitatively distinct ways that M could modify the effect of A on Y:

1. The causal effect of treatment A on mortality Y is in the same direction (i.e., harmful or beneficial) in both stratum $M = 1$ and stratum $M = 0$.

2. The direction of the causal effect of treatment A on mortality Y in stratum $M = 1$ is the opposite of that in stratum $M = 0$ (i.e., there is qualitative effect modification).

3. Treatment A has a causal effect on Y in one stratum of M but no causal effect in the other stratum, e.g., A only kills individuals with $M = 0$.

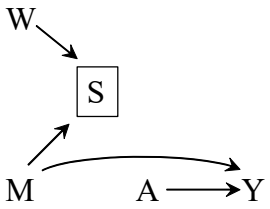


Figure 6.15

That is, Figure 6.11—as well as all the other figures discussed in this section—is equally valid to depict a setting with or without effect modification by M.

In the above example, the effect modifier M had a causal effect on the outcome. Many effect modifiers, however, do not have a causal effect on the outcome. Rather, they are surrogates for variables that have a causal effect on the outcome. Figure 6.13 includes the variable "cost of the treatment" S (1: high, 0: low), which is affected by "quality of care" M but has itself no effect on mortality Y. An analysis stratified by S will generally detect effect modification by S even though the variable that truly modifies the effect of A on Y is M. The variable S is a *surrogate effect modifier* whereas the variable M is a *causal effect modifier* (see Section 4.2). Because causal and surrogate effect modifiers are often indistinguishable in practice, the concept of effect modification comprises both. As discussed in Section 4.2, some prefer to use the neutral term "heterogeneity of causal effects," rather than "effect modification," to avoid confusion. For example, someone might be tempted to interpret the statement "cost modifies the effect of heart transplant on mortality because the effect is more beneficial when the cost is higher" as an argument to increase the price of medical care without necessarily increasing its quality.

See VanderWeele and Robins (2007b) for a finer classification of effect modification via causal diagrams.

A surrogate effect modifier is simply a variable associated with the causal effect modifier. Figure 6.13 depicts the setting in which such association is due to the effect of the causal effect modifier on the surrogate effect modifier. However, such association may also be due to shared common causes or conditioning on common effects. For example, Figure 6.14 includes the variables "place of residence" (1: Greece, 0: Rome) U and "passport-defined nationality" P (1: Greece, 0: Rome). Place of residence U is a common cause of both quality of care M and nationality P. Thus P will behave as a surrogate effect modifier because P is associated with the causal effect modifier M. Another example: Figure 6.15 includes the variables "cost of care" S and "use of bottled mineral water (rather than tap water) for drinking at the hospital" W. Use of mineral water W affects cost S but not mortality Y in developed countries. If the study were restricted to low-cost hospitals ($S = 0$), then use of mineral water W would be generally associated with medical care M, and thus W would behave as a surrogate effect modifier. In summary, surrogate effect modifiers can be associated with the causal effect modifier by structures including common causes, conditioning on common effects, or cause and effect.

Some intuition for the association between W and M in low-cost hospitals $S = 0$: suppose that low-cost hospitals that use mineral water need to offset the extra cost of mineral water by spending less on components of medical care that decrease mortality. Then use of mineral water would be inversely associated with quality of medical care in low-cost hospitals.

Causal diagrams are in principle agnostic about the presence of interaction between two treatments A and E. However, causal diagrams can encode information about interaction when augmented with nodes that represent sufficient-component causes (see Chapter 5), i.e., nodes with deterministic arrows from the treatments to the sufficient-component causes. Because the presence of interaction affects the magnitude and direction of the association due to conditioning on common effects, these augmented causal diagrams are discussed in Chapter 8.

Chapter 7
CONFOUNDING

Suppose an investigator conducted an observational study to answer the causal question "does one's looking up to the sky make other pedestrians look up too?" She found an association between a first pedestrian's looking up and a second one's looking up. However, she also found that pedestrians tend to look up when they hear a thunderous noise above. Thus it was unclear what was making the second pedestrian look up, the first pedestrian's looking up or the thunderous noise? She concluded the effect of one's looking up was confounded by the presence of a thunderous noise.

In randomized experiments treatment is assigned by the flip of a coin, but in observational studies treatment (e.g., a person's looking up) may be determined by many factors (e.g., a thunderous noise). If those factors affect the risk of developing the outcome (e.g., another person's looking up), then the effects of those factors become entangled with the effect of treatment. We then say that there is confounding, which is just a form of lack of exchangeability between the treated and the untreated. Confounding is often viewed as the main shortcoming of observational studies. In the presence of confounding, the old adage "association is not causation" holds even if the study population is arbitrarily large. This chapter provides a definition of confounding and reviews the methods to adjust for it.

7.1 The structure of confounding

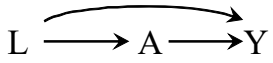


Figure 7.1

The structure of confounding can be represented by using causal diagrams. For example, the diagram in Figure 7.1 (same as Figure 6.1) depicts a treatment A, an outcome Y, and their shared (or common) cause L. This diagram shows two sources of association between treatment and outcome: 1) the path $A \rightarrow Y$ that represents the causal effect of A on Y, and 2) the path $A \leftarrow L \rightarrow Y$ between A and Y that is mediated by the common cause L. The path $A \leftarrow L \rightarrow Y$ that links A and Y through their common cause L is an example of a *backdoor path*.

In a causal DAG, a backdoor path is a noncausal path between treatment and outcome that remains even if all arrows pointing from treatment to other variables (in graph-theoretic terms, the descendants of treatment) are removed. That is, the path has an arrow pointing into treatment.

If the common cause L did not exist in Figure 7.1, then the only path between treatment and outcome would be $A \rightarrow Y$, and thus the entire association between A and Y would be due to the causal effect of A on Y. That is, the associational risk ratio $\Pr[Y = 1|A = 1] / \Pr[Y = 1|A = 0]$ would equal the causal risk ratio $\Pr\left[Y^{a=1} = 1\right] / \Pr\left[Y^{a=0} = 1\right]$; association would be causation. But the presence of the common cause L creates an additional source of association between the treatment A and the outcome Y, which we refer to as confounding for the effect of A on Y. Because of confounding, the associational risk ratio does not equal the causal risk ratio; association is not causation.

Examples of confounding abound in observational research. Consider the following examples of confounding for the effect of various kinds of treatments on health outcomes:

- Occupational factors: The effect of working as a firefighter A on the risk of death Y will be confounded if "being physically fit" L is a cause of both being an active firefighter and having a lower mortality risk. This

bias, depicted in the causal diagram in Figure 7.1, is often referred to as a *healthy worker bias*.

- Clinical decisions: The effect of drug A (say, aspirin) on the risk of disease Y (say, stroke) will be confounded if the drug is more likely to be prescribed to individuals with certain condition L (say, heart disease) that is both an indication for treatment and a risk factor for the disease. Heart disease L is a risk factor for stroke Y because L has a direct causal effect on Y as in Figure 7.1 or, as in Figure 7.2, because both L and Y are caused by atherosclerosis U, an unmeasured variable. This bias is known as *confounding by indication* or *channeling*, the last term often being reserved to describe the bias created by patient-specific risk factors L that encourage doctors to use certain drug A within a class of drugs.

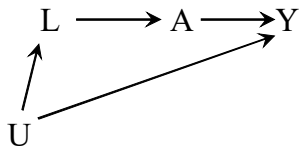


Figure 7.2

- Lifestyle: The effect of behavior A (say, exercise) on the risk of Y (say, death) will be confounded if the behavior is associated with another behavior L (say, cigarette smoking) that has a causal effect on Y and tends to co-occur with A. The structure of the variables L, A, and Y is depicted in the causal diagram in Figure 7.3, in which the unmeasured variable U represents the sort of personality and social factors that lead to both lack of exercise and smoking. Another frequent problem: subclinical disease U results both in lack of exercise A and an increased risk of clinical disease Y. This form of confounding is often referred to as *reverse causation.*

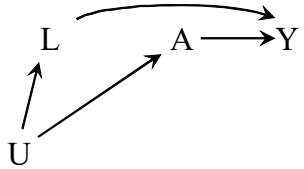


Figure 7.3

- Genetic factors: The effect of a DNA sequence A on the risk of developing certain trait Y will be confounded if there exists a DNA sequence L that has a causal effect on Y and is more frequent among people carrying A. This bias, also represented by the causal diagram in Figure 7.3, is known as *linkage disequilibrium* or *population stratification*, the last term often being reserved to describe the bias arising from conducting studies in a mixture of individuals from different ethnic groups. Thus the variable U can stand for ethnicity or other factors that result in linkage of DNA sequences.

- Social factors: The effect of income at age 65 A on the level of disability at age 75 Y will be confounded if the level of disability at age 55 L affects both future income and disability level. This bias may be depicted by the causal diagram in Figure 7.1.

- Environmental exposures: The effect of airborne particulate matter A on the risk of coronary heart disease Y will be confounded if other pollutants L whose levels co-vary with those of A cause coronary heart disease. This bias is also represented by the causal diagram in Figure 7.3, in which the unmeasured variable U represent weather conditions that affect the levels of all types of air pollution.

In all these cases, the bias has the same structure: it is due to the presence of a cause (L or U) that is shared by the treatment A and the outcome Y, which results in an unblocked backdoor path between A and Y. We refer to the bias caused by shared causes as confounding, and we use other names to refer to biases caused by structural reasons other than the presence of shared causes. For example, we say that selection bias is the result of conditioning on shared effects. For simplicity of presentation, we assume throughout this chapter that other sources of bias (e.g., selection bias, measurement error, and random variability) are absent.

Some authors prefer to replace the unmeasured common cause U (and the two arrows leaving it) by a bidirectional edge between the measured variables that U causes.

7.2 Confounding and exchangeability

We have defined confounding structurally as the bias resulting from the presence of common causes of—or open backdoor paths between—treatment and outcome. It is also possible to provide a definition of confounding strictly in terms of counterfactuals, with no explicit reference to common causes . In fact, that is precisely what we did in previous chapters in which we described the (confounding) bias that results from lack of exchangeability of the treated and the untreated.

See Greenland and Robins (1986, 2009) for a detailed discussion on the relations between confounding and exchangeability.

Suppose positivity and consistency hold. Then, in the absence of bias due to selection (Chapter 8) or measurement (Chapter 9), the following two questions are equivalent:

- under what conditions can confounding be eliminated in the analysis?
- under what conditions can the causal effect of treatment A on outcome Y be identified?

Pearl (1995) proposed the backdoor criterion for nonparametric identification of causal effects. All backdoor paths are blocked if treatment and outcome are d-separated given the measured covariates in a graph in which the arrows out of A are removed.

An important result from causal graphs theory, known as the *backdoor criterion*, is that the causal effect of treatment A on the outcome Y is identifiable if all backdoor paths between them can be blocked by conditioning on variables that are not affected by—non-descendants of—treatment A. Thus the two settings in which causal effects are identifiable are

1. *No common causes of treatment and outcome.* If, like in Figure 6.2, there are no common causes of treatment and outcome, and hence no backdoor paths that need to be blocked, we say that there is no confounding.
2. *Common causes but enough measured variables to block all backdoor paths.* If, like in Figure 7.1, the backdoor path through the common cause L can be blocked by conditioning on some measured covariates (in this example, L itself) which are non-descendants of treatment, we say that there is confounding but there is no residual confounding whose elimination would require adjustment for unmeasured variables. For brevity, we say that there is *no unmeasured confounding.*

Early statistical descriptions of confounding were provided by Yule (1903) for discrete variables and by Pearson et al. (1899) for continuous variables. Yule described the association due to confounding as "ficticious", "illusory", and "apparent". Pearson et al. (1899) referred to it as a "spurious" correlation. However, there is nothing ficticious, illusory, apparent, or spurious about these associations. Associations due to common causes are quite real associations, though they cannot be causally interpreted. Or, in Yule's words, they are associations "to which the most obvious physical meaning must not be assigned."

The first setting is expected in marginally randomized experiments in which all individuals have the same probability of receiving treatment. In these experiments confounding is not expected to occur because treatment is solely determined by the flip of a coin—or its computerized upgrade: the random number generator—and the flip of the coin cannot be a cause of the outcome. That is, when the treatment is unconditionally and randomly assigned, the treated and the untreated are expected to be exchangeable because no common causes exist or, equivalently, because there are no open backdoor paths. Marginal exchangeability, i.e., $Y^a \perp\!\!\!\perp A$, is equivalent to no common causes, whether measured or unmeasured, of treatment and outcome. The average causal effect $\mathrm{E}[Y^{a=1}] - \mathrm{E}[Y^{a=0}]$ is then calculated without adjustment for any variables.

The second setting is expected in conditionally randomized experiments in which the probability of receiving treatment is the same for all individuals with the same value of risk factor L but, by design, this probability varies across values of L. The design of these experiments guarantees the presence of confounding, because L is a common cause of treatment and outcome, that is, there are open backdoor paths. However, in conditionally randomized experiments confounding is not expected conditional on—within levels of—the

covariates L. Conditional exchangeability, i.e., $Y^a \perp\!\!\!\perp A|L$, is equivalent to being able to block all backdoor paths.

Take our heart transplant study, a conditionally randomized experiment, as an example. Individuals who received a transplant ($A = 1$) are different from the untreated ($A = 0$) because, if the treated had remained untreated, their risk of death Y would have been higher than that of those that were actually untreated—the treated had a higher frequency of severe heart disease L, a common cause of A and Y. Thus the consequence of common causes of treatment and outcome is that the treated and the untreated are conditionally exchangeable given L. Then the average causal effect in any stratum l of L is given by the stratum-specific risk difference $\mathrm{E}[Y^{a=1}|L = l] - \mathrm{E}[Y^{a=0}|L = l]$. Therefore the average causal effect $\mathrm{E}[Y^{a=1}] - \mathrm{E}[Y^{a=0}]$ may be calculated by adjusting for the measured variables L via standardization or IP weighting. This second setting is also what one hopes for in observational studies in which many variables L have been measured.

Under conditional exchangeability, $\mathrm{E}[Y^{a=1}] - \mathrm{E}[Y^{a=0}] = \sum_l \mathrm{E}[Y|L = l, A = 1] \Pr[L = l] - \sum_l \mathrm{E}[Y|L = l, A = 0] \Pr[L = l]$.

The backdoor criterion answers three questions: 1) does confounding exist?, 2) can confounding be eliminated?, and 3) what variables are necessary to eliminate the confounding? The answer to the first question is affirmative if there exist unblocked backdoor paths between treatment and outcome; the answer to the second question is affirmative if all those backdoor paths can be blocked using the measured variables; the answer to the third question is any minimal set of variables that, when conditioned on, block all backdoor paths. We say that L is a *sufficient set for confounding adjustment* when conditioning on the set of measured variables L (that are non-descendants of A) blocks all backdoor paths—that is, the treated and the untreated are exchangeable within levels of L.

Formal proofs of the results involving the backdoor criterion are given by Pearl (1995, 2000).

The backdoor criterion, however, does not answer questions regarding the magnitude or direction of confounding. It is logically possible that some unblocked backdoor paths are weak (e.g., if L does not have a large effect on either A or Y) and thus induce little bias, or that several strong backdoor paths induce bias in opposite directions and thus result in a weak net bias. Because unmeasured confounding is not an "all or nothing" issue, in practice, it is important to consider the expected direction and magnitude of the bias (see Fine Point 7.1).

The variables L that are used to reduce confounding via standardization or IP weighting are often referred to as *confounders*. We now review several definitions of confounder.

7.3 Confounders

Confounding is the bias that results from the presence of causes shared by treatment A and outcome Y, which results in open backdoor paths between A and Y. It is then natural to define a confounder as a variable that can be used to block an (otherwise open) backdoor path between treatment and outcome. Equivalently, for the causal diagrams discussed in this paper, a confounder can be defined as any variable L that can be used to help eliminate confounding.

Robins and Morgenstern (1987, Section 2H) defined C to be a confounder given data on F if $L = (C, F)$ is a sufficient set for confounding adjustment but F, or any subset of F, is not. This definition of confounder is closely related, but not exactly equal, to ours (VanderWeele and Shpitser, 2013).

In contrast with this structural definition, a confounder was traditionally defined as any variable that meets the following three conditions: 1) it is associated with the treatment, 2) it is associated with the outcome conditional on the treatment (with "conditional on the treatment" often replaced by "in the untreated"), and 3) it does not lie on a causal pathway between treatment and

Fine Point 7.1

The strength and direction of confounding bias. Suppose you conducted an observational study to identify the effect of heart transplant A on death Y and that you assumed no unmeasured confounding. A thoughtful critic says "the inferences from this observational study may be incorrect because of potential confounding due to cigarette smoking L." A crucial question is whether the bias results in an attenuated or an exaggerated estimate of the effect of heart transplant. For example, suppose that the risk ratio from your study was 0.6 (heart transplant was estimated to reduce mortality during the follow-up by 40%) and that, as the reviewer suspected, cigarette smoking L is a common cause of A (cigarette smokers are less likely to receive a heart transplant) and Y (cigarette smokers are more likely to die). Because there are fewer cigarette smokers ($L = 1$) in the heart transplant group ($A = 1$) than in the other group ($A = 0$), one would have expected to find a lower mortality risk in the group $A = 1$ even under the null hypothesis of no effect of treatment A on Y. Adjustment for cigarette smoking will therefore move the effect estimate upwards (say, from 0.6 to 0.7). In other words, lack of adjustment for cigarette smoking resulted in an exaggeration of the beneficial average causal effect of heart transplant.

An approach to predict the direction of confounding bias is the use of signed causal diagrams. Consider the causal diagram in Figure 7.1 with dichotomous L, A, and Y variables. A positive sign over the arrow from L to A is added if L has a positive average causal effect on A (i.e., if the probability of $A = 1$ is greater among those with $L = 1$ than among those with $L = 0$), otherwise a negative sign is added if L has a negative average causal effect on A (i.e., if the probability of $A = 1$ is greater among those with $L = 0$ than among those with $L = 1$). Similarly a positive or negative sign is added over the arrow from L to Y. If both arrows are positive or both arrows are negative, then the confounding bias is said to be positive, which implies that effect estimate will be biased upwards in the absence of adjustment for L. If one arrow is positive and the other one is negative, then the confounding is said to be negative, which implies that the effect estimate will be biased downwards in the absence of adjustment for L. Unfortunately, this simple rule may fail in more complex causal diagrams or when the variables are non dichotomous. See VanderWeele, Hernán, and Robins (2008) for a more detailed discussion of signed diagrams in the context of average causal effects.

Regardless of the sign of confounding, another key issue is the magnitude of the bias. Biases that are not large enough to affect the conclusions of the study may be safely ignored in practice, whether the bias is upwards or downwards. A large confounding bias requires a strong confounder-treatment association and a strong confounder-outcome association (conditional on the treatment). For discrete confounders, the magnitude of the bias depends also on prevalence of the confounder (Cornfield et al. 1959, Walker 1991). If the confounders are unknown, one can only guess what the magnitude of the bias is. Educated guesses can be organized by conducting sensitivity analyses (i.e., repeating the analyses under several assumptions regarding the magnitude of the bias), which may help quantify the maximum bias that is reasonably expected. See Greenland (1996a), Robins, Rotnitzky, and Scharfstein (1999), and Greenland and Lash (2008) for detailed descriptions of sensitivity analyses for unmeasured confounding.

An informal definition: 'A confounder is any variable that can be used to help eliminate confounding.'
Note this definition is not circular because we have previously provided a definition of confounding. Another example of a non-circular definition: "A musician is a person who plays music," stated after we have defined what music is.

outcome. According to this traditional definition, all so defined confounders should be adjusted for in the analysis. However, this traditional definition of confounder may lead to inappropriate adjustment for confounding. To see why, let us compare the structural and traditional definitions of confounder in Figures 7.1-7.4. For simplicity, these four figures depict settings in which investigators need no data beyond the measured variables L for confounding adjustment (with F being the empty set), and in which the variables L are affected by neither the treatment A nor the outcome Y.

In Figure 7.1 there is confounding because the treatment A and the outcome Y share the cause L, i.e., because there is an open backdoor path between A and Y through L. However, this backdoor path can be blocked by conditioning on L. Thus, if the investigators collected data on L for all individuals, there is no unmeasured confounding given L. We say that L is a confounder because it is needed to eliminate confounding. Let us now turn to the traditional definition of confounder. The variable L is associated with the treatment (because it

has a causal effect on A), is associated with the outcome conditional on the treatment (because it has a direct causal effect on Y), and it does not lie on the causal pathway between treatment and outcome. Then, according to the traditional definition, L is a confounder and it should be adjusted for. There is no discrepancy between the structural and traditional definitions of confounder under the causal diagram in Figure 7.1.

In Figure 7.2 there is confounding because the treatment A and the outcome Y share the unmeasured cause U, i.e., there is a backdoor path between A and Y through U. (Unlike the variables L, A, and Y, the variable U was not measured by the investigators.) This backdoor path could be theoretically blocked, and thus confounding eliminated, by conditioning on U, had data on this variable been collected. However, this backdoor path can also be blocked by conditioning on L. Thus, there is no unmeasured confounding given L. We say that L is a confounder because it is needed to eliminate confounding, even though the confounding resulted from the presence of U. Let us now turn to the traditional definition of confounder. The variable L is associated with the treatment (because it has a causal effect on A), is associated with the outcome conditional on the treatment (because it shares the cause U with Y), and it does not lie on the causal pathway between treatment and outcome. Then, according to the traditional definition, L is a confounder and it should be adjusted for. Again, there is no discrepancy between the structural and traditional definitions of confounder in Figure 7.2.

In Figure 7.3 there is also confounding because the treatment A and the outcome Y share the cause U, and the backdoor path can also be blocked by conditioning on L. Therefore there is no unmeasured confounding given L, and we say that L is a confounder. According to the traditional definition, L is also a confounder and should be adjusted for because L is associated with the treatment (it shares the cause U with A), is associated with the outcome conditional on the treatment (it has a causal effect on Y), and it does not lie on the causal pathway between treatment and outcome. Again, there is no discrepancy between the structural and traditional definitions of confounder for the causal diagram in Figure 7.3.

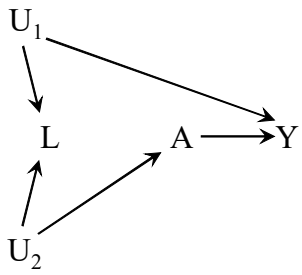


Figure 7.4

The key figure is Figure 7.4. In this causal diagram there are no common causes of treatment A and outcome Y, and therefore there is no confounding. The backdoor path between A and Y through L ($A \leftarrow U_2 \rightarrow L \leftarrow U_1 \rightarrow Y$) is blocked because L is a collider on that path. Thus all the association between A and Y is due to the effect of A on Y: association is causation. For example, suppose A represents physical activity, Y cervical cancer, U_1 a pre-cancer lesion, L a diagnostic test (Pap smear) for pre-cancer, and U_2 a health-conscious personality (more physically active, more visits to the doctor). Then, under the causal diagram in Figure 7.4, the effect of physical activity A on cancer Y is unconfounded and there is no need to adjust for L (adjustment for either U_1 or U_2 is impossible, as these are unmeasured variables.)

The bias induced in Figure 7.4 was described by Greenland et al (1999), and referred to as M-bias (Greenland 2003) because the structure of the variables involved in it—U_2, L, U_1—resembles a letter M lying on its side.

In fact, adjustment for L would induce bias. Let us say that we decide to adjust for L by, for example, restricting the analysis to women with a negative test ($L = 0$). Conditioning on the collider L opens the backdoor path between A and Y ($A \leftarrow U_2 \rightarrow L \leftarrow U_1 \rightarrow Y$), which was previously blocked by the collider itself. Thus the association between A and Y would be a mixture of the association due to the effect of A on Y and the association due to the open backdoor path. Association would not be causation any more. Although there is no unconditional bias, there is conditional bias for at least one stratum of L. We refer to this bias as selection bias because it arises from selecting a particular stratum of L in which the association between A and Y is calculated

Technical Point 7.1

Fixing the traditional definition of confounder. Figures 7.4 and 7.5 depict two examples in which the traditional definition of confounder misleads investigators into adjusting for a variable when adjustment for such variable is not only superfluous but also harmful. The traditional definition fails because it relies on two incorrect statistical criteria—conditions 1) and 2)—and one incorrect causal criterion—condition 3). To "fix" the traditional definition one needs to do two things:

1. Replace condition 3) by the condition that "there exist variables L and U such that there is conditional exchangeability within their joint levels $Y^a \perp\!\!\!\perp A|L, U$. If this new condition holds, it will quite generally be the case that L is not on a causal pathway between A and Y.

2. Replace conditions 1) and 2) by the following condition: U can be decomposed into two disjoint subsets U_1 and U_2 (i.e., $U = U_1 \cup U_2$ and $U_1 \cap U_2$ is empty) such that (i) U_1 and A are not associated within strata of L, and (ii) U_2 and Y are not associated within joint strata of A, L, and U_1. The variables in U_1 may be associated with the variables in U_2. U_1 can always be chosen to be the largest subset of U that is unassociated with treatment.

If these two new conditions are met we say U is a non-confounder given data on L. These conditions were proposed by Robins (1997,Theorem 4.3) and further discussed by Greenland, Pearl, and Robins (1999, pp. 45-46, note the condition that $U = U_1 \cup U_2$ was inadvertently left out). These conditions overcome the difficulties found in Figures 7.4 and 7.5 because they allow to dismiss variables as non-confounders. For example, Greenland, Pearl, and Robins applied these conditions to Figure 7.4 to show that there is no confounding.

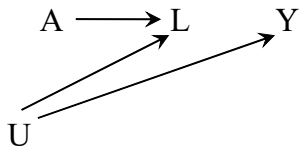


Figure 7.5

Figure 7.5 is another nonconfounding example in which the traditional criteria lead to selection bias due to adjustment for L. The traditional criteria would not have resulted in bias had condition 3) been replaced by the condition that L is not caused by treatment, i.e., it is a non-descendant of A.

(see Chapter 8).

Though there is no confounding, L meets the criteria for a traditional confounder: it is associated with the treatment (it shares the cause U_2 with A), it is associated with the outcome conditional on the treatment (it shares the cause U_1 with Y), and it does not lie on the causal pathway between treatment and outcome. Hence, according to the traditional definition, L is considered a confounder that should be adjusted for, even in the absence of confounding! Again, the result of trying to adjust for the nonexistent confounding would be selection bias.

In this example the standard definition of confounder fails because it misleads investigators into adjusting for a variable when adjustment for such variable is not only superfluous but also harmful. This problem arises because the standard definition treats the concept of confound*er*, rather than that of confound*ing*, as the primary concept. In contrast, the structural definition first establishes the presence of confounding—common causes—and then identifies the confounders that are necessary to adjust for confounding in the analysis. Confounding is an absolute concept—common causes of treatment and outcome either exist or do not exist in a particular region of the universe—whereas confounder is a relative one—L may be needed to block a backdoor path only when U is not measured. See also Fine Point 7.2.

Furthermore, our example shows that confounding is a causal concept and that associational or statistical criteria are insufficient to characterize confounding. The standard definition of confounder that relies almost exclusively on statistical considerations may lead, as shown by Figure 7.4, to the wrong advice: adjust for a "confounder" even when confounding does not exist. In contrast, the structural definition of confounding emphasizes that causal inference from observational data requires a priori causal assumptions or beliefs, which are derived from subject-matter knowledge rather than statistical as-

Fine Point 7.2

Surrogate confounders. Consider now the causal diagram in Figure 7.6. There is confounding for the effect of A on Y because of the presence of the unmeasured common cause U. The measured variable L is a proxy or surrogate for U. For example, the unmeasured variable socioeconomic status U may confound the effect of physical activity A on the risk of cardiovascular disease Y. Income L is a surrogate for the often ill-defined variable socioeconomic status. Should we adjust for the variable L? On the one hand, it can be said that L is not a confounder because it does not lie on a backdoor path between A and Y. On the other hand, adjusting for the measured L, which is associated with the unmeasured U, may indirectly adjust for some of the confounding caused by U. In the extreme, if L were perfectly correlated with U then it might make no difference whether one conditions on L or on U. Indeed if L is binary and is a nondiferentially missclassified (see Chapter 9) version of U, conditioning on L will result in a partial blockage of the backdoor path $A \leftarrow U \rightarrow Y$ under some weak conditions (Ogburn and VanderWeele 2012). Therefore we will typically prefer to adjust, rather than not to adjust, for L.

We refer to variables that can be used to reduce confounding bias even though they are not on a backdoor path as *surrogate confounders*. A strategy to fight confounding is to measure as many surrogate confounders as possible and adjust for all of them.

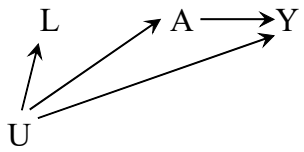


Figure 7.6

sociations detected in the data. One important advantage of the structural definition is that it prevents inconsistencies between beliefs and actions. For example, if you believe Figure 7.4 is the true causal diagram—and therefore that there is no confounding for the effect of A on Y—then you will not adjust for the variable L.

In an attempt to eliminate the problem described for Figure 7.4, some authors have proposed a modified definition of confounder that replaces the traditional condition "2) it is associated with the outcome conditional on the treatment" by the condition "2) it is a cause of the outcome." This modified definition of confounder indeed prevents inappropriate adjustment for L in Figure 7.4, but only to create a new problem by not considering L a confounder—that needs to be adjusted for—in Figure 7.2. Thus this modification of the traditional definition of confounder may lead to lack of adjustment for confounding. See Technical Point 7.1 for a detailed description of how to fix the traditional definition of confounder.

A note on terminology. Our structural definition of confounding was "bias due to common causes of A and Y," which results in an open backdoor between A and Y. An alternative way to structurally define confounding could then be "bias due to an open backdoor between A and Y." This alternative definition is identical to ours except that it labels the bias in Figure 7.4 as confounding rather than as selection bias. In other words, the alternative definition considers confounding as "any bias that is eliminated by a randomized assignment of A" (in the absence of random variability). The choice of one definition over the other is just a matter of taste with no practical implications. For example, the above discussion on bias remains unaltered regarding of how we label the bias in Figure 7.4. Given that the choice between the definitions of confounding "bias due to common causes of A and Y" and "bias due to an open backdoor between A and Y" is inconsequential, we arbitrarily chose the former for this chapter, but some readers may prefer the latter. Fortunately, nothing important in causal inference hinges on this choice. The next chapter provides more detail on the distinction between confounding and selection bias.

Hernán, Hernández-Díaz, and Robins (2004) discuss the blurred border between confounding and selection bias—the, M-bias introduced above—using a hypothetical study conducted among firefighters. We review this example in Chapter 8.

7.4 Single-world intervention graphs

Exchangeability is translated into graph language as the lack of open paths between the treatment A and outcome Y nodes—other than those originating from A—that would result in an association between A and Y. Chapters 7–9 describe different ways in which lack of exchangeability can be represented in causal diagrams. For example, in this chapter we discuss confounding, a violation of exchangeability due to the presence of an open backdoor path between treatment and outcome.

To a non-mathematician, the relation between exchangeability $Y^a \perp\!\!\!\perp A$ and the backdoor criterion seems rather magical: there appears to be no obvious relationship between counterfactual independences and the absence of backdoor paths because counterfactuals are not included as variables on causal diagrams.

SWIGs overcome the shortcomings of previously proposed twin causal diagrams (Balke and Pearl 1994).

A new type of graphs—Single-world intervention graphs (SWIGs)— unify the counterfactual and graphical approaches by explicitly including the counterfactual variables on the graph. A SWIG depicts the variables and causal relations that would be observed in a hypothetical world in which all individuals received treatment level a. That is, a SWIG is a *graph* that represents a counterfactual *world* created by a *single intervention*. In contrast, a standard causal diagram represents the variables and causal relations that are observed in the actual world. A SWIG can then be viewed as a function that transforms a given causal diagram under a given intervention. The following examples describe this transformation.

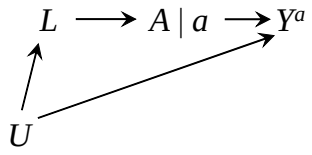


Figure 7.7

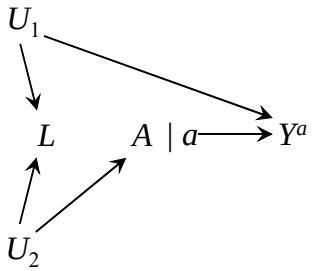


Figure 7.8

Suppose the causal diagram in Figure 7.2 represents the observed study data. The SWIG in Figure 7.7 is a transformation of Figure 7.2 that represents the data from a hypothetical intervention in which all individuals receive the same treatment level a. The treatment node is split into left and right sides. The right side encodes the treatment value a under the intervention; the left side encodes the value of treatment A that would have been observed in the absence of intervention, i.e., *the natural value of treatment*. Note that A does not have an arrow into a because the value a is the same for all individuals. The outcome is Y^a, the value of Y in the hypothetical study. The remaining variables are temporally prior to A. Thus these variables and A take the same value as in the observational study. Conditional exchangeability $Y^a \perp\!\!\!\perp A|L$ holds because all paths between Y^a and A are blocked after conditioning on L.

Consider now the causal diagram in Figure 7.4 and the SWIG in Figure 7.8. Marginal exchangeability $Y^a \perp\!\!\!\perp A$ holds because, on the SWIG, all paths between Y^a and A are blocked (without conditioning on L). In contrast, conditional exchangeability $Y^a \perp\!\!\!\perp A|L$ does not hold because, on the SWIG, the path $Y^a \longleftarrow U_1 \longrightarrow L \longleftarrow U_2 \longrightarrow A$ is open when the collider L is conditioned on. This is why the marginal A-Y association is causal, but the conditional A-Y association given L is not, and thus any method that adjusts for L results in bias. These examples show how SWIGs unify the counterfactual and graphical approaches (see also Fine Point 7.3).

A practical example of the application of expert knowledge of the causal structure to confounding evaluation was described by Hernán et al (2002).

Knowledge of the causal structure is a prerequisite to label a variable as a confounder, and thus to decide which variables need to be adjusted for. In observational studies, investigators measure many variables L in an attempt to ensure that the treated and the untreated are conditionally exchangeable given the covariates L. The underlying assumption is that, even though common causes may exist (confounding), the measured variables L are sufficient to block all backdoor paths (no unmeasured confounding). Of course, there is no guarantee that this attempt will be successful, which makes causal inference

Fine Point 7.3

Confounders cannot be descendants of treatment, but can be in the future of treatment. Consider the causal DAG in Figure 7.9. L is a descendant of treatment A that blocks all backdoor paths from A to Y. Unlike in Figures 7.4 and 7.5, conditioning on L does not cause selection bias because no collider path is opened. Rather, because the causal effect of A on Y is solely through the intermediate variable L, conditioning on L completely blocks this pathway. This example shows that adjusting for a variable L that blocks all backdoor paths does not eliminate bias when L is a descendant of A.

Since conditional exchangeability $Y^a \perp\!\!\!\perp A|L$ implies the adjustment for L eliminates all bias, it must be the case thatconditional exchangeability fails to hold and the average treatment effect $\mathrm{E}[Y^{a=1}] - \mathrm{E}[Y^{a=0}]$ cannot be identified in this example. This failure can be verified by analyzing the SWIG in Figure 7.10, which depicts a counterfactual world in which A has been set to the value a. In this world, the factual variable L is replaced by the counterfactual variable L^a, that is, the value of L that would have been observed if all individuals had received treatment value a. Since L^a blocks all paths from Y^a to A we conclude that $Y^a \perp\!\!\!\perp A|L^a$ holds, but we cannot conclude that conditional exchangeability $Y^a \perp\!\!\!\perp A|L$ holds as L is not even on the graph. (Under an FFRCISTG, any independence that cannot be read off the SWIG cannot be assumed to hold.) Therefore, we cannot ensure that the average treatment effect $\mathrm{E}[Y^{a=1}] - \mathrm{E}[Y^{a=0}]$ is identified from data on (L, A, Y).

Note that the problem arises because L is a descendant of A, not because L is in the future of A. If, in Figure 7.9, the arrow from A to L did not exist, then L would be a non-descendant of A that blocks all the backdoor paths. Therefore adjusting for L would eliminate all bias, even if L were still in the future of A. What matters is the topology of the causal diagram (which variables cause which variables), not the time sequence of the nodes.

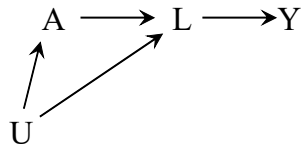


Figure 7.9

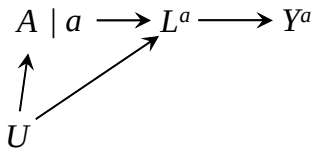


Figure 7.10

from observational data a risky undertaking.

There is a scientific consequence to the potential confounding in observational studies. Suppose you conducted an observational study to identify the effect of heart transplant A on death Y and that you assumed no unmeasured confounding given disease severity L. A critic of your study says "the inferences from this observational study may be incorrect because of potential confounding." The critic is not making a scientific statement, but a logical one. Since the findings from *any* observational study may be confounded, it is obviously true that those of your study can be confounded. If the critic's intent was to provide evidence about the shortcomings of your particular study, he failed. His criticism is noninformative because he simply restated a characteristic of observational research that you and the critic already knew before the study was conducted.

To appropriately criticize your study, the critic needs to work harder and engage in a truly scientific conversation. For example, the critic may cite experimental or observational findings that contradict your findings, or he can say something along the lines of "the inferences from this observational study may be incorrect because of potential confounding due to cigarette smoking, a common cause through which a backdoor path may remain open". This latter option provides you with a testable challenge to your assumption of no unmeasured confounding. The burden of the proof is again yours. Your next move is to try and adjust for smoking. The next section reviews the methods to adjust for confounding when, as in Figures 7.1-7.3, enough confounders L are measured to block all backdoor paths between treatment and outcome.

Though the above discussion was restricted to bias due to confounding, the absence of biases due to selection and measurement is also needed for valid causal inference from observational data (as discussed in the next chapters). But, unlike the expectation of no unmeasured confounding, these other biases

may arise in *both* randomized experiments and observational studies.

7.5 How to adjust for confounding

Randomization is the preferred method to control confounding because a random assignment of treatment is expected to produce exchangeability of the treated and the untreated, either marginally or conditionally. In marginally randomized experiments, no common causes of treatment and outcome are expected to exist and thus the unadjusted association measure is expected to equal the effect measure. In conditionally randomized experiments given covariates L, the common causes (i.e., the covariates L) are measured and thus the adjusted (via standardization or IP weighting) association measure is expected to equal the effect measure. Subject-matter knowledge to identify adjustment variables is unnecessary in ideal randomized experiments.

On the other hand, subject-matter knowledge is key in observational studies in order to identify and measure adjustment variables. Causal inference from observational data relies on the uncheckable assumption that we have used our expert knowledge to identify and measure a set of variables L that is a *sufficient set for confounding adjustment*, that is, a set of non-descendants of treatment that includes enough variables to block all backdoor paths. Under this assumption of no unmeasured confounding or of conditional exchangeability given L, standardization and IP weighting can be used to compute the average causal effect in the population.

As discussed in Section 4.6, standardization and IP weighting are not the only methods used to adjust for confounding in observational studies. Methods for confounding adjustment can be classified into the two following categories:

The 'g' in g-methods stands for 'generalized'.

- G-methods: G-formula (the general form of standardization), IP weighting, G-estimation. Methods that exploit conditional exchangeability in subsets defined by L to estimate the causal effect of A on Y in the entire population or in any subset of the population. In our heart transplant study, we used g-methods to adjust for confounding by disease severity L in Sections 2.4 (standardization) and 2.5 (IP weighting). The causal risk ratio in the population was 1. G-methods are described in detail in Part II and Part III

The parametric and semiparametric extensions of g-methods are the parametric g-formula (standardization), IP weighting of marginal structural models, and g-estimation of nested structural models. The parametric and semiparametric extension of stratification is conventional regression. See Part II.

- Stratification-based methods: Stratification, Restriction, Matching. Methods that exploit conditional exchangeability in subsets defined by L to estimate the association between A and Y in those subsets only. In our heart transplant study, we used stratification-based methods to adjust for confounding by disease severity L in Sections 4.4 (stratification, restriction) and 4.5 (matching). The causal risk ratio was 1 in all the subsets of the population that we studied because there was no effect-measure modification.

Under the assumption of conditional exchangeability given L, g-methods simulate the A-Y association in the population if backdoor paths involving the measured variables L did not exist; the simulated A-Y association can then be entirely attributed to the effect of A on Y. For example, IP weighting achieves this by creating a pseudo-population in which treatment A is independent of the measured confounders L, that is, by "deleting" the arrow from L to A. The practical implications of "deleting" the arrow from measured confounders L to

treatment A will become apparent when we discuss time-varying treatments and confounders in Part III.

Stratification-based methods estimate the association between treatment and outcome in one or more subsets of the population in which the treated and the untreated are assumed to be exchangeable. Hence the A-Y association in each subset is entirely attributed to the effect of A on Y. In graph terms, stratification/restriction do not delete the arrow from L to A but rather compute the conditional effect in a subset of the observed population (in which there is an arrow from L to A), which is represented by adding a box around variable L. Matching works by computing the effect in a selected subset of the observed population, which is represented by adding a selection node that is conditioned on (see Fine Point 6.2 and Chapter 8). A common variation of restriction, stratification, and matching replaces each individual's measured variables L by the individual's estimated probability of receiving treatment $\Pr[A = 1|L]$: the propensity score (Chapter 15).

A common variation of restriction, stratification, and matching replaces each individual's measured variables L by the individual's estimated probability of receiving treatment $\Pr[A = 1|L]$: the *propensity score* (Rosenbaum and Rubin 1983). See Chapter 15.

Causal diagrams in this chapter include only fixed treatments that do not vary over time, but the structural definitions of confounding and confounders can be generalized to the case of time-varying treatments. When the treatment is time-varying, then so can be the confounders.In settings with time-varying confounders and treatments, g-methods are the methods of choice to adjust for confounding because stratification-based methods for confounding adjustment may result in selection bias. The bias of stratification-based methods is described in Part III.

A time-varying confounder is a time-varying variable that can be used to help eliminate confounding for the effect of a time-varying treatment.

All the above methods require conditional exchangeability given the measured covariates L to identify the effect of treatment A on outcome Y, i.e., the condition that the investigator has measured enough variables L to block all backdoor paths between A and Y. When interested in the effect in the entire population, conditional exchangeability is required in all strata defined by L; when interested in the effect in a subset of the population, conditional exchangeability is required in that subset only. Achieving conditional exchangeability may be an unrealistic goal in many observational studies but, as discussed in Section 3.2, expert knowledge can be used to get as close as possible to that goal.

Technically, g-estimation requires the slightly weaker assumption that the magnitude of unmeasured confounding given L is known, of which the assumption of no unmeasured confounding is a particular case. See Chapter 14.

In addition, expert knowledge can be used to avoid adjusting for variables that may introduce bias. At the very least, investigators should generally avoid adjustment for variables affected by either the treatment or the outcome. Of course, thoughtful and knowledgeable investigators could believe that two or more causal structures, possibly leading to different conclusions regarding confounding and confounders, are equally plausible. In that case they would perform multiple analyses and explicitly state the assumptions about causal structure required for the validity of each. Unfortunately, one can never be certain that the set of causal structures under consideration includes the true one; this uncertainty is unavoidable with observational data.

The existence of common causes of treatment and outcome, and thus the definition of confounding, does not depend on the adjustment method. We do not say that measured confounding exists simply because the adjusted estimate is different from the unadjusted estimate. In fact, adjustment for measured confounding will generally imply a change in the estimate, but not necessarily the other way around. Changes in estimates may occur for reasons other than confounding, including the introduction of selection bias when adjusting for nonconfounders (see Chapter 8) and the use of noncollapsible effect measures (see Fine Point 4.3). Attempts to define confounding based on change in estimates have been long abandoned because of these problems.

Technical Point 7.2

Difference-in-differences and negative outcome controls. Suppose we want to compute the average causal effect of aspirin A (1: yes; 0: no) on blood pressure Y, but there are unmeasured common causes U of A and Y such as history of heart disease. Then we cannot compute the effect via standardization or IP weighting because there is unmeasured confounding. But there is an alternative method that, under some conditions, may adjust for the unmeasured confounding: the use of negative outcome controls (also known as "placebo tests").

Suppose further that, for each individual in the population, we have also measured the value of the outcome right before treatment was available in the population. We refer to this pre-treatment outcome C as a negative outcome control. As depicted in Figure 7.11, U is a cause of both Y and C and treatment A is obviously not a cause of the pre-treatment outcome C. Now, even though the causal effect of A on C is known to be zero, the contrast $\mathrm{E}[C|A=1] - \mathrm{E}[C|A=0]$ is not zero because of confounding by U. In fact, $\mathrm{E}[C|A=1] - \mathrm{E}[C|A=0]$ measures the magnitude of confounding for the effect of A on C on the additive scale. If the magnitude of additive confounding for the effect of A on the negative outcome control C is the same as for the effect of A on the true outcome Y, then we can compute the effect of A on Y in the treated. Specifically, under the assumption of additive equi-confounding $\mathrm{E}\left[Y^0|A=1\right] - \mathrm{E}\left[Y^0|A=0\right] = \mathrm{E}[C|A=1] - \mathrm{E}[C|A=0]$, the effect is

$$\mathrm{E}\left[Y^1 - Y^0|A=1\right] = (\mathrm{E}[Y|A=1] - \mathrm{E}[Y|A=0]) - (\mathrm{E}[C|A=1] - \mathrm{E}[C|A=0])$$

That is, the effect in the treated is equal to the association between treatment A and outcome Y (which is a mixture of the causal effect and confounding) minus the confounding as measured by the association between treatment A and the negative outcome control C.

This method for confounding adjustment is known as difference-in-differences (Card 1990, Meyer et al. 1995, Angrist and Krueger 1999). In practice. the method is often combined with adjustment for measured covariates using parametric or semiparametric approaches (Abadie 2005). However, as explained by Sofer et al. (2016), the difference-in-differences method is a somewhat restrictive approach for using negative outcome controls: it requires measurement of the outcome both pre- and post-treatment (or at least that the true outcome Y and the C are measured on the same scale) and it requires additive equi-confounding. Sofer et al. (2016) describe more general methods that allow for Y and C to be on different scales, rely on weaker versions of equi-confounding, and incorporate adjustment for measured covariates. For a general introduction to the use of negative outcome controls to detect confounding, see Lipsitch et al (2010) and Flanders et al (2011).

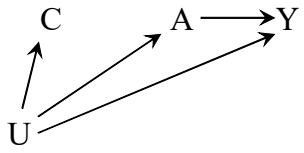


Figure 7.11

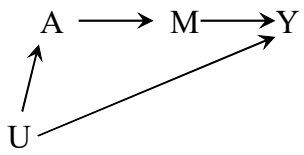


Figure 7.12

Confounding can sometimes be handled by methods that do not require conditional exchangeability of the treated and the untreated within levels of the measured covariates. These alternative methods are helpful in cases in which investigators have not been able to measure a sufficient number of confounders. Some examples of these methods are difference-in-differences (Technical Point 7.2), instrumental variable estimation (Chapter 16), the frontdoor criterion (Technical Point 7.3), and others. Unfortunately, these methods are not the panacea for confounding for two main reasons.

First, the validity of the methods requires assumptions that, like conditional exchangeability, are unverifiable. Therefore, in practice, the validity of the resulting effect estimates is not guaranteed. The choice of methods will depend on the availability of confounder data, and on the investigators's subject-matter knowledge about which unverifiable assumptions—either conditional exchangeability or the alternative conditions—are more likely to hold in a particular setting.

Second, the alternative methods cannot be generally employed for causal questions involving time-varying treatments. As a result, these methods are disqualified from consideration for many research problems that are concerned with the effects of time-varying treatments. This book focuses on the confound-

Technical Point 7.3

The frontdoor criterion. The causal diagram in Figure 7.12 depicts a setting in which the treatment A and the binary outcome Y share an unmeasured cause U, and in which there is a variable M that fully mediates the effect of A on Y and that shares no unmeasured cases with neither A nor Y. Under this causal structure, a data analyst cannot directly use standardization (nor IP weighting) to compute the counterfactual risks $\Pr\left[Y^{a=1}=1\right]$ and $\Pr\left[Y^{a=0}=1\right]$ because the variable U, which is necessary to block the backdoor path between A and Y, is not available. Therefore, the average causal effect of A on Y cannot be identified using these methods. Note, however, that one can readily compute (i) the effect of A on M because there is no confounding for that effect, and (ii) the effect of M on Y because A blocks the only backdoor path.

Pearl (1995) showed that, under the causal structure depicted by Figure 7.12, $\Pr[Y^a=1] = \sum_m \Pr[M^a=m]\Pr[Y^m=1]$ and thus one can apply standardization in two steps to estimate $\Pr[Y^a=1]$. The first step computes $\Pr[M^a=m]$ as $\Pr[M=m|A=a]$ and the second step computes $\Pr[Y^m=1]$ as $\sum_{a'}\Pr[Y=1|M=m,A=a']\Pr[A=a']$. Then the two quantities are combined to compute $\Pr[Y^a=1]$ as

$$\sum_m \Pr[M=m|A=a]\sum_{a'}\Pr[Y=1|M=m,A=a']\Pr[A=a']$$

Pearl refers to this identification formula as frontdoor adjustment because it relies on the existence of a path from A and Y that, contrary to a backdoor path, goes through a descendant M of A that is a cause of Y and does not share causes with other variables. Pearl often uses the term backdoor adjustment to refer to the identification formula that we refer to as standardization.

ing adjustment methods that can be extended to time-varying treatments and confounders.

After having explored confounding in this chapter, the next chapter presents another potential source of lack of exchangeability between the treated and the untreated: selection of individuals into the analysis.

Chapter 8
SELECTION BIAS

Suppose an investigator conducted a randomized experiment to answer the causal question "does one's looking up to the sky make other pedestrians look up too?" She found a strong association between her looking up and other pedestrians' looking up. Does this association reflect a causal effect? Well, by definition of randomized experiment, confounding bias is not expected in this study. However, there was another potential problem: The analysis included only those pedestrians that, after having been part of the experiment, gave consent for their data to be used. Shy pedestrians (those less likely to look up anyway) and pedestrians in front of whom the investigator looked up (who felt tricked) were less likely to participate. Thus participating individuals in front of whom the investigator looked up (a reason to decline participation) are less likely to be shy (an additional reason to decline participation) and therefore more likely to lookup. That is, the process of selection of individuals into the analysis guarantees that one's looking up is associated with other pedestrians' looking up, regardless of whether one's looking up actually makes others look up.

An association created as a result of the process by which individuals are selected into the analysis is referred to as selection bias. Unlike confounding, this type of bias is not due to the presence of common causes of treatment and outcome, and can arise in both randomized experiments and observational studies. Like confounding, selection bias is just a form of lack of exchangeability between the treated and the untreated. This chapter provides a definition of selection bias and reviews the methods to adjust for it.

8.1 The structure of selection bias

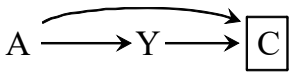


Figure 8.1

Pearl (1995) and Spirtes et al (2000) used causal diagrams to describe the structure of bias resulting from selection of individuals.

The term "selection bias" encompasses various biases that arise from the procedure by which individuals are selected into the analysis. Here we focus on bias that would arise even if the treatment had a null effect on the oucome, that is, selection bias under the null (as described in Section 6.5). The structure of selection bias can be represented by using causal diagrams like the one in Figure 8.1, which depicts dichotomous treatment A, outcome Y, and their common effect C. Suppose Figure 8.1 represents a study to estimate the effect of folic acid supplements A given to pregnant women shortly after conception on the fetus's risk of developing a cardiac malformation Y (1: yes, 0: no) during the first two months of pregnancy. The variable C represents death before birth. A cardiac malformation increases mortality (arrow from Y to C), and folic acid supplementation decreases mortality by reducing the risk of malformations other than cardiac ones (arrow from A to C). The study was restricted to fetuses who survived until birth. That is, the study was conditioned on no death $C = 0$ and hence the box around the node C.

The diagram in Figure 8.1 shows two sources of association between treatment and outcome: 1) the open path $A \rightarrow Y$ that represents the causal effect of A on Y, and 2) the open path $A \rightarrow C \leftarrow Y$ that links A and Y through their (conditioned on) common effect C. An analysis conditioned on C will generally result in an association between A and Y. We refer to this induced association between the treatment A and the outcome Y as selection bias due to conditioning on C. Because of selection bias, the associational risk ratio $\Pr[Y = 1|A = 1, C = 0]/\Pr[Y = 1|A = 0, C = 0]$ does not equal the causal

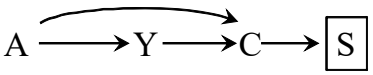


Figure 8.2

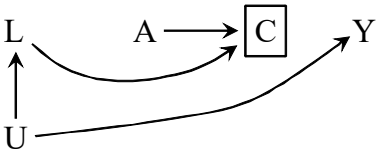


Figure 8.3

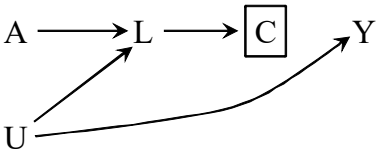


Figure 8.4

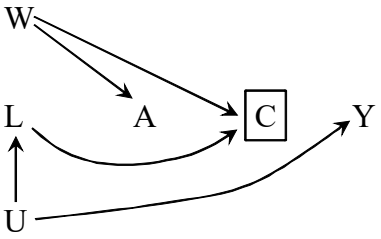


Figure 8.5

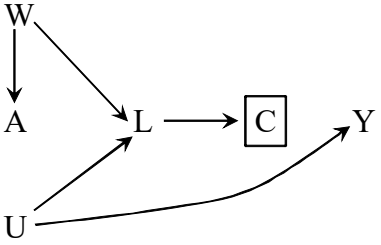


Figure 8.6

risk ratio $\Pr\left[Y^{a=1}=1\right]/\Pr\left[Y^{a=0}=1\right]$; association is not causation. If the analysis were not conditioned on the common effect (collider) C, then the only open path between treatment and outcome would be $A \rightarrow Y$, and thus the entire association between A and Y would be due to the causal effect of A on Y. That is, the associational risk ratio $\Pr[Y=1|A=1]/\Pr[Y=1|A=0]$ would equal the causal risk ratio $\Pr\left[Y^{a=1}=1\right]/\Pr\left[Y^{a=0}=1\right]$; association would be causation.

The causal diagram in Figure 8.2 shows another example of selection bias. This diagram includes all variables in Figure 8.1 plus a node S representing parental grief (1: yes, 0: no), which is affected by vital status at birth. Suppose the study was restricted to non grieving parents $S=0$ because the others were unwilling to participate. As discussed in Chapter 6, conditioning on a variable S affected by the collider C also opens the path $A \rightarrow C \leftarrow Y$.

Both Figures 8.1 and 8.2 depict examples of selection bias in which the bias arises because of conditioning on a common effect of treatment and outcome: C in Figure 8.1 and S in Figure 8.2. This bias arises regardless of whether there is an arrow from A to Y, that is, it is selection bias under the null. Remember that causal stuctures that result in bias under the null also cause bias when the treatment has a non-null effect. Both confounding due to common causes of treatment and outcome (see previous chapter) and selection bias due to conditioning on common effects of treatment and outcome are examples of bias under the null. However, selection bias under the null can be defined more generally as illustrated by Figures 8.3 to 8.6.

Consider the causal diagram in Figure 8.3, which represents a follow-up study of HIV-positive individuals to estimate the effect of certain antiretroviral treatment A on the 3-year risk of death Y (to reduce clutter, there is no arrow from A to Y). The unmeasured variable U represents high level of immunosuppression (1: yes, 0: no). Individuals with $U=1$ have a greater risk of death. Individuals who drop out from the study or are otherwise lost to follow-up are censored ($C=1$). Individuals with $U=1$ are more likely to be censored because the severity of their disease prevents them from participating in the study. The effect of U on censoring C is mediated by the presence of symptoms (fever, weight loss, diarrhea, and so on), CD4 count, and viral load in plasma, all included in L, which could or could not be measured. (The role of L, when measured, in data analysis is discussed in Section 8.5; in this section, we take L to be unmeasured.) Individuals receiving treatment are at a greater risk of experiencing side effects, which could lead them to dropout, as represented by the arrow from A to C. The square around C indicates that the analysis is restricted to individuals who remained uncensored ($C=0$) because those are the only ones in which Y can be assessed.

According to the rules of d-separation, conditioning on the collider C opens the path $A \rightarrow C \leftarrow L \leftarrow U \rightarrow Y$ and thus association flows from treatment A to outcome Y, i.e., the associational risk ratio is not equal to 1 even though the causal risk ratio is equal to 1. Figure 8.3 can be viewed as a simple transformation of Figure 8.1: the association between Y and C resulting from a direct effect of Y on C in Figure 8.1 is now the result of U, a common cause of Y and C. Some intuition for this bias: If a treated individual with treatment-induced side effects (and thereby at a greater risk of dropping out) did in fact not drop out ($C=0$), then it is generally less likely that a second independent cause of dropping out (e.g., $U=1$) was present. Therefore, an inverse association between A and U would be expected in those who did not drop out ($C=0$). Because U is positively associated with the outcome Y, restricting the analysis to individuals who did not drop out of this study

induces an inverse association between A and Y.

The bias in Figure 8.3 is an example of selection bias that results from conditioning on the censoring variable C, which is a common effect of treatment A and *a cause U of* the outcome Y, rather than of the outcome itself. We now present three additional causal diagrams that could lead to selection bias by differential loss to follow up. In Figure 8.4 prior treatment A has a direct effect on symptoms L. Restricting the study to the uncensored individuals again implies conditioning on the common effect C of A and U, thereby introducing an association between treatment and outcome. Figures 8.5 and 8.6 are variations of Figures 8.3 and 8.4, respectively, in which there is a common cause W of A and another measured variable. W indicates unmeasured lifestyle/personality/educational variables that determine both treatment (arrow from W to A) and either attitudes toward attending study visits (arrow from W to C in Figure 8.5) or threshold for reporting symptoms (arrow from W to L in Figure 8.6).

Figures 8.5 and 8.6 show examples of M-bias.

We have described some different causal structures, depicted in Figures 8.1-8.6, that may lead to selection bias. In all these cases, the bias is the result of selection on a common effect of two other variables in the diagram, i.e., a collider. We will use the term selection bias to refer to all biases that arise from conditioning on a common effect of two variables, one of which is either the treatment or a cause of treatment, and the other is either the outcome or a cause of the outcome. We now describe some examples of selection bias that share this structure.

More generally, selection bias can be defined as the bias resulting from conditioning on the common effect of two variables, one of which is either the treatment or associated with the treatment, and the other is either the outcome or associated with the outcome (Hernán, Hernández-Díaz, and Robins 2004).

8.2 Examples of selection bias

Consider the following examples of bias due to the mechanism by which individuals are selected into the analysis:

- *Differential loss to follow-up*: This is precisely the bias described in the previous section and summarized in Figures 8.3-8.6. It is also referred to as bias due to *informative censoring*.

- *Missing data bias*, *nonresponse bias*: The variable C in Figures 8.3-8.6 can represent missing data on the outcome for any reason, not just as a result of loss to follow up. For example, individuals could have missing data because they are reluctant to provide information or because they miss study visits. Regardless of the reasons why data on Y are missing, restricting the analysis to individuals with complete data ($C = 0$) may result in bias.

- *Healthy worker bias*: Figures 8.3–8.6 can also describe a bias that could arise when estimating the effect of an occupational exposure A (e.g., a chemical) on mortality Y in a cohort of factory workers. The underlying unmeasured true health status U is a determinant of both death Y and of being at work C (1: no, 0: yes). The study is restricted to individuals who are at work ($C = 0$) at the time of outcome ascertainment. (L could be the result of blood tests and a physical examination.) Being exposed to the chemical reduces the probability of being at work in the near future, either directly (e.g., exposure can cause disabling asthma), like in Figures 8.3 and 8.4, or through a common cause W (e.g., certain

Fine Point 8.1

Selection bias in case-control studies. Figure 8.1 can be used to represent selection bias in a case-control study. Suppose a certain investigator wants to estimate the effect of postmenopausal estrogen treatment A on coronary heart disease Y. The variable C indicates whether a woman in the study population (the underlying cohort, in epidemiologic terms) is selected for the case-control study (1: no, 0: yes). The arrow from disease status Y to selection C indicates that cases in the population are more likely to be selected than noncases, which is the defining feature of a case-control study. In this particular case-control study, the investigator decided to select controls ($Y = 0$) preferentially among women with a hip fracture. Because treatment A has a protective causal effect on hip fracture, the selection of controls with hip fracture implies that treatment A now has a causal effect on selection C. This effect of A on C is represented by the arrow $A \rightarrow C$. One could add an intermediate node F (representing hip fracture) between A and C, but that is unnecessary for our purposes.

In a case-control study, the association measure (the treatment-outcome odds ratio) is by definition conditional on having been selected into the study ($C = 0$). If individuals with hip fracture are oversampled as controls, then the probability of control selection depends on a consequence of treatment A (as represented by the path from A to C) and "inappropriate control selection" bias will occur. Again, this bias arises because we are conditioning on a common effect C of treatment and outcome. A heuristic explanation of this bias follows. Among individuals selected for the study ($C = 0$), controls are more likely than cases to have had a hip fracture. Therefore, because estrogens lower the incidence of hip fractures, a control is less likely to be on estrogens than a case, and hence the A-Y odds ratio conditional on $C = 0$ would be greater than the causal odds ratio in the population. Other forms of selection bias in case-control studies, including some biases described by Berkson (1946) and incidence-prevalence bias, can also be represented by Figure 8.1 or modifications of it, as discussed by Hernán, Hernández-Díaz, and Robins (2004).

exposed jobs are eliminated for economic reasons and the workers laid off) like in Figures 8.5 and 8.6.

Berkson (1955) described the structure of bias due to self-selection.

- *Self-selection bias*, *volunteer bias*: Figures 8.3-8.6 can also represent a study in which C is agreement to participate (1: no, 0: yes), A is cigarette smoking, Y is coronary heart disease, U is family history of heart disease, and W is healthy lifestyle. (L is any mediator between U and C such as heart disease awareness.) Under any of these structures, selection bias may be present if the study is restricted to those who volunteered or elected to participate ($C = 0$).

Robins, Hernán, and Rotnitzky (2007) used causal diagrams to describe the structure of bias due to the effect of pre-study treatments on selection into the study.

- *Selection affected by treatment received before study entry*: Suppose that C in Figures 8.3-8.6 represents selection into the study (1: no, 0: yes) and that treatment A took place before the study started. If treatment affects the probability of being selected into the study, then selection bias is expected. The case of selection bias arising from the effect of treatment on selection into the study can be viewed as a generalization of self-selection bias. This bias may be present in any study that attempts to estimate the causal effect of a treatment that occurred before the study started or in which treatment includes a pre-study component. For example, selection bias may arise when treatment is measured as the lifetime exposure to certain factor (medical treatment, lifestyle behavior...) in a study that recruited 50 year-old participants. In addition to selection bias, it is also possible that there exists unmeasured confounding for the pre-study component of treatment if confounders were only measured during the study.

In addition to the biases described here, as well as in Fine Point 8.1 and Technical Point 8.1, causal diagrams have been used to characterize various

other biases that arise from conditioning on a common effect. These examples show that selection bias may occur in *retrospective studies*—those in which data on treatment A are collected *after* the outcome Y occurs—and in *prospective studies*—those in which data on treatment A are collected *before* the outcome Y occurs. Further, these examples show that selection bias may occur both in observational studies and in randomized experiments.

For example, selection bias may be induced by attempts to eliminate ascertainment bias (Robins 2001), to estimate direct effects (Cole and Hernán 2002), and by conventional adjustment for variables affected by previous treatment (see Part III).

Take Figures 8.3 and 8.4, which could depict either an observational study or an experiment in which treatment A is randomly assigned, because there are no common causes of A and any other variable. Individuals in *both* randomized experiments and observational studies may be lost to follow-up or drop out of the study before their outcome is ascertained. When this happens, the risk $\Pr[Y = 1|A = a]$ cannot be computed because the value of the outcome Y is unknown for the censored individuals ($C = 1$). Therefore only the risk among the uncensored $\Pr[Y = 1|A = a, C = 0]$ can be computed. This restriction of the analysis to the uncensored individuals may induce selection bias because uncensored individuals who remained through the end of the study ($C = 0$) may not be exchangeable with individuals that were lost ($C = 1$).

Hence a key difference between confounding and selection bias: randomization protects against confounding, but not against selection bias when the selection occurs after the randomization. On the other hand, no bias arises in randomized experiments from selection into the study before treatment is assigned. For example, only volunteers who agree to participate are enrolled in randomized clinical trials, but such trials are not affected by volunteer bias because participants are randomly assigned to treatment only after agreeing to participate ($C = 0$). Thus none of Figures 8.3-8.6 can represent volunteer bias in a randomized trial. Figures 8.3 and 8.4 are eliminated because treatment cannot cause agreement to participate C. Figures 8.5 and 8.6 are eliminated because, as a result of the random treatment assignment, there cannot exist a common cause of treatment and any other variable.

8.3 Selection bias and confounding

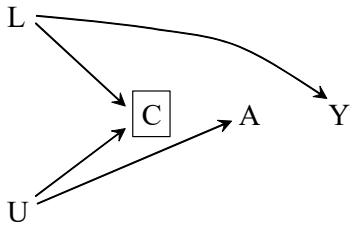


Figure 8.7

For the same reason, social scientists often refer to unmeasured confounding as *selection on unobservables*.

In this and the previous chapter, we describe two reasons why the treated and the untreated may not be exchangeable: 1) the presence of common causes of treatment and outcome, and 2) conditioning on common effects of treatment and outcome (or causes of them). We refer to biases due to the presence of common causes as "confounding" and to those due to conditioning on common effects as "selection bias." This structural definition provides a clear-cut classification of confounding and selection bias, even though it might not coincide perfectly with the traditional terminology of some disciplines. For example, statisticians and econometricians often use the term "selection bias" to refer to both types of biases; the rationale is that in both cases the bias is due to selection: selection of individuals into the anaysis (the structural "selection bias") or selection of individuals into a treatment (the structural "confounding"). Our goal, however, is not to be normative about terminology, but rather to emphasize that, regardless of the particular terms chosen, there are two distinct causal structures that lead to bias.

The end result of both structures is lack of exchangeability between the treated and the untreated—which implies that these two biases occur even under the null. For example, consider a study restricted to firefighters that aims to estimate the causal effect of being physically active A on the risk

Technical Point 8.1

The built-in selection bias of hazard ratios. The causal DAG in Figure 8.8 describes a randomized experiment of the effect of heart transplant A on death at times 1 (Y_1) and 2 (Y_2). The arrow from A to Y_1 represents that transplant decreases the risk of death at time 1. The lack of an arrow from A to Y_2 indicates that A has no direct effect on death at time 2. That is, heart transplant does not influence the survival status at time 2 of any individual who would survive past time 1 when untreated (and thus when treated). U is an unmeasured haplotype that decreases the individual's risk of death at all times. Because of the absence of confounding, the associational risk ratios $aRR_{AY_1} = \frac{\Pr[Y_1=1|A=1]}{\Pr[Y_1=1|A=0]}$ and $aRR_{AY_2} = \frac{\Pr[Y_2=1|A=1]}{\Pr[Y_2=1|A=0]}$ are unbiased measures of the effect of A on death at times 1 and 2, respectively. Note that, even though A has no direct effect on Y_2, aRR_{AY_2} will be less than 1 because it is a measure of the effect of A on total mortality through time 2.

Consider now the time-specific hazard ratio (which, for all practical purposes, is equivalent to the rate ratio). In discrete time, the hazard of death at time 1 is the probability of dying at time 1 and thus the associational hazard ratio is the same as aRR_{AY_1}. However, the hazard at time 2 is the probability of dying at time 2 among those who survived past time 1. Thus, the associational hazard ratio at time 2 is then $aRR_{AY_2|Y_1=0} = \frac{\Pr[Y_2=1|A=1,Y_1=0]}{\Pr[Y_2=1|A=0,Y_1=0]}$. The square around Y_1 in Figure 8.8 indicates this conditioning. Treated survivors of time 1 are less likely than untreated survivors of time 1 to have the protective haplotype U (because treatment can explain their survival) and therefore are more likely to die at time 2. That is, conditional on Y_1, treatment A is associated with a higher mortality at time 2. Thus, the hazard ratio at time 1 is less than 1, whereas the hazard ratio at time 2 is greater than 1, i.e., the hazards have crossed. We conclude that the hazard ratio at time 2 is a biased estimate of the direct effect of treatment on mortality at time 2. The bias is selection bias arising from conditioning on a common effect Y_1 of treatment A and of U, which is a cause of Y_2 that opens the associational path $A \rightarrow Y_1 \leftarrow U \rightarrow Y_2$ between A and Y_2. In the survival analysis literature, an unmeasured cause of death that is marginally unassociated with treatment such as U is often referred to as a *frailty*.

In contrast, the conditional hazard ratio $aRR_{AY_2|Y_1=0,U}$ is 1 within each stratum of U because the path $A \rightarrow Y_1 \leftarrow U \rightarrow Y_2$ is now blocked by conditioning on the noncollider U. Thus, the conditional hazard ratio correctly indicates the absence of a direct effect of A on Y_2. That the unconditional hazard ratio $aRR_{AY_2|Y_1=0}$ differs from the stratum-specific hazard ratios $aRR_{AY_2|Y_1=0,U}$, even though U is independent of A, shows the noncollapsibility of the hazard ratio (Greenland, 1996b). Unfortunately, the unbiased measure $aRR_{AY_2|Y_1=0,U}$ of the direct effect of A on Y_2 cannot be computed because U is unobserved. In the absence of data on U, it is impossible to know whether A has a direct effect on Y_2. That is, the data cannot determine whether the true causal DAG generating the data was that in Figure 8.8 or in Figure 8.9. All of the above applies to both observational studies and randomized experiments.

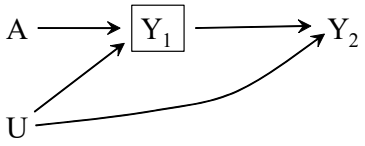


Figure 8.8

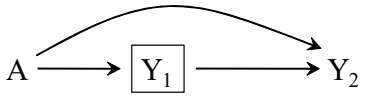


Figure 8.9

of heart disease Y as represented in Figure 8.7. For simplicity, we assume that, unknown to the investigators, A does not cause Y. Parental socioeconomic status L affects the risk of becoming a firefighter C and, through childhood diet, of heart disease Y. Attraction toward activities that involve physical activity (an unmeasured variable U) affects the risk of becoming a firefighter and of being physically active (A). U does not affect Y, and L does not affect A. According to our terminology, there is no confounding because there are no common causes of A and Y. Thus, the associational risk ratio $\Pr[Y=1|A=1] / \Pr[Y=1|A=0]$ is expected to equal the causal risk ratio $\Pr\left[Y^{a=1}=1\right] / \Pr\left[Y^{a=0}=1\right] = 1$.

However, in a study restricted to firefighters ($C = 0$), the associational and causal risk ratios would differ because conditioning on a common effect C of causes of treatment and outcome induces selection bias resulting in lack of exchangeability of the treated and untreated firefighters. To the study investigators, the distinction between confounding and selection bias is moot because, regardless of nomenclature, they must adjust for L to make the treated and the untreated firefighters comparable. This example demonstrates that a structural classification of bias does not always have consequences for the

analysis of a study. Indeed, for this reason, many epidemiologists use the term "confounder" for any variable L on which one has to adjust for, regardless of whether the lack of exchangeability is the result of conditioning on a common effect or the result of a common cause of treatment and outcome.

There are, however, advantages of adopting a structural approach to the classification of sources of non exchangeability. First, the structure of the problem frequently guides the choice of analytical methods to reduce or avoid the bias. For example, in longitudinal studies with time-varying treatments, identifying the structure allows us to detect situations in which adjustment for confounding via stratification would introduce selection bias (see Part III). In those cases, g-methods are a better alternatives. Second, even when understanding the structure of bias does not have implications for data analysis (like in the firefighters' study), it could still help study design. For example, investigators running a study restricted to firefighters should make sure that they collect information on joint risk factors for the outcome Y and for the selection variable C (i.e., becoming a firefighter), as described in the first example of confounding in Section 7.1. Third, selection bias resulting from conditioning on pre-treatment variables (e.g., being a firefighter) could explain why certain variables behave as "confounders" in some studies but not others. In our example, parental socioeconomic status L would not necessarily need to be adjusted for in studies not restricted to firefighters. Finally, causal diagrams enhance communication among investigators and may decrease the occurrence of misunderstandings.

The choice of terminology usually has no practical consequences, but disregard for the causal structure may lead to apparent paradoxes. For example, the so-called Simpson's paradox (1951) was the result of ignoring the difference between common causes and common effects. Interestingly, Blyth (1972) failed to grasp the causal structure of the paradox in Simpson's example and misrepresented it as an extreme case of confounding. Because most people read Blyth's paper but not Simpson's paper, the misunderstanding was perpetuated. See Hernán, Clayton, and Keiding (2011) for details.

As an example of the last point, consider the "*healthy worker bias*". We described this bias in the previous section as an example of a bias that arises from conditioning on the variable C, which is a common effect of (a cause of) treatment and (a cause of) the outcome. Thus the bias can be represented by the causal diagrams in Figures 8.3-8.6. However, the term "healthy worker bias" is also used to describe the bias that occurs when comparing the risk in certain group of workers with that in a group of individuals from the general population.

This second bias can be depicted by the causal diagram in Figure 7.1 in which L represents health status, A represents membership in the group of workers, and Y represents the outcome of interest. There are arrows from L to A and Y because being healthy affects job type and risk of subsequent outcome, respectively. In this case, the bias is caused by the common cause L and we would refer to it as confounding. The use of causal diagrams to represent the structure of the "healthy worker bias" prevents any confusions that may arise from employing the same term for different sources of non-exchangeability.

All the above considerations ignore the magnitude or direction of selection bias confounding. However, it is possible that some noncausal paths opened by conditioned on a collider are weak and thus induce little bias. Because selection bias is not an "all or nothing" issue, in practice, it is important to consider the expected direction and magnitude of the bias (see Fine Point 8.2).

8.4 Selection bias and censoring

Suppose an investigator conducted a marginally randomized experiment to estimate the average causal effect of wasabi intake on the one-year risk of death ($Y = 1$). Half of the 60 study participants were randomly assigned to eating meals supplemented with wasabi ($A = 1$) until the end of follow-up or

death, whichever occurred first. The other half were assigned to meals that contained no wasabi ($A = 0$). After 1 year, 17 individuals died in each group. That is, the associational risk ratio $\Pr[Y = 1|A = 1] / \Pr[Y = 1|A = 0]$ was 1. Because of randomization, the causal risk ratio $\Pr\left[Y^{a=1} = 1\right] / \Pr\left[Y^{a=0} = 1\right]$ is also expected to be 1. (If ignoring random variability bothers you, please imagine the study had 60 million patients rather than 60.)

Unfortunately, the investigator could not observe the 17 deaths that occurred in each group because many patients were lost to follow-up, or censored, before the end of the study (i.e., death or one year after treatment assignment). The proportion of censoring ($C = 1$) was higher among patients with heart disease ($L = 1$) at the start of the study and among those assigned to wasabi supplementation ($A = 1$). In fact, only 9 individuals in the wasabi group and 22 individuals in the other group were not lost to follow-up. The investigator observed 4 deaths in the wasabi group and 11 deaths in the other group. That is, the associational risk ratio $\Pr[Y = 1|A = 1, C = 0] / \Pr[Y = 1|A = 0, C = 0]$ was $(4/9)/(11/22) = 0.89$ among the uncensored. The risk ratio of 0.89 in the uncensored differs from the causal risk ratio of 1 in the entire population: There is selection bias due to conditioning on the common effect C.

The causal diagram in Figure 8.3 depicts the relation between the variables L, A, C, and Y in the randomized trial of wasabi. U represents atherosclerosis, an unmeasured variable, that affects both heart disease L and death Y. Figure 8.3 shows that there are no common causes of A and Y, as expected in a marginally randomized experiment, and thus there is no need to adjust for confounding to compute the causal effect of A on Y. On the other hand, Figure 8.3 shows that there is a common cause U of C and Y. The presence of this backdoor path $C \leftarrow L \leftarrow U \rightarrow Y$ implies that, were the investigator interested in estimating the causal effect of censoring C on Y (which is null in Figure 8.3), she would have to adjust for confounding due to the common cause U. The backdoor criterion says that such adjustment is possible because the measured variable L can be used to block the backdoor path $C \leftarrow L \leftarrow U \rightarrow Y$.

The causal contrast we have considered so far is "the risk if everybody had been treated", $\Pr\left[Y^{a=1} = 1\right]$, versus "the risk if everybody had remained untreated", $\Pr\left[Y^{a=0} = 1\right]$, and this causal contrast does not involve C at all. Why then are we talking about confounding for the causal effect of C? It turns out that the causal contrast of interest needs to be modified in the presence of censoring or, in general, of selection. Because selection bias would not exist if everybody had been uncensored $C = 0$, we would like to consider a causal contrast that reflects what would have happened in the absence of censoring.

Let $Y^{a=1,c=0}$ be an individual's counterfactual outcome if he had received treatment $A = 1$ *and* he had remained uncensored $C = 0$. Similarly, let $Y^{a=0,c=0}$ be an individual's counterfactual outcome if he had not received treatment $A = 0$ *and* he had remained uncensored $C = 0$. Our causal contrast of interest is now "the risk if everybody had been treated and had remained uncensored", $\Pr\left[Y^{a=1,c=0} = 1\right]$, versus "the risk if everybody had remained untreated and uncensored", $\Pr\left[Y^{a=0,c=0} = 1\right]$.

For example, we may want to compute the causal risk ratio $\mathrm{E}\left[Y^{a=1,c=0}\right] / \mathrm{E}\left[Y^{a=0,c=0}\right]$ or the causal risk difference $\mathrm{E}\left[Y^{a=1,c=0}\right] - \mathrm{E}\left[Y^{a=0,c=0}\right]$.

Often it is reasonable to assume that censoring does not have a causal effect on the outcome (an exception would be a setting in which being lost to follow-up prevents people from getting additional treatment). Because of the lack of effect of censoring C on the outcome Y, one might imagine that the definition of causal effect could ignore censoring, i.e., that we could omit the superscript $c = 0$. However, omitting the superscript would obscure the fact that considerations about confounding for C become central when computing the causal effect on A on Y in the presence of selection bias. In fact, when

In causal diagrams with no arrow from censoring C to the observed outcome Y, we could replace Y by the counterfactual outcome $Y^{c=0}$ and add arrows $Y^{c=0} \longrightarrow Y$ and $C \longrightarrow Y$.

conceptualizing the causal contrast of interest in terms of $Y^{a=0,c=0}$, we can think of censoring C as just another treatment. That is, the goal of the analysis is to compute the causal effect of a joint intervention on A and C. To eliminate selection bias for the effect of treatment A, we need to adjust for confounding for the effect of treatment C.

Since censoring C is now viewed as a treatment, it follows that we will need to (i) ensure that the identifiability conditions of exchangeability, positivity, and consistency hold for C as well as for A, and (ii) use analytical methods that are identical to those we would have to use if we wanted to estimate the effect of censoring C. Under these identifiability conditions and using these methods, selection bias can be eliminated via analytic adjustment and, in the absence of measurement error and confounding, the causal effect of treatment A on outcome Y can be identified. The next section explains how to do so.

8.5 How to adjust for selection bias

Though selection bias can sometimes be avoided by an adequate design (see Fine Point 8.1), it is often unavoidable. For example, loss to follow up, self-selection, and, in general, missing data leading to bias can occur no matter how careful the investigator. In those cases, the selection bias needs to be explicitly corrected in the analysis. This correction can sometimes be accomplished by IP weighting (or by standardization), which is based on assigning a weight W^C to each selected individual ($C = 0$) so that she accounts in the analysis not only for herself, but also for those like her, i.e., with the same values of L and A, who were not selected ($C = 1$). The IP weight W^C is the inverse of the probability of her selection $\Pr[C = 0|L, A]$.

We have described IP weights to adjust for confounding, $W^A = 1/f(A|L)$, and selection bias. $W^C = 1/\Pr[C = 0|A, L]$. When both confounding and selection bias exist, the product weight $W^A W^C$ can be used to adjust simultaneously for both biases under assumptions described in Chapter 12 and Part III.

To describe the application of IP weighting for selection bias adjustment consider again the wasabi randomized trial described in the previous section. The tree graph in Figure 8.10 presents the trial data. Of the 60 individuals in the trial, 40 had ($L = 1$) and 20 did not have ($L = 0$) heart disease at the time of randomization. Regardless of their L status, all individuals had a 50/50 chance of being assigned to wasabi supplementation ($A = 1$). Thus 10 individuals in the $L = 0$ group and 20 in the $L = 1$ group received treatment $A = 1$. This lack of effect of L on A is represented by the lack of an arrow from L to A in the causal diagram of Figure 8.3. The probability of remaining uncensored varies across branches in the tree. For example, 50% of the individuals without heart disease that were assigned to wasabi ($L = 0$, $A = 1$), whereas 60% of the individuals with heart disease that were assigned to no wasabi ($L = 1$, $A = 0$), remained uncensored. This effect of A and L on C is represented by arrows from A and L into C in the causal diagram of Figure 8.3. Finally, the tree shows how many people would have died ($Y = 1$) both among the uncensored and the censored individuals. Of course, in real life, investigators would never know how many deaths occurred among the censored individuals. It is precisely the lack of this knowledge which forces investigators to restrict the analysis to the uncensored, opening the door for selection bias. Here we show the deaths in the censored to document that, as depicted in Figure 8.3, treatment A is marginally independent on Y, and censoring C is independent of Y within levels of L. It can also be checked that the risk ratio in the entire population (inaccessible to the investigator) is 1 whereas the risk ratio in the uncensored (accessible to the investigator) is 0.89.

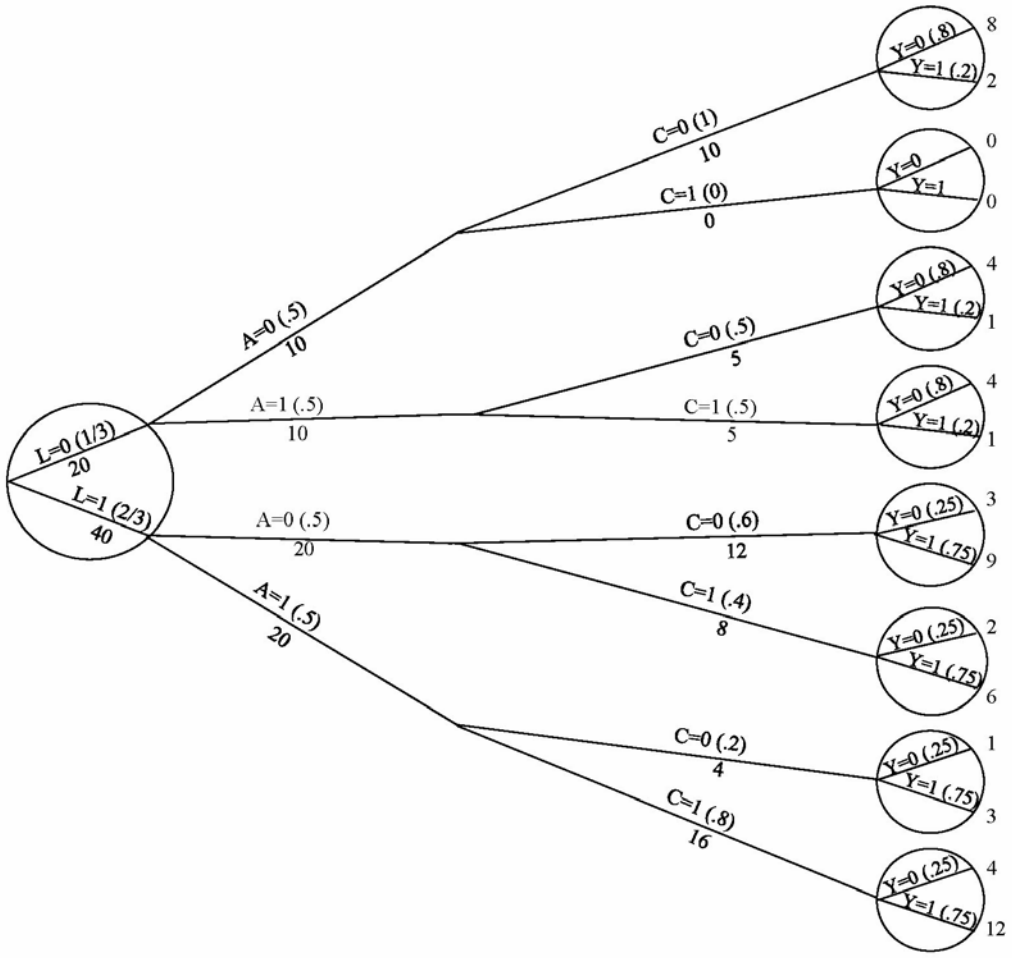


Figure 8.10

Let us now describe the intuition behind the use of IP weighting to adjust for selection bias. Look at the bottom of the tree in Figure 8.10. There are 20 individuals with heart disease ($L = 1$) who were assigned to wasabi supplementation ($A = 1$). Of these, 4 remained uncensored and 16 were lost to follow-up. That is, the conditional probability of remaining uncensored in this group is 1/5, i.e., $\Pr[C = 0|L = 1, A = 1] = 4/20 = 0.2$. In an IP weighted analysis the 16 censored individuals receive a zero weight (i.e., they do not contribute to the analysis), whereas the 4 uncensored individuals receive a weight of 5, which is the inverse of their probability of being uncensored (1/5). IP weighting replaces the 20 original individuals by 5 copies of each of the 4 uncensored individuals. The same procedure can be repeated for the other branches of the tree, as shown in Figure 8.11, to construct a pseudo-population of the same size as the original study population but in which nobody is lost to follow-up. (We let the reader derive the IP weights for each branch of the tree.) The associational risk ratio in the pseudo-population is 1, the same as the risk ratio $\Pr\left[Y^{a=1,c=0} = 1\right] / \Pr\left[Y^{a=0,c=0} = 1\right]$ that would have been computed in the original population if nobody had been censored.

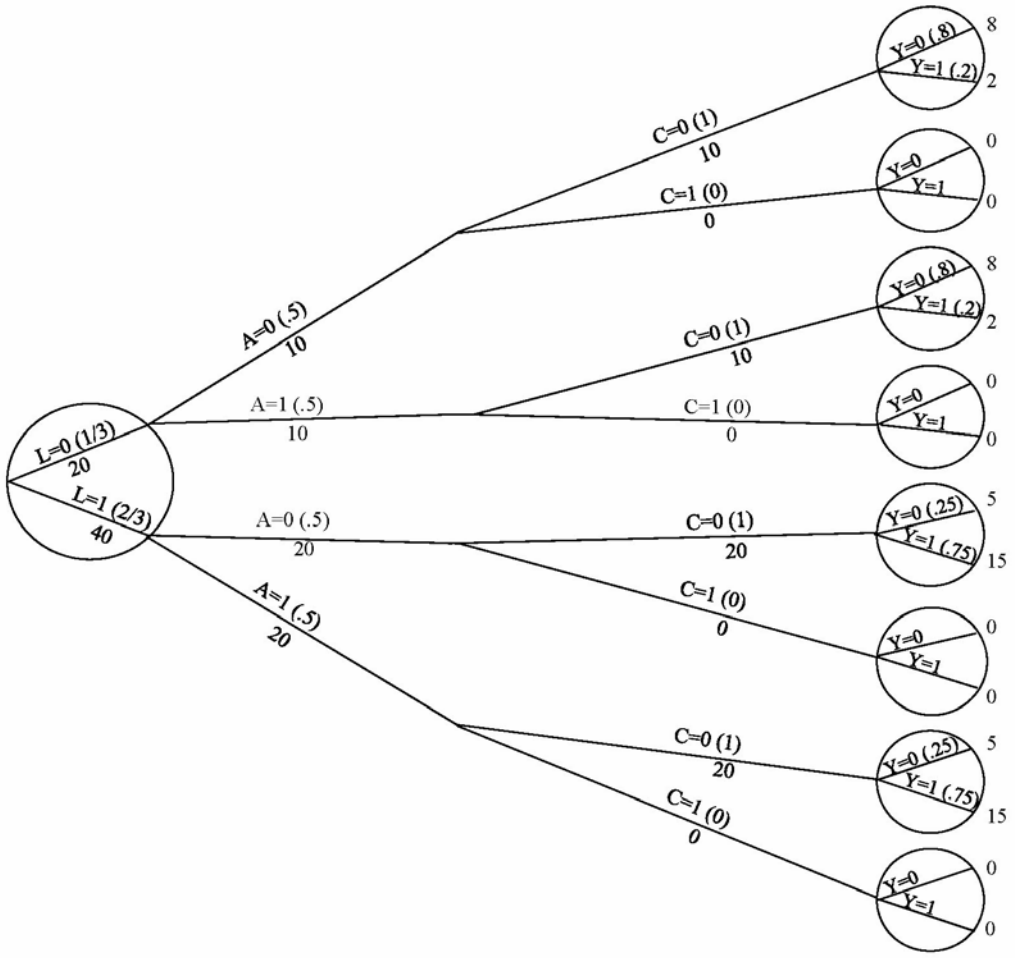


Figure 8.11

The association measure in the pseudo-population equals the effect measure in the original population if the following three identifiability conditions are met.

First, the average outcome in the uncensored individuals must equal the unobserved average outcome in the censored individuals with the same values of A and L. This provision will be satisfied if the probability of selection $\Pr[C = 0|L = 1, A = 1]$ is calculated conditional on treatment A and on all additional factors that independently predict both selection and the outcome, that is, if the variables in A and L are sufficient to block all backdoor paths between C and Y. Unfortunately, one can never be sure that these additional factors were identified and recorded in L, and thus the causal interpretation of the resulting adjustment for selection bias depends on this untestable *exchangeability* assumption.

Second, IP weighting requires that all conditional probabilities of being uncensored given the variables in L must be greater than zero. Note this *positivity* condition is required for the probability of being uncensored ($C = 0$) but not for the probability of being censored ($C = 1$) because we are not interested in inferring what would have happened if study individuals had

been censored, and thus there is no point in constructing a pseudo-population in which everybody is censored. For example, the tree in Figure 8.10 shows that $\Pr[C = 1|L = 0, A = 0] = 0$, but this zero does not affect our ability to construct a pseudo-population in which nobody is censored.

The third condition is consistency, including *well-defined interventions*. IP weighting is used to create a pseudo-population in which censoring C has been abolished, and in which the effect of the treatment A is the same as in the original population. Thus, the pseudo-population effect measure is equal to the effect measure had nobody been censored. This effect measure may be relatively well defined when censoring is the result of loss to follow up or non-response, but not when censoring is defined as the occurrence of a *competing event*. For example, in a study aimed at estimating the effect of certain treatment on the risk of Alzheimer's disease, death from other causes (cancer, heart disease, and so on) is a competing event. Defining death as a form of censoring is problematic: we might not wish to base our effect estimates on a pseudo-population in which all other causes of death have been removed, because it is unclear even conceptually what sort of intervention would produce such a population. Also, no feasible intervention could possibly remove just one cause of death without affecting the others as well.

A *competing event* is an event that prevents the outcome of interest from happening. A typical example of competing event is death because, once an individual dies, no other outcomes can occur.

Finally, one could argue that IP weighting is not necessary to adjust for selection bias in a setting like that described in Figure 8.3. Rather, one might attempt to remove selection bias by stratification (i.e., by estimating the effect measure conditional on the L variables) rather than by IP weighting. Stratification could yield unbiased conditional effect measures within levels of L because conditioning on L is sufficient to block the backdoor path from C to Y. That is, the conditional risk ratio

$$\Pr[Y = 1|A = 1, C = 0, L = l] \,/\, \Pr[Y = 1A = 0, C = 0, L = l]$$

can be interpreted as the effect of treatment among the uncensored with $L = l$. For the same reason, under the null, stratification would work (i.e., it would provide an unbiased conditional effect measure) if the data can be represented by the causal structure in Figure 8.5. Stratification, however, would not work under the structure depicted in Figures 8.4 and 8.6. Take Figure 8.4. Conditioning on L blocks the backdoor path from C to Y but also opens the path $A \rightarrow L \leftarrow U \rightarrow Y$ from A to Y because L is a collider on that path. Thus, even if the causal effect of A on Y is null, the conditional (on L) risk ratio would be generally different from 1. And similarly for Figure 8.6. In contrast, IP weighting appropriately adjusts for selection bias under Figures 8.3-8.6 because this approach is not based on estimating effect measures conditional on the covariates L, but rather on estimating unconditional effect measures after reweighting the individuals according to their treatment and their values of L.

This is the first time we discuss a situation in which stratification cannot be used to validly compute the causal effect of treatment, even if the three conditions of exchangeability, positivity, and consistency hold. We will discuss other situations with a similar structure in Part III when considering the effect of time-varying treatments.

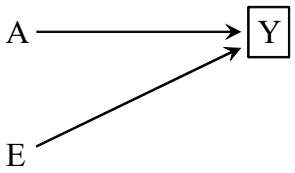


Figure 8.12

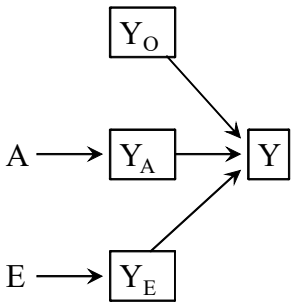


Figure 8.13

8.6 Selection without bias

The causal diagram in Figure 8.12 represents a hypothetical study with dichotomous variables surgery A, certain genetic haplotype E, and death Y.

Technical Point 8.2

Multiplicative survival model. When the conditional probability of survival $\Pr[Y=0|E=e,A=a]$ given A and E is equal to a product $g(e)h(a)$ of functions of e and a, we say that a multiplicative survival model holds. A multiplicative survival model

$$\Pr[Y=0|E=e,A=a]=g(e)h(a)$$

is equivalent to a model that assumes the survival ratio $\Pr[Y=0|E=e,A=a]/\Pr[Y=0|E=e,A=0]$ does not depend on e and is equal to $h(a)$. The data follow a multiplicative survival model when there is no interaction between A and E on the multiplicative scale as depicted in Figure 8.13. Note that if $\Pr[Y=0|E=e,A=a]=g(e)h(a)$, then $\Pr[Y=1|E=e,A=a]=1-g(e)h(a)$ does not follow a multiplicative mortality model. Hence, when A and E are conditionally independent given $Y=0$, they will be conditionally dependent given $Y=1$.

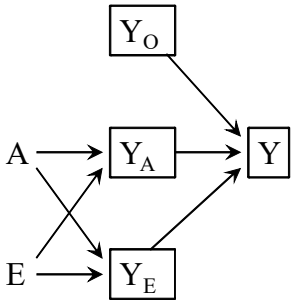


Figure 8.14

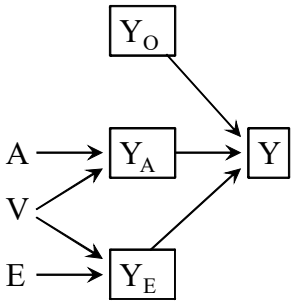


Figure 8.15

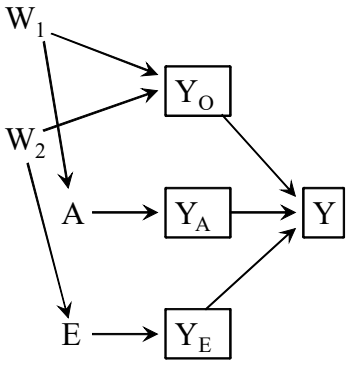


Figure 8.16

According to the rules of d-separation, surgery A and haplotype E are (i) marginally independent, i.e., the probability of receiving surgery is the same for people with and without the genetic haplotype, and (ii) associated conditionally on Y, i.e., the probability of receiving surgery varies by haplotype when the study is restricted to, say, the survivors ($Y=0$).

Indeed conditioning on the common effect Y of two independent causes A and E always induces a conditional association between A and E in at least one of the strata of Y (say, $Y=1$). However, there is a special situation under which A and E remain conditionally independent within the other stratum (say, $Y=0$).

Suppose A and E affect survival through totally independent mechanisms in such a way that E cannot possibly modify the effect of A on Y, and vice versa. For example, suppose that the surgery A affects survival through the removal of a tumor, whereas the haplotype E affects survival through increasing levels of low-density lipoprotein-cholesterol levels resulting in an increased risk of heart attack (whether or not a tumor is present). In this scenario, we can consider 3 cause-specific mortality variables: death from tumor Y_A, death from heart attack Y_E, and death from any other causes Y_O. The observed mortality variable Y is equal to 1 (death) when Y_A or Y_E or Y_O is equal to 1, and Y is equal to 0 (survival) when Y_A and Y_E and Y_O equal 0. The causal diagram in Figure 8.13, an expansion of that in Figure 8.12, represents a causal structure linking all these variables. We assume data on underlying cause of death (Y_A, Y_E, Y_O) are not recorded and thus the only measured variables are those in Figure 8.12 (A, E, Y).

Because the arrows from Y_A, Y_E and Y_O to Y are deterministic, conditioning on observed survival ($Y=0$) is equivalent to simultaneously conditioning on $Y_A=0$, $Y_E=0$, and $Y_O=0$ as well, i.e., conditioning on $Y=0$ implies $Y_A=Y_E=Y_O=0$. As a consequence, we find by applying d-separation to Figure 8.13 that A and E are conditionally independent given $Y=0$, i.e., the path, between A and E through the conditioned on collider Y is blocked by conditioning on the noncolliders Y_A, Y_E and Y_O. On the other hand, conditioning on death $Y=1$ does not imply conditioning on any specific values of Y_A, Y_E and Y_O as the event $Y=1$ is compatible with 7 possible unmeasured events: $(Y_A=1,Y_E=0,Y_O=0)$, $(Y_A=0,Y_E=1,Y_O=0)$, $(Y_A=0,Y_E=0,Y_O=1)$, $(Y_A=1,Y_E=1,Y_O=0)$, $(Y_A=0,Y_E=1,Y_O=1)$, $(Y_A=1,Y_E=0,Y_O=1)$, and $(Y_A=1,Y_E=1,Y_O=1)$. Thus, the path between A and E through the conditioned on collider Y is not blocked: A and E are associated given $Y=1$.

Fine Point 8.2

The strength and direction of selection bias. We have referred to selection bias as an "all or nothing" issue: either bias exists or it doesn't. In practice, however, it is important to consider the expected direction and magnitude of the bias.

The direction of the conditional association between 2 marginally independent causes A and E within strata of their common effect Y depends on how the two causes A and E interact to cause Y. For example, suppose that, in the presence of an undiscovered background factor U that is unassociated with A or E, having either $A = 1$ or $E = 1$ is sufficient and necessary to cause death (an "or" mechanism), but that neither A nor E causes death in the absence of U. Then among those who died ($Y = 1$), A and E will be negatively associated, because it is more likely that an individual with $A = 0$ had $E = 1$ because the absence of A increases the chance that E was the cause of death. (Indeed, the logarithm of the conditional odds ratio $OR_{AE|Y=1}$ will approach minus infinity as the population prevalence of U approaches 1.0.) This "or" mechanism was the only explanation given in the main text for the conditional association of independent causes within strata of a common effect; nonetheless, other possibilities exist.

For example, suppose that in the presence of the undiscovered background factor U, having both $A = 1$ and $E = 1$ is sufficient and necessary to cause death (an "and" mechanism) and that neither A nor E causes death in the absence of U. Then, among those who die, those with $A = 1$ are more likely to have $E = 1$, i.e., A and E are positively correlated. A standard DAG such as that in Figure 8.12 fails to distinguish between the case of A and E interacting through an "or" mechanism from the case of an "and" mechanism. Causal DAGs with sufficient causation structures (VanderWeele and Robins, 2007c) overcome this shortcoming.

Regardless of the direction of selection bias, another key issue is its magnitude. Biases that are not large enough to affect the conclusions of the study may be safely ignored in practice, whether the bias is upwards or downwards. Generally speaking, a large selection bias requires strong associations between the collider and both treatment and outcome. Greenland (2003) studied the magnitude of selection bias under the null, which he referred to as *collider-stratification bias*, in several scenarios.

In contrast with the situation represented in Figure 8.13, the variables A and E will not be independent conditionally on $Y = 0$ when one of the situations represented in Figures 8.14-8.16 occur. If A and E affect survival through a common mechanism, then there will exist an arrow either from A to Y_E or from E to Y_A, as shown in Figure 8.14. In that case, A and E will be dependent within both strata of Y. Similarly, if Y_A and Y_E are not independent because of a common cause V as shown in Figure 8.15, A and E will be dependent within both strata of Y. Finally, if the causes Y_A and Y_O, and Y_E and Y_O, are not independent because of common causes W_1 and W_2 as shown in Figure 8.16, then A and E will also be dependent within both strata of Y. When the data can be summarized by Figure 8.13, we say that the data follow a *multiplicative survival model* (see Technical Point 8.2).

Augmented causal DAGs, introduced by Hernán, Hernández-Díaz, and Robins (2004), can be extended to represent the sufficient causes described in Chapter 5 (VanderWeele and Robins, 2007c).

What is interesting about Figure 8.13 is that by adding the unmeasured variables Y_A, Y_E and Y_O, which functionally determine the observed variable Y, we have created an augmented causal diagram that succeeds in representing both the conditional independence between A and E given $Y = 0$ and the their conditional dependence given $Y = 1$.

In summary, conditioning on a collider always induces an association between its causes, but this association could be restricted to certain levels of the common effect. In other words, it is theoretically possible that selection on a common effect does not result in selection bias when the analysis is restricted to a single level of the common effect. Collider stratification is not always a source of selection bias.

Chapter 9
MEASUREMENT BIAS

Suppose an investigator conducted a randomized experiment to answer the causal question "does one's looking up to the sky make other pedestrians look up too?" She found a weak association between her looking up and other pedestrians' looking up. Does this weak association reflect a weak causal effect? By definition of randomized experiment, confounding bias is not expected in this study. In addition, no selection bias was expected because all pedestrians' responses—whether they did or did not look up—were recorded. However, there was another problem: the investigator's collaborator who was in charge of recording the pedestrians' responses made many mistakes. Specifically, the collaborator missed half of the instances in which a pedestrian looked up and recorded these responses as "did not look up." Thus, even if the treatment (the investigator's looking up) truly had a strong effect on the outcome (other people's looking up), the misclassification of the outcome will result in a dilution of the association between treatment and the (mismeasured) outcome.

We say that there is measurement bias when the association between treatment and outcome is weakened or strengthened as a result of the process by which the study data are measured. Since measurement errors can occur under any study design—including randomized experiments and observational studies—measurement bias need always be considered when interpreting effect estimates. This chapter provides a description of biases due to measurement error.

9.1 Measurement error

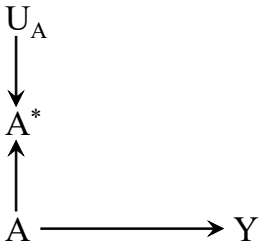


Figure 9.1

In previous chapters we implicitly made the unrealistic assumption that all variables were perfectly measured. Consider an observational study designed to estimate the effect of a cholesterol-lowering drug A on the risk of liver disease Y. We often expect that treatment A will be measured imperfectly. For example, if the information on drug use is obtained by medical record abstraction, the abstractor may make a mistake when transcribing the data, the physician may forget to write down that the patient was prescribed the drug, or the patient may not take the prescribed treatment. Thus, the treatment variable in our analysis data set will not be the *true* use of the drug, but rather the *measured* use of the drug. We will refer to the measured treatment as A^* (read A-star), which will not necessarily equal the true treatment A for a given individual. The psychological literature sometimes refers to A as the "construct" and to A^* as the "measure" or "indicator." The challenge in observational disciplines is making inferences about the unobserved construct (e.g., cholesterol-lowering drug use) by using data on the observed measure (e.g., information on statin use from medical records).

Measurement error for discrete variables is known as *misclassification*.

The causal diagram in Figure 9.1 depicts the variables A, A^*, and Y. For simplicity, we chose a setting with neither confounding nor selection bias for the causal effect of A on Y. The true treatment A affects both the outcome Y and the measured treatment A^*. The causal diagram also includes the node U_A to represent all factors other than A that determine the value of A^*. We refer to U_A as the *measurement error* for A. Note that the node U_A is unnecessary in discussions of confounding (it is not part of a backdoor path) or selection bias (no variables are conditioned on) and therefore we omitted it from the

Technical Point 9.1

Independence and nondifferentiality. Let $f(\cdot)$ denote a probability density function (PDF). The measurement errors U_A for treatment and U_Y for outcome are independent if their joint PDF equals the product of their marginal PDFs, i.e., $f(U_Y, U_A) = f(U_Y)f(U_A)$. The measurement error U_A for the treatment is nondifferential if its PDF is independent of the outcome Y, i.e., $f(U_A|Y) = f(U_A)$. Analogously, the measurement error U_Y for the outcome is nondifferential if its PDF is independent of the treatment A, i.e., $f(U_Y|A) = f(U_Y)$.

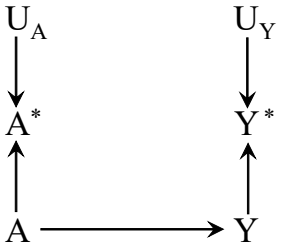


Figure 9.2

causal diagrams in Chapters 7 and 8. For the same reasons, the determinants of the variables A and Y are not included in Figure 9.1.

Besides treatment A, the outcome Y can be measured with error too. The causal diagram in Figure 9.2 includes the measured outcome Y^*, and the measurement error U_Y for Y. Figure 9.2 illustrates a common situation in practice. One wants to compute the average causal effect of the treatment A on the outcome Y, but these variables A and Y have not been, or cannot be, measured correctly. Rather, only the mismeasured versions A^* and Y^* are available to the investigator who aims at identifying the causal effect of A on Y.

Figure 9.2 also represents a setting in which there is neither confounding nor selection bias for the causal effect of treatment A on outcome Y. According to our reasoning in previous chapters, association is causation in this setting. We can compute any association measure and endow it with a causal interpretation. For example, the associational risk ratio $\Pr[Y = 1|A = 1] / \Pr[Y = 1|A = 0]$ is equal to the causal risk ratio $\Pr\left[Y^{a=1} = 1\right] / \Pr\left[Y^{a=0} = 1\right]$. Our implicit assumption in previous chapters, which we now make explicit, was that perfectly measured data on A and Y were available.

We now consider the more realistic setting in which treatment and outcome are measured with error. Then there is no guarantee that the measure of association between A^* and Y^* will equal the measure of causal effect of A on Y. The associational risk ratio $\Pr[Y^* = 1|A^* = 1] / \Pr[Y^* = 1|A^* = 0]$ will generally differ from the causal risk ratio $\Pr\left[Y^{a=1} = 1\right] / \Pr\left[Y^{a=0} = 1\right]$. We say that there is *measurement bias* or *information bias*. In the presence of measurement bias, the identifiability conditions of exchangeability, positivity, and consistency are insufficient to compute the causal effect of treatment A on outcome Y.

9.2 The structure of measurement error

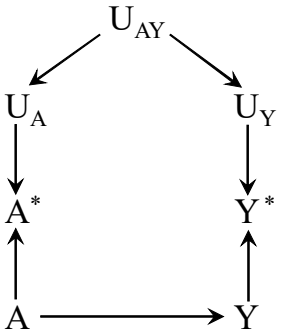


Figure 9.3

The causal structure of confounding can be summarized as the presence of common causes of treatment and outcome, and the causal structure of selection bias can be summarized as conditioning on common effects of treatment and outcome (or of their causes). Measurement bias arises in the presence of measurement error, but there is no single structure to summarize measurement error. This section classifies the structure of measurement error according to two properties—*independence* and *nondifferentiality*—that we describe below (see Technical Point 9.1 for formal definitions).

The causal diagram in Figure 9.2 depicts the measurement errors U_A and U_Y for both treatment A and outcome Y, respectively. According to the rules of d-separation, the measurement errors U_A and U_Y are independent because

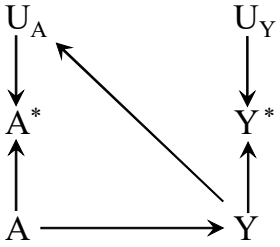


Figure 9.4

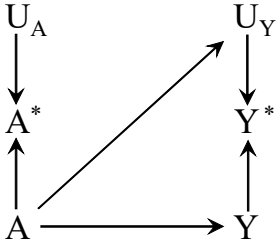


Figure 9.5

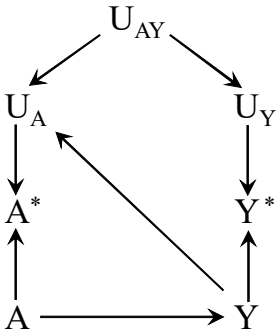


Figure 9.6

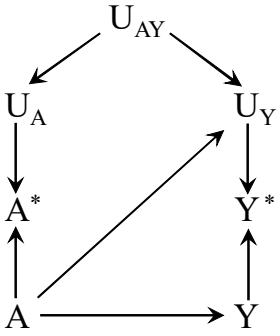


Figure 9.7

the path between them is blocked by colliders (either A^* or Y^*). Independent errors are expected to arise if, for example, information on both drug use A and liver toxicity Y was obtained from electronic medical records in which data entry errors occurred haphazardly. In other settings, however, the measurement errors for exposure and outcome may be dependent, as depicted in Figure 9.3. For example, dependent measurement errors will occur if the information were obtained retrospectively by phone interview and an individual's ability to recall her medical history (U_{AY}) affected the measurement of both A and Y.

Both Figures 9.2 and 9.3 represent settings in which the error for treatment U_A is independent of the true value of the outcome Y, and the error for the outcome U_Y is independent of the true value of treatment. We then say that the measurement error for treatment is nondifferential with respect to the outcome, and that the measurement error for the outcome is nondifferential with respect to the treatment. The causal diagram in Figure 9.4 shows an example of independent but differential measurement error in which the true value of the outcome affects the measurement of the treatment (i.e., an arrow from Y to U_A). Some examples of differential measurement error of the treatment follow.

Suppose that the outcome Y were dementia rather than liver toxicity, and that drug use A were ascertained by interviewing study participants. Since the presence of dementia affects the ability to recall A, one would expect an arrow from Y to U_A. Similarly, one would expect an arrow from Y to U_A in a study to compute the effect of alcohol use during pregnancy A on birth defects Y if alcohol intake is ascertained by recall after delivery—because recall may be affected by the outcome of the pregnancy. The resulting measurement bias in these two examples is often referred to as *recall bias*. A bias with the same structure might arise if blood levels of drug A^* are used in place of actual drug use A, and blood levels are measured after liver toxicity Y is present—because liver toxicity affects the measured blood levels of the drug. The resulting measurement bias is often referred to as *reverse causation bias*.

The causal diagram in Figure 9.5 shows an example of independent but differential measurement error in which the true value of the treatment affects the measurement of the outcome (i.e., an arrow from A to U_Y). A differential measurement error of the outcome will occur if physicians, suspecting that drug use A causes liver toxicity Y, monitored patients receiving drug more closely than other patients. Figures 9.6 and 9.7 depict measurement errors that are both dependent and differential, which may result from a combination of the settings described above.

In summary, we have discussed four types of measurement error: independent nondifferential (Figure 9.2), dependent nondifferential (Figure 9.3), independent differential (Figures 9.4 and 9.5), and dependent differential (Figures 9.6 and 9.7). The particular structure of the measurement error determines the methods that can be used to correct for it. For example, there is a large literature on methods for measurement error correction when the measurement error is independent nondifferential. In general, methods for measurement error correction rely on a combination of modeling assumptions and validation samples, i.e., subsets of the data in which key variables are measured with little or no error. The description of methods for measurement error correction is beyond the scope of this book. Rather, our goal is to highlight that the act of measuring variables (like that of selecting individuals) may introduce bias (see Fine Point 9.1 for a discussion of its strength and direction). Realistic causal diagrams need to simultaneously represent biases arising from confounding, selection, and measurement. The best method to fight bias due to mismeasurement is, obviously, to improve the measurement procedures.

Fine Point 9.1

The strength and direction of measurement bias. In general, measurement error will result in bias. A notable exception is the setting in which A and Y are unassociated and the measurement error is independent and nondifferential: If the arrow from A to Y did not exist in Figure 9.2, then both the A-Y association and the A^*-Y^* association would be null. In all other circumstances, measurement bias may result in an A^*-Y^* association that is either further from or closer to the null than the A-Y association. Worse, for non-dichotomous treatments, measurement bias may result in A^*-Y^* and A-Y associations in opposite directions. This association or trend reversal may occur even under the independent and nondifferential measurement error structure of Figure 9.2 when the mean of A^* is a nonmonotonic function of A. See Dosemeci, Wacholder, and Lubin (1990) and Weinberg, Umbach, and Greenland (1994) for details. VanderWeele and Hernán (2009) described a more general framework using signed causal diagrams.

The magnitude of the measurement bias depends on the magnitude of the measurement error. That is, measurement bias generally increases with the strength of the arrows from U_A to A^* and from U_Y to Y^*. Causal diagrams do not encode quantitative information, and therefore they cannot be used to describe the magnitude of the bias.

9.3 Mismeasured confounders

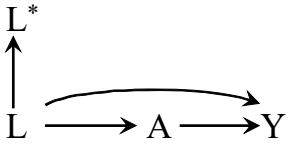


Figure 9.8

Besides the treatment A and the outcome Y, the confounders L may also be measured with error. Mismeasurement of confounders will result in bias even if both treatment and outcome are perfectly measured. To see this, consider the causal diagram in Figure 9.8, which includes the variables drug use A, liver disease Y, and history of hepatitis L. Individuals with prior hepatitis L are less likely to be prescribed drug A and more likely to develop liver disease Y. As discussed in Chapter 7, there is confounding for the effect of the treatment A on the outcome Y because there exists an open backdoor path $A \leftarrow L \rightarrow Y$, but there is no unmeasured confounding given L because the backdoor path $A \leftarrow L \rightarrow Y$ can be blocked by conditioning on L. That is, there is exchangeability of the treated and the untreated conditional on the confounder L, and one can apply IP weighting or standardization to compute the average causal effect of A on Y. The standardized, or IP weighted, risk ratio based on L, Y, and A will equal the causal risk ratio $\Pr\left[Y^{a=1}=1\right] / \Pr\left[Y^{a=0}=1\right]$.

Again the implicit assumption in the above reasoning is that the confounder L was perfectly measured. Suppose investigators did not have access to the study participants' medical records. Rather, to ascertain previous diagnoses of hepatitis, investigators had to ask participants via a questionnaire. Since not all participants provided an accurate recollection of their medical history—some did not want anyone to know about it, others had memory problems or simply made a mistake when responding to the questionnaire—the confounder L was measured with error. Investigators had data on the mismeasured variable L^* rather than on the variable L. Unfortunately, the backdoor path $A \leftarrow L \rightarrow Y$ cannot be generally blocked by conditioning on L^*. The standardized (or IP weighted) risk ratio based on L^*, Y, and A will generally differ from the causal risk ratio $\Pr\left[Y^{a=1}=1\right] / \Pr\left[Y^{a=0}=1\right]$. We then say that there is *measurement bias* or information bias.

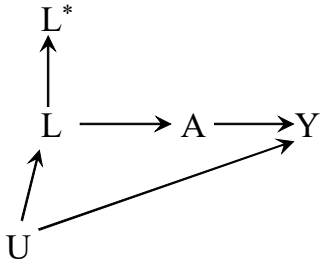


Figure 9.9

The causal diagram in Figure 9.9 shows an example of confounding of the causal effect of A on Y in which L is not the common cause shared by A and Y. Here too mismeasurement of L leads to measurement bias because the backdoor path $A \leftarrow L \leftarrow U \rightarrow Y$ cannot be generally blocked by conditioning on L^*. (Note that Figures 9.8 and 9.9 do not include the measurement error U_L because the particular structure of this error is not relevant to our discussion.)

Alternatively, one could view the bias due to mismeasured confounders in Figures 9.8 and 9.9 as a form of unmeasured confounding rather than as a form of measurement bias. In fact the causal diagram in Figure 9.8 is equivalent to that in Figure 7.5. One can think of L as an unmeasured variable and of L^* as a surrogate confounder (see Fine Point 7.2). The particular choice of terminology—unmeasured confounding versus bias due to mismeasurement of the confounders—is irrelevant for practical purposes.

Mismeasurement of confounders may also result in apparent effect modification. As an example, suppose that all study participants who reported a prior diagnosis of hepatitis ($L^* = 1$) and half of those who reported no prior diagnosis of hepatitis ($L^* = 0$) did actually have a prior diagnosis of hepatitis ($L = 1$). That is, the true and the measured value of the confounder coincide in the stratum $L^* = 1$, but not in the stratum $L^* = 0$. Suppose further that treatment A has no effect on any individual's liver disease Y, i.e., the sharp null hypothesis holds. When investigators restrict the analysis to the stratum $L^* = 1$, there will be no confounding by L because all participants included in the analysis have the same value of L (i.e., $L = 1$). Therefore they will find no association between A and Y in the stratum $L^* = 1$. However, when the investigators restrict the analysis to the stratum $L^* = 0$, there will be confounding by L because the stratum $L^* = 0$ includes a mixture of individuals with both $L = 1$ and $L = 0$. Thus the investigators will find an association between A and Y as a consequence of uncontrolled confounding by L. If the investigators are unaware of the fact that there is mismeasurement of the confounder in the stratum $L^* = 0$ but not in the stratum $L^* = 1$, they could naively conclude that both the association measure in the stratum $L^* = 0$ and the association measure in the stratum $L^* = 1$ can be interpreted as effect measures. Because these two association measures are different, the investigators will say that L^* is a modifier of the effect of A on Y even though no effect modification by the true confounder L exists.

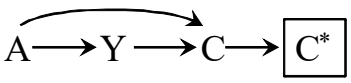


Figure 9.10

Finally, it is also possible that a collider C is measured with error as represented in Figure 9.10. In this setting, conditioning on the mismeasured collider C^* will generally introduce selection bias because C^* is a common effect of the treatment A and the outcome Y.

9.4 Intention-to-treat effect: the effect of a misclassified treatment

Consider a marginally randomized experiment to compute the causal effect of heart transplant on 5-year mortality Y. So far in this book we have used the notation $A = 1$ to refer to the study participants who were assigned and therefore received treatment (heart transplant in this example), and $A = 0$ to the others. This notation is appropriate for ideal randomized experiments in which all participants assigned to treatment actually received treatment, and in which all participants assigned to no treatment actually did not receive treatment. This notation, however is not detailed enough for real randomized experiments in which participants may not comply with the assigned treatment.

In real randomized experiments we need to distinguish between two treatment variables: the assigned treatment Z (1 if the person is assigned to transplant, 0 otherwise) and the received treatment A (1 if the person receives a transplant, 0 otherwise). For a given individual, the value of Z and A may differ because of lack of adherence to the assigned treatment. For example, an individual randomly assigned to receive a heart transplant ($Z = 1$) may

not receive it ($A = 0$) because he refuses to undergo the surgical procedure, or an individual assigned to medical therapy only ($Z = 0$) may still obtain a transplant ($A = 1$) outside of the study. In that sense, when individuals do not adhere to their assigned treatment, the assigned treatment Z is a misclassified version of the treatment A that was truly received by the study participants. Figure 9.11 represents a randomized experiment with Z, A, and Y (the variable U in discussed in the next section).

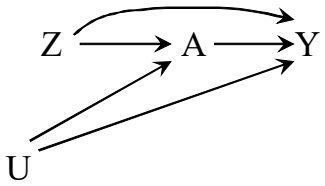


Figure 9.11

But there is a key difference between the assigned treatment Z in randomized experiments and the misclassified treatments A^* that we have considered so far. The mismeasured treatment A^* in Figures 9.1-9.7 does not have a causal effect on the outcome Y. The association between A^* and Y is entirely due to their common cause A. Indeed, in observational studies, one generally expects no causal effect of the measured treatment A^* on the outcome, even if the true treatment A has a causal effect. On the other hand, as shown in Figure 9.11, the assigned treatment Z in randomized experiments can have a causal effect on the outcome Y through two different pathways.

First, treatment assignment Z may affect the outcome Y simply because it affects the received treatment A. Individuals assigned to heart transplant are more likely to receive a heart transplant, as represented by the arrow from Z to A. If receiving a heart transplant has a causal effect on mortality, as represented by the arrow from A to Y, then assignment to heart transplant has a causal effect on the outcome Y through the pathway $Z \rightarrow A \rightarrow Y$.

Second, treatment assignment Z may affect the outcome Y through pathways that are not mediated by received treatment A. For example, awareness of the assigned treatment might lead to changes in the behavior of study participants: patients who are aware of receiving a transplant may spontaneously change their diet in an attempt to keep their new heart healthy, doctors may take special care of patients who were not assigned to a heart transplant... These behavioral changes are represented by the direct arrow from Z to Y.

Hence, the causal effect of the assigned treatment Z is not equal to the effect of received treatment A because the magnitude of the effect of Z depends not only on the strength of the arrow $A \longrightarrow Y$ (the effect of the received treatment), but also on the strength of the arrows $Z \longrightarrow A$ (the degree of adherence to the assigned treatment in the study) and $Z \longrightarrow Y$ (the concurrent behavioral changes).

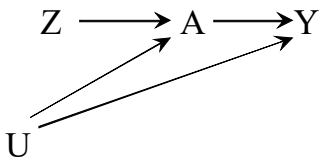


Figure 9.12

Other studies cannot be effectively blinded because known side effects of a treatment will make apparent who is taking it.

Often investigators try to partly "de-contaminate" the effect of Z by eliminating the arrow $Z \rightarrow Y$ as shown in Figure 9.12, which depicts the *exclusion restriction* of no direct arrow from Z to Y (see Fine Point 9.2). To do so, they withhold knowledge of the assigned treatment Z from participants and their doctors. For example, if Z were aspirin the investigators would administer an aspirin pill to those randomly assigned to $Z = 1$, and a *placebo* (an identical pill except that it does not contain aspirin) to those assigned to $Z = 0$. Because participants and their doctors do not know whether the pill they are given is the active treatment or a placebo, they are are said to be "blinded" and the study is referred to as a *double-blind placebo-controlled* randomized experiment. A double-blind treatment assignment, however, is often unfeasible. For example, in our heart transplant study, there is no practical way of administering a convincing placebo for open heart surgery.

Again, a key point is that the effect of Z does not measure "the effect of treating with A" but rather "the effect of assigning participants to being treated with A" or "the effect of having the intention of treating with A," which is why the causal effect of randomized assignment Z is referred to as the *intention-to-treat effect*. Yet, despite its dependence on adherence and other

Technical Point 9.2

The exclusion restriction. If the exclusion restriction holds, then there is no direct arrow from assigned treatment Z to the outcome Y, that is, that all of the effect of Z on Y is mediated through the received treatment A. Let $Y^{z,a}$ be the counterfactual outcome under randomized treatment assignment z and actual treatment received a. Formally, we say that the exclusion restriction holds when $Y^{z=0,a} = Y^{z=1,a}$ for all individuals and all values a and, specifically, for the value A observed for each individual. Instrumental variable methods (see Chapter 16) rely critically on the exclusion restriction being true.

factors, the effect of treatment assignment Z is the effect that investigators pursue in most randomized experiments. Why would one be interested in the effect of assigned treatment Z rather than in the effect of the treatment truly received A? The next section provides some answers to this question.

9.5 Per-protocol effect

In randomized experiments, the *per-protocol effect* is the causal effect of treatment that would have been observed if all individuals had adhered to their assigned treatment as specified in the protocol of the experiment. If all study participants happen to adhere to the assigned treatment, the values of assigned treatment Z and received treatment A coincide for all participants, and therefore the per-protocol effect can be equivalently defined as either the average causal effect of Z or of A. As explained in Chapter 2, in ideal experiments with perfect adherence, the treated ($A = 1$) and the untreated ($A = 0$) are exchangeable, $Y^a \perp\!\!\!\perp A$, and association is causation. The associational risk ratio $\Pr[Y = 1|A = 1]/\Pr[Y = 1|A = 0]$ is expected to equal the causal risk ratio $\Pr[Y^{a=1} = 1]/\Pr[Y^{a=0} = 1]$, which measures the per-protocol effect on the risk ratio scale.

Consider now a setting in which some individuals do not adhere to the assigned treatment so that their values of assigned treatment Z and received treatment A differ. For example, suppose that the most severely ill individuals in the $Z = 0$ group tend to seek a heart transplant ($A = 1$) outside of the study. If that occur, then the group $A = 1$ would include a higher proportion of severely ill individuals than the group $A = 0$: the groups $A = 1$ and $A = 0$ would not be exchangeable, and thus association between A and Y would not be causation. The associational risk ratio $\Pr[Y = 1|A = 1]/\Pr[Y = 1|A = 0]$ would not equal the causal per-protocol risk ratio $\Pr[Y^{a=1} = 1]/\Pr[Y^{a=0} = 1]$.

The setting described in the previous paragraph is represented by Figure 9.11, with U representing severe illness (1: yes, 0: no). As indicated by the backdoor path $A \leftarrow U \rightarrow Y$, there is confounding for the effect of A on Y. Because the reasons why participants receive treatment A include prognostic factors U, computing the per-protocol effect requires adjustment for confounding. That is, computation of the per-protocol effect requires viewing the randomized experiment as an observational study. If the factors U remain unmeasured, the effect of received treatment A cannot be correctly computed. See Fine Point 9.2 for a description of approaches to quantify the per-protocol effect when the prognostic factors that predict adherence are measured.

In contrast, there is no confounding for the effect of assigned treatment

Fine Point 9.2

Per-protocol analyses. In randomized trials, two common attempts to estimate the per-protocol effect of treatment A are 'as treated' and 'per protocol' analyses.

A conventional as-treated analysis compares the distribution of the outcome Y in those who received treatment ($A = 1$) versus those who did not receive treatment ($A = 0$), regardless of their treatment assignment Z. Clearly, a conventional as-treated comparison will be confounded if the reasons that moved participants to take treatment were associated with prognostic factors U that were not measured, as in Figures 9.11 and 9.12. On the other hand, consider a setting in which all backdoor paths between A and Y can be blocked by conditioning on measured factors L, as in Figure 9.13. Then an as-treated analysis will succeed in estimating the per-protocol effect if it appropriately measures and adjusts for the factors L.

A conventional per-protocol analysis—also referred to as an on-treatment analysis—only includes individuals who adhered to the study protocol: the so-called per-protocol population of participants with $A = Z$. The analysis then compares, in the per-protocol population only, the distribution of the outcome Y in those with were assigned to treatment ($Z = 1$) versus those who were not assigned to treatment ($Z = 0$). That is, a conventional per-protocol analysis, which is just an intention-to-treat analysis restricted to the per-protocol population, will generally result in a biased estimate of the per-protocol effect. To see why, consider the causal diagram in Figure 9.14, which includes an indicator of selection S into the per-protocol population: $S = 1$ if $A = Z$ and $S = 0$ otherwise. Selection bias will arise unless the per-protocol analysis appropriately measures and adjusts for the factors L.

That is, as-treated and per-protocol analyses are observational analyses of a randomized experiment and, like any observational analysis, require appropriate adjustment for confounding and selection bias to obtain valid estimates of the per-protocol effect. For examples and additional discussion, see Hernán and Hernández-Díaz (2012).

Z. Because Z is randomly assigned, exchangeability $Y^z \perp\!\!\!\perp Z$ holds for the assigned treatment Z even if it does not hold for the received treatment A. There are no backdoor paths from Z to Y in Figure 9.11. Association between Z and Y implies a causal effect of Z on Y, whether or not all individuals adhere to the assigned treatment. The associational risk ratio $\Pr[Y = 1|Z = 1]/\Pr[Y = 1|Z = 0]$ equals the causal intention-to-treat risk ratio $\Pr[Y^{z=1} = 1]/\Pr[Y^{z=0} = 1]$.

The analysis that estimates the unadjusted association between Z and Y to estimate the intention-to-treat *effect* is referred to as an intention-to-treat analysis. See Fine Point 9.4 for more on intention-to-treat analyses.

The lack of confounding largely explains why the intention-to-treat effect is privileged in many randomized experiments: "the effect of having the intention of treating with A" may not measure the treatment effect that we want—"the effect of treating with A" or the per-protocol effect—but it is easier to compute correctly than the per-protocol effect. As often occurs when a less interesting quantity is easier to compute than a more interesting quantity, we tend to come up with arguments to justify the use of the less interesting quantity. The intention-to-treat effect is no exception. We now discuss why several well-known justifications for the intention-to-treat effect need to be taken with a grain of salt. See also Fine Point 9.4.

A common justification for the intention-to-treat effect is that it preserves the null. That is, if treatment A has a null effect on Y, then assigned treatment Z will also have a null effect on Y. *Null preservation* is a key property because it ensures no effect will be declared when no effect exists. More formally, under the sharp causal null hypothesis and the exclusion restriction, it can be shown that $\Pr[Y = 1|Z = 1]/\Pr[Y = 1|Z = 0] = \Pr[Y^{a=1} = 1]/\Pr[Y^{a=0} = 1] = 1$. However, this equality is not true when the exclusion restriction does not hold, as represented in Figure 12. In those cases—experiments that are not double-blind placebo-controlled—the effect of A may be null while the effect of Z is non-null. To see that, mentally erase the arrow $A \longrightarrow Y$ in Figure 9.11: there

In statistical terms, the intention-to-treat analysis provides a valid—though perhaps underpowered—α-level test of the null hypothesis of no average treatment effect.

Fine Point 9.3

Pseudo-intention-to-treat analysis. The intention-to-treat effect can only be directly computed from an intention-to-treat analysis if there are no losses to follow-up or other forms of censoring. When some individuals do not complete the follow-up, their outcomes are unknown and thus the analysis needs to be restricted to individuals with complete follow-up. Thus, we can only conduct a *pseudo-intention-to-treat analysis* $\Pr[Y=1|Z=1,C=0]/\Pr[Y=1|Z=0,C=0]$ where $C=0$ indicates that an individual remained uncensored until the measurement of Y. As described in Chapter 8, censoring may induce selection bias and thus the pseudo-intention-to-treat estimate may be a biased estimate, in either direction, of the intention-to-treat effect. In the presence of loss to follow-up or other forms of censoring, the analysis of randomized experiments requires appropriate adjustment for selection bias even to compute the intention-to-treat effect. For additional discussion, see Little et al (2012).

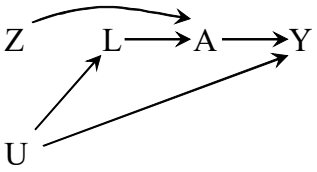


Figure 9.13

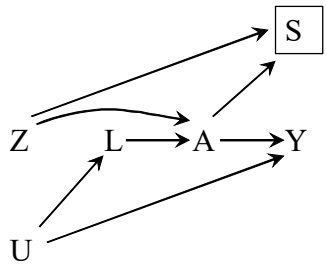


Figure 9.14

is still an arrow from Z to Y.

A related justification for the intention-to-treat effect is that its value is guaranteed to be closer to the null than the value of the per-protocol effect. The intuition is that imperfect adherence results in an attenuation—not an exaggeration—of the effect. Therefore, the intention-to-treat risk ratio $\Pr[Y=1|Z=1]/\Pr[Y=1|Z=0]$ will have a value between 1 and that of the per-protocol risk ratio $\Pr[Y^{a=1}=1]/\Pr[Y^{a=0}=1]$. The intention-to-treat effect can thus be interpreted as a lower bound for the per-protocol effect, i.e., as a conservative effect estimate. There are, however, three problems with this answer.

First, this justification assumes monotonicity of effects (see Technical Point 5.2), that is, that the treatment effect is in the same direction for all individuals. If this were not the case and the degree of non-adherence were high, then the per-protocol effect may be closer to the null than the intention-to-treat effect. For example, suppose that 50% of the individuals assigned to treatment did not adhere (e.g., because of mild adverse effects after taking a couple of pills), and that the direction of the effect is opposite in those who did and did not adhere. Then the intention-to-treat effect would be anti-conservative.

Second, suppose the effects are monotonic. The intention-to-treat effect may be conservative in placebo-controlled experiments, but not necessarily in head-to-head trials in which individuals are assigned to two active treatments. Suppose individuals with a chronic and painful disease were randomly assigned to either an expensive drug ($Z=1$) or ibuprofen ($Z=0$). The goal was to determine which drug results in a lower risk of severe pain Y after 1 year of follow-up. Unknown to the investigators, both drugs are equally effective to reduce pain, that is, the per-protocol (causal) risk ratio $\Pr[Y^{a=1}=1]/\Pr[Y^{a=0}=1]$ is 1. However, adherence to ibuprofen happened to be lower than adherence to the expensive drug because of a mild, easily palliated side effect. As a result, the intention-to-treat risk ratio $\Pr[Y=1|Z=1]/\Pr[Y=1|Z=0]$ was greater than 1, and the investigators wrongly concluded that ibuprofen was less effective than the expensive dug to reduce severe pain.

A similar argument against intention-to-treat analyses applies to non-inferiority trials, in which the goal is to demonstrate that one treatment is not inferior to the other.

Third, suppose the intention-to-treat effect is indeed conservative. Then the intention-to-treat effect is a dangerous effect measure when the goal is evaluating a treatment's safety: one could naïvely conclude that a treatment A is safe because the intention-to-treat effect of Z on the adverse outcome is close to null, even if treatment A causes the adverse outcome in a significant fraction of the patients. The explanation may be that many individuals assigned to $Z=1$ did not take, or stopped taking, the treatment before developing the

Fine Point 9.4

Effectiveness versus efficacy. Some authors refer to the per-protocol effect, e.g., $\Pr[Y^{a=1}=1]/\Pr[Y^{a=0}=1]$ as the treatment's "efficacy," and to the intention-to-treat effect, e.g., $\Pr[Y^{z=1}=1]/\Pr[Y^{z=0}=1]$, as the treatment's "effectiveness." A treatment's "efficacy" closely corresponds to what we have referred to as the average causal effect of treatment A in an ideal randomized experiment. In contrast, a treatment's "effectiveness" would correspond to the effect of assigning treatment Z in a setting in which the interventions under study will not be optimally implemented, typically because a fraction of study individuals will not adhere. Using this terminology, it is often argued that "effectiveness" is the most realistic measure of a treatment's effect because "effectiveness" includes any effects of treatment assignment Z not mediated through the received treatment A, and already incorporates the fact that people will not perfectly adhere to the assigned treatment. A treatment's "efficacy," on the other hand, does not reflect a treatment's effect in real conditions. Thus it is claimed that one is justified to report the intention-to-treat effect as the primary finding from a randomized experiment not only because it is easy to compute, but also because "effectiveness" is the truly interesting effect measure.

Unfortunately, the above argumentation is problematic. First, the intention-to-treat effect measures the effect of assigned treatment under the adherence conditions observed in a particular experiment. The actual adherence in real life may be different (e.g., participants in a study may adhere better if they are closely monitored), and may actually be affected by the findings from that particular experiment (e.g., people will be more likely to adhere to a treatment after they learn it works). Second, the above argumentation implies that we should refrain from conducting double-blind randomized clinical trials because, in real life, both patients and doctors are aware of the received treatment. Thus a true "effectiveness" measure should incorporate the effects stemming from assignment awareness (e.g., behavioral changes) that are eliminated in double-blind randomized experiments. Third, individual patients who are planning to adhere to the treatment prescribed by their doctors will be more interested in the per-protocol effect than in the intention-to-treat effect. For more details, see the discussion by Hernán and Hernández-Díaz (2012).

adverse outcome.

Thus the exclusive reporting of intention-to-treat effect estimates as the findings from a randomized experiment is hard to justify for experiments with substantial non-adherence, and for those aiming at estimating harms rather than benefits. Unfortunately, computing the per-protocol effect requires adjustment for confounding under the assumption of exchangeability conditional on the measured covariates, or via instrumental variable estimation (a particular case of g-estimation, see Chapter 16) under alternative assumptions.

For a non-technical discussion of per-protocol effects in complex randomized experiments, see Hernán and Robins (2017).

Our discussion of per-protocol has been necessarily oversimplified because we have not yet introduced time-varying treatments in this book. When, as often happens, treatment can vary over time in a randomized experiment, we define the per-protocol effect as the effect that would have been observed if everyone had adhered to their assigned treatment strategy throughout the follow-up. Part III describes the concepts and methods that are required to define and estimate per-protocol effects in the general case.

In summary, in the analysis of randomized experiments there is trade-off between bias due to potential unmeasured confounding—when choosing the per-protocol effect—and misclassification bias—when choosing the intention-to-treat effect. Reporting only the intention-to-treat effect implies preference for misclassification bias over confounding, a preference that needs to be justified in each application.

Chapter 10
RANDOM VARIABILITY

Suppose an investigator conducted a randomized experiment to answer the causal question "does one's looking up to the sky make other pedestrians look up too?" She found an association between her looking up and other pedestrians' looking up. Does this association reflect a causal effect? By definition of randomized experiment, confounding bias is not expected in this study. In addition, no selection bias was expected because all pedestrians' responses—whether they did or did not look up—were recorded, and no measurement bias was expected because all variables were perfectly measured. However, there was another problem: the study included only 4 pedestrians, 2 in each treatment group. By chance, 1 of the 2 pedestrians in the "looking up" group, and neither of the 2 pedestrians in the "looking straight" group, was blind. Thus, even if the treatment (the investigator's looking up) truly had a strong average effect on the outcome (other people's looking up), half of the individuals in the treatment group happened to be immune to the treatment. The small size of the study population led to a dilution of the estimated effect of treatment on the outcome.

There are two qualitatively different reasons why causal inferences may be wrong: systematic bias and random variability. The previous three chapters described three types of systematic biases: selection bias, measurement bias—both of which may arise in observational studies and in randomized experiments—and unmeasured confounding—which is not expected in randomized experiments. So far we have disregarded the possibility of bias due to random variability by restricting our discussion to huge study populations. In other words, we have operated as if the only obstacles to identify the causal effect were confounding, selection, and measurement. It is about time to get real: the size of study populations in etiologic research rarely precludes the possibility of bias due to random variability. This chapter discusses random variability and how we deal with it.

10.1 Identification versus estimation

The first nine chapters of this book are concerned with the computation of causal effects in study populations of near infinite size. For example, when computing the causal effect of heart transplant on mortality in Chapter 2, we only had a twenty-person study population but we regarded each individual in our study as representing 1 billion identical individuals. By acting as if we could obtain an unlimited number of individuals for our studies, we could ignore random fluctuations and could focus our attention on systematic biases due to confounding, selection, and measurement. Statisticians have a name for problems in which we can assume the size of the study population is effectively infinite: *identification* problems.

Thus far we have reduced causal inference to an identification problem. Our only goal has been to identify (or, as we often said, to compute) the average causal effect of treatment A on the outcome Y. The concept of identifiability was first described in Section 3.1—and later discussed in Sections 7.2 and 8.4—where we also introduced some conditions required to identify causal effects even if the size of the study population could be made arbitrarily large. These so-called identifying conditions were exchangeability, positivity, and consistency.

Our ignoring random variability may have been pedagogically convenient to introduce systematic biases, but also extremely unrealistic. In real research

projects the study population is not effectively infinite and hence, we cannot ignore the possibility of random variability. To this end let us return to our twenty-person study of heart transplant and mortality in which 7 of the 13 treated individuals died.

Suppose our study population of 20 can be conceptualized as being a random sample from a *super-population* so large compared with the study population that we can effectively regard it as infinite. Then it is natural to want to make inferences about the super-population. For example, we may want to make inferences about the super-population probability (or proportion) $\Pr[Y = 1|A = a]$. We refer to the parameter of interest in the super-population, the probability $\Pr[Y = 1|A = a]$ in this case, as the *estimand*. An *estimator* is a rule that takes the data from any sample from the super-population and produces a numerical value for the estimand. This numerical value for a particular sample is the *estimate* from that sample. The sample proportion of individuals that develop the outcome among those receiving treatment level a, $\widehat{\Pr}[Y = 1 \mid A = a]$, is an estimator of the super-population probability $\Pr[Y = 1|A = a]$. The estimate from our sample is $\widehat{\Pr}[Y = 1 \mid A = a] = 7/13$. More specifically, we say that 7/13 is a *point estimate*. The value of the estimate will depend on the particular 20 individuals randomly sampled from the super-population.

As informally defined in Chapter 1, an estimator is *consistent* for a particular estimand if the estimates get (arbitrarily) closer to the parameter as the sample size increases (see Technical Point 10.1 for the formal definition). Thus the sample proportion $\widehat{\Pr}[Y = 1 \mid A = a]$ consistently estimates the super-population probability $\Pr[Y = 1|A = a]$, i.e., the larger the number n of individuals in our study population, the smaller the magnitude of $\Pr[Y = 1|A = a] - \widehat{\Pr}[Y = 1 \mid A = a]$ is expected to be. Previous chapters were exclusively concerned with identification; from now on we will be concerned with statistical *estimation*.

For an introduction to statistics, see the book by Wasserman (2004). For a more detailed introduction, see Casella and Berger (2002).

Even consistent estimators may result in point estimates that are far from the super-population value. Large differences between the point estimate and the super-population value are much more likely to happen when the size of the study population is small compared with that of the super-population. Therefore it makes sense to have more confidence in estimates that originate from larger study populations. Statistical theory allows one to quantify this confidence in the form of a confidence interval around the point estimate. The larger the size of the study population, the narrower the confidence interval. A common way to construct a 95% confidence interval for a point estimate is to use a 95% Wald confidence interval centered at a point estimate. It is computed as follows.

First, estimate the standard error of the point estimate under the assumption that our study population is a random sample from a much larger super-population. Second, calculate the upper limit of the 95% Wald confidence interval by adding 1.96 times the estimated standard error to the point estimate, and the lower limit of the 95% confidence interval by subtracting 1.96 times the estimated standard error from the point estimate. For example, consider our estimator $\widehat{\Pr}[Y = 1 \mid A = a] = \hat{p}$ of the super-population parameter $\Pr[Y = 1|A = a] = p$. Its standard error is $\sqrt{\frac{p(1-p)}{n}}$ (the standard error of a binomial) and thus its estimated standard error is $\sqrt{\frac{\hat{p}(1-\hat{p})}{n}} = \sqrt{\frac{(7/13)(6/13)}{13}} = 0.138$. Recall that the Wald 95% confidence interval for a parameter θ based on an estimator $\widehat{\theta}$ is $\widehat{\theta} \pm 1.96 \times \widehat{se}\left(\widehat{\theta}\right)$ where $\widehat{se}\left(\widehat{\theta}\right)$ is an estimate of the (exact or

large sample) standard error of $\widehat{\theta}$. Therefore the 95% Wald confidence interval for our estimate is 0.27 to 0.81. The length and centering of the 95% Wald confidence interval will vary from sample to sample.

A Wald confidence interval centered at $\hat{p}$ can only be guaranteed to be valid in large samples. For simplicity, here we assume that our sample size was sufficiently large for the validity of our Wald interval.

A 95% confidence interval is *calibrated* if the estimand is contained in the interval in 95% of random samples, conservative if the estimand is contained in more than 95% of samples, and anticonservative if contained in less than 95%. We will say that a confidence interval is *valid* if it is either calibrated or conservative, i.e. it covers the true parameter at least 95% of the time. We would like to choose the valid interval whose length is narrowest.

The validity of confidence intervals is based on the variability of estimates over samples of the super-population, but we only see one of those samples when we conduct a study. Why should we care about what would have happened in other samples that we did not see? One answer is that the definition of confidence interval also implies the following. Suppose we and all of our colleagues keep conducting research studies for the rest of our lifetimes. In each new study, we construct a valid 95% confidence interval for the parameter of interest. Then, at the end of our lives, we can look back at all the studies we conducted, and conclude that the parameters of interest were trapped in—or covered by—the confidence interval in at least 95% of our studies. Unfortunately, we will have no way of identifying the 5% of our studies in which the confidence interval failed to include the super-population quantity.

Importantly, the 95% confidence interval from a single study does not imply that there is a 95% probability that the estimand is in the interval. In our example, we cannot conclude that the probability that the estimand lies between the values 0.27 and 0.81 is 95%. The estimand is fixed, which implies that either it is or it is not included in the interval (0.27, 0.81). The probability that the estimand is included in that interval is either 0 or 1. A confidence interval only has a *frequentist* interpretation. Its level (e.g., 95%) refers to the frequency with which the interval will *trap* the unknown super-population quantity of interest over a collection of studies (or in hypothetical repetitions of a particular study).

In contrast with a frequentist 95% confidence interval, a Bayesian 95% credible interval can be interpreted as "there is a 95% probability that the estimand is in the interval", but probability is defined as degree-of-belief. For the relation between confidence intervals and credible intervals, see Fine Point 11.1

Confidence intervals are often classified as either *small-sample* or *large-sample* (equivalently, asymptotic) confidence intervals. A small-sample valid (conservative or calibrated) confidence interval is one that is valid at all sample sizes for which it is defined. Small-sample calibrated confidence intervals are sometimes called *exact* confidence intervals. A large-sample valid confidence interval is one that is valid only in large samples. A large-sample exact 95% confidence interval is one whose coverage becomes arbitrarily close to 95% as the sample size increases. The Wald confidence interval for $\Pr[Y = 1|A = a] = p$ mentioned above is a large-sample valid confidence interval, but not a small-sample valid interval. (There do exist small-sample valid confidence intervals for p, but they are not often used in practice.) When the sample size is small, a valid large-sample confidence interval, such as the Wald 95% confidence interval of our example above, may not be valid. In this book, when we use the term 95% confidence interval, we mean a large-sample valid confidence interval, like a Wald interval, unless stated otherwise. See also Fine Point 10.1.

There are many valid large-sample confidence intervals other than the Wald interval (Casella and Berger, 2002). One of these might be preferred over the Wald interval, which can be badly anti-conservative in small samples (Brown et al, 2001).

However, not all estimators can be used to center a valid Wald confidence interval, even in large samples. Most users of statistics will consider an estimator unbiased if it can center a valid Wald interval and biased if it cannot (see Technical Point 10.1 for details). For now, we will equate the term bias with the inability to center Wald confidence intervals.

Fine Point 10.1

Honest confidence intervals. The smallest sample size at which a large-sample, valid 95% confidence interval covers the true parameter at least 95% of the time may depend on the value of the true parameter. We say a large-sample valid 95% confidence interval is *uniform* or *honest* if there exists a sample size n at which the interval is guaranteed to cover the true parameter value at least 95% of the time, whatever be the value of the true parameter. For a large-sample, honest confidence interval, the smallest such n is generally unknown and is difficult to determine even by simulation. See Robins and Ritov (1997) for technical details.

In the remainder of the text, when we refer to confidence intervals, we will generally mean large-sample honest confidence intervals. Note that, by definition, any small-sample valid confidence interval is uniform or honest for all n for which the interval is defined.

10.2 Estimation of causal effects

Suppose our heart transplant study was a marginally randomized experiment, and that the 20 individuals were a random sample of all individuals in a nearly infinite super-population of interest. Suppose further that all individuals in the super-population were randomly assigned to either $A = 1$ or $A = 0$, and that all of them adhered to their assigned treatment. Exchangeability of the treated and the untreated would hold in the super-population, i.e., $\Pr[Y^a = 1] = \Pr[Y = 1|A = a]$, and therefore the causal risk ratio $\Pr[Y^{a=1} = 1]/\Pr[Y^{a=0} = 1]$ equals the associational risk ratio $\Pr[Y = 1|A = 1]/\Pr[Y = 1|A = 0]$ in the super-population.

Because our study population is a random sample of the super-population, the sample proportion of individuals that develop the outcome among those with observed treatment value $A = a$, $\widehat{\Pr}[Y = 1 \mid A = a]$, is a consistent estimator of the super-population probability $\Pr[Y = 1|A = a]$. Because of exchangeability in the super-population, the sample proportion $\widehat{\Pr}[Y = 1 \mid A = a]$ is also a consistent estimator of $\Pr[Y^a = 1]$. Thus testing the causal null hypothesis $\Pr[Y^{a=1} = 1] = \Pr[Y^{a=0} = 1]$ boils down to comparing, via standard statistical procedures, the sample proportions $\widehat{\Pr}[Y = 1 \mid A = 1] = 7/13$ and $\widehat{\Pr}[Y = 1 \mid A = 0] = 3/7$. Standard statistical methods can also be used to compute 95% confidence intervals for the causal risk ratio and risk difference in the super-population, which are estimated by $(7/13)/(3/7)$ and $(7/13) - (3/7)$, respectively. Slightly more involved, but standard, statistical procedures are used in observational studies to obtain confidence intervals for standardized, IP weighted, or stratified association measures.

There is an alternative way to think about sampling variability in randomized experiments. Suppose only individuals in the study population, not all individuals in the super-population, are randomly assigned to either $A = 1$ or $A = 0$. Because of the presence of random sampling variability, we do not expect that exchangeability will exactly hold in our sample. For example, suppose that only the 20 individuals in our study were randomly assigned to either heart transplant ($A = 1$) or medical treatment ($A = 0$). Each individual can be classified as good or bad prognosis at the time of randomization. We say that the groups $A = 0$ and $A = 1$ are exchangeable if they include exactly the same proportion of individuals with bad prognosis. By chance, it is possible that 2 out of the 13 individuals assigned to $A = 1$ and 3 of the 7 individuals assigned to $A = 0$ had bad prognosis. However, if we increased the size of our sample then there is a high probability that the *relative* imbalance between

Technical Point 10.1

Bias and consistency in statistical inference. We have discussed systematic bias (due to unknown sources of confounding, selection, or measurement error) and consistent estimators in earlier chapters. Here we discuss these and other concepts of bias, and describe how they are related.

To provide a formal definition of consistent estimator for an estimand θ, suppose we observe n independent, identically distributed (i.i.d.) copies of a vector-valued random variable whose distribution P lies in a set $\mathcal{M}$ of distributions (our model). Then the estimator $\widehat{\theta}_n$ is consistent for $\theta = \theta(P)$ if $\widehat{\theta}_n$ converges to θ in probability under P, i.e., $P \in \mathcal{M}$

$$\left| \Pr_P \left[\left\| \widehat{\theta}_n - \theta(P) \right\| > \varepsilon \right] \right| \to 0 \text{ as } n \to \infty \text{ for every } \varepsilon > 0.$$

The estimator $\widehat{\theta}_n$ is exactly unbiased under P if $\mathrm{E}_P\left[\widehat{\theta}_n\right] = \theta(P)$. The *exact bias* under P is the difference $\mathrm{E}_P\left[\widehat{\theta}_n\right] - \theta(P)$. Note that we denote the estimator by $\widehat{\theta}_n$ rather than by simply $\widehat{\theta}$ to emphasize that the estimate depends on the sample size n. On the other hand, the parameter $\theta(P)$ is a fixed, though unknown, quantity.

Systematic bias precludes both consistency and exact unbiasedness of an estimator. Because most studies have some degree of unknown systematic bias, we cannot actually expect that the 95% confidence intervals around the estimate $\hat{\theta}_n$ will really cover the parameter θ in at least 95% of the studies. That is, in reality, our actual intervals will generally be anti-conservative.

Consistent estimators are not guaranteed to center a valid Wald confidence interval. Most researchers (e.g., epidemiologists) will declare an estimator unbiased only if it can center a valid Wald confidence interval. As argued by Robins (1987), this definition of bias is essentially equivalent to the definition of uniform asymptotic unbiasedness because in general only uniformly asymptotic unbiased estimators can center a valid Wald interval. All inconsistent estimators (such as those resulting from unknown systematic bias), and some consistent estimators, are biased under this definition, which is the one we use in the main text.

the groups $A = 1$ and $A = 0$ would decrease.

Under this conceptualization, there are two possible targets for inference. First, investigators may be agnostic about the existence of a super-population and restrict their inference to the sample that was actually randomized. This is referred to as *randomization-based inference*, and requires taking into account some technicalities that are beyond the scope of this book. Second, investigators may still be interested in making inferences about the super-population from which the study sample was randomly drawn. From an inference standpoint, this latter case turns out to be mathematically equivalent to the conceptualization of sampling variability described at the start of this section in which the entire super-population was randomly assigned to treatment. That is, randomization followed by sampling is equivalent to sampling followed by randomization.

See Robins (1988) for a discussion of randomization-based inference.

In many cases we are not interested in the first target. To see why, consider a study that compares the effect of two first-line treatments on the mortality of cancer patients. After the study ends, we may determine that it is better to initiate one of the two treatments, but this information is now irrelevant to the actual study participants. The purpose of the study was not to guide the choice of treatment for patients in the study but rather for a group of individuals similar to—but larger than—the studied sample. Heretofore we have assumed that there is a larger group—the super-population—from which the study participants were randomly sampled. We now turn our attention to the concept of the super-population.

10.3 The myth of the super-population

As discussed in Chapter 1, there are two sources of randomness: sampling variability and nondeterministic counterfactuals. Consider our estimate $\widehat{\Pr}[Y = 1 \mid A = 1] = \hat{p} = 7/13$ of the super-population risk $\Pr[Y = 1|A = a] = p$. Nearly all investigators would report a binomial confidence $\hat{p} \pm 1.96\sqrt{\frac{\hat{p}(1-\hat{p})}{n}} = 7/13 \pm 1.96\sqrt{\frac{(7/13)(6/13)}{13}}$ for the probability p. If asked why these intervals, they would say it is to incorporate the uncertainty due to random variability. But these intervals are valid only if $\hat{p}$ has a binomial sampling distribution. So we must ask when would that happen. In fact there are two scenarios under which $\hat{p}$ has a binomial sampling distribution.

Robins (1988) discussed these two scenarios in more detail.

- *Scenario 1.* The study population is sampled at random from an essentially infinite super-population, sometimes referred to as the source or target population, and our estimand is the proportion $p = \Pr[Y = 1|A = 1]$ of treated individuals who developed the outcome in the super-population. It is then mathematically true that, in repeated random samples of size 13 from the treated individuals in the super-population, the number of individuals who develop the outcome among the 13 is a binomial random variable with success probability $\Pr[Y = 1|A = 1]$. As a result, the 95% Wald confidence interval calculated in the previous section is asymptotically exact for $\Pr[Y = 1|A = 1]$. This is the model we have considered so far.

- Scenario 2. The study population is not sampled from any super-population. Rather (i) each individual i among the 13 treated individuals has an individual nondeterministic (stochastic) counterfactual probability $p_i^{a=1}$ (ii) the observed outcome $Y_i = Y_i^{a=1}$ for subject i occurs with probability $p_i^{a=1}$ and (iii) $p_i^{a=1}$ takes the same value, say p, for each of the 13 treated individuals. Then the number of individuals who develop the outcome among the 13 treated is a binomial random variable with success probability p. As a result, the 95% confidence interval calculated in the previous section is asymptotically exact for p.

Scenario 1 assumes a hypothetical super-population. Scenario 2 does not. However, Scenario 2 is untenable because the probability $p_i^{a=1}$ of developing the outcome when treated will almost certainly vary among the 13 treated individuals due to between-individual differences in risk. For example we would expect the probability of death $p_i^{a=1}$ to have some dependence on an individual's genetic make-up. If the $p_i^{a=1}$ are nonconstant then the estimand of interest in the actual study population would generally be the average, say p, of the 13 $p_i^{a=1}$. But in that case the number of treated who develop the outcome is not a binomial random variable with success probability p, and the 95% confidence interval for p calculated in the previous section is not asymptotically exact (but rather asymptotically conservative.)

Therefore, any investigator who reports a binomial confidence interval for $\Pr[Y = 1|A = a]$, and who acknowledges that there exists between-individual variation in risk, must be implicitly assuming Scenario 1: the study individuals were sampled from a near-infinite super-population and that all inferences are concerned with quantities from that super-population. Under Scenario 1, the number with the outcome among the 13 treated is a binomial variable regardless of whether the underlying counterfactual is deterministic or stochastic.

Fine Point 10.2

Quantitative bias analysis. The width of the usual Wald-type confidence intervals is a function of the standard error of the estimator and thus reflects only uncertainty due to random error. However, the possible presence of systematic bias due to confounding, selection, or measurement is another important source of uncertainty around effect estimates. This uncertainty due to systematic bias is well recognized by investigators and usually a central part of the discussion section of scientific articles. However, most discussions revolve around informal judgments about the potential direction and magnitude of the systematic bias. Some authors argue that quantitative methods need to be used to produce intervals around the effect estimate that integrate random and systematic sources of uncertainty. These methods are referred to as quantitative bias analysis. See the book by Lash, Fox, and Fink (2009). Bayesian alternatives are discussed by Greenland and Lash (2008), and Greenland (2009a, 2009b).

An advantage of working under the hypothetical super-population scenario is that nothing hinges on whether the world is deterministic or nondeterministic. On the other hand, the super-population is generally a fiction; in most studies individuals are not randomly sampled from any near-infinite population. Why then has the myth of the super-population endured? One reason is that it leads to simple statistical methods.

A second reason has to do with generalization. As we mentioned in the previous section, investigators generally wish to generalize their findings about treatment effects from the study population (e.g., the 20 individuals in our heart transplant study) to some large target population (e.g., all immortals in the Greek pantheon). The simplest way of doing so is to assume the study population is a random sample from a large population of individuals who are potential recipients of treatment. Since this is a fiction, a 95% confidence interval computed under Scenario 1 should be interpreted as covering the super-population parameter had, often contrary to fact, the study individuals been sampled randomly from a near infinite super-population. In other words, confidence intervals obtained under Scenario 1 should be viewed as a what-if statements.

It follows from the above that an investigator might not want to entertain Scenario 1 if the size of the pool of potential recipients is not much larger than the size of the study population, or if there is selection bias, i.e., the target population of potential recipients is believed to differ from the study population to an extent that cannot be accounted for by sampling variability (see Fine Point 10.2).

We will accept that individuals were randomly sampled from a super-population, and explore the consequences of random variability for causal inference in that context. We first explore this question in a simple randomized experiment.

10.4 The conditionality "principle"

Table 10.1 summarizes the data from a randomized experiment to estimate the average causal effect of treatment A (1: yes, 0: no) on the 1-year risk of death Y (1: yes, 0: no). The experiment included 240 individuals, 120 in each treatment group. The associational risk ratio is $\Pr[Y = 1|A = 1]/\Pr[Y = 1|A = 0] = 24/42 = 0.57$. Suppose the experiment had been conducted in

a super-population of near-infinite size, the treated and the untreated would be exchangeable, i.e., $Y^a \perp\!\!\!\perp A$, and the associational risk ratio would equal the causal risk ratio $\Pr\left[Y^{a=1}=1\right] / \Pr\left[Y^{a=0}=1\right]$. Suppose the study investigators computed a 95% confidence interval $(0.37, 0.88)$ around the point estimate 0.57 and published an article in which they concluded that treatment was beneficial because it reduced the risk of death by 43%.

Table 10.1

	$Y=1$	$Y=0$
$A=1$	24	96
$A=0$	42	78

However, the study population had only 240 individuals and is therefore likely that, due to chance, the treated and the untreated are not perfectly exchangeable. Random assignment of treatment does not guarantee exact exchangeability within individuals in the trial; it only guarantees that any departures from exchangeability are due to random variability rather than to a systematic bias. In fact, one can view the uncertainty resulting from our ignorance of the chance correlation between unmeasured baseline risk factors and the treatment A in the study sample as contributing to the length 0.51 of the confidence interval.

A few months later the investigators remember that information on a third variable, cigarette smoking L (1: yes, 0: no), had also been collected and decide to take a look at it. The study data, stratified by L, is shown in Table 10.2. Unexpectedly, the investigators find that the probability of receiving treatment for smokers (80/120) is twice that for nonsmokers (40/120), which suggests that the treated and the untreated are not exchangeable and thus that some form of adjustment for smoking is necessary. When the investigators adjust via stratification, the associational risk ratio in smokers, $\Pr[Y=1|A=1, L=1] / \Pr[Y=1|A=0, L=1]$, is equal to 1. The associational risk ratio in nonsmokers, $\Pr[Y=1|A=1, L=0] / \Pr[Y=1|A=0, L=0]$, is also equal to 1. Treatment has no effect in both smokers and nonsmokers, even though the marginal risk ratio 0.57 suggested a net beneficial effect in the study population.

Table 10.2

$\mathbf{L=1}$	$Y=1$	$Y=0$
$A=1$	4	76
$A=0$	2	38

$\mathbf{L=0}$	$Y=1$	$Y=0$
$A=1$	20	20
$A=0$	40	40

These new findings are disturbing to the investigators. Either someone did not assign the treatment at random (malfeasance) or randomization did not result in approximate exchangeability (very very bad luck). A debate ensues among the investigators. Should they retract their article and correct the results? They all agree that the answer to this question would be affirmative if the problem were due to malfeasance. If that were the case, there would be confounding by smoking and the effect estimate should be adjusted for smoking. But they all agree that malfeasance is impossible given the study's quality assurance procedures. It is therefore clear that the association between smoking and treatment is entirely due to bad luck. Should they still retract their article and correct the results?

One investigator says that they should not retract the article. His argument goes as follows: "OK, randomization went wrong for smoking, but why should we privilege the adjusted over the unadjusted estimator? It is likely that imbalances on other unmeasured factors U cancelled out the effect of the chance imbalance on L, so that the unadjusted estimator is still the closer to the true value in the super-population." A second investigator says that they should retract the article and report the adjusted null result. Her argument goes as follows: "We should adjust for L because the strong association between L and A introduces confounding in our effect estimate. Within levels of L, we have mini randomized trials and the confidence intervals around the corresponding point estimates will reflect the uncertainty due to the possible U-A associations conditional on L."

To determine which investigator is correct, here are the facts of the matter. Suppose, for simplicity, the true causal risk ratio is constant across strata of

L, and suppose we could run the randomized experiment trillions of times. We then select only (i.e., condition on) those runs in which smoking L and treatment A are as strongly positively associated as in the observed data. We would find that the fraction of these runs in which any given risk factor U for Y was positively associated with A essentially equals the number of runs in which it was negatively associated. [This is true even if U and L are highly correlated in both the super-population and in the study data, and furthermore both are correlated with A in the study data.] As a consequence, the adjusted estimate of the treatment effect is unbiased but the unadjusted estimate is greatly biased when averaged over these runs. Unconditionally—over all the runs of the experiment—both the unadjusted and adjusted estimates are unbiased but the variance of the adjusted estimate is smaller than that of the unadjusted estimate. That is, the adjusted estimator is both conditionally unbiased and unconditionally more efficient. Hence either from the conditional or unconditional point of view, the Wald interval centered on the adjusted estimator is the correct analysis and the article needs to be retracted. The second investigator is correct.

The idea that one should condition on the observed L-A association is an example of what is referred to in the statistical literature as *the conditionality principle*. In statistics, the observed L-A association is said to be an ancillary statistic for the causal risk ratio. The conditionality principle states that inference on a parameter should be performed conditional on all ancillary statistics (see Technical Point 10.2 for details). The discussion in the preceding paragraph then implies that many researchers intuitively follow the conditionality principle when they consider an estimator to be biased if it cannot center a valid Wald confidence interval conditional on any ancillary statistics. That is, our previous definition of bias was not sufficiently restrictive. From now on, we will say that an estimator is unbiased if and only if it can center a valid Wald interval conditional on all ancillary statistics.

When confronted with the frequentist argument that "Adjustment for L is unnecessary because unconditionally—over all the runs of the experiment—the unadjusted estimate is unbiased," investigators that intuitively apply the conditionality principle would aptly respond "Why should the various L-A associations in other hypothetical studies affect what I do in my study? In my study L is a confounder and adjustment is needed to eliminate bias." This is a convincing argument for both randomized experiments and observational studies when, as above, the number of measured confounders is not large. When the number of measured variables is large however, following the conditionality principle is no longer a wise strategy.

10.5 The curse of dimensionality

If the investigators had measured 100 pre-treatment binary variables rather than only one, then the pre-treatment variable L formed by combining the 100 variables $L = (L_1, ..., L_{100})$ has 2^{100} strata. When, as in this case, there are many possible combinations of values of the pretreatment variables, we say that the data is of *high dimensionality*. For simplicity, suppose that there is no multiplicative effect modification by L, i.e., the super-population risk ratio $\Pr[Y = 1|A = 1, L = l]/\Pr[Y = 1|A = 0, L = l]$ is constant across the 2^{100} strata. In particular, suppose that the constant stratum-specific risk ratio is 1.

Technical Point 10.2

A formal statement of the conditionality principle. The likelihood for the observed data has three factors: the density of Y given A and L, the density of A given L, and the marginal density of L. Consider a simple example with one dichotomous L, exchangeability given L, and in which the parameter of interest is the stratum-specific causal risk ratio $sRR = \Pr(Y=1|L=l,A=1)/\Pr(Y=1|L=l,A=0)$ known to be constant across strata of L. Then the likelihood of the data is

$$\prod_{i=1}^{N}\prod_{i=1}^{N} f(Y_i|L_i,A_i;sRR,\mathbf{p}_0)\times f(A_i|L_i;\alpha)\times f(L_i;\rho)$$

where $p_0 = (p_{01},p_{02})$ with $p_{0l} = \Pr(Y=1|L=l,A=0)$, α, and ρ are nuisance parameters associated with the conditional density of Y given A and L, the conditional density of A given L, and the marginal density of L, respectively. See, for example, Casella and Berger (2002).

The data on A and L are said to be exactly ancillary for the parameter of interest when, as in this case, the distribution of the data conditional on these variables depends on the parameter of interest, but the joint density of A and L does not share parameters with $f(Y_i|L_i,A_i;sRR,\mathbf{p}_0)$. The conditionality principle states that one should always perform inference on the parameter of interest conditional on any ancillary statistics.

The investigators debate again whether to retract the article and report their estimate of the stratified risk ratio. They have by now agreed that they should follow the conditionality principle because the marginal risk ratio 0.57 is biased. However, they notice that, when there are 2^{100} strata, a 95% confidence interval for the conditional risk ratio is much less precise than the marginal risk ratio. This is exactly the opposite of what was found when L had only 2 strata. In fact, the 95% confidence interval may be so wide as to be completely uninformative.

To see why, note that, because 2^{100} is much larger than the number of individuals (240), there will at most be only a few strata of L that will contain both a treated and an untreated individual. Suppose only one of 2^{100} strata contains a single treated individual and a single untreated individual, and no other stratum contains both a treated and untreated individual. Then the 95% confidence interval for the risk ratio conditional on the observed distribution of A within the 2^{100} strata of L is $(0,\infty)$ because in the single stratum with both a treated and an untreated individual, the empirical risk ratio could be ∞, 0, or 1 depending on the value of Y for each individual.

What should the investigators do? By trying to do the right thing—following the conditionality principle—in the simple setting with one dichotomous variable, they put themselves in a corner for the high-dimensional setting. This is the *curse of dimensionality*: conditional on all 100 covariates the marginal estimator is still biased, but now the conditional estimator is uninformative. This shows that, just because conditionality is compelling in simple examples, it should not be raised to a principle since it cannot be carried through high-dimensional models. Though we have discussed this issue in the context of a randomized experiment, our discussion applies equally to observational studies.

Robins and Wasserman (1999) provide a technical description of the curse of dimensionality.

Finding a solution to the curse of dimensionality is not straightforward. One approach is to reduce the dimensionality of the data by excluding some variables from the analysis. Many procedures to eliminate variables from the analysis are *ad hoc*. For example, investigators often exclude variables in L that they believe to be unimportant or that happen to be weakly associated with the treatment A or the outcome Y in the study sample, where "weak association"

is defined by using some arbitrary threshold (e.g., a p-value greater than 0.10).

Many software packages use automatic procedures to select the covariates to include in a model such as forward selection, backward selection, stepwise selection. These procedures do not preserve the interpretation of frequentist confidence intervals (see Chapter REF). When *ad hoc* or automatic procedures are employed, 95% confidence intervals tend to be too narrow and thus invalid: they fail to cover the causal parameter of interest at least 95% of the time. The degree of undercoverage will be greater when there is some degree of confounding in the super-population since, in that case, Wald confidence intervals will not be centered on an unbiased estimator of the causal effect.

Multiple authors have studied the problems of *ad hoc* or automatic variable selection. See Greenland (2008) for a list of citations.

Unfortunately, there is not much we can do about the curse of dimensionality because the statistical theory to provide correct (honest) confidence intervals for high-dimensional data is still under development. In practice, the most common approach to deal with the curse of dimensionality is to specify low-dimensional, parsimonious statistical models. Using such models results in increased precision of the estimates at the expense of potential bias if the models are incorrect. Part II of this book is devoted to models for causal inference.

Technical Point 10.3

Comparison between adjusted and unadjusted estimators. Consider a setting in which the marginal risk ratio RR and the stratified risk ratios sRR within any level of the variables L are equal. This would be the case in a randomized experiment, in which A and L are known to be independent in the super-population, with no multiplicative effect modification by L. The maximum likelihood estimator (MLE) $\widehat{sRR}_{MLE}$ of the stratified risk ratio sRR , which corresponds to the conditional estimator discussed in the text, is an unconditionally efficient (i.e., the most precise) estimator when the sample size n is much greater than the dimension of the nuisance parameter $\mathbf{p}_0$ (see Technical Point 10.2).

Because of the likelihood factorization , the MLE $\widehat{sRR}_{MLE}$ depends only on the first factor of the likelihood $\prod_{i=1}^{N} f\left(Y_i|L_i, A_i; sRR, \mathbf{p}_0\right)$. That is, the MLE does not care about how L and A were generated. In particular, it does not matter whether α is known as in a randomized experiment, or unknown as in an observational study. Since the MLE is more efficient than the marginal risk ratio estimator $\widehat{RR}$ that ignores data on L, even statisticians who do not accept the conditionality principle will still prefer the stratified over the marginal estimator.

The reason that MLE is both unconditionally more efficient and conditionally less biased than the marginal estimator is not a coincidence. In fact, both properties of the MLE are logically equivalent. To show this we use the facts that $\widehat{RR}$ and $\widehat{sRR}_{MLE}$ have the same conditional variance, i.e., $var\left(\widehat{RR}|\mathbf{A},\mathbf{L}\right) = var\left(\widehat{sRR}_{MLE}|\mathbf{A},\mathbf{L}\right)$ and that the MLE is unbiased conditional on $(\mathbf{A},\mathbf{L}) = (A_i,L_i)$, $i = 1,...,n$, i.e., $\mathrm{E}\left\{\widehat{sRR}_{MLE}|\mathbf{A},\mathbf{L}\right\} = sRR$. It then follows from the identities

$$var\left(\widehat{RR}\right) = \mathrm{E}\left[var\left(\widehat{RR}|\mathbf{A},\mathbf{L}\right)\right] + var\left[\mathrm{E}\left\{\widehat{RR}|\mathbf{A},\mathbf{L}\right\}\right]$$
$$var\left(\widehat{sRR}_{MLE}\right) = \mathrm{E}\left[var\left(\widehat{sRR}_{MLE}|\mathbf{A},\mathbf{L}\right)\right]$$

that $var\left(\widehat{RR}\right) > var\left(\widehat{sRR}_{MLE}\right)$ if and only if $\mathrm{E}\left\{\widehat{RR}|\mathbf{A},\mathbf{L}\right\} > 0$ with positive probability. The above expectations and variances are asymptotic; a more precise statement was provided by Robins and Morgenstern (1987).

But this argument breaks down with high-dimensional data. To see this, consider the case where L has 2^{100} joint strata so the dimension of the nuisance parameter $\mathbf{p}_0$ is 2^{100}. Because the MLE needs to estimate each of the 2^{100} nuisance parameters, little or no information is left in the data to estimate the parameter of interest RR so the unconditional variance of the MLE will be very large, even infinite. (Also, the MLE will fail to be asymptotically unbiased conditional on $\mathbf{A},\mathbf{L}$**)**. The variance of the marginal estimator is essentially unaffected by the dimension of $\mathbf{p}$ and thus will be more efficient than the MLE. The MLE is only guaranteed to be more efficient than the marginal estimator when the ratio of number of individuals to the number of parameters is large (a frequently used rule of thumb is a minimum ratio of 10, though the minimum ratio depends on the characteristics of the data). Note the marginal estimator uses prior information not used by the conditional estimator. In our example, the marginal estimator uses the information that A and L are known not to be associated in the super-population. Without this prior information the marginal estimator would not be an unbiased estimator of the sRR.
