CAUSAL INFERENCE

What If

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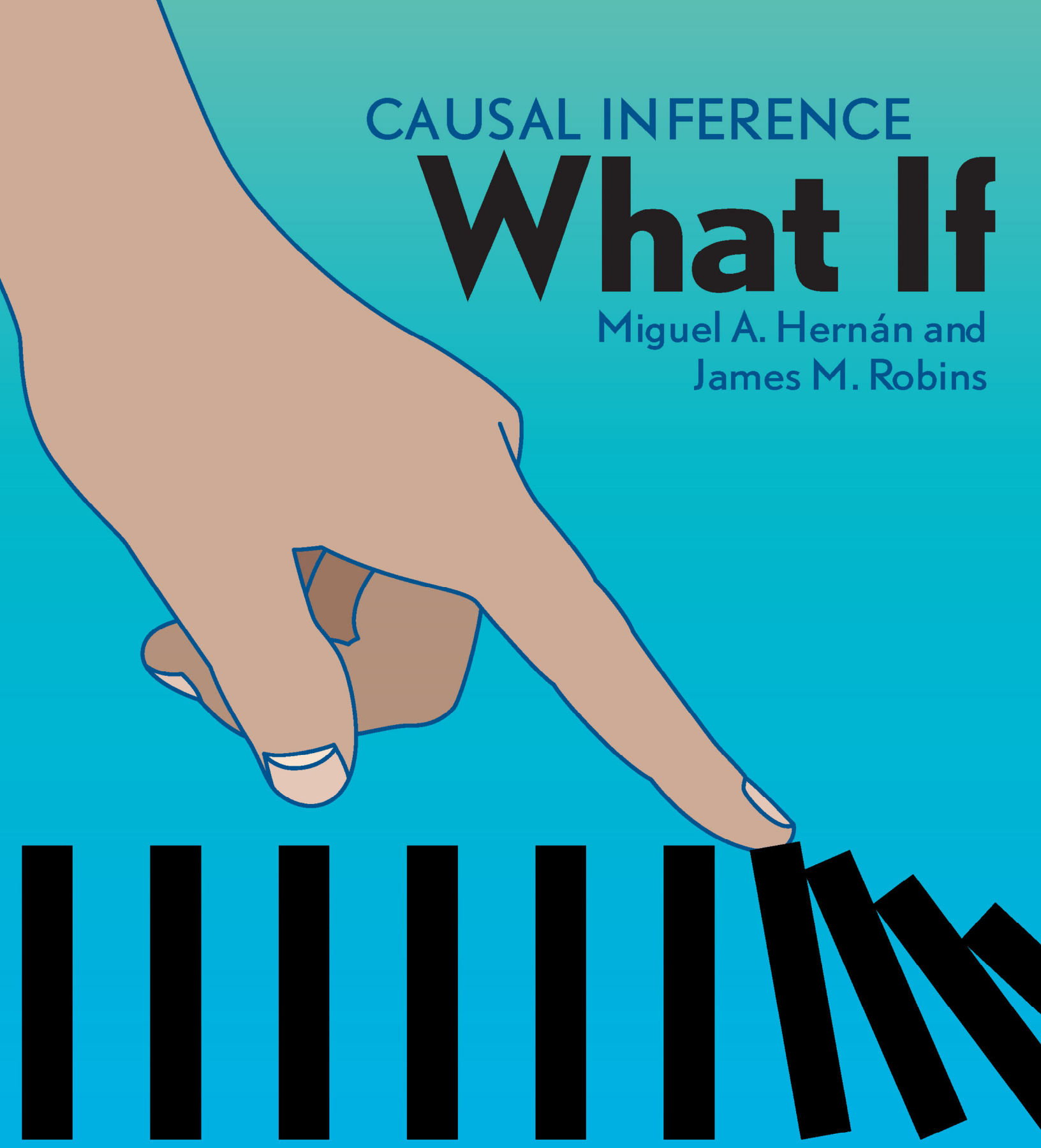

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INTRODUCTION: TOWARDS LESS CASUAL CAUSAL INFERENCES

Causal Inference is an admittedly pretentious title for a book. A complex scientific task, causal inference relies on triangulating evidence from multiple sources and on the application of a variety of methodological approaches. No book can possibly provide a comprehensive description of all methodologies for causal inference across the sciences. The authors of any *Causal Inference* book will have to choose which aspects of causal inference methodology they want to emphasize.

The title of this introduction reflects our own choices: a book that helps scientists—especially health and social scientists—generate and analyze data to make causal inferences that are explicit about both the causal question and the assumptions underlying the data analysis. Unfortunately, the scientific literature is plagued by studies in which the causal question is not explicitly stated and the investigators' unverifiable assumptions are not declared. This casual attitude towards causal inference has led to a great deal of confusion. For example, it is not uncommon to find studies in which the effect estimates are hard to interpret because the data analysis methods cannot appropriately answer the causal question (were it explicitly stated) under the investigators' assumptions (were they declared).

In this book, we stress the need to take the causal question seriously enough to articulate it, and to delineate the separate roles of data and assumptions for causal inference. Once these foundations are in place, causal inferences become necessarily less casual, which helps prevent confusion. The book describes various data analysis approaches to estimate the causal effect of interest under a particular set of assumptions when data are collected on each individual in a population. A key message of the book is that causal inference cannot be reduced to a collection of recipes for data analysis.

The book is divided in three parts of increasing difficulty: Part I is about causal inference without models (i.e., nonparametric identification of causal effects), Part II is about causal inference with models (i.e., estimation of causal effects with parametric models), and Part III is about causal inference from complex longitudinal data (i.e., estimation of causal effects of time-varying treatments). Throughout the text, we have interspersed Fine Points and Technical points that elaborate on certain topics mentioned in the main text. Fine Points are designed to be accessible to all readers while Technical Points are designed for readers with intermediate training in statistics. The book provides a cohesive presentation of concepts and methods for causal inference that are currently scattered across journals in several disciplines. We expect that it will be of interest to all professionals that make causal inferences, including epidemiologists, statisticians, psychologists, economists, sociologists, political scientists, computer scientists...

This is not a philosophy book. We remain agnostic about metaphysical concepts like causality and cause. Instead, we focus on the identification and estimation of causal effects in populations, that is, numerical quantities that measure changes in the distribution of an outcome under different interventions. For example, we discuss how to estimate the risk of death in patients

with serious heart failure if they received a heart transplant versus if they did not. Through actionable causal inference, we want to help decision makers make better decisions.

We are grateful to many people who have made this book possible. Stephen Cole, Sander Greenland, Jay Kaufman, Eleanor Murray, Sonja Swanson, Tyler VanderWeele, and Jan Vandenbroucke provided detailed comments. Goodarz Danaei, Kosuke Kawai, Martin Lajous, and Kathleen Wirth helped create the NHEFS dataset. The sample code in Part II was developed by Roger Logan in SAS, Eleanor Murray and Roger Logan in Stata, Joy Shi and Sean McGrath in R, and James Fiedler in Python. Roger Logan has also been our LaTeX wizard. Randall Chaput helped create the figures in Chapters 1 and 2. Josh McKible designed the book cover. Rob Calver, our patient publisher, encouraged us to write the book and supported our decision to make it freely available online.

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Part I

Causal inference without models

Chapter 1
A DEFINITION OF CAUSAL EFFECT

As a human being, you are already innately familiar with causal inference's fundamental concepts. Through sheer existence, you know what a causal effect is, understand the difference between association and causation, and you have used this knowledge consistently throughout your life. Had you not, you'd be dead. Without basic causal concepts, you would not have survived long enough to read this chapter, let alone learn to read. As a toddler, you would have jumped right into the swimming pool after seeing those who did were later able to reach the jam jar. As a teenager, you would have skied down the most dangerous slopes after seeing those who did won 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 not at 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 will be used 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 versus 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

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 because we are assuming that individual counterfactual outcomes are deterministic (see Technical Point 1.2).

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

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).

For each individual, one of the counterfactual outcomes—the one that corresponds to the treatment value that the individual did receive—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 $Y_i^a = Y_i^A = Y_i$

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. Because of missing data, individual effects cannot be identified, that is, they cannot be expressed as a function of the observed 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. Focus 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 $\Pr[Y^{a=1} = 1] = 10/20 = 0.5$. Similarly, from the other column of Table 1.1, we can conclude that half of

Fine Point 1.1

Interference. Our definition of a counterfactual outcome implicitly assumes 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 on other individuals' treatment values. When there is interference, "the causal effect of heart transplant on Zeus's outcome" is not well defined. 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

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 $\Pr[Y^{a=0} = 1] = 10/20 = 0.5$. 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 outcomes 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. 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 ($a = 1$)" and "not receiving a heart transplant ($a = 0$)." When more than two actions are possible (i.e., the treatment is not dichotomous), the particular

Fine Point 1.2

Multiple versions of treatment. Our definition of a counterfactual outcome under treatment value a also implicitly assumes 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, 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. When there are multiple versions of treatment, "the causal effect of heart transplant on Zeus's outcome" is not well defined. 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: $\mathrm{E}[Y^{a=1}] \neq \mathrm{E}[Y^{a=0}]$

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." This causal effect is well defined even if counterfactual outcomes under other interventions are not well defined or 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 functionals, including medians, variances, hazards, or CDFs of counterfactual outcomes. In general, a population causal effect can be defined as a contrast of any functional of the marginal distributions of counterfactual outcomes under different actions or treatment values. For example the population causal effect on the variance is defined as $var(Y^{a=1}) - var(Y^{a=0})$, which is zero for the population in Table 1.1 since the distribution of $Y^{a=1}$ and $Y^{a=0}$ are identical—both having 6 deaths out of 20. In fact, the equality of these distributions imply that for any functional (e.g., mean, variance, median, hazard,etc.), the population causal effect on the functional is zero. However, in contrast to the mean, the difference in population variances $var(Y^{a=1}) - var(Y^{a=0})$ does not in general equal the variance of the individual causal effects $var(Y^{a=1} - Y^{a=0})$. For example, in Table 1.1, since $Y^{a=1} - Y^{a=0}$ is not constant (-1 for 6 individuals, 1 for 6 individuals and 0 for 8 individuals), $var(Y^{a=1} - Y^{a=0}) > 0 = var(Y^{a=1}) - var(Y^{a=0})$. We will be able to identify (i.e., compute) $var(Y^{a=1}) - var(Y^{a=0})$ from the data collected in a randomized trial, but not $var(Y^{a=1} - Y^{a=0})$ because we can never simultaneously observe both $Y^{a=1}$ and $Y^{a=0}$ for any individual, and thus the covariance of $Y^{a=1}$ and $Y^{a=0}$ is not identified. The above discussion is true not only for the variance but for for any nonlinear functional (e.g., median, hazard).

1.3 Measures of causal effect

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.

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.

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,

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:

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

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). Like the causal risk difference, the NNT applies to the population and time interval on which it is based. For a discussion of the relative advantages and disadvantages of the NNT as an effect measure, see Grieve (2003).

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 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 evaluate the empirical evidence regarding the causal null hypothesis $\Pr[Y^{a=1} = 1] = \Pr[Y^{a=0} = 1]$ (see Chapter 10 for details).

2nd source of random error: Nondeterministic counterfactuals

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 nor 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.

Thus, in causal inference, random error derives from sampling variability,

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 an individual-specific 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 now 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, $\mathrm{E}[Y^a] = \mathrm{E}\left[\int y\, d\Theta_{Y^a}(y)\right] = \int y\, d\mathrm{E}[\Theta_{Y^a}(y)] = \int y\, dF_{Y^a}(y)$, where $F_{Y^a}(\cdot) = \mathrm{E}\left[\Theta_{Y_i^a}(\cdot)\right]$.

If the counterfactual outcomes are binary and nondeterministic, the causal risk ratio in the population $\frac{\mathrm{E}\left[Q_{Y^{a=1}}(1)\right]}{\mathrm{E}\left[Q_{Y^{a=0}}(1)\right]}$ 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 $W = \frac{Q_{Y^{a=0}}(1)}{\mathrm{E}\left[Q_{Y^{a=0}}(1)\right]}$, provided $Q_{Y^{a=0}}(1)$ is never equal to 0 (i.e., deterministic) for anyone in the population.

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 irrespective 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 are

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

(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.

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

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 will 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.

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.

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).

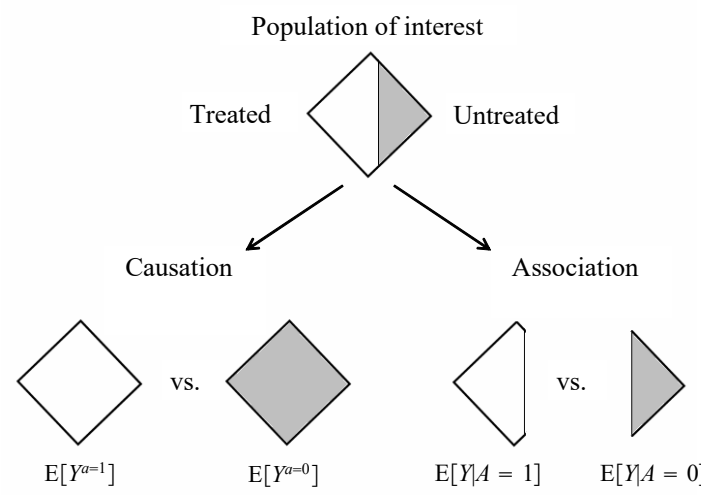


Figure 1.1

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. That is, inferences about causation are concerned with *what if* questions in counterfactual worlds, such as "what would be the risk if everybody had been treated?" and "what would be the risk if everybody had been untreated?", whereas inferences about association are concerned with questions in the actual world, such as "what is the risk in the treated?" and "what is the risk in the untreated?"

We can use the notation we have developed thus far to formalize this 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 an action (your looking up) affects an outcome (other people's looking up) in a specific population (say, residents of Madrid in 2019). 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 experiments. Suppose we want to estimate the individual 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 asked Zeus to call a lightning strike ($a = 1$). His blood pressure was elevated after doing so. This morning we asked Zeus to refrain from using his lightning bolt ($a = 0$). His blood pressure did not increase. We have conducted a *crossover 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. However, we now show that his argument would generally be incorrect unless the very strong assumptions 1)-3) given in the next paragraph are true.

In crossover experiments, individuals are observed during two or more periods, say $t = 0$ and $t = 1$. An individual i receives a different treatment value A_{it} in each period t. Let $Y_{i1}^{a_0 a_1}$ be the (deterministic) counterfactual outcome at $t = 1$ for individual i if treated with a_1 at $t = 1$ and a_0 at $t = 0$. Let $Y_{i0}^{a_0}$ be defined similarly for $t = 0$. The individual causal effect $Y_{it}^{a_t=1} - Y_{it}^{a_t=0}$ can be identified if the following three conditions hold: i) no carryover effect of treatment: $Y_{it=1}^{a_0,a_1} = Y_{it=1}^{a_1}$, ii) the individual causal effect does not depend on time: $Y_{it}^{a_t=1} - Y_{it}^{a_t=0} = \alpha_i$ for $t = 0, 1$, and iii) the counterfactual outcome under no treatment does not depend on time: $Y_{it}^{a_t=0} = \beta_i$ for $t = 0, 1$. Under these conditions, if the individual is treated at time 1 ($A_{i1} = 1$) but not time 0 ($A_{i0} = 0$) then, by consistency, $Y_{i1} - Y_{i0}$ is the individual causal effect because $Y_{i1} - Y_{i0} = Y_{i1}^{a_1=1} - Y_{i0}^{a_0=0} = Y_{i1}^{a_1=1} - Y_{i1}^{a_1=0} + Y_{i1}^{a_1=0} - Y_{i0}^{a_0=0} = \alpha_i + \beta_i - \beta_i = \alpha_i$. Similarly if $A_{i1} = 0$ and $A_{i0} = 1$, $Y_{i0} - Y_{i1} = \alpha_i$ is the individual level causal effect.

Condition (i) implies that the outcome $Y_{it}^{a_t}$ has an abrupt onset that completely resolves by the next time period. Hence, crossover experiments cannot be used to study the effect of heart transplant, an irreversible action, on death, an irreversible outcome. See also Fine Point 3.2.

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 $\frac{7/13}{3/7} = 1.26$. 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.

If $A = 1$, the $Y^{a=0}$ is missing data and if $A = 0$, the $Y^{a=1}$ is missing data. Data are missing completely at random (MCAR) if $\Pr[A = a|L, Y^{a=1}, Y^{a=0}] = \Pr[A = a]$, which holds in a marginally randomized experiment. Data are missing at random (MAR) if the probability of $A = a$ conditional on the full data $(L, Y^{a=1}, Y^{a=0})$ only depends on the data that woud be observed (L, Y^a) if $A = a$, that is, $\Pr[A = a|L, Y^{a=1}, Y^{a=0}] = \Pr[A = a|L, Y^a]$, which holds in a conditional randomized experiment. 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 or 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 experiments 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 a similar 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 that 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

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

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.

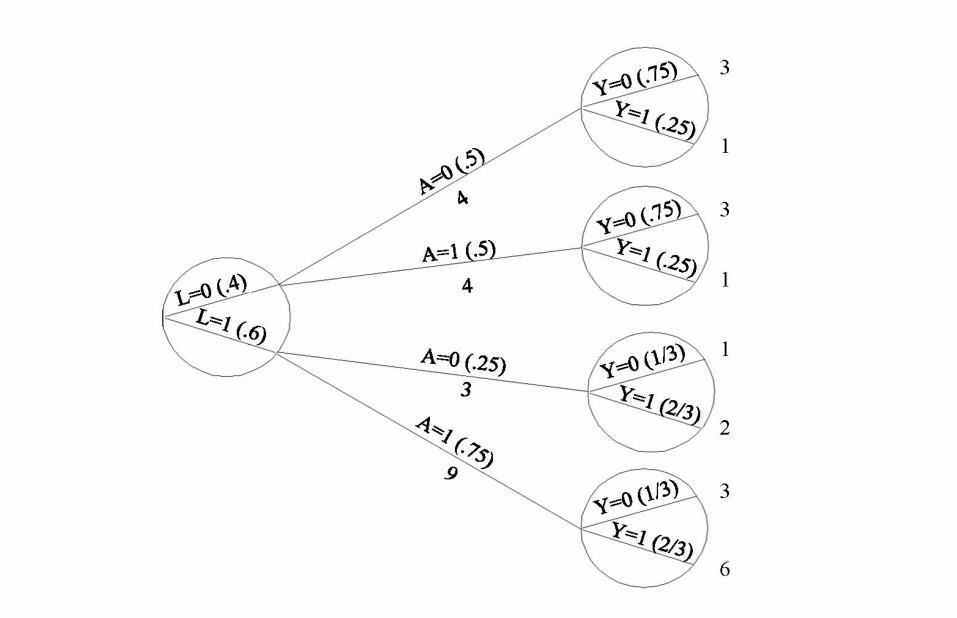


Figure 2.1

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 $\Pr[Y = 1|A = 1]$ 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.

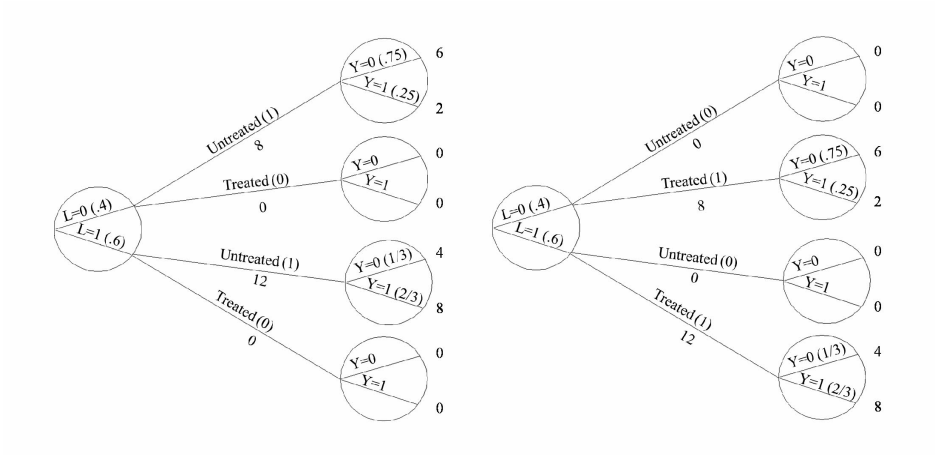


Figure 2.2

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.

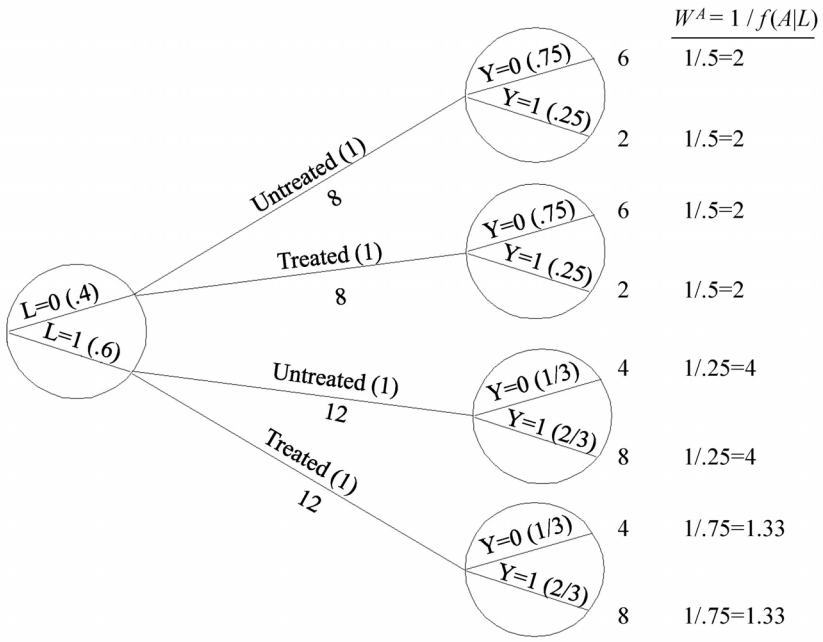


Figure 2.3

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 A is discrete with finite number of values and 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 $\mathrm{E}\left[\frac{I(A=a)}{f[a|L]}\middle| L\right] = 1$)

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

When treatment is continuous, which is an unlikely design choice in conditionally randomized experiments, $\mathrm{E}[I(A=a)Y/f(A|L)]$ is no longer equal to $\sum_l \mathrm{E}[Y|A=a,L=l]\Pr[L=l]$ and thus is biased for $\mathrm{E}[Y^a]$ even under exchangeability. To see this, one can calculate that $\mathrm{E}[I(A=a)/f(a|l)|L=l]$ is equal to 0 rather than 1 if we take $f(a|l)$ to be a (version) of the conditional density of A given $L=l$ (with respect to Lebesgue measure). On the other hand, if we continue to take $f(a|l)$ to be $\mathrm{pr}(A=a|L=l)$, the denominator $f(a|L=l)$ is zero on a set with probability 1 so positivity fails. In Section 12.4 we discuss how IP weighting can be generalized to accomodate continuous treatments. In Technical Point 3.1, we discuss that the results above do not hold in the absence of positivity, even for discrete A.

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 measured covariates L—though we often 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.

Informally, an observational study can be conceptualized as a conditionally randomized experiment if the following conditions hold:

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 measured covariates L

3. the probability of receiving every value of treatment conditional on L 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, then we can use the methods described in the previous chapter—IP weighting or standardization—to identify causal effects from observational studies. We therefore refer to these conditions as *identifiability* conditions or assumptions. 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 identifiability 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 identifiability conditions hold by design. That is, for a conditionally randomized experiment, we would only need the data in Table 3.1 to compute the causal risk ratio of 1. In contrast, to identify the causal risk ratio from an observational study, we would need to assume that the identifiability conditions held, which of course may not be true. 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 under a particular set of assumptions if these assumptions imply that 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 under the assumptions 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 three identifiability conditions for nonparametric identification of average causal effects. In Chapter 16, we describe alternative identifiability conditions which suffice for nonparametric identification of 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

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.

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.

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

Fine Point 3.2

Crossover randomized experiments. In Fine Point 2.1, we described crossover experiments in which an individual is observed during two or more periods—say $t = 0$ and $t = 1$—and the individual receives a different treatment value in each period. We showed that individual causal effects can be identified in crossover experiments when the following three strong conditions hold: i) no carryover effect of treatment: $Y_{it=1}^{a_0,a_1} = Y_{it=1}^{a_1}$, ii) the individual causal effect does not depend on time: $Y_{it}^{a_t=1} - Y_{it}^{a_t=0} = \alpha_i$ for $t = 0, 1$, and iii) the counterfactual outcome under no treatment does not depend on time: $Y_{it}^{a_t=0} = \beta_i$ for $t = 0, 1$. No randomization was required. We now turn our attention to crossover randomized experiments in which the order of treatment values that an individual receives is randomly assigned.

Randomized treatment assignment becomes important when, due to possible temporal effects, we do not assume iii) holds. For simplicity, assume that every individual is randomized to either ($A_{i1} = 1$, $A_{i0} = 0$) or ($A_{i1} = 0$, $A_{i0} = 1$) with probability 0.5. Let $Y_{i1}^{a_1=0} - Y_{i0}^{a_0=0} = r_i$. Then, under i) and ii) and consistency, if $A_{i0} = 0$ and $A_{i1} = 1$, then $Y_{i1} - Y_{i0} = \alpha_i + r_i$, and if $A_{i1} = 0$ and $A_{i0} = 1$, then $Y_{i0} - Y_{i1} = \alpha_i - r_i$. Because r_i is unknown we can no longer identify individual causal effects but, since A_{i1} and A_{i0} are randomized and therefore independent of r_i, the mean of $(Y_{i1} - Y_{i0})\, A_{i1} + (Y_{i0} - Y_{i1})\, A_{i0}$ estimates the average causal effect, i.e., $\mathrm{E}[\alpha_i]$. If we only assume i), then this mean estimates the average of the average treament effects at times 0 and 1, i.e., $(\mathrm{E}[\alpha_{i1}] + \mathrm{E}[\alpha_{i0}])/2$, where $\alpha_{it} = Y_{it}^{a_t=1} - Y_{it}^{a_t=0}$.

In conclusion, if assumption 1) of no carryover effect holds, then a crossover experiment can be used to estimate average causal effects. However, for the type of treatments and outcomes we study in this book, the assumption of no carryover effect is implausible.

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.

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.

a lower probability of receiving treatment $A = 1$. When the distribution of smoking, an important outcome predictor, differs between the treated (with lower proportion of smokers $U = 1$) and the untreated (with higher proportion of smokers) in the stratum $L = 1$, 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 analyzing an observational study under 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.

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 positivity 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.

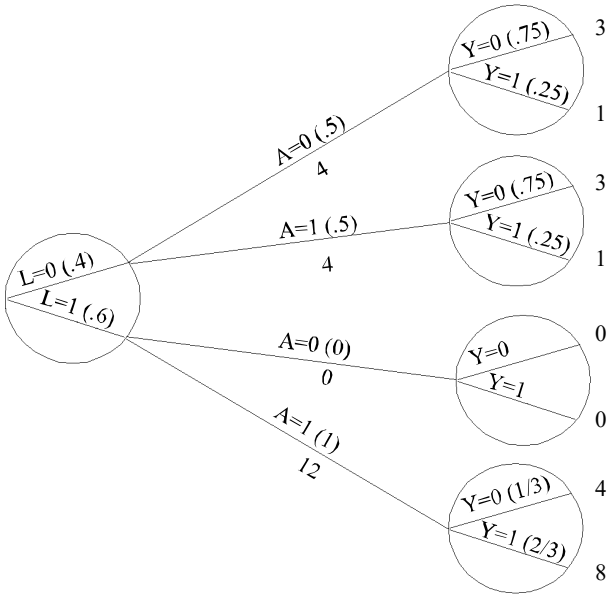


Figure 3.1

3.4 Consistency: First, define the counterfactual outcome

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

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 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 definition 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.

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.

Consider again a randomized experiment to compute the causal 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, anesthesia, surgical technique, post-operative care, and immunosuppressive therapy. Had the protocol not specified these details, it is possible that each doctor had conducted a different version of the treatment "heart transplant", perhaps using her preferred surgical technique or immunosuppressive therapy.

A problem arises if different versions of treatment have different causal effects. 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. Therefore, when referring to "the causal effect of heart transplant A on mortality", we need to specifiy the versions a of treatment A that are of interest. If the treatment values a are not well defined, then the counterfactual outcomes Y^a are not well defined, which in turn means that the causal effect $\Pr[Y^{a=1}=1]-\Pr[Y^{a=0}=$

1] is not well defined. Ideally, the protocols of randomized experiments will precisely specify the treatment values a assigned to each individual, so that their counterfactual outcomes Y^a are well defined. In observational studies, investigators will 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.

For simplicity, we consider the usual definition of obesity (body mass index$\geq$30), More sophisticated definitions of adiposity might be desirable, but using them would complicate the exposition without fundamentally altering the main points.

Suppose that a colleague of ours wishes to quantify the causal effect of obesity A at age 40 on the risk of mortality Y by age 50 in a certain population. Formally, the causal effect is defined by a contrast between the risk if all individuals had been obese $\Pr[Y^{a=1} = 1]$ and the risk if all individuals had been nonobese $\Pr[Y^{a=0} = 1]$ at age 40. But what exactly is meant by "the risk if all individuals had been obese"? The answer is not clear because there are many different ways in which an individual could have become obese at age 40. For example, an individual might be obese at age 40 after having been obese for 20 years, or after having been obese for 2 years only. That is, there are multiple versions of the treatment $A = 1$ defined by duration, recency, and intensity of obesity. Because each of these versions may have a different effect on mortality, our colleague needs to provide a detailed definition of the version of obesity at age 40 that he is interested in. Otherwise, the "causal effect of obesity A at age 40 on mortality at age 50" will be ill-defined.

Part III of this book is devoted to interventions that, like interventions on obesity, are sustained over time. In this chapter we ignore the definitions (and notation) that are required for a formal discussion of sustained interventions.

But, even if our colleague were able to define the duration, recency, and intensity of obesity $A = 1$, other aspects of the intervention would also need to be specified. In particular, our colleague would need to specify *how* to intervene on body weight to ensure that each individual experiences treatment value $A = 1$. For example, he might consider a genetic modification to increase fat tissue in both waist and coronary arteries, or a regime of extreme physical inactivity with high caloric intake, or the replacement of the intestinal microbiota, or surgery, or a combination of these and other interventions. The problem is that each of these options may have different effects on mortality even if they all could somehow set adiposity at the same level.

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.

Take Zeus, who is obese at age 40 ($A = 1$) and had a fatal myocardial infarction at age 49 ($Y = 1$). Zeus had genes that predisposed him to large amounts of fat tissue in both his waist and his coronary arteries, so he died despite exercising moderately, keeping a healthy diet, and having a favorable intestinal microbiota. If, contrary to fact, his genes had been neutral but he had become obese ($A = 1$) after a lifetime of lack of exercise, too many calories in the diet, and an unfavorable intestinal microbiota, then he would not have died by age 50 ($Y = 0$). Therefore, what is Zeus's counterfactual outcome $Y^{a=1}$ under "obesity" $a = 1$? We have just said that he died under one set of circumstances that led to obesity $A = 1$, but would not have died under another set of circumstances that would have also led to obesity $A = 1$. The counterfactual outcome $Y^{a=1}$ under $a = 1$ is ill-defined.

The counterfactual outcome $Y^{a=0}$ if Zeus had been nonobese is also ill-defined. If Zeus 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, suppose a nonobese Zeus would have died by age 50 if he had been nonobese after a lifetime of exercise (cause of death: a bicycle accident), cigarette smoking (cause of death: lung cancer), or bariatric surgery (cause of death: adverse reaction to anesthesia), and would have survived if he had been nonobese after a lifetime of a healthy 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 "no obesity" $A = 0$ we are

considering, the counterfactual outcome $Y^{a=0}$ under $a = 0$ is ill-defined.

Ill-defined counterfactual outcomes result in vague causal questions. If our colleague is interested in the effect of obesity $A = 1$ on mortality, he will have to work harder to define the counterfactual outcomes $Y^{a=0}$ and $Y^{a=1}$. Another example: if interested in the causal effect of exercise, we might need to define the duration, frequency, intensity, and type of exercise (swimming, running, playing basketball...), how the time devoted to exercise would otherwise be spent (playing with your children, rehearsing with your band, watching television...), etc.

Questions about 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—are less vague. Because the treatment is "obesity as perceived by the employer," the mechanisms that led to obesity may be irrelevant.

Note that absolute precision in the definition of the treatment is not needed for useful causal inference. For example, for the causal effect of exercise, 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 "lifetime exercise," the direction of the running need not be specified. This and other aspects of the treatment are deemed to be irrelevant because varying them would not lead to different counterfactual outcomes. That is, we only need *sufficiently well-defined* interventions a for which no meaningful vagueness remains.

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.

Which begs the question of "How do we know that a treatment is sufficiently well-defined" or, equivalently, that no meaningful vagueness remains? The answer is "We don't." Declaring a 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. However, some vagueness is inherent to all causal questions. The vagueness of causal questions can be reduced by a more detailed specification of treatment, but cannot be completely eliminated. Yet the degree of vagueness is especially high in observational studies with causal questions involving biological (e.g., body weight, LDL-cholesterol) or social (e.g., socioeconomic status) "treatments."

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 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 colleague's 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. Refining the causal question, until it is agreed that no meaningful vagueness remains, is a fundamental component of causal inference. Declaring our interest in "the effect of obesity" is just a starting point for a discussion with our colleagues. During

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.

that discussion, we will sharpen the causal question by refining the specification of the treatment until, hopefully, a consensus is reached. The more precisely we define the treatment, 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.

3.5 Consistency: Second, link counterfactuals to the observed data

Inspired by the arguments in the previous section, our colleague decided to transform his vague causal question about the effect of obesity on mortality by age 50 into a more precise causal question. He is now interested in the following intervention ($a = 1$): "at age 18 and through age 40, put every individual on a stringent mandatory diet that guarantees that they would never weigh more than their weight at the age of 18 years." Specifically, each individual is weighed every day starting on the day before his eighteenth birthday. Whenever the weight is greater than the baseline weight at 18 years, the individual's caloric intake is restricted, without changing his usual mix of calorie sources and micronutrients, until the time (usually within 1–3 days) that the individual falls below baseline weight. Thus, ignoring errors of a kilogram or two, no individual would ever weigh more than his baseline weight through age 40. No instructions or restrictions are given concerning exercise at any time or diet during non-calorie-restricted periods. The comparison intervention ($a = 0$) is "do not intervene."

This hypothetical intervention was described by Robins (2008). The hypothetical intervention was restricted to men in order to avoid the complicating issue of how much weight gain to allow during pregnancy.

Suppose experts agree that these treatment values $a = 1$ and $a = 0$ are sufficiently well-defined and, therefore, that no meaningful vagueness remains in the specification of the counterfactual outcomes $Y^{a=1}$ and $Y^{a=0}$. We can now shift our attention to the equal sign in the consistency condition $Y^a = Y$

for individuals with $A = a$.

To fix ideas, let us consider Ares, who maintained an approximately constant weight between the ages of 18 and 40 years despite not receiving our colleague's stringent intervention $a = 1$. Rather, Ares maintained his baseline weight because of a mixture of good genes (from Hera) and vigorous physical activity (from frequent war combat). Thus Ares's observed treatment value was not $A = 1$ and therefore his observed outcome Y does not necessarily equal the counterfactual outcome $Y^{a=1}$ that he would have experienced if he had received our colleague's hypothetical intervention $a = 1$.

To preserve the link between the counterfactual outcomes $Y^{a=1}$ and the observed outcomes Y, we have to ensure that only individuals receiving treatment version $a = 1$ are considered as treated individuals ($A = 1$) in the analysis, and similarly for the untreated. The implication is that, if we want to quantify the causal effect $\Pr[Y^{a=1} = 1] - \Pr[Y^{a=0} = 1]$ using observational data, we need data in which some individuals received treatment values consistent with $a = 1$ and $a = 0$, that is, we need (unconditional) positivity. Being able to describe a well-defined intervention a, as our colleague did, is not helpful if the intervention cannot be linked to the observed data, that is, if we cannot reasonably assume that the equality $Y^a = Y$ holds for at least some individuals.

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

But restriction to the treatment value a of interest is impossible when, as it often happens, our data are not sufficiently rich. This problem would arise, for example, in an "obesity study" that collects data on body weight at age 40, but no data on the individual's lifetime history of weight, exercise, and diet.

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*. In some cases, this may be a good approximation. For example, if interested in the 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 treatment "blood pressure" is unnecessary to link the potential and observed outcomes. In other cases, however, the validity of the assumption is more questionable. 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 implicitly 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 that are absent in the data (this section). Detecting a mismatch between the treatment values of interest and the data at hand requires a careful characterization of the versions of treatment that operate in the population. Such characterization may be 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.

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).

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

In this Section and throughout the book, the term causal effect refers to a contrast between average counterfactual outcomes under different treatment values. Therefore, for each causal effect, we can imagine a (hypothetical) randomized experiment to quantify it. We refer to that hypothetical experiment as the target experiment or the *target trial*. When conducting the target trial is not feasible, ethical, or timely, we resort to causal analyses of observational data. 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 observational estimates and the numerical results that the target trial would have yielded (had it 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. (See Fine Point 3.4 for how to use observational data to compute the proportion of cases attributable to treatment.)

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.

Therefore "what randomized experiment are you trying to emulate?" is a key question for causal inference from observational data. For each causal effect that we wish to estimate 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, interventions (or treatment strategies), outcome, follow-up, causal contrast, and statistical analysis. Here we focus on the treatment strategies or, in the language of this chapter, the interventions that will be compared across groups. As discussed in the previous two sections, investigators will first specify the interventions of interest and then identify individuals who receive them in the data.

Consider the causal effect of "weight loss" on mortality in individuals who are obese and do not smoke at age 40. The first step for investigators is to make their causal question less vague. For example, they might 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 does not matter how the weight loss is achieved. 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, say, obese versus nonobese individuals at age 40. That comparison corresponds implicitly to a target trial in which obese individuals are instantaneously transformed into individuals with 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 (as long as A temporally precedes Y). For example, when considering the effect of obesity, they claim that it is not necessary to carefully specify the target trial. In contrast to our view that specifying the target trial is necessary for interpreting numerical effect es-

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 $\Pr[Y^{a=1}=1]-\Pr[Y^{a=0}=1]$, which 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 latter contrast 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.

The excess fraction is generally different from the *etiologic fraction*, another version of the attributable fraction which is defined as the proportion of cases mechanically caused by exposure. For example, suppose the untreated would have had 7 cases if they have been treated, but these 7 cases would not have contained the 1 exposed case that actually occurred, i.e., treatment prevents 7 cases but produces 1 case. Also suppose that, if untreated, the treated would have had only 1 case but different from the 7 cases they actually had. Then the excess fraction would not be equal to the etiologic fraction. Here the excess fraction is a lower bound on the etiologic fraction. Because the etiologic fraction does not rely on the concept of excess cases, it can only be computed in randomized experiments under strong assumptions (Greenland and Robins, 1988).

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

timates, these authors question the need for such quantitative interpretation. Their argument goes like this:

> 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 required for achieving that transformation is unspecified.

This is an appealing, but risky, argument. Accepting it raises an important 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 forgo characterizing 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 greatly 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. As discussed above, a more reasonable, even if not completely well-defined, intervention may be to reduce body mass index by 5% annually. 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 treatments 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 treatments 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 treatments 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?),

For an extended discussion about the differences between prediction and causal inference, which is a form of counterfactual prediction, see Hernán, Hsu, and Healy (2019).

Technical Point 3.2

Cheating consistency. Consider a compound treatment R with multiple, relevant versions of treatment. 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; VanderWeele and Hernán, 2013): 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 exchangeability and positivity.

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 realistic interventions (e.g., 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.

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.

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

	V	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 V for sex: $V = 1$ for females (referred to as women in this book) and $V = 0$ 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 $V = 1$. In this subset of the population, the risk of death under treatment is $\Pr[Y^{a=1} = 1|V = 1] = 6/10 = 0.6$ and the risk of death under no treatment is $\Pr[Y^{a=0} = 1|V = 1] = 4/10 = 0.4$. 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 $V = 0$. In this subset of the population, the risk of death under treatment is $\Pr[Y^{a=1} = 1|V = 0] = 4/10 = 0.4$ and the risk of death under no treatment is $\Pr[Y^{a=0} = 1|V = 0] = 6/10 = 0.6$. 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:
$\mathrm{E}[Y^{a=1} - Y^{a=0}|V = 1] \neq \mathrm{E}[Y^{a=1} - Y^{a=0}|V = 0]$

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

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.

We are now ready to provide a definition of effect modifier. We say that V is a modifier of the effect of A on Y when the average causal effect of A on Y varies across levels of V. 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 V 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 V. Sex V 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 V. We only consider variables V that are not affected by treatment A as effect modifiers.

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

In Table 4.1 the causal risk ratio is greater than 1 in women ($V = 1$) and less than 1 in men ($V = 0$). Similarly, the causal risk difference is greater than 0 in women ($V = 1$) and less than 0 in men ($V = 0$). That is, there is *qualitative effect modification* because the average causal effects in the subsets $V = 1$ and $V = 0$ 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 V because the causal risk difference among individuals with $V = 1$ equals that among individuals with $V = 0$, i.e., $0.9 - 0.8 = 0.1 = 0.2 - 0.1$. However, in this study there is multiplicative effect modification by V because the causal risk ratio among individuals with $V = 1$ differs from that among individuals with $V = 0$, 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.

4.2 Stratification to identify effect modification

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

A stratified analysis is the natural way to identify effect modification. To determine whether V modifies the causal effect of A on Y, one computes the causal effect of A on Y in each level (stratum) of the variable V. 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 V. 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 V 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 V because, if treatment assignment was random and unconditional, exchangeability is expected in every subset of the population. Thus the causal risk difference in women, $\Pr[Y^{a=1} = 1|V = 1] - \Pr[Y^{a=0} = 1|V = 1]$, is equal to the associational risk difference in women, $\Pr[Y = 1|A = 1, V = 1] - \Pr[Y = 1|A = 0, V = 1]$. And similarly for men. Thus, to identify effect modification by V 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 V. Stratification can be used to compute average causal effects in subsets of the population, but not individual effects (see Fine Points 2.1 and 3.2).

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 ($V = 1$) and 20 are Roman ($V = 0$). 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 $V = 0$

	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 V modifies the effect of A on Y. The goal is to compute the causal effect of A on Y in the Greeks, $\Pr[Y^{a=1} = 1|V = 1] - \Pr[Y^{a=0} = 1|V = 1]$, and in the Romans, $\Pr[Y^{a=1} = 1|V = 0] - \Pr[Y^{a=0} = 1|V = 0]$. If these two causal risk differences differ, we will say that there is additive effect modification by

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 V even if V 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).

V. And similarly for the causal risk ratios if interested in multiplicative effect modification.

The procedure to compute the conditional risks $\Pr[Y^{a=1} = 1|V = v]$ and $\Pr[Y^{a=0} = 1|V = v]$ in each stratum v has two stages: 1) stratification by V, and 2) standardization by L (or, equivalently, IP weighting with weights depending on L). We computed the standardized risks in the Greek stratum ($V = 1$) in Chapter 2: the causal risk difference was 0 and the causal risk ratio was 1. Using the same procedure in the Roman stratum ($V = 0$), we can compute the risks $\Pr[Y^{a=1} = 1|V = 0] = 0.6$ and $\Pr[Y^{a=0} = 1|V = 0] = 0.3$. (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 $V = 0$. Because these effect measures differ from those in the stratum $V = 1$, we say that there is both additive and multiplicative effect modification by nationality V 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 $V = 0$ and $V = 1$.

Step 2 can be ignored when V 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 V modifies the effect of heart transplant A on the risk of death Y. However, we have made no claims about the causal mechanisms involved in such effect modification. In fact, it is possible that nationality is simply a marker for the causal factor that is truly responsible for the modification of the 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. An intervention to improve the quality of heart surgery in Rome could 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 V does not necessarily imply that V 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 V" rather than "effect modification by V." The next chapter introduces "interaction," a concept related to effect modification, that does attribute a causal role to the variables involved.

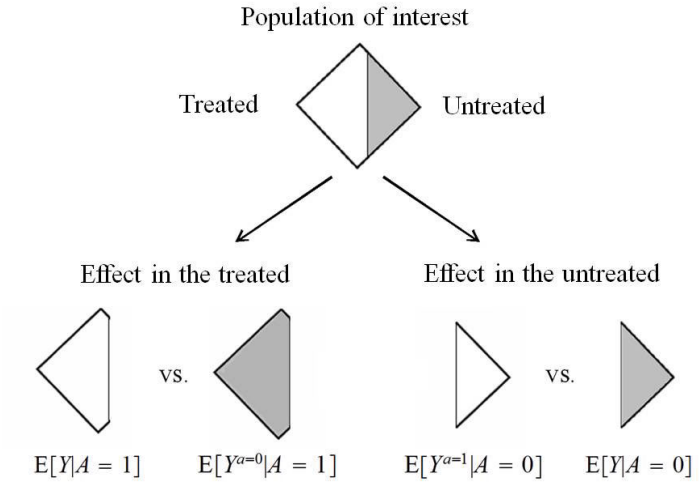


Figure 4.1

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 V even in randomized experiments.

First, if a factor V modifies the effect of treatment A on the outcome Y then the average causal effect will differ between populations with different prevalence of V. For example, the average causal effect in the population of Table 4.1 is harmful in women and beneficial in men, that is, there is qualitative effect modification. 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. In the presence of non-qualitative effect modification, the magnitude, but not the direction, of the average causal effect may vary across populations. As examples of non-qualitative effect modification, consider the effects of asbestos exposure (which differ between smokers and nonsmokers) and of universal health care (which 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."

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 mean $\mathrm{E}\left[Y^a|A = a'\right]$ via standardization, and via IP weighting, under the above assumptions of partial exchangeability:

- Standardization: $\mathrm{E}[Y^a|A = a']$ is equal to $\sum_l \mathrm{E}\left[Y|A = a, L = l\right] \Pr\left[L = l|A = a'\right]$. See Miettinen (1972) and Greenland and Rothman (2008) for a discussion of standardized risk ratios.
- IP weighting: $\mathrm{E}[Y^a|A = a']$ is equal to the IP weighted mean $\dfrac{\mathrm{E}\left[\dfrac{I\left(A=a\right)Y}{f\left(A|L\right)} \Pr\left[A = a'|L\right]\right]}{\mathrm{E}\left[\dfrac{I\left(A=a\right)}{f\left(A|L\right)} \Pr\left[A = a'|L\right]\right]}$ with weights $\dfrac{\Pr\left[A = a'|L\right]}{f\left(A|L\right)}$. For dichotomous A, this equality was derived by Sato and Matsuyama (2003). See Hernán and Robins (2006) for further details.

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 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.

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.

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 described in Fine Point 4.2). These unmeasured effect modifiers are not variables needed to achieve exchangeability, but just risk factors for the outcome. Therefore, transportability of effects across populations is a more difficult problem than the identification of causal effects in a single population: one would need to stratify not just on all those things required to achieve exchangeability (which you might have information about, say, by interviewing those who decide how to allocate the treatment) but on unmeasured causes of the outcome for which there is much less information.

Hence, 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 transported 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 ($V = 0$), and a harmful effect in women ($V = 1$). 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 $V = 0$ and also by 10% in individuals with $V = 1$, i.e., there is no additive effect modification by V because the causal risk difference is 0.1 in all levels of V. Thus, an intervention to treat all patients would be equally effective in reducing risk in both strata of V, despite the fact that there is multiplicative effect modification. In fact, if there is a nonzero causal effect in at least one stratum of V and the counterfactual risk $\Pr[Y^{a=0} = 1|V = v]$ varies with v, 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 $V = 1$ equals 0.8, the maximum possible causal risk ratio in the $V = 1$ stratum is $1/0.8 = 1.25$. Thus the causal risk ratio in the stratum $V = 1$ is guaranteed to differ from the causal risk ratio of 2 in the $V = 0$ stratum. In these situations, the presence of multiplicative effect modification is simply the consequence of different risk under no treatment $\Pr[Y^{a=0} = 1|V = v]$ across levels of V. Therefore, as a general rule, it is more informative to report the (absolute) counterfactual risks $\Pr[Y^{a=1} = 1|V = v]$ and $\Pr[Y^{a=0} = 1|V = v]$ in every level v of V, rather than simply their ratio or difference.

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. 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 factor L via both standardization and IP weighting.

The present chapter adds another potential goal to the analysis: to identify

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.
- 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.
- Interference: In the main text we have focused on settings with no interference (Fine Point 1.1). However, one must remember that interference may exist because treating one individual may affect the outcome of others 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. Therefore, the patterns of contacts among individuals may affect the magnitude of the causal effect. 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.

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, 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.

effect modification by variables V. To achieve this goal, we need to stratify by V before adjusting for L. For example, in this chapter we stratified by nationality V before adjusting for 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 V.

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

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 $Y^a \perp\!\!\!\perp A|L$, then $\Pr[Y = 1|A = a, L = 0] = \Pr[Y^a = 1|L = 0]$

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 $V = 0$ because nationality V, 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 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 V 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. When positivity fails in some strata of the population, restriction is used to limit causal inference to those strata of the original population in which positivity holds (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 via 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

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

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 and positivity 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 of the above methods requires exchangeability and positivity in that subset only; to estimate the marginal effect in the entire population, exchangeability and positivity are required in all levels of L.

In the absence of effect modification, the effect measures (risk ratio or risk difference) 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.

Technical Point 4.3

Relation between marginal and conditional risk ratios. Suppose we wish to determine under which conditions the marginal risk ratio $\Pr\left[Y^{a=1}=1\right]/\Pr\left[Y^{a=0}=1\right]$ will be less than 1 given that we know the values of the conditional risk ratios $\Pr\left[Y^{a=1}=1|L=l\right]/\Pr\left[Y^{a=0}=1|L=l\right]$ for each stratum l. To do so, note that $\Pr\left[Y^{a=1}=1\right]/\Pr\left[Y^{a=0}=1\right] = \sum_l \left\{\Pr\left[Y^{a=1}=1|L=l\right]/\Pr\left[Y^{a=0}=1|L=l\right]\right\} w(l)$, with $w(l) = \left\{\Pr\left[Y^{a=0}=1|L=l\right]\Pr\left[L=l\right]\right\}/\Pr\left[Y^{a=0}=1\right]$ and $\sum_l w(l) = 1$. Substituting for $w(1)$ and $w(0)$ followed by some algebraic manipulations will provide the condition under which the inequality $\Pr\left[Y^{a=1}=1\right]/\Pr\left[Y^{a=0}=1\right] < 1$ holds.

In our data example, $\Pr\left[Y^{a=1}=1|L=l\right]/\Pr\left[Y^{a=0}=1|L=l\right]$ is 0.5 for $L=1$ and 2.0 for $L=0$. Therefore the marginal risk ratio will be less than 1 if and only if $\Pr\left[Y^{a=0}=1|L=1\right]/\Pr\left[Y^{a=0}=1|L=0\right] > 2\Pr\left[L=0\right]/\Pr\left[L=1\right]$.

Table 4.4

	V	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.

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 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 the ratio $\Pr\left[Z^{a=0}=1|L=1\right]/\Pr\left[Z^{a=0}=1|L=0\right]$ of the counterfactual risk under no treatment in the critical group to that in the noncritical group exceeds 2 times the odds $\Pr\left[L=0\right]/\Pr\left[L=1\right]$ of being in the noncritical group (see Technical Point 4.3). 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. As we have discussed earlier, individual causal effects can only be identified under extreme assumptions. See Fine Points 2.1 and 3.2.

Fine Point 4.3

Collapsibility and the odds ratio. In the absence of multiplicative effect modification by V, 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 $\Pr[Y^{a=1}=1|V=v]/\Pr[Y^{a=0}=1|V=v]$ in every stratum v of V. 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 $V=1$ and $V=0$ 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 V 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 $\Pr[Y=1|V=v,A=1]/\Pr[Y=1|V=v,A=0]$ is 2 for men $(V=0)$ and 3 for women $(V=1)$. The (conditional) causal odds ratio $\dfrac{\Pr[Y=1|V=v,A=1]/\Pr[Y=0|V=v,A=1]}{\Pr[Y=1|V=v,A=0]/\Pr[Y=0|V=v,A=0]}$ is 6 for men $(V=0)$ and 6 for women $(V=1)$. 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 V is an independent risk factor for Y and, as in our randomized experiment, A is independent of V (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. See also Technical Point 6.2.

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 V is a modifier of the effect of A on Y when the average causal effect of A on Y varies across levels of V. Note the concept of effect modification refers to the causal effect of A, not to the causal effect of V. 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 V modifies the effect of A we are not considering V 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 $Y^{a,v}$. 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 V can now be applied to identify interaction of A and E by simply replacing the effect modifier V 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 V (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 V, but we never required any identifying assumptions for the effect of V because we were not interested in using our data to compute the causal effect of V on Y. In Section 4.2 we argued on substantive grounds that V is a surrogate effect modifier; that is, V does not act on the outcome and therefore does not interact with A—no action, no interaction. But V is a modifier of the effect of A on Y because V 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).

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 $Y^{a=0,e=1} = Y^{a=0,e=0} = 1$.

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)

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)

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 $\left(Y^{a=0,e=1}=0, Y^{a=0,e=0}=1\right)$.

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 $(A=1)$ 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

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 (2010a) reviews empirical tests for compositional epistasis.

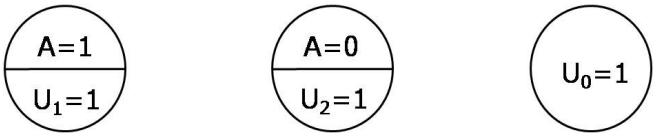
$A = 0$ only results in death if individuals have an ejection fraction less than 20%. We refer to the smallest set of background factors that, together with $A = 0$, are sufficient to produce the outcome as U_2. The simultaneous absence of treatment ($A = 0$) and presence of low ejection fraction ($U_2 = 1$) 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 nor 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.

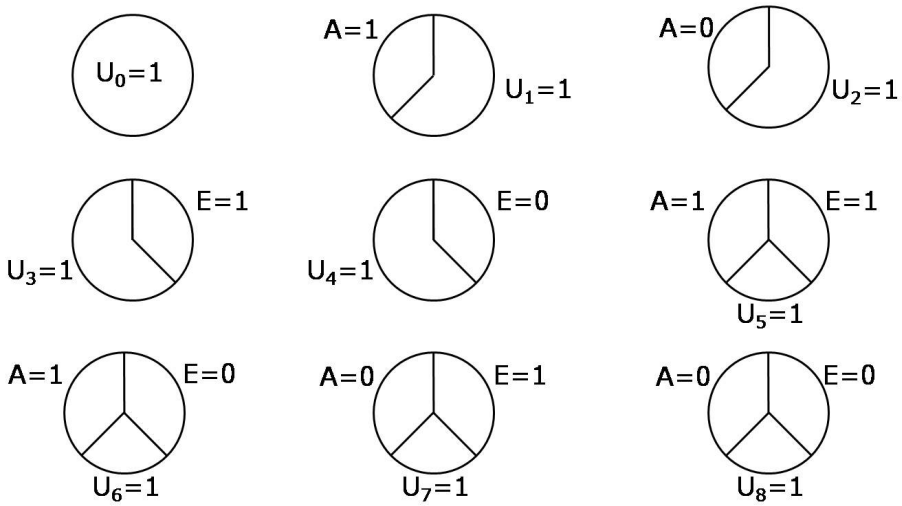


Figure 5.2

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.

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. 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

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).

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 $E = 1$ 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

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.

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

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.

5.6 Counterfactuals or sufficient-component causes?

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

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 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 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.

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

Fine Point 5.4

More on the attributable fraction. Fine Point 3.4 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.

of the magnitude of causal effects on the distribution of background factors (effect modifiers), and the relationship between effect modification, interaction, and synergism.

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. More recent extensions of the sufficient-component-cause framework to stochastic settings and to categorical and ordinal treatments might lead to an increased application of this approach to realistic data analysis. Finally, even allowing for these extensions of the sufficient-component-cause framework, we may rarely have the large amount of data needed to study the fine distinctions it makes.

VanderWeele (2010b) provided extensions to 3-level treatments. VanderWeele and Robins (2012) explored the relationship between stochastic counterfactuals and stochastic sufficient causes.

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.

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.

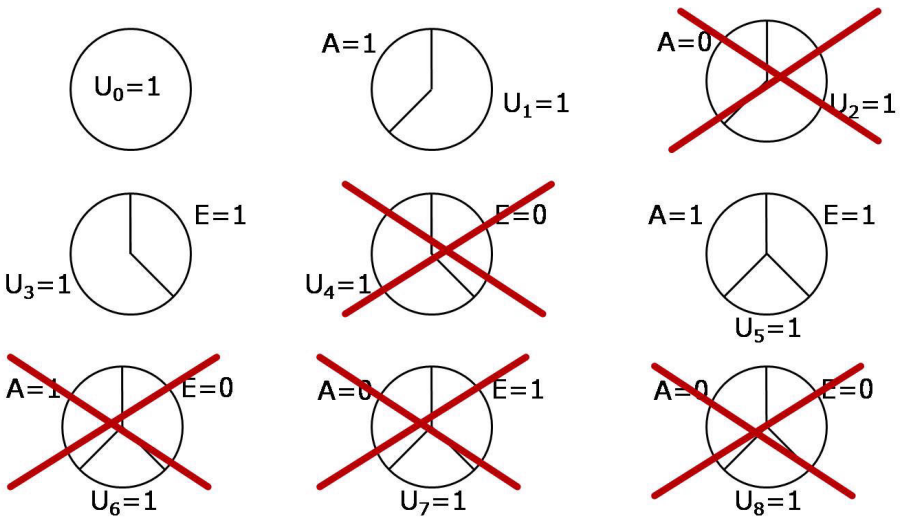


Figure 5.3

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.

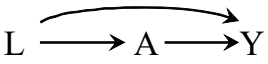


Figure 6.1

The presence of an arrow pointing from a particular variable V to another variable W indicates 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. Alternatively, the lack of an arrow means that we know 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 disease severity affects the probability of receiving a heart transplant. 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.

Directed acyclic graphs have applications other than causal inference. Here we focus on *causal* directed acyclic graphs. A defining property of causal DAGs

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 ordering convention that if $m > j$, V_m is not an ancestor of V_j. We define the distribution of V to be Markov with respect to a DAG G (equivalently, the distribution factors according to a DAG G) if, for each j, V_j is independent of its non-descendants conditional on its parents.

A causal DAG is a DAG in which 1) the lack of an arrow from node V_j to V_m (i.e., V_j is not a parent of 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

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

is that, conditional on its direct causes, any variable on the DAG is independent of any other variable for which it is not a cause. This assumption, referred to as the causal Markov assumption, implies that in a causal DAG the common causes of any pair of variables in the graph must be also in the graph. For a formal definition of causal DAGs, 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 all 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.

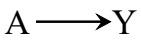


Figure 6.2

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 has as parent disease severity L *and 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 include the underlying counterfactual variables on the graph. Therefore the link between graphs and counterfactuals has traditionally remained hidden. A recently developed 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.

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

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

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.

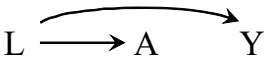


Figure 6.3

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 edges such that the route visits no variable more than once. A path is causal if it consists entirely of edges with their arrows pointing in the same direction. Otherwise it is noncausal.

Technical Point 6.2

Counterfactual models associated with a causal DAG. In this book, 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. An NPSEM implies that any variable V_j on the graph can be intervened on, as counterfactuals in which V_j has been set to a specific value v_j are assumed to exist. 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 direct cause of V_3.

Robins (1986) called this NPSEM a finest causally interpreted structural tree graph (FCISTGs) "as fine as the data". Pearl (2000) showed how to represent this model with a DAG. Robins (1986) also proposed more realistic causally interpreted structural tree graphs 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 of Technical Point 6.1 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. Robins (1986) showed this assumption implies that the causal Markov assumption holds. An NPSEM-IE is an FFRCISTG but not vice-versa because an NPSEM-IE makes many more independence assumptions than an FFRCISTG (Robins and Richardson 2011).

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 whenever we do not mention the underlying counterfactual model.

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 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 $A \rightarrow L \leftarrow Y$ because two arrowheads collide on this node.

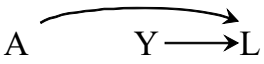


Figure 6.4

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). She 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

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.

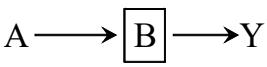


Figure 6.5

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 $A \rightarrow B \rightarrow Y$.

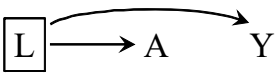


Figure 6.6

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.

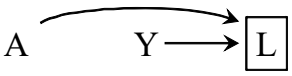


Figure 6.7

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

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

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 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.

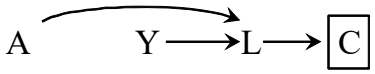


Figure 6.8

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.

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

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 (or of its descendants). 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.

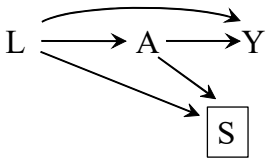


Figure 6.9

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 consistency 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 the next section (and in Chapters 7 and 8) we discuss how the exchangeability condition is translated into graph language.

Fine Point 6.1

D-separation. 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. 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 non-collider that has been conditioned on is blocked. 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. 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. 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 non-collider 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. Two variables are d-separated if all paths between them are blocked (otherwise they are d-connected). Two sets of variables are 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 d-separated 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 d-separated because the only path between them is blocked by the collider L.

The relationship between statistical independence and the purely graphical concept of d-separation relies on the causal Markov assumption (Technical Point 6.1): In a causal DAG, any variable is independent of its non-descendants conditional on its parents. Pearl (1988) proved the following fundamental theorem: The causal Markov assumption implies that, given any three disjoint sets A, B, C of variables, if A is d-separated from B conditional on C, then A is statistically independent of B given C. The assumption that the converse holds, i.e., that A is d-separated from B conditional on C if A is statistically independent of B given C, is a separate assumption—the faithfulness assumption described in Fine Point 6.2. Under faithfulness, A is conditionally independent of Y given B in Figure 6.5, A is not conditionally independent of Y given L in Figure 6.7, and A is not conditionally independent of Y given C in Figure 6.8. The d-separation rules ('d-' stands for directional) to infer associational statements from causal diagrams were formalized by Pearl (1995). An equivalent set of graphical rules, known as "moralization", was developed by Lauritzen et al. (1990).

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

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 hypothetical 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. Positivity is concerned with arrows into the treatment nodes, and well-defined interventions are only concerned with arrows leaving the treatment nodes.

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

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 $A \rightarrow Y$ (as in Figure 6.2) indicates that A has a causal effect on the outcome Y of at least one individual in the population. Thus, we would generally expect that, under Figure 6.2, the average causal effect of A on Y, $\Pr[Y^{a=1} = 1] \neq \Pr[Y^{a=0} = 1]$, and the association between A and Y, $\Pr[Y = 1|A = 1] \neq \Pr[Y = 1|A = 0]$, are not null. 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.

Formally, faithfulness is the assumption that, for three disjoint sets A, B, C on a causal DAG, (where C may be the empty set), A independent of B given C implies A is d-separated from B given C. 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 are open. In this book we will assume faithfulness unless we say otherwise. Faithfulness is also assumed when the goal of the data analysis is discovering the causal structure (see Fine Point 6.3)

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

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. However, we will give a different status to treatment nodes when using SWIGs—causal diagrams with nodes representing counterfactual variables—in subsequent chapters.

The different status of treatment nodes compared with other nodes was also graphically explicit in the causal trees introduced in Chapter 2, in which non-treatment branches corresponding to non-treatment 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 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 $R = r$.

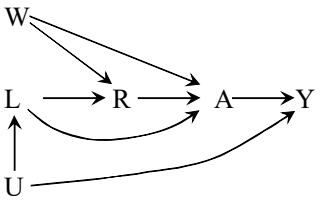


Figure 6.10

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.

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. (In this chapter, due to the assumption of an infinite sample size, bias refers to systematic bias.) 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 can use causal diagrams to classify systematic bias according to its source, and thus to sharpen discussions about bias.

Take the crucial source of bias that we have discussed in previous chapters: lack of exchangeability between the treated and the untreated. For the average causal effect in the entire population, we say that there is (unconditional) bias when $\Pr[Y^{a=1} = 1] - \Pr[Y^{a=0} = 1] \neq \Pr[Y = 1|A = 1] - \Pr[Y = 1|A = 0]$, which is the case when (unconditional) exchangeability $Y^a \perp\!\!\!\perp A$ does not hold.

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 (Spirtes et al., 2000).

We now briefly discuss causal discovery under the assumption that the observed data arose from an unknown causal DAG that includes, in addition to the observed variables, an unknown number of unobserved variables U. Causal discovery requires that we assume faithfulness so that statistical independencies in the observed data distribution imply missing causal arrows on the DAG. Even assuming faithfulness, 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 many causal diagrams: B causes C ($B \rightarrow C$), C causes B, ($C \rightarrow B$), B and C share an unmeasured cause U ($B \longleftarrow U \rightarrow C$), B and C have an unobserved common effect U that has been conditioned on, and various combinations. If we knew the time sequence of B and C, we could only rule out causal diagrams with either $B \rightarrow C$ (if C predates B) or $C \rightarrow B$ (if B predates C).

There are, however, some settings in which learning causal structure from data appears 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 finds 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 analysis is $Z \rightarrow A \rightarrow Y$ with perhaps a common cause U of Z and A in addition to (or in place of) the arrow from Z to A. This is because, if either Z was a parent of Y or shared a cause with Y, or an unmeasured common cause of A and Y was present, then Z and Y could not have been statistically independent given A (assuming faithfulness). Thus, to explain the marginal dependency of Y and A, there must be a causal arrow from A to Y. In summary, the causal DAG learned implies that Z is not a direct cause (parent) of Y, that no unmeasured common cause of A and Y exists, and that, in fact, the average causal effect of A on Y is identified by $\mathrm{E}[Y|A=1] - \mathrm{E}[Y|A=0]$.

The problem is, of course, that we do not have an infinite sample size. Robins et al. (2003) showed that, due to sampling variability, there is no finite sample size at which results of independence tests can, with high probability, distinguish between the hypotheses "A is a cause of Y" and "A does not cause Y". Therefore, if we impose no assumption beyond faithfulness on the unknown graph, we can never have confidence that we have discovered the presence or absence of a causal effect from data. See the book by Peters et al. (2017) for alternative approaches to causal discovery.

When there is systematic bias, no estimator can be consistent. Review Chapter 1 for a definition of consistent estimator.

Absence of (unconditional) bias implies that the association measure (e.g., associational risk ratio or difference) in the population is a consistent estimate of the corresponding effect measure (e.g., causal risk ratio or difference) in the population.

Lack of exchangeability results in bias even when the null hypothesis of no causal effect of treatment on the outcome holds. That is, even if the treatment had no causal effect on the outcome, treatment and outcome would be associated in the data. We then say that lack of exchangeability leads to *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 (i.e., off the null) but not under the null, as described by Greenland (1977) and Hernán (2017). See also Chapter 18.

For the average causal effects within levels of L, we say that there is conditional bias whenever $\Pr[Y^{a=1}=1|L=l] - \Pr[Y^{a=0}=1|L=l]$ differs from $\Pr[Y=1|L=l, A=1] - \Pr[Y=1|L=l, A=0]$ for at least one stratum

l, which is generally the case when conditional exchangeability $Y^a \perp\!\!\!\perp A|L = l$ does not hold for all a and l.

So far in this book we have referred to lack of exchangeability multiple times. However, we have yet to explore the causal structures that generate lack of exchangeability. With causal diagrams added to our methodological arsenal, we will be able to describe how lack of exchangeability 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. Many epidemiologists use the term *confounding* to refer to this bias.

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

Chapter 7 will focus on confounding bias due to the presence of common causes, and Chapter 8 on selection bias due to conditioning on common effects. Again, both are examples of bias under the null due to lack of exchangeability.

Chapter 9 will focus on another source of bias: 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. As we will see, some types of measurement bias also cause bias under the null.

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

Therefore, in the next three chapters we turn our attention to the three types of systematic bias—confounding, selection, and measurement. These biases may arise both in observational studies *and* in randomized experiments. The susceptibility to bias of randomized experiments may not be obvious from previous chapters, in which we conceptualized observational studies as some sort of imperfect randomized experiments, while only considering ideal randomized experiments with no participants lost during the follow-up, all participants adhering to their assigned treatment, and unknown treatment assignment for both study participants and investigators. While our quasi-mythological characterization of randomized experiments was helpful for teaching purposes, real randomized experiments rarely look like that. The remaining chapters of Part I will elaborate on the sometimes fuzzy boundary between experimenting and observing.

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.

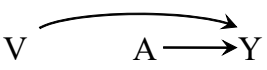


Figure 6.11

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 ($V = 1$) or normal ($V = 0$) quality of care, compute the stratified risk differences in each level of V as described in Chapter 4, and indeed confirm that there is effect modification by V on the additive scale. The causal diagram in Figure 6.11 includes the effect modifier V with an arrow into the outcome Y but no arrow into treatment A (which is randomly assigned and thus independent of V). Two important caveats.

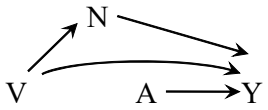


Figure 6.12

First, the causal diagram in Figure 6.11 would still be a valid causal diagram if it did not include V because V is not a common cause of A and Y. It is only because the causal question makes reference to V (i.e., what is the average causal effect of A on Y *within levels of* V?), that V needs to be included on the causal diagram. Other variables measured along the path between "quality of care" V 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 V on Y.

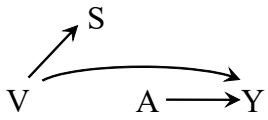


Figure 6.13

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

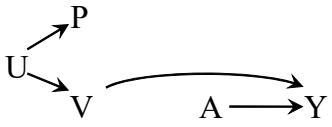


Figure 6.14

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

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

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

That is, valid causal graphs such as Figure 6.11 fail to distinguish between the above three different qualitative types of effect modification by V.

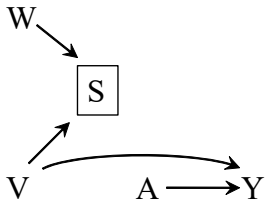


Figure 6.15

In the above example, the effect modifier V 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" V but has itself no effect on mortality Y. An analysis stratified by S (but not by V) will generally detect effect modification by S even though the variable that truly modifies the effect of A on Y is V. The variable S is a *surrogate effect modifier* whereas the variable V 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 V and nationality P. Thus P will behave as a surrogate effect modifier because P is associated with the causal effect modifier V. Another (admittedly silly) example to illustrate this issue: 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 V, 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 V 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

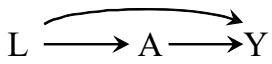


Figure 7.1

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 (the descendants of treatment) are removed. That is, the path has an arrow pointing into treatment.

The structure of confounding, the bias due to common causes of treatment and outcome, 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 includes 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*.

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*.

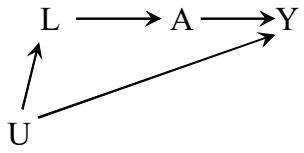


Figure 7.2

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.

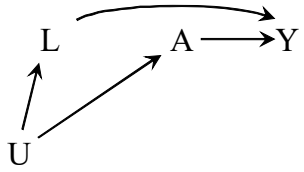


Figure 7.3

- 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.

- 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* when L is unknown.

- 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.

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 as treatment effects. Or, in Yule's words, they are associations "to which the most obvious physical meaning must not be assigned."

- 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 open backdoor path between A and Y. We refer to the bias caused by shared causes of treatment and outcome as confounding, and we use other names to refer to biases caused by structural reasons other than the presence of shared causes of treatment and outcome. For simplicity of presentation, we assume throughout this chapter that all nodes in the causal DAGs are perfectly measured, that there are no selection nodes S with a box

around them (that is, the data are a random sample from the population of interest), and that random variability is absent. Causal DAGs with selection nodes will be discussed in Chapter 8, and causal DAGs with mismeasured nodes in Chapter 9. Random variability is discussed in Chapter 10.

7.2 Confounding and exchangeability

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

We now link the concept of confounding, which we have defined using causal diagrams, with the concept of exchangeability, which we have defined using counterfactuals in earlier chapters. For simplicity of presentation throughout this chapter, suppose that positivity and consistency hold, and that all causal DAGs include perfectly measured nodes that are not conditioned on.

When exchangeability $Y^a \perp\!\!\!\perp A$ holds, as in a marginally randomized experiment in which all individuals have the same probability of receiving treatment, the average causal effect can be identified without adjustment for any variables. For a binary treatment A, the average causal effect $\mathrm{E}[Y^{a=1}] - \mathrm{E}[Y^{a=0}]$ is calculated as the difference of conditional means $\mathrm{E}[Y|A=1] - \mathrm{E}[Y|A=0]$.

When exchangeability $Y^a \perp\!\!\!\perp A$ does not hold but conditional exchangeability $Y^a \perp\!\!\!\perp A|L$ does, as in a conditionally randomized experiment in which the probability of receiving treatment varies across values of L, the average causal effect can also be identified. However, as we described in Chapter 2, identification of the causal effect $\mathrm{E}[Y^{a=1}] - \mathrm{E}[Y^{a=0}]$ in the population requires adjustment for the variables L via standardization or IP weighting. Also, as we described in Chapter 4, conditional exchangeability also allows the identification of the conditional causal effects $\mathrm{E}[Y^{a=1}|L=l] - \mathrm{E}[Y^{a=0}|L=l]$ for any value l via stratification.

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

In practice, if we believe confounding is likely, a key question arises: can we determine whether there exists a set of measured covariates L for which conditional exchangeability holds? Answering this question is difficult because thinking in terms of conditional exchangeability $Y^a \perp\!\!\!\perp A|L$ is often not intuitive in complex causal systems.

In this chapter, we will see that answering this question is possible if one knows the causal DAG that generated the data. To do so, suppose that we know the true causal DAG (for now, it doesn't matter how we know it: perhaps we have sufficient subject-matter knowledge, or perhaps an omniscient god gave it to us). How does the causal DAG allow us to determine whether there exists a set of variables L for which conditional exchangeability holds? There are two main approaches: (i) the backdoor criterion applied to the causal DAG and (ii) the transformation of the causal DAG into a SWIG. Though the use of SWIGs is a more direct approach, it also requires a bit more machinery so we are going to first explain the backdoor criterion; we will describe the SWIG approach in Section 7.5.

Pearl (1995, 2000) proposed the backdoor criterion for nonparametric identification of causal effects.

A set of covariates L satisfies the *backdoor criterion* if all backdoor paths between A and Y are blocked by conditioning on L and L contains no variables that are descendants of treatment A. Under faithfulness and a further condition discussed in Technical Point 7.1, conditional exchangeability $Y^a \perp\!\!\!\perp A|L$ holds if and only if L satisfies the backdoor criterion. (A simple proof of this fact will be given below based on SWIGs.) Hence, we can now answer any query we may have about whether, for a given set of covariates L, conditional exchangeability given L holds. Thus, by trying every subset of measured non-descendants of treatment, we can answer the question of whether conditional exchangeability

Technical Point 7.1

Does conditional exchangeability imply the backdoor criterion? That L satisfies the backdoor criterion always implies conditional exchangeability given L, even in the absence of faithfulness. In the main text we also said that, given faithfulness, conditional exchangeability given L implies that L satisfies the backdoor criterion. This last sentence is true under an FFRCISTG model (see Technical Point 6.2). In contrast, under an NPSEM-IE model, conditional exchangeability can hold even if the backdoor criterion does not, as is the case in a causal DAG with nodes A, L, Y and arrows $A \rightarrow L$, $A \rightarrow Y$. In this book we always assume an FFRCISTG model and faithfulness, unless stated otherwise.

This difference between causal models is due to the fact that the NPSEM-IE, unlike an FFRCISTG model, assumes cross-world independencies between counterfactuals. However a cross-world independence can never be verified, even in principle, by any randomized experiment, which was the very reason that Robins (1986, 1987) did not assume cross-world independence in his FFRCISTG model. For further discussion, see Chapter 22.

holds for any subset. (In fact, algorithms exist that can greatly reduce the number of subsets that must be tried in order to answer the question.)

Let us now relate the backdoor criterion (i.e., exchangeability) to confounding. The two settings in which the backdoor criterion is satisfied are

1. *No common causes of treatment and outcome.* In Figure 6.2, there are no common causes of treatment and outcome, and hence no backdoor paths that need to be blocked. Then the set of variables that satisfies the backdoor criterion is the empty set and we say that there is no confounding.

2. *Common causes of treatment and outcome but a subset L of measured non-descendants of A suffices to block all backdoor paths.* In Figure 7.1, the set of variables that satisfies the backdoor criterion is L. Thus, we say that there is confounding, but that there is no residual confounding whose elimination would require adjustment for unmeasured variables (which, of course, is not possible). For brevity, we say that there is *no unmeasured confounding.*

The first setting describes a marginally randomized experiment in which confounding is not expected because treatment assignment is solely determined by the flip of a coin—or its computerized upgrade: the random number generator—and the flip of the coin cannot cause the outcome. That is, when the treatment is unconditionally 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 of treatment and outcome.

The second setting describes a conditionally randomized experiment in which the probability of receiving treatment is the same for all individuals with the same value of L but, by design, this probability varies across values of L. This experimental design guarantees confounding if L is (i) a risk factor for the outcome Y and (ii) either a cause of the outcome (as in Figure 7.1) or the descendant of an unmeasured cause of the outcome as in Figure 7.2. Hence, there are open backdoor paths. However, conditioning on the covariates L will block all backdoor paths and therefore conditional exchangeability, i.e., $Y^a \perp\!\!\!\perp A|L$, will hold. We say that a set L of measured non-descendants of A is a *sufficient set for confounding adjustment* when conditioning on L blocks all backdoor paths—that is, the treated and the untreated are exchangeable within levels of L.

Take our heart transplant study, a conditionally randomized experiment, as an example. Individuals who received a transplant ($A = 1$) are different from the others ($A = 0$) because, had the treated 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. The presence of common causes of treatment and outcome implies that the treated and the untreated are not marginally exchangeable but are conditionally exchangeable given L. This second setting is also what one hopes for in observational studies in which many variables L have been measured.

The backdoor criterion 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).

7.3 Confounding and the backdoor criterion

We now describe several examples of the application of the backdoor criterion to determine whether the causal effect of A on Y is identifiable and, if so, which variables are required to ensure conditional exchangeability. Remember that all causal DAGs in this chapter include perfectly measured nodes that are not conditioned on.

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.

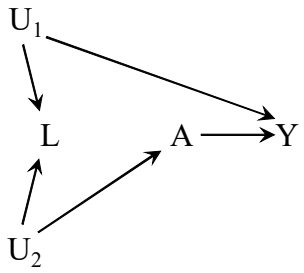


Figure 7.4

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.

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.

Now consider 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 to compute either $\Pr[Y^{a=1}]$ or $\Pr[Y^{a=0}]$ and thus to compute the causal effect in the population.

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), Greenland and Lash (2008), and VanderWeele and Arah (2011) for detailed descriptions of sensitivity analyses for unmeasured confounding.

An informal definition for Figures 7.1 to 7.4: 'A confounder is any variable that can be used to adjust for 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.

Suppose, as in the last four examples, that data on L, A, and Y suffice to identify the causal effect. In such setting we define L to be a confounder if the data on A and Y do not suffice for identification (i.e., we have structural confounding). We define L to be a non-confounder if data on A, Y alone suffice for identification. These definitions are equivalent to defining L as a confounder if there is conditional exchangeability but not unconditional exchangeability (i.e., structural confounding) and as a non-confounder if there is unconditional exchangeability.

Thus, in Figures 7.1-7.3, L is a confounder because $\Pr[Y^a = 1]$ is identified by the standardized risk $\sum_l \Pr[Y = 1|A = a, L = l] \Pr[L = l]$. In Figures 7.2 and 7.3, L is not a common cause of A and Y, yet we still say that L is a confounder because it is needed to block the open backdoor path attributable to the unmeasured common cause U of A and Y. In Figure 7.4, L is a non-confounder and the identifying formula for $\Pr[Y^a = 1]$ is just the conditional mean $\Pr[Y = 1|A = a]$.

The possibility of identification of unconditional effects without identification of conditional effects was non-graphically demonstrated by Greenland and Robins (1986). The conditional bias 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.

If U_1 caused U_2, or U_2 caused U_1, or an unmeasured U_3 caused both, there would exist a common cause of A and Y, and we would have neither unconditional nor conditional exchangeability given L.

The definition of collider is path-specific: L is a collider on the path $A \leftarrow U_2 \rightarrow L \leftarrow U_1 \rightarrow Y$, but not on the path $A \leftarrow L \leftarrow U_1 \rightarrow Y$.

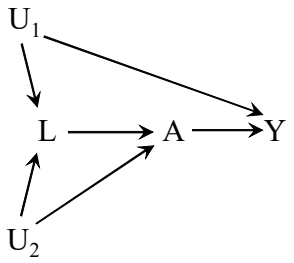


Figure 7.5

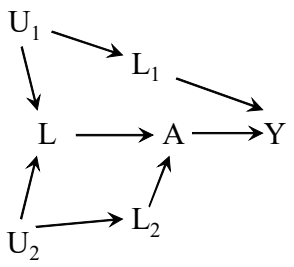


Figure 7.6

Interestingly, in Figure 7.4, conditional exchangeability given L does not hold and thus the counterfactual risks $\Pr[Y^a = 1|L = l]$ are not equal to the stratum-specific risks $\Pr[Y = 1|A = a, L = l]$, and the conditional treatment effects with strata of L are not identified. Further, adjustment for L via standardization $\sum_l \Pr[Y = 1|A = a, L = l] \Pr[L = l]$ gives a biased estimate of $\Pr[Y^a]$. This follows from the fact that adjustment for L would induce bias because 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. This is the first example we have seen for which unconditional exchangeability holds but conditional exchangeability does not: the average causal effect is identified, but generally not the conditional causal effects within levels of L. We refer to the resulting bias in the conditional effect as selection bias because it it arises from selecting (conditioning) on the common effect L of two marginally independent variables U_1 and U_2, one of which is associated with A and the other with Y (see Chapter 8).

The causal diagram in Figure 7.5 is a variation of the one in Figure 7.4. The difference is that, in Figure 7.5, there is an arrow $L \rightarrow A$. The presence of this arrow creates an open backdoor path $A \leftarrow L \leftarrow U_1 \rightarrow Y$ because U_1 is a common cause of A and Y, and so confounding exists. Conditioning on L would block that backdoor path but would simultaneously open a backdoor path on which L is a collider ($A \leftarrow U_2 \rightarrow L \leftarrow U_1 \rightarrow Y$).

Therefore, in Figure 7.5, the bias is intractable: attempting to block the confounding path opens a selection bias path. There is neither unconditional exchangeability nor conditional exchangeability given L. A solution to the bias in Figure 7.5 would be to measure either (i) a variable L_1 between U_1 and either A or Y, or (ii) a variable L_2 between U_2 and either A or L. In the first case we would have conditional exchangeability given L_1. In the second case we would have conditional exchangeability given both L_2 and L. For example, Figure 7.6 includes the variable L_1 between U_1 and Y and the variable L_2 between U_2 and A. See Fine Point 7.2 for a discussion of identification of causal effects depending on what variables are measured in Figure 7.6.

The causal diagrams in this section depict two structural sources of lack of exchangeability that are due to the presence of open backdoor paths between treatment and outcome. The first source is the presence of common causes of treatment and outcome—which creates an open backdoor path. The second source is conditioning on a common effect—which may open a previously blocked backdoor path. For pedagogic purposes, we have reserved the term "confounding" for the first and "selection bias" for the latter. An alternative way to structurally define confounding could be the "bias due to an open backdoor path between A and Y." This alternative definition is identical to ours except that it labels the bias due to conditioning on L in Figure 7.4 as confounding rather than as selection bias. The alternative definition can be equivalently expressed as follows: confounding is "any systematic bias that would be eliminated by randomized assignment of A". To see this, note that the bias induced in Figure 7.4 by conditioning on L could not occur in an experiment in which treatment A is randomly assigned because the random assignment ensures the absence of an unmeasured U_2 that is a common cause of A and L and thus conditioning on L would no longer open a backdoor path.

One interesting distinction between these two definitions is the following. The existence of a common cause of treatment and the outcome (the structural

Fine Point 7.2

Identification of conditional and unconditional effects. Under any causal diagram, the causal effects that can be identified depend on the variables that are measured in addition to the treatment and the outcome. Take Figure 7.6 as an example. If we measure only L_2 (but not L and L_1), we have neither unconditional nor conditional exchangeability given L_2, and no causal effects can be identified. If we measure L_2 and L, we have conditional exchangeability given L_2 and L, but we do not have conditional exchangeability given either L_2 alone or L alone. However, we can identify:

- The conditional causal effects within joint strata of L_2 and L. The identifying formula for each of the counterfactual means is $\mathrm{E}[Y|A=a, L=l, L_2=l_2]$.
- The unconditional causal effect. The identifying formula for each of the counterfactual means is $\sum_{l,l_2} \mathrm{E}[Y|A=a, L=l, L_2=l_2] \Pr[L=l, L_2=l_2]$.
- The conditional causal effects within strata of L. The identifying formula for each of the counterfactual means is $\sum_{l_2} \mathrm{E}[Y|A=a, L=l, L_2=l_2] \Pr[L_2=l_2|L=l]$.
- The conditional causal effects within strata of L_2. The identifying formula for each of the counterfactual means is $\sum_{l} \mathrm{E}[Y|A=a, L=l, L_2=l_2] \Pr[L=l|L_2=l_2]$.

If we only measure L_1, then we have conditional exchangeability given L_1 so we can identify the conditional causal effects within strata of L_1 and the unconditional causal effect. If we measure L_1 and L, then we can also identify the conditional causal effects within joint strata of L_1 and L, and within strata of L alone. If we measure L, L_1, and L_2, then we can also identify the conditional effects within joint strata of all three variables.

definition of confounding) is a substantive fact about the study population and the world, independent of the method chosen to analyze the data. On the other hand, the definition of confounding as any bias that would have been eliminated by randomization implies that the existence of confounding depends on the method of analysis. In Figure 7.4, we have no confounding if we do not adjust for L, but we introduce confounding if we do adjust.

Nonetheless, the choice of one definition over the other is just a matter of taste with no practical implications as all our conclusions regarding identifiability are based solely on whether conditional and/or unconditional exchangeability holds and not on our definition of confounding. The next chapter provides more detail on the distinction between structural confounding and selection bias.

7.4 Confounding and confounders

In the previous section, we have described how to use causal diagrams to decide whether confounding exists and, if so, to identify whether a given set of measured variables L is a sufficient set for confounding adjustment. The procedure requires a priori knowledge of the causal DAG that includes all causes—both measured and unmeasured—shared by the treatment A and the outcome Y. Once the causal diagram is known, we simply need to apply the backdoor criterion to determine what variables need to be adjusted for.

In contrast, the traditional approach to handle confounding was based mostly on observed associations rather than on prior causal knowledge. The traditional approach first labels variables that meet certain (mostly) associa-

Technically, investigators do not need structural knowledge. They only need to know a set of variables that guarantees conditional exchangeability. However, acquring the structural knowledge—and therefore drawing the causal diagram—is arguably the most natural approach to reason about conditional exchangeability.

tional conditions as confounders and then mandates that these so-called confounders are adjusted for in the analysis. Confounding is said to exist when the adjusted estimate differs from the unadjusted estimate.

Under the traditional approach, a confounder was defined as a 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 outcome. However, this traditional approach may lead to inappropriate adjustment. To see why, let us revisit Figures 7.1-7.4.

In Figure 7.1, 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. In Figure 7.2, 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. In Figure 7.3, 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.

Therefore, according to the traditional approach, L is a confounder in the settings represented by Figures 7.1-7.3 and it needs be adjusted for. That was also our conclusion when using the backdoor criterion in the previous section. For Figures 7.1-7.3, there is no discrepancy between the traditional, mostly associational approach and the application of the backdoor criterion to the causal diagram.

Now consider Figure 7.4 again in which there is no confounding and L is a non-confounder by the definition given in Section 7.3. However, 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 approach, L is a confounder that should be adjusted for, even in the absence of confounding! But, as we saw above, adjustment for L results in a biased estimator of the causal effect in the population due to selection bias. Figure 7.7 is another example in which the traditional approach leads to inappropriate adjustment for L by inducing selection bias.

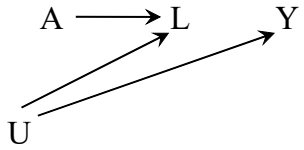


Figure 7.7

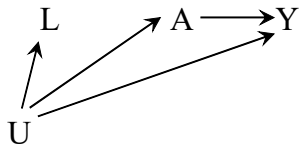


Figure 7.8

These examples show that associational or statistical criteria are insufficient to characterize confounding. An approach based on a definition of confounder that relies almost exclusively on statistical considerations may lead, as shown by Figures 7.4 and 7.7, to the wrong advice: adjust for a "confounder" even when structural confounding does not exist. To eliminate this problem for Figure 7.4, a follower of the traditional approach might replace the associational condition "(2) it is associated with the outcome conditional on the treatment" by the structural condition "(2) it is a cause of the outcome." This modified definition of confounder 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. See Technical Point 7.2.

The traditional approach misleads investigators into adjusting for variables when adjustment is harmful. The problem arises because the traditional approach starts by defining confounders in the absence of sufficient causal knowledge about the sources of confounding, and then mandates adjustment for

Fine Point 7.3

Surrogate confounders. Under the causal DAG in Figure 7.8, 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 would make no difference whether one conditions on L or on U. Indeed if L is binary and is a nondifferentially 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 (Greenland 1980, 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 (and so could never completely eliminate confounding) as *surrogate confounders*. A possible strategy to fight confounding is to measure as many surrogate confounders as possible and adjust for all of them. See Chapter 18 for discussion.

those so-called confounders. If the adjusted and unadjusted estimates differ, the traditional approach declares the existence of confounding. However, change in estimates may occur for reasons other than confounding, including selection bias when adjusting for non-confounders (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.

In contrast, a structural approach starts by explicitly identifying the sources of confounding—the common causes of treatment and outcome that, were they all measured, would be sufficient to adjust for confounding—and then identifies a sufficient set of adjustment variables.

The structural approach makes clear that including a particular variable in a sufficient set depends on the variables already included in the set. For example, in Figures 7.2 and 7.3 the set of variables L is needed to block a backdoor path because the set of variables U is not measured. We could then say that the variables in L are confounders. However, if the variables U had been measured and used to block the backdoor path, then the variables L would not be confounders given U (see also Fine Point 7.3). Given a causal DAG, confounding is an absolute concept whereas confounder is a relative one.

VanderWeele and Shpitser (2013) also proposed a formal definition of confounder.

A structural approach to confounding emphasizes that causal inference from observational data requires a priori causal knowledge. This causal knowledge is summarized in a causal DAG that encodes the researchers' beliefs or assumptions about the causal network. Of course, there is no guarantee that the researchers' causal DAG is correct and thus it is possible that, contrary to the researchers' beliefs, their chosen set of adjustment variables fails to eliminate confounding or introduces selection bias. However, the structural approach to confounding has two important advantages. First, 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, regardless of what non-structural definitions of confounder may say. Second, the researchers' assumptions about confounding become explicit and therefore can be explicitly criticized by other investigators.

Technical Point 7.2

Fixing the traditional definition of confounder. Figures 7.4 and 7.7 depict two graphical examples in which the traditional non-graphical definition of confounder and confounding 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 $Y^a \perp\!\!\!\perp A|L, U$. This new condition is stronger than the earlier condition because it effectively implies that L is not on a causal pathway between A and Y and that $\mathrm{E}[Y^a|L = l, U = u]$ is identified by $\mathrm{E}[Y|L = l, U = u, A = a]$.
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 7.7 because they allow us to dismiss variables as non-confounders (Robins 1997). For example, Greenland, Pearl, and Robins applied these conditions to Figure 7.4 to show that there is no confounding.

7.5 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.

The equivalence between unconditional exchangeability $Y^a \perp\!\!\!\perp A$ and the backdoor criterion seems rather magical: there appears to be no obvious relationship between counterfactual independence and the absence of backdoor paths because counterfactuals are not included as variables on causal diagrams. Since graphs are so useful for evaluating independencies via d-separation, it seems natural to want to construct graphs that include counterfactuals as nodes, so that unconditional and conditional exchangeability can be directly read off the graph.

A new type of graph—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, the variables on a standard causal diagram represent 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.

Robins and Richardson (2013) showed that SWIGs overcome some of the shortcomings of previously proposed twin causal diagrams (Balke and Pearl 1994).

Suppose the causal diagram in Figure 7.2 represents the observed study

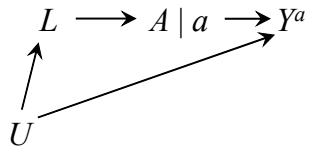


Figure 7.9

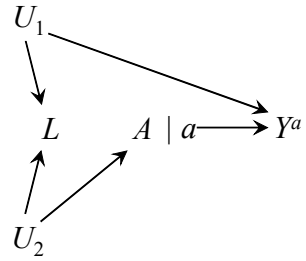


Figure 7.10

Under an FFRCISTG model, it can be shown that d-separation also implies statistical independence on the SWIG.

data. The SWIG in Figure 7.9 is a transformation of Figure 7.2 that represents a world in which all individuals have received an intervention that sets their treatment to the fixed value a.

In the SWIG, the treatment node is split into left and right sides which are to be regarded as separate nodes (variables) once split. The right side encodes the treatment value a under the intervention and inherits all the arrows that were out of A in the original causal DAG. 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*. It inherits all nodes that were into A on the causal DAG because its causal inputs are the same in the intervened on (counterfactual) world as in the actual world. Note that A does not have an arrow into a because the value a is the same for all individuals, i.e., is a constant in the intervened on world.

We assume that the natural value of treatment A is well defined even though we are generally unable to measure it under intervention a. In some settings, though, A may be measurable: recent experiments suggest that electroencephalogram recordings can detect the choice individuals will make up to 1/2 second before individuals becomes conscious of their decision. If so, A could actually be measured via electroencephalogram, while still leaving 1/2 second to intervene and give treatment a.

In the SWIG, the outcome is Y^a, the value of Y in the intervened on world. Because the remaining variables are temporally prior to A, they are not affected by the intervention and therefore take the same value as in the observed world. i.e., they are not labelled as a counterfactual variable. In fact, any variable that is a non-descendant of A need not be labelled as a counterfactual because, under the faithfulness assumption (which we make), treatment has no causal effect on its non-descendants for any individual. Under our causal model, conditional exchangeability $Y^a \perp\!\!\!\perp A|L$ holds because all paths between Y^a and A are blocked after conditioning on L, i.e., Y^a and A are d-separated given L.

Consider now the causal diagram in Figure 7.4 and the SWIG in Figure 7.10. 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. In fact it is straightforward to see that, on the SWIG, Y^a is d-separated from A given L if and only if L is a non-descendant of A that blocks all backdoor paths from A to Y (see also Fine Point 7.4).

7.6 Confounding adjustment

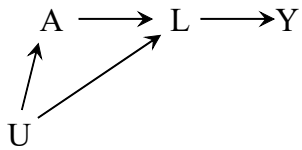


Figure 7.11

In the absence of randomization, causal inference relies on the uncheckable assumption that we have measured a set of variables L that is a *sufficient set for confounding adjustment*, that is, a set of non-descendants of treatment A that includes enough variables to block all backdoor paths from A to Y. Under this assumption of conditional exchangeability given L, standardization and IP weighting can be used to compute the average causal effect in the population. But, as discussed in Section 4.6, standardization and IP weighting are not the only available methods to adjust for confounding in observational

Fine Point 7.4

Confounders cannot be descendants of treatment, but can be in the future of treatment. Consider the causal DAG in Figure 7.11. L is a descendant of treatment A that blocks all backdoor paths from A to Y. Unlike in Figures 7.4 and 7.7, 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 that the adjustment for L eliminates all bias, it must be the case that conditional 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 7.12, 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).

The problem arises because L is a descendant of A, not because L is in the future of A. If, in Figure 7.11, the arrow from A to L did not exist, then L would be a non-descendant of A that blocks all the backdoor paths. Analogously, on the SWIG in Figure 7.12, we can replace L^a by L as A is no longer a cause of L (note Y^a and A are now d-separated by L). 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. Rosenbaum (1984) and Robins (1986, section 11) give non-graphical discussions of the control of confounding by temporally post-treatment variables.

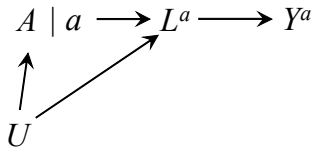


Figure 7.12

studies. Methods that adjust for confounders L can be classified into two broad categories:

- G-methods: standardization, IP weighting, and g-estimation. These methods (the 'g' stands for 'generalized.') exploit conditional exchangeability given 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). Part II describes model-based extensions of g-methods: the parametric g-formula (standardization), IP weighting of marginal structural models, and g-estimation of nested structural models.

- Stratification-based methods: Stratification (including restriction) and matching. These methods exploit conditional exchangeability given L to estimate the association between A and Y in subsets defined by L. In our heart transplant study, we used stratification-based methods to adjust for confounding by disease severity L in Sections 4.4 (stratification) and 4.5 (matching). Part II describes the model-based extension of stratification: conventional outcome regression.

A common variation of stratification and matching replaces each individual's 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.

G-methods simulate the A-Y association in the population if backdoor paths involving the measured variables L did not exist. 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. In contrast, stratification-based methods do not delete the arrow from L to A but rather compute the conditional effect in a subset of the

observed population, which is represented by adding a selection box. The advantage of "deleting" the arrow from confounders L to treatment A will become apparent when we discuss time-varying treatments in Part III. In settings with time-varying treatments, and therefore time-varying confounders, g-methods are the methods of choice to adjust for confounding because stratification-based methods may result in selection bias. The bias of stratification-based methods is described in Chapter 20.

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.

All the above methods require conditional exchangeability given L. However, confounding can sometimes be handled by methods that do not require conditional exchangeability. Some examples of these methods are difference-in-differences (Technical Point 7.3), instrumental variable estimation (Chapter 16), the front door criterion (Technical Point 7.4), and others. Unfortunately, these methods require alternative assumptions that, like conditional exchangeability, are unverifiable. Therefore, in practice, the validity of the resulting effect estimates is not guaranteed. Also, these 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. For time-fixed treatment, the choice of adjustment method will depend on which unverifiable assumptions—either conditional exchangeability or the alternative conditions—are believed more likely to hold in a particular setting.

Achieving conditional exchangeability may be an unrealistic goal in many observational studies but, as discussed in Section 3.2, expert knowledge about the causal structure can be used to get as close as possible to that goal. Therefore, in observational studies, investigators measure many variables L (which are non-descendants of treatment) in an attempt to ensure that the treated and the untreated are conditionally exchangeable. The hope is that, even though common causes may exist (confounding), the measured variables L are sufficient to block all backdoor paths (no unmeasured confounding). However, there is no guarantee that this attempt will be successful, which makes causal inference from observational data a risky undertaking.

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

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.

There is a scientific consequence to the always present threat of 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.

Technical Point 7.3

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 7.13, 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).

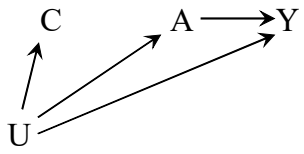


Figure 7.13

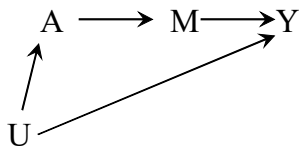


Figure 7.14

To appropriately criticize your study, the critic needs to 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.

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. But, unlike confounding, these other biases may arise in *both* randomized experiments and observational studies. 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.

Technical Point 7.4

The front door criterion. The causal diagram in Figure 7.14 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 causes with either A or 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 the methods described in previous chapters. However, Pearl (1995) showed that $\Pr[Y^a=1]$ is identified by the so-called *front door formula*

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

Pearl refers to this identification formula as front door 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 completely mediates the effect of A on Y. Pearl often uses the term backdoor formula to refer to the identification formula that we refer to as standardization or, more generally, the g-formula (Robins 1986).

A proof of the front door identification formula follows. Note that $\Pr[Y^a=1] = \sum_m \Pr[M^a=m] \Pr[Y^a=1|M^a=m]$ and that, under Figure 7.14, $\Pr[M^a=m] = \Pr[M=m|A=a]$ because there is no confounding for the effect of A on M (i.e., $A \perp\!\!\!\perp M^a$), and $\Pr[Y^a=1|M^a=m] = \sum_{a'} \Pr[Y=1|M=m,A=a'] \Pr[A=a']$. To prove the last equality, first note that $\Pr[Y^a=1|M^a=m] = \Pr[Y^m=1]$ because (i) $Y^a = Y^m$ when $M^a = m$ (A affects Y only through M in Figure 7.14) and (ii) $Y^m \perp\!\!\!\perp M^a$ by d-separation on a SWIG under the joint intervention in which M is set to m and A to a. Finally, by conditional exchangeability $Y^m \perp\!\!\!\perp M|A$ on the SWIG where we intervene on M alone, $\Pr[Y^m=1] = \sum_{a'} \Pr[Y=1|M=m,A=a'] \Pr[A=a']$.

The above proof requires well-defined counterfactual outcomes Y^m under interventions on M. We now provide a second proof in which we assume that only counterfactual outcomes Y^a under interventions on A are well-defined. To do so, we reinterpret the causal DAG in Figure 7.14 as a statistical DAG and use the SWIG independence $D^a \perp\!\!\!\perp A|N$, where $D=(Y,M)$ and $N=U$ are the descendants and non-descendants of A, respectively. Then $\Pr[Y^a=y] =$
$= \sum_m \sum_u \Pr[Y^a=y, M^a=m, U=u]$
$= \sum_m \sum_u \Pr[Y^a=y, M^a=m|A=a, U=u] \Pr[U=u]$ (by exchangeability)
$= \sum_m \sum_u \Pr[Y=y, M=m|A=a, U=u] \Pr[U=u]$ (by consistency)
$= \sum_m \sum_u \Pr[Y=y|M=m, A=a, U=u] \Pr[M=m|A=a, U=u] \Pr[U=u]$
$= \sum_m \Pr[M=m|A=a] \sum_u \Pr[Y=y|M=m, U=u] \{\sum_{a'} \Pr[U=u|A=a'] \Pr[A=a']\}$
by $U \perp\!\!\!\perp M|A$ and $A \perp\!\!\!\perp Y|M,U$
$= \sum_m \Pr[M=m|A=a] \sum_{a'} \{\sum_u \Pr[Y=y|M=m, A=a', U=u] \Pr[U=u|M=m, A=a']\} \Pr[A=a']$
by $U \perp\!\!\!\perp M|A$ and $A \perp\!\!\!\perp Y|M,U$
$= \sum_m \Pr[M=m|A=a] \sum_{a'} \Pr[Y=y|M=m, A=a'] \Pr[A=a']$.

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 look up. 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

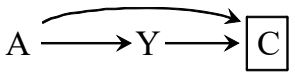


Figure 8.1

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 outcome, 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

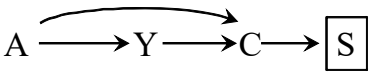


Figure 8.2

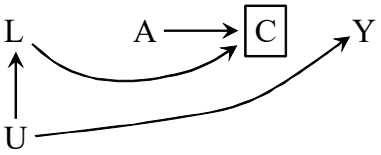


Figure 8.3

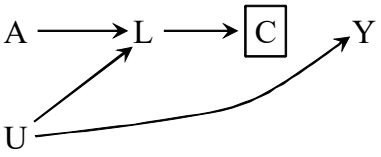


Figure 8.4

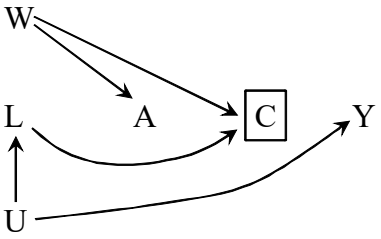


Figure 8.5

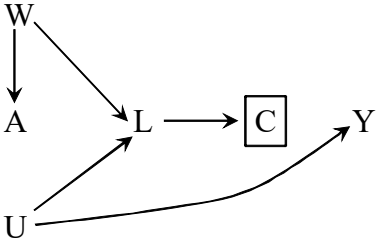


Figure 8.6

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 structures 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

The distinction between the two structures leading to lack of exchangeability is not universally made across disciplines. Lack of conditional exchangeability due to any cause is often referred as "weak ignorability" or "ignorable treatment assignment" in statistics (Rosenbaum and Rubin, 1983), "selection on observables" in the social sciences (Barnow et al., 1980), and "ommitted variable bias" or "endogeneity" in econometrics (Imbens, 2004).

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

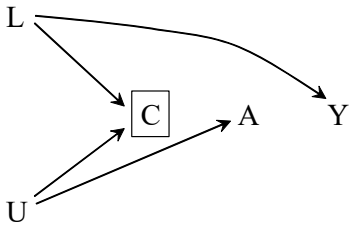


Figure 8.7

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. Their 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. 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 non-collider 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.

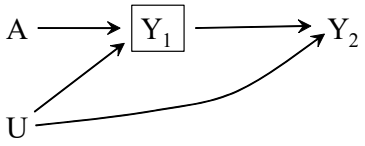


Figure 8.8

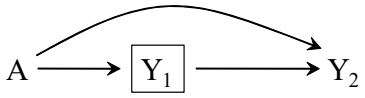


Figure 8.9

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 that needs to be adjusted 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 alternative. 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 and confounding. However, it is possible that some noncausal paths opened by conditioning 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

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 $C \longrightarrow Y$.

the causal effect of A on Y in the presence of selection bias. In fact, when conceptualizing the causal contrast of interest in terms of $Y^{a,c=0}$, 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 of 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.

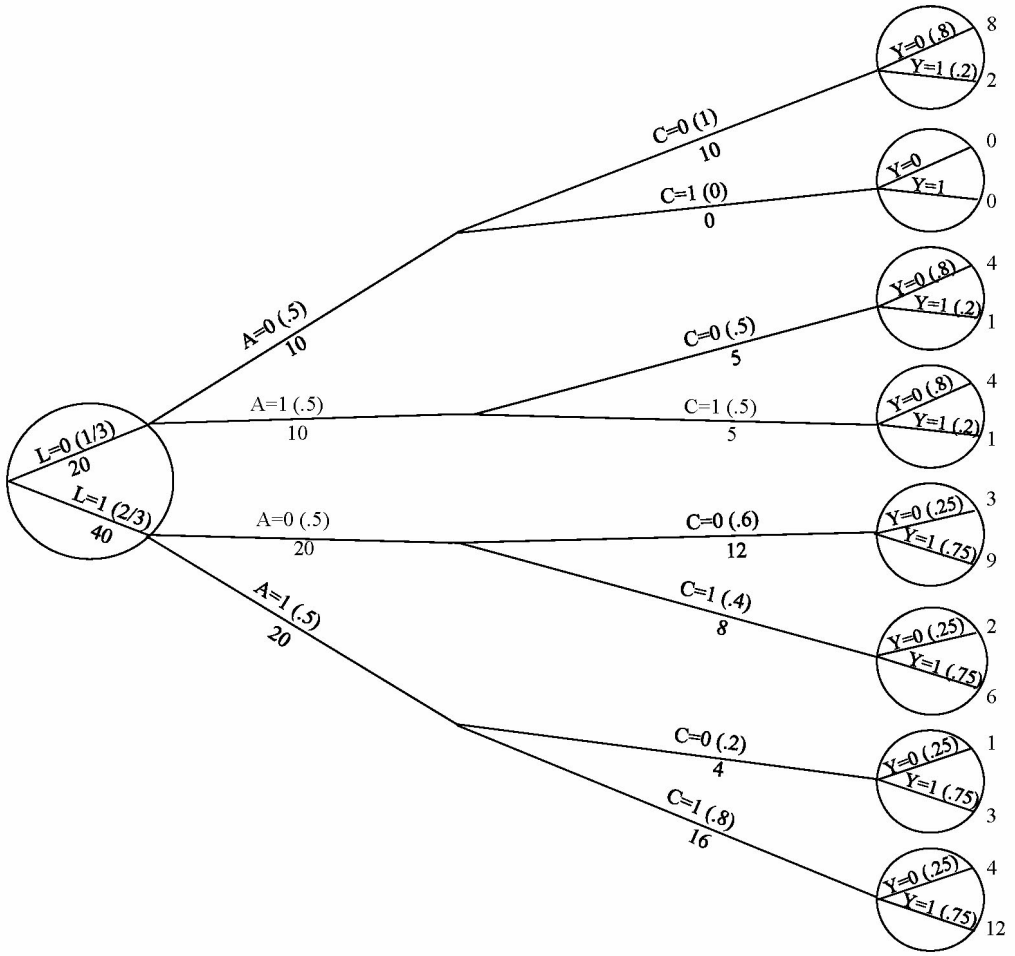


Figure 8.10

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.

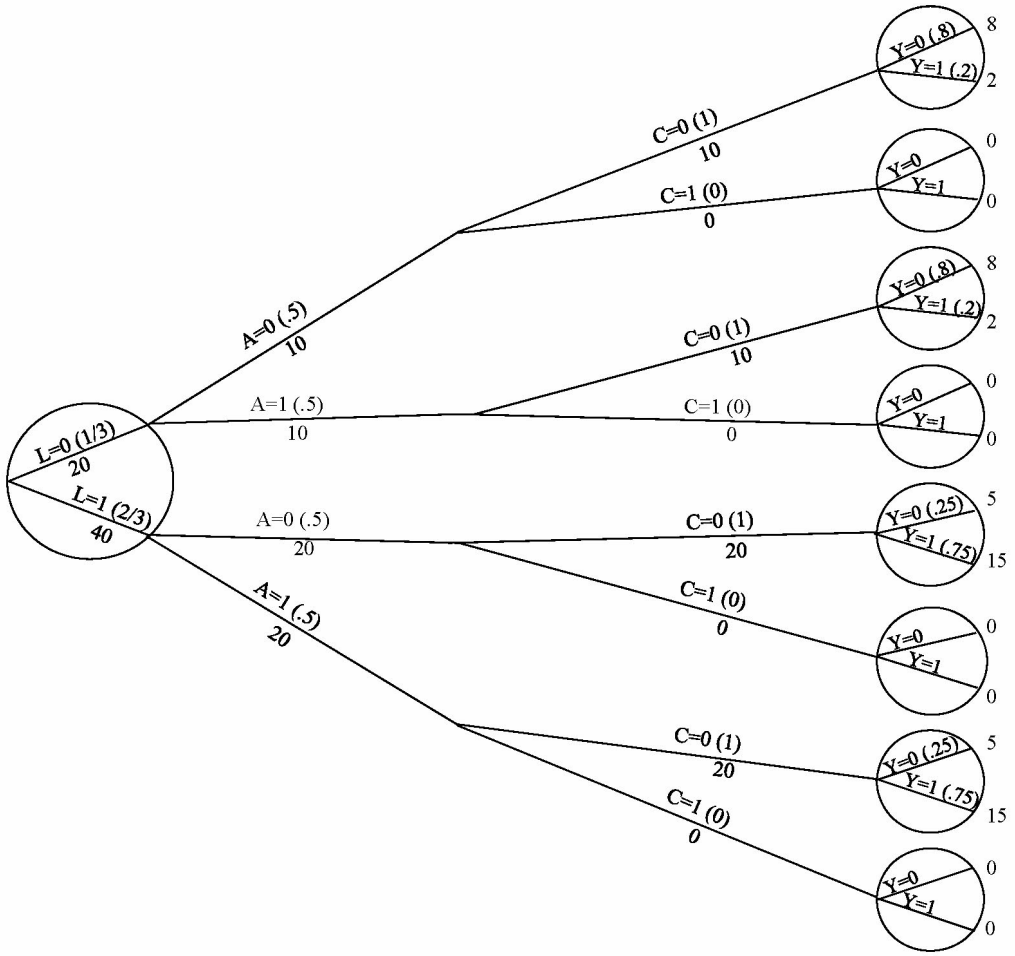


Figure 8.11

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

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

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.

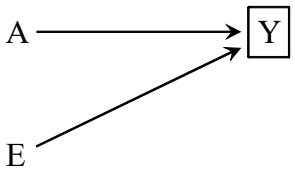


Figure 8.12

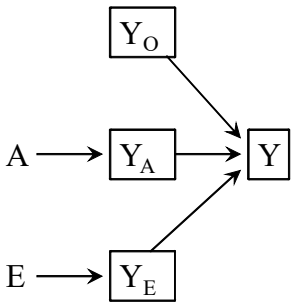


Figure 8.13

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.

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. 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 $Y=1$.

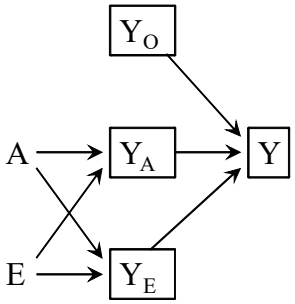


Figure 8.14

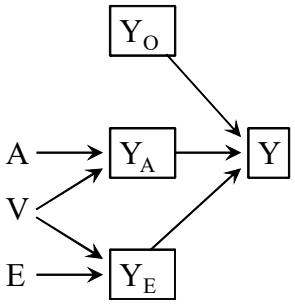


Figure 8.15

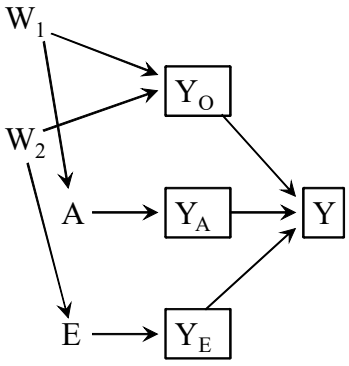


Figure 8.16

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., when conditioning on collider $Y=0$, the path between A and E through Y is blocked by conditioning on the non-colliders 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, A and E are associated given $Y=1$, i.e., when conditioning on collider $Y=1$, the path between A and E through Y is not blocked.

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

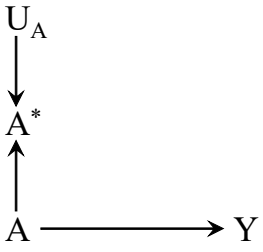


Figure 9.1

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., $f(U_Y|A) = f(U_Y)$.

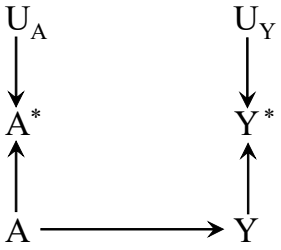


Figure 9.2

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

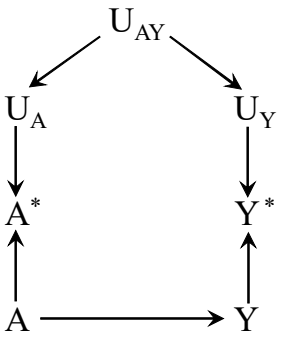


Figure 9.3

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

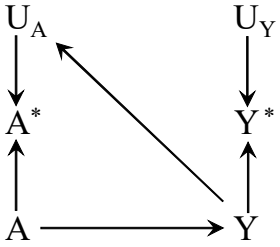


Figure 9.4

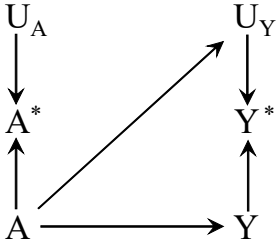


Figure 9.5

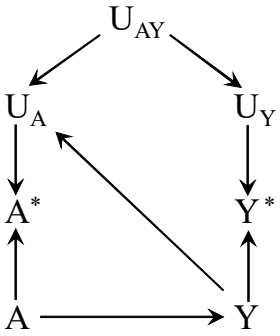


Figure 9.6

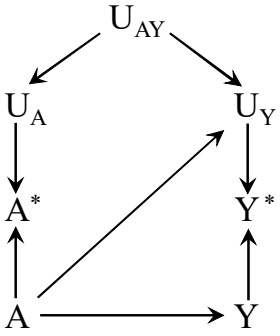


Figure 9.7

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

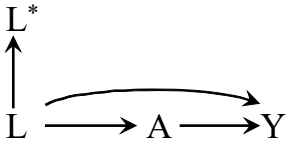


Figure 9.8

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.

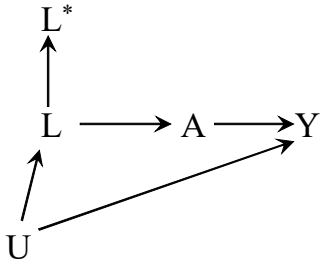


Figure 9.9

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 7.6. 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.

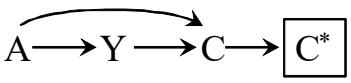


Figure 9.10

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 is discussed in the next section).

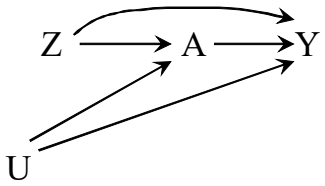


Figure 9.11

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).

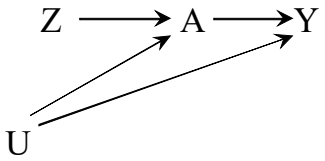


Figure 9.12

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 Technical 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 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 occurs, 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 who 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).

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.

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 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.

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.

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 9.11. 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

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).

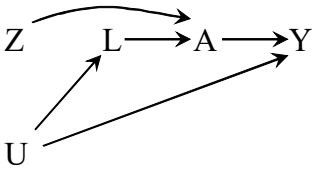


Figure 9.13

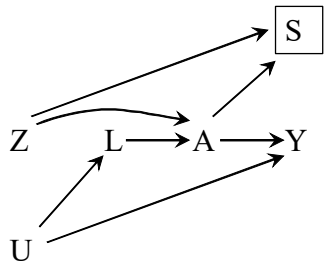


Figure 9.14

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 drug 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 generally 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. Further, suppose our goal is 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 of a proportion 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. In the absence of systematic biases, 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 $\widehat{\theta}$ and 1.96 is the upper 97.5% quantile of a standard normal distribution with mean 0 and variance 1. 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 $\hat{p}$ is only guaranteed to be valid in large samples. For simplicity, here we assume that our sample size is 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 otherwise. We will say that a confidence interval is *valid* if, for any value of the true parameter, the interval 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 width is narrowest.

The validity of confidence intervals is defined in terms of the frequency of coverage in repeated samples from 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 important 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 that were conducted, and conclude that the parameters of interest were trapped in—or covered by—the confidence interval in at least 95% of the studies. Unfortunately, we will have no way of identifying the (up to) 5% of the 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 particular interval (0.27, 0.81). In this sense, 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". However, for a Bayesian, probability is defined not as a frequency over hypothetical repetitions but as degree-of-belief. In this book we adopt the frequency definition of probability. See Fine Point 11.2 for more on Bayesian intervals.

Confidence intervals are often classified as either *small-sample* or *large-sample* 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 (equivalently, asymptotic) valid confidence interval is one that is valid only in large samples. A large-sample calibrated 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 calibrated 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 consistent 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

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 unknown 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. We demand honest intervals because, in the absence of uniformity, at any finite sample size there may be data generating distributions under which the coverage of the true parameter is much less than 95%. Unfortunately, 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 valid confidence intervals, we will mean large-sample honest confidence intervals. By definition, any small-sample valid confidence interval is uniform or honest for all n for which the interval is defined.

cannot (see Technical Point 10.1 for details). For now, we will equate the term bias with the inability to center valid Wald confidence intervals. Also, bear in mind that confidence intervals only quantify uncertainty due to random error, and thus the confidence we put on confidence intervals may be excessive in the presence of systematic biases (see Fine Point 10.2 for details).

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 difference $\Pr[Y^{a=1} = 1] - \Pr[Y^{a=0} = 1]$ equals the associational risk difference $\Pr[Y = 1|A = 1] - \Pr[Y = 1|A = 0]$ 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 an unbiased 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 an unbiased 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 difference and causal risk ratio 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 $A = 1$

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 $\theta = \theta(P)$ in model $\mathcal{M}$ if $\widehat{\theta}_n$ converges to θ in probability for every $P \in \mathcal{M}$ i.e.

$$\Pr_P\left[|\widehat{\theta}_n - \theta(P)| > \varepsilon\right] \to 0 \text{ as } n \to \infty \text{ for every } \varepsilon > 0, P \in \mathcal{M}.$$

The estimator $\widehat{\theta}_n$ is exactly unbiased in model $\mathcal{M}$ if, for every $P \in \mathcal{M}, \mathrm{E}_P\left[\widehat{\theta}_n\right] = \theta(P)$. The exact bias under P is the difference $\mathrm{E}_P\left[\widehat{\theta}_n\right] - \theta(P)$. 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 depending on $P \in \mathcal{M}$. When P is the distribution generating the data in our study, we often suppress the P in the notation and , e.g., write $\mathrm{E}\left[\widehat{\theta}_n\right] = \theta$. For many parameters θ, such as the risk ratio $\Pr[Y=1|A=1]/\Pr[Y=1|A=0]$, exactly unbiased estimators do not exist.

A systematically biased estimator is neither consistent nor exactly unbiased. Robins and Morgenstern (1987) argue that most applied researchers (e.g., epidemiologists) will declare an estimator unbiased only if it can center a valid Wald confidence interval. They show that under this definition, an estimator is only unbiased if it is uniformly asymptotic normal and unbiased (UANU), as only UANU estimators can center valid standard Wald intervals for $\theta(P)$ under the model $\mathcal{M}$. An estimator $\widehat{\theta}_n$ is UANU in model $\mathcal{M}$ if there exists sequences $\sigma_n(P)$ such that the z-statistic $\left(\widehat{\theta}_n - \theta(P)\right)/\sigma_n(P)$ converges uniformly to a standard normal random variable in the following sense: for $t \in R$,

$$\sup_{P \in \mathcal{M}} \left|\Pr_P\left[n^{1/2}\left(\widehat{\theta}_n - \theta(P)\right)/\sigma_n(P) < t\right] - \Phi(t)\right| \to 0 \text{ as } n \to \infty$$

where $\Phi(t)$ is the standard normal cumulative distribution function (Robins and Ritov,1997).

All inconsistent estimators and some consistent estimators (see Chapter 18 for examples), are biased under this definition. In the text, whenever we say an estimator is unbiased (without further qualification) we mean that it is UANU.

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 ($A = 0$). Suppose further that 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 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

See Robins (1988) for a discussion of randomization-based inference.

Fine Point 10.2

Uncertainty from systematic biases. 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. The larger the study population, the smaller the random error is both absolutely and as a proportion of total uncertainty, and hence the more the usual Wald confidence interval will understate the true uncertainty.

The stated 95% confidence in a 95% confidence interval becomes overconfidence as population size increases because the interval excludes uncertainty due to systematic biases, which are not diminished by increasing the sample size. As a consequence, some authors advocate referring to such intervals by a less confident name, calling them *compatibility intervals* instead. The renaming recognizes that such intervals can only show us which effect sizes are highly compatible with the data under our adjustment assumptions and methods (Amrhein et al. 2019; Greenland 2019). The compatibility concept is weaker than the confidence concept, for it does not demand complete confidence that our adjustment removes all systematic biases.

Regardless of the name of the intervals, the uncertainty due to systematic bias is 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).

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 random sampling is equivalent to random sampling followed by randomization.

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. Below we discuss both.

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 interval $\hat{p} \pm 1.96\sqrt{\frac{\hat{p}(1-\hat{p})}{n}} = 7/13 \pm 1.96\sqrt{\frac{(7/13)(6/13)}{13}}$ 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

Robins (1988) discussed these two scenarios in more detail.

happen. In fact there are two scenarios under which $\hat{p}$ has a binomial sampling distribution.

The term i.i.d. used in Technical Point 10.1 means that our data were a random sample of size n from a super-population.

- *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 calibrated 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 calibrated 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 calibrated but 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.

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 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 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. Here 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 trial 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 difference is $\Pr[Y=1|A=1]-\Pr[Y=1|A=0]=\frac{24}{120}-\frac{42}{120}=-0.15$. 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 difference would equal the causal risk difference $\Pr\left[Y^{a=1}=1\right]-\Pr\left[Y^{a=0}=1\right]$. Suppose the study investigators computed a 95% confidence interval $(-0.26,-0.04)$ around the point estimate -0.15 and published an article in which they concluded that treatment was beneficial because it reduced the risk of death by 15 percentage points.

The estimated variance of the unadjusted estimator is $\frac{\frac{24}{120}\frac{96}{120}}{120}+\frac{\frac{42}{120}\frac{78}{120}}{120}=\frac{31}{9600}$. The Wald 95% confidence interval is then $-0.15 \pm \left(\frac{31}{9600}\right)^{1/2} \times 1.96 = (-0.26,-0.04)$.

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 for the sample consisting of the 240 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 0.22 of the confidence interval.

A few months later the investigators learn 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 adjustment for smoking is necessary. When the investigators adjust via stratification, the associational risk difference in smokers, $\Pr[Y=1|A=1,L=1]-\Pr[Y=1|A=0,L=1]$, is equal to 0. The associational risk difference in nonsmokers, $\Pr[Y=1|A=1,L=0]-\Pr[Y=1|A=0,L=0]$, is also equal to 0. Treatment has no effect in both smokers and nonsmokers, even though the marginal risk difference -0.15 suggested a net beneficial effect in the study

Table 10.1

	$Y=1$	$Y=0$
$A=1$	24	96
$A=0$	42	78

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

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 $Y^a \perp\!\!\!\perp A|L$, the stratum-specific risk difference $sRD = \Pr(Y = 1|L = l, A = 1) - \Pr(Y = 1|L = l, A = 0)$ known to be constant across strata of L, and in which the parameter of interest is the stratum-specific causal risk difference. Then the likelihood of the data is

$$\prod_{i=1}^{n} f(Y_i|L_i, A_i; sRD, p_0) \times f(A_i|L_i; \alpha) \times f(L_i; \rho)$$

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 $f(Y_i|L_i, A_i; sRD, p_0)$. The conditionality principle states that one should always perform inference on the parameter of interest conditional on any ancillary statistics. Thus one should condition on the ancillary statistic $\{A_i, L_i; i = 1, .., n\}$. Analogously, if the risk ratio (rather than the risk difference) were known to be constant across strata of L, $\{A_i, L_i; i = 1, .., n\}$ remains ancillary for the risk ratio.

The estimated variance of the adjusted estimator is described in Technical Point 10.5. The Wald 95% confidence interval is then $(-0.076, 0.076)$.

population.

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: "Okay, 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 difference 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

Technical Point 10.3

Approximate ancillarity. Suppose that the stratum-specific risk difference (sRD_l) is known to vary over strata of L. Under our usual identifiability assumptions, the causal risk difference in the population is identified by the standardized risk difference

$$RD_{std} = \sum_l \left[\Pr\left(Y=1|L=l,A=1;\upsilon\right) - \Pr\left(Y=1|L=l,A=0;\upsilon\right)\right] f\left(l;\rho\right)$$

which depends on the parameters $\upsilon = \{sRD_l, p_{0,l}; l=0,1\}$ and ρ (see Technical Point 10.2). In unconditionally randomized experiments, RD_{std} equals the associational RD, $\Pr\left(Y=1|A=1\right) - \Pr\left(Y=1|A=0\right)$, because $A \perp\!\!\!\perp L$ in the super-population. Due to the dependence of RD_{std} on ρ, $\{A_i, L_i; i=1,..,n\}$ is no longer exactly ancillary and in fact no exact ancillary exists.

Consider the statistic $\widetilde{S} = \widehat{OR}_{AL} - OR_{AL}$ where $OR_{AL} = OR_{AL}\left(\alpha\right) = \frac{\Pr(A=1|L=1;\alpha)\Pr(A=0|L=0;\alpha)}{\Pr(A=1|L=0;\alpha)\Pr(A=0|L=1;\alpha)}$is the A-L odds ratio in the super-population, and $\widehat{OR}_{AL}$ is OR_{AL} but with the the population proportions $\Pr\left(A=a|L=l;\alpha\right)$ replaced by the empirical sample proportions $\widehat{\Pr}\left(A=a|L=l\right)$. $\widetilde{S}$ is asymptotically normal with mean 0. Let $\widehat{S} = \widetilde{S}/\widehat{se}(\widetilde{S})$, where $\widehat{se}(\widetilde{S})$ is an estimate of the standard error of $\widetilde{S}$. The distribution of $\widehat{S}$ converges to a standard normal distribution in large samples, so that $\widehat{S}$ quantifies the A-L association in the data on a standardized scale. For example, if $\widehat{S}=2$, then $\widehat{S}$ is two standard deviations above its (asymptotic) expected value of 0.

When the true value of OR_{AL} is known, $\widehat{S}$ is referred to as an approximate (or large sample) ancillary statistic. To see why, consider a randomized experiment with $OR_{AL}=1$. Then $\widehat{S}$, like an exact ancillary statistic, i) can be computed from the data (i.e., $\widehat{S} = \left(\widehat{OR}_{AL} - 1\right)/\widehat{se}(\widetilde{S})$), ii) $\widehat{S} = \widehat{S}\left(\alpha\right)$ depends on a parameter α that does not occur in the estimand of interest, iii) the likelihood factors into a term $f\left(A|L;\alpha\right)$ that depends only on α and a term $f\left(Y|L,A;\upsilon\right)f\left(L;\rho\right)$ that does not depend on α, and iv) conditional on $\widehat{S}$, the adjusted estimate of RD_{std} is unbiased, while the unadjusted estimate of RD_{std} is biased (Technical Point 10.4 defines and compares adjusted and unadjusted estimators). Any other statistic that quantifies the A-L association in the data, e.g., $\frac{\widehat{\Pr}(A=1|L=1)}{\widehat{\Pr}(A=1|L=0)} - 1$, can be used in place of $\widetilde{S}$.

Now consider a continuity principle wherein inferences about an estimand should not change discontinuously in response to an arbitrarily small known change in the data generating distribution (Buehler 1982). If one accepts both the conditionality and continuity principles, then one should condition on an approximate ancillary statistic. For example, when $OR_{AL}=1$ is known, the continuity principle would be violated if, following the conditionality principle, we treated the unadjusted estimate of RD_{std} as biased when sRD_l was known to be a constant, but treated it as unbiased when the sRD_l were almost constant. We will say that a researcher who always conditions on both exact and approximate ancillaries follows the extended conditionality principle.

would find that, within each level of L, 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.) 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 better analysis and the article needs to be retracted. The second investigator is correct.

The unconditional efficiency of the adjusted estimator results from the adjusted estimator being the maximum likelihood estimator (MLE) of the risk difference when data on L are available.

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*

Technical Point 10.4

Comparison between adjusted and unadjusted estimators. The adjusted estimator of RD_{std} in Technical Point 10.3 is the maximum likelihood estimator $\widehat{RD}_{MLE}$, which replaces the population proportions in the RD_{std} by their sample proportions. The unadjusted estimator of RD_{std} is $\widehat{RD}_{UN} = \widehat{\Pr}(Y=1|A=1) - \widehat{\Pr}(Y=1|A=0)$. Unconditionally, both $\widehat{RD}_{MLE}$ and $\widehat{RD}_{UN}$ are asymptotically normal and unbiased for RD_{std} with asymptotic variances $aVar\left(\widehat{RD}_{MLE}\right)$ and $aVar\left(\widehat{RD}_{UN}\right)$.

In the text we stated that $\widehat{RD}_{UN}$ is both unconditionally inefficient and conditionally biased. We now explain that both properties are logically equivalent. Robins and Morgenstern (1987) prove that $\widehat{RD}_{MLE}$ has the same asymptotic distribution conditional on the approximate ancillary $\widehat{S}$ as it does unconditionally, which implies $aVar\left(\widehat{RD}_{MLE}\right) = aVar\left(\widehat{RD}_{MLE}|\widehat{S}\right)$. They also show that $aVar\left(\widehat{RD}_{MLE}\right)$ equals $aVar\left(\widehat{RD}_{UN}\right) - \left[aCov\left(\widehat{S}, \widehat{RD}_{UN}\right)\right]^2$. Hence $\widehat{RD}_{UN}$ is unconditionally inefficient if and only if $aCov\left(\widehat{S}, \widehat{RD}_{UN}\right) \neq 0$, i.e., $\widehat{S}$ and $\widehat{RD}_{UN}$ are correlated unconditionally. Further, the conditional asymptotic bias $a\,\mathrm{E}\left[\widehat{RD}_{UN}|\widehat{S}\right] - RD_{std}$ is shown to equal $aCov\left(\widehat{S}, \widehat{RD}_{UN}\right)\widehat{S}$. Hence, $\widehat{RD}_{UN}$ is conditionally biased if and only if it is unconditionally inefficient.

It can be shown that $aCov\left(\widehat{S}, \widehat{RD}_{UN}\right) = 0$ if and only if $L \perp\!\!\!\perp Y|A$. Therefore, when data on a measured risk factor for Y are available, $\widehat{RD}_{MLE}$ is preferred over $\widehat{RD}_{UN}$.

principle. In statistics, the observed L-A association is said to be an ancillary statistic for the causal risk difference. The conditionality principle states that inference on a parameter should be performed conditional on ancillary statistics (see Technical Points 10.2 and 10.3 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. For such researchers, our previous definition of bias was not sufficiently restrictive. They would say that an estimator is unbiased if and only if it can center a valid Wald interval conditional on ancillary statistics. Technical Point 10.5 argues that most researchers implicitly follow the conditionality principle.

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 acts as 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. However, when the number of measured confounders is large, strictly following the conditionality principle is no longer a wise strategy.

10.5 The curse of dimensionality

The derivations in previous sections above are based on an asymptotic theory that assumed the number of strata of L was small compared with the sample size. In this section, we study the cases in which the number of strata of a

Technical Point 10.5

Most researchers intuitively follow the extended conditionality principle. Consider again the randomized trial data in Table 10.2. Assuming without loss of generality that the sRD is constant over the strata of a dichotomous L, the estimated variance of the MLE of sRD is $\widehat{V}_0\widehat{V}_1/\left(\widehat{V}_0+\widehat{V}_1\right)$ where $\widehat{V}_l$ is the estimated variance of $\widehat{RD}_l$.

Two possible choices for $\widehat{V}_1$ are $\widehat{V}_1^{obs}=\frac{\frac{4}{80}\frac{76}{80}}{80}+\frac{\frac{2}{40}\frac{38}{40}}{40}=1.78\times10^{-3}=$ and $\widehat{V}_1^{\exp}=\frac{\frac{4}{80}\frac{76}{80}}{60}+\frac{\frac{2}{40}\frac{38}{40}}{60}=1.58\times10^{-3}$ that differ only in that $\widehat{V}_1^{obs}$ divides by the observed number of individuals in stratum $L=1$ with $A=1$ and $A=0$ (80 and 40, respectively) while $\widehat{V}_1^{\exp}$divides by the expected number of subjects (60) given that $A\perp\!\!\!\perp L$. Mathematically, $\widehat{V}_1^{obs}$is the variance estimator based on the observed information and $\widehat{V}_1^{\exp}$ is the estimator based on the expected information.

In our experience, nearly all researchers would choose $\widehat{V}_1^{obs}$ over $\widehat{V}_1^{\exp}$as the appropriate variance estimator. Results of Efron and Hinkley (1982) and Robins and Morgenstern (1987) imply that such researchers are implicitly conditioning on an approximate ancillary $\widehat{S}$ and thus, whether aware of this fact or not, are following the extended conditionality principle. Specifically, these authors proved that that the variance of $\widehat{RD}_l$, and thus of the MLE, conditioned on an approximate ancillary $\widehat{S}$ differs from the unconditional variance by order $n^{-3/2}$. (As noted in Technical Point 10.4, the conditional and unconditional asymptotic variance of an MLE are equal, as equality of asymptotic variances implies equality only up to order n^{-1}.) Further, they showed that the variance estimator based on the observed information differs from the conditional variance by less than order $n^{-3/2}$, while an estimator based on the expected information differs from the unconditional variance by less than $n^{-3/2}$. Thus, a preference for $\widehat{V}_1^{obs}$ over $\widehat{V}_1^{\exp}$ implies a preference for conditional over unconditional inference.

vector L can be very large, even much larger than the sample size.

Suppose 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 pre-treatment variables, we say that the data is of *high dimensionality*. For simplicity, suppose that there is no additive effect modification by L, i.e., the super-population risk difference $\Pr[Y=1|A=1,L=l]-\Pr[Y=1|A=0,L=l]$ is constant across the 2^{100} strata. In particular, suppose that the constant stratum-specific risk difference is 0.

The investigators debate again whether to retract the article and report their estimate of the stratified risk difference. They have by now agreed that they should follow the conditionality principle because the unadjusted risk difference -0.15 is conditionally biased. However, they notice that, when there are 2^{100} strata, a 95% confidence interval for the risk difference based on the adjusted estimator is much wider than that based on the unadjusted estimator. This is exactly the opposite of what was found when L had only two strata. In fact, the 95% confidence interval based on the adjusted estimator 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 common risk difference based on the adjusted estimator is $(-1,1)$, and therefore completely uninformative, because in the single stratum with both a treated and an untreated individual, the empirical risk difference could be -1, 0, or 1 depending on the value of Y for each individual. In contrast, the 95% confidence interval for the common risk difference

Technical Point 10.6

Can the curse of dimensionality be reversed? In high-dimensional settings with many strata of L, informative conditional inference for the common risk difference given the exact ancillary statistic $\{A_i, L_i; i = 1, ..n\}$ is not possible regardless of the estimator used. This is not true for unconditional inference in marginally randomized experiments. For example, the unconditional statistical behavior of the unadjusted estimator $\widehat{RD}_{UN}$ is unaffected by the dimension of L. In particular, it remains unbiased with the width of the associated Wald 95% confidence interval proportional to $1/n^{1/2}$. Because $\widehat{RD}_{UN}$ relies on prior information not used by the MLE, it is an unbiased estimator of the common risk difference only it is known that $A \perp\!\!\!\perp L$ in the super-population.

However, even unconditionally, the confidence intervals associated with the MLE, i.e., the adjusted estimator, remain uninformative. This raises the question of whether data on L can be used to construct an estimator that is also unconditionally unbiased but that is more efficient that the unadjusted estimator. In Chapter 18 we show that this is indeed possible.

based on the unadjusted estimator remains $(-0.26, -0.04)$ as above because its width is unaffected by the fact that more covariates were measured. These results reflect the fact that the adjusted estimator is only guaranteed to be more efficient than the unadjusted estimator when the ratio of number of individuals to the number of unknown 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).

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 for high-dimensional models. Though we have discussed this issue in the context of a randomized experiment, our discussion applies equally to observational studies. See Technical Point 10.6

Robins and Wasserman (1999) provide a technical description of the curse of dimensionality.

Finding a solution to the curse of dimensionality is a difficult problem and an active area of research. In Chapter 18 we review this research and offer some practical guidance. Chapters 11 through 17 provide necessary background information on the use of models for causal inference.

Part II

Causal inference with models

Chapter 11
WHY MODEL?

Do not worry. No more chapter introductions around the effect of your looking up on other people's looking up. We squeezed that example well beyond what seemed possible. In Part II of this book, most examples involve real data. The data sets can be downloaded from the book's web site.

Part I was mostly conceptual. Calculations were kept to a minimum, and could be carried out by hand. In contrast, the material described in Part II requires the use of computers to fit regression models, such as linear and logistic models. Because this book cannot provide a detailed introduction to regression techniques, we assume that readers have a basic understanding and working knowledge of these commonly used models. Our web site provides links to computer code in R, SAS, Stata, and Python to replicate the analyses described in the text. The CODE margin notes specify the portion of the code that is relevant to the analysis described in the text.

This chapter describes the differences between the nonparametric estimators used in Part I and the parametric (model-based) estimators used in Part II. It also reviews the concept of smoothing and, briefly, the bias-variance trade-off involved in any modeling decision. The chapter motivates the need for models in data analysis, regardless of whether the analytic goal is causal inference or, say, prediction. We will take a break from causal considerations until the next chapter. Please bear in mind that the statistical literature on modeling is vast; this chapter can only highlight some of the key issues.

11.1 Data cannot speak for themselves

Consider a study population of 16 individuals infected with the human immunodeficiency virus (HIV). Unlike in Part I of this book, we will not view these individuals as representatives of 1 billion individuals identical to them. Rather, these are just 16 individuals randomly sampled from a large, possibly hypothetical super-population: the target population.

At the start of the study each individual receives a certain level of a treatment A (antiretroviral therapy), which is maintained during the study. At the end of the study, a continuous outcome Y (CD4 cell count, in cells/mm^3) is measured in all individuals. We wish to consistently estimate the mean of Y among individuals with treatment level $A = a$ in the population from which the 16 individuals were randomly sampled. That is, the *estimand* is the unknown population parameter $\mathrm{E}[Y|A = a]$.

As defined in Chapter 10, an *estimator* $\widehat{\mathrm{E}}[Y|A = a]$ of $\mathrm{E}[Y|A = a]$ is some function of the data that is used to estimate the unknown population parameter. Informally, a consistent estimator $\widehat{\mathrm{E}}[Y|A = a]$ meets the requirement that "the larger the sample size, the closer the estimate to the population value $\mathrm{E}[Y|A = a]$." Two examples of possible estimators $\widehat{\mathrm{E}}[Y|A = a]$ are (i) the sample average of Y among those receiving $A = a$, and (ii) the value of the first observation in the dataset that happens to have the value $A = a$. The sample average of Y among those receiving $A = a$ is a consistent estimator of the population mean; the value of the first observation with $A = a$ is not. In practice we require all estimators to be consistent, and therefore we use the sample average to estimate the population mean.

See Chapter 10 for a rigorous definition of a consistent estimator.

Suppose treatment A is a dichotomous variable with two possible values: no

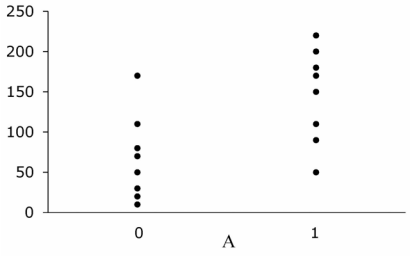


Figure 11.1

CODE: Program 11.1

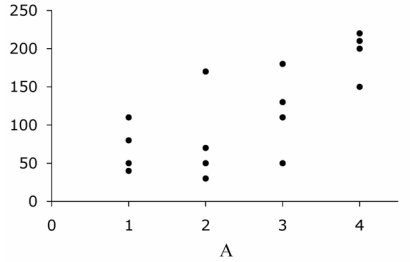


Figure 11.2

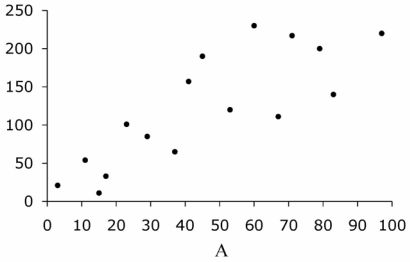


Figure 11.3

treatment ($A = 0$) and treatment ($A = 1$). Half of the individuals were treated ($A = 1$). Figure 11.1 is a scatter plot that displays each of the 16 individuals as a dot. The height of the dot indicates the value of the individual's outcome Y. The 8 treated individuals are placed along the column $A = 1$, and the 8 untreated along the column $A = 0$. As defined in Chapter 10, an *estimate* of the mean of Y among individuals with level $A = a$ in the population is the numerical result of applying the estimator—in our case, the sample average—to a particular data set.

Our estimate of the population mean in the treated is the sample average 146.25 for those with $A = 1$, and our estimate of the population mean in the untreated is the sample average 67.50 in those with $A = 0$. Under exchangeability of the treated and the untreated, the difference $146.25 - 67.50$ would be interpreted as an estimate of the average causal effect of treatment A on the outcome Y in the target population. However, this chapter is not about making causal inferences. Our current goal is simply to motivate the need for models when trying to estimate population quantities like the mean $\mathrm{E}[Y|A = a]$, irrespective of whether the estimates do or do not have a causal interpretation.

Now suppose treatment A is a polytomous variable that can take 4 possible values: no treatment ($A = 1$), low-dose treatment ($A = 2$), medium-dose treatment ($A = 3$), and high-dose treatment ($A = 4$). A quarter of the individuals received each treatment level. Figure 11.2 displays the outcome value for the 16 individuals in the study population. To estimate the population means in the 4 groups defined by treatment level, we compute the corresponding sample averages. The estimates are 70.0, 80.0, 117.5, and 195.0 for $A = 1$, $A = 2$, $A = 3$, and $A = 4$, respectively.

Figures 11.1 and 11.2 depict examples of discrete (categorical) treatment variables with 2 and 4 categories, respectively. Because the number of study individuals is fixed at 16, the number of individuals per category decreases as the number of categories increases. The sample average in each category is still an exactly unbiased estimator of the corresponding population mean, but the probability that the sample average is close to the corresponding population mean decreases as the number of individuals in each category decreases. The length of the 95% confidence intervals (see Chapter 10) for the category-specific means will be greater for the data in Figure 11.2 than for the data in Figure 11.1.

Finally, suppose that treatment A is a variable representing the dose of treatment in mg/day, and that it takes integer values from 0 to 100 mg. Figure 11.3 displays the outcome value for each of the 16 individuals. Because the number of possible values of treatment is much greater than the number of individuals in the study, there are many values of A that no individual received. For example, there are no individuals with treatment dose $A = 90$ in the study population.

This creates a problem: how can we estimate the mean of the outcome Y among individuals with treatment level $A = 90$ in the target population? The estimator we used for the data in Figures 11.1 and 11.2—the treatment-specific sample average—is undefined for treatment levels for which there are zero individuals in Figure 11.3. If treatment A were a truly continuous variable, then the sample average would be undefined for nearly all treatment levels. (A continuous variable A can be viewed as a categorical variable with an uncountably infinite number of categories.)

The above description shows that we cannot always let the data "speak for themselves" to obtain a meaningful estimate. Rather, we often need to

supplement the data with a model, as we describe in the next section.

11.2 Parametric estimators of the conditional mean

We want to estimate the mean of Y among individuals with treatment level $A = 90$, i.e., $\mathrm{E}[Y|A = 90]$, from the data in Figure 11.3. Suppose we expect the mean of Y among individuals with treatment level $A = 90$ to lie between the mean among individuals with $A = 80$ and the mean among individuals with $A = 100$. In fact, suppose we knew that the treatment-specific population mean of Y is a linear function of the value of treatment A throughout the range of A. More precisely, we know that the mean of Y, $\mathrm{E}[Y|A]$, increases (or decreases) from some value θ_0 for $A = 0$ by θ_1 units per unit of A. Or, more compactly,

$$\mathrm{E}[Y|A] = \theta_0 + \theta_1 A$$

More generally, the restriction on the shape of the relation is known as the *functional form* and, by some authors, as the *dose-response curve*. We do not use the latter term because it suggests that the dose of treatment causally effects the response, which could be false in the presence of confounding.

This equation is a restriction on the shape of conditional mean function $\mathrm{E}[Y|A]$. This particular restriction is referred to as a *linear mean model*, and the quantities θ_0 and θ_1 are referred to as the *parameters of the model*. Models that describe the conditional mean function in terms of a finite number of parameters are referred to as parametric conditional mean models. In our example, the parameters θ_0 and θ_1 define a straight line that crosses (intercepts) the vertical axis at θ_0 and that has a slope θ_1. That is, the model specifies that all conditional mean functions are straight lines, though their intercepts and slopes may vary.

We are now ready to combine the data in Figure 11.3 with our parametric mean model to estimate $\mathrm{E}[Y|A = a]$ for all values a from 0 to 100. The first step is to obtain estimates $\hat{\theta}_0$ and $\hat{\theta}_1$ of the parameters θ_0 and θ_1. The second step is to use these estimates to estimate the mean of Y for any value $A = a$. For example, to estimate the mean of Y among individuals with treatment level $A = 90$, we use the expression $\widehat{\mathrm{E}}[Y|A = 90] = \hat{\theta}_0 + 90\hat{\theta}_1$. The estimate $\widehat{\mathrm{E}}[Y|A]$ for each individual is referred to as the *predicted value*.

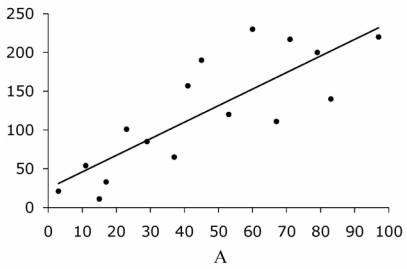


Figure 11.4

CODE: Program 11.2

Under the assumption that the variance of the residuals does not depend on A (homoscedasticity), the Wald 95% confidence intervals are $(-21.2, 70.3)$ for θ_0, $(1.28, 2.99)$ for θ_1, and $(172.1, 261.6)$ for $\mathrm{E}[Y|A = 90]$.

An exactly unbiased estimator of θ_0 and θ_1 can be obtained by the method of *ordinary least squares*. A nontechnical motivation of the method follows. Consider all possible candidate straight lines for Figure 11.3, each of them with a different combination of values of intercept θ_0 and slope θ_1. For each candidate line, one can calculate the vertical distance from each dot to the line (the *residual*), square each of those 16 residuals, and then sum the 16 squared residuals. The line for which the sum is the smallest is the "least squares" line, and the parameter values $\hat{\theta}_0$ and $\hat{\theta}_1$ of this "least squares" line are the "least squares" estimates. The values $\hat{\theta}_0$ and $\hat{\theta}_1$ can be easily computed using linear algebra, as described in any statistics textbook.

In our example, the parameter estimates are $\hat{\theta}_0 = 24.55$ and $\hat{\theta}_1 = 2.14$, which define the straight line shown in Figure 11.4. The predicted mean of Y among individuals with treatment level $A = 90$ is therefore $\widehat{\mathrm{E}}[Y|A = 90] = 24.55 + 90 \times 2.14 = 216.9$. Because ordinary least squares estimation uses all data points to find the best line, the mean of Y in the group $A = a$, i.e., $\mathrm{E}[Y|A = a]$, is estimated by borrowing information from individuals who have values of treatment A not equal to a.

So what is a model? A model is defined by an a priori restriction on the joint distribution of the data. Our linear conditional mean model says that the

conditional mean function $\mathrm{E}[Y|A]$ is a straight line, which restricts its shape. For example, the model restricts the mean of Y for $A = 90$ to be between the mean of Y for $A = 80$ and the mean of Y for $A = 100$. This restriction is encoded by the parameters θ_0 and θ_1. A parametric conditional mean model is, through its a priori restrictions, adding information to compensate for the lack of sufficient information in the data.

Parametric estimators—those based on a parametric conditional mean model—allow us to estimate quantities that cannot be estimated otherwise, e.g., the mean of Y among individuals in the target population with treatment level $A = 90$ when no such individuals exist in the study population. But this is not a free lunch. When using a parametric model, the inferences are correct only if the restrictions encoded in the model are correct, i.e. if the model is correctly specified. Thus model-based causal inference—to which a large fraction of the remainder of this book is devoted—relies on the condition of (approximately) *no model misspecification*. Because parametric models are rarely, if ever, perfectly specified, a certain degree of model misspecification is almost always expected. This can be at least partially rectified by using nonparametric estimators, which we describe in the next section.

11.3 Nonparametric estimators of the conditional mean

Let us return to the data in Figure 11.1. Treatment A is dichotomous and we want to consistently estimate the mean of Y in the treated $\mathrm{E}[Y|A = 1]$ and in the untreated $\mathrm{E}[Y|A = 0]$. Suppose we have become so enamored with models that we decide to use one to estimate these two quantities. Again we proposed a linear model

$$\mathrm{E}[Y|A] = \theta_0 + \theta_1 A$$

where $\mathrm{E}[Y|A = 0] = \theta_0 + 0 \times \theta_1 = \theta_0$ and $\mathrm{E}[Y|A = 1] = \theta_0 + 1 \times \theta_1 = \theta_0 + \theta_1$. We use the least squares method to obtain estimates of the parameters θ_0 and θ_1. These estimates are $\hat{\theta}_0 = 67.5$ and $\hat{\theta}_1 = 78.75$. We therefore estimate $\widehat{\mathrm{E}}[Y|A = 0] = 67.5$ and $\widehat{\mathrm{E}}[Y|A = 1] = 146.25$. Note that our model-based estimates of the mean of Y are identical to the sample averages we calculated in Section 11.1. This is not a coincidence but an expected finding.

CODE: Program 11.2

In this book we define "model" as an a priori mathematical restriction on the possible states of nature (Robins, Greenland 1986). Part I was entitled "Causal inference without models" because it only described saturated models.

Let us take a second look at the model $\mathrm{E}[Y|A] = \theta_0 + \theta_1 A$ with a dichotomous treatment A. If we rewrite the model as $\mathrm{E}[Y|A = 1] = \mathrm{E}[Y|A = 0] + \theta_1$, we see that the model simply states that the mean in the treated $\mathrm{E}[Y|A = 1]$ is equal to the mean in the untreated $\mathrm{E}[Y|A = 0]$ plus a quantity θ_1, where θ_1 may be negative, positive or zero. But this statement is of course always true! The model imposes no restrictions whatsoever on the values of $\mathrm{E}[Y|A = 1]$ and $\mathrm{E}[Y|A = 0]$. Therefore $\mathrm{E}[Y|A = a] = \theta_0 + \theta_1 A$ with a dichotomous treatment A is not a model because it lets the data speak for themselves, just like the sample average does. "Models" which do not impose restrictions on the distribution of the data are *saturated models*. Because they formally look like models even if they do not fit our definition of model, saturated models are ordinarily referred to as models too.

Generally, the model is saturated whenever the number of parameters in a conditional mean model is equal to the number of unknown conditional means in the population. For example, the linear model $\mathrm{E}[Y|A] = \theta_0 + \theta_1 A$ has two parameters and, when A is dichotomous, there exist two unknown conditional means: the means $\mathrm{E}[Y|A = 1]$ and $\mathrm{E}[Y|A = 0]$. Since the values of the two

Fine Point 11.1

Fisher consistency. Our definition of a nonparametric estimator in the main text coincides with what is known in statistics as a *Fisher consistent estimator* (Fisher 1922). That is, an estimator of a population quantity that, when calculated using the entire population rather than a sample, yields the true value of the population parameter. By definition, a Fisher consistent estimator lacks any model restrictions but, as discussed in the text, a Fisher consistent estimate may not exist for many population quantities. Technically, Fisher consistent estimators are the nonparametric maximum likelihood estimators of population quantities under a saturated model.

In the statistical literature, the term nonparametric estimator is sometimes used to refer to estimators that are not Fisher consistent but that impose very weak restrictions, such as kernel regression models. See Technical Point 11.1 for details.

A saturated model has the same number of unknowns on both sides of the equal sign.

parameters are not restricted by the model, neither are the values of the means. As a contrast, consider the data in Figure 11.3 where A can take values from 0 to 100. The linear model $\mathrm{E}[Y|A] = \theta_0 + \theta_1 A$ has two parameters but estimates 101 quantities, i.e., $\mathrm{E}[Y|A = 0], \mathrm{E}[Y|A = 1], ..., \mathrm{E}[Y|A = 100]$. The only hope for unbiasedly estimating 101 quantities with these two parameters is to be fortunate to have all 101 means $\mathrm{E}[Y|A = a]$ lie along a straight line. When a model has only a few parameters but it is used to estimate many population quantities, we say that the model is *parsimonious*.

Here we define nonparametric estimators of the conditional mean function as those that produce estimates from the data without any a priori restrictions on the conditional mean function (see Fine Point 11.1 for a more rigorous definition). An example of a nonparametric estimator of the population mean $\mathrm{E}[Y|A = a]$ for a dichotomous treatment is its empirical version, the sample average or, equivalently, the saturated model described in this section. When A is discrete with 100 levels and no individual in the sample has $A = 90$, no nonparametric estimator of $\mathrm{E}[Y|A = 90]$ exists. All methods for causal inference that we described in Part I of this book—standardization, IP weighting, stratification, matching—were based on nonparametric estimators of population quantities under a saturated model because they did not impose any a priori restrictions on the value of the effect estimates. In contrast, most methods for causal inference described in Part II of this book rely on estimators that are parametric estimators of some part of the distribution of the data. Parametric estimation and other approaches to borrow information are our only hope when, as is often the case, data are unable to speak for themselves.

For causal inference, identifiability assumptions are the assumptions that we would have to make even if we had an infinite amount of data. Modeling assumptions are the assumptions that we have to make precisely because we do not have an infinite amount of data.

11.4 Smoothing

Consider again the data in Figure 11.3 and the linear model $\mathrm{E}[Y|A] = \theta_0 + \theta_1 A$. The parameter θ_1 is the difference in mean outcome per unit of treatment dose A. Because θ_1 is a single number, the model specifies that the difference in mean outcome Y per unit of treatment A must be constant throughout the entire range of A, that is, the model requires the conditional mean outcome to follow a straight line as a function of treatment dose A. Figure 11.4 shows the best-fitting straight line.

But one can imagine situations in which the difference in mean outcome is larger for a one-unit change at low doses of treatment, and smaller for a one-

unit change at high doses. This would be the case if, once the treatment dose reaches certain level, higher doses have an increasingly small effect. Under this scenario, the model $\mathrm{E}[Y|A] = \theta_0 + \theta_1 A$ is incorrect. However, linear models can be made more flexible.

Caution: Often the term "linear" is used with two different meanings. A model is *linear* when it is expressed as a linear combination of parameters and functions of the variables, even if the latter are nonlinear functions (e.g., higher powers or logarithms) of the covariates.

For example, suppose we fit the model $\mathrm{E}[Y|A] = \theta_0 + \theta_1 A + \theta_2 A^2$, where $A^2 = A \times A$ is A-squared, to the data in Figure 11.3. This is still referred to as a linear model because the conditional mean is expressed as a linear combination, i.e., as the sum of the products of each covariate (A and A^2) with its associated coefficient (the parameters θ_1 and θ_2) plus an intercept (θ_0). However, whenever θ_2 is not zero, the parameters θ_0, θ_1, and θ_2 now define a curve—a parabola—rather than a straight line. We refer to θ_1 as the parameter for the linear term A, and to θ_2 as the parameter for the quadratic term A^2.

The curve under the 3-parameter linear model $\mathrm{E}[Y|A] = \theta_0 + \theta_1 A + \theta_2 A^2$ can be found via ordinary least squares estimation applied to the data in Figure 11.3. The estimated curve is shown in Figure 11.5. The parameter estimates are $\hat{\theta}_0 = -7.41$, $\hat{\theta}_1 = 4.11$, and $\hat{\theta}_2 = -0.02$. The predicted mean of Y among individuals with treatment level $A = 90$ is obtained from the expression $\widehat{\mathrm{E}}[Y|A = 90] = \hat{\theta}_0 + 90\hat{\theta}_1 + 90 \times 90\hat{\theta}_2 = 197.1$.

CODE: Program 11.3
Under the homoscedasticity assumption, the Wald 95% confidence interval for $\widehat{\mathrm{E}}[Y|A = 90]$ is $(142.8, 251.5)$.

We could keep adding parameters for a cubic term ($\theta_3 A^3$), a quartic term ($\theta_4 A^4$)... until we reach a 15th-degree term ($\theta_{15} A^{15}$). At that point the number of parameters in our model equals the number of data points (individuals). The shape of the curve would change as the number of parameters increases. In general, the more parameters in the model, the more inflection points will appear.

That is, the curve generally becomes more "wiggly," or less smooth, as the number of parameters increase. A linear model with 2 parameters—a straight line—is the smoothest model. A linear model with as many parameters as data points is the least smooth model because it has as many possible inflection points as data points. In fact, such model interpolates the data, i.e., each data point in the sample lies on the estimated conditional mean function.

Often modeling can be viewed as a procedure to transform noisy data into more or less smooth curves. This smoothing occurs because the model borrows information from many data points to predict the outcome value at a particular combination of values of the covariates. The smoothing results from $\mathrm{E}[Y|A = a]$ being estimated by borrowing information from individuals with A not equal to a. All parametric estimators incorporate some degree of smoothing.

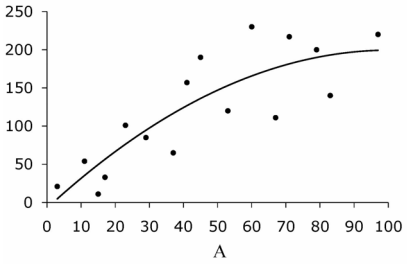


Figure 11.5

The degree of smoothing depends on how much information is borrowed across individuals. The 2-parameter model $\mathrm{E}[Y|A] = \theta_0 + \theta_1 A$ estimates $\mathrm{E}[Y|A = 90]$ by borrowing information from all individuals in the study population to find the least squares straight line. A model with as many parameters as individuals does not borrow any information to estimate $\mathrm{E}[Y|A]$ at the values of A that occur in the data, though it borrows information (by interpolation) for values of A that do not occur in the data.

We used a model for continuous outcomes as an example. The same reasoning applies to models for dichotomous outcomes such as logistic models (see Technical Point 11.1)

Intermediate degrees of smoothing can be achieved by using an intermediate number of parameters or, more generally, by restricting the number of individuals that contribute to the estimation. For example, to estimate $\mathrm{E}[Y|A = 90]$ we could decide to fit a 2-parameter model $\mathrm{E}[Y|A] = \theta_0 + \theta_1 A$ restricted to individuals with treatment doses between 80 and 100. That is, we would only borrow information from individuals in a 10-unit window of $A = 90$. The wider the window around $A = 90$, the more smoothing would be achieved.

In our simplistic examples above, all models included a single covariate (with either a single parameter for A or two parameters for A and A^2) so that

Fine Point 11.2

Model dimensionality and the relation between frequentist and Bayesian intervals. In frequentist statistical inference, probability is defined as frequency. In Bayesian inference, probability is defined as degree-of-belief—a concept very different from probability as frequency. Chapter 10 described the confidence intervals used in frequentist statistical inference. Bayesian statistical inference uses credible intervals, which have a more natural interpretation: A Bayesian 95% credible interval means that, given the observed data, "there is a 95% probability that the estimand is in the interval". However, in part because of the requirement to specify the investigators' degree of belief, Bayesian inference is less commonly used than frequentist inference.

Interestingly, in simple, low-dimensional parametric models with large sample sizes, 95% Bayesian credible intervals are also 95% frequentist confidence intervals, whereas in high-dimensional or nonparametric models, a Bayesian 95% credible interval may not be a 95% confidence interval as it may trap the estimand much less than 95% of the time. The underlying reason for these results is that Bayesian inference requires the specification of a prior distribution for all unknown parameters. In low-dimensional parametric models the information in the data swamps that contained in reasonable priors. As a result, inference is relatively insensitive to the particular prior distribution selected. However, this is no longer the case in high-dimensional models. Therefore if the true parameter values that generated the data are unlikely under the chosen prior distribution, the center of Bayes credible interval will be pulled away from the true parameters and towards the parameter values given the greatest probability under the prior.

the curves can be represented on a two-dimensional book page. In realistic applications, models often include many different covariates so that the curves are really hyperdimensional surfaces. Regardless of the dimensionality of the problem, the concept of smoothing remains invariant: the fewer parameters in the model, the smoother the prediction (response) surface will be.

11.5 The bias-variance trade-off

In previous sections we have used the 16 individuals in Figure 11.3 to estimate the mean outcome Y among people receiving a treatment dose of $A = 90$ in the target population, $\mathrm{E}[Y|A = 90]$. Since nobody in the study population received $A = 90$, we could not let the data speak for themselves. So we combined the data with a linear model. The estimate $\widehat{\mathrm{E}}[Y|A = 90]$ varied with the model. Under the 2-parameter model $\mathrm{E}[Y|A] = \theta_0 + \theta_1 A$, the estimate was 216.9 (95% confidence interval: 172.1, 261.6). Under the 3-parameter model $\mathrm{E}[Y|A] = \theta_0 + \theta_1 A + \theta_2 A^2$, the estimate was 197.1 (95% confidence interval: 142.8, 251.5). We used two different parametric models that yielded two different estimates. Which one is better? Is 216.9 or 197.1 closer to the mean in the target population?

If the relation is truly curvilinear, then the estimate from the 2-parameter model will be biased because this model assumes a straight line. On the other hand, if the relation is truly a straight line, then the estimates from both models will be valid. This is so because the 3-parameter model $\mathrm{E}[Y|A] = \theta_0 + \theta_1 A + \theta_2 A^2$ is correctly specified whether the relation follows a straight line (in which case $\theta_2 = 0$) or a parabolic curve (in which case $\theta_2 \neq 0$). One safe strategy would be to use the 3-parameter model $\mathrm{E}[Y|A] = \theta_0 + \theta_1 A + \theta_2 A^2$ rather than the 2-parameter model $\mathrm{E}[Y|A] = \theta_0 + \theta_1 A$. Because the 3-parameter model is correctly specified under both a straight line and a parabolic curve, it is less likely to be biased. In general, the larger the number of parameters in the

model, the fewer restrictions the model imposes; the less smooth the model, the more protection afforded against bias from model misspecification.

Although less smooth models may yield a less biased estimate, they also result in a larger variance, i.e., wider 95% confidence intervals around the estimate. For example, the estimated 95% confidence interval around $\widehat{\mathrm{E}}[Y|A = 90]$ was much wider when we used the 3-parameter model than when we used the 2-parameter model. However, when the estimate $\widehat{\mathrm{E}}[Y|A = 90]$ based on the 2-parameter model is biased, the standard (nominal) 95% confidence interval is not calibrated, that is, it does not cover the true parameter $\mathrm{E}[Y|A = 90]$ 95% of the time.

Fine Point 11.2 discusses the implications of model dimensionality for frequentist and Bayesian intervals.

This bias-variance trade-off is at the heart of many data analyses. Investigators using models need to decide whether some protection against bias—by, say, adding more parameters to the model—is worth the cost in terms of variance. Though some formal procedures exist to aid these decisions, in practice many investigators decide which model to use based on criteria like tradition, interpretability of the parameters, and software availability. In this book we will usually assume that our parametric models are correctly specified. This is an unrealistic assumption, but it allows us to focus on the problems that are specific to causal analyses. Model misspecification is, after all, a problem that can arise in any sort of data analysis, regardless of whether the estimates are endowed with a causal interpretation. In practice, careful investigators will always question the validity of their models, and will conduct an analysis to assess the sensitivity of their estimates to model specification.

We are now ready to describe the use of models for causal inference.

Technical Point 11.1

A taxonomy of commonly used models. The main text describes linear conditional mean models of the form $\mathrm{E}[Y|X] = \theta X \equiv \sum_{i=0}^{p} \theta_i X_i$ where X is a vector of covariates $X_0, X_1, ...X_p$ with $X_0 = 1$ for all n individuals. These models are a subset of larger class of conditional mean models which have two components: a linear functional form or predictor $\sum_{i=0}^{p} \theta_i X_i$ and a link function $g\{\cdot\}$ such that $g\{\mathrm{E}[Y|X]\} = \sum_{i=1}^{p} \theta_i X_i$.

The linear conditional mean models described in the main text uses the identity link function. Conditional mean models for outcomes with strictly positive values (e.g., counts, the numerator of incidence rates) often use the log link function to ensure that all predicted values will be greater than zero, i.e., $\log\{\mathrm{E}[Y|X]\} = \sum_{i=0}^{p} \theta_i X_i$ so $\mathrm{E}[Y|X] = \exp\left(\sum_{i=0}^{p} \theta_i X_i\right)$. Conditional mean models for dichotomous outcomes (i.e., those that only take values 0 and 1) often use a logit link i.e., $\log\left\{\frac{\mathrm{E}[Y|\mathbf{X}]}{1-\mathrm{E}[Y|\mathbf{X}]}\right\} = \sum_{i=0}^{p} \theta_i X_i$, so that $\mathrm{E}[Y|X] = \mathrm{expit}\left(\sum_{i=0}^{p} \theta_i X_i\right)$. This link ensures that all predicted values will be greater than 0 and less than 1. Conditional mean models that use the logit function are referred to as logistic regression models, and they are widely used in this book. For these links (referred to as canonical links) we can estimate θ by maximum likelihood under a normal model for the identity link, a Poisson model for the log link, and a logistic regression model for the logit link. These estimates are consistent for θ as long as the conditional mean model for $\mathrm{E}[Y|X]$ is correct. Generalized estimating equation (GEE) models, often used to deal with repeated measures, are a further example of a conditional mean model (Liang and Zeger, 1986).

Conditional mean models only specify a parametric form for $\mathrm{E}[Y|X]$ but do not otherwise restrict the distribution of $Y|X$ or the marginal distribution of X. Therefore, when X or Y are continuous, a parametric conditional mean model is a semiparametric model for the joint distribution of the data (X, Y) because parts of the distribution are modeled parametrically whereas others are left unrestricted. The model is semiparametric because the set of all unrestricted components of the joint distribution cannot be represented by a finite number of parameters.

Conditional mean models themselves can be generalized by relaxing the assumption that $\mathrm{E}[Y|X]$ takes a parametric form. For example, a kernel regression model does not impose a specific functional form on $\mathrm{E}[Y|X]$ but rather estimates $\mathrm{E}[Y|X = x]$ for any x by $\sum_{i=1}^{n} w_h(x - X_i) Y_i / \sum_{i=1}^{n} w_h(x - X_i)$ where $w_h(z)$ is a positive function, known as a kernel function, that attains its maximum value at $z = 0$ and decreases to 0 as $|z|$ gets large at a rate that depends on the parameter h subscripting w. As another example, generalized additive models (GAMs) replace the linear combination $\sum_{i=0}^{p} \theta_i X_i$ of a conditional mean model by a sum of smooth functions $\sum_{i=0}^{p} f_i(X_i)$. The model can be estimated using a backfitting algorithm with $f_i(\cdot)$ estimated at iteration k by, for example, kernel regression (Hastie and Tibshirani 1990).

In the text we discuss smoothing with parametric models which specify an a priori functional form for $\mathrm{E}[Y|X = x]$, such as a parabola. In estimating $\mathrm{E}[Y|X = x]$, the model may borrow information from values of X that are far from x. In contrast, kernel regression models do not specify an a priori functional form and borrow information only from values of X near to x when estimating $\mathrm{E}[Y|X = x]$. A kernel regression model is an example of a "non-parametric" regression model. This use of the term "nonparametric" differs from our previous usage. Our nonparametric estimators of $\mathrm{E}[Y|X = x]$ only used those individuals for whom X equalled x exactly; no information was borrowed even from close neighbors. Here "nonparametric" estimators of $\mathrm{E}[Y|X = x]$ use individuals with values of X near to x. How near is controlled by a smoothing parameter referred to as the bandwidth h.

Chapter 12
IP WEIGHTING AND MARGINAL STRUCTURAL MODELS

Part II is organized around the causal question "what is the average causal effect of smoking cessation on body weight gain?" In this chapter we describe how to use IP weighting to estimate this effect from observational data. Though IP weighting was introduced in Chapter 2, we only described it as a nonparametric method. We now describe the use of models together with IP weighting which, under additional assumptions, will allow us to tackle high-dimensional problems with many covariates and nondichotomous treatments.

To estimate the effect of smoking cessation on weight gain we will use real data from the NHEFS, an acronym that stands for (ready for a long name?) National Health and Nutrition Examination Survey Data I Epidemiologic Follow-up Study. The NHEFS was jointly initiated by the National Center for Health Statistics and the National Institute on Aging in collaboration with other agencies of the United States Public Health Service. A detailed description of the NHEFS, together with publicly available data sets and documentation, can be found at `wwwn.cdc.gov/nchs/nhanes/nhefs/`. For this and future chapters, we will use a subset of the NHEFS data that is available from this book's web site. We encourage readers to improve upon and refine our analyses.

12.1 The causal question

We restricted the analysis to individuals with known sex, age, race, weight, height, education, alcohol use and intensity of smoking at the baseline (1971-75) and follow-up (1982) visits, and who answered the medical history questionnaire at baseline. See Fine Point 12.1.

Table 12.1

Mean baseline characteristics	A = 1	A = 0
Age, years	46.2	42.8
Men, %	54.6	46.6
White, %	91.1	85.4
University, %	15.4	9.9
Weight, kg	72.4	70.3
Cigarettes/day	18.6	21.2
Years smoking	26.0	24.1
Little exercise, %	40.7	37.9
Inactive life, %	11.2	8.9

Our goal is to estimate the average causal effect of smoking cessation (the treatment) A on weight gain (the outcome) Y. To do so, we will use data from 1566 cigarette smokers aged 25-74 years who, as part of the NHEFS, had a baseline visit and a follow-up visit about 10 years later. Individuals were classified as treated $A = 1$ if they reported having quit smoking before the follow-up visit, and as untreated $A = 0$ otherwise. Each individual's weight gain Y was measured (in kg) as the body weight at the follow-up visit minus the body weight at the baseline visit. Most people gained weight, but quitters gained more weight on average. The average weight gain was $\widehat{\mathrm{E}}[Y|A=1] = 4.5$ kg in the quitters, and $\widehat{\mathrm{E}}[Y|A=0] = 2.0$ kg in the non-quitters. The difference $\mathrm{E}[Y|A=1] - \mathrm{E}[Y|A=0]$ was therefore estimated to be 2.5, with a 95% confidence interval from 1.7 to 3.4. A conventional statistical test of the null hypothesis that this difference was equal to zero yielded a P-value< 0.001.

We define $\mathrm{E}[Y^{a=1}]$ as the mean weight gain that would have been observed if all individuals in the population had quit smoking before the follow-up visit, and $\mathrm{E}[Y^{a=0}]$ as the mean weight gain that would have been observed if all individuals in the population had not quit smoking. We define the average causal effect on the additive scale as $\mathrm{E}[Y^{a=1}] - \mathrm{E}[Y^{a=0}]$, that is, the difference in mean weight that would have been observed if everybody had been treated compared with untreated. This is the causal effect that we will be primarily concerned with in this and the next chapters.

The associational difference $\mathrm{E}[Y|A=1] - \mathrm{E}[Y|A=0]$, which we estimated in the first paragraph of this section, is generally different from the causal difference $\mathrm{E}[Y^{a=1}] - \mathrm{E}[Y^{a=0}]$. The former will not generally have a causal interpretation if quitters and non-quitters differ with respect to characteristics that affect weight gain. For example, quitters were on average 4 years older than non-quitters (quitters were 44% more likely to be above age 50 than non

Fine Point 12.1

Setting a bad example. Our smoking cessation example is convenient: it does not require deep subject-matter knowledge and the data are publicly available. One price we have to pay for this convenience is potential selection bias.

We classified individuals as treated $A = 1$ if they reported (i) being smokers at baseline in 1971-75, and (ii) having quit smoking in the 1982 survey. Condition (ii) implies that the individuals included in our study did not die and were not otherwise lost to follow-up between baseline and 1982 (otherwise they would not have been able to respond to the survey). That is, we selected individuals into our study conditional on an event—responding the 1982 survey—that occurred after the start of the treatment—smoking cessation. If treatment affects the probability of selection into the study, we might have selection bias as described in Chapter 8. (Because different individuals quit smoking at different times, A is actually a time-varying treatment, which we will ignore throughout Part II. Time-varying treatments are discussed in Part III.)

A randomized experiment of smoking cessation would not have this problem. Each individual would be assigned to either smoking cessation or no smoking cessation at baseline, so that their treatment group would be known even if the individual did not make it to the 1982 visit. In Section 12.6 we describe how to deal with potential selection bias due to censoring or missing data for the outcome—something that may occur in both observational studies and randomized experiments—but the situation described in this Fine Point is different: the missing data concerns the treatment itself. This selection bias can be handled through sensitivity analysis, as was done by Hernán et al. (2008, Appendix 3).

The choice of this example allows us to describe, in our own analysis, a ubiquitous problem in published analyses of observational data: a misalignment of treatment assignment and eligibility at the start of follow-up (Hernán et al. 2016). Though we decided to ignore this issue in order to keep our analysis simple, didactic convenience would not be a good excuse to avoid dealing with this bias in real life.

Fine Point 7.3 defined surrogate confounders.

quitters), and older people gained less weight than younger people, regardless of whether they did or did not quit smoking. We say that age is a (surrogate) confounder of the effect of A on Y and our analysis needs to adjust for age. The unadjusted estimate 2.5 might underestimate the true causal effect $\mathrm{E}[Y^{a=1}] - \mathrm{E}[Y^{a=0}]$.

CODE: Program 12.1 computes the descriptive statistics shown in this section

As shown in Table 12.1, quitters and non-quitters also differed in their distribution of other variables such as sex, race, education, baseline weight, and intensity of smoking. If these variables are confounders, then they also need to be adjusted for in the analysis. In Chapter 18 we discuss strategies for confounder selection. Here we assume that the following 9 variables, all measured at baseline, are sufficient to adjust for confounding: sex (0: male, 1: female), age (in years), race (0: white, 1: other), education (5 categories), intensity and duration of smoking (number of cigarettes per day and years of smoking), physical activity in daily life (3 categories), recreational exercise (3 categories), and weight (in kg). That is, L represents a vector of 9 measured covariates. In the next section we use IP weighting to adjust for these covariates.

12.2 Estimating IP weights via modeling

IP weighting creates a pseudo-population in which the arrow from the covariates L to the treatment A is removed. More precisely, the pseudo-population has the following two properties: A and L are statistically independent and the mean $\mathrm{E}_{ps}[Y|A = a]$ in the pseudo-population equals the standardized mean $\sum_l \mathrm{E}[Y|A = a, L = l] \Pr[L = l]$ in the actual population. These properties are

true even if conditional exchangeability $Y^a \perp\!\!\!\perp A|L$ does not hold in the actual population (see Technical Point 2.3). Now, if conditional exchangeability $Y^a \perp\!\!\!\perp A|L$ holds in the actual population, then these properties imply that (i) the mean of Y^a is the same in both populations, (ii) unconditional exchangeability (i.e., no confounding) holds in the pseudo-population, (iii) the counterfactual mean $\mathrm{E}[Y^a]$ in the actual population is equal to $\mathrm{E}_{ps}[Y|A=a]$ in the pseudo-population, and (iv) association is causation in the pseudo-population. Please reread Chapter 2 if you need a refresher on IP weighting.

Informally, the pseudo-population is created by weighting each individual by the inverse (reciprocal) of the conditional probability of receiving the treatment level that she indeed received. The individual-specific IP weights for treatment A are defined as $W^A = 1/f(A|L)$. For our dichotomous treatment A, the denominator $f(A|L)$ of the IP weight is the probability of quitting conditional on the measured confounders, $\Pr[A=1|L]$, for the quitters, and the probability of not quitting conditional on the measured confounders, $\Pr[A=0|L]$, for the non-quitters. We only need to estimate $\Pr[A=1|L]$ because $\Pr[A=0|L] = 1 - \Pr[A=1|L]$.

The conditional probability of treatment $\Pr[A=1|L]$ is known as the *propensity score*. More about propensity scores in Chapter 15.

In Section 2.4 we estimated the quantity $\Pr[A=1|L]$ nonparametrically: we simply counted how many people were treated ($A=1$) in each stratum of L, and then divided this count by the number of individuals in the stratum. All the information required for this calculation was taken from a causally interpreted structured tree with 4 branches (2 for L times 2 for A). But nonparametric estimation of $\Pr[A=1|L]$ is out of the question when, as in our example, we have high-dimensional data with many confounders, some of them with many levels. Even if we were willing to recode all 9 confounders except age to a maximum of 6 categories each, our tree would still have over 2 million branches. And many more millions if we use the actual range of values of duration and intensity of smoking, and weight. We cannot obtain meaningful nonparametric stratum-specific estimates when there are 1566 individuals distributed across millions of strata. We need to resort to modeling.

The curse of dimensionality was introduced in Chapter 10.

To obtain parametric estimates of $\Pr[A=1|L]$ in each of the millions of strata defined by L, we fit a logistic regression model for the probability of quitting smoking with all 9 confounders included as covariates. We used linear and quadratic terms for the (quasi-)continuous covariates age, weight, intensity and duration of smoking, and we included no product terms between the covariates. That is, our model restricts the possible values of $\Pr[A=1|L]$ such that, on the logit scale, the conditional relation between the continuous covariates and the risk of quitting can be represented by a parabolic curve, and each covariate's contribution to the (logit of the) risk is independent of that of the other covariates. Under these parametric restrictions, we were able to obtain an estimate $\widehat{\Pr}[A=1|L]$ for each combination of L values, and therefore for each of the 1566 individuals in the study population.

CODE: Program 12.2
The estimated IP weights W^A ranged from 1.05 to 16.7, and their mean was 2.00.

The next step is computing the difference $\widehat{\mathrm{E}}_{ps}[Y|A=1] - \widehat{\mathrm{E}}_{ps}[Y|A=0]$ in the pseudo-population created by the estimated IP weights. If there is no confounding for the effect of A in the pseudo-population and the model for $\Pr[A=1|L]$ is correct, association is causation and an unbiased estimator of the associational difference $\mathrm{E}_{ps}[Y|A=1] - \mathrm{E}_{ps}[Y|A=0]$ in the pseudo-population is also an unbiased estimator of the causal difference $\mathrm{E}[Y^{a=1}] - \mathrm{E}[Y^{a=0}]$ in the actual population.

$\mathrm{E}[Y|A] = \theta_0 + \theta_1 A$ is a saturated model because it has 2 parameters, θ_0 and θ_1, to estimate two quantities, $\mathrm{E}[Y|A=1]$ and $\mathrm{E}[Y|A=0]$. In this model, $\theta_1 = \mathrm{E}[Y|A=1] - \mathrm{E}[Y|A=0]$.

Our approach to estimate $\mathrm{E}_{ps}[Y|A=1] - \mathrm{E}_{ps}[Y|A=0]$ in the pseudo-population was to fit the (saturated) linear mean model $\mathrm{E}[Y|A] = \theta_0 + \theta_1 A$ by weighted least squares, with individuals weighted by their estimated IP weights $\widehat{W}$: $1/\widehat{\Pr}[A=1|L]$ for the quitters, and $1/\left(1 - \widehat{\Pr}[A=1|L]\right)$ for the

Technical Point 12.1

Horvitz-Thompson estimators. In Technical Point 3.1, we defined the "apparent" IP weighted mean for treatment level a, $\mathrm{E}\left[\frac{I(A=a)Y}{f(A|L)}\right]$, which is equal to the counterfactual mean $\mathrm{E}[Y^a]$ under positivity and exchangeability. This IP weighted mean is consistently estimated by the original Horvitz-Thompson (1952) estimator $\widehat{\mathrm{E}}\left[\frac{I(A=a)Y}{f(A|L)}\right]$. In this chapter, however, we estimated $\mathrm{E}[Y^a]$ via the IP weighted least squares estimate $\hat{\theta}_0+\hat{\theta}_1 a$, a modified Horvitz-Thompson estimator often referred to as Hajek estimator $\frac{\widehat{\mathrm{E}}\left[\frac{I(A=a)Y}{f(A|L)}\right]}{\widehat{\mathrm{E}}\left[\frac{I(A=a)}{f(A|L)}\right]}$ (Hajek 1971, Robins 1998).

The Hajek estimator is an unbiased estimator of $\frac{\mathrm{E}\left[\frac{I(A=a)Y}{f(A|L)}\right]}{\mathrm{E}\left[\frac{I(A=a)}{f(A|L)}\right]}$ which, under positivity, is equal to $\mathrm{E}\left[\frac{I(A=a)Y}{f(A|L)}\right]$ because $\mathrm{E}\left[\frac{I(A=a)}{f(A|L)}\right] = 1$. In practice, the Hajek estimator is preferred because, unlike the Horvitz-Thompson estimator, it is guaranteed to lie between 0 and 1 for dichotomous Y.

On the other hand, if positivity does not hold, then the ratio $\frac{\mathrm{E}\left[\frac{I(A=a)Y}{f(A|L)}\right]}{\mathrm{E}\left[\frac{I(A=a)}{f(A|L)}\right]}$ equals $\sum_l \mathrm{E}[Y|A=a,L=l,L\in Q(a)]\Pr[L=l|L\in Q(a)]$ and, if exchangeability holds, it equals $\mathrm{E}[Y^a|L\in Q(a)]$,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, as discussed in Technical Point 3.1, the difference between Hajek estimators with $a=1$ versus $a=0$ does not have a causal interpretation in the absence of positivity.

non-quitters. The parameter estimate $\hat{\theta}_1$ was 3.4. That is, we estimated that quitting smoking increases weight by $\hat{\theta}_1 = 3.4$ kg on average. See Technical Point 12.1 for a formal definition of the estimator.

To obtain a 95% confidence interval around the point estimate $\hat{\theta}_1 = 3.4$ we need a method that takes the IP weighting into account. One possibility is to use statistical theory to derive the corresponding variance estimator. This approach requires that the data analyst programs the estimator, which is not generally available in standard statistical software. A second possibility is to approximate the variance by nonparametric bootstrapping (see Technical Point 13.1). This approach requires appropriate computing resources, or lots of patience, for large databases. A third possibility is to use the robust variance estimator (e.g., as used for GEE models with an independent working correlation) that is a standard option in most statistical software packages. The 95% confidence intervals based on the robust variance estimator are valid but, unlike the above analytic and bootstrap estimators, conservative—they cover the super-population parameter more than 95% of the time. The conservative 95% confidence interval around $\hat{\theta}_1$ was $(2.4, 4.5)$. In this chapter, all confidence intervals for IP weighted estimates are conservative. If the model for $\Pr[A=1|L]$ is misspecified, the estimates of θ_0 and θ_1 will be biased and, like we discussed in the previous chapter, the confidence intervals may cover the true values less than 95% of the time.

The weighted least squares estimates $\hat{\theta}_0$ and $\hat{\theta}_1$ with weight W of θ_0 and θ_1 are the minimizers of $\sum_i \widehat{W}_i[Y_i-(\theta_0+\theta_1 A_i)]^2$. If $\widehat{W}_i = 1$ for all individuals i, we obtain the ordinary least squares estimates described in the previous chapter.

The estimate $\widehat{\mathrm{E}}[Y|A=a] = \hat{\theta}_0 + \hat{\theta}_1 a$ is equal to $\frac{\sum_{i=1} Y_i \widehat{W}_i}{\sum_{i=1} \widehat{W}_i}$ where the sum is over all subjects with $A=a$.

12.3 Stabilized IP weights

The goal of IP weighting is to create a pseudo-population in which there is no association between the covariates L and treatment A. The IP weights $W^A = 1/f(A|L)$ simulate a pseudo-population in which all members of the study population are replaced by two copies of themselves. One copy receives treatment value $A = 1$ and the other copy receives treatment value $A = 0$. In Chapter 2 we showed how the original study population in Figure 2.1 was transformed into the pseudo-population in Figure 2.3. Note that the expected mean of the weights W^A is 2 because, heuristically, in the pseudo-population all individuals are included both under treatment and under no treatment.

However, there are other ways to create a pseudo-population in which A and L are independent. For example, a pseudo-population in which all individuals have a probability of receiving $A = 1$ equal to 0.5 and a probability of receiving $A = 0$ also equal to 0.5, regardless of their values of L. Such pseudo-population is constructed by using IP weights $0.5/f(A|L)$. This pseudo-population would be of the same size as the study population and it would be algebraically equal to the pseudo-population of the previous paragraph if all weights are divided by 2. Hence, the expected mean of the weights $0.5/f(A|L)$ is 1 and the effect estimate obtained in the pseudo-population created by weights $0.5/f(A|L)$ is equal to that obtained in the pseudo-population created by weights $1/f(A|L)$. (You can check this empirically by using the data in Figure 2.1, or see the proof in Technical Point 12.2.) The same goes for any other IP weights $p/f(A|L)$ with $0 < p \leq 1$. The weights $W^A = 1/f(A|L)$ are just one particular example of IP weights with $p = 1$.

Let us take our reasoning a step further. The key requirement for confounding adjustment is that, in the pseudo-population, the probability of treatment A does not depend on the confounders L. We can achieve this requirement by assigning treatment with the same probability p to everyone in the pseudo-population. But we can also achieve it by creating a pseudo-population in which different people have different probabilities of treatment, as long as the probability of treatment does not depend on the value of L. For example, a common choice is to assign to the treated the probability of receiving treatment $\Pr[A = 1]$ in the original population, and to the untreated the probability of not receiving treatment $\Pr[A = 0]$ in the original population. Thus the IP weights are $\Pr[A = 1]/f(A|L)$ for the treated and $\Pr[A = 0]/f(A|L)$ for the untreated or, more compactly, $f(A)/f(A|L)$.

The average causal effect in the treated subpopulation can be estimated by using IP weights in which the numerator is $\Pr[A = 1|L]$. See Technical Point 4.1.

Figure 12.1 shows the pseudo-population that is created by the IP weights $f(A)/f(A|L)$ when applied to the data in Figure 2.1, where $\Pr[A = 1] = 13/20 = 0.65$ and $\Pr[A = 0] = 7/20 = 0.35$. Under the identifiability conditions of Chapter 3, the pseudo-population resembles a hypothetical randomized experiment in which 65% of the individuals in the study population have been randomly assigned to $A = 1$, and 35% to $A = 0$. Note that, to preserve the 65/35 ratio, the number of individuals in each branch cannot be integers. Fortunately, non-whole people are no big deal in mathematics.

The IP weights $f(A)/f(A|L)$ range from 0.33 to 4.30, whereas the IP weights $1/f(A|L)$ range from 1.05 to 16.7. The stabilizing factor $f(A)$ in the numerator is responsible for the narrower range of the $f(A)/f(A|L)$ weights. The IP weights $W^A = 1/f(A|L)$ are referred to as *nonstabilized weights*, and the IP weights $SW^A = f(A)/f(A|L)$ are referred to as *stabilized weights*. The mean of the stabilized weights is expected to be 1 because the size of the pseudo-population equals that of the study population.

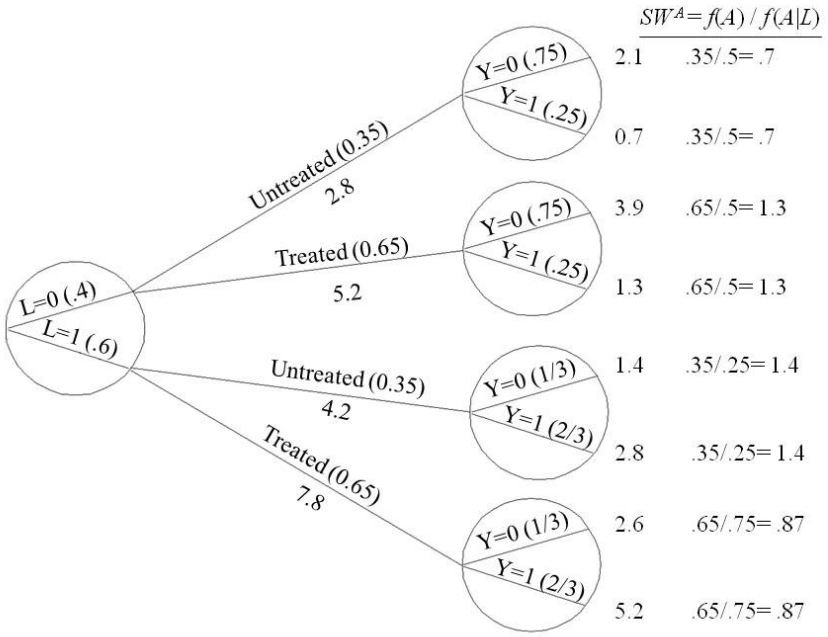


Figure 12.1

In data analyses one should always check that the estimated weights SW^A have mean 1 (Hernán and Robins 2006a). Deviations from 1 indicate model misspecification or possible violations, or near violations, of positivity. See Fine Point 12.2 for more on checking positivity.

CODE: Program 12.3
The estimated IP weights SW^A ranged from 0.33 to 4.30, and their mean was 1.00.

Let us now re-estimate the effect of quitting smoking on body weight by using the stabilized IP weights SW^A. First, we need an estimate of the conditional probability $\Pr[A = 1|L]$ to construct the denominator of the weights. We use the same logistic model we used in Section 12.2 to obtain a parametric estimate $\widehat{\Pr}[A = 1|L]$ for each of the 1566 individuals in the study population. Second, we need to estimate $\Pr[A = 1]$ for the numerator of the weights. We can obtain a nonparametric estimate by the ratio 403/1566 or, equivalently, by fitting a saturated logistic model for $\Pr[A = 1]$ with an intercept and no covariates. Finally, we estimate the causal difference $\mathrm{E}[Y^{a=1}] - \mathrm{E}[Y^{a=0}]$ by fitting the mean model $\mathrm{E}[Y|A] = \theta_0 + \theta_1 A$ with individuals weighted by their estimated stabilized IP weights: $\widehat{\Pr}[A = 1] / \widehat{\Pr}[A = 1|L]$ for the quitters, and $\left(1 - \widehat{\Pr}[A = 1]\right) / \left(1 - \widehat{\Pr}[A = 1|L]\right)$ for the non-quitters. Under our assumptions, we estimated that quitting smoking increases weight by $\hat{\theta}_1 = 3.4$ kg (95% confidence interval: 2.4, 4.5) on average. This is the same estimate we obtained earlier using the nonstabilized IP weights W^A rather than the stabilized IP weights SW^A.

If nonstabilized and stabilized IP weights result in the same estimate, why use stabilized IP weights then? Because stabilized weights typically result in narrower 95% confidence intervals than nonstabilized weights. However, the statistical superiority of the stabilized weights can only occur when the (IP weighted) model is not saturated. In our above example, the two-parameter model $\mathrm{E}[Y|A] = \theta_0 + \theta_1 A$ was saturated because treatment A could only take 2 possible values. In many settings (e.g., time-varying or continuous treatments), the weighted model cannot possibly be saturated and therefore stabilized weights are used. The next section describes the use of stabilized weights for a continuous treatment.

Fine Point 12.2

Checking positivity. In our study, there are 4 white women aged 66 years and none of them quit smoking. That is, the probability of $A = 1$ conditional on (a subset of) L is 0. Positivity, a condition for IP weighting, is empirically violated. There are two possible ways in which positivity can be violated:

- Structural violations: The type of violations described in Chapter 3. Individuals with certain values of L cannot possibly be treated (or untreated). An example: when estimating the effect of exposure to certain chemicals on mortality, being off work is an important confounder because people off work are more likely to be sick and to die, and a determinant of chemical exposure—people can only be exposed to the chemical while at work. That is, the structure of the problem guarantees that the probability of treatment conditional on being off work is exactly 0 (a structural zero). We'll always find zero cells when conditioning on that confounder.
- Random violations: The type of violations described in the first paragraph of this Fine Point. Our sample is finite so, if we stratify on several confounders, we will start finding zero cells at some places even if the probability of treatment is *not* really zero in the target population. This is a random, not structural, violation of positivity because the zeroes appear randomly at different places in different samples of the target population. An example: our study happened to include 0 treated individuals in the strata "white women age 66" and "white women age 67", but it included a positive number of treated individuals in the strata "white women age 65" and "white women age 69."

Each type of positivity violation has different consequences. In the presence of structural violations, causal inferences cannot be made about the entire population using IP weighting or standardization. The inference needs to be restricted to strata in which structural positivity holds. See Technical Point 12.1 for details. In the presence of random violations, we used our parametric model to estimate the probability of treatment in the strata with random zeroes using data from individuals in the other strata. In other words, we use parametric models to smooth over the zeroes. For example, the logistic model used in Section 12.2 estimated the probability of quitting in white women aged 66 by interpolating from all other individuals in the study. Every time we use parametric estimation of IP weights in the presence of zero cells—like we did in estimating $\hat{\theta}_1 = 3.4$—, we are effectively assuming random nonpositivity.

12.4 Marginal structural models

This is a (saturated) marginal structural mean model for a dichotomous treatment A.

Consider the following linear model for the mean outcome under treatment level a

$$\mathrm{E}[Y^a] = \beta_0 + \beta_1 a$$

This model is different from all models we have considered so far: the outcome variable of this model is counterfactual—and hence generally unobserved. Therefore the model cannot be fit to the data of any real-world study. Models for the marginal mean of a counterfactual outcome are referred to as *marginal structural mean models*.

The parameters for treatment in structural mean models correspond to average causal effects. In the above model, the parameter β_1 is equal to $\mathrm{E}[Y^{a=1}] - \mathrm{E}[Y^{a=0}]$ because $\mathrm{E}[Y^a] = \beta_0$ under $a = 0$ and $\mathrm{E}[Y^a] = \beta_0 + \beta_1$ under $a = 1$. In previous sections, we have estimated the average causal effect of smoking cessation A on weight change Y defined as $\mathrm{E}[Y^{a=1}] - \mathrm{E}[Y^{a=0}]$. In other words, we have estimated the parameter β_1 of a marginal structural model.

Specifically, we used IP weighting to construct a pseudo-population, and then fit the model $\mathrm{E}[Y|A] = \theta_0 + \theta_1 A$ to the pseudo-population data by using IP weighted least squares. Under our assumptions, association is causation in the pseudo-population. That is, the parameter θ_1 from the IP weighted

associational model $\mathrm{E}[Y|A] = \theta_0 + \theta_1 A$ can be endowed with the same causal interpretation as the parameter β_1 from the structural model $\mathrm{E}[Y^a] = \beta_0 + \beta_1 a$. It follows that a consistent estimate $\hat{\theta}_1$ of the associational parameter in the pseudo-population is also a consistent estimator of the causal effect $\beta_1 = \mathrm{E}[Y^{a=1}] - \mathrm{E}[Y^{a=0}]$ in the population.

The marginal structural model $\mathrm{E}[Y^a] = \beta_0 + \beta_1 a$ is saturated because smoking cessation A is a dichotomous treatment. That is, the model has 2 unknowns on both sides of the equation: $\mathrm{E}[Y^{a=1}]$ and $\mathrm{E}[Y^{a=0}]$ on the left-hand side, and β_0 and β_1 on the right-hand side. Thus sample averages computed in the pseudo-population were enough to estimate the causal effect of interest.

A desirable property of marginal structural models is *null preservation* (see Chapter 9): when the null hypothesis of no average causal effect is true, a marginal structural model is never misspecified. For example, under marginal structural model $\mathrm{E}[Y^a] = \beta_0 + \beta_1 a + \beta_2 a^2$, a Wald test on two degrees of freedom of the joint hypothesis $\beta_1 = \beta_2 = 0$ is a valid test of the null hypothesis.

But treatments are often polytomous or continuous. For example, consider the new treatment A "change in smoking intensity" defined as number of cigarettes smoked per day in 1982 minus number of cigarettes smoked per day at baseline. Treatment A can now take many values, e.g., -25 if an individual decreased his number of daily cigarettes by 25, 40 if an individual increased his number of daily cigarettes by 40. Let us say that we are interested in estimating the difference in average weight change under different changes in treatment intensity in the 1162 individuals who smoked 25 or fewer cigarettes per day at baseline. That is, we want to estimate $\mathrm{E}[Y^a] - \mathrm{E}[Y^{a'}]$ for any values a and a'.

A (nonsaturated) marginal structural mean model for a continuous treatment A.

Because treatment A can take dozens of values, a saturated model with as many parameters becomes impractical. We will have to consider a nonsaturated structural model to specify the dose-response curve for the effect of treatment A on the mean outcome Y. If we believe that a parabola appropriately describes the dose-response curve, then we would propose the marginal structural model

$$\mathrm{E}[Y^a] = \beta_0 + \beta_1 a + \beta_2 a^2$$

where $a^2 = a \times a$ is a-squared and $\mathrm{E}[Y^{a=0}] = \beta_0$ is the average weight gain under $a = 0$, i.e., under no change in smoking intensity between baseline and 1982.

Suppose we want to estimate the average causal effect of increasing smoking intensity by 20 cigarettes per day compared with no change, i.e., $\mathrm{E}[Y^{a=20}] - \mathrm{E}[Y^{a=0}]$. According to our structural model, $\mathrm{E}[Y^{a=20}] = \beta_0 + 20\beta_1 + 400\beta_2$, and thus $\mathrm{E}[Y^{a=20}] - \mathrm{E}[Y^{a=0}] = 20\beta_1 + 400\beta_2$. Now we need to estimate the parameters β_1 and β_2. To do so, we need to estimate IP weights SW^A to create a pseudo-population in which there is no confounding by L, and then fit the associational model $\mathrm{E}[Y|A] = \theta_0 + \theta_1 A + \theta_2 A^2$ to the pseudo-population data.

To estimate the stabilized weights $SW^A = f(A)/f(A|L)$ we need to estimate $f(A|L)$. For a dichotomous treatment A, $f(A|L)$ is a probability so we used a logistic model to estimate $\Pr[A = 1|L]$. For a continuous treatment A, $f(A|L)$ is a probability density function (PDF). Unfortunately, PDFs are generally hard to estimate correctly, which is why using IP weighting for continuous treatments will often be dangerous. In our example, we assumed that the density $f(A|L)$ was normal (Gaussian) with mean $\mu_L = \mathrm{E}[A|L]$ and constant variance σ^2. We then used a linear regression model to estimate the mean $\mathrm{E}[A|L]$ and variance of residuals σ^2 for all combinations of values of L. We also assumed that the density $f(A)$ in the numerator was normal. One should be careful when using IP weighting for continuous treatments because the effect estimates may be exquisitely sensitive to the choice of the model for the conditional density $f(A|L)$.

CODE: Program 12.4
The estimated SW^A ranged from 0.19 to 5.10 with mean 1.00. We assumed constant variance (homoscedasticity), which seemed reasonable after inspecting a residuals plot. Other choices of distribution (e.g., truncated normal with heteroscedasticity) resulted in similar estimates.

Our IP weighted estimates of the parameters of the marginal structural

model were $\hat{\beta}_0 = 2.005$, $\hat{\beta}_1 = -0.109$, and $\hat{\beta}_2 = 0.003$. According to these estimates, the mean weight gain (95% confidence interval) would have been 2.0 kg (1.4, 2.6) if all individuals had kept their smoking intensity constant, and 0.9 kg (−1.7, 3.5) if all individuals had increased smoking by 20 cigarettes/day between baseline and 1982.

One can also consider a marginal structural model for a dichotomous outcome. For example, if interested in the causal effect of quitting smoking A (1: yes, 0: no) on the risk of death D (1: yes, 0: no) by 1992, one could consider a *marginal structural logistic model* like

This is a saturated marginal structural logistic model for a dichotomous treatment. For a continuous treatment, we would specify a non-saturated logistic model.

$$\text{logit}\Pr[D^a = 1] = \alpha_0 + \alpha_1 a$$

where $\exp(\alpha_1)$ is the causal odds ratio of death for quitting versus not quitting smoking. The parameters of this model are consistently estimated, under our assumptions, by fitting the logistic model $\text{logit}\Pr[D = 1|A] = \theta_0 + \theta_1 A$ to the pseudo-population created by IP weighting. We estimated the causal odds ratio to be $\exp\left(\hat{\theta}_1\right) = 1.0$ (95% confidence interval: 0.8, 1.4).

CODE: Program 12.5

12.5 Effect modification and marginal structural models

Marginal structural models do not include covariates when the target parameter is the average causal effect in the population. However, one may include covariates—which may be non-confounders—in a marginal structural model to assess effect modification. Suppose it is hypothesized that the effect of smoking cessation varies by sex V (1: woman, 0: man). To examine this hypothesis, we add the covariate V to our marginal structural mean model:

$$\mathrm{E}[Y^a|V] = \beta_0 + \beta_1 a + \beta_2 V a + \beta_3 V$$

Additive effect modification is present if $\beta_2 \neq 0$. Technically, this is not a marginal model any more—because it is conditional on V—but the term "marginal structural model" is still applied.

The parameter β_3 does not generally have a causal interpretation as the effect of V. Remember that we are assuming exchangeability, positivity, and consistency for treatment A, not for sex V!

We can estimate the model parameters by fitting the linear regression model $\mathrm{E}[Y|A,V] = \theta_0 + \theta_1 A + \theta_2 V A + \theta_3 V$ via weighted least squares with IP weights W^A or SW^A. The vector of covariates L needs to include V—even if V is not a confounder—and any other variables that are needed to ensure exchangeability within levels of V.

Because we are considering a model for the effect of treatment within levels of V, we now have the choice to use either $f[A]$ or $f[A|V]$ in the numerator of the stabilized weights. IP weighting based on the stabilized weights $SW^A(V) = \dfrac{f[A|V]}{f[A|L]}$ generally results in narrower confidence intervals around the effect estimates. Some intuition for the increased statistical efficiency of $SW^A(V)$: with V in the conditioning event of both the numerator and the denominator, the numerical value of numerator and denominator gets closer, which results in added stabilization for (less variability in) the IP weights and therefore narrower 95% confidence intervals. We estimate $SW^A(V)$ using the same approach as for SW^A, except that we add the covariate V to the logistic model for the numerator of the weights.

The particular subset V of L that an investigator chooses to include in the marginal structural model should only reflect the investigator's substantive interest. For example, a variable V should be included in the marginal structural

model only if the investigator both believes that V may be an effect modifier and has greater substantive interest in the causal effect of treatment within levels of the covariate V than in the entire population. In our example, we found no strong evidence of effect modification by sex as the 95% confidence interval around the parameter estimate $\hat{\theta}_2$ was $(-2.2, 1.9)$. If the investigator chooses to include all variables L in the marginal structural model, then the stabilized weights $SW^A(L)$ equal 1 and no IP weighting is necessary because the (unweighted) outcome regression model, if correctly specified, fully adjusts for all confounding by L (see Chapter 15). For this reason, in a slightly humorous vein, we refer to a marginal structural model that conditions on all variables L needed for exchangeability as a *faux marginal structural model*.

CODE: Program 12.6

If we were interested in the interaction between 2 treatments A and B (as opposed to effect modification of treatment A by variable V; see Chapter 5), we would include parameters for both A and B in the marginal structural model, and would estimate IP weights with the joint probability of both treatments in the denominator. We would assume exchangeability, positivity, and consistency for A and B.

In Part I we discussed that effect modification and confounding are two logically distinct concepts. Nonetheless, many students have difficulty understanding the distinction because the same statistical methods—stratification (Chapter 4) or regression (Chapter 15)—are often used both for confounder adjustment and detection of effect modification. Thus, there may be some advantage to teaching these concepts using marginal structural models, because then methods for confounder adjustment (IP weighting) are distinct from methods for detection of effect modification (adding treatment-covariate product terms to a marginal structural model).

12.6 Censoring and missing data

When estimating the causal effect of smoking cessation A on weight gain Y, we restricted the analysis to the 1566 individuals with a body weight measurement at the end of follow-up in 1982. There were, however, 63 additional individuals who met our eligibility criteria but were excluded from the analysis because their weight in 1982 was not known. Selecting only individuals with nonmissing outcome values—that is, censoring from the analysis those with missing values—may introduce selection bias, as discussed in Chapter 8.

Let censoring C be an indicator for measurement of body weight in 1982: 1 if body weight is unmeasured (i.e., the individual is censored), and 0 if body weight is measured (i.e., the individual is uncensored). Our analysis was necessarily restricted to uncensored individuals, i.e., those with $C = 0$, because those were the only ones with known values of the outcome Y. That is, in sections 12.2 and 12.4 we did not fit the (weighted) outcome regression model $\mathrm{E}[Y|A] = \theta_0 + \theta_1 A$, but rather the model $\mathrm{E}[Y|A, C = 0] = \theta_0 + \theta_1 A$ restricted to individuals with $C = 0$.

Unfortunately, even under the null, selecting only uncensored individuals for the analysis is expected to induce bias when C is either a collider on a pathway between treatment A and the outcome Y, or the descendant of one such collider. See the causal diagrams in Figures 8.3 to 8.6. Our data are consistent with the structure depicted by those causal diagrams: treatment A is associated with censoring C—5.8% of quitters versus 3.2% nonquitters were censored—and at least some predictors of Y are associated with C—the average baseline weight was 76.6 kg in the censored versus 70.8 in the uncensored.

Because censoring due to loss to follow-up can introduce selection bias, we are generally interested in the causal effect if nobody in the study population had been censored. In our example, the goal becomes estimating the mean weight gain if everybody had quit smoking and nobody's outcome had been censored, $\mathrm{E}[Y^{a=1,c=0}]$, and the mean weight gain if nobody had quit smoking

and nobody's outcome had been censored $\mathrm{E}[Y^{a=0,c=0}]$. Then the causal effect of interest is $\mathrm{E}[Y^{a=1,c=0}] - \mathrm{E}[Y^{a=0,c=0}]$, a joint effect of A and C as we discussed in Chapter 8. The use of the superscript $c = 0$ makes it explicit the causal contrast that many have in mind when they refer to the causal effect of treatment A, even if they choose not to use the superscript $c = 0$.

The IP weights for censoring and treatment are $W^{A,C} = 1/f\left(A, C = 0|L\right)$, where the joint density of A and C is factored as $f\left(A, C = 0|L\right) = f\left(A|L\right) \times \Pr\left[C = 0|L, A\right]$.

This causal effect can be estimated by using IP weights $W^{A,C} = W^A \times W^C$ in which $W^C = 1/\Pr\left[C = 0|L, A\right]$ for the uncensored individuals and $W^C = 0$ for the censored individuals. The IP weights $W^{A,C}$ adjust for both confounding and selection bias under the identifiability conditions of exchangeability for the joint treatment (A, C) conditional on L—that is, $Y^{a,c=0} \perp\!\!\!\perp (A, C)\,|L$—, joint positivity for $(A = a, C = 0)$, and consistency. If some of the variables in L are affected by treatment A, e.g., as in Figure 8.4, the conditional independence $Y^{a,c=0} \perp\!\!\!\perp (A, C)\,|L$ will not generally hold. In Part III we show that there are alternative exchangeability conditions that license us to use IP weighting to estimate the joint effect of A and C when some components of L are affected by treatment.

Some variables in L may have zero coefficients in the model for $f\left(A|L\right)$ but not in the model for $\Pr\left[C = 0|L, A\right]$, or vice versa. Nonetheless, in large samples, it is always more efficient to keep all variables L that independenty predict the outcome in both models.

Remember that the weights $W^C = 1/\Pr\left[C = 0|L, A\right]$ create a pseudo-population with the same size as that of the original study population *before* censoring, and in which there is no arrow from either L or A into C. In our example, the estimates of IP weights for censoring W^C will create a pseudo-population with (approximately) $1566 + 63 = 1629$ in which, under our assumptions, there is no selection bias because there is no selection. That is, we fit the weighted model $\mathrm{E}[Y|A, C = 0] = \theta_0 + \theta_1 A$ with weights $W^{A,C}$ to estimate the parameters of the marginal structural model $\mathrm{E}[Y^{a,c=0}] = \beta_0 + \beta_1 a$ in the entire population.

The estimated IP weights SW^C have mean 1 when the model for $\Pr\left[C = 0|A\right]$ is correctly specified. See Technical Point 12.2 for more on stabilized IP weights.

Alternatively, one can use *stabilized* IP weights $SW^{A,C} = SW^A \times SW^C$. The censoring weights $SW^C = \Pr\left[C = 0|A\right] / \Pr\left[C = 0|L, A\right]$ create a pseudo-population of the same size as the original study population *after* censoring, and in which there is no arrow from L into C. In our example, the estimates of IP weights for censoring SW^C will create a pseudo-population of (approximately) 1566 uncensored individuals. That is, the stabilized weights do not eliminate censoring in the pseudo-population, they make censoring occur at random with respect to the measured covariates L. Therefore, under our assumption of conditional exchangeability of censored and uncensored individuals given L (and A), the proportion of censored individuals in the pseudo-population is identical to that in the study population: there is selection but no selection bias.

To obtain parametric estimates of $\Pr\left[C = 0|L, A\right]$ in our example, we fit a logistic regression model for the probability of being uncensored to the 1629 individuals in the study population. The model included the same covariates we used earlier to estimate the weights for treatment. Under these parametric restrictions, we obtained an estimate $\widehat{\Pr}\left[C = 0|L, A\right]$ and an estimate of SW^C for each of the 1566 uncensored individuals. Using the stabilized weights $SW^{A,C} = SW^A \times SW^C$ we estimated that quitting smoking increases weight by $\hat{\theta}_1 = 3.5$ kg (95% confidence interval: 2.5, 4.5) on average. This is almost the same estimate we obtained earlier using IP weights SW^A, which suggests that either there is no selection bias by censoring or that our measured covariates are unable to eliminate it.

CODE: Program 12.7
The estimated IP weights $SW^{A,C}$ ranged from 0.35 to 4.09, and their mean was 1.00.

We now describe an alternative to IP weighting to adjust for confounding and selection bias: standardization.

Technical Point 12.2

More on stabilized weights. The stabilized weights $SW^A = \frac{f[A]}{f[A|L]}$ are part of the larger class of stabilized weights $\frac{g[A]}{f[A|L]}$, where $g[A]$ is any function of A that is not a function of L. When unsaturated structural models are used, weights $\frac{g[A]}{f[A|L]}$ are preferable over weights $\frac{1}{f[A|L]}$ because there exist functions $g[A]$ (often $f[A]$) that can be used to construct more efficient estimators of the causal effect in a nonsaturated marginal structural model. We now show that the IP weighted mean with weights $\frac{g[A]}{f[A|L]}$ is equal to the counterfactual mean $\mathrm{E}[Y^a]$.

First note that the IP weighted mean $\mathrm{E}\left[\frac{I(A=a)Y}{f(A|L)}\right]$ using weights $1/f[A|L]$, which is equal to $\mathrm{E}[Y^a]$, can also be expressed as $\frac{\mathrm{E}\left[\frac{I(A=a)Y}{f(A|L)}\right]}{\mathrm{E}\left[\frac{I(A=a)}{f(A|L)}\right]}$ because $\mathrm{E}\left[\frac{I(A=a)}{f(A|L)}\right] = 1$. Similarly, the IP weighted mean using weights $\frac{g[A]}{f[A|L]}$ can be expressed as $\frac{\mathrm{E}\left[\frac{I(A=a)Y}{f(A|L)}g(A)\right]}{\mathrm{E}\left[\frac{I(A=a)}{f(A|L)}g(A)\right]}$, which is also equal to $\mathrm{E}[Y^a]$. The proof proceeds as in Technical Point 2.2 to show that the numerator $\mathrm{E}\left[\frac{I(A=a)Y}{f(A|L)}g(A)\right] = \mathrm{E}[Y^a]\,g(a)$, and that the denominator $\mathrm{E}\left[\frac{I(A=a)}{f(A|L)}g(A)\right] = g(a)$.

Chapter 13
STANDARDIZATION AND THE PARAMETRIC G-FORMULA

In this chapter we describe how to use standardization to estimate the average causal effect of smoking cessation on body weight gain. We use the same observational data set as in the previous chapter. Though standardization was introduced in Chapter 2, we only described it as a nonparametric method. We now describe the use of models together with standardization, which will allow us to tackle high-dimensional problems with many covariates and nondichotomous treatments. As in the previous chapter, we provide computer code to conduct the analyses.

In practice, investigators will often have a choice between IP weighting and standardization as the analytic approach to obtain effect estimates from observational data. Both methods are based on the same identifiability conditions, but on different modeling assumptions.

13.1 Standardization as an alternative to IP weighting

In the previous chapter we estimated the average causal effect of smoking cessation A (1: yes, 0: no) on weight gain Y (measured in kg) using IP weighting. In this chapter we will estimate the same effect using standardization. Our analyses will also be based on NHEFS data from 1629 cigarette smokers aged 25-74 years who had a baseline visit and a follow-up visit about 10 years later. Of these, 1566 individuals had their weight measured at the follow-up visit and are therefore uncensored ($C = 0$).

We define $\mathrm{E}[Y^{a,c=0}]$ as the mean weight gain that would have been observed if all individuals had received treatment level a and if no individuals had been censored. The average causal effect of smoking cessation can be expressed as the difference $\mathrm{E}[Y^{a=1,c=0}] - \mathrm{E}[Y^{a=0,c=0}]$, that is, the difference in mean weight that would have been observed if everybody had been treated and uncensored compared with untreated and uncensored.

As shown in Table 12.1, quitters ($A = 1$) and non-quitters ($A = 0$) differ with respect to the distribution of predictors of weight gain. The observed associational difference $\mathrm{E}[Y|A = 1, C = 0] - \mathrm{E}[Y|A = 0, C = 0] = 2.5$ is expected to differ from the causal difference $\mathrm{E}[Y^{a=1,c=0}] - \mathrm{E}[Y^{a=0,c=0}]$. Again we assume that the vector of variables L is sufficient to adjust for confounding and selection bias, and that L includes the baseline variables sex (0: male, 1: female), age (in years), race (0: white, 1: other), education (5 categories), intensity and duration of smoking (number of cigarettes per day and years of smoking), physical activity in daily life (3 categories), recreational exercise (3 categories), and weight (in kg).

As in the previous chapter, we will assume that the components of L required to adjust for C are unaffected by A. Otherwise, we would need to use the more general approach described in Part III.

One way to adjust for the variables L is IP weighting, which creates a pseudo-population in which the distribution of the variables in L is the same in the treated and in the untreated. Then, under the assumptions of exchangeability and positivity given L, we estimate $\mathrm{E}[Y^{a,c=0}]$ by simply computing $\widehat{\mathrm{E}}[Y|A = a, C = 0]$ as the average outcome in the pseudo-population. If A were a continuous treatment (contrary to our example), we would also need a structural model to estimate $\mathrm{E}[Y|A, C = 0]$ in the pseudo-population for all possible values of A. IP weighting requires estimating the joint distribution of

Fine Point 13.1

Structural positivity. Lack of structural positivity precludes the identification of the average causal effect in the entire population when using IP weighting. Positivity is also necessary for standardization because, when $\Pr[A = a|L = l] = 0$ and $\Pr[L = l] \neq 0$, then the conditional mean outcome $\mathrm{E}[Y|A = a, L = l]$ is undefined.

But the practical impact of deviations from positivity may vary greatly between IP weighted and standardized estimates that rely on parametric models. When using standardization, one can ignore the lack of positivity if one is willing to rely on parametric extrapolation. That is, one can fit a model for $\mathrm{E}[Y|A, L]$ that will smooth over the strata with structural zeroes. This smoothing will introduce bias into the estimation, and therefore the nominal 95% confidence intervals around the estimates will cover the true effect less than 95% of the time. Also, note the different purpose of modeling in this setting with structural positivity: we model not because we lack enough data, but because we want to estimate a quantity that cannot be identified even with an infinite amount of data (because of structural non-positivity). This is an important distinction.

In general, in the presence of violations or near-violations of positivity, the standard error of the treatment effect will be smaller for standardization than for IP weighting. This does not necessarily mean that standardization is preferred over IP weighting; the difference in the biases may swamp the differences in standard errors.

treatment and censoring. For the dichotomous treatment smoking cessation, we estimated $\Pr[A = a, C = 0|L]$ and computed IP probability weights with this joint probability in the denominator.

Technical Point 2.3 proves that, under conditional exchangeability, positivity, and consistency, the standardized mean in the treated equals the mean if everyone had been treated. The extension to censoring is trivial: just replace $A = a$ by $(A = a, C = 0)$ in the proof and definitions.

As discussed in Chapter 2, an alternative to IP weighting is standardization. Under exchangeability and positivity conditional on the variables in L, the standardized mean outcome in the uncensored treated is a consistent estimator of the mean outcome if everyone had been treated and had remained uncensored $\mathrm{E}[Y^{a=1,c=0}]$. Analogously, the standardized mean outcome in the uncensored untreated is a consistent estimator of the mean outcome if everyone had been untreated and had remained uncensored $\mathrm{E}[Y^{a=0,c=0}]$. See Fine Point 13.1 for a discussion of the relative impact of deviations from positivity in IP weighting and in standardization.

To compute the standardized mean outcome in the uncensored treated, we first need to compute the mean outcomes in the uncensored treated in each stratum l of the confounders L, i.e., the conditional means $\mathrm{E}[Y|A = 1, C = 0, L = l]$ in each of the strata l. In our smoking cessation example, we would need to compute the mean weight gain Y among those who quit smoking and remained uncensored in each of the (possibly millions of) strata defined by the combination of values of the 9 variables in L.

The standardized mean in the uncensored treated is then the weighted average of these conditional means using as weights the prevalence of each value l in the study population, i.e., $\Pr[L = l]$. That is, the conditional mean from the stratum with the greatest number of individuals has the greatest weight in the computation of the standardized mean. The standardized mean in the uncensored untreated is computed analogously except that the $A = 1$ in the conditioning event is replaced by $A = 0$.

The average causal effect in the treated can be estimated by standardization as described in Technical Point 4.1. One just needs to replace $\Pr[L = l]$ by $\Pr[L = l|A = 1]$ in the expression to the right.

More compactly, the standardized mean in the uncensored who received treatment level a is

$$\sum_l \mathrm{E}[Y|A = a, C = 0, L = l] \times \Pr[L = l]$$

When, as in our example, some of the variables in L are continuous, one needs to replace $\Pr[L = l]$ by the probability density function (PDF) $f_L[l]$, and the above sum becomes an integral.

The next two sections describe how to estimate the conditional means of the outcome Y and the distribution of the confounders L, the two types of quantities required to estimate the standardized mean.

13.2 Estimating the mean outcome via modeling

Ideally, we would estimate the set of conditional means $\mathrm{E}[Y|A=1,C=0,L=l]$ nonparametrically. We would compute the average outcome among the uncensored treated in each of the strata defined by different combination of values of the variables L. This is precisely what we did in Section 2.3, where all the information required for this calculation was taken from Table 2.2.

But nonparametric estimation of $\mathrm{E}[Y|A=1,C=0,L=l]$ is out of the question when, as in our current example, we have high-dimensional data with many confounders, some of them with multiple levels. We cannot obtain meaningful nonparametric stratum-specific estimates of the mean outcome in the treated when there are only 403 treated individuals distributed across millions of strata. We need to resort to modeling. The same rationale applies to the conditional mean outcome in the uncensored untreated $\mathrm{E}[Y|A=0,C=0,L=l]$.

To obtain parametric estimates of $\mathrm{E}[Y|A=a,C=0,L=l]$ in each of the millions of strata defined by L, we fit a linear regression model for the mean weight gain with treatment A and all 9 confounders in L included as covariates. We used linear and quadratic terms for the (quasi-)continuous covariates age, weight, intensity and duration of smoking. That is, our model restricts the possible values of $\mathrm{E}[Y|A=a,C=0,L=l]$ such that the conditional relation between the continuous covariates and the mean outcome can be represented by a parabolic curve. We included a product term between smoking cessation A and intensity of smoking. That is, our model imposes the restriction that each covariate's contribution to the mean is independent of that of the other covariates, except that the contribution of smoking cessation A varies linearly with intensity of prior smoking.

CODE: Program 13.1

Under these parametric restrictions, we obtained an estimate $\widehat{\mathrm{E}}[Y|A=a,C=0,L=l]$ for each combination of values of A and L, and therefore for each of the 403 uncensored treated $(A=1,C=0)$ and each of the 1163 uncensored untreated $(A=0,C=0)$ individuals in the study population. For example, we estimated that individuals with the combination of values {non-quitter, male, white, age 26, college dropout, 15 cigarettes/day, 12 years of smoking habit, moderate exercise, very active, weight 112 kg} had a mean weight gain of 0.34 kg (the individual with unique identifier 24770 happened to have these combination of values, you may take a look at his predicted value). Overall, the mean of the estimated weight gain was 2.6 kg, same as the mean of the observed weight gain, which ranged from -41.3 to 48.5 kg across different combinations of covariates.

In general, the standardized mean of Y is written as $\int \mathrm{E}\left[Y|A=a,C=0,L=l\right]\, dF_L\left(l\right)$ where $F_L\left(\cdot\right)$ is the joint cumulative distribution function (CDF) of the random variables in L. When, as in this chapter, L is a vector of baseline covariates unaffected by treatment, we can average over the observed values of L to nonparametrically estimate this integral.

Remember that our goal is to estimate the standardized mean $\sum_l \mathrm{E}[Y|A=a,C=0,L=l]\times\Pr\left[L=l\right]$ in the treated $(A=1)$ and in the untreated $(A=0)$. More formally, the standardized mean should be written as an integral because some of the variables in L are essentially continuous, and thus their distribution cannot be represented by a probability function. Regardless of these notational issues, we have already estimated the means $\mathrm{E}[Y|A=a,C=0,L=l]$ for all values of treatment A and confounders L.

The next step is standardizing these means to the distribution of the confounders L for all values l.

13.3 Standardizing the mean outcome to the confounder distribution

Second block: All untreated

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

Third block: All treated

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

The standardized mean is a weighted average of the conditional means $\mathrm{E}[Y|A = a, C = 0, L = l]$. When all variables in L are discrete, each mean receives a weight equal to the proportion of individuals with values $L = l$, i.e., $\Pr[L = l]$. In principle, these proportions $\Pr[L = l]$ could be calculated nonparametrically from the data: we would divide the number of individuals in the strata defined by $L = l$ by the total number of individuals in the population. This is precisely what we did in Section 2.3, where all the information required for this calculation was taken from Table 2.2. However, this method becomes tedious for high-dimensional data with many confounders, some of them with multiple levels, as in our smoking cessation example.

Fortunately, we do not need to estimate $\Pr[L = l]$. We only need to estimate $\mathrm{E}[Y|A = a, C = 0, L = l]$ for the l value of each individual i in the study, and then compute the average $\frac{1}{n}\sum_{i=1}^{n} \widehat{\mathrm{E}}[Y|A = a, C = 0, L_i]$ where n is the number of individuals in the study. This is so because the weighted mean $\sum_l \mathrm{E}[Y|A = a, C = 0, L = l] \Pr[L = l]$ can also be written as the double expectation $\mathrm{E}[\mathrm{E}[Y|A = a, C = 0, L]]$.

We now describe a simple computational method to estimate the standardized means $\sum_l \mathrm{E}[Y|A = a, C = 0, L = l] \times \Pr[L = l]$ in the treated ($A = 1$) and in the untreated ($A = 0$) with many confounders, without ever explicitly estimating $\Pr[L = l]$. We first apply the method to the data in Table 2.2, in which there was no censoring, the confounder L is only one variable with two levels, and Y is a dichotomous outcome, i.e., the mean $\mathrm{E}[Y|A = a, C = 0, L = l]$ is the risk $\Pr[Y = 1|A = a, L = l]$ of developing the outcome. Then we apply it to the real data with censoring and many confounders. The method has 4 steps: expansion of dataset, outcome modeling, prediction, and standardization by averaging.

Table 2.2 has 20 rows, one per individual in the study. We now create a new dataset in which the data of Table 2.2 is copied three times. That is, the analytic dataset has 60 rows in three blocks of 20 individuals each. We leave the first block of 20 rows as is, i.e., the first block is identical to the data in Table 2.2. We modify the data of the second and third blocks as shown in the margin. In the second block, we set the value of A to 0 (untreated) for all 20 individuals; in the third block we set the value of A to 1 (treated) for all individuals. In the second and third blocks, we delete the data on the outcome for all individuals, i.e., the variable Y is assigned a missing value. As described below, we will use the second block to estimate the standardized mean in the untreated and the third block for the standardized mean in the treated.

Next we use the 3-block dataset to fit a regression model for the mean outcome given treatment A and the confounder L. We add a product term $A \times L$ to make the model saturated. Note that only the rows in the first block of the dataset (the actual data) will contribute to the estimation of the parameters of the model because the outcome is missing for all rows in the second and third blocks.

The next step is to use the parameter estimates from the first block to predict the outcome values for all rows in the second and third blocks. (That is, we combine the values of the columns L and A with the regression estimates to impute the missing value for the outcome Y.) The predicted outcome values for the second block are the mean estimates for each combination of values of L and $A = 0$, and the predicted values for the third block are the mean estimates

for each combinations of values of L and $A = 1$.

Finally, we compute the average of all predicted values in the second block. Because 60% of rows have value $L = 1$ and 40% have value $L = 0$, this average gives more weight to rows with $L = 1$. That is, the average of all predicted values in the second block is precisely the standardized mean outcome in the untreated. We are done. To estimate the standardized mean outcome in the treated, we compute the average of all predicted values in the third block.

CODE: Program 13.2

The above procedure yields exactly the same estimates of the standardized means (0.5 for both of them) as the direct calculation in Section 2.3. Both approaches are completely nonparametric. In this chapter we did not directly estimate the distribution of L, but rather average over the observed values of L, i.e., its empirical distribution.

The use of the empirical distribution for standardizing is the way to go in more realistic examples, like our smoking cessation study, with high-dimensional L. The procedure for our study is analogous to the one described above for the data in Table 2.2. We add the second and third blocks to the dataset, fit the regression model for $\mathrm{E}[Y|A = a, C = 0, L = l]$ as described in the previous section, and generate the predicted values. The average predicted value in the second block—the standardized mean in the untreated—was 1.66, and the average predicted value in the third block—the standardized mean in the treated—was 5.18. Therefore, our estimate of the causal effect $\mathrm{E}[Y^{a=1,c=0}] - \mathrm{E}[Y^{a=0,c=0}]$ was $5.18 - 1.66 = 3.5$ kg. To obtain a 95% confidence interval for this estimate we used a statistical technique known as bootstrapping (see Technical Point 13.1). In summary, we estimated that quitting smoking increases body weight by 3.5 kg (95% confidence interval: 2.6, 4.5).

CODE: Program 13.3

CODE: Program 13.4

13.4 IP weighting or standardization?

We have now described two ways in which modeling can be used to estimate the average causal effect of a treatment: IP weighting (previous chapter) and standardization (this chapter). In our smoking cessation example, both yielded almost exactly the same effect estimate. Indeed Technical Point 2.3 proved that the standardized mean equals the IP weighted mean.

Why are we then bothering to estimate the standardized mean in this chapter if we had already estimated the IP weighted mean in the previous chapter? It turns out that the IP weighted and the standardized mean are only exactly equal when no models are used to estimate them. Otherwise they are expected to differ. To see this, consider the quantities that need to be modeled to implement either IP weighting or standardization. IP weighting models $\Pr[A = a, C = 0|L]$, which we estimated in the previous chapter by fitting parametric logistic regression models for $\Pr[A = a|L]$ and $\Pr[C = 0|A = a, L]$. Standardization models the conditional means $\mathrm{E}[Y|A = a, C = 0, L = l]$, which we estimated in this chapter using a parametric linear regression model.

In practice some degree of misspecification is inescapable in all models, and model misspecification will introduce some bias. But the misspecification of the treatment model (IP weighting) and the outcome model (standardization) will not generally result in the same magnitude and direction of bias in the effect estimate. Therefore the IP weighted estimate will generally differ from the standardized estimate because unavoidable model misspecification will affect the point estimates differently. Large differences between the IP weighted and standardized estimate will alert us to the presence of serious model misspec-

Technical Point 13.1

Bootstrapping. Effect estimates are presented with measures of random variability, such as the standard error or the 95% confidence interval, which is a function of the standard error. (We discussed the foundations of variability in Chapter 10.) Because of the computational difficulty to obtain exact estimates, in practice standard error estimates are often based on large-sample approximations, which rely on asymptotic considerations. However, sometimes even large-sample approximations are too complicated to be calculated. The bootstrap is an alternative method for estimating standard errors and computing 95% confidence intervals. The simplest version of the bootstrap, which we used to compute the 95% confidence interval around the effect estimate of smoking cessation, is sketched below.

Take the study population of 1629 individuals. Sample with replacement 1629 individuals from the study population, so that some of the original individuals may appear more than once while others may not be included at all. This new sample of size 1629 is referred to as a "bootstrap sample." Compute the effect of interest in the bootstrap sample (e.g., by using standardization as described in the main text). Now create a second bootstrap sample by again sampling with replacement 1629 individuals. Compute the effect of interest in the second bootstrap sample using the same method as for the first bootstrap sample. By chance, the first and second bootstrap sample will generally include a different number of copies of each individual, and therefore will result in different effect estimates. Repeat the procedure in a large number (say, 1000) of bootstrap samples. It turns out that the standard deviation of the 1000 effect estimates in the bootstrap samples consistently estimates the standard error of the effect estimate in the study population. The 95% confidence interval is then computed by using the usual normal approximation: ±1.96 times the estimate of the standard error. See, for example, Wasserman (2004) for an introduction to the statistical theory underlying the bootstrap.

We used this bootstrap method with 1000 bootstrap samples to obtain the 95% confidence interval described in the main text for the standardized mean difference. Though the bootstrap is a simple method, it can be computationally intensive for very large datasets. It is therefore common to see published estimates that are based on only 200-500 bootstrap samples (which would have resulted in an almost identical confidence interval in our example). Finally, note that the bootstrap is a general method for large samples. We could have also used it to compute a 95% confidence interval for the IP weighted estimates from marginal structural models in the previous chapter.

ification in at least one of the estimates. Small differences do not guarantee absence of serious model misspecification, but will be reassuring—though logically possible, it is unlikely that badly misspecified models resulting in bias of similar magnitude and direction for both methods.

In our smoking cessation example, both the IP weighted and the standardized estimates are similar. After rounding to one decimal place, the estimated weight gain due to smoking cessation was 3.5 kg regardless of whether we fit a model for treatment A (IP weighting) or for the outcome Y (standardization). In neither case we fit a model for the confounders L, as we did not need the distribution of the confounders to obtain the IP weighted estimate, and we just used the empirical distribution of L (a nonparametric method) to compute the standardized estimate.

Both IP weighting and standardization are estimators of the g-formula, a general method for causal inference first described in 1986. (Part III provides a definition of the g-formula in settings with time-varying treatments.) We say that standardization is a *plug-in g-formula* estimator because it simply replaces the conditional mean outcome in the g-formula by its estimates. When, like in this chapter, those estimates come from parametric models, we refer to the method as the *parametric g-formula*. Because here we were only interested in the average causal effect, we only had to estimate the conditional mean outcome. More generally, the parametric g-formula uses estimates of any functions of the distribution of the outcome (e.g., functionals like the probability density function or PDF) within levels of A and L to compute its standardized

Fine Point 13.2

A doubly robust estimator. The previous chapter describes IP weighting, a method that requires a correct model for treatment A conditional on the confounders L. This chapter describes standardization, a method that requires a correct model for the outcome Y conditional on treatment A and the confounders L. How about a method that requires a correct model for *either* treatment A *or* outcome Y? That is precisely what doubly robust estimation does. Under the usual identifiability assumptions, a doubly robust estimator consistently estimates the causal effect if at least one of the two models is correct (and one need not know which of the two models is correct). That is, doubly robust estimators give us two chances to get it right.

There are many types of doubly robust estimators. Here we describe a doubly robust estimator proposed by Bang and Robins (2005) for the average causal effect of a dichotomous treatment A on an outcome Y. For simplicity, we consider a setting without censoring.

To obtain a doubly robust estimate of the average causal effect, first estimate the IP weight $W^A = 1/f(A|L)$ as described in the previous chapter. Then fit an outcome regression model like the one described in this chapter—a generalized linear model with a canonical link—for $\mathrm{E}[Y|A = a, L = l, R]$ that adds the covariate R, where $R = W^A$ if $A = 1$ and $R = -W^A$ if $A = 0$. Finally, use the predicted values from the outcome model to obtain the standardized mean outcomes under $A = 1$ and $A = 0$. The difference of the standardized mean outcomes is now doubly robust. That is, under exchangeability and positivity given L, this estimator consistently estimates the average causal effect if either the model for the treatment or the model for the outcome is correct, without knowing which of the two models is the correct one.

Robins (1986) described the generalization of standardization to time-varying treatments and confounders, and named it the *g-computation algorithm formula*. Because this name is very long, some authors have abbreviated to *g-formula* and others to *g-computation*. Even though g-formula and g-computation are synonyms, this book uses only the former term because the latter term is frequently confused with g-estimation, a different method described in Chapter 14.

value. In the absence of time-varying confounders (see Part III), the parametric g-formula does not require parametric modeling of the distribution of the confounders.

Often there is no need to choose between IP weighting and the parametric g-formula. When both methods can be used to estimate a causal effect, just use both methods. Also, whenever possible, use doubly robust methods (see Fine Point 13.2 and Technical Point 13.2) that combine models for treatment and for outcome in the same approach.

Finally, note that we used the parametric g-formula to estimate the average causal effect in the entire population of interest. Had we been interested in the average causal effect in a particular subset of the population, we could have restricted our calculations to that subset. For example, if we had been interested in potential effect modification by sex, we would have estimated the standardized means in men and women separately. Both IP weighting and the parametric g-formula can be used to estimate average causal effects in either the entire population or a subset of it.

13.5 How seriously do we take our estimates?

We spent Part I of this book reviewing the definition of average causal effect, the assumptions required to estimate it, and many potential biases. The discussion was purely conceptual, the data examples hypersimplistic. A key message was that a causal analysis of observational data is sharper when explicitly emulating a (hypothetical) randomized experiment—the target trial.

The analyses in this and the previous chapter are our first attempts at estimating causal effects from real data. Using both IP weighting and the parametric g-formula we estimated that the mean weight gain would have

been 5.2 kg if everybody had quit smoking compared with 1.7 kg if nobody had quit smoking. Both methods estimated that quitting smoking increases weight by 3.5 kg (95% confidence interval: 2.5, 4.5) on average in this particular population. In the next chapters we will see that similar estimates are obtained when using g-estimation, outcome regression, and propensity scores.

The compatibility of estimates across methods is reassuring because each method's estimate is based on different modeling assumptions. However, observational effect estimates are always open to serious criticism. Even if we do not wish to transport our effect estimate to other populations (Chapter 4) and even if there is no interference between individuals, the validity of our estimates for the target population requires many conditions. We classify these conditions in three groups.

First, the identifiability conditions of exchangeability, positivity, and consistency (Chapter 3) need to hold for the observational study to resemble the target trial. The quitters and the non-quitters need to be exchangeable conditional on the 9 measured covariates L (see Fine Point 14.2). Unmeasured confounding (Chapter 7) or selection bias (Chapter 8, Fine Point 12.2) would prevent conditional exchangeability. Positivity requires that the distribution of the covariates L in the quitters fully overlaps with that in the non-quitters. Fine Point 13.1 discussed the different impact of deviations from positivity for nonparametric IP weighting and standardization. Regarding consistency, note that there are multiple versions of both quitting smoking (e.g., quitting progressively, quitting abruptly) and not quitting smoking (e.g., increasing intensity of smoking by 2 cigarettes per day, reducing intensity but not to zero). Our effect estimate corresponds to a somewhat vague hypothetical intervention in the target population that randomly assigns these versions of treatment with the same frequency as they actually have in the study population. Other hypothetical interventions might result in a different effect estimate.

Methods based on outcome regression (including douby robust methods) can be used in the absence of positivity, under the assumption that the outcome model is correctly specified to extrapolate beyond the data. See Fine Point 13.1.

Second, all variables used in the analysis need to be correctly measured. Measurement error in the treatment A, the outcome Y, or the confounders L will generally result in bias (Chapter 9).

Third, all models used in the analysis need to be correctly specified (Chapter 11). Suppose that the correct functional form for the continuous covariate age in the treatment model is not the parabolic curve we used but rather a curve represented by a complex polynomial. Then, even if all the confounders had been correctly measured and included in L, IP weighting would not fully adjust for confounding. Model misspecification has a similar effect as measurement error in the confounders.

This dependence of the numerical estimate on the exact interventions is important when the estimates are used to guide decision making, e.g., in public policy or clinical medicine (Hernán 2016).

The validity of our causal inferences requires the following conditions

- exchangeability
- positivity
- consistency
- no measurement error
- no model misspecification

Ensuring that each of these conditions hold, at least approximately, is the investigator's most important task. If these conditions could be guaranteed to hold, then the data analysis would be trivial. The problem is, of course, that one cannot ever expect that any of these conditions will hold perfectly. Unmeasured confounders, nonoverlapping confounder distributions, ill-defined interventions, mismeasured variables, and misspecified models will typically lurk behind our estimates. Some of these problems may be addressed empirically, but others will remain a matter of subject-matter judgement, and therefore open to criticism that cannot be refuted by our data. For example, we can propose different model specifications but we cannot adjust for variables that were not measured.

Causal inferences rely on the above conditions, which are heroic and not empirically testable. We replace the lack of data on the distribution of the counterfactual outcomes by the assumption that the above conditions are approximately met. The more our study deviates from those conditions, the

more biased our effect estimate may be. Therefore a healthy skepticism of causal inferences drawn from observational data is necessary. In fact, a key step towards less casual causal inferences is the realization that the discussion should primarily revolve around each of the above assumptions. We only take our effect estimates as seriously as we take the conditions that are needed to endow them with a causal interpretation.

Technical Point 13.2

The bias of doubly robust estimators. Suppose we have a dichotomous treatment A, an outcome Y, and a vector of measured variables L that satisfy positivity and exchangeability (consistency is assumed). For simplicity we consider estimation of the counterfactual mean outcome under treatment $\mathrm{E}[Y^{a=1}]$ rather than the average causal effect. Then $\mathrm{E}[Y^{a=1}]$ can be written as either $\mathrm{E}[b(L)]$, where $b(L) = \mathrm{E}[Y|A = 1, L]$, or $\mathrm{E}[\frac{AY}{\pi(L)}]$, where $\pi(L) = \Pr[A = 1|L]$. In this chapter, we described a plug-in g-formula estimator $\frac{1}{n}\sum_{i=1}^{n}\hat{b}(L_i)$ that replaces the conditional mean outcome by its estimate from a (say, linear) regression model for $b(L)$ and averages it over all n individuals in the study. In the previous chapter, we described a Horvitz-Thompson IP weighted estimator $\frac{1}{n}\sum_{i=1}^{n}\frac{A_iY_i}{\hat{\pi}(L_i)}$ that replaces the probability of treatment by its estimate from a (say, logistic) regression model for $\pi(L)$ and averages it over the n individuals. The bias of the plug-in g-formula estimator will be large if the estimate $\hat{b}(L)$ is far from $b(L)$, and the bias of the IP weighted estimator will be large if $\hat{\pi}(L)$ is far from $\pi(L)$.

A doubly robust estimator of $\mathrm{E}[Y^{a=1}]$ appropriately combines the estimate $\hat{b}(L)$ from the outcome model and the estimate $\hat{\pi}(L)$ from the treatment model. There are many forms of doubly robust estimators, like the one described in Fine Point 13.2 for the average causal effect. All doubly robust estimators involve a correction of the outcome regression model by a function that involves the treatment model (the first-order influence function), which can also be viewed as a correction of the Horvitz-Thompson estimator by a function that involves the outcome regression model. For example, consider the following doubly robust estimator of $\mathrm{E}[Y^{a=1}]$:

$$\widehat{\mathrm{E}}[Y^{a=1}]_{DR} = \frac{1}{n}\sum_{i=1}^{n}\left[\hat{b}(L_i) + \frac{A_i}{\hat{\pi}(L_i)}\left(Y_i - \hat{b}(L_i)\right)\right],$$

which can also be written as $\frac{1}{n}\sum_{i=1}^{n}\left[\frac{A_iY_i}{\hat{\pi}(L_i)} - \left(\frac{A_i}{\hat{\pi}(L_i)} - 1\right)\hat{b}(L_i)\right]$.

Under exchangeability and positivity, the bias of this doubly robust estimator of $\mathrm{E}[Y^{a=1}]$ is small if either the estimate $\hat{b}(L)$ is close to $b(L)$ or the estimate $\hat{\pi}(L)$ is close to $\pi(L)$. Specifically, the bias $\mathrm{E}\left[\widehat{\mathrm{E}}[Y^{a=1}]_{DR} - \mathrm{E}[Y^{a=1}]\right]$ of $\widehat{\mathrm{E}}[Y^{a=1}]_{DR}$ in large samples is

$$\mathrm{E}\left[\pi(L)\left(\frac{1}{\pi(L)} - \frac{1}{\pi^*(L)}\right)(b(L) - b^*(L))\right],$$

where $\pi^*(l)$ and $b^*(l)$ are the probability limits of $\hat{\pi}(l)$ and $\hat{b}(l)$ and $\pi^*(l) = \pi(l)$ when the treatment model is correct and $b^*(l) = b(l)$ when the outcome model is correct. Thus the large sample (i.e., asymptotic) bias is zero when either the outcome model or the treatment model is correct (and we do not need to know which one). Of course, one does not expect any parametric model to be correctly specified if the vector L is very high-dimensional and thus even the bias of our doubly robust estimator may be large.

However, all doubly robust estimators have the property that the bias depends on the product of the error $\frac{1}{\pi(l)} - \frac{1}{\hat{\pi}(l)}$ in the estimation of $\frac{1}{\pi(l)}$ with the error $b(l) - \hat{b}(l)$ in the estimation of $b(l)$. As we discuss in Chapter 18, this property—which is known as second-order bias—allows us to construct doubly-robust estimators of $\mathrm{E}[Y^{a=1}]$ that may have small bias by estimating $\pi(l)$ and $b(l)$ with machine learning estimators rather than with standard parametric models. This is because, in high-dimensional settings in which large amounts of data are available, machine learning estimators based on complex algorithms, produce more accurate estimators of $\pi(l)$ and $b(l)$ than standard parametric models which have a small number of parameters compared to the sample size.

Chapter 14
G-ESTIMATION OF STRUCTURAL NESTED MODELS

In the previous two chapters, we described IP weighting and standardization to estimate the average causal effect of smoking cessation on body weight gain. In this chapter we describe a third method to estimate the average causal effect: g-estimation. We use the same observational NHEFS data and provide simple computer code to conduct the analyses.

IP weighting, standardization, and g-estimation are often collectively referred to as *g*-methods because they are designed for application to *g*eneralized treatment contrasts involving treatments that vary over time. The application of g-methods to treatments that do not vary over time in Part II of this book may then be overkill since there are alternative, simpler approaches. However, by presenting g-methods in a relatively simple setting, we can focus on their main features while avoiding the more complex issues described in Part III.

IP weighting and standardization were introduced in Part I (Chapter 2) and then described with models in Part II (Chapters 12 and 13, respectively). In contrast, we have waited until Part II to describe g-estimation. There is a reason for that: describing g-estimation is facilitated by the specification of a structural model, even if the model is saturated. Models whose parameters are estimated via g-estimation are known as *structural nested models*. The three g-methods are based on different modeling assumptions.

14.1 The causal question revisited

As in previous chapters, we restricted the analysis to NHEFS individuals with known sex, age, race, weight, height, education, alcohol use and intensity of smoking at the baseline (1971-75) and follow-up (1982) visits, and who answered the medical history questionnaire at baseline.

In the last two chapters we have applied IP weighting and standardization to estimate the average causal effect of smoking cessation (the treatment) A on weight gain (the outcome) Y. To do so, we used data from 1566 cigarette smokers aged 25-74 years who were classified as treated $A = 1$ if they quit smoking, and as untreated $A = 0$ otherwise. We assumed that exchangeability of the treated and the untreated was achieved conditional on the L variables: sex, age, race, education, intensity and duration of smoking, physical activity in daily life, recreational exercise, and weight. We defined the average causal effect on the difference scale as $\mathrm{E}[Y^{a=1,c=0}] - \mathrm{E}[Y^{a=0,c=0}]$, that is, the difference in mean weight that would have been observed if everybody had been treated and uncensored compared with untreated and uncensored.

The quantity $\mathrm{E}[Y^{a=1,c=0}] - \mathrm{E}[Y^{a=0,c=0}]$ measures the average causal effect in the entire population. But sometimes one can be interested in the average causal effect in a subset of the population. For example, one may want to estimate the average causal effect in women—$\mathrm{E}[Y^{a=1,c=0}|woman] - \mathrm{E}[Y^{a=0,c=0}|woman]$—, in individuals aged 45, in those with low educational level, etc. To estimate the effect in a subset of the population one can use marginal structural models with product terms (see Chapter 12) or apply standardization to that subset only (Chapter 13).

Suppose that the investigator is interested in estimating the causal effect of smoking cessation A on weight gain Y in each of the strata defined by combinations of values of the variables L. In our example, there are many such strata. One of them is the stratum {non-quitter, male, white, age 26, college dropout, 15 cigarettes/day, 12 years of smoking habit, moderate exercise, very active, weight 112 kg}. As described in Chapter 4, investigators could partition

the study population into mutually exclusive subsets or non-overlapping strata, each of them defined by a particular combination of values l of the variables in L, and then estimate the average causal effect in each of the strata. In Section 12.5 we explain that an alternative approach is to add all variables L, together with product terms between each component of L and treatment A, to the marginal structural model. Then the stabilized weights $SW^A(L)$ equal 1 and no IP weighting is necessary because the (unweighted) outcome regression model, if correctly specified, fully adjusts for all confounding by L (see Chapter 15).

In this chapter we will use g-estimation to estimate the average causal effect of smoking cessation A on weight gain Y in each strata defined by the covariates L. This conditional effect is represented by $\mathrm{E}[Y^{a,c=0}|L] - \mathrm{E}[Y^{a=0,c=0}|L]$. Before describing g-estimation, we will present structural nested models and rank preservation, and, in the next section, articulate the condition of exchangeability given L in a new way.

14.2 Exchangeability revisited

You may find the first paragraph of this section repetitious and unnecessary given our previous discussions of conditional exchangeability. If that is the case, we could not be happier.

As a reminder (see Chapter 2), in our example, conditional exchangeability implies that, in any subset of the study population in which all individuals have the same values of L, those who did not quit smoking ($A = 0$) would have had the same mean weight gain as those who did quit smoking ($A = 1$) if they had not quit, and vice versa. In other words, conditional exchangeability means that the outcome distribution in the treated and the untreated would be the same if both groups had received the same treatment level. When the distribution of the outcomes Y^a under treatment level a is the same for the treated and the untreated, each of the counterfactual outcomes Y^a is independent of the actual treatment level A, within levels of the covariates, or $Y^a \perp\!\!\!\perp A|L$ for both $a = 1$ and $a = 0$.

Take the counterfactual outcome under no treatment $Y^{a=0}$. When conditional exchangeability holds, knowing the value of $Y^{a=0}$ does not help differentiate between quitters and nonquitters with a particular value of L. That is, the conditional (on L) probability of being a quitter is the same for all values of the counterfactual outcome $Y^{a=0}$. Mathematically, we write

$$\Pr[A = 1|Y^{a=0}, L] = \Pr[A = 1|L]$$

which is an equivalent definition of conditional exchangeability for a dichotomous treatment A.

Expressing conditional exchangeability in terms of the conditional probability of treatment will be helpful when we describe g-estimation later in this chapter. Specifically, suppose we propose the following parametric logistic model for the probability of treatment

$$\operatorname{logit}\Pr[A = 1|Y^{a=0}, L] = \alpha_0 + \alpha_1 Y^{a=0} + \alpha_2 L$$

For simplicity, in this book we do not distinguish between vector and scalar parameters. This is an abuse of notation, but we believe it does not create any confusion.

where α_2 is a vector of parameters, one for each component of L. If L has p components $L_1, ...L_p$ then $\alpha_2 L = \sum_{j=1}^{p} \alpha_{2j} L_j$. This model is the same one we used to estimate the denominator of the IP weights in Chapter 12, except that this model also includes the counterfactual outcome $Y^{a=0}$ as a covariate.

Of course, we can never fit this model to a real data set because we do not know the value of the variable $Y^{a=0}$ for all individuals. But suppose for

a second that we had data on $Y^{a=0}$ for all individuals, and that we fit the above logistic model. If there is conditional exchangeability and the model is correctly specified, what estimate would you expect for the parameter α_1? Pause and think about it before going on (the response can be found near the end of this paragraph) because we will be estimating the parameter α_1 when implementing g-estimation. If you have already guessed what its value should be, you have already understood half of g-estimation. Yes, the expected value of the estimate of α_1 is zero because $Y^{a=0}$ does not predict A conditional on L. We now introduce the other half of g-estimation: the structural model.

14.3 Structural nested mean models

We are interested in estimating the average causal effect of treatment A within levels of L, that is, $\mathrm{E}[Y^{a=1}|L] - \mathrm{E}[Y^{a=0}|L]$. (For simplicity, suppose there is no censoring until later in this section.) Note that we can also represent this effect by $\mathrm{E}[Y^{a=1} - Y^{a=0}|L]$ because the difference of the means is equal to the mean of the differences. If there were no effect-measure modification by L, these differences would be constant across strata, i.e., $\mathrm{E}[Y^{a=1} - Y^{a=0}|L] = \beta_1$ where β_1 would be the average causal effect in each stratum and also in the entire population. Our structural model for the conditional causal effect would be $\mathrm{E}[Y^a - Y^{a=0}|L] = \beta_1 a$.

More generally, there may be effect modification by L. For example, the causal effect of smoking cessation may be greater among heavy smokers than among light smokers. To allow for the causal effect to depend on L we can add a product term to the structural model, i.e., $\mathrm{E}[Y^a - Y^{a=0}|L] = \beta_1 a + \beta_2 aL$, where β_2 is a vector of parameters. Under conditional exchangeability $Y^a \perp\!\!\!\perp A|L$, the conditional effect will be the same in the treated and in the untreated because the treated and the untreated are, on average, the same type of people within levels of L. Thus, under exchangeability, the structural model can also be written as

$$\mathrm{E}[Y^a - Y^{a=0}|A = a, L] = \beta_1 a + \beta_2 aL$$

Robins (1991) first described the class of structural nested models. These models are "nested" when the treatment is time-varying. See Part III for an explanation.

which is referred to as a *structural nested mean model*. The parameters β_1 and β_2 (again, a vector), which are estimated by g-estimation, quantify the average causal effect of smoking cessation A on Y within levels of A and L.

In Chapter 13 we considered parametric models for the mean outcome Y that, like structural nested models, were also conditional on treatment A and covariates L. Those outcome models were the basis for standardization when estimating the parametric g-formula. In contrast with those parametric models, structural nested models are semiparametric because they are agnostic about both the intercept and the main effect of L—that is, there is no parameter β_0 and no parameter β_3 for a term $\beta_3 L$. As a result of leaving these parameters unspecified, structural nested models make fewer assumptions and can be more robust to model misspecification than the parametric g-formula. See Fine Point 14.1 for a description of the relation between structural nested models and the marginal structural models of Chapter 12.

In the presence of censoring, our causal effect of interest is not $\mathrm{E}[Y^{a=1} - Y^{a=0}|A, L]$ but $\mathrm{E}[Y^{a=1,c=0} - Y^{a=0,c=0}|A, L]$, that is, the average causal effect if everybody had remained uncensored. Estimating this difference requires adjustment for both confounding and selection bias (due to censoring $C = 1$) for the effect of treatment A. As described in the previous two chapters, IP

Fine Point 14.1

Relation between marginal structural models and structural nested models. Consider a *marginal structural mean model* for the average outcome under treatment level a within levels of the dichotomous covariate V, a component of L,

$$\mathrm{E}[Y^a|V] = \beta_0 + \beta_1 a + \beta_2 aV + \beta_3 V$$

The sum $\beta_1 + \beta_2 v$ is the average causal effect $\mathrm{E}[Y^{a=1} - Y^{a=0}|V = v]$ in the stratum $V = v$, and the sum $\beta_0 + \beta_3 v$ is the mean counterfactual outcome under no treatment $\mathrm{E}[Y^{a=0}|V = v]$ in the stratum $V = v$. Suppose the only inferential goal is the average causal effect $\beta_1 + \beta_2 v$, i.e., we are not interested in estimating $\beta_0 + \beta_3 v = \mathrm{E}[Y^{a=0}|V = v]$. Then we would write the model as $\mathrm{E}[Y^a|V] = \mathrm{E}[Y^{a=0}|V] + \beta_1 a + \beta_2 aV$ or, equivalently, as

$$\mathrm{E}[Y^a - Y^{a=0}|V] = \beta_1 a + \beta_2 aV$$

which is referred to as a *semiparametric marginal structural mean model* because, unlike the marginal structural models in Chapter 12, it leaves the mean counterfactual outcomes under no treatment $\mathrm{E}[Y^{a=0}|V]$ completely unspecified.

To estimate the parameters of this semiparametric marginal structural model in the absence of censoring, we first create a pseudo-population with IP weights $SW^A(V) = f(A|V)/f(A|L)$. In this pseudo-population there is only confounding by V and therefore the semiparametric marginal structural model is a structural nested model whose parameters are estimated by g-estimation with V substituted by L and each individual's contribution weighted by $SW^A(V)$. Therefore, in settings without time-varying treatments, structural nested models are identical to semiparametric marginal structural models that leave the mean counterfactual outcomes under no treatment unspecified. Because marginal structural mean models include more parameters than structural nested mean models, the latter may be more robust to model misspecification.

Consider the special case of a semiparametric marginal structural mean model within levels of *all* variables in L, rather than only a subset V so that $SW^A(V)$ are equal to 1 for all individuals. That is, let us consider the model $\mathrm{E}[Y^a - Y^{a=0}|L] = \beta_1 a + \beta_2 aL$, which we refer to as a faux semiparametric marginal structural model. Under conditional exchangeability, this model is the structural nested mean model we use in this chapter.

Technically, IP weighting is not necessary to adjust for selection bias when using g-estimation with a time-fixed treatment that does not affect any variable in L, and an outcome measured at a single time point. That is, if as we have been assuming $Y^a \perp\!\!\!\perp (A, C)\,|L$, we can apply g-estimation to the uncensored subjects without having to IP weight.

weighting and standardization can be used to adjust for these two biases. G-estimation, on the other hand, can only be used to adjust for confounding, not selection bias.

Thus, when using g-estimation, one first needs to adjust for selection bias due to censoring by IP weighting. In practice, this means that we first estimate nonstabilized IP weights for censoring to create a pseudo-population in which nobody is censored, and then apply g-estimation to the pseudo-population. In our smoking cessation example, we will use the nonstabilized IP weights $W^C = 1/\Pr[C = 0|L, A]$ that we estimated in Chapter 12. Again we assume that the vector of variables L is sufficient to adjust for both confounding and selection bias.

All the g-estimation analyses described in this chapter incorporate IP weights to adjust for the potential selection bias due to censoring. Under the assumption that the censored and the uncensored are exchangeable conditional on the measured covariates L, the structural nested mean model $\mathrm{E}[Y^a - Y^{a=0}|A = a, L] = \beta_1 a + \beta_2 aL$, when applied to the pseudo-population created by the IP weights W^C, is really a structural model in the absence of censoring:

$$\mathrm{E}[Y^{a,c=0} - Y^{a=0,c=0}|A = a, L] = \beta_1 a + \beta_2 aL$$

For simplicity, we will omit the superscript $c = 0$ hereafter in this chapter.

Technical Point 14.1

Multiplicative structural nested mean models. In the text we only consider additive structural nested mean models. When the outcome variable Y can only take positive values, a multiplicative structural nested mean model is preferred. An example of a multiplicative structural nested mean model is

$$\log\left(\frac{\mathrm{E}[Y^a|A=a,L]}{\mathrm{E}[Y^{a=0}|A=a,L]}\right)=\beta_1 a+\beta_2 aL$$

which can be fit by g-estimation with $H(\psi^\dagger)$ defined to be $Y\exp\left[-\psi_1^\dagger a-\psi_2^\dagger aL\right]$.

The above multiplicative model can also be used for binary (0, 1) outcome variables as long as the probability of $Y=1$ is small in all strata of L. Otherwise, the model might predict probabilities greater than 1. If the probability is not small, one can consider a structural nested logistic model for a dichotomous outcome Y such as

$$\operatorname{logit}\Pr[Y^a=1|A=a,L]-\operatorname{logit}\Pr[Y^{a=0}=1|A=a,L]=\beta_1 a+\beta_2 aL$$

Unfortunately, structural nested logistic models do not generalize easily to time-varying treatments and their parameters cannot be estimated using the g-estimation algorithm described in the text. For details, see Robins (1999) and Tchetgen Tchetgen and Rotnitzky (2011).

Unlike IP weighting, g-estimation cannot be easily extended to estimate the parameters of structural logistic models for dichotomous outcomes. See Technical Point 14.1.

In this chapter we will use g-estimation of a structural nested mean model to estimate the effect of the dichotomous treatment "smoking cessation", but structural nested models can also be used for continuous treatment variables—like "change in smoking intensity" (see Chapter 12). For continuous variables, the model needs to specify the dose-response function for the effect of treatment A on the mean outcome Y. For example, $\mathrm{E}[Y^a-Y^{a=0}|A=a,L]=\beta_1 a+\beta_2 a^2+\beta_3 aL+\beta_4 a^2 L$, or $\mathrm{E}[Y^a-Y^{a=0}|A=a,L]$ could be a smooth function, e.g., splines, of A and L.

We now turn our attention to the concept of rank preservation, which will help us describe g-estimation of structural nested models.

14.4 Rank preservation

CODE: Program 14.1

In our smoking cessation example, all individuals can be ranked according to the value of their observed outcome Y. Subject 23522 is ranked first with weight gain of 48.5 kg, individual 6928 is ranked second with weight gain 47.5 kg... and individual 23321 is ranked last with weight gain of −41.3 kg. Similarly we could think of ranking all individuals according to the value of their counterfactual outcome under treatment $Y^{a=1}$ if the value of $Y^{a=1}$ were known for all individuals rather than only for those who were actually treated. Suppose for a second that we could actually rank everybody according to $Y^{a=1}$ and also according to $Y^{a=0}$. We would then have two lists of individuals ordered from larger to smaller value of the corresponding counterfactual outcome. If both lists are in identical order we say that there is *rank preservation*.

When the effect of treatment A on the outcome Y is exactly the same, on the additive scale, for all individuals in the study population, we say that *additive rank preservation* holds. For example, if smoking cessation increases everybody's body weight by exactly 3 kg, then the ranking of individuals according to $Y^{a=0}$ would be equal to the ranking according to $Y^{a=1}$, except

that in the latter list all individuals will be 3 kg heavier. A particular case of additive rank preservation occurs when the *sharp null hypothesis* is true (see Chapter 1), i.e., if treatment has no effect on the outcomes of any individual in the study population. For the purposes of structural nested mean models we will care about additive rank preservation within levels of L. This *conditional additive rank preservation* holds if the effect of treatment A on the outcome Y is exactly the same for all individuals with the same values of L.

An example of an (additive conditional) rank-preserving structural model is

$$Y_i^a - Y_i^{a=0} = \psi_1 a + \psi_2 a L_i \quad \text{for all individuals } i$$

where $\psi_1 + \psi_2 l$ is the constant causal effect for all individuals with covariate values $L = l$. That is, for every individual i with $L = l$, the value of $Y_i^{a=1}$ is equal to $Y_i^{a=0} + \psi_1 + \psi_2 l$. An individual's counterfactual outcome under no treatment $Y_i^{a=0}$ is shifted by $\psi_1 + \psi_2 l$ to obtain the value of her counterfactual outcome under treatment.

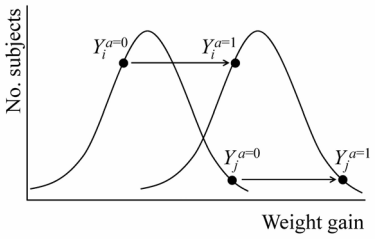


Figure 14.1

Figure 14.1 shows an example of additive rank preservation within the stratum $L = l$. The bell-shaped curves represent the distribution of the counterfactual outcomes $Y^{a=0}$ (left curve) and $Y^{a=1}$ (right curve). The two dots in the upper part of the figure represent the values of the two counterfactual outcomes for individual i, and the two dots in the lower part represent the values of the two counterfactual outcomes for individual j. The arrows represent the shifts from $Y^{a=0}$ to $Y^{a=1}$, which are equal to $\psi_1 + \psi_2 l$ for all individuals in this stratum. Figure 14.2 shows an example of rank preservation within another stratum $L = l'$. The distribution of the counterfactual outcomes is different from that in stratum $L = l$. For example, the mean of $Y^{a=0}$ in Figure 14.1 is to the left of the mean of $Y^{a=0}$ in Figure 14.2, which means that, on average, individuals in stratum $L = l$ have a smaller weight gain under no smoking cessation than individuals in stratum $L = l'$. The shift from $Y^{a=0}$ to $Y^{a=1}$ is $\psi_1 + \psi_2 l'$ for all individuals with $L = l'$, as shown for individuals p and q.

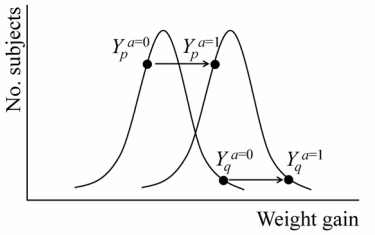


Figure 14.2

For most treatments and outcomes, the individual causal effect is not expected to be constant—not even approximately constant—across individuals with the same covariate values, and thus (additive conditional) rank preservation is scientifically implausible. In our example we do not expect that smoking cessation affects equally the body weight of all individuals with the same values of L. Some people are—genetically or otherwise—more susceptible to the effects of smoking cessation than others, even within levels of the covariates L. The individual causal effect of smoking cessation will vary across people: after quitting smoking some individuals will gain a lot of weight, some will gain little, and others may even lose some weight. Reality may look more like the situation depicted in Figure 14.3, in which the shift from $Y^{a=0}$ to $Y^{a=1}$ varies across individuals with the same covariate values, and even ranks are not preserved since the outcome for individual i is less than that for individual j when $a = 0$ but not when $a = 1$.

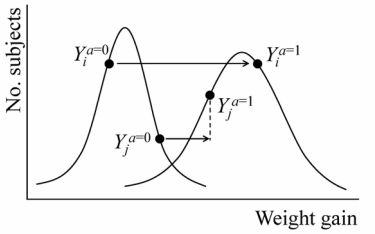


Figure 14.3

Because of the implausibility of rank preservation, one should not generally use methods for causal inference that rely on it. In fact none of the methods we consider in this book require rank preservation. For example, the marginal structural mean models from Chapter 12 are models for average causal effects, not for individual causal effects, and thus they do not assume rank preservation. The estimated average causal effect of smoking cessation on weight gain was 3.5 kg (95% confidence interval: 2.5, 4.5). This average effect is agnostic as to whether rank preservation of individual causal effects holds. Similarly, the structural nested mean model in the previous section made no assumptions about rank preservation.

A structural nested mean model is well defined in the absence of rank preservation. For example, one could propose a model for the setting depicted in Figure 14.3 to estimate the average causal effect within strata of L. Such average causal effect will generally differ from the individual causal effects.

The additive rank-preserving model in this section makes a much stronger assumption than non-rank-preserving models: the assumption of constant treatment effect for all individuals with the same value of L. There is no reason why we would want to use such an unrealistic rank-preserving model in practice. And yet we use it in the next section to introduce g-estimation because g-estimation is easier to understand for rank-preserving models, and because the g-estimation procedure is actually the same for rank-preserving and non-rank-preserving models. Note that the (conditional additive) rank-preserving structural model is a structural mean model—the mean of the individual shifts from $Y^{a=0}$ to $Y^{a=1}$ is equal to each of the individual shifts within levels of L.

14.5 G-estimation

This section links the material in the previous three sections. Suppose the goal is estimating the parameters of the structural nested mean model $\mathrm{E}[Y^a - Y^{a=0}|A = a, L] = \beta_1 a$. For simplicity, we first consider a model with a single parameter β_1. Because the model lacks product terms $\beta_2 aL$, we are effectively assuming that the average causal effect of smoking cessation is constant across strata of L, i.e., no additive effect modification by L.

We also assume that the additive rank-preserving model $Y_i^a - Y_i^{a=0} = \psi_1 a$ is correctly specified for all individuals i. Then the individual causal effect ψ_1 is equal to the average causal effect β_1 in which we are interested. We write the rank-preserving model as $Y^a - Y^{a=0} = \psi_1 a$, without a subscript i to index individuals because the model is the same for all individuals. For reasons that will soon be obvious, we write the model in the equivalent form

$$Y^{a=0} = Y^a - \psi_1 a$$

The first step in g-estimation is linking the model to the observed data. To do so, remember that an individual's observed outcome Y is, by consistency, the counterfactual outcome $Y^{a=1}$ if the person received treatment $A = 1$ or the counterfactual outcome $Y^{a=0}$ if the person received no treatment $A = 0$. Therefore, if we replace the fixed value a in the structural model by each individual's value A—which will be 1 for some and 0 for others—then we can replace the counterfactual outcome Y^a by the individual's observed outcome $Y^A = Y$. The rank-preserving structural model then implies an equation in which each individual's counterfactual outcome $Y^{a=0}$ is a function of his observed data on treatment and outcome and the unknown parameter ψ_1:

$$Y^{a=0} = Y - \psi_1 A$$

If this model were correct and we knew the value of ψ_1 then we could calculate the counterfactual outcome under no treatment $Y^{a=0}$ for each individual in the study population. But we don't know ψ_1. Estimating it is precisely the goal of our analysis.

Let us play a game. Suppose a friend of yours knows the value of ψ_1 but he only tells you that ψ_1 is one of the following: $\psi^\dagger = -20$, $\psi^\dagger = 0$, or $\psi^\dagger = 10$. He challenges you: "Can you identify the true value ψ_1 among the 3 possible values $\psi^\dagger$?" You accept the challenge. For each individual, you compute

$$H(\psi^\dagger) = Y - \psi^\dagger A$$

for each of the three possible values $\psi^\dagger$. The newly created variables $H(-20)$, $H(0)$, and $H(10)$ are candidate counterfactuals. Only one of them is the counterfactual outcome $Y^{a=0}$. More specifically, $H(\psi^\dagger) = Y^{a=0}$ if $\psi^\dagger = \psi_1$. In this game, choosing the correct value of ψ_1 is equivalent to choosing which one of the three candidate counterfactuals $H(\psi^\dagger)$ is the true counterfactual $Y^{a=0} = H(\psi_1)$. Can you think of a way to choose the right $H(\psi^\dagger)$?

Remember from Section 14.2 that the assumption of conditional exchangeability can be expressed as a logistic model for treatment given the counterfactual outcome and the covariates L. When conditional exchangeability holds, the parameter α_1 for the counterfactual outcome should be zero. So we have a simple method to choose the true counterfactual out of the three variables $H(\psi^\dagger)$. We fit three separate logistic models

Rosenbaum (1987) proposed a version of this procedure for non-time-varying treatments.

$$\text{logit}\Pr[A = 1|H(\psi^\dagger), L] = \alpha_0 + \alpha_1 H(\psi^\dagger) + \alpha_2 L,$$

one per each of the three candidates $H(\psi^\dagger)$. The candidate $H(\psi^\dagger)$ with $\alpha_1 = 0$ is the counterfactual $Y^{a=0}$, and the corresponding $\psi^\dagger$ is the true value ψ_1. For example, suppose that $H(\psi^\dagger = 10)$ is unassociated with treatment A given the covariates L. Then our estimate $\hat{\psi}_1$ of ψ_1 is 10. We are done. That was g-estimation.

Important: G-estimation does not test whether conditional exchangeability holds; it assumes that conditional exchangeability holds.

In practice, however, we need to g-estimate the parameter ψ_1 in the absence of a friend who knows the right answer and likes to play games. Therefore we will need to search over all possible values $\psi^\dagger$ until we find the one that results in an $H(\psi^\dagger)$ with $\alpha_1 = 0$. Because not all possible values can be tested—there is an infinite number of values $\psi^\dagger$ in any given interval—we can conduct a fine search over the possible range of $\psi^\dagger$ values (e.g., from -20 to 20 by increments of 0.01). The finer the search, the closer to the true estimate $\hat{\psi}_1$ we will get, but also the greater the computational demands.

CODE: Program 14.2

In our smoking cessation example, we first computed each individual's value of the 31 candidates $H(2.0)$, $H(2.1)$, $H(2.2)$, ...$H(4.9)$, and $H(5.0)$ for values $\psi^\dagger$ between 2.0 and 5.0 by increments of 0.1. We then fit 31 separate logistic models for the probability of smoking cessation. These models were exactly like the one used to estimate the denominator of the IP weights in Chapter 12, except that we added to each model one of the 31 candidates $H(\psi^\dagger)$. The parameter estimate $\hat{\alpha}_1$ for $H(\psi^\dagger)$ was closest to zero for values $H(3.4)$ and $H(3.5)$. A finer search found that the minimum value of $\hat{\alpha}_1$ (which was essentially zero) was for $H(3.446)$. Thus, our g-estimate $\hat{\psi}_1$ of the average causal effect $\psi_1 = \beta_1$ of smoking cessation on weight gain is 3.4 kg.

We calculated the P-value from a Wald test. Any other valid test may be used. For example, we could have used a Score test, which simplifies the calculations (it doesn't require fitting multiple models) and, in large samples, is essentially equivalent to a Wald test.

To compute a 95% confidence interval around our g-estimate of 3.4, we used the P-value for a test of $\alpha_1 = 0$ in the logistic models fit above. As expected, the P-value was 1—it was actually 0.998—for $\psi^\dagger = 3.446$, which is the value $\psi^\dagger$ that results in a candidate $H(\psi^\dagger)$ with a parameter estimate $\hat{\alpha}_1 = 0$. Of the 31 logistic models that we fit for $\psi^\dagger$ values between 2.0 and 5.0, the P-value was greater than 0.05 in all models with $H(\psi^\dagger)$ based on $\psi^\dagger$ values between approximately 2.5 and 4.5. That is, the test did not reject the null hypothesis at the 5% level for the subset of $\psi^\dagger$ values between 2.5 and 4.5. By inverting the test results, we concluded that the limits of the 95% confidence interval around 3.4 are 2.5 and 4.5. Another option to compute the 95% confidence interval is bootstrapping of the g-estimation procedure.

More generally, the 95% confidence interval for a g-estimate is determined by finding the set of values of $\psi^\dagger$ that result in a P-value> 0.05 when testing for $\alpha_1 = 0$. The 95% confidence interval is obtained by inversion of the statistical test for $\alpha_1 = 0$, with the limits of the 95% confidence interval being the limits

Fine Point 14.2

Sensitivity analysis for unmeasured confounding. G-estimation relies on the fact that $\alpha_1 = 0$ *if* conditional exchangeability given L holds. Now consider a setting in which conditional exchangeability does not hold. For example, suppose that the probability of quitting smoking A is lower for individuals whose spouse is a smoker, and that the spouse's smoking status is associated with important determinants of weight gain Y not included in L. That is, there is unmeasured confounding by spouse's smoking status. Because now the variables in L are insufficient to achieve exchangeability of the treated and the untreated, the treatment A and the counterfactual $Y^{a=0}$ are associated conditional on L. That is, $\alpha_1 \neq 0$ and we cannot apply g-estimation as described in the main text.

But g-estimation does not require that $\alpha_1 = 0$. Suppose that, because of unmeasured confounding by the spouse's smoking status, α_1 is expected to be 0.1 rather than 0. Then we can apply g-estimation as described in the text except that we will test whether $\alpha_1 = 0.1$ rather than whether $\alpha_1 = 0$. G-estimation does not require that conditional exchangeability given L holds, but that the magnitude of nonexchangeability—the value of α_1—is known. This property of g-estimation can be used to conduct sensitivity analyses for unmeasured confounding.

If we believe that L may not sufficiently adjust for confounding, then we can repeat our g-estimation analysis under different scenarios of unmeasured confounding, represented by a range of values of α_1, and plot the effect estimates under each of them. Such plot shows how sensitive our effect estimate is to unmeasured confounding of different direction and magnitude. One practical problem for this approach is how to quantify the unmeasured confounding on the α_1 scale, e.g., is 0.1 a lot of unmeasured confounding? Robins, Rotnitzky, and Scharfstein (1999) provide technical details on sensitivity analysis for unmeasured confounding using g-estimation.

In the presence of censoring, the fit of the logistic models is necessarily restricted to uncensored individuals ($C = 0$), and the contribution of each individual is weighted by the estimate of his/her IP weight SW^C. See Technical Point 14.2.

of the set of values $\psi^\dagger$ with P-value> 0.05. In our example, the statistical test was based on a robust variance estimator because of the use of IP weighting to adjust for censoring. Therefore our 95% confidence interval is conservative in large samples, i.e., it will trap the true value *at least* 95% of the time. In large samples, bootstrapping would result in a non-conservative, and thus possibly narrower, 95% confidence interval for the g-estimate.

Back to non-rank-preserving models. The g-estimation algorithm (i.e., the computer code implementing the procedure) for ψ_1 produces a consistent estimate of the parameter β_1 of the mean model, assuming the mean model is correctly specified (that is, if the average treatment effect is equal in all levels of L). This is true regardless of whether the individual treatment effect is constant, that is, regardless of whether the conditional additive rank preservation holds. In other words, the validity of the g-estimation algorithm does not actually require that $H(\beta_1) = Y^{a=0}$ for all individuals, where β_1 is the parameter value in the mean model. Rather, the algorithm only requires that $H(\beta_1)$ and $Y^{a=0}$ have the same conditional mean given L.

Interestingly, the above g-estimation procedure can be readily modified to incorporate a sensitivity analysis for unmeasured confounding, as described in Fine Point 14.2.

14.6 Structural nested models with two or more parameters

We have so far considered a structural nested mean model with a single parameter β_1. The lack of product terms $\beta_2 aL$ implies that we believe that the average causal effect of smoking cessation does not vary across strata of L. The structural nested model will be misspecified—and thus our causal inferences will be wrong—if there is indeed effect modification by some components V of

L but we failed to add a product term $\beta_2 aV$. This is in contrast with the saturated marginal structural model $\mathrm{E}[Y^a] = \beta_0 + \beta_1 a$, which is not misspecified if we fail to add terms $\beta_2 aV$ and $\beta_3 V$ even if there is effect modification by V. Marginal structural models that do not condition on V estimate the average causal effect in the population, whereas those that condition on V estimate the average causal effect within levels of V. Structural nested models estimate, by definition, the average causal effect within levels of the confounders L, not the average causal effect in the population. Omitting product terms in structural nested models when there is effect modification will generally lead to bias due to model misspecification.

As discussed in Chapter 12, a desirable property of marginal structural models is *null preservation*: when the null hypothesis of no average causal effect is true, the model is never misspecified. Structural nested models preserve the null too. In contrast, although the parametric g-formula preserves the null for time-fixed treatments, it loses this property in the time-varying setting (see Part III).

Fortunately, the g-estimation procedure described in the previous section can be generalized to models with product terms. For example, suppose we believe that the average causal effect of smoking cessation depends on the baseline level of smoking intensity V. We may then consider the structural nested mean model $\mathrm{E}[Y^a - Y^{a=0}|A = a, L] = \beta_1 a + \beta_2 aV$ and, for g-estimation purposes, the corresponding rank-preserving model $Y_i^a - Y_i^{a=0} = \psi_1 a + \psi_2 aV_i$. Because the structural model has two parameters, ψ_1 and ψ_2, we also need to include two parameters in the IP weighted logistic model for $\Pr[A = 1|H(\psi^\dagger), L]$ with $\psi^\dagger = \left(\psi_1^\dagger, \psi_2^\dagger\right)$. For example, we could fit the logistic model

$$\operatorname{logit}\Pr[A = 1|H(\psi^\dagger), L] = \alpha_0 + \alpha_1 H(\psi^\dagger) + \alpha_2 H(\psi^\dagger)V + \alpha_3 L$$

and find the combination of values of $\psi_1^\dagger$ and $\psi_2^\dagger$ that result in a $H(\psi^\dagger)$ that is independent of treatment A conditional on the covariates L. That is, we need to search the combination of values $\psi_1^\dagger$ and $\psi_2^\dagger$ that make both α_1 and α_2 equal to zero.

Because the model has two parameters, the search must be conducted over a two-dimensional space. Thus a systematic, brute force search will be more involved than that described in the previous section. Less computationally intensive approaches, known as directed search methods, for approximate searching are available in statistical software. For linear mean models like the one discussed here—but not, for example, for certain survival analysis models—the estimate can be directly calculated using a formula, i.e., the estimator has *closed form* and a search over the possible values of the parameters is not necessary (see Technical Point 14.2 for details). In our smoking cessation example, the g-estimates were $\hat{\psi}_1 = 2.86$ and $\hat{\psi}_2 = 0.03$. The corresponding 95% confidence intervals can be calculated by using the P-value of a joint test for $\alpha_1 = \alpha_2 = 0$ or, more simply, by bootstrapping.

The Nelder-Mead Simplex method is an example of a directed search method.

CODE: Program 14.3

In the more general case, we would consider a model that allows the average causal effect of smoking cessation to vary across *all* strata of the variables in L. For dichotomous variables, the corresponding rank-preserving model $Y_i^a - Y_i^{a=0} = \psi_1 a + a\sum_{j=1}^{p} \psi_{2j} L_{ij}$ has $p + 1$ parameters $\psi_1, \psi_{21,\ldots}\psi_{2p}$, where ψ_{2j} is the parameter corresponding to the product term aL_j and L_j represents one of the p components of L. The average causal effect in the entire study population can then be calculated as $\psi_1 + \frac{1}{n}\sum_i \sum_{j=1}^{p} \psi_{2j} L_{ij}$, where n is the number of individuals in the study. In practice, structural nested models with multiple parameters have rarely been used.

You may argue that structural nested models with multiple parameters may not be necessary. If all variables L are discrete and the study population is large, one could fit separate 1-parameter models to each subset of the population defined by joint levels of the covariates contained in the vector L.

In fact, structural nested models of any type have rarely been used, partly because of the lack of user-friendly software and partly because the extension of these models to survival analysis requires some additional considerations (see Chapter 17). We now review two methods that are arguably the most commonly used approaches to adjust for confounding: outcome regression and propensity scores.

Technical Point 14.2

G-estimation of structural nested mean models. Consider the structural nested model $\mathrm{E}[Y^a - Y^{a=0}|A = a, L] = \beta_1 a$. A consistent estimate of β_1 can be obtained by g-estimation under the assumptions described in the text. Specifically, our estimate of β_1 is the value of $H(\psi^\dagger)$ that minimizes the association between $H(\psi^\dagger)$ and A. When we base our g-estimate on the score test (see, for example, Casella and Berger 2002), this procedure is equivalent to finding the parameter value $\psi^\dagger$ that solves the estimating equation

$$\sum_{i=1}^{n} \mathrm{I}\left[C_i = 0\right] W_i^C H_i(\psi^\dagger) \left(A_i - \mathrm{E}\left[A|L_i\right]\right) = 0$$

where the indicator $\mathrm{I}\left[C_i = 0\right]$ takes value 1 for individual i if $C_i = 0$ and takes value 0 otherwise, and the IP weight W_i^C and the expectation $\mathrm{E}\left[A|L_i\right] = \Pr\left[A = 1|L_i\right]$ are replaced by their estimates. $\mathrm{E}\left[A|L_i\right]$ can be estimated from a logistic model for treatment conditional on the covariates L in which individual i contribution is weighted by W_i^C if $C_i = 0$ and it is zero otherwise. [Because A and L are observed on all individuals, we could also estimate $\mathrm{E}\left[A|L_i\right]$ by an unweighted logistic regression of A on L using all individuals.]

The solution to the equation has a closed form and can therefore be calculated directly, i.e., no search over the parameter space is required. Specifically, using the fact that $H_i(\psi^\dagger) = Y_i - \psi^\dagger A_i$ we obtain that $\hat{\psi}_1$ equals

$$\sum_{i=1}^{n} \mathrm{I}\left[C_i = 0\right] W_i^C Y_i \left(A_i - \mathrm{E}\left[A|L_i\right]\right) / \sum_{i=1}^{n} \mathrm{I}\left[C_i = 0\right] W_i^C A_i \left(A_i - \mathrm{E}\left[A|L_i\right]\right)$$

If ψ is D-dimensional, we multiply the left-hand side of the estimating equation by a D-dimensional vector function of L. The choice of the function affects the statistical efficiency of the estimator, but not its consistency. That is, although all choices of the function will result in valid confidence intervals, the length of the confidence interval will depend on the function. Robins (1994) provided a formal description of structural nested mean models, and derived the function that minimizes confidence interval length.

A natural question is whether we can further increase efficiency by replacing $H_i(\psi^\dagger)$ by a nonlinear function, such as $\left[H_i(\psi^\dagger)\right]^3$, in the above estimating equation and still preserve consistency of the estimate. Nonlinear functions of $H_i(\psi^\dagger)$ cannot be used in our estimating equation for models that, like the structural nested mean models described in this chapter, impose only mean independence conditional on L, i.e., $\mathrm{E}\left[H(\beta_1)|A, L\right] = \mathrm{E}\left[H(\beta_1)|L\right]$, for identification. Nonlinear functions of $H_i(\psi^\dagger)$ can be used for models that impose distributional independence, i.e., $H(\beta_1) \perp\!\!\!\perp A|L$, like structural nested distribution models (not described in this chapter) that map percentiles of the distribution of Y^a given $(A = a, L)$ into percentiles of the distribution of Y^0 given $(A = a, L)$.

The estimator of ψ is consistent only if the models used to estimate $\mathrm{E}\left[A|L\right]$ and $\Pr\left[C = 1|A, L\right]$ are both correct. We can construct a more robust estimator by replacing $H(\psi^\dagger)$ by $H(\psi^\dagger) - \mathrm{E}\left[H(\psi^\dagger)|L\right]$ in the estimating equation, and then estimating the latter conditional expectation by fitting an unweighted linear model for $\mathrm{E}\left[H(\psi^\dagger)|L\right] = \mathrm{E}\left[Y^{a=0}|L\right]$ among the uncensored individuals. If this model is correct then the estimate of ψ solving the modified estimating equation remains consistent even if both the above models for $\mathrm{E}\left[A|L\right]$ and $\Pr\left[C = 1|A, L\right]$ are incorrect. Thus we obtain a consistent estimator of ψ if either (i) the model for $\mathrm{E}\left[H(\psi^\dagger)|L\right]$ or (ii) both models for $\mathrm{E}\left[A|L\right]$ and $\Pr\left[C = 1|A, L\right]$ are correct, without knowing which of (i) or (ii) is correct. We refer to such an estimator as being doubly robust. Robins (2000) described a closed-form of the doubly robust estimator for the linear structural nested mean model.

Chapter 15
OUTCOME REGRESSION AND PROPENSITY SCORES

Outcome regression and various versions of propensity score analyses are the most commonly used parametric methods for causal inference. You may rightly wonder why it took us so long to include a chapter that discusses these methods. So far we have described IP weighting, standardization, and g-estimation—the g-methods. Presenting the most commonly used methods after the least commonly used ones seems an odd choice on our part. Why didn't we start with the simpler and widely used methods based on outcome regression and propensity scores? Because these methods do not work in general.

More precisely, the simpler outcome regression and propensity score methods—as described in a zillion publications that this chapter cannot possibly summarize—work fine in simpler settings, but these methods are not designed to handle the complexities associated with causal inference with time-varying treatments. In Part III we will again discuss g-methods but will say less about conventional outcome regression and propensity score methods. This chapter is devoted to causal methods that are commonly used but have limited applicability for complex longitudinal data.

15.1 Outcome regression

In the last three chapters we have described IP weighting, standardization, and g-estimation to estimate the average causal effect of smoking cessation (the treatment) A on weight gain (the outcome) Y. We also described how to estimate the average causal effect within subsets of the population, either by restricting the analysis to the subset of interest or by adding product terms in marginal structural models (Chapter 12) and structural nested models (Chapter 14). Take structural nested models. These models include parameters for the product terms between treatment A and the variables L, but no parameters for the variables L themselves. This is an attractive property of structural nested models because we are interested in the causal effect of A on Y within levels of L but not in the (noncausal) relation between L and Y. A method—g-estimation of structural nested models—that is agnostic about the functional form of the L-Y relation is protected from bias due to misspecifying this relation.

Reminder: We defined the average causal effect as $\mathrm{E}[Y^{a=1,c=0}] - \mathrm{E}[Y^{a=0,c=0}]$. We assumed that exchangeability of the treated and the untreated was achieved conditional on the L variables sex, age, race, education, intensity and duration of smoking, physical activity in daily life, recreational exercise, and weight.

On the other hand, if we were willing to specify the L-Y association within levels of A, we would consider the structural model

$$\mathrm{E}[Y^{a,c=0}|L] = \beta_0 + \beta_1 a + \beta_2 aL + \beta_3 L$$

where β_2 and β_3 are vector parameters. The average causal effects of smoking cessation A on weight gain Y in each stratum of L are a function of β_1 and β_2, the mean counterfactual outcomes under no treatment in each stratum of L are a function of β_0 and β_3. The parameter β_3 is usually referred as the main effect of L, but the use of the word effect is misleading because β_3 may not have an interpretation as the causal effect of L (there may be confounding for L). The parameter β_3 simply quantifies how the mean of the counterfactual $Y^{a=0,c=0}$ varies as a function of L, as we can see in our structural model. See

In Chapter 12, we referred to this model as a *faux marginal structural model* because it has the form of a marginal structural model but IP weighting is not required to estimate its parameters. The stabilized IP weights $SW^A(L)$ are all equal to 1 because the model is conditional on the entire vector L rather than on a subset V of L.

Fine Point 15.1

Nuisance parameters. Suppose our goal is to estimate the causal parameters $\beta_1$and β_2. If we do so by fitting the outcome regression model $\mathrm{E}[Y^{a,c=0}|L] = \beta_0+\beta_1 a+\beta_2 aL+\beta_3 L$, our estimates of $\beta_1$and β_2 will in general be consistent only if $\beta_0 + \beta_3 L$ correctly models the dependence of the mean $\mathrm{E}[Y^{a=0,c=0}|L]$ on L. We refer to the parameters β_0 and β_3 as *nuisance parameters* because they are not our parameters of primary interest.

On the other hand, if we estimate $\beta_1$and β_2 by g-estimation of the structural nested model $\mathrm{E}[Y^{a,c=0}-Y^{a=0,c=0}|L] = \beta_1 a+\beta_2 aL$, then our estimates of $\beta_1$and β_2 will in general be consistent only if the conditional probability of treatment given L $\Pr[A = 1|L]$ is correct. That is, the parameters of the treatment model such as $\operatorname{logit}\Pr[A = 1|L] = \alpha_0 + \alpha_1 L$ are now the nuisance parameters.

For example, bias would arise in the outcome regression model if a covariate L is modeled with a linear term $\beta_3 L$ when it should actually be linear and quadratic $\beta_3 L+\beta_4 L^2$. Structural nested models are not subject to misspecification of an outcome regression model because the L-Y relation is not specified in the structural model. However, bias would arise when using g-estimation of structural nested models if the L-A relation is misspecified in the treatment model. Symmetrically, outcome regression models are not subject to misspecification of a treatment model. For fixed treatments that do not vary over time, deciding what method to use boils down to deciding which nuisance parameters—those in the outcome model or in the treatment model—we believe can be more accurately estimated. When possible, a better alternative is to use doubly robust methods (see Fine Point 13.2).

Fine Point 15.1 for a discussion of parameters that, like β_0 and β_3, do not have a causal interpretation.

The counterfactual mean outcomes if everybody in stratum l of L had been treated and remained uncensored, $\mathrm{E}[Y^{a=1,c=0}|L = l]$, are equal to the corresponding mean outcomes in the uncensored treated, $\mathrm{E}[Y|A = 1, C = 0, L = l]$, under exchangeability, positivity, and well-defined interventions. And analogously for the untreated. Therefore the parameters of the above structural model can be estimated via ordinary least squares by fitting the *outcome regression* model

$$\mathrm{E}[Y|A, C = 0, L] = \alpha_0 + \alpha_1 A + \alpha_2 AL + \alpha_3 L$$

as described in Section 13.2. Like stratification in Chapter 3, outcome regression adjusts for confounding by estimating the causal effect of treatment in each stratum of L. If the variables L are sufficient to adjust for confounding (and selection bias) and the outcome model is correctly specified, no further adjustment is needed. That is, the parameters α of the regression model equal the parameters β of the structural model.

β_0 and β_3 specify the dependence of $Y^{a=0,c=0}$ on L, which is required when the model is used to estimate (i) the mean counterfactual outcomes and (ii) the conditional (within levels of L) effect on the multiplicative rather than additive scale.

In Section 13.2, outcome regression was an intermediate step towards the estimation of a standardized outcome mean. Here, outcome regression is the end of the procedure. Rather than standardizing the estimates of the conditional means to estimate a marginal mean, we just compare the conditional mean estimates. In Section 13.2, we fit a regression model with only one product term in β_2 (between A and smoking intensity). That is, a model in which we a priori set most product terms equal to zero. Using the same model as in Section 13.2, here we obtained the parameter estimates $\hat{\beta}_1 = 2.6$ and $\hat{\beta}_2 = 0.05$. As an example, the effect estimate $\widehat{\mathrm{E}}[Y|A = 1, C = 0, L]-\widehat{\mathrm{E}}[Y|A = 0, C = 0, L]$ was 2.8 (95% confidence interval: 1.5, 4.1) for those smoking 5 cigarettes/day, and 4.4 (95% confidence interval: 2.8, 6.1) for 40 cigarettes/day. A common approach to outcome regression is to assume that there is no effect modification by any variable in L. Then the model is fit without any product terms and $\hat{\beta}_1$ is an estimate of both the conditional and marginal average causal effects

CODE: Program 15.1

of treatment. In our example, a model without any product terms yielded the estimate 3.5 (95% confidence interval: 2.6, 4.3) kg.

In this chapter we did not need to explain how to fit an outcome regression model because we had already done it in Chapter 13 when estimating the components of the parametric g-formula. It is equally straightforward to use outcome regression for discrete outcomes, e.g., for a dichotomous outcome Y one could fit a logistic model for $\Pr[Y = 1|A = a, C = 0, L]$.

15.2 Propensity scores

When using IP weighting (Chapter 12) and g-estimation (Chapter 14), we estimated the probability of treatment given the covariates L, $\Pr[A = 1|L]$, for each individual. Let us refer to this conditional probability as $\pi(L)$. The value of $\pi(L)$ is close to 0 for individuals who have a low probability of receiving treatment and is close to 1 for those who have a high probability of receiving treatment. That is, $\pi(L)$ measures the propensity of individuals to receive treatment given the information available in the covariates L. No wonder that $\pi(L)$ is referred to as the *propensity score*.

CODE: Program 15.2
Here we only consider propensity scores for dichotomous treatments. Propensity score methods, other than IP weighting and g-estimation and other related doubly-robust estimators, are difficult to generalize to non-dichotomous treatments.

In an ideal randomized trial in which half of the individuals are assigned to treatment $A = 1$, the propensity score $\pi(L) = 0.5$ for all individuals. Also note that $\pi(L) = 0.5$ for any choice of L. In contrast, in observational studies some individuals may be more likely to receive treatment than others. Because treatment assignment is beyond the control of the investigators, the true propensity score $\pi(L)$ is unknown, and therefore needs to be estimated from the data.

In our example, we can estimate the propensity score $\pi(L)$ by fitting a logistic model for the probability of quitting smoking A conditional on the covariates L. This is the same model that we used for IP weighting and g-estimation. Under this model, individual 22941 was estimated to have the lowest estimated propensity score (0.053), and individual 24949 the highest (0.793). Figure 15.1 shows the distribution of the estimated propensity score in quitters $A = 1$ (bottom) and nonquitters $A = 0$ (top). As expected, those who quit smoking had, on average, a greater estimated probability of quitting (0.312) than those who did not quit (0.245). If the distribution of $\pi(L)$ were the same for the treated $A = 1$ and the untreated $A = 0$, then there would be no confounding due to L, i.e., there would be no open path from L to A on a causal diagram.

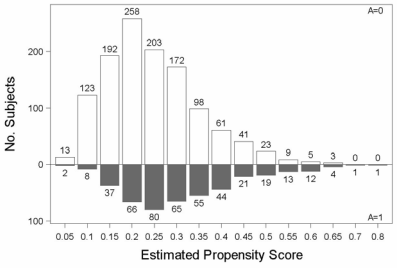


Figure 15.1

In the study population, due to sampling variability, the true propensity score only approximately "balances" the covariates L. The estimated propensity score based on a correct model gives better balance in general.

Individuals with the same propensity score $\pi(L)$ will generally have different values of some covariates L. For example, two individuals with $\pi(L) = 0.2$ may differ with respect to smoking intensity and exercise, and yet they may be equally likely to quit smoking given all the variables in L. That is, both individuals have the same conditional probability of ending up in the treated group $A = 1$. If we consider all individuals with a given value of $\pi(L)$ in the super-population, this group will include individuals with different values of L (e.g., different values of smoking intensity and exercise), but the distribution of L will be the same in the treated and the untreated, that is, $A \perp\!\!\!\perp L|\pi(L)$. We say the propensity score balances the covariates between the treated and the untreated.

Of course, the propensity score only balances the measured covariates L, which does not prevent residual confounding by unmeasured factors. Randomization balances both the measured and the unmeasured covariates, and thus

Technical Point 15.1

Balancing scores and prognostic scores. As discussed in the text, the propensity score $\pi(L)$ balances the covariates between the treated and the untreated. In fact, the propensity score $\pi(L)$ is the simplest example of a balancing score. More generally, a balancing score $b(L)$ is any function of the covariates L such that $A \perp\!\!\!\perp L|b(L)$. That is, for each value of the balancing score, the distribution of the covariates L is the same in the treated and the untreated. Rosenbaum and Rubin (1983) proved that exchangeability and positivity based on the variables L implies exchangeability and positivity based on a balancing score $b(L)$. If it is sufficient to adjust for L, then it is sufficient to adjust for a balancing score $b(L)$, including the propensity score $\pi(L)$. The causal diagram in Figure 15.2 depicts the propensity score for the setting represented in Figure 7.1: the $\pi(L)$ can be viewed as an intermediate node between L and A with a deterministic arrow from L to $\pi(L)$. By noting that $\pi(L)$ blocks all backdoor paths from A to L we have given a proof of the sufficiency of adjusting for $\pi(L)$.

An alternative to a balancing score $b(L)$ is a prognostic score $s(L)$, i.e., a function of the covariates L such that $Y^{a=0} \perp\!\!\!\perp L|s(L)$. Adjustment methods can be developed for both balancing scores and prognostic scores, but methods for prognostic scores require stronger assumptions and cannot be readily extended to time-varying treatments. See Hansen (2008) and Abadie et al (2013) for a discussion of prognostic scores.

it is the preferred method to eliminate confounding. See Technical Point 15.1 for a formal definition of a balancing score.

If L is sufficient to adjust for confounding and selection bias, then $\pi(L)$ is sufficient too. This result was derived by Rosenbaum and Rubin in a seminal paper published in 1983.

Like all methods for causal inference that we have discussed, the use of propensity score methods requires the identifying conditions of exchangeability, positivity, and consistency. The use of propensity score methods is justifed by the following key result: Exchangeability of the treated and the untreated within levels of the covariates L implies exchangeability within levels of the propensity score $\pi(L)$. That is, conditional exchangeability $Y^a \perp\!\!\!\perp A|L$ implies $Y^a \perp\!\!\!\perp A|\pi(L)$. Further, positivity within levels of the propensity score $\pi(L)$—which means that no individual has a propensity score equal to either 1 or 0—holds if and only if positivity within levels of the covariates L, as defined in Chapter 2, holds.

In a randomized experiment, the estimated $\pi(L)$ adjusts for both systematic and random imbalances in covariates, and thus does better than adjustment for the true $\pi(L)$ which ignores random imbalances.

Under exchangeability and positivity within levels of the propensity score $\pi(L)$, the propensity score can be used to estimate causal effects using stratification (including outcome regression), standardization, and matching. The next two sections describe how to implement each of these methods. As a first step, we must start by estimating the propensity score $\pi(L)$ from the observational data and then proceeding to use the estimated propensity score in lieu of the covariates L for stratification, standardization, or matching.

15.3 Propensity stratification and standardization

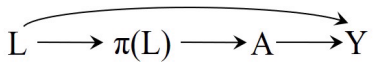


Figure 15.2

The average causal effect among individuals with a particular value s of the propensity score $\pi(L)$, i.e., $\mathrm{E}[Y^{a=1,c=0}|\pi(L) = s] - \mathrm{E}[Y^{a=0,c=0}|\pi(L) = s]$ is equal to $\mathrm{E}[Y|A = 1, C = 0, \pi(L) = s] - \mathrm{E}[Y|A = 0, C = 0, \pi(L) = s]$ under the identifying conditions. This conditional effect might be estimated by restricting the analysis to individuals with the value s of the true propensity score. However, the propensity score $\pi(L)$ is generally a continuous variable that can take any value between 0 and 1. It is therefore unlikely that two individuals will have exactly the same value s. For example, only individual 22005 had an estimated $\pi(L)$ of 0.6563, which means that we cannot estimate the causal

effect among individuals with $\pi(L) = 0.6563$ by comparing the treated and the untreated with that particular value.

One approach to deal with the continuous propensity score is to create strata that contain individuals with similar, but not identical, values of $\pi(L)$. The deciles of the estimated $\pi(L)$ is a popular choice: individuals in the population are classified in 10 strata of approximately equal size, then the causal effect is estimated in each of the strata. In our example, each decile contained approximately 162 individuals. The effect of smoking cessation on weight gain ranged across deciles from 0.0 to 6.6 kg, but the 95% confidence intervals around these point estimates were wide.

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We could have also obtained these effect estimates by fitting an outcome regression model for $\mathrm{E}[Y|A, C = 0, \pi(L)]$ that included as covariates treatment A, 9 indicators for the deciles of the estimated $\pi(L)$ (one of the deciles is the reference level and is already incorporated in the intercept of the model), and 9 product terms between A and the indicators. Most applications of outcome regression with deciles of the estimated $\pi(L)$ do not include the product terms, i.e., they assume no effect modification by $\pi(L)$. In our example, a model without product terms yields an effect estimate of 3.5 kg (95% confidence interval: 2.6, 4.4). See Fine Point 15.2 for more on effect modification by the propensity score.

Stratification on deciles or other functions of the propensity score raises a potential problem: in general the distribution of the continuous $\pi(L)$ will differ between the treated and the untreated within some strata (e.g., deciles). If, for example, the average $\pi(L)$ were greater in the treated than in the untreated in some strata, then the treated and the untreated might not be exchangeable in those strata. This problem did not arise in previous chapters, when we used functions of the propensity score to estimate the parameters of structural models via IP weighting and g-estimation, because those methods used the numerical value of the estimated probability rather than a categorical transformation like deciles. Similarly, the problem does not arise when using outcome regression for $\mathrm{E}[Y|A, C = 0, \pi(L)]$ with the estimated propensity score $\pi(L)$ as a continuous covariate rather than as a set of indicators. When we used this latter approach in our example the effect estimate was 3.6 (95% confidence interval: 2.7, 4.5) kg.

Caution: the denominator of the IP weights for a dichotomous treatment A is *not* the propensity score $\pi(L)$, but a function of $\pi(L)$. The denominator is $\pi(L)$ for the treated $(A = 1)$ and $1 - \pi(L)$ for the untreated $(A = 0)$.

The validity of our inference depends on the correct specification of the relationship between $\pi(L)$ and the mean outcome Y (which we assumed to be linear). However, because the propensity score is a one-dimensional summary of the multi-dimensional L, it is easy to guard against misspecification of this relationship by fitting flexible models, e.g., cubic splines rather than a single linear term for the propensity score. Note that IP weighting and g-estimation were agnostic about the relationship between propensity score and outcome.

Though the propensity score is one-dimensional, we still need to estimate it from a model that regresses treatment on a high-dimensional L. The same applies to IP weighting and g-estimation.

When our parametric assumptions for $\mathrm{E}[Y|A, C = 0, \pi(L)]$ are correct, plus exchangeability and positivity hold, the model estimates the average causal effects within all levels s of the propensity score $\mathrm{E}[Y^{a=1,c=0}|\pi(L) = s] - \mathrm{E}[Y^{a=0,c=0}|\pi(L) = s]$. If we were interested in the average causal effect in the entire study population $\mathrm{E}[Y^{a=1,c=0}] - \mathrm{E}[Y^{a=0,c=0}]$, we would standardize the conditional means $\mathrm{E}[Y|A, C = 0, \pi(L)]$ by using the distribution of the propensity score. The procedure is the same one described in Chapter 13 for continuous variables, except that we replace the variables L by the estimated $\pi(L)$. Note that the procedure can naturally incorporate a product term between treatment A and the estimated $\pi(L)$ in the outcome model. In our example, the standardized effect estimate was 3.6 (95% confidence interval: 2.7, 4.6) kg.

CODE: Program 15.4

15.4 Propensity matching

After propensity matching, the matched population has the $\pi(L)$ distribution of the treated, of the untreated, or any other arbitrary distribution.

The process of matching on the propensity score $\pi(L)$ is analogous to matching on a single continuous variable L, a procedure described in Chapter 4. There are many forms of propensity matching. All of them attempt to form a matched population in which the treated and the untreated are exchangeable because they have the same distribution of $\pi(L)$. For example, one can match the untreated to the treated: each treated individual is paired with one (or more) untreated individuals with the same propensity score value. The subset of the original population comprised by the treated-untreated pairs (or sets) is the *matched population*. Under exchangeability and positivity given $\pi(L)$, association measures in the matched population are consistent estimates of effect measures, e.g., the associational risk ratio in the matched population consistently estimates the causal risk ratio in the matched population.

A drawback of matching used to be that nobody knew how to compute the variance of the effect estimate. That is no longer the case thanks to the work of Abadie and Imbens (2006).

Again, it is unlikely that two individuals will have exactly the same values of the propensity score $\pi(L)$. In our example, propensity score matching will be carried out by identifying, for each treated individual, one (or more) untreated individuals with a *close* value of $\pi(L)$. A common approach is to match treated individuals with a value s of the estimated $\pi(L)$ with untreated individuals who have a value $s \pm 0.05$, or some other small difference. For example, treated individual 1089 (estimated $\pi(L)$ of 0.6563) might be matched with untreated individual 1088 (estimated $\pi(L)$ of 0.6579). There are numerous ways of defining closeness, and a detailed description of these definitions is beyond the scope of this book.

Defining closeness in propensity matching entails a bias-variance tradeoff. If the closeness criteria are too loose, individuals with relatively different values of $\pi(L)$ will be matched to each other, the distribution of $\pi(L)$ will differ between the treated and the untreated in the matched population, and exchangeability will not hold. On the other hand, if the closeness criteria are too tight and many individuals are excluded by the matching procedure, there will be approximate exchangeability but the effect estimate may have wider 95% confidence intervals.

Remember: positivity is now defined within levels of the propensity score, i.e., $\Pr[A = a|\pi(L) = s] > 0$ for all s such that $\Pr[\pi(L) = s]$ is nonzero.

The definition of closeness is also related to that of positivity. In our smoking cessation example, the distributions of the estimated $\pi(L)$ in the treated and the untreated overlapped throughout most of the range (see Figure 15.1). Only 2 treated individuals (0.01% of the study population) had values greater than those of any untreated individual. When using outcome regression on the estimated $\pi(L)$ in the previous section, we effectively assumed that the lack of untreated individuals with high $\pi(L)$ estimates was due to chance—random nonpositivity—and thus included all individuals in the analysis. In contrast, most propensity matched analyses would not consider those two treated individuals close enough to any of the untreated individuals, and would exclude them. Matching does not distinguish between random and structural nonpositivity.

The above discussion illustrates how the matched population may be very different from the target (super)population. In theory, propensity matching can be used to estimate the causal effect in a well characterized target population. For example, when matching each treated individual with one or more untreated individuals and excluding the unmatched untreated, one is estimating the effect in the treated (see Fine Point 15.2). In practice, however, propensity matching may yield an effect estimate in a hard-to-describe subset of the study population. For example, under a given definition of closeness, some treated individuals cannot be matched with any untreated individuals

and thus they are excluded from the analysis. As a result, the effect estimate corresponds to a subset of the population that is defined by the values of the estimated propensity score that have successful matches.

That propensity matching forces investigators to restrict the analysis to treatment groups with overlapping distributions of the estimated propensity score is often presented as a strength of the method. One surely would not want to have biased estimates because of violations of positivity, right? However, leaving aside issues related to random variability (see above), there is a price to be paid for restrictions based on the propensity score. Suppose that, after inspecting Figure 15.1, we conclude that we can only estimate the effect of smoking cessation for individuals with an estimated propensity score less than 0.67. Who are these people? It is unclear because individuals do not come with a propensity score tattooed on their forehead. Because the matched population is not well characterized, it is hard to assess the transportability of the effect estimate to other populations.

Even if every subject came with her propensity score tattooed on her forehead, the population could still be ill-characterized because the same propensity score value may mean different things in different settings.

When positivity concerns arise, restriction based on real-world variables (e.g., age, number of cigarettes) leads to a more natural characterization of the causal effect. In our smoking cessation example, the two treated individuals with estimated $\pi(L) > 0.67$ were the only ones in the study who were over age 50 and had smoked for less than 10 years. We could exclude them and explain that our effect estimate only applies to smokers under age 50 and to smokers 50 and over who had smoked for at least 10 years. This way of defining the target population is more natural than defining it as those with estimated $\pi(L) < 0.67$.

Using propensity scores to detect the overlapping range of the treated and the untreated may be useful, but simply restricting the study population to that range is a lazy way to ensure positivity. The automatic positivity ensured by propensity matching needs to be weighed against the difficulty of assessing transportability when restriction is solely based on the value of the estimated propensity scores.

15.5 Propensity models, structural models, predictive models

In Part II of this book we have described two different types of models for causal inference: propensity models and structural models. Let us now compare them.

Propensity models are models for the probability of treatment A given the variables L used to try to achieve conditional exchangeability. We have used propensity models for matching and stratification in this chapter, for IP weighting in Chapter 12, and for g-estimation in Chapter 14. The parameters of propensity models are nuisance parameters (see Fine Point 15.1) without a causal interpretation because a variable L and treatment A may be associated for many reasons—not only because the variable L causes A. For example, the association between L and A can be interpreted as the effect of L on A under Figure 7.1, but not under Figure 7.2. Yet propensity models are useful for causal inference, often as the basis of the estimation of the parameters of structural models, as we have described in this and previous chapters.

Structural models describe the relation between the treatment A and some component of the distribution (e.g., the mean) of the counterfactual outcome Y^a, either marginally or within levels of the variables L. For continuous treatments, a structural model is often referred to as a dose-response model. The parameters for treatment in structural models are not nuisance parameters:

Fine Point 15.2

Effect modification and the propensity score. A reason why matched and unmatched estimates may differ is effect modification. As an example, consider the common setting in which the number of untreated individuals is much larger than the number of treated individuals. Propensity matching often results in almost all treated individuals being matched and many untreated individuals being unmatched and therefore excluded from the analysis. When this occurs, the distribution of causal effect modifiers in the matched population will resemble that in the treated. Therefore, the effect in the matched population will be closer to the effect in the treated than to the effect that would have been estimated by methods that use data from the entire population. See Technical Point 4.1 for alternative ways to estimate the effect of treatment in the treated via IP weighting and standardization.

Effect modification across propensity strata may be interpreted as evidence that decision makers know what they are doing, e.g. that doctors tend to treat patients who are more likely to benefit from treatment (Kurth et al 2006). However, the presence of effect modification by $\pi(L)$ may complicate the interpretation of the estimates. Consider a situation with qualitative effect modification: "Doctor, according to our study, this drug is beneficial for patients who have a propensity score between 0.11 and 0.93 when they arrive at your office, but it may kill those with propensity scores below 0.11," or "Ms. Minister, let's apply this educational intervention to children with propensity scores below 0.57 only." The above statements are of little policy relevance because, as discussed in the main text, they are not expressed in terms of the measured variables L.

Finally, besides effect modification, there are other reasons why matched estimates may differ from the overall effect estimate: violations of positivity in the non-matched, an unmeasured confounder that is more/less prevalent (or that is better/worse measured) in the matched population than in the unmatched population, etc. As discussed for individual variables L in Chapter 4, remember that effect modification might be explained by differences in residual confounding across propensity strata.

they have a direct causal interpretation as outcome differences under different treatment values a. We have described two classes of structural models: marginal structural models and structural nested models. Marginal structural models include parameters for treatment, for the variables V that may be effect modifiers, and for product terms between treatment and variables V. The choice of V reflects only the investigator's substantive interest in effect modification (see Section 12.5). If no covariates V are included, then the model is truly marginal. If all variables L are included as possible effect modifiers, then the marginal structural model becomes a faux marginal structural model. Structural nested models include parameters for treatment and for product terms between treatment A and all variables in L that are effect modifiers.

See Fine Point 14.1 for a discussion of the relation between structural nested models and faux semiparametric marginal structural models, and other subtleties.

We have presented outcome regression as a method to estimate the parameters of faux marginal structural models for causal inference. However, outcome regression is also widely used for purely predictive, as opposed to causal, purposes. For example, online retailers use sophisticated outcome regression models to predict which customers are more likely to purchase their products. The goal is not to determine whether your age, sex, income, geographic origin, and previous purchases have a causal effect on your current purchase. Rather, the goal is to identify those customers who are more likely to make a purchase so that specific marketing programs can be targeted to them. It is all about association, not causation. Similarly, doctors use algorithms based on outcome regression to identify patients at high risk of developing a serious disease or dying. The parameters of these predictive models do not necessarily have any causal interpretation and all covariates in the model have the same status, i.e., there are no treatment variable A and variables L.

A study found that Facebook Likes predict sexual orientation, political views, and personality traits (Kosinski et al, 2013). Low intelligence was predicted by, among other things, a "Harley Davidson" Like. This is purely predictive, not necessarily causal.

The dual use of outcome regression in both causal inference method and

in prediction has led to many misunderstandings. One of the most important misunderstandings has to do with variable selection procedures. When the interest lies exclusively on outcome prediction, investigators may want to select *any* variables that, when included as covariates in the model, improve its predictive ability. Many well-known variable selection procedures—e.g., forward selection, backward elimination, stepwise selection—and more recent developments in machine learning are used to enhance prediction. These are powerful tools for investigators who are interested in prediction, especially when dealing with very high-dimensional data.

Unfortunately, statistics courses and textbooks have not always made a sharp difference between causal inference and prediction. As a result, these variable selection procedures for predictive models have often been applied to causal inference models. A possible result of this mismatch is the inclusion of superfluous—or even harmful—covariates in propensity models and structural models. Specifically, the application of predictive algorithms to causal inference models may result in inflated variances.

It is not uncommon for propensity analyses to report measures of predictive power like Mallows's Cp. The relevance of these measures for causal inference is questionable.

The problem arises because of the widespread, but mistaken, belief that propensity models should predict treatment A as well as possible. Propensity models do not need to predict treatment very well. They just need to include the variables L that guarantee exchangeability. Covariates that are strongly associated with treatment, but are not necessary to guarantee exchangeability, do not help reduce bias. If these covariates were included in L, adjustment can actually result in estimates with very large variances.

Consider the following example. Suppose all individuals in a certain study attend either hospital Aceso or hospital Panacea. Doctors in hospital Aceso give treatment $A = 1$ to 99% of the individuals, and those in hospital Panacea give $A = 0$ to 99% of the individuals. Suppose the variable Hospital has no effect on the outcome (except through its effect on treatment A) and is therefore not necessary to achieve conditional exchangeability. Say we decide to add Hospital as a covariate in our propensity model anyway. The propensity score $\pi(L)$ in the target population is about 0.99 for individuals in hospital Aceso and 0.01 for those in hospital Panacea, but by chance we may end up with a study population in which everybody in hospital Aceso has $A = 1$ or everybody in hospital Panacea has $A = 0$ for some strata defined by L. That is, our effect estimate may have a near-infinite variance without any reduction in confounding. That treatment is now very well predicted is irrelevant for causal inference purposes.

If we perfectly predicted treatment, then all treated individuals would have $\pi(L) = 1$ and all untreated individuals would have $\pi(L) = 0$. There would be no overlap and the analysis would be impossible.

Besides variance inflation, a predictive attitude towards variable selection for causal inference models—both propensity models and outcome regression models—may also result in self-inflicted bias. For example, the inclusion of colliders as covariates may result in systematic bias even if colliders may be effective covariates for purely predictive purposes. We will return to these issues in Chapter 18.

All causal inference methods based on models—propensity models and structural models—require no misspecification of the functional form for the covariates. To reduce the possibility of model misspecification, we use flexible specifications, e.g., cubic splines rather than linear terms. In addition, these causal inference methods require the conditions of exchangeability, positivity, and well-defined interventions for unbiased causal inferences. In the next chapter we describe a very different type of causal inference method that does not require exchangeability as we know it.

Chapter 16
INSTRUMENTAL VARIABLE ESTIMATION

The causal inference methods described so far in this book rely on a key untestable assumption: all variables needed to adjust for confounding and selection bias have been identified and correctly measured. If this assumption is incorrect—and it will always be to a certain extent—there will be residual bias in our causal estimates.

It turns out that there exist other methods that can validly estimate causal effects under an alternative set of assumptions that do not require measuring all adjustment factors. Instrumental variable estimation is one of those methods. Economists and other social scientists reading this book can breathe now. We are finally going to describe a very common method in their fields, a method that is unlike any other we have discussed so far.

16.1 The three instrumental conditions

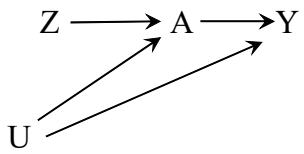

Figure 16.1

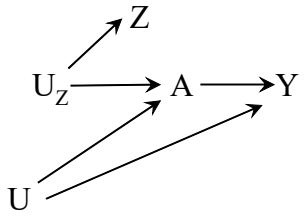

Figure 16.2

Condition (ii) would not be guaranteed if, for example, participants were inadvertently unblinded by side effects of treatment.

The causal diagram in Figure 16.1 depicts the structure of a double-blind randomized trial with noncompliance: Z is the randomization assignment indicator (1: treatment, 0: placebo), A is an indicator for receiving treatment (1: yes, 0: no), Y the outcome, and U all factors (some unmeasured) that affect both the outcome and the adherence to the assigned treatment.

Suppose we want to consistently estimate the average causal effect of A on Y. Whether we use IP weighting, standardization, g-estimation, stratification, or matching, we need to correctly measure, and adjust for, variables that block the backdoor path $A \leftarrow U \rightarrow Y$, i.e., we need to ensure conditional exchangeability of the treated and the untreated. Unfortunately, all these methods will result in biased effect estimates if some of the necessary variables are unmeasured, imperfectly measured, or misspecified in the model.

Instrumental variable (IV) methods are different: they may be used to identify the average causal effect of A on Y in this randomized trial, even if we did not measure the variables normally required to adjust for the confounding caused by U. To perform their magic, IV methods need an instrumental variable Z, or an *instrument*. A variable Z is an instrument because it meets three instrumental conditions:

(i) Z is associated with A

(ii) Z does not affect Y except through its potential effect on A

(iii) Z and Y do not share causes

See Technical Point 16.1 for a more rigorous definition of these conditions.

In the double-blind randomized trial described above, the randomization indicator Z is an instrument. Condition (i) is met because trial participants are more likely to receive treatment if they were assigned to treatment, condition (ii) is expected by the double-blind design, and condition (iii) is expected by the random assignment of Z.

Figure 16.1 depicts a special case in which the instrument Z has a causal effect on the treatment A. We then refer to Z as a *causal instrument*. Other instruments do not have a causal effect on treatment A. The variable Z in Figure 16.2 also meets the instrumental conditions with the Z-A association (i) now resulting from the cause U_Z shared by Z and A. We then refer to

Technical Point 16.1

The instrumental conditions, formally. Instrumental condition (i), sometimes referred to as the *relevance* condition, is non-null association between Z and A, or $Z \perp\!\!\!\perp A$ does not hold.

Instrumental condition (ii), commonly known as the *exclusion restriction*, is the condition of "no direct effect of Z on Y." At the individual level, condition (ii) is $Y_i^{z,a} = Y_i^{z',a} = Y_i^a$ for all z, z', all a, all individuals i. However, for some results presented in this chapter, only the population level condition (ii) is needed, i.e., $\mathrm{E}\left[Y^{z,a}\right] = \mathrm{E}\left[Y^{z',a}\right]$. Both versions of condition (ii) are trivially true for proxy instruments.

Instrumental condition (iii) can be written as *marginal exchangeability* $Y^{a,z} \perp\!\!\!\perp Z$ for all a, z, which holds in the SWIGs corresponding to Figures 16.1, 16.2, and 16.3. Together with condition (ii) at the individual level, it implies $Y^a \perp\!\!\!\perp Z$. A stronger condition (iii) is joint exchangeability, or $\{Y^{z,a}; a \in [0,1], z \in [0,1]\} \perp\!\!\!\perp Z$ for dichotomous treatment and instrument. See Technical Point 2.1 for a discussion on different types of exchangeability and Technical Point 16.2 for a description of results that require each version of exchangeability. Both versions of condition (iii) are expected to hold in randomized experiments in which the instrument Z is the randomized assignment.

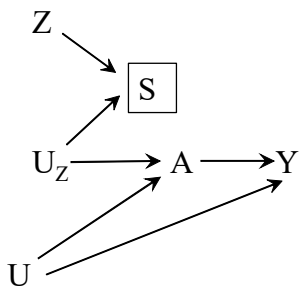

Figure 16.3

Condition (i) is met if the candidate instrument Z "price in state of birth" is associated with smoking cessation A through the unmeasured variable U_Z "price in place of residence".

U_Z as the unmeasured causal instrument and to Z as the measured *surrogate* or *proxy instrument*. (That Z and Y have U_Z as a common cause does not violate condition (iii) because U_Z is a causal instrument; see Technical Point 16.1.) Figure 16.3 depicts another case of proxy instrument Z in a selected population: the Z-A association arises from conditioning on a common effect S of the unmeasured causal instrument U_Z and the proxy instrument Z. Both causal and proxy instruments can be used for IV estimation, with some caveats described in Section 16.4.

In previous chapters we have estimated the effect of smoking cessation on weight change using various causal inference methods applied to observational data. To estimate this effect using IV methods, we need an instrument Z. Since there is no randomization indicator in an observational study, consider the following candidate for an instrument: the price of cigarettes. It can be argued that this variable meets the three instrumental conditions if (i) cigarette price affects the decision to quit smoking, (ii) cigarette price affects weight change only through its effect on smoking cessation, and (iii) no common causes of cigarette price and weight change exist. Fine Point 16.1 reviews some proposed instruments in observational studies.

To fix ideas, let us propose an instrument Z that takes value 1 when the average price of a pack of cigarettes in the U.S. state where the individual was born was greater than \$1.50, and takes value 0 otherwise. Unfortunately, we cannot determine whether our variable Z is actually an instrument. Of the three instrumental conditions, only condition (i) is empirically verifiable. To verify this condition we need to confirm that the proposed instrument Z and the treatment A are associated, i.e., that $\Pr[A = 1|Z = 1] - \Pr[A = 1|Z = 0] > 0$. The probability of quitting smoking is 25.8% among those with $Z = 1$ and 19.5% among those with $Z = 0$; the risk difference $\Pr[A = 1|Z = 1] - \Pr[A = 1|Z = 0]$ is therefore 6%. When, as in this case, Z and A are weakly associated, Z is often referred as a *weak instrument* (more on weak instruments in Section 16.5).

On the other hand, conditions (ii) and (iii) cannot be empirically verified. To verify condition (ii), we would need to prove that Z can only cause the outcome Y through the treatment A. We cannot prove it by conditioning on A, which is a collider on the pathway $Z \longleftarrow U_Z \rightarrow A \longleftarrow U \rightarrow Y$, because that would induce an association between Z and Y even if condition (ii) held

Fine Point 16.1

Candidate instruments in observational studies. Many variables have been proposed as instruments in observational studies and it is not possible to review all of them here. Three commonly used categories of candidate instruments are

- Genetic factors: The proposed instrument Z is a genetic variant that is associated with treatment A and that, supposedly, is only related with the outcome Y through A. For example, when estimating the effects of alcohol intake on the risk of coronary heart disease, Z can be a polymorphism associated with alcohol metabolism (say, ALDH2 in Asian populations). Causal inference from observational data via IV estimation using genetic variants is part of the framework known as *Mendelian randomization* (Katan 1986, Davey Smith and Ebrahim 2004, Didelez and Sheehan 2007, VanderWeele et al. 2014).
- Preference: The proposed instrument Z is a measure of the physician's (or a care provider's) preference for one treatment over the other. The idea is that a physician's preference influences the prescribed treatment A without having a direct effect on the outcome Y. For example, when estimating the effect of prescribing COX-2 selective versus non-selective nonsteroidal anti-inflammatory drugs on gastrointestinal bleeding, U_Z can be the physician's prescribing preference for drug class (COX-2 selective or non-selective). Because U_Z is unmeasured, investigators replace it in the analysis by a (measured) surrogate instrument Z, such as "last prescription issued by the physician before current prescription" (Korn and Baumrind 1998, Earle et al. 2001, Brookhart and Schneeweiss 2007).
- Access: The proposed instrument Z is a measure of access to the treatment. The idea is that access impacts the use of treatment A but does not directly affect the outcome Y. For example, physical distance or travel time to a facility has been proposed as an instrument for treatments available at such facilities (McClellan et al. 1994, Card 1995, Baiocchi et al. 2010). Another example: calendar period has been proposed as an instrument for a treatment whose accessibility varies over time (Hoover et al. 1994, Detels et al. 1998). In the main text we use "price of the treatment", another measure of access, as a candidate instrument.

Conditions (ii) and (iii) can sometimes be empirically falsified by using data on instrument, treatment, and outcome. However, falsification tests only reject the conditions for a small subset of violations. For most violations, the test has no statistical power, even for an arbitrarily large sample size (Bonet 2001, Glymour et al. 2012).

true. And we cannot, of course, prove that condition (iii) holds because we can never rule out confounding for the effect of any variable. We can only assume that conditions (ii) and (iii) hold. IV estimation, like all methods we have studied so far, is based on untestable assumptions.

In observational studies we cannot prove that our proposed instrument Z is truly an instrument. We refer to Z as a proposed or *candidate instrument* because we can never guarantee that the structures represented in Figures 16.1 and 16.2 are the ones that actually occur. The best we can do is to use subject-matter knowledge to build a case for why the proposed instrument Z may be reasonably assumed to meet conditions (ii) and (iii); this is similar to how we use subject-matter knowledge to justify the identifying assumptions of the methods described in previous chapters.

But let us provisionally assume that Z is an instrument. Now what? Can we now see the magic of IV estimation in action? Can we consistently estimate the average causal effect of A on Y without having to identify and measure the confounders? Sadly, the answer is no without further assumptions. An instrument by itself does not allow us to identify the average causal effect of smoking cessation A on weight change Y, but only identifies certain upper and lower bounds. Typically, the bounds are very wide and often include the null value (see Technical Point 16.2).

In our example, these bounds are not very helpful. They would only confirm what we already knew: smoking cessation can result in weight gain, weight loss, or no weight change. Unfortunately, that is all an instrument can offer unless

Technical Point 16.2

Bounds: Partial identification of causal effects. For a dichotomous outcome Y, the average causal effect $\Pr\left[Y^{a=1}=1\right]-\Pr\left[Y^{a=0}=1\right]$ can take values between -1 (if all individuals develop the outcome unless they were treated) and 1 (if no individuals develop the outcome unless treated). The bounds of the average causal effect are $(-1,1)$. The distance between these bounds can be cut in half by using the data: because for each individual we know the value of either her counterfactual outcome $Y^{a=1}$ (if the individual was actually treated) or $Y^{a=0}$ (if the individual was actually untreated), we can compute the causal effect after assigning the most extreme values possible to each individual's unknown counterfactual outcome. This will result in bounds of the average causal effect that are narrower but still include the null value 0. For a continuous outcome Y, deriving bounds requires the specification of the minimum and maximum values for the outcome; the width of the bounds will vary depending on the chosen values.

The bounds for $\Pr\left[Y^{a=1}=1\right]-\Pr\left[Y^{a=0}=1\right]$ can be further narrowed when there exists a variable Z that meets instrumental condition (ii) at the population level and marginal exchangeability (iii) (Robins 1989; Manski 1990). The width of these so-called *natural bounds*, $\Pr[A=1|Z=0]+\Pr[A=0|Z=1]$, is narrower than that of the bounds identified from the data alone. Sometimes narrower bounds—the so-called *sharp bounds*—can be achieved when marginal exchangeability is replaced by joint exchangeability (Balke and Pearl 1997; Richardson and Robins 2014).

The conditions necessary to achieve the sharp bounds can also be derived from the SWIGs under joint interventions on z and a corresponding to any of the causal diagrams depicted in Figures 16.1, 16.2, and 16.3. Richardson and Robins (2010, 2014) showed that the conditions $Y^{a,z}\perp\!\!\!\perp(Z,A)\,|U$ and $Z\perp\!\!\!\perp U$, together with a population level condition (ii) within levels of U, i.e., $\mathrm{E}\left[Y^{z,a}|U\right]=\mathrm{E}\left[Y^{z',a}|U\right]$, are sufficient to obtain the sharp bounds. Specifically, these conditions imply $Z\perp\!\!\!\perp U$, $Y\perp\!\!\!\perp Z|U,A$, and that $\mathrm{E}\left[Y^{z,a}\right]$ is given by the g-formula $\int\mathrm{E}\left[Y|A=a,U=u\right]dF(u)$ ignoring Z, which reflects that Z has no direct effect on Y within levels of U. Dawid (2003) proved that these latter conditions lead to the sharp bounds. Under further assumptions, Richardson and Robins derived yet narrower bounds. See also Richardson, Evans, and Robins (2011).

Unfortunately, all these partial identification methods (i.e., methods for bounding the effect) are often relatively uninformative because the bounds are wide. Swanson et al (2018) review partial identification methods for binary instruments, treatments, and outcomes. Swanson et al. (2015c) describe a real-world application of several partial identification methods and discuss their relative advantages and disadvantages.

There is a way to decrease the width of the bounds: making parametric assumptions about the form of the effect of A on Y. Under sufficiently strong assumptions described in Section 16.2, the upper and lower bounds converge into a single number and the average causal effect is point identified.

one is willing to make additional unverifiable assumptions. Sections 16.3 and 16.4 review additional conditions under which the IV estimand is the average causal effect. Before that, we review the methods to do so.

16.2 The usual IV estimand

We will focus on dichotomous instruments, which are the commonest ones. For a continuous instrument Z, the usual IV estimand is $\frac{Cov(Y,Z)}{Cov(A,Z)}$, where Cov means covariance.

When a dichotomous variable Z is an instrument, i.e., meets the three instrumental conditions (i)-(iii), and an additional condition (iv) described in the next section holds, then the average causal effect of treatment on the additive scale $\mathrm{E}\left[Y^{a=1}\right]-\mathrm{E}\left[Y^{a=0}\right]$ is identified and equals

$$\frac{\mathrm{E}\left[Y|Z=1\right]-\mathrm{E}\left[Y|Z=0\right]}{\mathrm{E}\left[A|Z=1\right]-\mathrm{E}\left[A|Z=0\right]},$$

which is the *usual IV estimand* for a dichotomous instrument. (Note $\mathrm{E}\left[A|Z=1\right]=\Pr\left[A=1|Z=1\right]$ for a dichotomous treatment). Technical Point 16.3 provides

a proof of this result in terms of an additive structural mean model, but you might want to wait until the next section before reading it.

In randomized experiments, the IV estimator is the ratio of two effects of Z: the effect of Z on Y and the effect of Z on A. Each of these effects can be consistently estimated without adjustment because Z is randomly assigned.

To intuitively understand the usual IV estimand, consider again the randomized trial from the previous section. The numerator of the IV estimand—the average causal effect of Z on Y—is the intention-to-treat effect, and the denominator—the average causal effect of Z on A—is a measure of adherence to, or compliance with, the assigned treatment. When there is perfect compliance, the denominator is equal to 1, and the effect of A on Y equals the effect of Z on Y. As compliance worsens, the denominator starts to get closer to 0, and the effect of A on Y becomes greater than the effect of Z on Y. The greater the rate of noncompliance, the greater the difference between the effect of A on Y—the IV estimand—and the effect of Z on Y.

The IV estimand bypasses the need to adjust for the confounders by inflating the intention-to-treat effect in the numerator. The magnitude of the inflation increases as compliance decreases, i.e., as the Z-A risk difference gets closer to zero. The same rationale applies to the instruments used in observational studies, where the denominator of the IV estimator may equal either the causal effect of the causal instrument Z on A (Figure 16.1), or the noncausal association between the proxy instrument Z and the treatment A (Figures 16.2 and 16.3).

Also known as the Wald estimator (Wald 1940).

The standard IV estimator is the ratio of the estimates of the numerator and the denominator of the usual IV estimand. In our smoking cessation example with a dichotomous instrument Z (1: state with high cigarette price, 0: otherwise), the numerator estimate $\widehat{\mathrm{E}}[Y|Z=1]-\widehat{\mathrm{E}}[Y|Z=0]$ equals $2.686-2.536=0.1503$ and the denominator $\widehat{\mathrm{E}}[A|Z=1]-\widehat{\mathrm{E}}[A|Z=0]$ equals $0.2578-0.1951=0.0627$. Therefore, the usual IV estimate is the ratio $0.1503/0.0627=2.4$ kg. Under the three instrumental conditions (i)-(iii) plus condition (iv) from next section, this is an estimate of the average causal effect of smoking cessation on weight gain in the population.

CODE: Program 16.1
For simplicity, we exclude individuals with missing outcome or instrument. In practice, we could use IP weighting to adjust for possible selection bias before using IV estimation.

We estimated the numerator and denominator of the IV estimand by simply calculating the four sample averages $\widehat{\mathrm{E}}[A|Z=1]$, $\widehat{\mathrm{E}}[A|Z=0]$, $\widehat{\mathrm{E}}[Y|Z=1]$, and $\widehat{\mathrm{E}}[Y|Z=0]$. Equivalently, we could have fit two (saturated) linear models to estimate the differences in the denominator and the numerator. The model for the denominator would be $\mathrm{E}[A|Z]=\alpha_0+\alpha_1 Z$, and the model for the numerator $\mathrm{E}[Y|Z]=\beta_0+\beta_1 Z$.

Linear models are used as an alternative method to calculate the standard IV estimator: the *two-stage-least-squares estimator*. The procedure is as follows. First, fit the first-stage treatment model $\mathrm{E}[A|Z]=\alpha_0+\alpha_1 Z$, and generate the predicted values $\widehat{\mathrm{E}}[A|Z]$ for each individual. Second, fit the second-stage outcome model $\mathrm{E}[Y|Z]=\beta_0+\beta_1\widehat{\mathrm{E}}[A|Z]$. The parameter estimate $\widehat{\beta}_1$ will always be numerically equivalent to the standard IV estimate. Thus, in our example, the two-stage-least-squares estimate was again 2.4 kg.

CODE: Program 16.2

The 2.4 point estimate has a very large 95% confidence interval: -36.5 to 41.3. This is expected for our proposed instrument because the Z-A association is weak and there is much uncertainty in the first-stage model. A commonly used rule of thumb is to declare an instrument as weak if the F-statistic from the first-stage model is less than 10 (it was a meager 0.8 in our example). We will revisit the problems raised by weak instruments in Section 16.5.

The two-stage-least-squares estimator and its variations forces investigators to make strong parametric assumptions. Some of these assumptions can be avoided by using additive or multiplicative structural mean models, like the ones described in Technical Points 16.3 and 16.4, for IV estimation. The

CODE: Program 16.3

parameters of structural mean models can be estimated via g-estimation. The trade-offs involved in the choice between two-stage-least-squares linear models and structural mean models are similar to those involved in the choice between outcome regression and structural nested models for non-IV estimation (see Chapters 14 and 15).

Anyway, the above estimators are only valid when the usual IV estimand can be interpreted as the average causal effect of treatment A on the outcome Y. For that to be true, a fourth identifying condition needs to hold in addition to the three instrumental conditions.

16.3 A fourth identifying condition: homogeneity

The three instrumental conditions (i)-(iii) are insufficient to ensure that the IV estimand is the average causal effect of treatment A on Y. A fourth condition, *effect homogeneity* (iv), is needed. Here we describe four possible homogeneity conditions (iv) in order of (historical) appearance.

The most extreme, and oldest, version of homogeneity condition (iv) is constant effect of treatment A on outcome Y across individuals. In our example, this constant effect condition would hold if smoking cessation made every individual in the population gain (or lose) the same amount of body weight, say, exactly 2.4 kg. A constant effect is equivalent to additive rank preservation which, as we discussed in Section 14.4, is scientifically implausible for most treatments and outcomes—and impossible for dichotomous outcomes, except under the sharp null or universal harm (or benefit). In our example, we expect that, after quitting smoking, some individuals will gain a lot of weight, some will gain little, and others may even lose some weight. Therefore, we are not generally willing to accept the homogeneity assumption of constant effect as a reasonable condition (iv).

Yet additive rank preservation was implicitly assumed in many early IV analyses using the two-stage-least-squares estimator.

A second, less extreme homogeneity condition (iv) for dichotomous Z and A is equality of the average causal effect of A on Y across levels of Z in both the treated and in the untreated, i.e., $\mathrm{E}\left[Y^{a=1} - Y^{a=0} | Z = 1, A = a\right] = \mathrm{E}\left[Y^{a=1} - Y^{a=0} | Z = 0, A = a\right]$ for $a = 0, 1$. This additive homogeneity condition (iv) was the one used in the mathematical proof of Technical Point 16.3. An alternative homogeneity condition on the multiplicative scale is discussed in Technical Point 16.4. (This multiplicative homogeneity condition leads to an IV estimand that is different from the usual IV estimand.)

Even when instrumental condition (iii) $Y^a \perp\!\!\!\perp Z$ holds—as in the SWIGs corresponding to Figures 16.1, 16.2, and 16.3— $Y^a \perp\!\!\!\perp Z|A$ does not generally hold. Therefore the treatment effect may depend on instrument Z, i.e., the less extreme homogeneity condition may not hold.

The above homogeneity condition is expressed in terms that are not naturally intuitive. How can subject-matter experts provide arguments in support of a constant average causal effect within levels of the proposed instrument Z and the treatment A in any particular study? More natural—even if still untestable—homogeneity conditions (iv) would be stated in terms of effect modification by possibly known (even if unmeasured) confounders U. One such condition is that U is not an additive effect modifier, i.e., that the average causal effect of A on Y is the same at every level of the unmeasured confounder U or $\mathrm{E}\left[Y^{a=1}|U\right] - \mathrm{E}\left[Y^{a=0}|U\right] = \mathrm{E}\left[Y^{a=1}\right] - \mathrm{E}\left[Y^{a=0}\right]$. This third homogeneity condition (iv) is often implausible because some unmeasured confounders may also be effect modifiers. For example, the magnitude of weight gain after smoking cessation may vary with prior intensity of smoking, which may itself be an unmeasured confounder for the effect of smoking cessation on weight gain.

Also, Hernán and Robins (2006b) showed that, if U is an additive effect modifier), then it would not be reasonable for us to believe that the previous additive homogeneity condition (iv) holds.

Another type of homogeneity condition (iv) is that the Z-A association on

Technical Point 16.3

Additive structural mean models and IV estimation. Consider the following saturated, additive structural mean model for a dichotomous treatment A and an instrument Z as depicted in Figures 16.1, 16.2, or 16.3:

$$\mathrm{E}\left[Y^{a=1} - Y^{a=0} | A = 1, Z\right] = \beta_0 + \beta_1 Z$$

This model can also be written as $\mathrm{E}\left[Y - Y^{a=0} | A, Z\right] = A\left(\beta_0 + \beta_1 Z\right)$. The parameter β_0 is the average causal effect of treatment among the treated individuals with $Z = 0$, and $\beta_0 + \beta_1$ is the average causal effect of treatment among the treated individuals with $Z = 1$. Thus β_1 quantifies additive effect modification by Z.

If we a priori assume that there is no additive effect modification by Z, then $\beta_1 = 0$ and β_0 is exactly the usual IV estimand (Robins 1994). That is, the usual IV estimand is the parameter of an additive structural mean model for the effect of treatment on the treated under no effect modification by Z.

The proof is simple. When Z is an instrument, condition (ii) holds, which implies $\mathrm{E}\left[Y^{a=0} | Z = 1\right] = \mathrm{E}\left[Y^{a=0} | Z = 0\right]$. Using the structural model notation, this conditional mean independence can be rewritten as $\mathrm{E}\left[Y - A\left(\beta_0 + \beta_1\right) | Z = 1\right] = \mathrm{E}\left[Y - A\beta_0 | Z = 0\right]$. Solving the above equation with $\beta_1 = 0$ we have

$$\beta_0 = \frac{\mathrm{E}\left[Y | Z = 1\right] - \mathrm{E}\left[Y | Z = 0\right]}{\mathrm{E}\left[A | Z = 1\right] - \mathrm{E}\left[A | Z = 0\right]}$$

You may wonder why we a priori set $\beta_1 = 0$. The reason is that we have an equation with two unknowns (β_0 and β_1) and that equation exhausts the constraints on the data distribution implied by the three instrumental conditions. Since we need an additional constraint, which by definition will be untestable, we arbitrarily choose $\beta_1 = 0$ (rather than, say, $\beta_1 = 2$). This is what we mean when we say that an instrument is insufficient to identify the average causal effect.

Therefore, to conclude that the average causal effect of treatment in the treated $\beta_0 = \mathrm{E}\left[Y^{a=1} - Y^{a=0} | A = 1, Z = z\right] = \mathrm{E}\left[Y^{a=1} - Y^{a=0} | A = 1\right]$ equals the average causal effect in the study population $\mathrm{E}\left[Y^{a=1}\right] - \mathrm{E}\left[Y^{a=0}\right]$—and thus that the usual IV estimand is $\mathrm{E}\left[Y^{a=1}\right] - \mathrm{E}\left[Y^{a=0}\right]$—we must assume that the effects of treatment in the treated and in the untreated are identical, which is an additional untestable assumption. Hence, under the additional assumption $\beta_1 = 0$, $\beta_0 = \mathrm{E}\left[Y^{a=1} - Y^{a=0} | A = 1, Z = z\right] = \mathrm{E}\left[Y^{a=1} - Y^{a=0} | A = 1\right]$ for any z is the average causal effect of treatment in the treated. To conclude that β_0 is the average causal effect in the study population $\mathrm{E}\left[Y^{a=1}\right] - \mathrm{E}\left[Y^{a=0}\right]$—and thus that $\mathrm{E}\left[Y^{a=1}\right] - \mathrm{E}\left[Y^{a=0}\right]$ is the usual IV estimand—we must assume that the effects of treatment are identical in the treated *and* in the untreated, i.e., the parameter for Z is also 0 in the structural model for $A = 0$. This is an additional untestable assumption.

Wang and Tchetgen-Tchetgen (2018) proposed these last two homogeneity conditions.

the additive scale is constant across levels of the confounders U, i.e., $\mathrm{E}\left[A | Z = 1, U\right] - \mathrm{E}\left[A | Z = 0, U\right] = \mathrm{E}\left[A | Z = 1\right] - \mathrm{E}\left[A | Z = 0\right]$. Unlike the previous three versions of homogeneity conditions, this one is not guaranteed to hold under the sharp causal null. On the other hand, this version has some testable implications: For dichotomous A, if some of the confounders are measured, then it must be the case that the difference is the same across levels of the measured confounders; for a continuous A, if we are willing to make additional assumptions about linearity, then the variance of the treatment A must be constant across levels of the instrument Z. Otherwise, the condition would not hold.

Because of the perceived implausibility of the homogeneity conditions in many settings, the possibility that IV methods can validly estimate the average causal effect of treatment seems questionable. There are two approaches that bypass the homogeneity conditions.

One approach is the introduction of baseline covariates in the models for IV estimation. To do so, it is safer to use structural mean models, which impose fewer parametric assumptions than two-stage-linear-squares estimators. The inclusion of covariates in a structural mean model allows the treatment effect

Technical Point 16.4

Multiplicative structural mean models and IV estimation. Consider the following saturated, multiplicative (log-linear) structural mean model for a dichotomous treatment A

$$\frac{\mathrm{E}\left[Y^{a=1}|A=1,Z\right]}{\mathrm{E}\left[Y^{a=0}|A=1,Z\right]} = \exp\left(\beta_0 + \beta_1 Z\right),$$

which can also be written as $\mathrm{E}\left[Y|A,Z\right] = \mathrm{E}\left[Y^{a=0}|A,Z\right]\exp\left[A\left(\beta_0+\beta_1 Z\right)\right]$. For a dichotomous Y, $\exp\left(\beta_0\right)$ is the causal risk ratio in the treated individuals with $Z=0$ and $\exp\left(\beta_0+\beta_1\right)$ is the causal risk ratio in the treated with $Z=1$. Thus β_1 quantifies multiplicative effect modification by Z. If we a priori assume that $\beta_1 = 0$—and additionally assume no multiplicative effect modification by Z in the untreated—then the causal effect on the multiplicative (risk ratio) scale is $\mathrm{E}\left[Y^{a=1}\right]/\mathrm{E}\left[Y^{a=0}\right] = \exp\left(\beta_0\right)$, and the causal effect on the additive (risk difference) scale is

$$\mathrm{E}\left[Y^{a=1}\right] - \mathrm{E}\left[Y^{a=0}\right] = \mathrm{E}\left[Y|A=0\right]\left(1-\mathrm{E}\left[A\right]\right)\left[\exp\left(\beta_0\right)-1\right] + \mathrm{E}\left[Y|A=1\right]\mathrm{E}\left[A\right]\left[1-\exp\left(-\beta_0\right)\right]$$

The proof, which relies on the instrumental conditions, can be found in Robins (1989) and Hernán and Robins (2006b).

That is, if we assume a multiplicative structural mean model with no multiplicative effect modification by Z in the treated and in the untreated, then the average causal effect $\mathrm{E}\left[Y^{a=1}\right] - \mathrm{E}\left[Y^{a=0}\right]$ remains identified, but no longer equals the usual IV estimator. As a consequence, our estimate of $\mathrm{E}\left[Y^{a=1}\right] - \mathrm{E}\left[Y^{a=0}\right]$ will depend on whether we assume no additive or multiplicative effect modification by Z. Unfortunately, it is not possible to determine which, if either, assumption is true even if we had an infinite sample size (Robins 1994) because, when considering saturated additive or multiplicative structural mean models, we have more unknown parameters to estimate than equations to estimate them with. That is precisely why we need to make modelling assumptions such as homogeneity.

Also, models can be used to incorporate multiple proposed instruments simultaneously, to handle continuous treatments, and to estimate causal risk ratios when the outcome is dichotomous (see Palmer et al. 2011 for a review).

in the treated to vary with Z by imposing constraints on how the treatment effect varies within levels of the covariates. See Section 16.5. and Technical Point 16.5 for more details on structural mean models with covariates.

Another approach is to use an alternative condition (iv) that does not require effect homogeneity. When combined with the three instrumental conditions (i)-(iii), this alternative condition allows us to endow the usual IV estimand with a causal interpretation, even though it does not suffice to identify the average causal effect in the population. We review this alternative condition (iv) in the next section.

16.4 An alternative fourth condition: monotonicity

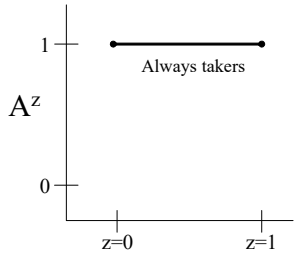

Figure 16.4

Consider again the double-blind randomized trial with randomization indicator Z, treatment A, and outcome Y. For each individual in the trial, the counterfactual variable $A^{z=1}$ is the value of treatment—1 or 0—that an individual would have taken if he had been assigned to receive treatment ($z=1$). The counterfactual variable $A^{z=0}$ is analogously defined as the treatment value if the individual had been assigned to receive no treatment ($z=0$).

If we knew the values of the two counterfactual treatment variables $A^{z=1}$ and $A^{z=0}$ for each individual, we could classify all individuals in the study population into four disjoint subpopulations:

1. *Always-takers*: Individuals who will always take treatment, regardless of the treatment group they were assigned to. That is, individuals with

Technical Point 16.5

More general structural mean models. Consider an additive structural mean model that allows for continuous and/or multivariate treatments A, instruments Z, and pre-instrument covariates V. Such model assumes

$$\mathrm{E}\left[Y - Y^{a=0}|Z, A, V\right] = \gamma\left(Z, A, V; \psi\right)$$

where $\gamma\left(Z, A, V; \psi\right)$ is a known function, ψ is an unknown (possibly vector-valued) parameter, and $\gamma\left(Z, A = 0, V; \psi\right) = 0$. That is, an additive structural mean model is a model for the average causal effect of treatment level A compared with treatment level 0 among the subset of individuals at level Z of the instrument and level V of the confounders whose observed treatment is precisely A. The parameters of this model can be identified via g-estimation under the conditional counterfactual mean independence assumption $\mathrm{E}\left[Y^{a=0}|Z = 1, V\right] = \mathrm{E}\left[Y^{a=0}|Z = 0, V\right]$.

Analogously, a general multiplicative structural mean model assumes

$$\mathrm{E}\left[Y|Z, A, V\right] = \mathrm{E}\left[Y^{a=0}|Z, A, V\right] \exp\left[\gamma\left(Z, A, V; \psi\right)\right]$$

where $\gamma\left(Z, A, V; \psi\right)$ is a known function, ψ is an unknown parameter vector, and $\gamma\left(Z, A = 0, V; \psi\right) = 0$. The parameters of this model can also be identified via g-estimation under analogous conditions. Identification conditions and efficient estimators for structural mean models were discussed by Robins (1994) and reviewed by Vansteelandt and Goetghebeur (2003). More generally, g-estimation of nested additive and multiplicative structural mean models can extend IV methods for time-fixed treatments and confounders to settings with time-varying treatments and confounders.

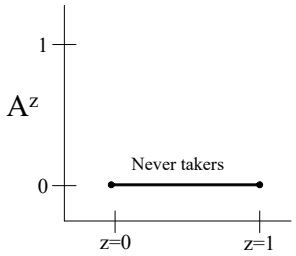

Figure 16.5

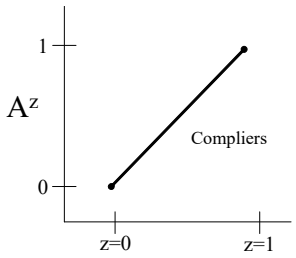

Figure 16.6

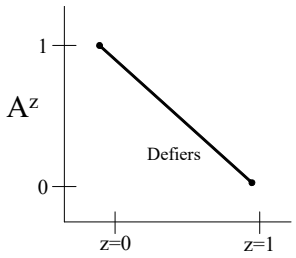

Figure 16.7

both $A^{z=1} = 1$ and $A^{z=0} = 1$.

2. *Never-takers*: Individuals who will never take treatment, regardless of the treatment group they were assigned to. That is, individuals with both $A^{z=1} = 0$ and $A^{z=0} = 0$.

3. *Compliers* or cooperative: Individuals who will take treatment when assigned to treatment, and no treatment when assigned to no treatment. That is, individuals with $A^{z=1} = 1$ and $A^{z=0} = 0$.

4. *Defiers* or contrarians: Individuals who will take no treatment when assigned to treatment, and treatment when assigned to no treatment. That is, individuals with $A^{z=1} = 0$ and $A^{z=0} = 1$.

Note that these subpopulations—often referred as *compliance types* or *principal strata*—are not generally identified. If we observe that an individual was assigned to $Z = 1$ and took treatment $A = 1$, we do not know whether she is a complier or an always-taker. If we observe that an individual was assigned to $Z = 1$ and took treatment $A = 0$, we do not know whether he is a defier or a never-taker.

When no defiers exist, we say that there is monotonicity because the instrument Z either does not change treatment A—as shown in Figure 16.4 for always-takers and Figure 16.5 for never-takers—or increases the value of treatment A—as shown in Figure 16.6 for compliers. For defiers, the instrument Z would decrease the value of treatment A—as shown in Figure 16.7. More generally, monotonicity holds when $A^{z=1} \geq A^{z=0}$ for all individuals.

Now let us replace any of the homogeneity conditions from the last section by the monotonicity condition, which will become our new condition (iv). Then the usual IV estimand does not equal the average causal effect of treatment $\mathrm{E}\left[Y^{a=1}\right] - \mathrm{E}\left[Y^{a=0}\right]$ any more. Rather, under monotonicity (iv), the usual IV

estimand equals the average causal effect of treatment in the compliers, that is

$$\mathrm{E}\left[Y^{a=1} - Y^{a=0} | A^{z=1} = 1, A^{z=0} = 0\right].$$

Technical Point 16.6 shows a proof for this equality under the assumption that Z was effectively randomly assigned. As a sketch of the proof, the equality between the usual IV estimand and the effect in the compliers holds because the effect of assignment Z on Y—the numerator of the IV estimand—is a weighted average of the effect of Z in each of the four principal strata. However, the effect of Z on Y is exactly zero in always-takers and never-takers because the effect of Z is entirely mediated through A and the value of A in those subpopulations is fixed, regardless of the value of Z they are assigned to. Also, no defiers exist under monotonicity (iv). Therefore the numerator of the IV estimand is the effect of Z on Y in the compliers—which is the same as the effect of A on Y in the compliers—times the proportion of compliers in the population, which is precisely the denominator of the usual IV estimand.

The "compliers average causal effect" (CACE) is an example of a local average treatment effect (LATE) in a subpopulation, as opposed to the global average causal effect in the entire population. Greenland (2000) refers to compliers as cooperative, and to defiers as non-cooperative, to prevent confusion with the common concept of (observed) compliance in randomized trials.

In observational studies, the usual IV estimand can also be used to estimate the effect in the compliers in the absence of defiers. Technically, there are no compliers or defiers in observational studies because the proposed instrument Z is not treatment assignment, but the term compliers refers to individuals with $(A^{z=1} = 1, A^{z=0} = 0)$ and the term defiers to those with $(A^{z=1} = 0, A^{z=0} = 1)$. In our smoking cessation example, the compliers are the individuals who would quit smoking in a state with high cigarette price and who would not quit smoking in a state with low price. Conversely, the defiers are the individuals who would not quit smoking in a state with high cigarette price and who would quit smoking in a state with low price. If no defiers exist and the causal instrument is dichotomous (see below and Technical Point 16.6), then 2.4 kg is the IV effect estimate in the compliers.

The replacement of homogeneity by monotonicity was welcomed in the mid-1990s as the salvation of IV methods. While homogeneity is often an implausible condition (iv), monotonicity appeared credible in many settings. IV methods under monotonicity (iv) cannot identify the average causal effect in the population, only in the subpopulation of compliers, but that seemed a price worth paying in order to keep powerful IV methods in our toolbox. However, the estimation of the average causal effect of treatment in the compliers under monotonicity (iv) has been criticized on several grounds.

Deaton (2010) on the effect in the compliers: "This goes beyond the old story of looking for an object where the light is strong enough to see; rather, we have control over the light, but choose to let it fall where it may and then proclaim that whatever it illuminates is what we were looking for all along."

First, the relevance of the effect in the compliers is questionable. The subpopulation of compliers is not identified and, even though the proportion of compliers in the population can be calculated (it is the denominator of the usual IV estimand, see Technical Point 16.6), it varies from instrument to instrument and from study to study. Therefore, causal inferences about the effect in the compliers are difficult to use by decision makers. Should they prioritize the administration of treatment $A = 1$ to the entire population because treatment has been estimated to be beneficial among the compliers, which happen to be 6% of the population in our example but could be a smaller or larger group in the real world? What if treatment is not as beneficial in always-takers and never-takers, the majority of the population? Unfortunately, the decision maker cannot know who is included in the 6%. Rather than arguing that the effect of the compliers is of primary interest, it may be more honest to accept that interest in this estimand is not the result of its practical relevance, but rather of the (often erroneous) perception that it is easy to identify.

A mitigating factor is that, under strong assumptions, investigators can characterize the compliers in terms of their distribution of the observed variables (Angrist and Pischke 2009, Baiocchi et al 2014).

Second, monotonicity is not always a reasonable assumption in observational studies. The absence of defiers seems a safe assumption in randomized

trials: we do not expect that some individuals will provide consent for participation in a trial with the perverse intention to do exactly the opposite of what they are asked to do. Further, monotonicity is ensured by design in trials in which those assigned to no treatment are prevented from receiving treatment, i.e., there are no always-takers or defiers. However, monotonicity is harder to justify for some instruments proposed in observational studies. Consider the proposed instrument "physician preference" to estimate the treatment effect in patients attending a clinic where two physicians with different preferences work. The first physician usually prefers to prescribe the treatment, but she makes exceptions for her patients with diabetes (because of some known contraindications). The second usually prefers to not prescribe the treatment, but he makes exceptions for his more physically active patients (because of some perceived benefits). Any patient who was both physically active and diabetic would have been treated contrary to both of these physicians' preferences, and therefore would be labeled as a defier. That is, monotonicity is unlikely to hold when the decision to treat is the result of weighing multiple criteria or dimensions of encouragement that include both risks and benefits. In these settings, the proportion of defiers may not be negligible.

The example to the right was proposed by Swanson and Hernán (2014). Also Swanson et al (2015a) showed empirically the existence in defiers in an observational setting.

The situation is even more complicated for the proxy instruments Z represented by Figures 16.2 and 16.3. If the causal instrument U_Z is continuous (e.g., the true, unmeasured physician's preference), then the standard IV estimand using a dichotomous proxy instrument Z (e.g., some measured surrogate of preference) is not the effect in a particular subpopulation of compliers. Rather, the standard IV estimand identifies a particular weighted average of the effect in all individuals in the population, which makes it difficult to interpret. Therefore the interpretation of the IV estimand as the effect in the compliers is questionable when the proposed dichotomous instrument is not causal, even if monotonicity held for the continuous causal instrument U_Z (see Technical Point 16.6 for details).

Definition of monotonicity for a continuous causal instrument U_Z: A^{u_z} is a non-decreasing function of u_z on the support of U_Z (Angrist and Imbens 1995, Heckman and Vytlacil 1999).

Last, but definitely not least important, the partitioning of the population into four subpopulations or principal strata may not be justifiable. In many realistic settings, the subpopulation of compliers is an ill-defined subset of the population. For example, using the proposed instrument "physician preference" in settings with multiple physicians, all physicians with the same preference level *who could have seen a patient* would have to treat the patient in the exact same way. This is not only an unrealistic assumption, but also essentially impossible to define in many observational studies in which it is unknown which physicians could have seen a patient. A stable partitioning into compliers, defiers, always takers and never takers also requires deterministic counterfactuals (not generally required to estimate average causal effects), no interference (e.g., I may be an always-taker, but decide not to take treatment when my friend doesn't), absence of multiple versions of treatment and other forms of heterogeneity (a complier in one setting, or for a particular instrument, may not be a complier in another setting).

Swanson et al (2015) discuss the difficulties to define monotonicity, and introduce the concept of global and local monotonicity in observational studies.

In summary, if the effect in the compliers is considered to be of interest, relying on monotonicity (iv) seems a promising approach in double-blind randomized trials with two arms and all-or-nothing compliance, especially when one of the arms will exhibit full adherence by design. However, caution is needed when using this approach in more complex settings and observational studies, even if the proposed instrument were really an instrument.

Sommer and Zeger (1991), Imbens and Rubin (1997), and Greenland (2000) describe examples of full compliance in the control group.

Fine Point 16.2

Defining weak instruments. There are two related, but different, definitions of weak instrument in the literature:

1. An instrument is weak if the true value of the Z-A association—the denominator of the IV estimand—is "small."
2. An instrument is weak if the F-statistic associated to the observed Z-A association is "small," typically meaning less than 10.

In our smoking cessation example, the proposed instrument met both definitions: the risk difference was only 6% and the F-statistic was a meager 0.8.

The first definition, based on the true value of the Z-A association, reminds us that, even if we had an infinite sample, the IV estimator greatly amplifies any biases in the numerator when using a proposed weak instrument (the second problem of weak instruments in the main text). The second definition, based on the statistical properties of the Z-A association, reminds us that, even if we had a perfect instrument Z, the IV estimator can be biased in finite samples (the third problem of weak instruments in the main text).

16.5 The three instrumental conditions revisited

The previous sections have discussed the relative advantages and disadvantages of choosing monotonicity or homogeneity as the condition (iv). Our discussion implicitly assumed that the proposed instrument Z was in fact an instrument. However, in observational studies, the proposed instrument Z will fail to be a valid instrument if it violates either of the instrumental conditions (ii) or (iii), and will be a weak instrument if it only barely meets condition (i). In all these cases, the use of IV estimation may result in substantial bias even if condition (iv) held perfectly. We now discuss each of the three instrumental conditions.

Condition (i), a Z-A association, is empirically verifiable. Before declaring Z as their proposed instrument, investigators will check that Z is associated with treatment A. However, when the Z-A association is weak as in our smoking cessation example, the instrument is said to be weak (see Fine Point 16.2). Three serious problems arise when the proposed instrument is weak.

In the context of linear models, Martens et al (2006) showed that instruments are guaranteed to be weak in the presence of strong confounding, because a strong A-U association leaves little residual variation for a strong A-U_Z, or A-Z, association.

First, weak instruments yield effect estimates with wide 95% confidence intervals, as in our smoking cessation example in Section 16.2. Second, weak instruments amplify bias due to violations of conditions (ii) and (iii). A proposed instrument Z which is weakly associated with treatment A yields a small denominator of the IV estimator. Therefore, violations of conditions (ii) and (iii) that affect the numerator of the IV estimator (e.g., unmeasured confounding for the instrument, a direct effect of the instrument) will be greatly exaggerated. In our example, any bias affecting the numerator of the IV estimator would be multiplied by approximately 15.9 (1/0.0627). Third, even in large samples, weak instruments introduce bias in the standard IV estimator and result in underestimation of its variance. That is, the effect estimate is in the wrong place and the width of the confidence interval around it is too narrow.

Bound, Jaeger and Baker (1995) documented this bias. Their paper was followed by many others that investigated the shortcomings of weak instruments.

To understand the nature of this third problem, consider a randomly generated dichotomous variable Z. In an infinite population, the denominator of the IV estimand will be exactly zero—there is a zero association between treatment A and a completely random variable—and the IV estimate will be undefined. However, in a study with a finite sample, chance will lead to an association between the randomly generated Z and the unmeasured confounders

U—and therefore between Z and treatment A—that is weak but not exactly zero. If we propose this random Z as an instrument, the denominator of the IV estimator will be very small rather than zero. As a result the numerator will be incorrectly inflated, which will yield potentially very large bias. In fact, our proposed instrument "Price higher than \$1.50" behaves like a randomly generated variable. Had we decided to define Z as price higher than \$1.60, \$1.70, \$1.80, or \$1.90, the IV estimate would have been 41.3, −40.9, −21.1, or −12.8 kg, respectively. In each case, the 95% confidence interval around the estimate was huge, though still an underestimate of the true uncertainty. Given how much bias and variability weak instruments may create, a strong proposed instrument that slightly violates conditions (ii) and (iii) may be preferable to a less invalid, but weaker, proposed instrument.

CODE: Program 16.4

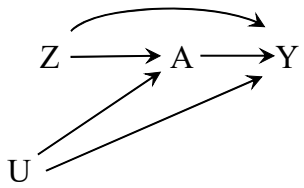

Figure 16.8

Condition (ii), the absence of a direct effect of the instrument on the outcome, cannot be verified from the data. A deviation from condition (ii) can be represented by a direct arrow from the instrument Z to the outcome Y, as shown in Figure 16.8. This direct effect of the instrument that is not mediated through treatment A will contribute to the numerator of the IV estimator, and it will be incorrectly inflated by the denominator as if it were part of the effect of treatment A. Condition (ii) may be violated when a continuous or multivalued treatment A is replaced in the analysis by a coarser (e.g., dichotomized) version A^*. Figure 16.9 shows that, even if condition (ii) holds for the original treatment A, it does not have to hold for its dichotomized version A^*, because the path $Z \rightarrow A \rightarrow Y$ represents a direct effect of the instrument Z that is not mediated through the treatment A^* whose effect is being estimated in the IV analysis. In practice, many treatments are replaced by coarser versions for simplicity of interpretation. Coarsening of treatment is problematic for IV estimation, but not necessarily for the methods discussed in previous chapters.

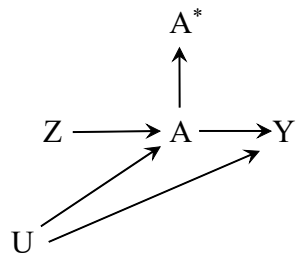

Figure 16.9

Condition (iii), no confounding for the effect of the instrument on the outcome, is also unverifiable. Figure 16.10 shows confounding due to common causes of the proposed instrument Z and outcome Y that are (U_1) and are not (U_2) shared with treatment A. In observational studies, the possibility of confounding for the proposed instrument always exists (same as for any other variable not under the investigator's control). Confounding contributes to the numerator of the IV estimator and is incorrectly inflated by the denominator as if it were part of the effect of treatment A on the outcome Y.

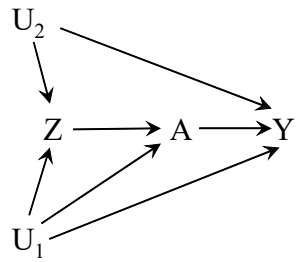

Figure 16.10

Sometimes condition (iii), and the other conditions too, can appear more plausible within levels of the measured covariates. Rather than making the unverifiable assumption that there is absolutely no confounding for the effect of Z on Y, we might feel more comfortable making the unverifiable assumption that there is no unmeasured confounding for the effect of Z on Y within levels of the measured pre-instrument covariates V. We could then apply IV estimation repeatedly in each stratum of V, and pool the IV effect estimates under the assumption that the effect in the population (under homogeneity) or in the compliers (under monotonicity) is constant within levels of V. Alternatively we could include the variables V as covariates in the two-stage modeling. In our example, this reduced the size of the effect estimate and increased its 95% confidence interval.

CODE: Program 16.5

Another frequent strategy to support condition (iii) is to check for balanced distributions of the measured confounders across levels of the proposed instrument Z. The idea is that, if the measured confounders are balanced, it may be more likely that the unmeasured ones are balanced too. However, this practice may offer a false sense of security: even small imbalances can lead to counterintuitively large biases because of the bias amplification discussed

above.

A violation of condition (iii) may occur even in the absence of confounding for the effect of Z on Y. The formal version of condition (iii) requires exchangeability between individuals with different levels of the proposed instrument. Such exchangeability may be violated because of either confounding (see above) or selection bias. A surprisingly common way in which selection bias may be introduced in IV analyses is the exclusion of individuals with certain values of treatment A. For example, if individuals in the population may receive treatment levels $A = 0$, $A = 1$, or $A = 2$, an IV analysis restricted to individuals with $A = 1$ or $A = 2$ may yield a non-null effect estimate even if the true causal effect is null. This exclusion does not introduce bias in non-IV analyses whose goal is to estimate the effect of treatment $A = 1$ versus $A = 2$.

Swanson et al (2015b) describe this selection bias in detail.

All the above problems related to conditions (i)-(iii) are exacerbated in IV analyses that use simultaneously multiple proposed instruments in an attempt to alleviate the weakness of a single proposed instrument. Unfortunately, the larger the number of proposed instruments, the more likely that some of them will violate one of the instrumental conditions.

16.6 Instrumental variable estimation versus other methods

IV estimation differs from all previously discussed methods in at least three aspects.

First, IV estimation requires modeling assumptions even if infinite data were available. This is not the case for previous methods like IP weighting or standardization: If we had treatment, outcome, and confounder data from all individuals in the super-population, we would simply calculate the average treatment effect as we did in Part I of this book, nonparametrically. In contrast, even if we had data on instrument, treatment, and outcome from all individuals in the super-population, IV estimation effectively requires the use of modeling assumptions in order to identify the average causal effect in the population. The homogeneity condition (iv) is mathematically equivalent to setting to zero the parameter corresponding to a product term in a structural mean model (see Technical Point 16.1). That is, IV estimation cannot be nonparametric—models are required for identification—which explains why the method was not discussed in Part I of this book.

IV estimation is not the only method that requires modeling for identification of causal effects. Other econometric approaches like *regression discontinuity analysis* (Thistlewaite and Campbell 1960) do too.

Second, relatively minor violations of conditions (i)-(iv) for IV estimation may result in large biases of unpredictable or counterintuitive direction. The foundation of IV estimation is that the denominator blows up the numerator. Therefore, when the conditions do not hold perfectly or the instrument is weak, there is potential for explosive bias in either direction. As a result, an IV estimate may often be more biased than an unadjusted estimate. In contrast, previous methods tend to result in slightly biased estimates when their identifiability conditions are only slightly violated, and adjustment is less likely to introduce a large bias. The exquisite sensitivity of IV estimates to departures from its identifiability conditions makes the method especially dangerous for novice users, and highlights the importance of sensitivity analyses. In addition, it is often easier to use subject-matter knowledge to think about unmeasured confounders of the effect of A on Y and how they may bias our estimates than to think about unmeasured confounders of the effect of Z on Y and how they and the existence of defiers or effect heterogeneity may bias our estimates.

Baiocchi and Small (2014) review some approaches to quantify how sensitive IV estimates are to violations of key assumptions.

Third, the ideal setting for the applicability of standard IV estimation is

more restrictive than that for other methods. As discussed in this chapter, standard IV estimation is better reserved for settings with lots of unmeasured confounding, a truly dichotomous and time-fixed treatment A, a strong and causal proposed instrument Z, and in which either effect homogeneity is expected to hold, or one is genuinely interested in the effect in the compliers and monotonicity is expected to hold. A consequence of these restrictions is that IV estimation is generally used to answer relatively simple causal questions, such as the contrast $A = 1$ versus $A = 0$. For this reason, IV estimation will not be a prominent method in Part III of this book, which is devoted to time-varying treatments and the contrast of complex treatment strategies that are sustained over time.

Transparency requires proper reporting of IV analyses. See some suggested guidelines by Brookhart et al (2010), Swanson and Hernán (2013), and Baiocchi and Small (2014).

Causal inference relies on transparency of assumptions and on triangulation of results from methods that depend on different sets of assumptions. IV estimation is therefore an attractive approach because it depends on a different set of assumptions than other methods. However, because of the wide 95% confidence intervals typical of IV estimates, the value added by using this approach will often be small. Also, users of IV estimation need to be critically aware of the limitations of the method. While this statement obviously applies to any causal inference method, the potentially counterintuitive direction and magnitude of bias in IV estimation requires especial attention.

Technical Point 16.6

Monotonicity and the effect in the compliers. Consider a dichotomous causal instrument Z, like the randomization indicator described in the text, and treatment A. Imbens and Angrist (1994) proved that the usual IV estimand equals the average causal effect in the compliers $\mathrm{E}\left[Y^{a=1} - Y^{a=0} | A^{z=1} - A^{z=0} = 1\right]$ under monotonicity (iv), i.e., when no defiers exist. Baker and Lindeman (1994) had a related proof for a binary outcome. See also Angrist, Imbens, and Rubin (1996), and the associated discussion, and Baker, Kramer, and Lindeman (2016). A proof follows.

The intention-to-treat effect can be written as the weighted average of the intention-to-treat effects in the four principal strata:

$$\begin{aligned}
\mathrm{E}\left[Y^{z=1} - Y^{z=0}\right] = {} & \mathrm{E}\left[Y^{z=1} - Y^{z=0} | A^{z=1} = 1, A^{z=0} = 1\right] \Pr\left[A^{z=1} = 1, A^{z=0} = 1\right] && \text{(always-takers)} \\
& + \mathrm{E}\left[Y^{z=1} - Y^{z=0} | A^{z=1} = 0, A^{z=0} = 0\right] \Pr\left[A^{z=1} = 0, A^{z=0} = 0\right] && \text{(never-takers)} \\
& + \mathrm{E}\left[Y^{z=1} - Y^{z=0} | A^{z=1} = 1, A^{z=0} = 0\right] \Pr\left[A^{z=1} = 1, A^{z=0} = 0\right] && \text{(compliers)} \\
& + \mathrm{E}\left[Y^{z=1} - Y^{z=0} | A^{z=1} = 0, A^{z=0} = 1\right] \Pr\left[A^{z=1} = 0, A^{z=0} = 1\right] && \text{(defiers)}
\end{aligned}$$

However, the intention-to-treat effect in both the always-takers and the never-takers is zero, because Z does not affect A in these two strata and, by individual-level condition (ii) of Technical Point 16.1, Z has no independent effect on Y. If we assume that no defiers exist, then the above sum is simplified to

$$\mathrm{E}\left[Y^{z=1} - Y^{z=0}\right] = \mathrm{E}\left[Y^{z=1} - Y^{z=0} | A^{z=1} = 1, A^{z=0} = 0\right] \Pr\left[A^{z=1} = 1, A^{z=0} = 0\right] \qquad \text{(compliers)}.$$

But, in the compliers, the effect of Z on Y equals the effect of A on Y (because $Z = A$), that is $\mathrm{E}\left[Y^{z=1} - Y^{z=0} | A^{z=1} = 1, A^{z=0} = 0\right] = \mathrm{E}\left[Y^{a=1} - Y^{a=0} | A^{z=1} = 1, A^{z=0} = 0\right]$. Therefore, the effect in the compliers is

$$\mathrm{E}\left[Y^{a=1} - Y^{a=0} | A^{z=1} = 1, A^{z=0} = 0\right] = \frac{\mathrm{E}\left[Y^{z=1} - Y^{z=0}\right]}{\Pr\left[A^{z=1} = 1, A^{z=0} = 0\right]}$$

which is the usual IV estimand if we assume that Z is randomly assigned, as random assignment implies $Z \perp\!\!\!\perp \{Y^{a,z}, A^z;\ z = 0, 1; a = 0, 1\}$. Under this joint independence and consistency, the intention-to-treat effect $\mathrm{E}\left[Y^{z=1} - Y^{z=0}\right]$ in the numerator equals $\mathrm{E}[Y|Z=1] - \mathrm{E}[Y|Z=0]$, and the proportion of compliers $\Pr\left[A^{z=1} = 1, A^{z=0} = 0\right]$ in the denominator equals $\Pr[A=1|Z=1] - \Pr[A=1|Z=0]$. To see why the latter equality holds, note that the proportion of always-takers $\Pr\left[A^{z=0} = 1\right] = \Pr[A=1|Z=0]$ and the proportion of never-takers $\Pr\left[A^{z=1} = 0\right] = \Pr[A=0|Z=1]$. Since, under monotonicity (iv), there are no defiers, the proportion of compliers $\Pr\left[A^{z=1} - A^{z=0} = 1\right]$ is the remainder $1 - \Pr[A=1|Z=0] - \Pr[A=0|Z=1] =$
$1 - \Pr[A=1|Z=0] - (1 - \Pr[A=1|Z=1]) = \Pr[A=1|Z=1] - \Pr[A=1|Z=0]$, which completes the proof.

The above proof only considers the setting depicted in Figure 16.1 in which the instrument Z is causal. When, as depicted in Figures 16.2 and 16.3, data on a surrogate instrument Z—but not on the causal instrument U_Z—are available, Hernán and Robins (2006b) proved that the average causal effect in the compliers (defined according to U_Z) is also identified by the usual IV estimator. Their proof depends critically on two assumptions: that Z is independent of A and Y given the causal instrument U_Z, and that U_Z is binary. However, this independence assumption has often little substantive plausibility unless U_Z is continuous. A corollary is that the interpretation of the IV estimand as the effect in the compliers is questionable in many applications of IV methods to observational data in which Z is at best a surrogate for U_Z.

Chapter 17
CAUSAL SURVIVAL ANALYSIS

In previous chapters we have been concerned with causal questions about the treatment effects on outcomes occurring at a particular time point. For example, we have estimated the effect of smoking cessation on weight gain measured in the year 1982. Many causal questions, however, are concerned with treatment effects on the time until the occurrence of an event of interest. For example, we may want to estimate the causal effect of smoking cessation on the time until death, whenever death occurs. This is an example of a *survival analysis*.

The use of the word "survival" does not imply that the event of interest must be death. The term "survival analysis", or the equivalent term "failure time analysis", is applied to any analyses about time to an event, where the event may be death, marriage, incarceration, cancer, flu infection, etc. Survival analyses require some special considerations and techniques because the failure time of many individuals may occur after the study has ended and is therefore unknown. This chapter outlines basic techniques for survival analysis in the simplified setting of time-fixed treatments.

17.1 Hazards and risks

Suppose we want to estimate the average causal effect of smoking cessation A (1: yes, 0: no) on the time to death T with time measured from the start of follow-up. This is an example of a *survival analysis*: the outcome is time to an event of interest that can occur at any time after the start of follow-up. In most follow-up studies, the event of interest is not observed to happen for all, or even the majority of, individuals in the study. This is so because most follow-up studies have a date after which there is no information on any individuals: the *administrative end of follow-up*.

After the administrative end of follow-up, no additional data can be used. Individuals who do not develop the event of interest before the administrative end of follow-up have their survival time administratively censored, that is, we know that they survived beyond the administrative end of follow-up, but we do not know for how much longer. For example, let us say that we conduct the above survival analysis among the 1629 cigarette smokers from the NHEFS who were aged 25-74 years at baseline and who were alive through 1982. For all individuals, the start of follow-up is January 1, 1983 and the administrative end of follow-up is December 31, 1992. We define the administrative censoring time to be the difference between the date of administrative end of follow-up and date at which follow-up begins. In our example, this time is the same—120 months—for all individuals because the start of follow-up and the administrative end of follow-up are the same for everybody. Of the 1629 individuals, only 318 individuals died before the end of 1992, so the survival time of the remaining 1311 individuals is administratively censored.

In a study with staggered entry (i.e., with a variable start of follow-up date) different individuals will have different administrative censoring times, even when the administrative end of follow-up date is common to all.

Administrative censoring is a problem intrinsic to survival analyses—studies of smoking cessation and death will rarely, if ever, follow a cohort of individuals until extinction—but administrative censoring is not the only type of censoring that may occur in survival analyses. Like any other causal analyses, survival analysis may also need to handle non-administrative types of censoring, such

Fine Point 17.1

Competing events. As described in Section 8.5, a competing event is an event (typically, death) that prevents the event of interest (e.g., stroke) from happening: individual who die from other causes (say, cancer) cannot ever develop stroke. In survival analyses, the key decision is whether to consider competing events a form of non-administrative censoring.

- If the competing event is considered a censoring event, then the analysis is effectively an attempt to simulate a population in which death from other causes is somehow either abolished or rendered independent of the risk factors for stroke. The resulting effect estimate is hard to interpret and may not correspond to a meaningful estimand (see Chapter 8). In addition, the censoring may introduce selection bias under the null, which would require adjustment (by, say, IP weighting) using data on the measured risk factors for the event of interest.
- If the competing event is not considered a censoring event, then the analysis effectively sets the time to event to be infinite. That is, dead individuals are considered to have probability zero of developing stroke between their death and the administrative end of follow-up. The estimate of the effect of treatment on stroke is hard to interpret because a non-null estimate may arise from a direct effect of treatment on death, which would prevent the occurrence of stroke.

An alternative to the handling of competing events is to create a composite event that includes both the competing event and the event of interest (e.g., death and stroke) and conduct a survival analysis for the composite event. This approach effectively eliminates the competing events, but fundamentally changes the causal question. Again, the resulting effect estimate is hard to interpret because a non-null estimate may arise from either an effect of treatment on stroke or on death. Another alternative is to restrict the inference to the principal stratum of individuals who would not die regardless of the treatment level they received. This approach targets a sort of local average effect, as defined in Chapter 16, which makes both interpretation and valid estimation especially challenging.

None of the above strategies provides a satisfactory solution to the problem of competing events. Indeed the presence of competing events raises logical questions about the meaning of the causal estimand that cannot be bypassed by statistical techniques. For a detailed description of approaches to handle competing events and their challenges, see the discussion by Young et al. (2019).

as loss to follow-up (e.g., dropout from the study) and competing events (see Fine Point 17.1). In previous chapters we have discussed how to adjust for the selection bias introduced by non-administrative censoring via standardization or IP weighting. The same approaches can be applied to survival analyses. Therefore, in this chapter, we will focus on administrative censoring. We defer a more detailed consideration of non-administrative censoring to Part III of the book because non-administrative censoring is generally a time-varying process, whereas the time of administrative censoring is fixed at baseline.

For simplicity, we assume that anyone without confirmed death survived the follow-up period. In reality, some individuals may have died but confirmation (by, say, a death certificate or a proxy interview) was not feasible. Also for simplicity, we will ignore the problem described in Fine Point 12.1.

In our example, the month of death T can take values subsequent from 1 (January 1983) to 120 (December 1992). T is known for 102 treated ($A = 1$) and 216 untreated ($A = 0$) individuals who died during the follow-up, and is administratively censored (that is, all we know is that it is greater than 120 months) for the remaining 1311 individuals. Therefore we cannot compute the mean survival $\widehat{\mathrm{E}}[T]$ as we did in previous chapters with the outcome of interest. Rather, in survival analysis we need to use other measures that can accommodate administrative censoring. Some common measures are the survival probability, the risk, and the hazard. Let us define these quantities, which are functions of the survival time T.

The *survival probability* $\Pr[T > k]$, or simply the survival at month k, is the proportion of individuals who survived through time k. If we calculate the

survivals at each month until the administrative end of follow-up $k_{end} = 120$ and plot them along a horizontal time axis, we obtain the *survival curve*. The survival curve starts at $\Pr[T > 0] = 1$ for $k = 0$ and then decreases monotonically—that is, it does not increase—with subsequent values of $k = 1, 2, ...k_{end}$. Alternatively, we can define *risk*, or cumulative incidence, at time k as one minus the survival $1 - \Pr[T > k] = \Pr[T \leq k]$. The cumulative incidence curve starts at $\Pr[T \leq 0] = 0$ and increases monotonically during the follow-up.

Other effect measures that can be derived from survival curves are years of life lost and the restricted mean survival time.

In survival analyses, a natural approach to quantify the treatment effect is to compare the survival or risk under each treatment level at some or all times k. Of course, in our smoking cessation example, a contrast of these curves may not have a causal interpretation because the treated and the untreated are probably not exchangeable. However, suppose for a second (actually, until Section 17.4) that quitters ($A = 1$) and non-quitters ($A = 0$) are marginally exchangeable. Then we can construct the survival curves shown in Figure 17.1 and compare $\Pr[T > k|A = 1]$ versus $\Pr[T > k|A = 0]$ for all times k. For example, the survival at 120 months was 76.2% among quitters and 82.0% among non-quitters. Alternatively, we could contrast the risks rather than the survivals. For example, the 120-month risk was 23.8% among quitters and 18.0% among non-quitters.

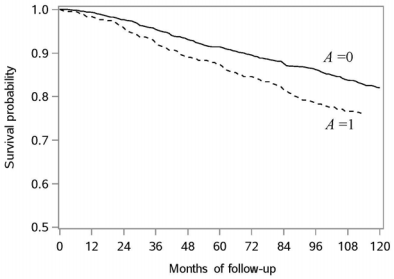

Figure 17.1

CODE: Program 17.1
A common statistical test to compare survival curves (the log-rank test) yielded a P-value= 0.005.

At any time k, we can also calculate the proportion of individuals who develop the event among those who had not developed it before k. This is the *hazard* $\Pr[T = k|T > k - 1]$. Technically, this is the discrete time hazard, that is, the hazard in a study in which time is measured in discrete intervals—as opposed to measured continuously. Because in real-world studies, time is indeed measured in discrete intervals (years, months, weeks, days...) rather than in a truly continuous fashion, here we will refer to the discrete time hazard as, simply, the hazard.

The risk and the hazard are different measures. The denominator of the risk—the number of individuals at baseline—is constant across times k and its numerator—all events between baseline and k—is cumulative. That is, the risk will stay flat or increase as k increases. On the other hand, the denominator of the hazard—the number of individuals alive at k—varies over time t and its numerator includes only recent events—those during interval k. That is, the hazard may increase or decrease over time. In our example, the hazard at 120 months was 0% among quitters (because the last death happened at 113 months in this group) and $1/986 = 0.10\%$ among non-quitters, and the hazard curves between 0 and 120 months had roughly the shape of a letter M.

A frequent approach to quantify the treatment effect in survival analyses is to estimate the ratio of the hazards in the treated and the untreated, known as the *hazard ratio*. However, the hazard ratio is problematic for the reasons described in Fine Point 17.2. Therefore, the survival analyses in this book privilege survival/risk over hazard. However, that does not mean that we should completely ignore hazards. The estimation of hazards is often a useful intermediate step for the estimation of survivals and risks.

17.2 From hazards to risks

In survival analyses, there are two main ways to arrange the analytic dataset. In the first data arrangement each row of the database corresponds to one person. This data format—often referred to as the long or wide format when

there are time-varying treatments and confounders—is the one we have used so far in this book. In the analyses of the previous section, the dataset had 1629 rows, one per individual.

In the second data arrangement each row of the database corresponds to a person-time. That is, the first row contains the information for person 1 at $k = 0$, the second row the information for person one at $k = 1$, the third row the information for person 1 at $k = 2$, and so on until the follow-up of person one ends. The next row contains the information of person 2 at $k = 0$, etc. This person-time data format is the one we will use in most survival analyses in this chapter and in all analysis with time-varying treatments in Part III. In our smoking cessation example, the person-time dataset has 176, 764 rows, one per person-month.

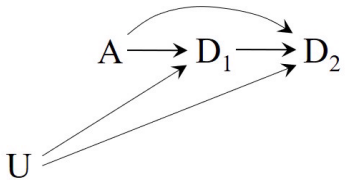

Figure 17.2

To encode survival information through k in the person-time data format, it is helpful to define a time-varying indicator of event D_k. For each person at each month k, the indicator D_k takes value 1 if $T \leq k$ and value 0 if $T > k$. The causal diagram in Figure 17.2 shows the treatment A and the event indicators D_1 and D_2 at times 1 and 2, respectively. The variable U represents the (generally unmeasured) factors that increase susceptibility to the event of interest. Note that sometimes these susceptibility factors are time-varying too. In that case, they can be depicted in the causal diagram as U_0, U_1..., and so on. Part III deals with the case in which the treatment itself is time-varying.

In the person-time data format, the row for a particular individual at time k includes the indicator D_{k+1}. In our example, the first row of the person-time dataset, for individual one at $k = 0$, includes the indicator D_1, which is 1 if the individual died during month 1 and 0 otherwise; the second row, for individual one at $k = 1$, includes the indicator D_2, which is 1 if the individual died during month 2 and 0 otherwise; and so on. The last row in the dataset for each individual is either her first row with $D_{k+1} = 1$ or the row corresponding to month 119.

By definition, everybody had to survive month 0 in order to be included in the dataset, i.e., $D_0 = 0$ for all individuals.

Using the time-varying outcome variable D_k, we can define survival at k as $\Pr[D_k = 0]$, which is equal to $\Pr[T > k]$, and risk at k as $\Pr[D_k = 1]$, which is equal to $\Pr[T \leq k]$. The hazard at k is defined as $\Pr[D_k = 1|D_{k-1} = 0]$. For $k = 1$ the hazard is equal to the risk because everybody is, by definition, alive at $k = 0$.

The survival probability at k is the product of the conditional probabilities of having survived each interval between 0 and k. For example, the survival at $k = 2$, $\Pr[D_2 = 0]$, is equal to survival probability at $k = 1$, $\Pr[D_1 = 0]$, times the survival probability at $k = 2$ conditional on having survived through $k = 1$, $\Pr[D_2 = 0|D_1 = 0]$. More generally, the survival at k is

$$\Pr[D_k = 0] = \prod_{m=1}^{k} \Pr[D_m = 0|D_{m-1} = 0]$$

That is, the survival at k equals the product of one minus the hazard at all previous times. If we know the hazards through k we can easily compute the survival at k (or the risk at k, which is just one minus the survival).

The hazard at k, $\Pr[D_k = 1|D_{k-1} = 0]$, can be estimated nonparametrically by dividing the number of cases during the interval k by the number of individuals alive at the end of interval $k - 1$. If we substitute this estimate into the above formula the resulting nonparametric estimate of the survival $\Pr[D_k = 0]$ at k is referred to as the Kaplan-Meier, or product-limit, estimator. Figure 17.1 was constructed using the Kaplan-Meier estimator, which is

Fine Point 17.2

The hazards of hazard ratios. When using the hazard ratio as a measure of causal effect, two important properties of the hazard ratio need to be taken into account.

First, because the hazards vary over time, the hazard ratio generally does too. That is, the ratio at time k may differ from that at time $k+1$. However, many published survival analyses report a single hazard ratio, which is usually the consequence of fitting a Cox proportional hazards model that assumes a constant hazard ratio by ignoring interactions with time. The reported hazard ratio is a weighted average of the k-specific hazard ratios, which makes it hard to interpret. If the risk is rare and censoring only occurs at a common administrative censoring time k_{end}, then the weight of the hazard ratio at time k is proportional to the total number of events among untreated individuals that occur at k. (Technically, the weights are equal to the conditional density at k of T given $A = 0$ and $T < k_{end}$.) Because it is a weighted average, the reported hazard ratio may be 1 even if the survival curves are not identical. In contrast to the hazard ratio, survival and risks are always presented as depending on time, e.g., the 5-year survival, the 120-month risk.

Second, even if we presented the time-specific hazard ratios, their causal interpretation is not straightforward. Suppose treatment kills all high-risk individuals by time k and has no effects on others. Then the hazard ratio at time $k+1$ compares the treated and the untreated individuals who survived through k. In the treated group, the survivors are all low-risk individuals (because the high-risk ones have already been killed by treatment); in the untreated group, the survivors are a mixture of high-risk and low-risk individuals (because treatment did not weed out the former). As a result the hazard ratio at $k+1$ will be less than 1 even though treatment is not beneficial for any individual.

This apparent paradox is an example of selection bias due to conditioning on a post-treatment variable (i.e., being alive at k) which is affected by treatment. For example, the hazard ratio at time 2 is the probability $\Pr[D_2 = 1|D_1 = 0, A]$ of the event at time 2 among those who survived time 1. As depicted in the causal diagram of Figure 17.3, the conditioning on the collider D_1 will generally open the path $A \rightarrow D_1 \leftarrow U \rightarrow D_2$ and therefore induce an association between treatment A and event D_2 among those with $D_1 = 0$. This built-in selection bias of hazard ratios does not happen if the survival curves are the same in the treated and the untreated, that is, if there are no arrows from A into the indicators for the event. Hernán (2010) described an example of this problem.

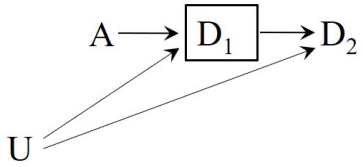

Figure 17.3

Functions other than the logit (e.g., the probit) can also be used to model dichotomous outcomes and therefore to estimate hazards.

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Although each person occurs in multiple rows of the person-time data structure, the standard error of the parameter estimates outputted by a routine logistic regression program will be correct if the hazards model is correct.

an excellent estimator of the survival curve, provided the total number of failures over the follow up period is reasonably large. Typically, the number of cases during each interval is low (or even zero) and thus the nonparametric estimates of the hazard $\Pr[D_k = 1|D_{k-1} = 0]$ at k will be very unstable. If our interest is in estimation of the hazard at a particular k, smoothing via a parametric model may be required (see Chapter 11 and Fine Point 17.3).

An easy way to parametrically estimate the hazards is to fit a logistic regression model for $\Pr[D_{k+1} = 1|D_k = 0]$ that, at each k, is restricted to individuals who survived through k. The fit of this model is straightforward when using the person-time data format. In our example, we can estimate the hazards in the treated and the untreated by fitting the logistic model

$$\text{logit}\ \Pr[D_{k+1} = 1|D_k = 0, A] = \theta_{0,k} + \theta_1 A + \theta_2 A \times k + \theta_3 A \times k^2$$

where $\theta_{0,k}$ is a time-varying intercept that can be estimated by some flexible function of time such as $\theta_{0,k} = \theta_0 + \theta_4 k + \theta_5 k^2$. The flexible time-varying intercept allows for a time-varying hazard and the product terms between treatment A and time ($\theta_2 A \times k + \theta_3 A \times k^2$) allow the hazard ratio to vary over time. See Technical Point 17.1 for details on how a logistic model approximates a hazards model.

We then compute estimates of the survival $\Pr[D_{k+1} = 0|A = a]$ by multiplying the estimates of one minus the estimates of $\Pr[D_{k+1} = 1|D_k = 0, A = a]$ provided by the logistic model, separately for the treated and the untreated. Figure 17.4 shows the survival curves obtained after parametric estimation of the hazards. These curves are a smooth version of those in Figure 17.1.

Fine Point 17.3

Models for survival analysis. Methods for survival analysis need to accommodate the expected censoring of failure times due to administrative end of follow-up.

Nonparametric approaches to survival analysis, like constructing Kaplan-Meier curves, make no assumptions about the distribution of the unobserved failure times due to administrative censoring. On the other hand, parametric models for survival analysis assume a particular statistical distribution (e.g., exponential, Weibull) for the failure times or hazards. The logistic model described in the main text to estimate hazards is an example of a parametric model.

Other models for survival analysis, like the Cox proportional hazards model and the accelerated failure time (AFT) model, do not assume a particular distribution for the failure times or hazards. In particular, these models are agnostic about the shape of the hazard when all covariates in the model have value zero—often referred to as the baseline hazard. These models, however, impose a priori restrictions on the relation between the baseline hazard and the hazard under other combinations of covariate values. As a result, these methods are referred to as *semiparametric* methods.

See the book by Hosmer, Lemeshow, and May (2008) for a review of applied survival analysis. More formal descriptions can be found in the books by Fleming and Harrington (2005) and Kalbfleisch and Prentice (2002).

The validity of this procedure requires no misspecification of the hazards model. In our example, this assumption seems plausible because we obtained essentially the same survival estimates as in the previous section when we estimated the survival in a fully nonparametric way. A 95% confidence interval around the survival estimates can be easily constructed via bootstrapping of the individuals in the population.

17.3 Why censoring matters

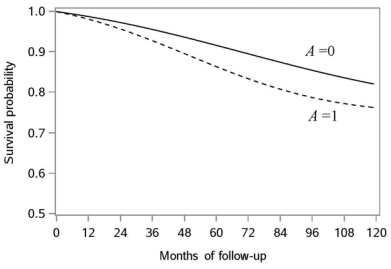

Figure 17.4

The only source of censoring in our study is a common administrative censoring time $k_{end} = 120$ that is identical for all individuals. In this simple setting the procedure described in the previous section to estimate the survival is overkill. One can simply estimate the survival probabilities $\Pr[D_{k+1} = 0|A = a]$ by the fraction of individuals who received treatment a and survived to $k + 1$, or by fitting separate logistic models for $\Pr[D_{k+1} = 0|A]$ at each time, for $k = 0, 1, ..., k_{end}$.

Now suppose that individuals start the follow-up at different dates—there is staggered entry into the study—but the administrative end of follow-up date is common to all. Because the administrative censoring time is the difference between the administrative end of follow-up and the time of start of follow-up, different individuals will have different administrative censoring times. In this setting it is helpful to define a time-varying indicator C_k for censoring by time k. For each person at each month k, the indicator C_k takes value 0 if the administrative end of follow-up is greater than k and takes value 1 otherwise. In the person-time data format, the row for a particular individual at time k includes the indicator C_{k+1}. We did not include this variable in our dataset because $C_{k+1} = 0$ for all individuals at all times k before 120 months. In the general case with random (i.e., individual-specific) administrative censoring, the indicator C_{k+1} will transition from 0 to 1 at different times k for different people.

Our goal is to estimate the survival curve that would have been observed if nobody had been censored before k_{end}, where k_{end} is the maximum administra-

Technical Point 17.1

Approximating the hazard ratio via a logistic model. The (discrete-time) hazard ratio $\frac{\Pr[D_{k+1}=1|D_k=0,A=1]}{\Pr[D_{k+1}=1|D_k=0,A=0]}$ is $\exp(\alpha_1)$ at all times $k+1$ in the hazards model $\Pr[D_{k+1}=1|D_k=0,A] = \Pr[D_{k+1}=1|D_k=0,A=0]\times\exp(\alpha_1 A)$. If we take logs on both sides of the equation, we obtain $\log\Pr[D_{k+1}=1|D_k=0,A] = \alpha_{0,k}+\alpha_1 A$ where $\alpha_{0,k} = \log\Pr[D_{k+1}=1|D_k=0,A=0]$.

Suppose the hazard at $k+1$ is small, i.e., $\Pr[D_{k+1}=1|D_k=0,A]\approx 0$. Then one minus the hazard at $k+1$ is close to one, and the hazard is approximately equal to the odds: $\Pr[D_{k+1}=1|D_k=0,A]\approx\frac{\Pr[D_{k+1}=1|D_k=0,A]}{\Pr[D_{k+1}=0|D_k=0,A]}$. We then have

$$\log\frac{\Pr[D_{k+1}=1|D_k=0,A]}{\Pr[D_{k+1}=0|D_k=0,A]} = \text{logit}\,\Pr[D_{k+1}=1|D_k=0,A]\approx\alpha_{0,k}+\alpha_1 A$$

That is, if the hazard is close to zero at $k+1$, we can approximate the log hazard ratio α_1 by θ_1 in a logistic model $\text{logit}\,\Pr[D_{k+1}=1|D_k=0,A] = \theta_{0,k}+\theta_1 A$ like the one we used in the main text (Thompson 1977). As a rule of thumb, the approximation is often considered to be accurate enough when $\Pr[D_{k+1}=1|D_k=0,A]<0.1$ for all k.

This rare event condition can almost always be guaranteed to hold: we just need to define a time unit k that is short enough for $\Pr[D_{k+1}=1|D_k=0,A]<0.1$. For example, if D_k stands for lung cancer, k may be measured in years; if D_k stands for infection with the common cold virus, k may be measured in days. The shorter the time unit, the more rows in the person-time dataset used to fit the logistic model.

tive censoring time in the study. That is, our goal is to estimate the survival $\Pr[D_k=0|A=a]$ that would have been observed if the value of the time-varying indicators D_k were known even after censoring. Technically, we can also refer to this quantity as $\Pr\left[D_k^{\overline{c}=\overline{0}}=0|A=a\right]$ where $\overline{c}=(c_1,c_2...c_{k_{end}})$. As discussed in Chapter 12, the use of the superscript $\overline{c}=\overline{0}$ makes explicit the quantity that we have in mind. We sometimes choose to omit the superscript $\overline{c}=\overline{0}$ when no confusion can arise. For simplicity, suppose that the time of start of follow-up was as if randomly assigned to each individual, which would be the case if there were no secular trends in any variable. Then the administrative censoring time, and therefore the indicator $\overline{C}$, is independent of both treatment and death time.

We cannot validly estimate this survival $\Pr[D_k=0|A=a]$ at time k by simply computing the fraction of individuals who received treatment level a and survived and were not censored through k. This fraction is a valid estimator of the joint probability $\Pr[C_{k+1}=0,D_{k+1}=0|A=a]$, which is not what we want. To see why, consider a study with $k_{end}=2$ and in which the following happens:

- $\Pr[C_1=0]=1$, i.e., nobody is censored by $k=1$
- $\Pr[D_1=0|C_0=0]=0.9$, i.e., 90% of individuals survive through $k=1$
- $\Pr[C_2=0|D_1=0,C_1=0]=0.5$, i.e., a random half of survivors is censored by $k=2$
- $\Pr[D_2=0|C_2=0,D_1=0,C_1=0]=0.9$, i.e., 90% of the remaining individuals survive through $k=2$

The fraction of uncensored survivors at $k=2$ is $1\times0.9\times0.5\times0.9=0.405$. However, if nobody had been censored, i.e., if $\Pr[C_2=0|D_1=0,C_1=0]=1$, the survival would have been $1\times0.9\times1\times0.9=0.81$. This example motivates how correct estimation of the survivals $\Pr[D_k=0|A=a]$ requires

the procedures described in the previous section. Specifically, under (as if) randomly assigned censoring, the survival $\Pr[D_k = 0|A = a]$ at k is

$$\prod_{m=1}^{k} \Pr[D_m = 0|D_{m-1} = 0, C_m = 0, A = a] \text{ for } k < k_{end}$$

The estimation procedure is the same as described above except that we either use a nonparametric estimate of, or fit a logistic model for, the cause-specific hazard $\Pr[D_{k+1} = 1|D_k = 0, C_{k+1} = 0, A = a]$.

Often we are not ready to assume that censoring is as if randomly assigned. When there is staggered entry, an individual's time of administrative censoring depends on the calendar time at study entry (later entries have shorter values of k_{end}) and calendar time may itself be associated with the outcome. Therefore, the above procedure will need to be adjusted for baseline calendar time. In addition, there may be other baseline prognostic factors that are unequally distributed between the treated ($A = 1$) and the untreated ($A = 0$), which also requires adjustment. The next sections extend the above procedure to incorporate adjustment for baseline confounders via g-methods. In Part III we extend the procedure to settings with time-varying treatments and confounders.

17.4 IP weighting of marginal structural models

When the treated and the untreated are not exchangeable, a direct contrast of their survival curves cannot be endowed with a causal interpretation. In our smoking cessation example, we estimated that the 120-month survival was lower in quitters than in non-quitters (76.2% versus 82.0%), but that does not necessarily imply that smoking cessation increases mortality. Older people are more likely to quit smoking and also more likely to die. This confounding by age makes smoking cessation look bad because the proportion of older people is greater among quitters than among non-quitters.

Let us define $D_k^{a,\overline{c}=\overline{0}}$ as a counterfactual time-varying indicator for death at k under treatment level a and no censoring. For simplicity of notation, we will write $D_k^{a,\overline{c}=\overline{0}}$ as D_k^a when, as in this chapter, it is clear that the goal is estimating the survival in the absence of censoring. For additional simplicity, in the remainder of this chapter we omit $C_k = 0$ from the conditioning event of the hazard at k, $\Pr[D_{k+1} = 0|D_k = 0, L = l, A]$. That is, we write all expressions as if all individuals had a common administrative censoring time, like in our smoking cessation example.

Suppose we want to compare the counterfactual survivals $\Pr\left[D_{k+1}^{a=1} = 0\right]$ and $\Pr\left[D_{k+1}^{a=0} = 0\right]$ that would have been observed if everybody had received treatment ($a = 1$) and no treatment ($a = 0$), respectively. That is, the causal contrast of interest is

$$\Pr\left[D_{k+1}^{a=1} = 0\right] \quad \text{vs.} \quad \Pr\left[D_{k+1}^{a=0} = 0\right] \quad \text{for } k = 0, 2, ...k_{end} - 1$$

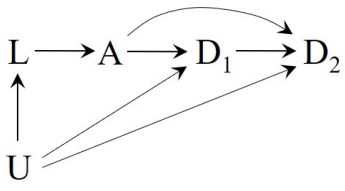

FIGURE 17.5

Because of confounding, this contrast may not be validly estimated by the contrast of the survivals $\Pr[D_{k+1} = 0|A = 1]$ and $\Pr[D_{k+1} = 0|A = 0]$ that we described in the previous sections. Rather, a valid estimation of the quantities $\Pr\left[D_{k+1}^a = 0\right]$ for $a = 1$ and $a = 0$ typically requires adjustment for confounders, which can be achieved through several methods. This section focuses on IP weighting.

Let us assume that the treated ($A = 1$) and the untreated ($A = 0$) are exchangeable within levels of the L variables, as represented in the causal diagram of Figure 17.5. Like in Chapters 12 to 15, L includes the variables sex, age, race, education, intensity and duration of smoking, physical activity in daily life, recreational exercise, and weight. We also assume positivity and consistency. The estimation of IP weighted survival curves has two steps.

CODE: Program 17.3

First, we estimate the stabilized IP weight SW^A for each individual in the study population. The procedure is exactly the same as the one described in Chapter 12. We fit a logistic model for the conditional probability $\Pr[A = 1|L]$ of treatment (i.e., smoking cessation) given the variables in L. The denominator of the estimated SW^A is $\widehat{\Pr}[A = 1|L]$ for treated individuals and $\left(1 - \widehat{\Pr}[A = 1|L]\right)$ for untreated individuals, where $\widehat{\Pr}[A = 1|L]$ is the predicted value from the logistic model. The numerator of the estimated weight SW^A is $\widehat{\Pr}[A = 1]$ for the treated and $\left(1 - \widehat{\Pr}[A = 1]\right)$ for the untreated, where $\widehat{\Pr}[A = 1]$ can be estimated nonparametrically or as the predicted value from a logistic model for the marginal probability $\Pr[A = 1]$ of treatment. See Chapter 11 for details on predicted values.

The application of the estimated weights SW^A creates a pseudo-population in which the variables in L are independent from the treatment A, which eliminates confounding by those variables. In our example, the weights had mean 1 (as expected) and ranged from 0.33 to 4.21.

Second, using the person-time data format, we fit a hazards model like the one described above except that individuals are weighted by their estimated SW^A. Technically, this IP weighted logistic model estimates the parameters of the marginal structural logistic model

$$\text{logit}\ \Pr\left[D^a_{k+1} = 0|D^a_k = 0\right] = \beta_{0,k} + \beta_1 a + \beta_2 a \times k + \beta_3 a \times k^2$$

That is, the IP weighted model estimates the time-varying hazards that would have been observed if all individuals in the study population had been treated ($a = 1$) and the time-varying hazards if they had been untreated ($a = 0$).

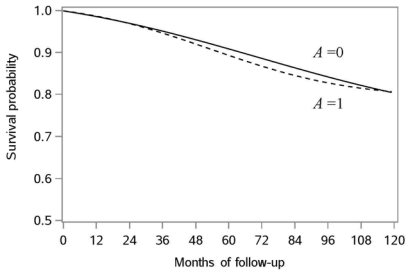

Figure 17.6

The estimates of $\Pr\left[D^a_{k+1} = 0|D^a_k = 0\right]$ from the IP weighted hazards models can then be multiplied over time (see previous section) to obtain an estimate of the survival $\Pr\left[D^a_{k+1} = 0\right]$ that would have been observed under treatment $a = 1$ and under no treatment $a = 0$. The resulting curves are shown in Figure 17.6.

In our example, the 120-month survival estimates were 80.7% under smoking cessation and 80.5% under no smoking cessation; difference 0.2% (95% confidence interval from −4.1% to 3.7% based on 500 bootstrap samples). Though the survival curve under treatment was lower than the curve under no treatment for most of the follow-up, the maximum difference never exceeded −1.4% with a 95% confidence interval from −3.4% to 0.7%. That is, after adjustment for the covariates L via IP weighting, we found little evidence of an effect of smoking cessation on mortality at any time during the follow-up. The validity of this procedure requires no misspecification of both the treatment model and the marginal hazards model.

17.5 The parametric g-formula

In the previous section we estimated the survival curve under treatment and under no treatment in the entire study population via IP weighting. To do

so, we adjusted for L and assumed exchangeability, positivity, and consistency. Another method to estimate the marginal survival curves under those assumptions is standardization based on parametric models, that is, the parametric g-formula.

The survival $\Pr\left[D_{k+1}^{a}=0\right]$ at $k+1$ under treatment level a is the weighted average of the survival conditional probabilities at $k+1$ within levels of the covariates L and treatment level $A=a$, with the proportion of individuals in each level l of L as the weights. That is, under exchangeability, positivity, and consistency, $\Pr\left[D_{k+1}^{a}=0\right]$ equals the standardized survival

$$\sum_{l}\Pr\left[D_{k+1}=0|L=l,A=a\right]\Pr\left[L=l\right].$$

For a formal proof, see Section 2.3.

Therefore, the estimation of the parametric g-formula has two steps. First, we need to estimate the conditional survivals $\Pr\left[D_{k+1}=0|L=l,A=a\right]$ using our administratively censored data. Second, we need to compute their weighted average over all values l of the covariates L. We describe each of these two steps in our smoking cessation example.

For the first step we fit a parametric hazards model like the one described in Section 17.2, except that the variables in L are included as covariates. If the model is correctly specified, it validly estimates the time-varying hazards $\Pr\left[D_{k+1}=1|D_{k}=0,L,A\right]$ within levels of treatment A and covariates L. The product of one minus the conditional hazards

$$\prod_{m=0}^{k}\Pr\left[D_{m+1}=0|D_{m}=0,L=l,A=a\right]$$

is equal to the conditional survival $\Pr\left[D_{k+1}=0|L=l,A=a\right]$. Because of conditional exchangeability given L, the conditional survival for a particular set of covariate values $L=l$ and $A=a$ can be causally interpreted as the survival that would have been observed if everybody with that set of covariates had received treatment value a. That is,

$$\Pr\left[D_{k+1}=0|L=l,A=a\right]=\Pr\left[D_{k+1}^{a}=0|L=l\right]$$

Therefore the conditional hazards can be used to estimate the survival curve under treatment ($a=1$) and no treatment ($a=0$) within each combination of values l of L. For example, we can use this model to estimate the survival curves under treatment and no treatment for white men aged 61, with college education, low levels of exercise, etc. However, our goal is estimating the marginal, not the conditional, survival curves under treatment and under no treatment.

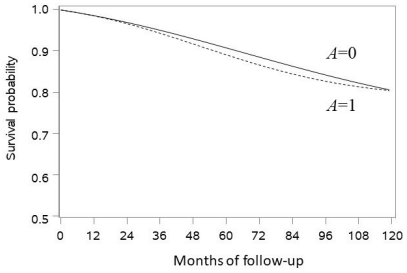

Figure 17.7

In Chapter 12 we referred to models conditional on all the covariates L as faux marginal structural models.

For the second step we compute the weighted average of the conditional survival across all values l of the covariates L, that is, we standardize the survival to the confounder distribution. To do so, we use the method described in Section 13.3 to standardize means: standardization by averaging after expansion of dataset, outcome modeling, and prediction. This method can be used even when some of the variables in L are continuous so that the sum over values l is formally an integral. The resulting curves are shown in Figure 17.7.

CODE: Program 17.4
The procedure is analogous to the one described in Chapter 13

In our example, the survival curve under treatment was lower than the curve under no treatment during the entire follow-up, but the maximum difference never exceeded -2.0% (95% confidence interval from -5.6% to 1.8%). The 120-month survival estimates were 80.4% under smoking cessation and 80.6% under

no smoking cessation; difference 0.2% (95% confidence interval from −4.6% to 4.1%). That is, after adjustment for the covariates L via standardization, we found little evidence of an effect of smoking cessation on mortality at any time during the follow-up. Note that the survival curves estimated via IP weighting (previous section) and the parametric g-formula (this section) are similar but not identical because they rely on different parametric assumptions: the IP weighted estimates require no misspecification of a model for treatment and a model for the unconditional hazards; the parametric g-formula estimates require no misspecification of a model for the conditional hazards.

17.6 G-estimation of structural nested models

The previous sections describe causal contrasts that compare survivals, or risks, under different levels of treatment A. The survival was computed from hazards estimated by logistic regression models. This approach is feasible when the analytic method is IP weighting of marginal structural models or the parametric g-formula, but not when the method is g-estimation of structural nested models. As explained in Chapter 14, structural nested models are models for conditional causal contrasts (e.g., the difference or ratio of covariate-specific means under different treatment levels), not for the components of those contrasts (e.g., each of the means under different treatment levels). Therefore we cannot estimate survivals or hazards using a structural nested model.

In fact, we may not even approximate a hazard ratio because structural nested logistic models do not generalize easily to time-varying treatments (Technical Point 14.1).

We can, however, consider a structural nested log-linear model to model the ratio of cumulative incidences (i.e., risks) under different treatment levels. *Structural nested cumulative failure time models* do precisely that (see Technical Point 17.2), but they are best used when failure is a rare event because log-linear models do not naturally impose an upper limit of 1 on the risk. For non-rare failures, we can instead consider a structural nested log-linear model to model the ratio of cumulative survival probabilities (i.e., 1− risk) under different treatment levels. *Structural nested cumulative survival time models* do precisely that (see Technical Point 17.2), but they are best used when survival is rare because log-linear models do not naturally impose an upper limit of 1 on the survival. A more general option is to use a structural nested model that models the ratio of survival times under different treatment options. That is, an accelerated failure time (AFT) model.

Tchetgen Tchetgen et al (2015) and Robins (1997b) describe survival analysis with instrumental variables that exhibit similar problems to those described here for structural nested models.

Let T_i^a be the counterfactual time of survival for individual i under treatment level a. The effect of treatment A on individual i's survival time can be measured by the ratio $T_i^{a=1}/T_i^{a=0}$ of her counterfactual survival times under treatment and under no treatment. If the survival time ratio is greater than 1, then treatment is beneficial because it increases the survival time; if the ratio is less than 1, then treatment is harmful; if the ratio is 1, then treatment has no effect. Suppose, temporarily, that the effect of treatment is the same for every individual in the population.

The 'nested' component is only evident when treatment is time-varying. See Chapter 21.

We could then consider the *structural nested accelerated failure time (AFT) model* $T_i^a/T_i^{a=0} = \exp(-\psi_1 a)$, where ψ_1 measures the expansion (or contraction) of each individual's survival time attributable to treatment. If $\psi_1 < 0$ then treatment increases survival time, if $\psi_1 > 0$ then treatment decreases survival time, if $\psi_1 = 0$ then treatment does not affect survival time. More generally, the effect of treatment may depend on covariates L so a more general structural AFT would be $T_i^a/T_i^{a=0} = \exp(-\psi_1 a - \psi_2 a L_i)$, with ψ_1 and ψ_2 (a vector) constant across individuals. Rearranging the terms, the model can be

The negative sign in front of ψ preserves the usual interpretation of positive parameters indicating harm and negative parameters indicating benefit.

Technical Point 17.2

Structural nested cumulative failure time (CFT) models and cumulative survival time (CST) models. For a time-fixed treatment, a (non-nested) structural CFT model is a model for the ratio of the counterfactual risk under treatment value a divided by the counterfactual risk under treatment value 0 conditional on treatment A and covariates L. The general form of the model is

$$\frac{\Pr\left[D_k^a = 1|L, A\right]}{\Pr\left[D_k^{a=0} = 1|L, A\right]} = \exp[\gamma_k(L, A; \psi)]$$

where $\gamma_k(L, A; \psi)$ is a function of treatment and covariate history indexed by the (possibly vector-valued) parameter ψ. For consistency, $\exp[\gamma_k(L, A; \psi)]$ must be 1 when $A = 0$ because then the two treatment values being compared are identical, and when there is no effect of treatment at time m on outcome at time k. An example of such a function is $\gamma_k(L, A; \psi) = \psi A$ so $\psi = 0$ corresponds to no effect, $\psi < 0$ to beneficial effect, and $\psi > 0$ to harmful effect.

Analogously, for a time-fixed treatment, a (non-nested) structural CST model is a model for the ratio of the counterfactual survival under treatment value a divided by the counterfactual survival under treatment level 0 conditional on treatment A and covariates L. The general form of the model is

$$\frac{\Pr\left[D_k^a = 0|L, A\right]}{\Pr\left[D_k^{a=0} = 0|L, A\right]} = \exp[\gamma_k(L, A; \psi)]$$

Although CFT and CST models differ only in whether we specify a multiplicative model for $\Pr\left[D_k^a = 1|L, A\right]$ versus for $\Pr\left[D_k^a = 0|L, A\right]$, the meaning of $\gamma_k(L, A; \psi)$ differs because a multiplicative model for risk is not a multiplicative model for survival, whenever the treatment effect is non-null. When we let the time index k be continuous rather than discrete, a structural CST model is equivalent to a structural additive hazards model (Tchetgen Tchetgen et al., 2015) as any model for $\Pr\left[D_k^a = 0|L, A\right] / \Pr\left[D_k^{a=0} = 0|L, A\right]$ induces a model for the difference in the time-specific hazards of T^a and $T^{a=0}$, and vice-versa.

The use of structural CFT models requires that, for all values of the covariates L, the conditional cumulative probability of failure under all treatment values satisfies a particular type of rare failure assumption. In this "rare failure" context, the structural CFT model has an advantage over AFT models: it admits unbiased estimating equations that are differentiable in the model parameters and thus are easily solved. Page (2005) and Picciotto et al. (2012) provided further details on structural CFT and CST models. For a time-varying treatment, this class of models can be viewed as a special case of the multivariate structural nested mean model (Robins 1994). See Technical Point 14.1.

written as

$$T_i^{a=0} = T_i^a \exp\left(\psi_1 a + \psi_2 a L_i\right) \quad \text{for all individuals } i$$

Following the same reasoning as in Chapter 14, consistency of counterfactuals implies the model $T_i^{a=0} = T_i \exp\left(\psi_1 A_i + \psi_2 A_i L_i\right)$, in which the counterfactual time T_i^a is replaced by the actual survival time $T_i^A = T_i$. The parameters ψ_1 and ψ_2 can be estimated by a modified g-estimation procedure (to account for administrative censoring) that we describe later in this section.

The above structural AFT is unrealistic because it is both deterministic and rank-preserving. It is deterministic because it assumes that, for each individual, the counterfactual survival time under no treatment $T^{a=0}$ can be computed without error as a function of the observed survival time T, treatment A, and covariates L. It is rank-preserving because, under this model, if individuals i would die before individual j had they both been untreated, i.e., $T_i^{a=0} < T_j^{a=0}$, then individual i would also die before individual j had they both been treated, i.e., $T_i^{a=1} < T_j^{a=1}$.

Because of the implausibility of rank preservation, one should not generally

use methods for causal inference that rely on it, as we discussed in Chapter 14. And yet again we will use a rank-preserving model here to describe g-estimation for structural AFT models because g-estimation is easier to understand for rank-preserving models, and because the g-estimation procedure is actually the same for rank-preserving and non-rank-preserving models.

Robins (1997b) described non-deterministic non-rank-preserving structural nested AFT models.

For simplicity, consider the simpler rank-preserving model $T_i^{a=0} = T_i \exp(\psi A_i)$ without a product term between treatment and covariates. G-estimation of the parameter ψ of this structural AFT model would be straightforward if administrative censoring did not exist, that is, if we could observe the time of death T for all individuals. In fact, in that case the g-estimation procedure would be the same as we described in Section 14.5. The first step would be to compute candidate counterfactuals $H_i(\psi^\dagger) = T_i \exp\left(\psi^\dagger A_i\right)$ under many possible values $\psi^\dagger$ of the causal parameter ψ. The second step would be to find the value $\psi^\dagger$ that results in a $H_i(\psi^\dagger)$ that is independent of treatment A in a logistic model for the probability of $A = 1$ with $H_i(\psi^\dagger)$ and the confounders L as covariates. Such value $\psi^\dagger$ would be the g-estimate of ψ.

However, this procedure cannot be implemented in the presence of administrative censoring at time K because $H_i(\psi^\dagger)$ cannot be computed for individuals with unknown T_i. One might then be tempted to restrict the g-estimation procedure to individuals with an observed survival time only, i.e., those with $T_i \leq K$. Unfortunately, that approach results in selection bias. To see why, consider the following oversimplified scenario.

We conduct a 60-month randomized experiment to estimate the effect of a dichotomous treatment A on survival time T. Only 3 types of individuals participate in our study. Type 1 individuals are those who, in the absence of treatment, would die at 36 months ($T^{a=0} = 36$). Type 2 individuals are those who in the absence of treatment, would die at 72 months ($T^{a=0} = 72$). Type 3 individuals are those who in the absence of treatment, would die at 108 months ($T^{a=0} = 108$). That is, type 3 individuals have the best prognosis and type 1 individuals have the worst one. Because of randomization, we expect that the proportions of type 1, type 2, and type 3 individuals are the same in each of the two treatment groups $A = 1$ and $A = 0$. That is, the treated and the untreated are expected to be exchangeable.

	Type		
	1	2	3
$T^{a=0}$	36	72	108
$T^{a=1}$	24	48	72

Table 17.1

Suppose that treatment $A = 1$ decreases the survival time compared with $A = 0$. Table 17.1 shows the survival time under treatment and under no treatment for each type of individual. Because the administrative end of follow-up is $K = 60$ months, the death of type 1 individuals will be observed whether they are randomly assigned to $A = 1$ or $A = 0$ (both survival times are less than 60), and the death of type 3 individuals will be administratively censored whether they are randomly assigned to $A = 1$ or $A = 0$ (both survival times are greater than 60). The death of type 2 individuals, however, will only be observed if they are assigned to $A = 1$. Hence an analysis that welcomes all individuals with non-administratively censored death times will have an imbalance of individual types between the treated and the untreated. Exchangeability will be broken because the $A = 1$ group will include type 1 and type 2 individuals, whereas the $A = 0$ group will include type 1 individuals only. Individuals in the $A = 0$ group will have, on average, a worse prognosis than those in the $A = 1$ group, which will make treatment look better than it really is. This selection bias (Chapter 8) arises when treatment has a non-null effect on survival time.

To avoid this selection bias, one needs to select individuals whose survival time would have been observed by the end of follow-up whether they had been treated or untreated, i.e., those with $T_i^{a=0} \leq K$ and $T_i^{a=1} \leq K$. In our example, we will have to exclude all type 2 individuals from the analysis in order

Technical Point 17.3

Artificial censoring. Let $K(\psi)$ be the minimum survival time under no treatment that could possibly correspond to an individual who actually died at time K (the administrative end of follow-up). For a dichotomous treatment A, $K(\psi) = \inf\{K\exp(\psi A)\}$, which implies that $K(\psi) = K\exp(\psi \times 0) = K$ if treatment contracts the survival time (i.e., $\psi > 0$), $K(\psi) = K\exp(\psi \times 1) = K\exp(\psi)$ if treatment expands the survival time (i.e., $\psi < 0$), and $K(\psi) = K\exp(0) = K$ if treatment does not affect survival time (i.e., $\psi = 0$).

All individuals who are administratively censored (i.e., $T > K$) have $\Delta(\psi) = 0$ because there is at least one treatment level (the one they actually received) under which their survival time is greater than K, i.e., $H(\psi) \geq K(\psi)$. Some of the individuals who are not administratively censored (i.e., $T \leq K$) also have $\Delta(\psi) = 0$ and are excluded from the analysis—they are artificially censored—to avoid selection bias.

The artificial censoring indicator $\Delta(\psi)$ is a function of $H(\psi)$ and K. Under conditional exchangeability given L, all such functions, when evaluated at the true value of ψ, are conditionally independent of treatment A given the covariates L. That is, g-estimation of the AFT model parameters can be performed based on $\Delta(\psi)$ rather than $H(\psi)$. Technically, $\Delta(\psi)$ is substituted for $H(\psi)$ in the estimating equation of Technical Point 14.2. For practical estimation details, see the Appendix of Hernán et al (2005).

This exclusion of uncensored individuals from the analysis is often referred to as *artificial censoring*.

to preserve exchangeability. That is, we will not only exclude administratively censored individuals with $T_i > K$, but also some uncensored individuals with known survival time $T_i \leq K$ because their survival time would have been greater than K if they had received a treatment level different from the one they actually received.

We then define an indicator $\Delta(\psi)$, which takes value 0 when an individual is excluded and 1 when she is not. The g-estimation procedure is then modified by replacing the variable $H(\psi^\dagger)$ by the indicator $\Delta(\psi^\dagger)$. See Technical Point 17.3 for details. In our example, the g-estimate $\hat{\psi}$ from the rank-preserving structural AFT model $T_i^{a=0} = T_i\exp(\psi A_i)$ was -0.047 (95% confidence interval: -0.223 to 0.333). The number $\exp\left(-\hat{\psi}\right) = 1.05$ can be interpreted as the median survival time that would have been observed if all individuals in the study had received $a = 1$ divided by the median survival time that would have been observed if all individuals in the study had received $a = 0$. This survival time ratio suggests little effect of smoking cessation A on the time to death.

CODE: Program 17.5
The point estimate of ψ is the value that corresponds to the minimum of the estimating function described in Technical Point 17.3.; the limits of the 95% confidence interval are the values that correspond to the value 3.84 (χ^2 with one degree of freedom) of the estimating function.

As we said in Chapter 14, structural nested models, including AFT models, have rarely been used in practice. A practical obstacle for the implementation of the method is the lack of user-friendly software. An even more serious obstacle in the survival analysis setting is that the parameters of structural AFT models need to be estimated through search algorithms that are not guaranteed to find a unique solution. This problem is exacerbated for models with two or more parameters ψ. As a result, the few published applications of this method tend to use simplistic AFT models that do not allow for the treatment effect to vary across covariate values.

This state of affairs is unfortunate because subject-matter knowledge (e.g., biological mechanisms) are easier to translate into parameters of structural AFT models than into those of structural hazards models. This is especially true when using non-deterministic and non-rank preserving structural AFT models.

Chapter 18
VARIABLE SELECTION FOR CAUSAL INFERENCE

In the previous chapters, we have described several adjustment methods to estimate the causal effect of a treatment A on an outcome Y, including stratification and outcome regression, standardization and the parametric g-formula, IP weighting, and g-estimation. Each of these methods carry out the adjustment in different ways but all these methods rely on the same condition: the set of adjustment variables L must include sufficient information to achieve conditional exchangeability between the treated $A = 1$ and the untreated $A = 0$—or, equivalently, to block all backdoor paths between A and Y without opening other biasing paths.

In practice, a common question is how to select the variables L for adjustment. This chapter offers some guidelines for variable selection when the goal of the data analysis is causal inference. Because the variable selection criteria for causal inference are not the same as for prediction, widespread procedures for variable selection in predictive analyses may not be directly transferable to causal analyses. This chapter summarizes the problems of incorrect variable selection in causal analyses and outlines some practical guidance.

18.1 The different goals of variable selection

As we have discussed throughout this book, valid causal inferences usually require adjustment for confounding and other biases. When an association measure between a treatment A and an outcome Y may be partly or fully explained by confounders L, adjustment for these confounders needs to be incorporated into the data analysis. Otherwise, the association measure cannot be interpreted as a causal effect measure.

Even if the outcome model includes all confounders for the effect of A on Y, the association between each confounder and the outcome cannot be causally interpreted because we do not adjust for the confounders of the confounders.

But if the goal of the data analysis is purely predictive, no adjustment for confounding is necessary. If we just want to quantify the association between smoking cessation A and weight gain Y, we simply estimate that association from the data by comparing the average weight gain between those who did and did not quit smoking. More generally, if we want to develop a predictive model for weight gain, we will want to include covariates (like smoking cessation, baseline weight, and annual income) that predict weight gain. We do not ask the question of whether those covariates are confounders because there is no treatment variable whose effect can be confounded. In predictive models, we do not try to endow any parameter estimates with a causal interpretation and therefore we do not try to adjust for confounding because the concept of confounding does not even apply.

Reminder: Confounding is a causal concept that does not apply when the estimand is an association rather than a causal effect.

The distinction between predictive/associational models and causal models was discussed in Section 15.5. For example, clinical investigators can use outcome regression to identify patients at high risk of developing heart failure. The goal is classification, which is a form of prediction. The parameters of these predictive models do not necessarily have any causal interpretation and all covariates in the model have the same status, i.e., there are no treatment variable A and variables L. For example, a prior hospitalization may be identified as a useful predictor of future heart failure, but nobody would suggest stop we hospitalizing people in order to prevent heart failures. Identifying patients with bad prognosis (prediction) is very different from identifying the

Fine Point 18.1

Variable selection procedures for regression models. Suppose we want to fit a regression model with predictive purposes, but the database includes so many potential predictors—perhaps even more than individuals—that including all of them in the model is either impossible or results in very unstable predictions. Several approaches exist to deal with this problem in regression models. A detailed description of these procedures can be found in many books. See, for example, the books by Hastie, Tibshirani, and Friedman (2009), and by Harrell (2015). Below we briefly outline some of the existing approaches.

One approach is to select a subset of the available variables. A conceptually simple way to find the best subset would be to first decide the number of variables in the model, then fit all possible combinations of models with that number of variables, and finally choose the best one according to some pre-specified criterion (e.g., Akaike's Information criterion). However, this approach becomes computationally infeasible for a large number of available variables. More efficient methods to select variables are forward selection (start with no variables and, in each step of the algorithm, add the variable that leads to the greatest improvement), backward elimination (start with all variables and, in each step, delete the variable that leads to the greatest improvement), and stepwise selection (a combination of forward selection and backward elimination). The variable selection algorithm ends when no further improvement is possible, with improvement again defined according to some pre-specified criterion. These algorithms are easy to implement but, on the other hand, they do not explore all possible subsets of variables.

An alternative to subset selection is shrinkage. The idea is to modify the estimation method by adding a "penalty" that forces the model parameter estimates (other than the intercept) to be closer to zero than they would have been in the absence of the penalty. That is, the parameter estimates are shrunk towards zero. As a result of this shrinkage, the variance decreases and the prediction becomes more stable. The two best known shrinkage methods are ridge regression and the *lasso* or "least absolute shrinkage and selection operator", which was proposed by Santosa and Symes (1986) and rediscovered by Tibshirani (1996). Unlike ridge regression, the lasso allows some parameter values to be exactly zero. Therefore, the lasso is both a shrinkage method and a subset selection method. The lasso has become the preferred variable selection method for regression models, as it generally outperforms stepwise selection in terms of prediction accuracy.

best course of action to prevent or treat a disease (causal inference).

For pure prediction, investigators may want to select *any* variables that improve predictive ability. The selection of these variables can be automated to obtain the best possible prediction using data from the population of interest. Some automatic variable selection algorithms, like the *lasso*, are designed for predictive regression models (see Fine Point 18.1) whereas others are implemented as part of non-regression algorithms (e.g., neural networks). All of them can use cross-validation (see Fine Point 18.2) to optimize predictive accuracy. Because some selection algorithms are "black-box" procedures, it is not always easy to explain how the variables are selected or why the algorithm works. However, that does not necessarily matter. A reasonable point of view is that, for purely predictive purposes in a particular population and setting, whatever works to improve prediction is fair game, regardless of interpretability.

In contrast, in a causal analysis, a thoughtful selection of confounders is needed before endowing the treatment parameter estimates with a causal interpretation. Automatic variable selection procedures may work for prediction, but not generally for causal inference. Variable selection algorithms may select variables that introduce bias in the effect estimate. There are several reasons why this bias may arise. Some of these reasons have been described earlier in the book; others have not been described yet. The next section summarizes all of them.

Fine Point 18.2

Overfitting and cross-validation. Overfitting is a common problem of all variable selection methods for regression models: The variables are selected to predict the data points as well as possible, without taking in consideration that some of the variation observed in the data is purely random. As a result, the model predicts very well for the individuals used to estimate the model parameters, but the model predicts poorly for future individuals who were not used to estimate the model parameters. The same problem arises in predictive algorithms such as random forests, neural networks, and other machine learning algorithms.

A straightforward solution to the overfitting problem is to split the sample in two parts: a training sample used to run the predictive algorithm (that is, to estimate the model parameters when using regression) and a validation sample used to evaluate the accuracy of the algorithm's predictions. For a sample size n, we use v individuals for the validation set and $n - v$ individuals for the training set. When using the lasso, the degree of shrinkage in the training sample may be guided by the model's performance in the validation sample.

The obvious downside of splitting the sample into training and validation subsamples is that the predictive algorithm only uses—e.g., the model parameters are estimated in—a subset of individuals, which increases the variance. A solution is to repeat the splitting process multiple times, which increases the effective number of individuals used by the predictive algorithm. Then one can evaluate the algorithm's predictive accuracy as the average over all the validation samples. This procedure is known as *cross-validation* or out-of-sample testing. Different forms of cross-validation exist.

A procedure referred to as "leave-v-out cross-validation" analyzes all possible partitions of the sample into training sample and validation sample of size v. However, examining all such partitions may become computationally infeasible for moderately large values of n and v. Therefore, in practice, it is common to choose $v = 1$, a procedure referred to as "leave-one-out cross-validation." When even leave-one-out cross-validation is too computationally intensive, one may consider a cross-validation procedure that does not exhaust all possible partitions. For example, in "k-fold cross validation," the sample is split into k subsamples of equal size. Then one of the subsamples is used as the validation sample and the other $k - 1$ subsamples as the training sample. The procedure is repeated k times, with $k = 10$ being a common choice. See the book by Hastie, Tibshirani, and Friedman (2009) for a description of cross-validation and related techniques.

18.2 Variables that induce or amplify bias

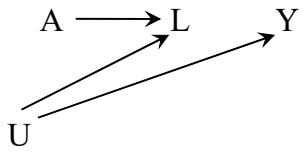

Figure 18.1

Collapsibility reminder: When adjusting for covariates using stratification, remember that the adjusted association measure may differ from the unadjusted association measure, even when no confounding exists. See Fine Point 4.3.

Imagine that we have unlimited computational power and a dataset with a quasi-infinite number of individuals (the rows of the dataset) and many variables measured for each individual (the columns of the data set), including treatment A, outcome Y, and a large number of variables X, some of which may be confounders of the effect of A on Y. In this setting, we can afford to adjust for as many variables in the dataset as we wish, without computational, numerical, or statistical constraints.

Say that we want to unbiasedly estimate the average causal effect of a binary treatment A on the outcome Y, that is, $\mathrm{E}\left[Y^{a=1}\right] - \mathrm{E}\left[Y^{a=0}\right]$. Then the goal of covariate adjustment is to eliminate as much confounding as possible by using the information contained in the measured variables X. We could easily adjust for all measured variables X via stratification/outcome regression, standardization/g-formula, IP weighting, or g-estimation. Are there any reasons to adjust for only a subset of X rather than simply adjust for all available variables X? The answer is yes. Even in this ideal setting, we want to ensure that some variables are not selected for adjustment because adjustment for those variables would induce bias. The next examples illustrate this point when some of the variables L in X are causally affected by A.

Suppose the causal structure of the problem is represented by the causal diagram of Figure 18.1 (same as Figure 7.7) in which the variable L is a collider.

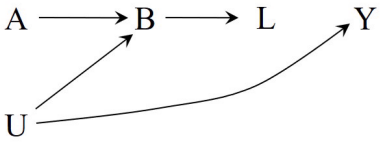

Figure 18.2

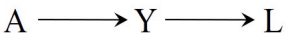

Figure 18.3

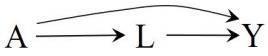

Figure 18.4

In Figure 18.4, adjusting for L blocks the path $A \rightarrow L \rightarrow Y$ but not the path $A \rightarrow Y$. Thus the A-Y association adjusted for L is a biased estimator of the total effect of A on Y but an unbiased estimator of the direct effect of A on Y that is not mediated through L (Schisterman et al. 2009).

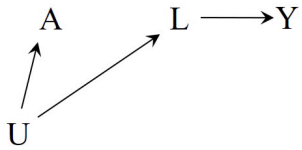

Figure 18.5

Here the average causal effect $\mathrm{E}[Y^{a=1}] - \mathrm{E}[Y^{a=0}] = 0$ is unbiasedly estimated by $\mathrm{E}[Y|A=1] - \mathrm{E}[Y|A=0]$ since there is no confounding by L. Suppose now we try to estimate the average causal effect by adjusting for L, e.g., via the g-formula $\sum_l \mathrm{E}[Y|A=1, L=l]\Pr(L=l) - \sum_l \mathrm{E}[Y|A=0, L=l]\Pr(L=l)$. This contrast differs from $\mathrm{E}[Y|A=1] - \mathrm{E}[Y|A=0]$—and thus is biased—because L is both conditionally associated with Y given A and marginally associated with A, so $\Pr(L=l) \neq \Pr(L=l|A)$. Because the A-Y association adjusted for L is expected to be non-null even though the causal effect of treatment A on the outcome Y is null, we say that there is *selection bias under the null*. The same bias is expected to arise when we adjust for a variable L that, as in the causal diagram of Figure 18.2, is a descendant of the collider B. You may want to review Chapter 8 for more examples of causal structures with colliders and their descendants.

Selection bias may also appear when adjusting for a noncollider affected by treatment, like the variable L in the causal diagram in Figure 18.3. Here the average causal effect $\mathrm{E}[Y^{a=1}] - \mathrm{E}[Y^{a=0}] \neq 0$ is also unbiasedly estimated by $\mathrm{E}[Y|A=1] - \mathrm{E}[Y|A=0]$ since there is no confounding by L. However, if we try to estimate the average causal effect by adjusting for L, the g-formula contrast will differ from $\mathrm{E}[Y|A=1] - \mathrm{E}[Y|A=0]$ for the same reasons as in the previous paragraph. Now suppose that the arrow from A to Y had been absent, that is, that the null hypothesis of no effect of A on Y were true and so $\mathrm{E}[Y^{a=1}] - \mathrm{E}[Y^{a=0}] = 0$. Then A and Y would be independent (both marginally and conditionally on L) and the g-formula contrast would be zero and thus unbiased. The key reason for this result is that, under the null, A no longer has a causal effect on L. That is, unlike in Figures 18.1 and 18.2, adjusting for L in Figure 18.3 results in selection bias only when A has a non-null causal effect on Y. We then say that there is *selection bias under the alternative* or off the null (see Section 6.5).

When the adjustment variable is affected by the treatment A *and* affects the outcome Y, we say that the variable is a mediator. Consider the causal diagram in Figure 18.4, which includes the mediator L on a causal path from the treatment A to the outcome Y. The A-Y association adjusted for the mediator L, or its descendants, will differ from the effect of treatment A on the outcome Y because the adjustment blocks the component of the effect that goes through L. Sometimes this problem is referred to as *overadjustment for mediators* when the average causal effect of A on Y is the contrast of interest.

The bias-inducing variables discussed above share a common feature: they are affected by treatment and therefore they are post-treatment variables. One might then think that we should always avoid adjustment for variables that occur after treatment A. The rule of not adjusting for post-treatment variables would be easy to follow because the temporal sequence of the adjustment variables and the treatment is usually known. Unfortunately, following this simple rule may result in the exclusion of useful adjustment variables, as we discussed in Fine Point 7.4. Consider the causal diagram in Figure 18.5. The variable L is a post-treatment variable, but it can be used to block the backdoor path between treatment A and outcome Y. Therefore, the A-Y association adjusted for L is an unbiased estimator of the effect of A on Y, whereas the unadjusted A-Y association is a biased estimator. The take home message is that causal graphs do not care about temporal order. Thus, when A does not affect L, the analysis must be the same whether L is temporally before or temporally after A.

The problem is that, even when we know the temporal order of the variables, we cannot determine from the data whether or not A affects L. In fact,

given the temporal ordering $A\ L\ Y$, any joint distribution of (A, L, Y) without any independencies is compatible with several causal graphs. So the decision whether to adjust for L must be based on information outside of the data. That is, whether to adjust for L cannot be determined via any automated procedures that rely exclusively on statistical associations. For example, as discussed in Chapter 7, there is no way to distinguish a collider from a confounder by using data only. Rather, the exclusion of bias-inducing variables from the adjustment set needs to be guided by subject-matter knowledge (if it exists) about the causal structure of the problem.

We next turn to the question of adjustment for variables L that are temporally prior to treatment A, that is, our temporal ordering is now $L\ A\ Y$. Suppose, for simplicity, that the sample size is very large, greatly exceeding the number of covariates X available for adjustment. As a consequence, the variance of any estimator will be negligible and the only issue is bias. In this setting it is commonly believed that an estimator that adjusts for all available pretreatment covariates will minimize the bias. However, this belief is wrong for two separate reasons.

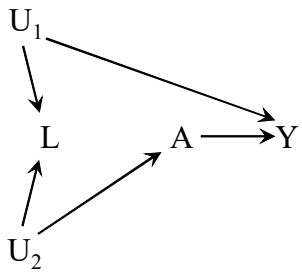

Figure 18.6

Consider the causal diagram of Figure 18.6 (same as Figure 7.4), which includes a pre-treatment variable L. Because L is a collider on a path from A to Y, adjusting for it will introduce selection bias, which we referred to as M-bias in Chapter 7. Again, the observed data cannot distinguish between confounders and colliders, so one must rely on whatever external information one may have to decide whether or not to adjust for a pre-treatment variable L. In fact, it is also possible that L is both a confounder and a collider—if there were an arrow from L to A in Figure 18.6—which implies that the average causal effect cannot be identified, regardless of whether we do or do not adjust for L.

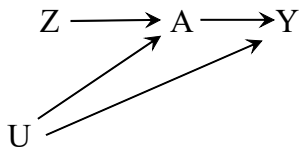

Figure 18.7

There is one additional reason to avoid indiscriminate adjustment for pretreatment variables: bias amplification, a phenomenon we have not yet described in this book. Consider the causal diagram of Figure 18.7 (same as Figure 16.1), which represents a setting in which the causal effect of treatment A on the outcome Y is confounded by the unmeasured variable U. Because U is not available in the data, we cannot adjust for U and the confounding is intractable. Adjustment for the variable Z—using the g-formula as above with L replaced by Z—does not eliminate confounding because Z is not on any backdoor path from the treatment A to the outcome Y. In fact, Z is an instrument—which can be used for instrumental variable estimation in some situations described in Chapter 16—and therefore useless for direct confounding adjustment by the g-formula.

Interestingly, even though Z cannot be used to adjust away the confounding bias due to U, adjustment for the instrument Z can amplify the confounding bias due to U. That is, the A-Y association adjusted for Z may be further from the effect of A on Y than the A-Y association not adjusted for Z. This bias amplification due to adjusting for an instrument Z, often referred to as Z-bias, is a reason to avoid adjustment for variables that, like Z, are instruments. Bias amplification, however, is not guaranteed: adjustment for Z could also reduce the bias due to confounding by the unmeasured variable U. Generally, it is not possible to know whether adjustment for an instrument will amplify or reduce bias.

Bias amplification is guaranteed if all the equations in the structural equation model corrresponding to the causal diagram are linear (Pearl 2011), but may also occur in more realistic settings (Ding et al. 2017).

In summary, even if we had no computational constraints and a quasi-infinite sample size, it is not advisable to adjust for all available variables X. Ideally, the adjustment set would not include any variables that may introduce or amplify bias. Because these bias-inducing variables cannot be empirically

An example of the application of expert knowledge to adjustment was described by Hernán et al (2002).

identified by purely statistical algorithms, expert knowledge is needed to guide variable selection.

18.3 Causal inference and machine learning

The next three sections reflect Miguel Hernán's informal interpretation (as of April 2019) of a set of theoretical lectures that James Robins delivered in Boston, Berlin, Rotterdam, and elsewhere beween 2018 and early 2019.

For the remainder of this chapter, we will assume that we have somehow succeeded at ensuring that X includes no variables that may induce or amplify bias (i.e., no variables that would destroy conditional exchangeability if adjusted for) while still including all confounders L of the average causal effect of A on Y (i.e., all variables needed to achieve conditional exchangeability). Our next problem is to estimate this effect $\mathrm{E}\left[Y^{a=1}\right] - \mathrm{E}\left[Y^{a=0}\right]$ in practice when X is very high-dimensional.

Depending on the adjustment method that we choose, the variables X will be used in different ways. When using the plug-in g-formula (standardization), we will estimate the mean outcome Y conditional on the variables X, which we refer to as $b(X)$; when using IP weighting, we will estimate the probability of treatment A conditional on the variables X, which we refer to as $\pi(X)$. We can produce estimates $\hat{b}(x)$ and $\hat{\pi}(x)$ via the sort of parametric models (e.g., linear and logistic regression) that we have described in Part II of this book. To reduce the possibility of model misspecification, we will want to fit richly parameterized models with multiple product terms and flexible functional forms (e.g., cubic splines) for the variables in X.

The use of traditional parametric models encounters a serious constraint in many practical applications. The number of parameters in those models will be very large compared with, or larger than, the sample size n. However, traditional parametric models can only have a small number of parameters compared with the sample size. Therefore, fitting richly parametrized models with terms for all variables in X will yield very imprecise $\hat{b}(x)$ and $\hat{\pi}(x)$ estimates, or may actually be impossible under the usual large sample approximations used to fit linear or logistic models when the number of parameters in the model is greater than the number of individuals n in the dataset. Also, as discussed in Section 15.5, X may include non-confounders that are strongly associated with the treatment A, which will result in quasi-violations of positivity when using methods that require fitting a model for $\pi(X)$.

Remember that some of the variables in X may not even be confounders so we do not need to adjust for them.

Possible ways forward are to fit the parametric models using the *lasso* (see Fine Point 18.1), a variable selection algorithm originally designed for predictive regression models, or to estimate the conditional expectations $b(X)$ and $\pi(X)$ using predictive machine learning algorithms such as tree-based algorithms (e.g., random forests) or neural networks (e.g., deep learning). In very high-dimensional databases, these and other machine learning algorithms can effectively incorporate thousands of parameters and thus outperform traditional parametric models for the accurate prediction of conditional expectations. But the use of predictive machine learning algorithms to estimate $b(X)$ and $\pi(X)$ raises two serious concerns.

Machine learning algorithms can use cross-validation (see Fine Point 18.2) to optimize predictive accuracy.

First, machine learning algorithms do not guarantee that the selected variables will eliminate confounding when using methods that require estimates of either the conditional mean outcome $b(X)$ (like the plug-in g-formula) or the probability of treatment $\pi(X)$ (like IP weighting). An improved approach is to use a doubly robust estimator that appropriately combines estimates of both $b(X)$ and $\pi(X)$. Doubly robust estimators may succeed because their bias, unlike that of non-doubly robust estimators, depends on the product of

Multiple authors have studied the problems of *ad hoc* or automatic variable selection for causal inference. See Greenland (2008) for a list of citations.

the error $\frac{1}{\pi(x)} - \frac{1}{\hat{\pi}(x)}$ in the estimation of $\frac{1}{\pi(x)}$ with the error $b(x) - \hat{b}(x)$ in the estimation of $b(x)$. Therefore, doubly robust estimators may have small bias when they are based on accurate estimates $\hat{b}(x)$ and $\hat{\pi}(x)$ obtained via machine learning estimators.

This property of doubly robust estimators is referred to as a *second-order bias*. See Technical Point 13.2 for details.

Second, machine learning algorithms are statistical black boxes with largely unknown statistical properties. That is, even if a doubly robust estimator is unbiased, the variance of the resulting estimate may be wrong. As a result, the calculated confidence intervals will lose their frequentist interpretation. Specifically, it is expected that 95% confidence intervals obtained via predictive machine learning will be too narrow and thus invalid: they fail to trap 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 (see Chapter 10).

Thus, the use of doubly robust estimators is key to combining causal inference with machine learning, but it is not sufficient. The next section describes two modifications to doubly robust estimation that tackle this second problem: sample splitting and cross-fitting.

18.4 Doubly robust machine learning estimators

Let us suppose that the use of predictive machine learning algorithms results in a small bias for a doubly robust estimator. Small bias means that the bias of the estimate is much smaller than its standard error. More precisely, the bias has to be less than $1/\sqrt{n}$. A small bias is easier to achieve with doubly robust estimators than with non-doubly estimators because, again, the bias of doubly robust estimators is the product of the errors $\frac{1}{\pi(x)} - \frac{1}{\hat{\pi}(x)}$ and $b(x) - \hat{b}(x)$. That is, even if each of the conditional expectations are estimated with an error larger than $1/\sqrt{n}$, the bias of the doubly robust estimator may still be sufficiently small for the construction of valid confidence intervals.

Then, in large samples (i.e., asymptotically) and under some weak conditions, we can define a consistent doubly robust estimator that will follow a normal distribution with mean at the true value of the causal parameter. That is, we will be able to construct valid confidence intervals for the doubly robust estimator with small bias. For this to be true, the doubly robust estimator needs to incorporate two procedures, sample splitting and cross-fitting, which we describe below.

We first describe sample splitting. First, we randomly divide the study population of n individuals into two halves: an estimation sample and a training sample, each with $n/2$ individuals. Second, we apply the predictive algorithms to the training sample in order to obtain estimators of $\hat{b}(x)$ and $\hat{\pi}(x)$ for the conditional expectations of outcome and treatment, respectively. Third, we compute the doubly robust estimator of the average causal effect in the estimation sample using the estimators of $\hat{b}(x)$ and $\hat{\pi}(x)$ from the training sample. We have now obtained a doubly robust machine learning estimate of the average causal effect in a random half of the study population.

We may refer to the training sample as the nuisance sample because we use it to estimate the nuisance regressions for $b(X)$ and $\pi(X)$. Fine Point 15.1 reviews the concept of nuisance parameters.

Sample splitting allows us to use standard statistical inference procedures based on the $n/2$ individuals in the estimation sample. Being able to construct a valid confidence interval is a good thing but, unfortunately, we lose half of the sample size in the process. As a result, our confidence interval will be wider than the one we would have obtained if we had been able to use the entire sample of n individuals. A way to overcome this problem is cross-fitting.

We now describe how cross-fitting recovers the statistical efficiency lost by

Sample splitting and cross-fitting are not new procedures. However, the idea of combining these procedures with machine learning has not been emphasized until recently.

sample splitting. First, we repeat the above procedure but swapping the roles of the estimation and training halves of the study population. That is, we use the half formerly reserved for estimation as the new training sample, and the half formerly used for training as the new estimation sample. We then compute the doubly robust estimator of the average causal effect in the new estimation sample using the estimators of $\hat{b}(x)$ and $\hat{\pi}(x)$ from the new training sample. We have now obtained a doubly robust machine learning estimate of the average causal effect in the other random half of the population.

The next step is to compute the average of the two doubly robust estimates from each half of the population. This average will be our doubly robust estimate of the effect in the entire study population. A 95% confidence interval around this estimate can be constructed by bootstrapping, either by adding and subtracting 1.96 times the bootstrap standard error or by using the 2.5 and 97.5 percentiles of the bootstrap estimates as the bounds of the interval.

We are done. Through sample splitting and cross-fitting, we can combine doubly robust estimation and machine learning to obtain causal effect estimates which have known statistical properties and which use all the available data. An active area of research is the development of procedures to detect whether the bias of doubly robust estimators is too large and, if so, to obtain estimates with smaller bias in the estimation sample without having to redo the machine learning component in the training sample.

18.5 Variable selection is a difficult problem

The methods outlined in the previous section invalidate the widespread belief that any data-based procedure to select adjustment variables will inevitably result in incorrect confidence intervals. As we have seen, the combination of causal inference methods with machine learning algorithms for confounder selection can, under certain conditions, result in correct statistical inference. However, doubly robust machine learning does not solve all our problems for at least four reasons.

First, in many applications, the available subject-matter knowledge may be insufficient to identify all important confounders or to rule out variables that induce or amplify bias. Thus there is no guarantee that doubly robust machine learning estimators will have a small bias.

Second, many machine learning algorithms are available but no algorithm is optimal in all settings. No mathematical theorem can show that one algorithm is generally better than another. The choice of algorithm should depend on the causal structure that gave rise to the data, but such causal structure may be unknown or hard to summarize for the development of practical recommendations.

Third, the implementation of doubly robust estimators is difficult—and computationally expensive when combined with machine learning—in high-dimensional settings with time-varying treatments. This is especially true for causal survival analysis. As a result, most published examples of causal inference from complex longitudinal data use single robust estimators, which are the ones emphasized in Part III of this book.

Fourth, doubly robust machine learning can yield a variance of the causal effect that equals the variance that would have been obtained if the true conditional expectations $b(X)$ and $\pi(X)$ were known. However, there is no guarantee that such variance will be small enough for meaningful causal inference.

Suppose that we obtain a doubly robust machine learning estimate of the causal effect, as described in the previous section, only to find out that its (correct) variance is too big to be useful. This will happen, even when we have done everything correctly, if some of the covariates in X are strongly associated with the treatment A. Then the estimate of the probability of treatment $\pi(X)$ may be near 0 or near 1 for individuals with a particular value of X. As a result, the effect estimate will have a very large variance and thus a very wide (but correct) 95% confidence interval. Since we do not like very wide 95% confidence intervals, even if they are correct, we may be tempted to throw out the variables in X that are causing the "problem" and then repeat the data analysis. If we did that, we would be fundamentally changing the game. Using the data to discard covariates in X that are associated with treatment, but not so much with the outcome, makes it no longer possible to guarantee that the 95% confidence interval around the effect estimate is valid. The tension between including all potential confounders to eliminate bias and excluding some variables to reduce the variance is hard to resolve.

This result raises a puzzling philosophical question: If the confidence interval is invalid when we use the data to rule out, say, 5 variables that make the variance too large, then why should the confidence interval be valid if we had happened to receive a dataset that did not include those 5 variables? Given that we always work with datasets in which some potential confounders are not recorded, how should we interpret confidence intervals in any observational analysis?

Given all of the above, developing a clear set of general guidelines for variable selection may not be possible. In fact, so much methodological research is ongoing around these issues that this chapter cannot possibly be prescriptive. The best scientific advice for causal inference may be to carry out multiple sensitivity analyses: implement several analytic methods and inspect the resulting effect estimates. If the various effect estimates are compatible, we will be more confident in the results. If the various effect estimates are not compatible, our job as researchers is to try to understand why.

Part III

Causal inference from complex longitudinal data

Chapter 19
TIME-VARYING TREATMENTS

So far this book has dealt with fixed treatments which do not vary over time. However, many causal questions involve treatments that vary over time. For example, we may be interested in estimating the causal effects of medical treatments, lifestyle habits, employment status, marital status, occupational exposures, etc. Because these treatments may take different values for a single individual over time, we refer to them as time-varying treatments.

Restricting our attention to time-fixed treatments during Parts I and II of this book helped us introduce basic concepts and methods. It is now time to consider more realistic causal questions that involve the contrast of hypothetical interventions that are played out over time. Part III extends the material in Parts I and II to time-varying treatments. This chapter describes some key terminology and concepts for causal inference with time-varying treatments. Though we have done our best to simplify those concepts (if you don't believe us, check out the causal inference literature), this is still one of the most technical chapters in the book. Unfortunately, further simplification would result in too much loss of rigor. But if you made it this far, you are qualified to understand this chapter.

19.1 The causal effect of time-varying treatments

Consider a time-fixed treatment variable A (1: treated, 0: untreated) at time zero of follow-up and an outcome variable Y measured 60 months later. We have previously defined the average causal effect of A on the outcome Y as the contrast between the mean counterfactual outcome $Y^{a=1}$ under treatment and the mean counterfactual outcome $Y^{a=0}$ under no treatment, that is, $\mathrm{E}\left[Y^{a=1}\right] - \mathrm{E}\left[Y^{a=0}\right]$. Because treatment status is determined at a single time (time zero) for everybody, the average causal effect does not need to make reference to the time at which treatment occurs. In contrast, causal contrasts that involve time-varying treatments need to incorporate time explicitly.

To see this, consider a time-varying dichotomous treatment A_k that may change at every month k of follow-up, where $k = 0, 1, 2...K$ with $K = 59$. For example, in a 5-year follow-up study of individuals infected with the human immunodeficiency virus (HIV), A_k takes value 1 if the individual receives antiretroviral therapy in month k, and 0 otherwise. No individuals received treatment before the start of the study at time 0, i.e., $A_{-1} = 0$ for all individuals.

For simplicity, we will provisionally assume that no individuals were lost to follow-up or died during this period, and we will also assume that all variables were perfectly measured.

We use an overbar to denote treatment history, that is, $\bar{A}_k = (A_0, A_1, ...A_k)$ is the history of treatment from time 0 to time k. When we refer to the entire treatment history through K, we often represent $\bar{A}_K$ as $\bar{A}$ without a time subscript. In our HIV study, an individual who receives treatment continuously throughout the follow-up has treatment history $\bar{A} = (A_0 = 1, A_1 = 1, ...A_{59} = 1) = (1, 1, ...1)$, or $\bar{A} = \bar{1}$. Analogously, an individual who never receives treatment during the follow-up has treatment history $\bar{A} = (0, 0, ...0) = \bar{0}$. Most individuals are treated during part of the follow-up only, and therefore have intermediate treatment histories with some 1s and some 0s—which we cannot represent as compactly as $\bar{1}$ and $\bar{0}$.

For compatibility with many published papers, we use zero-based indexing for time. That is, the first time of possible treatment is $k = 0$ rather than $k = 1$.

To keep things simple, our example considers an outcome measured at a fixed time. However, the concepts discussed in this chapter also apply to time-varying outcomes and failure time outcomes.

Suppose Y measures health status—with higher values of Y indicating better health—at the end of follow-up at time $K+1 = 60$. We would like to estimate the average causal effect of the time-varying treatment $\bar{A}$ on the outcome Y. But we can no longer define the average causal effect of a time-varying treatment as a contrast at a single time k, because the contrast $\mathrm{E}\left[Y^{a_k=1}\right] - \mathrm{E}\left[Y^{a_k=0}\right]$ quantifies the effect of treatment A_k at a single time k, not the effect of the time-varying treatment A_k at all times k between 0 and 59.

Remember: we use lower-case to denote possible realizations of a random variable, e.g., a_k is a realization of treatment A_k.

Indeed we will have to define the average causal effect as a contrast between the counterfactual mean outcomes under two treatment strategies that involve treatment at all times between the start ($k = 0$) and the end ($k = K$) of the follow-up. As a consequence, the average causal effect of a time-varying treatment is not uniquely defined. In the next section, we describe many possible definitions of average causal effect for a time-varying treatment.

19.2 Treatment strategies

A general counterfactual theory to compare treatment strategies was first articulated by Robins (1986, 1987, 1997a).

A treatment strategy—also referred to as a plan, policy, protocol, or regime—is a rule to assign treatment at each time k of follow-up. For example, two treatment strategies are "always treat" and "never treat" during the follow-up. The strategy "always treat" is represented by $\bar{a} = (1, 1, ...1) = \bar{1}$, and the strategy "never treat" is represented by $\bar{a} = (0, 0, ...0) = \bar{0}$. We can now define an average causal effect of $\bar{A}$ on the outcome Y as the contrast between the mean counterfactual outcome $Y^{\bar{a}=\bar{1}}$ under the strategy "always treat" and the mean counterfactual outcome $Y^{\bar{a}=\bar{0}}$ under the strategy "never treat", that is, $\mathrm{E}\left[Y^{\bar{a}=\bar{1}}\right] - \mathrm{E}\left[Y^{\bar{a}=\bar{0}}\right]$.

But there are many other possible causal effects for the time-varying treatment $\bar{A}$, each of them defined by a contrast of outcomes under two particular treatment strategies. For example, we might be interested in the average causal effect defined by the contrast $\mathrm{E}\left[Y^{\bar{a}}\right] - \mathrm{E}\left[Y^{\bar{a}'}\right]$ that compares the strategy "treat at every other month" $\bar{a} = (1, 0, 1, 0...)$ with the strategy "treat at all months except the first one" $\bar{a}' = (0, 1, 1, 1...)$. The number of possible contrasts is very large: we can define at least 2^K treatment strategies because there are 2^K possible combinations of values $(a_0, a_1, ...a_K)$ for a dichotomous a_k. In fact, as we next explain, these 2^K such strategies do not exhaust all possible treatment strategies.

To define even more treatment strategies in our HIV example, consider the time-varying covariate L_k which denotes CD4 cell count (in cells/μL) measured at month k in all individuals. The variable L_k takes value 1 when the CD4 cell count is low, which indicates a bad prognosis, and 0 otherwise. At time zero, all individuals have a high CD4 cell count, $L_0 = 0$. We could then consider the strategy "do no treat while $L_k = 0$, start treatment when $L_k = 1$ and treat continuously after that time". This treatment strategy is different from the ones considered in the previous paragraph because we cannot represent it by a rule $\bar{a} = (a_0, a_1, ...a_K)$ under which all individuals get the same treatment a_0 at time $k = 0$, a_1 at time $k = 1$, etc. Now, at each time, some individuals will be treated and others will be untreated, depending on the value of their evolving L_k. This is an example of a *dynamic treatment strategy*, a rule in which the treatment a_k at time k depends on the evolution of an individual's time-varying covariate(s) $\bar{L}_k$. Strategies $\bar{a}$ for which treatment does not depend

Fine Point 19.1

Deterministic and random treatment strategies. A dynamic treatment strategy is a rule $g = [g_0(\bar{a}_{-1}, l_0), \ldots\ g_K(\bar{a}_{K-1}, \bar{l}_K)]$, where $g_k(\bar{a}_{k-1}, \bar{l}_k)$ that specifies the treatment assigned at k to an individual with past history $(\bar{a}_{k-1}, \bar{l}_k)$. An example in our HIV study: $g_k(\bar{a}_{k-1}, \bar{l}_k)$ is 1 if an individual's CD4 cell count (a function of $\bar{l}_k$) was low at or before k; otherwise $g_k(\bar{a}_{k-1}, \bar{l}_k)$ is 0. A static treatment strategy is a rule $g = [g_0(\bar{a}_{-1}), \ldots\ g_K(\bar{a}_{K-1})]$, where $g_k(\bar{a}_{k-1})$ does not depend on $\bar{l}_k$. We will often abbreviate $g_k(\bar{a}_{k-1}, \bar{l}_k)$ as $g(\bar{a}_{k-1}, \bar{l}_k)$.

Most static and dynamic strategies we are interested in comparing are *deterministic treatment strategies*, which assign a particular value of treatment (0 or 1) to each individual at each time. More generally, we could consider *random treatment strategies* that do not assign a particular value of treatment, but rather a probability of receiving a treatment value. Random treatment strategies can be static (e.g., "independently at each month, treat individuals with probability 0.3 and do not treat with probability 0.7") or dynamic (e.g., "independently at each month, treat individuals whose CD4 cell count is low with probability 0.3, but do not treat individuals with high CD4 cell count").

We refer to the strategy g for which the mean counterfactual outcome $\mathrm{E}[Y^g]$ is maximized (when higher values of outcome are better) as the optimal treatment strategy. For a drug treatment, the optimal strategy will almost always be dynamic because treatment needs to be discontinued when toxicity develops. Also, no random strategy can ever be preferred to the optimal deterministic strategy. However, random strategies (i.e., ordinary randomized trials and sequentially randomized trials) remain scientifically necessary because, before the trial, it is unknown which deterministic regime is optimal. See Young et al. (2014) for a taxonomy of treatment strategies. In the text, except if noted otherwise, the letter g will refer only to deterministic treatment strategies.

on covariates are non-dynamic or *static treatment strategies*. See Fine Point 19.1 for a formal definition.

Causal inference with time-varying treatments involves the contrast of counterfactual outcomes under two or more treatment strategies. The average causal effect of a time-varying treatment is only well-defined if the treatment strategies of interest are specified. In our HIV example, we can define an average causal effect based on the difference $\mathrm{E}[Y^{\bar{a}}] - \mathrm{E}\left[Y^{\bar{a}'}\right]$ that contrasts strategy $\bar{a}$ (say, "always treat") versus strategy $\bar{a}'$ (say, "never treat"), or on the difference $\mathrm{E}[Y^{\bar{a}}] - \mathrm{E}[Y^g]$ that contrasts strategy $\bar{a}$ ("always treat") versus strategy g (say, "treat only after CD4 cell count is low"). Note we will often use g to represent any—static or dynamic—strategy. When we use it to represent a static strategy, we sometimes write $Y^{g=\bar{a}}$ rather than just Y^g or $Y^{\bar{a}}$.

That is, there is not a single definition of causal effect for time-varying treatments. Even when only two treatment options—treat or do not treat—exist at each time k, we can still define as many causal effects as pairs of treatment strategies exist. In the next section, we describe a study design under which all these causal effects can be validly estimated: the sequentially randomized experiment.

19.3 Sequentially randomized experiments

Recall that, by definition, a causal graph must always include all common causes of any two variables on the graph.

The causal diagrams in Figures 19.1, 19.2, and 19.3 summarize three situations that can occur in studies with time-varying treatments. In all three diagrams, A_k represents the time-varying treatment, L_k the set of measured variables, Y the outcome, and U_k the set of unmeasured variables at k that are common causes of at least two other variables on the causal graph. Because the covariates U_k are not measured, their values are unknown and therefore un-

Technical Point 19.1

On the definition of dynamic strategies. Each dynamic strategy $g = \left[g_0\left(\bar{a}_{-1}, \bar{l}_0\right), \ldots \; g_K\left(\bar{a}_{K-1}, \bar{l}_K\right)\right]$ that depends on past treatment and covariate history is associated with a dynamic strategy $g' = \left[g'_0\left(\bar{l}_0\right), \ldots \; g'_K\left(\bar{l}_K\right)\right]$ that depends only on past covariate history. By consistency (see Technical Point 19.2), an individual will have the same treatment, covariate, and outcome history when following strategy g from time zero as when following strategy g' from time zero. In particular, $Y^g = Y^{g'}$ and $\bar{L}^g(K) = \bar{L}^{g'}(K)$. Specifically, g' is defined in terms of g recursively by $g'_0(l_0) = g_0(\bar{a}_{-1} = 0, l_0)$ (by convention, $\bar{a}_{-1}$ can only take the value zero) and $g'_k\left(\bar{l}_k\right) = g_k\left[g'_k\left(\bar{l}_{k-1}\right), \bar{l}_k\right]$. For any strategy g for which treatment at each k already does not depend on past treatment history, g and g' are the identical set of functions. The above definition of g' in terms of g guarantees that an individual has followed strategy g through time t in the observed data, i.e., $A_k = g_k\left(\bar{A}_{k-1}, \bar{L}_k\right)$ for $k \leq t$, if and only if the individual has followed strategy g' through t, i.e., $A_k = g'_k\left(\bar{L}_k\right)$ for $k \leq t$.

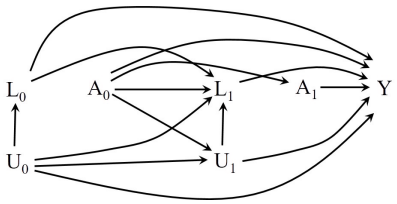

Figure 19.1

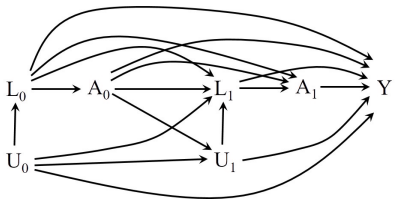

Figure 19.2

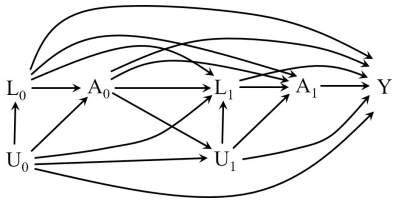

Figure 19.3

available for the analysis. In our HIV study, the time-varying covariate CD4 cell count L_k is a consequence of the true, but unmeasured, chronic damage to the immune system U_k. The greater an individual's immune damage U_k, the lower her CD4 cell count L_k and her health status Y. For simplicity, the causal diagrams include only the first two times of follow-up $k = 0$ and $k = 1$, and we will assume that all participants adhered to the assigned treatment (see Fine Point 19.2).

The causal diagram in Figure 19.1 lacks arrows from either the measured covariates $\bar{L}_k$ or the unmeasured covariates $\bar{U}_k$ into treatment A_k. The causal diagram in Figure 19.2 has arrows from the measured covariates $\bar{L}_k$, but not from the unmeasured covariates $\bar{U}_k$, into treatment A_k. The causal diagram in Figure 19.3 has arrows from both the measured covariates $\bar{L}_k$ and the unmeasured covariates $\bar{U}_k$ into treatment A_k.

Figure 19.1 could represent a randomized experiment in which treatment A_k at each time k is randomly assigned with a probability that depends only on prior treatment history. Our HIV study would be represented by Figure 19.1 if, for example, an individual's treatment value at each month k were randomly assigned with probability 0.5 for individuals who did not receive treatment during the previous month ($A_{k-1} = 0$), and with probability 1 for individuals who did receive treatment during the previous month k ($A_{k-1} = 1$). When interested in the contrast of static treatment strategies, Figure 19.1 is the proper generalization of no confounding by measured or unmeasured variables for time-varying treatments. Under this causal diagram, the counterfactual outcome mean $\mathrm{E}\left[Y^{\bar{a}}\right]$ if everybody had followed the static treatment strategy $\bar{a}$ is simply the mean outcome $\mathrm{E}\left[Y|\overline{A} = \bar{a}\right]$ among those who followed the strategy $\bar{a}$. (Interestingly, the same is not true for dynamic strategies. The counterfactual mean $\mathrm{E}\left[Y^g\right]$ under a dynamic strategy g that depends on the variables L is only the mean outcome among those who followed the strategy g if the probability of receiving treatment $A_k = 1$ is exactly 0.5 at all times k at which treatment A_k depends on $\overline{L}_k$. Otherwise, identifying $\mathrm{E}\left[Y^g\right]$ requires the application of g-methods to data on $\overline{L}$, $\overline{A}$, and Y under either Figure 19.1 or Figure 19.2.)

Figure 19.2 could represent a randomized experiment in which treatment A_k at each time k is randomly assigned by the investigators with a probability that depends on prior treatment *and* measured covariate history. Our study would be represented by Figure 19.2 if, for example, an individual's treatment value at each month k were randomly assigned with probability 0.4 for untreated

Fine Point 19.2

Per-protocol effects to compare treatment strategies. Many randomized trials assign individuals to a treatment at baseline with the intention that they will keep taking it during the follow-up, unless the treatment becomes toxic or otherwise contraindicated. That is, the protocol of the trial implicitly or explicitly aims at the comparison of dynamic treatment strategies, and the per-protocol effect (introduced in Section 9.5) is the effect that would have been observed if everybody had adhered to their assigned treatment *strategy*.

For example, the goal of a trial of statin therapy among healthy individuals may be the comparison of the dynamic strategies "initiate statin therapy at baseline and keep taking it during the study unless rhabdomyolysis occurs" versus "do not take statin therapy during the study unless LDL-cholesterol is high or coronary heart disease is diagnosed." Estimating the per-protocol effect in this randomized trial raises the same issues as any comparison of treatment strategies in an observational study. Specifically, valid estimation of the per-protocol effect generally demands that trial investigators collect post-randomization data on adherence to the strategy and on (time-varying) prognostic factors associated with adherence (Hernán and Robins 2017). Baseline randomization makes us expect baseline exchangeability for the assigned treatment strategy, not sequential exchangeability for the strategy that is actually received.

individuals with high CD4 cell count ($A_{k-1} = 0$, $L_k = 1$), 0.8 for untreated individuals with low CD4 cell count ($A_{k-1} = 0$, $L_k = 0$), and 0.5 for previously treated individuals, regardless of their CD4 cell count ($A_{k-1} = 1$). In Figure 19.2, there is confounding by measured, but not unmeasured, variables for the time-varying treatment.

An experiment in which treatment is randomly assigned at each time k to each individual is referred to as a *sequentially randomized experiment*. Therefore Figures 19.1 and 19.2 could represent sequentially randomized experiments. On the other hand, Figure 19.3 cannot represent a randomized experiment: the value of treatment A_k at each time k depends partly on unmeasured variables U which are causes of L_k and Y, but unmeasured variables obviously cannot be used by investigators to assign treatment. That is, a sequentially randomized experiment can be represented by a causal diagram with many time points $k = 0, 1...K$ and with no direct arrows from the unmeasured prognostic factors U into treatment A_k at any time k.

In observational studies, decisions about treatment often depend on outcome predictors such as prognostic factors. Therefore, observational studies will be typically represented by either Figure 19.2 or Figure 19.3 rather than Figure 19.1. For example, suppose our HIV follow-up study were an observational study (not an experiment) in which the lower the CD4 cell count L_k, the more likely a patient is to be treated. Then our study would be represented by Figure 19.2 if, at each month k, treatment decisions in the real world were made based on the values of prior treatment and CD4 cell count history ($\bar{A}_{k-1}$, $\bar{L}_k$), but not on the values of any unmeasured variables $\bar{U}_k$. Thus, an observational study represented by Figure 19.2 would differ from a sequentially randomized experiment only in that the assignment probabilities are unknown (but could be estimated from the data). Unfortunately, it is impossible to show empirically whether an observational study is represented by the causal diagram in either Figure 19.2 or Figure 19.3. Observational studies represented by Figure 19.3 have unmeasured confounding, as we describe later.

Sequentially randomized experiments are not frequently used in practice. However, the concept of sequentially randomized experiment is helpful to understand some key conditions for valid estimation of causal effects of time-varying treatments. The next section presents these conditions formally.

19.4 Sequential exchangeability

As described in Parts I and II, valid causal inferences about time-fixed treatments typically require conditional exchangeability $Y^a \perp\!\!\!\perp A|L$. When exchangeability $Y^a \perp\!\!\!\perp A|L$ holds, we can obtain unbiased estimates of the causal effect of treatment A on the outcome Y if we appropriately adjust for the variables in L via standardization, IP weighting, g-estimation, or other methods. We expect conditional exchangeability to hold in conditionally randomized experiments—a trial in which individuals are assigned treatment with a probability that depends on the values of the covariates L. Conditional exchangeability holds in observational studies if the probability of receiving treatment depends on the measured covariates L and, conditional on L, does not further depend on any unmeasured, common causes of treatment an outcome.

Similarly, causal inference with time-varying treatments requires adjusting for the time-varying covariates $\bar{L}_k$ to achieve conditional exchangeability at each time point, that is, sequential conditional exchangeability. For example, in a study with two time points, sequential conditional exchangeability is the combination of conditional exchangeability at both the first time and the second time of the study. That is, $Y^g \perp\!\!\!\perp A_0|L_0$ and $Y^g \perp\!\!\!\perp A_1|A_0 = g(L_0), L_0, L_1$. (For brevity, in this book we drop the word "conditional" and simply say sequential exchangeability.) We will refer this set of conditional independences as sequential exchangeability for Y^g under any—static or dynamic—strategy g that involves interventions on both components of the time-varying treatment (A_0, A_1).

For those with observed treatment history $[A_0 = g(L_0), A_1 = g(A_0, L_0, L_1)]$ equal to (i.e., compatible with) the treatment they would have received under strategy g through the end of follow-up, the counterfactual outcome Y^g is equal to the observed outcome Y and therefore also to the counterfactual outcome under the strategy $a_0 = A_0, a_1 = A_1$.

A sequentially randomized experiment—an experiment in which treatment A_k at each time k is randomly assigned with a probability that depends only on the values of their prior covariate history $\bar{L}_k$ and treatment history $\bar{A}_{k-1}$—implies sequential exchangeability for Y^g. That is, for any strategy g, the treated and the untreated at each time k are exchangeable for Y^g conditional on prior covariate history $\bar{L}_k$ and any observed treatment history $\bar{A}_{k-1} = g(\bar{A}_{k-2}, \bar{L}_{k-1})$ compatible with strategy g. Formally, *sequential exchangeability for* Y^g is defined as

$$Y^g \perp\!\!\!\perp A_k|\bar{A}_{k-1} = g(\bar{A}_{k-2}, \bar{L}_{k-1}), \bar{L}_k \text{ for all strategies } g \text{ and } k = 0, 1...K$$

In Figure 19.1, sequential unconditional exchangeability for Y holds, that is, $Y^{\bar{a}} \perp\!\!\!\perp A_k|\bar{A}_{k-1} = \bar{a}_{k-1}$ for all static strategies $\bar{a}$. Unconditional exchangeability implies that association is causation, i.e., $\mathrm{E}[Y^{\bar{a}}] = \mathrm{E}\left[Y|\bar{A} = \bar{a}\right]$.

This form of sequential exchangeability (there are others, as we will see) always holds in any causal graph which, like Figure 19.2, has no arrows from the unmeasured variables U into the treatment variables A. Therefore sequential exchangeability for Y^g holds in sequentially randomized experiments and observational studies in which the probability of receiving treatment at each time depends on their treatment and measured covariate history $\left(\bar{A}_{k-1}, \bar{L}_k\right)$ and, conditional on this history, does not depend on any unmeasured causes of the outcome.

Whenever we talk about identification of causal effects, the identifying formula will be the g-formula. In rare cases not relevant to our discussion, effects can be identified by formulas that are related to, but not equal to, the g-formula (e.g., Technical Point 7.3).

That is, in observational studies represented by Figure 19.2 the mean of the counterfactual outcome $\mathrm{E}[Y^g]$ under all strategies g is identified, whereas in observational studies represented by Figure 19.3 no mean counterfactual outcome $\mathrm{E}[Y^g]$ is identified. In observational studies represented by other causal diagrams, the mean counterfactual outcome $\mathrm{E}[Y^g]$ under some but not all strategies g is identified.

For example, consider an observational study represented by the causal diagram in Figure 19.4, which includes an unmeasured variable W_0. In our HIV example, W_0 could be an indicator for a scheduled clinic visit at time 0 that was not recorded in our database. In that case W_0 would be a cause shared by treatment A_0 and obtaining a (somewhat noisy) measurement L_1 of

Technical Point 19.2

Positivity and consistency for time-varying treatments. The positivity condition needs to be generalized from the fixed version "if $f_L(l) \neq 0$, $f_{A|L}(a|l) > 0$ for all a and l" to the sequential version

$$\text{If } f_{\bar{A}_{k-1},\bar{L}_k}\left(\bar{a}_{k-1},\bar{l}_k\right) \neq 0, \text{ then } f_{A_k|\bar{A}_{k-1},\bar{L}_k}\left(a_k|\bar{a}_{k-1},\bar{l}_k\right) > 0 \text{ for all } \left(\bar{a}_k,\bar{l}_k\right)$$

In a sequentially randomized experiment, positivity will hold if the randomization probabilities at each time k are never either 0 nor 1, no matter the past treatment and covariate history. If we are interested in a particular strategy g, the above positivity condition needs to only hold for treatment histories compatible with g, i.e., for each k, $a_k = g\left(\bar{a}_{k-1},\bar{l}_k\right)$.

The consistency condition also needs to be generalized from the fixed version "If $A = a$ for a given individual, then $Y^a = Y$ for that individual" to the sequential version

$$Y^{\bar{a}} = Y^{\bar{a}^*} \text{ if } \overline{a}^* = \overline{a};\ Y^{\bar{a}} = Y \text{ if } \overline{A} = \bar{a};\ \bar{L}_k^{\bar{a}} = \bar{L}_k^{\bar{a}^*} \text{ if } \overline{a}^*_{k-1} = \overline{a}_{k-1};\ \bar{L}_k^{\bar{a}} = \bar{L}_k \text{ if } \overline{A}_{k-1} = \overline{a}_{k-1}$$

where $\bar{L}_k^{\bar{a}}$ is the counterfactual L-history through time k under strategy $\overline{a}$. Technically, the identification of effects of time-varying treatments on Y requires weaker consistency conditions: "If $\overline{A} = \overline{a}$ for a given individual, then $Y^{\bar{a}} = Y$ for that individual" is sufficient for static strategies, and "For any strategy g, if $A_k = g_k\left(\overline{A}_{k-1},\overline{L}_k\right)$ at each time k for a given individual, then $Y^g = Y$" is sufficient for dynamic strategies. However, the stronger sequential consistency is a natural condition that we will always accept.

Note that, if we expect that the interventions "treat in month k" corresponding to $A_k = 1$ and "do not treat in month k" corresponding to $A_k = 0$ are sufficiently well defined at all times k, then all static and dynamic strategies involving A_k will be similarly well defined.

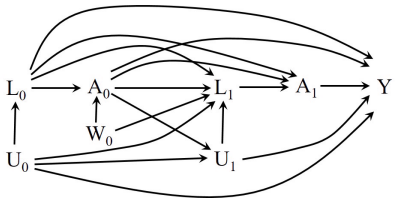

Figure 19.4

CD4 cell count, with U_1 representing the underlying but unknown true value of CD4 cell count. Even though W_0 is unmeasured, the mean counterfactual outcome is still identified under any static strategy $g = \bar{a}$; however, the mean counterfactual outcome $\mathrm{E}[Y^g]$ is not identified under any dynamic strategy g with treatment assignment depending on L_1. To illustrate why identification is possible under some but not all strategies, we will use SWIGs in the next section.

In addition to some form of sequential exchangeability, causal inference involving time-varying treatments also requires a sequential version of the conditions of positivity and consistency. In a sequentially randomized experiment, both sequential positivity and consistency are expected to hold (see Technical Point 19.2). Below we will assume that sequential positivity and consistency hold. Under the three identifiability conditions, we can identify the mean counterfactual outcome $\mathrm{E}[Y^g]$ under a strategy of interest g as long as we use methods that appropriately adjust for treatment and covariate history $\left(\bar{A}_{k-1},\bar{L}_k\right)$, such as the g-formula (standardization), IP weighting, and g-estimation.

19.5 Identifiability under some but not all treatment strategies

Pearl and Robins (1995) proposed a generalized backdoor criterion for static strategies. Robins (1997) extended the procedure to dynamic strategies.

In Chapter 7, we presented a graphical rule—the backdoor criterion—to assess whether exchangeability holds for a time-fixed treatment under a particular causal diagram. The backdoor criterion can be generalized for time-varying treatments. For example, for static strategies, a sufficient condition for identification of the causal effect of treatment strategies is that, at each time k, all backdoor paths into A_k that do not go through any future treatment are

blocked.

However, the *generalized backdoor criterion* does not directly show the connection between blocking backdoor paths and sequential exchangeability, because the procedure is based on causal directed acyclic graphs that do not include counterfactual outcomes. An alternative graphical check for identifiability of causal effects is based on SWIGs, also discussed in Chapter 7. SWIGs are especially helpful for time-varying treatments.

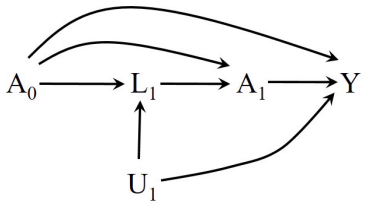

Figure 19.5

Consider the causal diagrams in Figures 19.5 and 19.6, which are simplified versions of those in Figures 19.2 and 19.4. We have omitted the nodes U_0 and L_0 and the arrow from A_0 to U_1. In addition, the arrow from L_1 to Y is absent so L_1 is no longer a direct cause of Y. Figures 19.5 and 19.6 (like Figures 19.2 and 19.4) differ in whether A_k and subsequent covariates L_t for $t > k$ share a cause W_k.

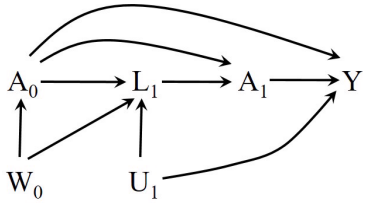

Figure 19.6

As discussed in Part I of this book, a SWIG represents a counterfactual world under a particular intervention. The SWIG in Figure 19.7 represents the world in Figure 19.5 if all individuals had received the static strategy (a_0, a_1), where a_0 and a_1 can take values 0 or 1. For example, Figure 19.7 can be used to represent the world under the strategy "always treat" $(a_0 = 1, a_1 = 1)$ or under the strategy "never treat" $(a_0 = 0, a_1 = 0)$. To construct this SWIG, we first split the treatment nodes A_0 and A_1. The right side of the split treatments represents the value of treatment under the intervention. The left side represents the value of treatment that would have been observed when intervening on all previous treatments. Therefore, the left side of A_0 is precisely A_0 because there are no previous treatments to intervene on, and the left side of A_1 is the counterfactual treatment $A_1^{a_0}$ that would be observed after setting A_0 to the value a_0. All arrows into a given treatment in the original causal diagram now point into the left side, and all arrows out of a given treatment now originate from the right side. The outcome variable is the counterfactual outcome Y^{a_0,a_1} and the covariates L are replaced by their corresponding counterfactual variables. Note that we write the counterfactual variable corresponding to L_1 under strategy (a_0, a_1) as $L_1^{a_0}$, rather than $L_1^{a_0,a_1}$, because a future intervention on A_1 cannot affect the value of earlier L_1.

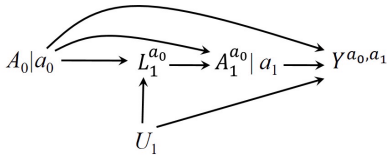

Figure 19.7

Unlike the directed acyclic graph in Figure 19.5, the SWIG in Figure 19.7 does include the counterfactual outcome, which means that we can visually check for exchangeability using d-separation.

In Figure 19.7, we can use d-separation to show that both $Y^{a_0,a_1} \perp\!\!\!\perp A_0$ and $Y^{a_0,a_1} \perp\!\!\!\perp A_1^{a_0} | A_0, L_1^{a_0}$ hold for any static strategy (a_0, a_1). Note that this second conditional independence holds even though there seems to be an open path $A_1^{a_0} \leftarrow a_0 \rightarrow L_1^{a_0} \leftarrow U_1 \rightarrow Y^{a_0,a_1}$. However, this path is actually blocked for the following reason. In the counterfactual world, a_0 is a constant and in probability statements constants are always implicitly conditioned on even though, by convention, they are not shown in the conditioning event. However, when checking d-separation we need to remember that constants are conditioned on, blocking the above path.

The second conditional independence $Y^{a_0,a_1} \perp\!\!\!\perp A_1^{a_0} | A_0, L_1^{a_0}$ implies, by definition, $Y^{a_0,a_1} \perp\!\!\!\perp A_1^{a_0} | A_0 = a_0, L_1^{a_0}$ in the subset of individuals who received treatment $A_0 = a_0$. Therefore, by consistency, we conclude that $Y^{a_0,a_1} \perp\!\!\!\perp A_0$ and $Y^{a_0,a_1} \perp\!\!\!\perp A_1 | A_0 = a_0, L_1$ holds under the causal diagram in Figure 19.5, which corresponds to the SWIG in Figure 19.7 where we can actually check for exchangeability. If there were multiple time points, we would say that

$$Y^{\bar{a}} \perp\!\!\!\perp A_k | \bar{A}_{k-1} = \bar{a}_{k-1}, \bar{L}_k \text{ for } k = 0, 1 ... K$$

We refer to the above condition as *static sequential exchangeability for* $Y^{\bar{a}}$,

$Y^{a_0,a_1} \perp\!\!\!\perp A_1^{a_0} | A_0 = a_0, L_1^{a_0}$ equals $Y^{a_0,a_1} \perp\!\!\!\perp A_1 | A_0 = a_0, L_1$ because, by consistency, $L_1^{a_0} = L_1$ and $A_1^{a_0} = A_1$ when $A_0 = a_0$.

Technical Point 19.3

The many forms of sequential exchangeability. Consider a sequentially randomized experiment of a time-varying treatment A_k with multiple time points $k = 0, 1, ...K$. The SWIG that represents this experiment is just a longer version of Figure 19.7. The following conditional independence can be directly read from the SWIG:

$$\left(Y^{\overline{a}}, \underline{L}^{\overline{a}}_{k+1}\right) \perp\!\!\!\perp A_k^{\overline{a}_{k-1}} | \bar{A}_{k-1}^{\overline{a}_{k-2}}, \bar{L}_k^{\overline{a}_{k-1}}$$

where $\underline{L}^{\overline{a}}_{k+1}$ is the counterfactual covariate history from time $k+1$ through the end of follow-up. The above conditional independence implies $\left(Y^{\overline{a}}, \underline{L}^{\overline{a}}_{k+1}\right) \perp\!\!\!\perp A_k^{\overline{a}_{k-1}} | \bar{A}_{k-1}^{\overline{a}_{k-2}} = \overline{a}_{k-1}, \bar{L}_k^{\overline{a}_{k-1}}$ for the particular instance $\bar{A}_{k-1}^{\overline{a}_{k-2}} = \overline{a}_{k-1}$, with $\overline{a}_{k-1}$ being a component of strategy $\overline{a}$. Because of consistency, the last conditional independence statement equals

$$\left(Y^{\overline{a}}, \underline{L}^{\overline{a}}_{k+1}\right) \perp\!\!\!\perp A_k | \bar{A}_{k-1} = \overline{a}_{k-1}, \bar{L}_k$$

When this statement holds for all $\overline{a}$, we say that there is *sequential exchangeability*. Interestingly, even though this sequential exchangeability condition only refers to static strategies $g = \overline{a}$, it is equivalent to the seemingly stronger

$$\left(Y^{g}, \underline{L}^{g}_{k+1}\right) \perp\!\!\!\perp A_k | \bar{A}_{k-1} = g\left(\bar{A}_{k-1}, \bar{L}_k\right), \bar{L}_k \text{ for all } g,$$

and, if positivity holds, is therefore sufficient to identify the outcome and covariate distribution under any static and dynamic strategies g (Robins 1986). This identification results from the joint conditional independence between $\left(Y^{\overline{a}}, \underline{L}^{\overline{a}}_{k+1}\right)$ and A_k. Note that, for dynamic strategies, sequential exchangeability does not follow from the separate independences $Y^{\overline{a}} \perp\!\!\!\perp A_k | \bar{A}_{k-1} = \overline{a}_{k-1}, \bar{L}_k$ and $\underline{L}^{\overline{a}}_{k+1} \perp\!\!\!\perp A_k | \bar{A}_{k-1} = \overline{a}_{k-1}, \bar{L}_k$.

Stronger conditional independences are expected to hold in a sequentially randomized experiment, but they (i) cannot be read from SWIGs and (ii) are not necessary for identification of the causal effects of treatment strategies in the population. For example, a sequentially randomized trial implies the stronger joint independence $\left\{Y^{\overline{a}}, \underline{L}^{\overline{a}}_{k+1}; \text{all } \overline{a}\right\} \perp\!\!\!\perp A_k | \bar{A}_{k-1}, \bar{L}_k$.

An even stronger condition that is expected to hold in sequentially randomized experiments is

$$\left(Y^{\bar{\mathcal{A}}}, \bar{L}^{\bar{\mathcal{A}}}\right) \perp\!\!\!\perp A_k | \bar{A}_{k-1}, \bar{L}_k$$

where, for a dichotomous treatment A_k, $\bar{\mathcal{A}}$ denotes the set of all 2^K static strategies $\bar{a}$, $Y^{\bar{\mathcal{A}}}$ denotes the set of all counterfactual outcomes $Y^{\bar{a}}$, and $\bar{L}^{\bar{\mathcal{A}}}$ denotes the set of all counterfactual covariate histories. Using a terminology analogous to that of Technical Point 2.1, we refer to this joint independence condition as *full sequential exchangeability*.

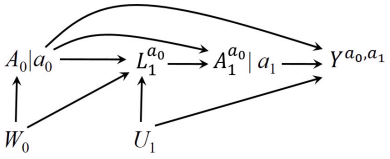

Figure 19.8

which is weaker than sequential exchangeability for Y^g, because it only requires conditional independence between counterfactual outcomes $Y^{\bar{a}}$ indexed by static strategies $g = \bar{a}$ and treatment A_k. Static sequential exchangeability is sufficient to identify the mean counterfactual outcome under any static strategy $g = \bar{a}$. See also Technical Point 19.3.

Static sequential exchangeability also holds under the causal diagram in Figure 19.6, as can be checked by applying d-separation to its corresponding SWIG in Figure 19.8. Therefore, in an observational study represented by Figure 19.6, we can identify the mean counterfactual outcome under any static strategy (a_0, a_1).

Let us return to Figure 19.5. Let us now assume that the arrow from L_1 to A_1 were missing. In that case, the arrow from $L_1^{a_0}$ to $A_1^{a_0}$ would also be missing from the SWIG in Figure 19.7. It would then follow by d-separation that sequential exchangeability holds unconditionally for A_0 and conditionally on A_0 for $A_1^{a_0}$, and therefore that the mean counterfactual outcome under any static strategy could be identified without data on L_1. Now let us assume that,

Fine Point 19.3

Dynamic strategies that depend on baseline covariates. For simplicity, the causal graphs depicted in this chapter do not include a baseline confounder L_0. If we included L_0 in Figure 19.9, then we could have considered a strategy in which the random variable representing the intervention $g_0(L_0)$ replaces g_0. Then, when checking d-separation between A_1^g and Y^g on the graph, $Y^g \perp\!\!\!\perp A_1^g | A_0, g_0(L_0), L_0, L_1^g$, we need to condition on the entire past, including $g_0(L_0)$. If we instantiate this expression at $A_0 = g_0(L_0)$, then the intervention variable can be removed from the conditioning event because $g_0(L_0)$ is now equal to the observed A_0 and thus is redundant. That is, we have now $Y^g \perp\!\!\!\perp A_1^g | A_0 = g_0(L_0), L_0, L_1^g$ which, by consistency, is $Y^g \perp\!\!\!\perp A_1 | A_0 = g_0(L_0), L_0, L_1$. This conditional independence is sequential exchangeability for Y^g and treatment A_1 when there is also a baseline confounder L_0.

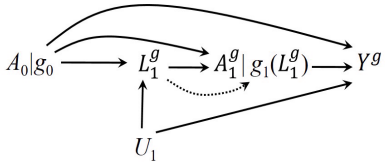

Figure 19.9

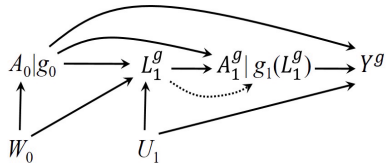

Figure 19.10

Technically, what we read from the SWIG is $Y^g \perp\!\!\!\perp A_1^g | A_0, L_1^g$ which, by consistency, implies $Y^g \perp\!\!\!\perp A_1 | A_0 = g_0, L_1$

in Figure 19.5, there was an arrow from U_1 to A_1. Then the SWIG in Figure 19.7 would include an arrow from U_1 to $A_1^{a_0}$, and that no form of sequential exchangeability would hold. Therefore the counterfactual mean would not be identified under any strategy.

We now discuss the SWIGs for Figures 19.5 and 19.6 under dynamic regimes. The SWIG in Figure 19.9 represents the world of Figure 19.5 under a dynamic treatment strategy $g = [g_0, g_1(L_1)]$ in which treatment A_0 is assigned a fixed value g_0 (either 0 or 1), and treatment A_1 at time $k = 1$ is assigned a value $g_1(L_1^g)$ that depends on the value of L_1^g that was observed after having assigned treatment value g_0 at time $k = 0$. For example, g may be the strategy "do no treat at time 0, treat at time 1 only if CD4 cell count is low, i.e., if $L_1^g = 1$". Under this strategy $g_0 = 0$ for everybody, and $g_1(L_1^g) = 1$ when $L_1^g = 1$ and $g_1(L_1^g) = 0$ when $L_1^g = 0$. Therefore the SWIG includes an arrow from L_1^g to $g_1(L_1^g)$. This arrow was not part of the original causal graph; it is the result of the intervention. We therefore draw this arrow differently from the others, even though we need to treat it as any other arrow when evaluating d-separation. The outcome in the SWIG is the counterfactual outcome Y^g under the dynamic treatment strategy g.

By applying d-separation to the SWIG in Figure 19.9, we find that both $Y^g \perp\!\!\!\perp A_0$ and $Y^g \perp\!\!\!\perp A_1 | A_0 = g_0, L_1^g$ hold for any strategy g. That is, sequential exchangeability for Y^g holds, which means that we can identify the mean counterfactual outcome under all strategies g (see also Fine Point 19.3). This result, however, does not hold for the causal diagram in Figure 19.6.

The SWIG in Figure 19.10 represents the world of Figure 19.6 under a dynamic treatment strategy $g = [g_0, g_1(L_1)]$. By applying d-separation to the SWIG in Figure 19.10, we find that $Y^g \perp\!\!\!\perp A_0$ does not hold because of the open path $A_0 \leftarrow W_0 \rightarrow L_1^g \rightarrow g_1(L_1^g) \rightarrow Y^g$. That is, sequential exchangeability for Y^g does not hold, which means that we cannot identify the mean counterfactual outcome for any strategy g.

In summary, in observational studies (or sequentially randomized trials) represented by Figure 19.5, sequential exchangeability for Y^g holds, and therefore the data can be used to validly estimate causal effects involving static and dynamic strategies. On the other hand, in observational studies represented by Figure 19.6, only the weaker condition for static strategies holds, and therefore the data can be used to validly estimate causal effects involving static strategies, but not dynamic strategies. Another way to think about this is that in the counterfactual world represented by the SWIG in Figure 19.10, the distribution of Y^g depends on the distribution of $g_1(L_1^g)$ and thus of L_1^g. However, the distribution of L_1^g is not identifiable due to the path $A_0 \leftarrow W_0 \rightarrow L_1^g$.

One last example. Consider Figure 19.11 which is equal to Figure 19.6 except for the presence of an arrow from L_1 to Y, and its corresponding SWIG under a static strategy in Figure 19.12. We can use d-separation to show that neither sequential exchangeability for Y^g nor static sequential exchangeability for $Y^{\bar{a}}$ hold. Therefore, in observational study represented by Figure 19.11, we cannot use the data to validly estimate causal effects involving any strategies.

19.6 Time-varying confounding and time-varying confounders

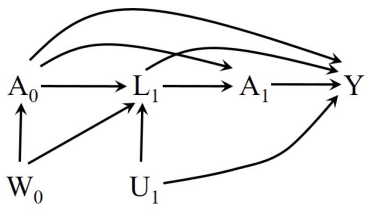

Figure 19.11

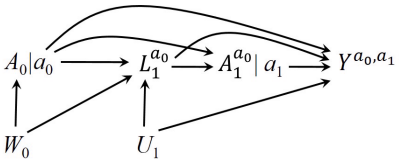

Figure 19.12

No form of sequential exchangeability is guaranteed to hold in observational studies. Achieving approximate exchangeability requires expert knowledge, which will guide investigators in the design of their studies to measure as many of the relevant variables $\bar{L}_k$ as possible. For example, in an HIV study, experts would agree that time-varying variables like CD4 cell count, viral load, symptoms need to be appropriately measured and adjusted for.

But the question "Are the measured covariates sufficient to ensure sequential exchangeability?" can never be answered with certainty. Yet we can use our expert knowledge to organize our beliefs about exchangeability and represent them in a causal diagram. Figures 19.1 to 19.4 are examples of causal diagrams that summarize different scenarios. Note that we drew these causal diagrams in the absence of selection (e.g., censoring by loss to follow-up) so that we can concentrate on confounding here.

Consider Figure 19.5. Like in Part I of this book, suppose that we are interested in the effect of the time-fixed treatment A_1 on the outcome Y. We say that there is confounding for the effect of A_1 on Y because A_1 and Y share the cause U, i.e., because there is an open backdoor path between A_1 and Y through U. To estimate this effect without bias, we need to adjust for confounders of the effect of the treatment A_1 on the outcome Y, as explained in Chapter 7. In other words, we need to be able to block all open backdoor paths between A_1 and Y. This backdoor path $A_1 \longleftarrow L_1 \longleftarrow U \longrightarrow Y$ cannot be blocked by conditioning on the common cause U because U is unmeasured and therefore unavailable to the investigators. However, this backdoor path can be blocked by conditioning on L_1, which is measured. Thus, if the investigators collected data on L_1 for all individuals, there would be no unmeasured confounding for the effect of A_1. We then say that L_1 is a confounder for the effect of A_1, even though the actual common cause of A_1 and Y was the unmeasured U (re-read Section 7.3 if you need to refresh your memory about confounding and causal diagrams).

A second backdoor path gets open after conditioning on collider L_1: $A_1 \longleftarrow A_0 \longrightarrow L_1 \longleftarrow U \longrightarrow Y$ This second backdoor path can be safely blocked by conditioning on prior treatment A_0, assuming it is available to investigators.

As discussed in Chapter 7, the confounders do not have to be direct causes of the outcome. In Figure 19.5, the arrow from the confounder L_1 to the outcome Y does not exist. Then the source of the confounding (i.e., the causal confounder) is the unmeasured common cause U. Nonetheless, because data on L_1 suffice to block the backdoor paths from A_1 to Y and thus to control confounding, we refer to L_1 as a confounder for the effect of A_1 on Y.

Now imagine the very long causal diagram that contains all time points $k = 0, 1, 2...$, and in which L_k affects subsequent treatments A_k, A_{k+1}... and shares unmeasured causes U_k with the outcome Y. Suppose that we want to estimate the causal effects on the outcome Y of treatment strategies defined by interventions on A_0, A_1, A_2. Then, at each time k, the covariate history $\bar{L}_k$ will be needed, together with the treatment history $\bar{A}_{k-1}$, to block the backdoor paths between treatment A_k and the outcome Y. Thus, no unmeasured

Fine Point 19.4

A definition of time-varying confounding. In the absence of selection bias, we say there is confounding for causal effects involving $\mathrm{E}[Y^{\bar{a}}]$ if $\mathrm{E}[Y^{\bar{a}}] \neq \mathrm{E}[Y|A = \bar{a}]$, that is, if the mean outcome had, contrary to fact, all individuals in the study followed strategy $\bar{a}$ differs from the mean outcome among the subset of individuals who followed strategy $\bar{a}$ in the actual study.

We say the confounding is solely time-fixed (i.e., wholly attributable to baseline covariates) if $\mathrm{E}[Y^{\bar{a}}|L_0] = \mathrm{E}[Y|A = \bar{a}, L_0]$, as would be the case if the only arrows pointing into A_1 in Figure 19.2 were from A_0 and L_0. In contrast, if the identifiability conditions hold, but $\mathrm{E}[Y^{\bar{a}}|L_0] \neq \mathrm{E}[Y|A = \bar{a}, L_0]$, we say that time-varying confounding is present. If the identifiability conditions do not hold, as in Figure 19.3, we say that there is unmeasured confounding.

A sufficient condition for no time-varying confounding is unconditional sequential exchangeability for $Y^{\bar{a}}$, that is, $Y^{\bar{a}} \perp\!\!\!\perp A_k | \bar{A}_{k-1} = \bar{a}_{k-1}$. This condition holds in sequentially randomized experiments, like the one represented in Figure 19.1, in which treatment A_k at each time k is randomly assigned with a probability that depends only on the values of prior treatment history $\bar{A}_{k-1}$. In fact, the causal diagram in Figure 19.1 can be greatly simplified. To do so, first note that L_1 is not a common cause of any two nodes in the graph so it can be omitted from the graph. Once L_1 is gone, then both L_0 and U_1 can be omitted too because they cease to be common causes of two nodes in the graph. In the graph without L_0, L_1, and U_1, the node U_0 can be omitted too. That is, the causal diagram in Figure 19.1 can be simplified to include only the nodes A_0, A_1 and Y.

Time-varying confounders are sometimes referred to as time-dependent confounders.

confounding for the effect of $\bar{A}$ requires that the investigators collected data on $\bar{L}_k$ for all individuals. We then say that the time-varying covariates in $\bar{L}_k$ are *time-varying confounders* for the effect of the time-varying treatment $\bar{A}$ on Y at several (or, in our example, all) times k in the study. See Fine Point 19.4 for a more precise definition of time-varying confounding.

Unfortunately, we cannot empirically confirm that all confounders, whether time-fixed or time-varying, are measured. That is, we cannot empirically differentiate between Figure 19.2 with no unmeasured confounding and Figure 19.3 with unmeasured confounding. Interestingly, even if all confounders were correctly measured and modeled, most adjustment methods may still result in biased estimates when comparing treatment strategies. The next chapter explains why g-methods are the appropriate approach to adjust for time-varying confounders.

Chapter 20
TREATMENT-CONFOUNDER FEEDBACK

The previous chapter identified sequential exchangeability as a key condition to identify the causal effects of time-varying treatments. Suppose that we have a study in which the strongest form of sequential exchangeability holds: the measured time-varying confounders are sufficient to validly estimate the causal effect of any treatment strategy. Then the question is what confounding adjustment method to use. The answer to this question highlights a key problem in causal inference about time-varying treatments: treatment-confounder feedback.

When treatment-confounder feedback exists, using traditional adjustment methods may introduce bias in the effect estimates. That is, even if we had all the information required to validly estimate the average causal effect of any treatment strategy, we would be generally unable to do so. This chapter describes the structure of treatment-confounder feedback and the reasons why traditional adjustment methods fail.

20.1 The elements of treatment-confounder feedback

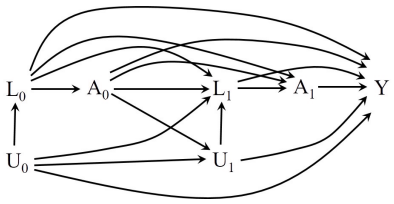

Figure 20.1

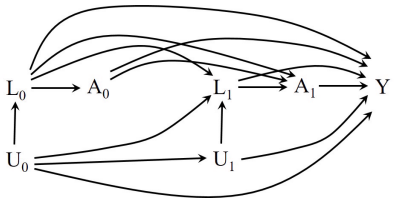

Figure 20.2

Consider again the sequentially randomized trial of HIV-positive individuals that we discussed in the previous chapter. For every person in the study, we have data on treatment A_k (1: treated, 0: untreated) and covariates L_k at each month of follow-up $k = 0, 1, 2...K$, and on an outcome Y that measures health status at month $K + 1$. The causal diagram in Figure 20.1, which is equal to the one in Figure 19.2, represents the first two months of the study. The time-varying covariates L_k are time-varying confounders. (As in the previous chapter, we are using this example without censoring so that we can focus on confounding.)

Something else is going on in Figure 20.1. Not only is there an arrow from CD4 cell count L_k to treatment A_k, but also there is an arrow from treatment A_{k-1} to future CD4 cell count L_k—because receiving treatment A_{k-1} increases future CD4 cell count L_k. That is, the confounder affects the treatment *and* the treatment affects the confounder. There is *treatment-confounder feedback* (see also Fine Point 20.1).

Note that time-varying confounding can occur without treatment-confounder feedback. The causal diagram in Figure 20.2. is the same as the one in Figure 20.1, except that the arrows from treatment A_{k-1} to future L_k and U_k have been deleted. In a setting represented by this diagram, the time-varying covariates L_k are time-varying confounders, but they are not affected by prior treatment. Therefore, there is time-varying confounding, but there is no treatment-confounder feedback.

Treatment-confounder feedback creates an interesting problem for causal inference. To state the problem in its simplest form, let us simplify the causal diagram in Figure 20.1 a bit more. Figure 20.3 is the smallest subset of Figure 20.1 that illustrates treatment-confounder feedback in a sequentially randomized trial with two time points. When drawing the causal diagram in Figure 20.3, we made two simplifications:

- Because our interest is in the implications of confounding by L_1, we

Fine Point 20.1

Representing feedback cycles with acyclic graphs. Interestingly, an *acyclic* graph—like the one in Figure 20.1—can be used to represent a treatment-confounder feedback loop or *cycle*. The trick to achieve this visual representation is to elaborate the treatment-confounder feedback loop in time. That is, $A_{k-1} \rightarrow L_k \rightarrow A_k \rightarrow L_{k+1}$ and so on.

The representation of feedback cycles with acyclic graphs also requires that time be considered as a discrete variable. That is, we say that treatment and covariates can change during each interval $[k, k+1)$ for $k = 0, 1, ...K$, but we do not specify when exactly during the interval the change takes place. This discretization of time is not a limitation in practice: the length of the intervals can be chosen to be as short as the granularity of the data requires. For example, in a study where individuals see their doctors once per month or less frequently (as in our HIV example), time may be safely discretized into month intervals. In other cases, year intervals or day intervals may be more appropriate. Also, as we said in Chapter 17, time is typically measured in discrete intervals (years, months, days) any way, so the discretization of time is often not even a choice.

did not bother to include a node L_0 for baseline CD4 cell count. Just suppose that treatment A_0 is marginally randomized and treatment A_1 is conditionally randomized given L_1.

- The unmeasured variable U_0 is not included.
- There is no arrow from A_0 to A_1, which implies that treatment is assigned using information on L_1 only.
- There are no arrows from A_0, L_1 and A_1 to Y, which would be the case if treatment has no causal effect on the outcome Y of any individual, i.e., the sharp null hypothesis holds.

None of these simplifications affect the arguments below. A more complicated causal diagram would not add any conceptual insights to the discussion in this chapter; it would just be harder to read.

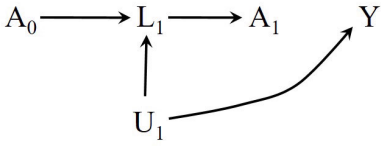

Figure 20.3

Now suppose that treatment has no effect on any individual's Y, which implies the causal diagram in Figure 20.3 is the correct one, but the investigators do not know it. Also suppose that we have data on treatment A_0 in month 0 and A_1 in month 1, on the confounder CD4 cell count L_1 at the start of month 1, and on the outcome Y at the end of follow-up. We wish to use these data to estimate the average causal effect of the static treatment strategy "always treat", $(a_0 = 1, a_1 = 1)$, compared with the static treatment strategy "never treat", $(a_0 = 0, a_1 = 0)$ on the outcome Y, that is, $\mathrm{E}\left[Y^{a_0=1,a_1=1}\right] - \mathrm{E}\left[Y^{a_0=0,a_1=0}\right]$. According to Figure 20.3, the true, but unknown to the investigator, average causal effect is 0 because there are no forward-directed paths from either treatment variable to the outcome. That is, one cannot start at either A_0 or A_1 and, following the direction of the arrows, arrive at Y.

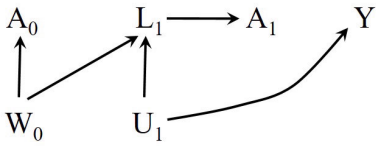

Figure 20.4

Figure 20.4 can depict a sequentially randomized trial because there are no direct arrows from the unmeasured U into the treatment variables. Therefore, as we discussed in the previous chapter, we should be able to use the observed data on A_0, L_1, A_1, and Y to conclude that $\mathrm{E}\left[Y^{a_0=1,a_1=1}\right] - \mathrm{E}\left[Y^{a_0=0,a_1=0}\right]$ is equal to 0. However, as we explain in the next section, we will not generally be able to correctly estimate the causal effect when we adjust for L_1 using traditional methods, like stratification, outcome regression, and matching. That is, in this example, an attempt to adjust for the confounder L_1 using these methods will generally result in an effect estimate that is different from 0, and thus invalid.

Figure 20.3 represents either a sequentially randomized trial or an observational study with no unmeasured confounding; Figure 20.4 represents an observational study.

In other words, when there are time-varying confounders and treatment-confounder feedback, traditional methods cannot be used to correctly adjust for those confounders. Even if we had sufficient longitudinal data to ensure sequential exchangeability, traditional methods would not generally provide a valid estimate of the causal effect of any treatment strategies. In contrast, g-methods appropriately adjust for the time-varying confounders even in the presence of treatment-confounder feedback.

This limitation of traditional methods applies to settings in which the time-varying confounders are affected by prior treatment as in Figure 20.3, but also to settings in which the time-varying confounders share causes W with prior treatment as in Figure 20.4, which is a subset of Figure 19.4. We refer to both Figures 20.3 and 20.4 (and Figures 19.2 and 19.4) as examples of treatment-confounder feedback. The next section explains why traditional methods cannot adequately handle treatment-confounder feedback.

20.2 The bias of traditional methods

This is an ideal trial with full adherence to the assigned treatment and no losses to follow-up.

To illustrate the bias of traditional methods, let us consider a (hypothetical) sequentially randomized trial with 32,000 HIV-positive individuals and two time points $k = 0$ and $k = 1$. Treatment $A_0 = 1$ is randomly assigned at baseline with probability 0.5. Treatment A_1 is randomly assigned in month 1 with a probability that depends only on the value of CD4 cell count L_1 at the start of month 1—0.4 if $L_1 = 0$ (high), 0.8 if $L_1 = 1$ (low). The outcome Y, which is measured at the end of follow-up, is a function of CD4 cell count, concentration of virus in the serum, and other clinical measures, with higher values of Y signifying better health.

Table 20.1

N	A_0	L_1	A_1	Mean Y
2400	0	0	0	84
1600	0	0	1	84
2400	0	1	0	52
9600	0	1	1	52
4800	1	0	0	76
3200	1	0	1	76
1600	1	1	0	44
6400	1	1	1	44

If there were additional times k at which treatment A_k were affected by L_k, then L_k would be a time-varying confounder

Table 20.1 shows the data from this trial. To save space, the table displays one row per combination of values of A_0, L_1, and A_1, rather than one row per individual. For each of the eight combinations, the table provides the number of subjects N and the mean value of the outcome $\mathrm{E}[Y|A_0, L_1, A_1]$. Thus, row 1 shows that the mean of the 2400 individuals with $(A_0 = 0, L_1 = 0, A_1 = 0)$ was $\mathrm{E}[Y|A_0 = 0, L_1 = 0, A_1 = 0] = 84$. In this sequentially randomized trial, the identifiability conditions—sequential exchangeability, positivity, and consistency—hold. By design, there are no confounders for the effect of A_0 on Y, and L_1 is the only confounder for the effect of A_1 on Y so (conditional on L_1) sequential exchangeability holds. By inspection of Table 20.1, we can conclude that the positivity condition is satisfied, because otherwise one or more of the eight rows would have zero individuals.

Figure 20.3 represents the null because there is no arrow from L_1 to Y. Otherwise, A_0 would have an effect on Y through L_1

The causal diagram in Figure 20.3 depicts this sequentially randomized experiment when the sharp null hypothesis holds. To check whether the data in Table 20.1 are consistent with the causal diagram in Figure 20.3, we can separately estimate the average causal effects of each of the time-fixed treatments A_0 and A_1 within levels of past covariates and treatment, which should all be null. In the calculations below, we will ignore random variability.

A quick inspection of the table shows that the average causal effect of treatment A_1 is indeed zero in all four strata defined by A_0 and L_1. Consider the effect of A_1 in the 4000 individuals with $A_0 = 0$ and $L_1 = 0$, whose data are shown in rows 1 and 2 of Table 20.1. The mean outcome among those who did not receive treatment at time 1, $\mathrm{E}[Y|A_0 = 0, L_1 = 0, A_1 = 0]$, is 84, and the mean outcome among those who did receive treatment at time 1,

Technical Point 20.1

G-null test. Suppose the sharp null hypothesis is true. Then any counterfactual outcome Y^g is the observed outcome Y. In this setting, sequential exchangeability for Y^g can be written as $Y \perp\!\!\!\perp A_0 | L_0$ and $Y \perp\!\!\!\perp A_1 | A_0 = g(L_0), L_0, L_1$ in a study with two time points. The first independence implies no causal effect of A_0 in any strata defined by L_0, and the second independence implies no causal effect of A_1 in any strata defined by L_1 and A_0. Therefore, under sequential exchangeability, a test of these conditional independences is a test of the sharp null. This is the g-null test.

Conversely, the g-null theorem (Robins 1986) says that, if these conditional independences hold, then the distribution of Y^g and therefore the mean $\mathrm{E}[Y^g]$ is the same for all g, and also equal to the distribution and mean of the observed Y. Note, however, that equality of distributions under all g only implies the sharp null hypothesis under a strong form of faithfulness that forbids perfect cancellations of effects. As discussed in Fine Point 6.2, we assume faithfulness throughout this book unless we say otherwise.

$\mathrm{E}[Y|A_0 = 0, L_1 = 0, A_1 = 1]$, is also 84. Therefore the difference

$$\mathrm{E}[Y|A_0 = 0, L_1 = 0, A_1 = 1] - \mathrm{E}[Y|A_0 = 0, L_1 = 0, A_1 = 0]$$

is zero. Because the identifiability conditions hold, this associational difference validly estimates the average causal effect

$$\mathrm{E}\left[Y^{a_1=1}|A_0 = 0, L_1 = 0\right] - \mathrm{E}\left[Y^{a_1=0}|A_0 = 0, L_1 = 0\right]$$

in the stratum $(A_0 = 0, L_1 = 0)$. Similarly, it is easy to check that the average causal effect of treatment A_1 on Y is zero in the remaining three strata $(A_0 = 0, L_1 = 1)$, $(A_0 = 1, L_1 = 0)$, $(A_0 = 1, L_1 = 1)$, by comparing the mean outcome between rows 3 and 4, rows 5 and 6, and rows 7 and 8, respectively.

We can now show that the average causal effect of A_0 is also zero. To do so, we need to compute the associational difference $\mathrm{E}[Y|A_0 = 1] - \mathrm{E}[Y|A_0 = 0]$ which, because of randomization, is a valid estimator of the causal contrast $\mathrm{E}\left[Y^{a_0=1}\right] - \mathrm{E}\left[Y^{a_0=0}\right]$. The mean outcome $\mathrm{E}[Y|A_0 = 0]$ among the $16,000$ individuals treated at time 0 is the weighted average of the mean outcomes in rows 1, 2, 3 and 4, which is 60. And $\mathrm{E}[Y|A_0 = 1]$, computed analogously, is also 60. Therefore, the average causal effect of A_0 is zero.

The weighted average is $\frac{2400}{16000} \times 84 + \frac{1600}{16000} \times 84 + \frac{2400}{16000} \times 52 + \frac{9600}{16000} \times 52 = 60$

We have confirmed that the causal effects of A_0 and A_1 (conditional on the past) are zero when we treat A_0 and A_1 separately as time-fixed treatments. What if we now treat the joint treatment (A_0, A_1) as a time-varying treatment and compare two treatment strategies? For example, let us say that we want to compare the strategies "always treat" versus "never treat", that is $(a_0 = 1, a_1 = 1)$ versus $(a_0 = 0, a_1 = 0)$. Because the identifiability conditions hold, the data in Table 20.1 should suffice to validly estimate this effect.

Because the effect for each of the individuals components of the strategy, a_0 and a_1, is zero, it follows from the g-null theorem that the average causal effect $\mathrm{E}\left[Y^{a_0=1,a_1=1}\right] - \mathrm{E}\left[Y^{a_0=0,a_1=0}\right]$ is zero. But is this what we conclude from the data if we use conventional analytic methods? To answer this question, let us conduct two data analyses. In the first one, we do not adjust for the confounder L_1, which should give us an incorrect effect estimate. In the second one, we do adjust for the confounder L_1 via stratification.

1. We compare the mean outcome in the 9600 individuals who were treated at both times (rows 6 and 8 of Table 20.1) with that in the 4800 individuals who were untreated at both times (rows 1 and 3). The respective averages are $\mathrm{E}[Y|A_0 = 1, A_1 = 1] = 54.7$, and $\mathrm{E}[Y|A_0 = 0, A_1 = 0] =$

$\mathrm{E}[Y|A_0 = 1, A_1 = 1]$
$\frac{3200}{9600} \times 76 + \frac{6400}{9600} \times 44 = 54.7$
$\mathrm{E}[Y|A_0 = 0, A_1 = 0]$
$\frac{2400}{4800} \times 84 + \frac{2400}{4800} \times 52 = 68.0$

68. The associational difference is $54.7 - 68 = -13.3$ which, if interpreted causally, would mean that not being treated at either time is better than being treated at both times. This analysis gives the wrong answer—a non-null difference—because $\mathrm{E}[Y|A_0 = a_0, A_1 = a_1]$ is not a valid estimator of $\mathrm{E}[Y^{a_0,a_1}]$. Adjustment for the confounder L_1 is needed.

2. We adjust for L_1 via stratification. That is, we compare the mean outcome in individuals who were treated with that in individuals who were untreated at both times, within levels of L_1. For example, take the stratum $L_1 = 0$. The mean outcome in the treated at both times, $\mathrm{E}[Y|A_0 = 1, L_1 = 0, A_1 = 1]$, is 76 (row 6). The mean outcome in the untreated at both times, $\mathrm{E}[Y|A_0 = 0, L_1 = 0, A_1 = 0]$, is 84 (row 1). The associational difference is $76 - 84 = -8$ which, if interpreted causally, would mean that, in the stratum $L_1 = 0$, not being treated at either time is better than being treated at both times. Similarly, the difference $\mathrm{E}[Y|A_0 = 1, L_1 = 1, A_1 = 1] - \mathrm{E}[Y|A_0 = 0, L_1 = 1, A_1 = 0]$ in the stratum $L_1 = 1$ is also -8.

Note that, because the effect is -8 in both strata of L_1, it is not possible that a weighted average of the stratum-specific effects will yield the correct value 0.

What? We said that the effect estimate should be 0, not -8. How is it possible that the analysis adjusted for the confounder also gives a wrong answer? This estimate reflects the bias of traditional methods to adjust for confounding when there is treatment-confounder feedback. The next section explains why the bias arises.

20.3 Why traditional methods fail

Table 20.1 shows data from a sequentially randomized trial with treatment-confounder feedback, as represented by the causal diagram in Figure 20.3. Even though no data on the unmeasured variable U_1 (immunosuppression level) is available, all three identifiability conditions hold: U_1 is not needed if we have data on the confounder L_1. Therefore, as discussed in Chapter 19, we should be able to correctly estimate causal effects involving any static or dynamic treatment strategies. And yet our analyses in the previous section did not yield the correct answer, whether or not we adjusted for L_1.

The problem was that we did not use the correct method to adjust for confounding. Stratification is a commonly used method to adjust for confounding, but it cannot handle treatment-confounder feedback. Stratification means estimating the association between treatment and outcome in subsets—strata—of the study population defined by the confounders—L_1 in our example. Because the variable L_1 can take only two values—1 if the CD4 cell count is low, and 0 otherwise—there are two such strata in our example. To estimate the causal effect in those with $L_1 = l$, we selected (i.e., conditioned or stratified on) the subset of the population with value $L_1 = l$.

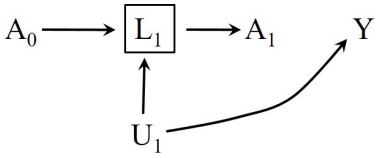

Figure 20.5

But stratification can have unintended effects when the association measure is computed within levels of a variable L_1 that is caused by prior treatment A_0. Indeed Figure 20.5 shows that conditioning on L_1—a collider—opens the path $A_0 \longrightarrow L_1 \longleftarrow U_1 \longrightarrow Y$. That is, stratification induces a noncausal association between the treatment A_0 at time 0 and the unmeasured variable U_1, and therefore between A_0 and the outcome Y, within levels of L_1. Among those with low CD4 count ($L_1 = 1$), being on treatment ($A_0 = 1$) becomes a marker for severe immunosuppression (high value of U_1); among those with a high level

Fine Point 20.2

Confounders on the causal pathway. Conditioning on confounders L_1 which are affected by previous treatment can create selection bias even if the confounder is not on a causal pathway between treatment and outcome. In fact, no such causal pathway exists in Figures 20.5 and 20.6.

On the other hand, in Figure 20.7 the confounder L_1 for subsequent treatment A_1 lies on a causal pathway from earlier treatment A_0 to outcome Y, i.e., the path $A_0 \longrightarrow L_1 \longrightarrow Y$. Were the potential for selection bias not present in Figure 20.7 (e.g., were U_1 not a common cause of L_1 and Y), the associational differences within strata of L_1 could be an unbiased estimate of the direct effect of A_0 on Y not through L_1, but still would not be an unbiased estimate of the overall effect of $\bar{A}$ on Y, because the effect of A_0 mediated through L_1 is not included.

It is sometimes said that variables on a causal pathway between treatment and outcome cannot be considered as confounders, because adjusting for those variables will result in a biased effect estimate. However, this characterization of confounders is inaccurate for time-varying treatments. Figure 20.7 shows that a confounder for subsequent treatment A_1 can be on a causal pathway between past treatment A_0 and the outcome. As for whether adjustment for confounders on a causal pathway induces bias for the effect of a treatment strategy, that depends on the choice of adjustment method. Stratification will indeed induce bias; g-methods will not.

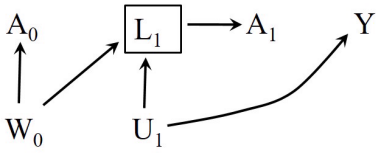

Figure 20.6

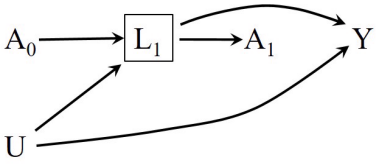

Figure 20.7

of CD4 ($L_1 = 0$), being off treatment ($A_0 = 0$) becomes a marker for milder immunosuppression (low value of U_1). Thus, the side effect of stratification is to induce an association between treatment A_0 and outcome Y.

In other words, stratification eliminates confounding for A_1 at the cost of introducing selection bias for A_0. The associational differences

$$\mathrm{E}\left[Y|A_0 = 1, L_1 = l, A_1 = 1\right] - \mathrm{E}\left[Y|A_0 = 0, L_1 = l, A_1 = 0\right]$$

may be different from 0 even if, as in our example, treatment has no effect on the outcome of any individuals at any time. This bias arises from choosing a subset of the study population by selecting on a variable L_1 affected by (a component A_0 of) the time-varying treatment. The net bias depends on the relative magnitude of the confounding that is eliminated and the selection bias that is created.

Technically speaking, the bias of traditional methods will occur not only when the confounders are affected by prior treatment (in randomized experiments or observational studies), but also when the confounders share an unmeasured cause W with prior treatment (in observational studies). In the observational study depicted in Figure 20.6, conditioning on the collider L_1 opens the path $A_0 \longleftarrow W_0 \longrightarrow L_1 \longleftarrow U_1 \longrightarrow Y$. For this reason, we referred to both settings in Figures 20.3 and 20.4—which cannot be distinguished using the observed data—as examples of treatment-confounder feedback.

The causal diagrams that we have considered to describe the bias of traditional methods are all very simple. They only represent settings in which treatment does not have a causal effect on the outcome. However, conditioning on a confounder in the presence of treatment-confounder feedback also induces bias when treatment has a non-null effect, as in Figure 20.7. The presence of arrows from A_0, A_1, or L_1 to Y does not change the fact that conditioning on L_1 creates an association between A_0 and Y that does not have a causal interpretation (see also Fine Point 20.2). Also, our causal diagrams had only two time points and a limited number of nodes, but the bias of traditional methods will also arise from high-dimensional data with multiple time points and variables. In fact, the presence of time-varying confounders affected by previous treatment at multiple times increases the possibility of a large bias.

In general, valid estimation of the effect of treatment strategies is only possible when the joint effect of the treatment components A_k can be estimated simultaneously and without bias. As we have just seen, this may be impossible to achieve using stratification, even when data on all time-varying confounders are available.

20.4 Why traditional methods cannot be fixed

We showed that stratification cannot be used as a confounding adjustment method when there is treatment-confounder feedback. But what about other traditional methods? For example, we could have used parametric outcome regression, rather than nonparametric stratification, to adjust for confounding. Would outcome regression succeed where plain stratification failed?

This question is particularly important for settings with high-dimensional data, because in high-dimensional settings we will be unable to conduct a simple stratified analysis like we did in the previous section. In Table 20.1, treatment A_k occurs at two months $k = 0, 1$, which means that there are only 2^2 static treatment strategies $\bar{a}$. But when the treatment A_k occurs at multiple points $k = 0, 1...K$, we will not be able to present a table with all the combinations of treatment values. If, as is not infrequent in practice, K is of the order of 100, then there are 2^{100} static treatment strategies $\bar{a}$, a staggering number that far exceeds the sample size of any study. The total number of treatment strategies is much greater when we consider dynamic strategies as well.

The number of data combinations is even greater because there are multiple confounders L_k measured at each time point k.

As we have been arguing since Chapter 11, we will need modeling to estimate average causal effects involving $\mathrm{E}[Y^{\bar{a}}]$ when there are many possible treatment strategies $\bar{a}$. To do so, we will need to hypothesize a dose-response function for the effect of treatment history $\bar{a}$ on the mean outcome Y. One possibility would be to assume that the effect of treatment strategies $\bar{a}$ increases linearly as a function of the cumulative treatment under each strategy. Under this assumption, all strategies that assign treatment for exactly three months have the same effect, regardless of the period when those three months of treatment occur, e.g., the first 3 months of follow-up, the last 3 months of follow-up, etc. The price paid for modelling is yet another threat to the validity of our estimates due to possible model misspecification of the dose-response function.

Unfortunately, regression modeling does not remove the bias of traditional methods in the presence of treatment-confounder feedback, as we now show. For the data in Table 20.1, let us define cumulative treatment $cum\left(\bar{A}\right) = A_0 + A_1$, which can take 3 values: 0 (if the individuals remains untreated at both times), 1 (if the subject is treated at time 1 only or at time 2 only), and 2 (if the subject is treated at both times). The treatment strategies of interest can then be expressed as "always treat" $cum\left(\bar{a}\right) = 2$, and "never treat" $cum\left(\bar{a}\right) = 0$, and the average causal effect as $\mathrm{E}\left[Y^{cum(\bar{a})=2}\right] - \mathrm{E}\left[Y^{cum(\bar{a})=0}\right]$. Again, any valid method should estimate that the value of this difference is 0.

Under the assumption that the mean outcome $\mathrm{E}\left[Y|\bar{A}, L_1\right]$ depends linearly on the covariate $cum\left(\bar{A}\right)$, we could fit the outcome regression model

$$\mathrm{E}\left[Y|\bar{A}, L_1\right] = \theta_0 + \theta_1 cum\left(\bar{A}\right) + \theta_2 L_1$$

The associational difference $\mathrm{E}\left[Y|cum\left(\bar{A}\right) = 2, L_1\right] - \mathrm{E}\left[Y|cum\left(\bar{A}\right) = 0, L_1\right]$ is equal to $\theta_1 \times 2$. (The model correctly assumes that the difference is the same in

the strata $L_1 = 1$ and $L_1 = 0$.) Therefore some might want to interpret $\theta_1 \times 2$ as the average causal effect of "always treat" versus "never treat" within levels of the covariate L_1. But such causal interpretation is unwarranted because, as Figure 20.5 shows, conditioning on L_1 induces an association between A_0, a component of treatment $cum\left(\bar{A}\right)$, and the outcome Y. This implies that θ_1—and therefore the associational difference of means—is non-zero even if the true causal effect is zero. A similar argument can be applied to matching. G-methods are needed to appropriately adjust for time-varying confounders in the presence of treatment-confounder feedback.

We invite readers to check for themselves that θ_1 is not zero by fitting this outcome regression model to the data in Table 20.1.

20.5 Adjusting for past treatment

One more thing before we discuss g-methods. For simplicity, we have so far described treatment-confounder feedback under simplified causal diagrams in which past treatment does not directly affect subsequent treatment. That is, the causal diagrams in Figures 20.3 and 20.4 did not include an arrow from A_0 to A_1. We now consider the more general case in which past treatment may directly affect subsequent treatment.

As an example, suppose doctors in our HIV study use information on past treatment history $\bar{A}_{k-1}$ when making a decision about whether to prescribe treatment A_k at time k. To represent this situation, we add an arrow from A_0 to A_1 to the causal diagrams in Figures 20.3 and 20.4, as depicted in Figures 20.8 and 20.9.

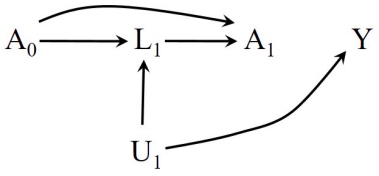

Figure 20.8

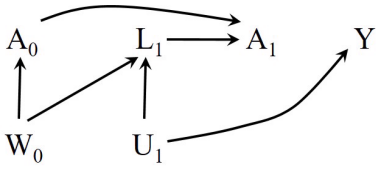

Figure 20.9

The causal diagrams in Figures 20.8 and 20.9 show that, in the presence of treatment-confounder feedback, conditioning on L_1 is insufficient to block all backdoor paths between treatment A_1 and outcome Y. Indeed conditioning on L_1 opens the path $A_1 \leftarrow A_0 \rightarrow L_1 \leftarrow U_1 \rightarrow Y$ in Figure 20.8, and the path $A_1 \leftarrow A_0 \leftarrow W_0 \rightarrow L_1 \leftarrow U_1 \rightarrow Y$ in Figure 20.9. Of course, regardless of whether treatment-confounder feedback exists, conditioning on past treatment history is always required when past treatment has a non-null effect on the outcome, as in the causal diagram of Figure 20.10. Under this diagram, treatment A_0 is a confounder of the effect of treatment A_1.

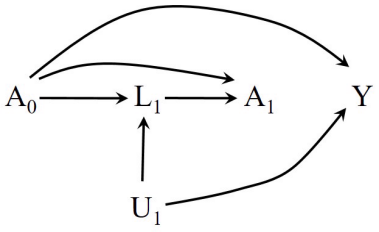

Figure 20.10

Therefore, sequential exchangeability at time k generally requires conditioning on treatment history $\bar{A}_{k-1}$ before k; conditioning only on the covariates L is not enough. That is why, in this and in the previous chapter, all the conditional independence statements representing sequential exchangeability were conditional on treatment history.

Past treatment plays an important role in the estimation of effects of time-fixed treatments too. Suppose we are interested in estimating the effect of the time-fixed treatment A_1—as opposed to the effect of a treatment strategy involving both A_0 and A_1—on Y. (Sometimes the effect of A_1 is referred to as the short-term effect of the time-varying treatment $\bar{A}$.) Then lack of adjustment for past treatment A_0 will generally result in selection bias if there is treatment-confounder feedback, and in confounding if past treatment A_0 directly affects the outcome Y. In other words, the difference $\mathrm{E}\left[Y|A_1 = 1, L_1\right] - \mathrm{E}\left[Y|A_1 = 0, L_1\right]$ would not be zero even if treatment A_1 had no effect on any individual's outcome Y, as in Figures 20.8-20.10. In practice, when making causal inferences about time-fixed treatments, bias may arise in analyses that compare current users ($A_1 = 1$) versus nonusers ($A_1 = 0$) of treatment. To avoid the bias, one can adjust for prior treatment history or restrict the analysis to individuals with a particular treatment history. This

is the idea behind "new-user designs" for time-fixed treatments: restrict the analysis to individuals who had not used treatment in the past.

The requirement to adjust for past treatment has additional bias implications when past treatment is mismeasured. As discussed in Section 9.3, a mismeasured confounder may result in effect estimates that are biased, either upwards or downwards. In our HIV example, suppose investigators did not have access to the study participants' medical records. Rather, to ascertain prior treatment, investigators had to ask participants via a questionnaire. Since not all participants provided an accurate recollection of their treatment history, treatment A_0 was measured with error. Investigators had data on the mismeasured variable A_0^* rather than on the variable A_0. To depict this setting in Figures 20.8-20.10, we add an arrow from the true treatment A_0 to the mismeasured treatment A_0^*, which shows that conditioning on A_0^* cannot block the biasing paths between A_1 and Y that go through A_0. Investigators will then conclude that there is an association between A_1 to Y, even after adjusting for A_0^* and L_1, despite the lack of an effect on A_1 on Y. Therefore, when treatment is time-varying, we find that, contrary to a widespread belief, mismeasurement of treatment—even if the measurement error is independent and non-differential—may cause bias under the null. This bias arises because past treatment is a confounder for the effect of subsequent treatment, even if past treatment has no causal effect on the outcome. Furthermore, under the alternative, this imperfect bias adjustment may result in an exaggerated estimate of the effect.

Chapter 21
G-METHODS FOR TIME-VARYING TREATMENTS

In the previous chapter we described a dataset with a time-varying treatment and treatment-confounder feedback. We showed that, when applied to this dataset, traditional methods for confounding adjustment could not correctly adjust for confounding. Even though the time-varying treatment had a zero causal effect on the outcome, traditional adjustment methods yielded effect estimates that were different from the null.

This chapter describes the solution to the bias of traditional methods in the presence of treatment-confounder feedback: the use of g-methods—the g-formula, IP weighting, g-estimation, and their doubly-robust generalizations. Using the same dataset as in the previous chapter, here we show that the three g-methods yield the correct (null) effect estimate. For time-fixed treatments, we described the g-formula in Chapter 13, IP weighting of marginal structural models in Chapter 12, and g-estimation of structural nested models in Chapter 15. Here we introduce each of the three g-methods for the comparison of static treatment strategies under the identifiability conditions described in Chapter 19: sequential exchangeability, positivity, and consistency.

21.1 The g-formula for time-varying treatments

Table 21.1

N	A_0	L_1	A_1	Mean Y
2400	0	0	0	84
1600	0	0	1	84
2400	0	1	0	52
9600	0	1	1	52
4800	1	0	0	76
3200	1	0	1	76
1600	1	1	0	44
6400	1	1	1	44

Consider again the data from the sequentially randomized experiment in Table 20.1 which, for convenience, we reproduce again here as Table 21.1. Suppose we are only interested in the effect of the time-fixed treatment A_1. That is, suppose we want to contrast the mean counterfactual outcomes $\mathrm{E}\left[Y^{a_1=1}\right]$ and $\mathrm{E}\left[Y^{a_1=0}\right]$. In Parts I and II we have showed that, under the identifiability conditions, each of the means $\mathrm{E}\left[Y^{a_1}\right]$ is a weighted average of the mean outcome $\mathrm{E}\left[Y|A_1 = a_1, L_1 = l_1\right]$ conditional on the (time-fixed) treatment and confounders. Specifically, $\mathrm{E}\left[Y^{a_1}\right]$ equals the weighted average

$$\sum_{l_1} \mathrm{E}\left[Y|A_1 = a_1, L_1 = l_1\right] f\left(l_1\right), \text{ where } f\left(l_1\right) = \Pr\left[L_1 = l_1\right].$$

This weighted average is the g-formula. Under conditional exchangeability given the time-fixed confounders L_1, the g-formula is the mean outcome standardized to the distribution of the confounders in the study population.

But, in the sequentially randomized experiment of Table 21.1, the treatment $\overline{A} = (A_0, A_1)$ is time-varying and, as we saw in the previous chapter, there is treatment-confounder feedback. That means that traditional adjustment methods cannot be relied on to unbiasedly estimate the causal effect of time-varying treatment $\overline{A}$. For example, traditional methods may not provide valid estimates of the mean outcome under "always treat" $\mathrm{E}\left[Y^{a_0=1,a_1=1}\right]$ and the mean outcome under "never treat" $\mathrm{E}\left[Y^{a_0=0,a_1=0}\right]$ even in a sequentially randomized experiment in which sequential exchangeability holds. In contrast, the g-formula can be used to calculate the counterfactual means $\mathrm{E}\left[Y^{a_0,a_1}\right]$ in a sequentially randomized experiment. To do so, the above expression of the g-formula for time-fixed treatments needs to be generalized.

The g-formula for $\mathrm{E}\left[Y^{a_0,a_1}\right]$ under the identifiability conditions (described in Chapter 19) will still be a weighted average, but now it will be a weighted

average of the mean outcome $\mathrm{E}[Y|A_0 = a_0, A_1 = a_1, L_1 = l_1]$ conditional on the time-varying treatment and confounders required to achieve sequential exchangeability. Specifically, the g-formula

$$\sum_{l_1} \mathrm{E}[Y|A_0 = a_0, A_1 = a_1, L_1 = l_1] f(l_1|a_0)$$

equals $\mathrm{E}[Y^{a_0,a_1}]$ under (static) sequential exchangeability for Y^{a_0,a_1}. That is, for a time-varying treatment, the g-formula estimator of the counterfactual mean outcome under the identifiability conditions is the mean outcome standardized to the distribution of the confounders in the study population, with every factor in the expression conditional on past treatment and covariate history. This conditioning on prior history is not necessary in the time-fixed case in which both treatment and confounders are measured at a single time point.

Note that the g-formula is only computable (i.e., well-defined) if, for any value l_1 such that $f(l_1|a_0) \neq 0$, there are individuals in the population with $(A_0 = a_0, A_1 = a_1, L_1 = l_1)$. This is equivalent to the definition of positivity given in Technical Point 19.2 and a generalization for time-varying treatments of the discussion of positivity in Technical Point 3.1.

Let us apply the g-formula to estimate the causal effect $\mathrm{E}\left[Y^{a_0=1,a_1=1}\right] - \mathrm{E}\left[Y^{a_0=0,a_1=0}\right]$ from the sequentially randomized experiment of Table 21.1. The g-formula estimate for the mean $\mathrm{E}\left[Y^{a_0=0,a_1=0}\right]$ is $84\times0.25+52\times0.75 = 60$. The g-formula estimate for the mean $\mathrm{E}\left[Y^{a_0=1,a_1=1}\right]$ is $76\times0.50+44\times0.50 = 60$. Therefore the estimate of the causal effect $\mathrm{E}\left[Y^{a_0=1,a_1=1}\right] - \mathrm{E}\left[Y^{a_0=0,a_1=0}\right]$ is 0, as expected. The g-formula succeeds where traditional methods failed.

In a study with 2 time points, the g-formula for "never treat" is $\mathrm{E}[Y|A_0 = 0, A_1 = 0, L_1 = 0] \times \Pr[L_1 = 0|A_0 = 0] + \mathrm{E}[Y|A_0 = 0, A_1 = 0, L_1 = 1] \times \Pr[L_1 = 1|A_0 = 0]$

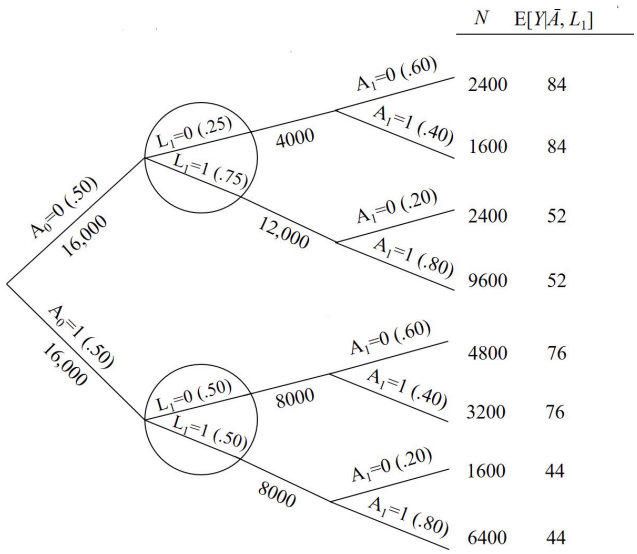

Figure 21.1

Another way to think of the g-formula is as a simulation. Under sequential exchangeability for Y and $\bar{L}$ jointly, the g-formula simulates the counterfactual outcome $Y^{\bar{a}}$ and covariate history $\bar{L}^{\bar{a}}$ that would have been observed if everybody in the study population had followed treatment strategy $\bar{a}$. In other words, the g-formula simulates (identifies) the joint distribution of the counterfactuals $\left(Y^{\bar{a}}, \bar{L}^{\bar{a}}\right)$ under strategy $\overline{a}$. To see this, first consider the causally-structured tree graph in Figure 21.1, which is an alternative representation of the data in Table 21.1. Under the aforementioned identifiability condition, the

g-formula can be viewed as a procedure to build a new tree in which all individuals follow strategy $\bar{a}$. For example, the causally-structured tree graph in Figure 21.2 shows the counterfactual population that would have been observed if all individuals have followed the strategy "always treat" $(a_0 = 1, a_1 = 1)$.

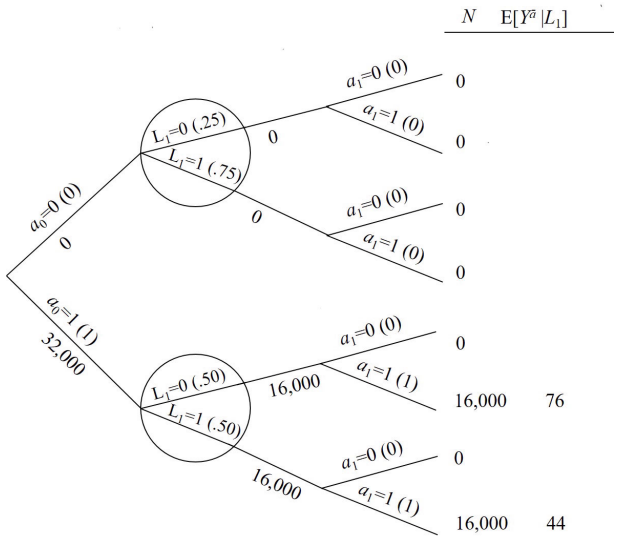

Figure 21.2

To simulate this counterfactual population we (i) assign probability 1 to receiving treatment $a_0 = 1$ and $a_1 = 1$ at times $k = 0$ and $k = 1$, respectively, and (ii) assign the same probability $\Pr[L_1 = l_1|A_0 = a_0]$ and the same mean $\mathrm{E}[Y|A_0 = a_0, A_1 = a_1, L_1 = l_1]$ as in the original study population.

Two important points. First, the value of the g-formula depends on what, if anything, has been included in L. As an example, suppose we do not collect data on L_1 because we believe, incorrectly, that our study is represented by a causal diagram like the one in Figure 20.8 after removing the arrow from L_1 to A_1. Thus we believe L_1 is not a confounder and hence not necessary for identification. Then the g-formula in the absence of data on L_1 becomes $\mathrm{E}[Y|A_0 = a_0, A_1 = a_1]$ because there is no covariate history to adjust for. However, because our study is actually represented by the causal graph in Figure 20.8. (under which treatment assignment A_1 is affected by L_1), the g-formula that fails to include L_1 no longer has a causal interpretation.

Second, even when the g-formula has a causal interpretation, each of its components may lack a causal interpretation. As an example, consider the causal diagram in Figure 20.9 under which only static sequential exchangeability holds. The g-formula that includes L_1 correctly identifies the mean of Y^a. Remarkably, regardless of whether we add arrows from A_0 and A_1 to Y, the g-formula continues to have a causal interpretation as $\mathrm{E}[Y^{\bar{a}}]$, even though neither of its components—$\mathrm{E}[Y|A_0 = a_0, A_1 = a_1, L_1 = l_1]$ and $\Pr[L_1 = l_1|A_0 = a_0]$—has any causal interpretation at all. That is, $\Pr[L_1 = l_1|A_0 = a_0] \neq \Pr\left[L_1^{a=0} = l_1\right]$ and $\mathrm{E}[Y|A_0 = a_0, A_1 = a_1, L_1 = l_1] \neq \mathrm{E}[Y^{a_0,a_1}|L_1^{a_0} = l_1]$. The last two inequalities will be equalities in a sequential randomized trial like the one represented in Figures 20.1 and 20.2.

Now let us generalize the g-formula to high-dimensional settings with multiples times k. The g-formula is

$$\sum_{\bar{l}} \mathrm{E}\left[Y|\bar{A} = \bar{a}, \bar{L} = \bar{l}\right] \prod_{k=0}^{K} f\left(l_k|\bar{a}_{k-1}, \bar{l}_{k-1}\right),$$

Under sequential exchangeability, $\Pr[L_1 = l_1|A_0 = a_0] = \Pr\left[L_1^{a=0} = l_1\right]$ and $\mathrm{E}[Y|A_0 = a_0, A_1 = a_1, L_1 = l_1] = \mathrm{E}[Y^{a_0,a_1}|L_1^{a_0} = l_1]$.

Thus the g-formula is $\sum_{l_1} \mathrm{E}[Y^{a_0,a_1}|L_1^{a_0} = l_1] \Pr\left[L_1^{a=0} = l_1\right]$, which equals $\mathrm{E}[Y^{a_0,a_1}|L_1^{a_0} = l_1]$ as required.

Under any of the causal diagrams shown in this book, the g-formula that includes all the unmeasured variables—such as U and W—is always correct. Unfortunately, the unmeasured variables are by definition unavailable to the investigators.

The g-formula for time-varying treatments was first described by Robins (1986, 1987).

Fine Point 21.1

Treatment and covariate history. When describing g-methods, we often refer to the treatment and covariate history that is required to achieve sequential exchangeability. For the g-formula, we say of its components is conditional on prior treatment and covariate history. For example, the factor corresponding to the probability of a discrete confounder L_2 at time $k = 2$

$$f\left(l_2|\overline{A}_1 = \bar{a}_1, \overline{L}_1 = \bar{l}_1\right) = \Pr\left[L_2 = l_2|A_0 = a_0, A_1 = a_1, L_0 = l_0, L_1 = l_1\right]$$

is conditional on treatment and confounders at prior times 0 and 1; the factor at time $k = 3$ is conditional on treatment and confounders at times 0, 1, and 2, and so on.

However, the term "history" is not totally accurate because, as explained in Fine Point 7.2, confounders can theoretically be in the future of treatment. Conversely, as explained along with Figure 7.4, adjusting for some variables in the past of treatment may introduce selection bias (sometimes referred to as M-bias). Therefore, the causally relevant "history" at time k needs to be understood as the set of treatment and confounders that are needed to achieve conditional exchangeability for treatment A_k. Usually, those confounders $\overline{L}_k$ will be in the past of treatment A_k so, for convenience, we will keep using the term "history" throughout the book.

where the sum is over all possible $\bar{l}$-histories ($\bar{l}_{k-1}$ is the history through time $k-1$). Under sequential exchangeability for $Y^{\bar{a}}$ given $\left(\bar{L}_k, \bar{A}_k\right)$ at each time k, this expression equals the counterfactual mean $\mathrm{E}\left[Y^{\bar{a}}\right]$ under treatment strategy $\bar{a}$. Fine Point 21.1 presents a more nuanced definition of the term "history". Technical Point 21.1 shows a more general expression for the g-formula, which can be used to compute densities, not just means.

In practice, however, the components of the g-formula cannot be directly computed if the data are high-dimensional, as is expected in observational studies with multiple confounders or time points. The quantities $\mathrm{E}\left[Y|\bar{A} = \bar{a}, \bar{L} = \bar{l}\right]$ and $f\left(l_k|\bar{a}_{k-1}, \bar{l}_{k-1}\right)$ will need to be estimated. For example, we can fit a linear regression model to estimate the conditional means $\mathrm{E}\left[Y|\bar{A} = \bar{a}, \bar{L} = \bar{l}\right]$ of the outcome variable at the end of follow-up, and logistic regression models to estimate the distribution of the discrete confounders L_k at each time $k \neq 0$ (the distribution of L_0 can be estimated without models as described in Section 13.3). The estimates from these models, $\widehat{\mathrm{E}}\left[Y|\bar{A} = \bar{a}, \bar{L} = \bar{l}\right]$ and $\widehat{f}\left(l_k|\bar{a}_{k-1}, \bar{l}_{k-1}\right)$, will then be plugged in into the g-formula. Since Chapter 13, we have referred to this estimator as the *plug-in g-formula* and, when the estimates used in the plug-in g-formula are based on parametric models, we have referred to the plug-in g-formula as the *parametric g-formula*.

For simplicity, this chapter presents a version of the g-formula under deterministic static strategies only. However, the g-formula can be used to compute the mean of the outcome under any treatment strategy: deterministic or random, static or dynamic. Let us define $f^{int}\left(a_k|\bar{a}_{k-1}, \bar{l}_k\right)$ as the conditional probability of treatment a_k at time k if the treatment strategy (or *int*ervention) of interest had been implemented in the population. Then, the general expression of the g-formula is

$$\sum_{\bar{l}} \mathrm{E}\left[Y|\bar{A} = \bar{a}, \bar{L} = \bar{l}\right] \prod_{k=0}^{K} f\left(l_k|\bar{a}_{k-1}, \bar{l}_{k-1}\right) \prod_{k=0}^{K} f^{int}\left(a_k|\bar{a}_{k-1}, \bar{l}_k\right).$$

Under a deterministic treatment strategy, $f^{int}\left(a_k|\bar{a}_{k-1}, \bar{l}_k\right)$ is always 1 and therefore does not need to be specified. For example, under the strategy "always treat" or $\bar{a} = (1, 1, ...1)$, the probability $f^{int}\left(1|\bar{a}_{k-1}, \bar{l}_k\right) = 1$ at all

Technical Point 21.1

The g-formula density for static strategies. The g-formula density for $\left(Y, \overline{L}\right)$ evaluated at $\left(y, \bar{l}\right)$ for a strategy $\bar{a}$ is

$$f\left(y|\bar{a}, \bar{l}\right) \prod_{k=0}^{K} f\left(l_k|\bar{a}_{k-1}, \bar{l}_{k-1}\right)$$

The g-formula density for Y is simply the marginal density of Y under the g-formula density for $\left(Y, \overline{L}\right)$:

$$\int f\left(y|\bar{a}, \bar{l}\right) \prod_{k=0}^{K} dF\left(l_k|\bar{a}_{k-1}, \bar{l}_{k-1}\right),$$

where the integral notation $\int$ is used—instead of the sum notation $\sum$—to accommodate settings in which L_k represents a vector of variables and some of the variables in the vector are continuous.

Given observed data $O = \left(\bar{A}, \overline{V}, Y\right)$ where $\overline{V}$ is the set of all measured variables other than treatment $\bar{A}$ and outcome Y, the inputs of the g-formula are (i) a treatment strategy $\bar{a}$, (ii) a causal DAG representing the observed data (and their unmeasured common causes), (iii) a subset $\overline{L}$ of $\overline{V}$ for which we wish to adjust, and (iv) a choice of a total ordering of $\overline{L}$, $\bar{A}$, and Y consistent with the topology of the DAG, i.e., an ordering such that each variable comes after its ancestors. The vector L_k consists of all variables in L after A_{k-1} and before A_k in the ordering. The chosen ordering will usually, but not always, be temporal. See Fine Point 21.1 and Pearl and Robins (1995) for additional subtleties that are beyond the scope of this book. When sequential exchangeability for $Y^{\bar{a}}$ and positivity holds for the chosen ordering, the g-formula density for Y equals the density of Y that would have been observed in the study population if all individuals had followed strategy $\bar{a}$. Otherwise, the g-formula can still be computed, but it lacks a causal interpretation.

Note that the g-formula density for $Y, \overline{L}$ under treatment strategy $\bar{a}$ differs from the joint distribution

$$f\left(y|\overline{A}_k = \bar{a}_k, \overline{L}_k = \bar{l}_k\right) \prod_{k=0}^{K} f\left(l_k|\overline{A}_{k-1} = \bar{a}_{k-1}, \overline{L}_{k-1} = \bar{l}_{k-1}\right) \prod_{k=0}^{K} f\left(a_k|\overline{A}_{k-1} = \bar{a}_{k-1}, \overline{L}_k = \bar{l}_k\right)$$

only in that each factor $f\left(a_k|\overline{A}_{k-1} = \bar{a}_{k-1}, \overline{L}_k = \bar{l}_k\right)$ is eliminated. Note that each of the remaining factors are evaluated at $\overline{A}_k = \bar{a}_k$ consistent with strategy $\bar{a}$.

CODE: The *gfoRmula* R package (Lin et al. 2019) is available through CRAN. The *GFORMULA* SAS macro is available through GitHub. See the book's web site.

k. However, under other types of treatment strategies, $f^{int}\left(a_k|\bar{a}_{k-1}, \bar{l}_k\right)$ is not 1 at all k and therefore needs to be included in the g-formula. For example, under the random static strategy "independently at each time k, treat individuals with probability 0.3 and do not treat with probability 0.7", $f^{int}\left(1|\bar{a}_{k-1}, \bar{l}_k\right) = 0.3$. Our publicly available software implements this general form of the g-formula and therefore can accommodate any treatment strategy.

21.2 IP weighting for time-varying treatments

Suppose we are only interested in the effect of the time-fixed treatment A_1 in Table 21.1. We then want to contrast the counterfactual mean outcomes $\mathrm{E}\left[Y^{a_1=1}\right]$ and $\mathrm{E}\left[Y^{a_1=0}\right]$. As we have seen in Chapter 12, under the identifiability conditions, each of the counterfactual means $\mathrm{E}\left[Y^{a_1}\right]$ is the mean $\mathrm{E}_{ps}\left[Y|A_1 = a_1\right]$ in the pseudo-population created by the subject-specific nonstabilized weights $W^{A_1} = 1/f\left(A_1|L_1\right)$ or the stabilized weights $SW^{A_1} = f\left(A_1\right)/f\left(A_1|L_1\right)$. The denominator of the IP weights is, informally, an individual's probability of receiving the treatment value that he or she received, condi-

tional on the individual's confounder values. One can estimate $\mathrm{E}_{ps}\left[Y|A_1=a_1\right]$ from the observed study data by the average of Y among subjects with $A_1=a_1$ in the pseudo-population.

When treatment and confounders are time-varying, these IP weights for time-fixed treatments need to be generalized. For a time-varying treatment $\overline{A}=(A_0,A_1)$ and time-varying covariates $\bar{L}=(L_0,L_1)$ at two time points, the nonstabilized IP weights are

$$W^{\bar{A}}=\frac{1}{f\left(A_0|L_0\right)}\times\frac{1}{f\left(A_1|A_0,L_0,L_1\right)}=\prod_{k=0}^{1}\frac{1}{f\left(A_k|\bar{A}_{k-1},\bar{L}_k\right)}$$

and the stabilized IP weights are

$$SW^{\bar{A}}=\frac{f\left(A_0\right)}{f\left(A_0|L_0\right)}\times\frac{f\left(A_1|A_0\right)}{f\left(A_1|A_0,L_0,L_1\right)}=\prod_{k=0}^{1}\frac{f\left(A_k|\bar{A}_{k-1}\right)}{f\left(A_k|\bar{A}_{k-1},\bar{L}_k\right)}$$

where $A_{-1}$is 0 by definition. The denominator of the IP weights for a time-varying treatment is, informally, an individual's probability of receiving the treatment history that he or she received, conditional on the individual's covariate history.

Suppose we want to contrast the counterfactual mean outcomes $\mathrm{E}\left[Y^{a_0=1,a_1=1}\right]$ and $\mathrm{E}\left[Y^{a_0=0,a_1=0}\right]$. Under the identifiability assumptions for static strategies, each counterfactual mean $\mathrm{E}\left[Y^{a_0,a_1}\right]$ is the mean $\mathrm{E}_{ps}\left[Y|A_0=a_0,A_1=a_1\right]$ in the pseudo-population created by the nonstabilized weights $W^{\bar{A}}$ or the stabilized weights $SW^{\bar{A}}$. The IP weighted estimator of each counterfactual mean is the average of Y among individuals with $\overline{A}=(A_0,A_1)$ in the pseudo-population.

Let us apply IP weighting to the data from Table 21.1. The causally-structured tree in Figure 21.3 is the tree graph in Figure 21.1 with additional columns for the nonstabilized IP weights $W^{\bar{A}}$ and the number of individuals in the corresponding pseudo-population N_W for each treatment and covariate history. The pseudo-population has a size of $128,000$, that is, the $32,000$ individuals in the original population multiplied by 4, the number of static strategies. Because there is no L_0 in this study, the denominator of the IP weights simplifies to $f\left(A_0\right)f\left(A_1|A_0,L_1\right)$.

The IP weighted estimator for the counterfactual mean $\mathrm{E}\left[Y^{a_0=0,a_1=0}\right]$ is the mean $\mathrm{E}_{ps}\left[Y|A_0=0,A_1=0\right]$ in the pseudo-population, which we estimate as the average outcome among the $32,000$ individuals with $(A_0=0,A_1=0)$ in the pseudo-population. From the tree in Figure 21.3, the estimate is $84\times\frac{8000}{32000}+52\times\frac{24000}{32000}=60$. Similarly, the IP weighted estimate of $\mathrm{E}\left[Y^{a_0=1,a_1=1}\right]$ is also 60. Therefore the estimate of the causal effect $\mathrm{E}\left[Y^{a_0=1,a_1=1}\right]-\mathrm{E}\left[Y^{a_0=0,a_1=0}\right]$ is 0, as expected. IP weighting, like the g-formula, succeeds where traditional methods failed.

The same estimate of 0 is obtained when using stabilized IP weights $SW^{\bar{A}}$ in Figure 21.3 (check for yourself). However, $\Pr_{ps}\left[A_k=1|\bar{A}_{k-1},\bar{L}_k\right]$ is $1/2$ in the nonstabilized pseudo-population and $\Pr\left[A_k=1|\bar{A}_{k-1}\right]$ in the stabilized pseudo-population.

Note that our nonparametric estimates of $\mathrm{E}\left[Y^{a_0,a_1}\right]$ based on the g-formula are precisely equal to those based on IP weighting. This equality has nothing to do with causal inference. That is, even if the identifiability conditions did not hold—so neither the g-formula nor IP weighting estimates have a causal interpretation—both approaches would yield the same mean in the population.

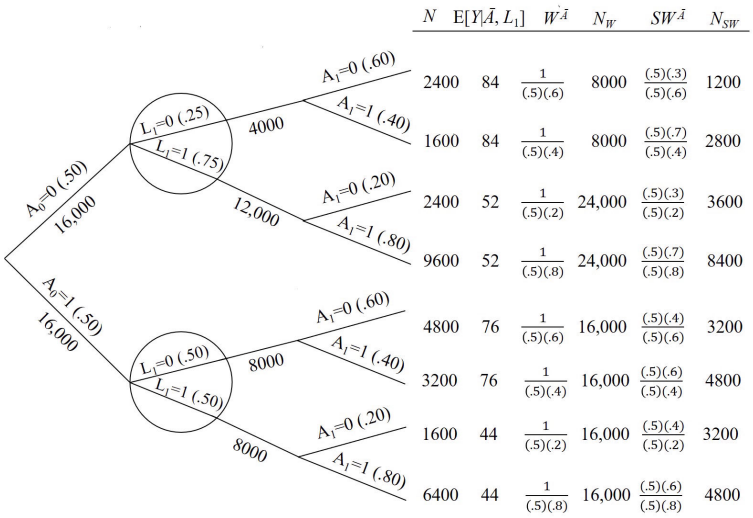

Figure 21.3

Let us generalize IP weighting to high-dimensional settings with multiple times $k = 0, 1...K$. The general form of the nonstabilized IP weights is

$$W^{\bar{A}} = \prod_{k=0}^{K} \frac{1}{f\left(A_k|\bar{A}_{k-1}, \bar{L}_k\right)}$$

and the general form of the stabilized IP weights is

$$SW^{\bar{A}} = \prod_{k=0}^{K} \frac{f\left(A_k|\bar{A}_{k-1}\right)}{f\left(A_k|\bar{A}_{k-1}, \bar{L}_k\right)}$$

When the identifiability conditions hold, these IP weights create a pseudo-population in which (i) the mean of $Y^{\bar{a}}$ is identical to that in the actual population, but (ii) like on Figure 19.1, the randomization probabilities at each time k are constant (nonstabilized weights) or depend at most on past treatment history (stabilized weights). Hence the average causal effect $\mathrm{E}\left[Y^{\bar{a}}\right] - \mathrm{E}\left[Y^{\bar{a}'}\right]$ is $\mathrm{E}_{ps}\left[Y|\overline{A} = \bar{a}\right] - \mathrm{E}_{ps}\left[Y|\overline{A} = \bar{a}'\right]$ because unconditional sequential exchangeability holds in both pseudo-populations.

In a true sequentially randomized trial, the quantities $f\left(A_k|\bar{A}_{k-1}, \bar{L}_k\right)$ are known by design. Therefore we can use them to compute nonstabilized IP weights and the estimates of $\mathrm{E}\left[Y^{\bar{a}}\right]$ and $\mathrm{E}\left[Y^{\bar{a}}\right] - \mathrm{E}\left[Y^{\bar{a}'}\right]$ are guaranteed to be unbiased. In contrast, in observational studies, the quantities $f\left(A_k|\bar{A}_{k-1}, \bar{L}_k\right)$ will need to be estimated from the data. When the data are high-dimensional, we can, for example, fit a logistic regression model to estimate the conditional probability of a dichotomous treatment $\Pr\left[A_k = 1|\bar{A}_{k-1}, \bar{L}_k\right]$ at each time k. The estimates $\widehat{f}\left(A_k|\bar{A}_{k-1}, \bar{L}_k\right)$ from these models will then replace $f\left(A_k|\bar{A}_{k-1}, \bar{L}_k\right)$ in $W^{\bar{A}}$. If the estimates $\widehat{f}\left(A_k|\bar{A}_{k-1}, \bar{L}_k\right)$ are based on a misspecified logistic model for the $\Pr\left[A_k = 1|\bar{A}_{k-1}, \bar{L}_k\right]$, the resulting estimates of $\mathrm{E}\left[Y^{\bar{a}}\right]$ and $\mathrm{E}\left[Y^{\bar{a}}\right] - \mathrm{E}\left[Y^{\bar{a}'}\right]$ will be biased. For stabilized weights $SW^{\bar{A}}$ we must also obtain an estimate of $\widehat{f}\left(A_k|\bar{A}_{k-1}\right)$ for the numerator. Even if this estimate is based on a misspecified model, the estimates of $\mathrm{E}\left[Y^{\bar{a}}\right]$ and $\mathrm{E}\left[Y^{\bar{a}}\right] - \mathrm{E}\left[Y^{\bar{a}'}\right]$ remain unbiased, although the distribution of treatment in the stabilized pseudo-population will differ from that in the observed population.

In practice, the most common approach is to fit a single model for $\Pr\left[A_k = 1|\bar{A}_{k-1}, \bar{L}_k\right]$ rather than a separate model at each time k. The model includes a function of time k—often referred to as a time-varying intercept—as a covariate.

There is no logical guarantee of no model misspecification even when the estimates from both parametric approaches are similar, as they may both be biased in the same direction.

Suppose that we obtain two estimates of $\mathrm{E}[Y^{\bar{a}}]$, one using the parametric g-formula and another one using IP weights estimated via parametric models, and that the two estimates differ by more than can be reasonably explained by sampling variability (the sampling variability of the difference of the estimates can be quantified by bootstrapping). We can then conclude that the parametric models used for the g-formula or the parametric models used for IP weighting (or both) are misspecified. This conclusion is always true, regardless of whether the identifiability assumptions hold. An implication is that one should always estimate $\mathrm{E}[Y^{\bar{a}}]$ using both methods and, if the estimates differ substantially (according to some prespecified criterion), reexamine all the models and modify them where necessary. In the next section, we describe how doubly-robust estimators can help deal with model misspecification.

Also, as we discussed in the previous section, it is not infrequent that the number of unknown quantities $\mathrm{E}[Y^{\bar{a}}]$ far exceeds the sample size. Thus we need to specify a model that combines information from many strategies to help estimate a given $\mathrm{E}[Y^{\bar{a}}]$. For example, we can hypothesize that the effect of treatment history $\bar{a}$ on the mean outcome increases linearly as a function of the cumulative treatment $cum(\bar{a}) = \sum_{k=0}^{K} a_k$ under strategy $\bar{a}$. This hypothesis is encoded in the *marginal structural mean model*

This marginal structural model is unsaturated. Remember, saturated models have an equal number of unknowns on both sides of the equation.

$$\mathrm{E}\left[Y^{\bar{a}}\right] = \beta_0 + \beta_1 cum(\bar{a})$$

for all $\overline{a}$, which is a more general version of the marginal structural mean model for time-fixed treatments discussed in Chapter 12. There are 2^K different unknown quantities on the left hand side of model, one for each of the 2^K different strategies $\bar{a}$, but only 2 unknown parameters β_0 and β_1 on the right hand side. The parameter β_1 measures the average causal effect of the time-varying treatment $\bar{A}$. The average causal effect $\mathrm{E}[Y^{\bar{a}}] - \mathrm{E}\left[Y^{\bar{a}=\overline{0}}\right]$ is equal to $\beta_1 \times cum(\bar{a})$.

As discussed in Chapter 12, to estimate the parameters of the marginal structural model, we fit the ordinary linear regression model

$$\mathrm{E}\left[Y|\overline{A}\right] = \theta_0 + \theta_1 cum\left(\overline{A}\right)$$

in the pseudo-population, that is, we use weighted least squares with weights being estimates of either $SW^{\bar{A}}$ or $W^{\bar{A}}$. Under the identifiability conditions, the estimate of the associational parameter θ_1 is consistent for the causal parameter β_1. As described in Chapter 12, the variance of $\widehat{\beta}_1$—and thus of the contrast $\mathrm{E}[Y^{\bar{a}}] - \mathrm{E}\left[Y^{\bar{a}=\overline{0}}\right]$—can be estimated by the nonparametric bootstrap or by computing its analytic variance (which requires additional statistical analysis and programming). We can also construct a conservative 95% confidence interval by using the robust variance estimator of $\widehat{\beta}_1$, which is directly outputted by most statistical software packages. For a non-saturated marginal structural model the width of the intervals will typically be narrower when the model is fit with the weights $SW^{\bar{A}}$ than with the weights $W^{\bar{A}}$, so the $SW^{\bar{A}}$ weights are preferred.

Of course, the estimates of $\mathrm{E}[Y^{\bar{a}}]$ will be incorrect if the marginal structural mean model is misspecified, that is, if the mean counterfactual outcome depends on the treatment strategy through a function of the time-varying treatment other than cumulative treatment $cum(\bar{a})$ (say, cumulative treatment only in the final 5 months $\sum_{k=K-5}^{K} a_k$) or depends nonlinearly (say, quadratically) on

Technical Point 21.2

The g-null paradox. When using the parametric g-formula, model misspecification will result in biased estimates of $\mathrm{E}\left[Y^{\bar{a}}\right]$, even if the identifiability conditions hold. Suppose there is treatment-confounder feedback and the sharp null hypothesis of no effect of treatment on Y is true, that is,

$$Y^{\bar{a}} - Y^{\bar{a}'} = 0 \text{ with probability 1 for all } \bar{a}' \text{ and } \bar{a}.$$

Then the value of the g-formula for $\mathrm{E}\left[Y^{\bar{a}}\right]$ is the same for any strategy $\bar{a}$, even though $\mathrm{E}\left[Y|\bar{A}=\bar{a},\bar{L}=\bar{l}\right]$ and $f\left(l_k|\bar{a}_{k-1},\bar{l}_{k-1}\right)$ both depend on $\bar{a}$. Now suppose we use standard non-saturated parametric models $\mathrm{E}\left[Y|\bar{A}=\bar{a},\bar{L}=\bar{l};\theta\right]$ and $f\left(l_k|\bar{a}_{k-1},\bar{l}_{k-1};\varphi\right)$ based on distinct (i.e., variation-independent) parameters θ and φ to estimate the components of the g-formula. Then Robins and Wasserman (1997) showed that, when L_k has any discrete components, these models cannot all be correctly specified because the estimated value of the g-formula for $\mathrm{E}\left[Y^{\bar{a}}\right]$ will generally depend on $\bar{a}$. As a consequence, inference based on the estimated g-formula might theoretically result in the sharp null hypothesis being falsely rejected, even in a sequentially randomized experiment. This phenomenon is referred to as the null paradox of the estimated g-formula for time-varying treatments. See Cox and Wermuth (1999) for additional discussion. Fortunately, the g-null paradox has not prevented the parametric g-formula to estimate null effects in practice, presumably because the bias induced by the paradox is small compared with typical random variability.

In contrast, and as described in Chapters 12 and 14, neither IP weighting of marginal structural mean models nor g-estimation of structural nested mean models suffer from the null paradox in a sequentially randomized experiment where the treatment probabilities are known by design. These methods preserve the null because the models are correctly specified no matter what functional form we choose for treatment. For example, the marginal structural mean model $\mathrm{E}\left[Y^{\bar{a}}\right] = \beta_0 + \beta_1 cum\left(\bar{a}\right)$ is correctly specified under the null because, in that case, $\beta_1 = 0$ and $\mathrm{E}\left[Y^{\bar{a}}\right]$ would not depend on the function of $\bar{a}$. Also, any structural nested mean model $\gamma_k\left(\overline{a}_{k-1},\overline{l}_k,\beta\right)$ is also correctly specified under the null with $\beta = 0$ being the true parameter value and $\gamma_k\left(\overline{a}_{k-1},\overline{l}_k,\beta\right) = 0$, regardless of the function of past treatment and covariate history.

cumulative treatment. However, if we fit the model

$$\mathrm{E}\left[Y|\overline{A}\right] = \theta_0 + \theta_1 cum\left(\overline{A}\right) + \theta_2 cum_{-5}\left(\overline{A}\right) + \theta_3 cum\left(\overline{A}\right)^2$$

with weights $SW^{\bar{A}}$ or $W^{\bar{A}}$, a Wald test on two degrees of freedom of the joint hypothesis $\theta_2 = \theta_3 = 0$ is a test of the null hypothesis that our marginal structural model is correctly specified. That is, IP weighting of marginal structural models is not subject to the g-null paradox described in Technical Point 21.2. In practice, one might choose to use a marginal structural model that includes different summaries of treatment history $\overline{A}$ as covariates, and that uses flexible functions like, say, cubic splines.

This test will generally have good statistical power against the particular directions of misspecification mentioned above, especially if the weights $SW^{\bar{A}}$ are used.

Finally, as we discussed in Section 12.5, we can use a marginal structural model to explore effect modification by a subset V of the covariates in L_0. For example, for a dichotomous baseline variable V, we would elaborate our marginal structural mean model as

$$\mathrm{E}\left[Y^{\bar{a}}|V\right] = \beta_0 + \beta_1 cum\left(\bar{a}\right) + \beta_2 V + \beta_3 cum\left(\bar{a}\right) V$$

The parameters of this model can be estimated by fitting the ordinary linear regression model $\mathrm{E}\left[Y|\overline{A},V\right] = \theta_0 + \theta_1 cum\left(\overline{A}\right) + \theta_2 V + \theta_3 V cum\left(\overline{A}\right)$ by weighted least squares with IP weights $W^{\bar{A}}$ or, better, $SW^{\bar{A}}\left(V\right) = \prod_{k=0}^{K} \frac{f\left(A_k|\bar{A}_{k-1},V\right)}{f\left(A_k|\bar{A}_{k-1},\bar{L}_k\right)}$. In the presence of treatment-confounder feedback, V can only include baseline variables. If V had components of L_k for $k > 0$ then the parameters $\theta_1$and θ_3

could be different from 0 even if treatment had no effect on the mean outcome at any time.

We now describe a doubly robust estimator of marginal structural mean models.

21.3 A doubly robust estimator for time-varying treatments

Doubly robust estimators give us two chances to get it right when, as in most observational studies, there are many confounders and non-saturated models are required.

Part II briefly mentioned doubly robust methods that combine IP weighting and the g-formula. As we know, IP weighting requires a correct model for treatment A conditional on the confounders L, and the g-formula requires a correct model for the outcome Y conditional on treatment A and the confounders L. Doubly robust methods require a correct model for *either* treatment A *or* outcome Y. If at least one of the two models is correct (and one need not know which of the two models is correct), a doubly robust estimator consistently estimates the causal effect. Technical Point 13.2 described a doubly robust estimator for the average causal effect of a time-fixed treatment A on an outcome Y. In this section, we first review this doubly robust estimator for time-fixed treatments and then extend it to time-varying treatments.

Suppose we are only interested in the effect of a time-fixed treatment A, that is, the difference of counterfactual means $\mathrm{E}\left[Y^{a_1=1}\right] - \mathrm{E}\left[Y^{a_1=0}\right]$, under exchangeability, positivity, and consistency in a setting with many confounders L. One possibility is to fit an outcome model for $\mathrm{E}[Y|A=a, L=l]$ and then standardize (parametric g-formula); another possibility is to fit a treatment model for $\Pr[A=1|L]$ and then use it to compute weights $W^A = 1/f\left(A|L\right)$ (IP weighting). A doubly robust method estimates both models and combines them. The doubly robust procedure has three steps.

The use of the "clever covariate" D to achieve double robustness was first proposed by Bang and Robins (2005) for both time-fixed and time-varying treatments.

The first step is to use the predicted values $\widehat{\Pr}\left[A=1|L\right]$ from the treatment model to compute the IP weight estimates $\hat{W}^A$. The second step is to compute the predicted values $\widehat{\mathrm{E}}\left[Y|A=a, L=l, R\right]$ from a modified outcome model that includes the covariate R, where $R = \hat{W}^A$ if $A=1$ and $R = -\hat{W}^A$ if $A=0$. The third step is to standardize the mean of the predicted value $\widehat{\mathrm{E}}\left[Y|A=a, L=l, R\right]$ under $A=1$ and under $A=0$. The difference of the standardized mean outcomes is a doubly robust estimator of the causal effect $\mathrm{E}\left[Y^{a_1=1}\right] - \mathrm{E}\left[Y^{a_1=0}\right]$. That is, under the identifiability conditions, this estimator validly estimates the average causal effect if either the model for the treatment or for the outcome is correct.

Let us now extend this doubly robust estimator to settings with time-varying treatments in which we are interested in comparing the counterfactual means $\mathrm{E}\left[Y^{\bar{a}}\right]$ and $\mathrm{E}\left[Y^{\bar{a}'}\right]$ under two treatment strategies $\bar{a}$ and $\bar{a}'$. The doubly robust procedure to estimate $\mathrm{E}\left[Y^{\bar{a}}\right]$ for a time-varying treatment follows the same 3 steps as the procedure to estimate $\mathrm{E}\left[Y^{a}\right]$ for a time-fixed treatment. However, as we will see, the second step is a bit more involved because it requires the fitting of sequential regression models. Next we describe how to obtain a doubly robust estimator of $\mathrm{E}\left[Y^{\bar{a}}\right]$ under the treatment strategy "always treated".

The first step requires fitting a regression model for $\Pr\left[A_k=1|\bar{A}_{k-1}, \bar{L}_k\right]$ and then use the predicted values from this model to estimate the time-varying IP weights $W^{\bar{A}_m} = \prod_{k=0}^{m} \frac{1}{f\left(A_k|\bar{A}_{k-1}, \bar{L}_k\right)}$ at each time m, where $f\left(A_k|\bar{A}_{k-1}, \bar{L}_k\right) = \Pr\left[A_k=1|\bar{A}_{k-1}, \bar{L}_k\right]$ for person-times with $A_k=1$ and $f\left(A_k|\bar{A}_{k-1}, \bar{L}_k\right) = \Pr\left[A_k=0|\bar{A}_{k-1}, \bar{L}_k\right]$ for person-times with $A_k=0$. That is, for each indi-

vidual, we estimate a different weight for each time point rather than a single weight at the end of follow-up as in the previous section. For example, if we fit the parametric model $\Pr\left[A_k = 1|\bar{A}_{k-1}, \bar{L}_k\right] = \alpha_{0,k} + \alpha_1 A_{k-1} + \alpha_2 L_k$, then, in our example of Table 21.1 with two time points, the predicted values are $\widehat{\Pr}\left[A_1 = 1|A_0, \bar{L}_1\right] = \hat{\alpha}_{0,1} + \hat{\alpha}_1 A_0 + \hat{\alpha}_2 L_1$ and $\widehat{\Pr}\left[A_0 = 1|L_0\right] = \hat{\alpha}_{0,0} + \hat{\alpha}_2 L_0$ (because $A_{-1} \equiv 0$). We then compute the time-varying IP weight estimates $\hat{W}^{\bar{A}_m} = \prod_{k=0}^{m} \frac{1}{\hat{f}\left(A_k|\bar{A}_{k-1}, \bar{L}_k\right)}$. In addition, we also compute the modified IP weight $\hat{W}^{\bar{A}_{m-1}, a_m=1} = \hat{W}^{\bar{A}_{m-1}} \times \frac{1}{\hat{f}\left(a_m=1|\bar{A}_{m-1}, \bar{L}_m\right)}$ in which the treatment value at time m is set to the corresponding treatment value under the strategy "always treated". We have reached the end of Step 1.

The second step requires fitting a separate outcome regression model at each time m, starting from the last time K and going down towards $m = 0$. This sequence of regression models has two peculiarities. First, the time-varying IP weight estimate $\hat{W}^{\bar{A}_m}$ is included as a covariate. Second, the outcome of the model is Y only at the last time K. At all other times m, the outcome of the model is a variable $\hat{T}_{m+1}$ that is generated by the previous regression at time $m + 1$.

Because doubly robust estimation for time-varying treatments relies on a sequential outcome regression, we need to fit the regression models at each time m sequentially rather than simultaneously.

For example, suppose we decide to fit the regression model

$$\mathrm{E}\left[\hat{T}_{m+1}|\bar{A}_m, \bar{L}_m\right] = \theta_{0,m} + \theta_1 cum\left(\overline{A}_m\right) + \theta_2 L_m + \theta_3 \hat{W}_m^A$$

where treatment history $\bar{A}_m$ is summarized by cumulative treatment as in the marginal structural mean model of the previous section, and covariate history $\bar{L}_m$ is summarized by its most recent value L_m. To define the variable $\hat{T}_{m+1}$, let us consider the simple case with 2 time points only, i.e., with $K = 1$. (Technical Point 21.3 provides the general definition for multiple times.)

Start by fitting the model $\mathrm{E}\left[\hat{T}_2|\bar{A}_1, \bar{L}_1\right] = \mathrm{E}\left[Y|\bar{A}_1, \bar{L}_1\right] = \theta_{0,1} + \theta_1 cum\left(\overline{A}_1\right) + \theta_2 L_1 + \theta_3 \hat{W}^{\bar{A}_1}$ with $\hat{T}_2 = Y$. Use the parameter estimates $\hat{\theta}$ to calculate the predicted value from this model with A_1 set to 1, as it should be under the strategy "always treated", which implies that $\hat{W}^{\bar{A}_1}$ needs to be replaced by $\hat{W}^{A_0, a_1=1}$. The predicted value for each individual i is therefore $\hat{T}_{1i} = \hat{\theta}_{0,1} + \hat{\theta}_1 \times 2 + \hat{\theta}_2 L_{1i} + \hat{\theta}_3 \hat{W}_i^{A_0, a_1=1}$. This predicted value $\hat{T}_1$ is the new outcome variable to be used in the next regression model. Now fit the model $\mathrm{E}\left[\hat{T}_1|A_0, L_0\right] = \theta_{0,0} + \theta_1 A_0 + \theta_2 L_0 + \theta_3 \hat{W}^{A_0}$ and calculate again the predicted value with A_0 set to 1, which is $\hat{T}_{0i} = \hat{\theta}_{0,1} + \hat{\theta}_1 \times 1 + \hat{\theta}_2 L_{0i} + \hat{\theta}_3 \hat{W}_i^{a_0=1}$ for individual i. We have reached the end of Step 2 as there are no more time points.

The third step is to standardize the mean of $\hat{T}_0$, which we do by simply computing its average across all individuals. This average $\widehat{\mathrm{E}}\left[\hat{T}_0\right]$ is a valid doubly robust estimator of the counterfactual mean $\mathrm{E}\left[Y^{a_0=1, a_1=1}\right]$. That is, under conditional exchangeability and positivity given $\bar{L}_m$, this estimator validly estimates the average causal effect if one of the three following statements holds: (i) the treatment model is correct at all times, (ii) the outcome model is correct at all times, or (iii) the treatment model is correct for time 0 to k and the outcome model is correct for times $k + 1$ to K, for any $k < K$. This last statement is known as $k + 1$ robustness.

$k + 1$ robustness was described by Molina et al. (2017).

To estimate the counterfactual mean $\mathrm{E}\left[Y^{a_0=0, a_1=0}\right]$ under the treatment strategy "never treated", repeat the above steps using $(a_0 = 0, a_1 = 0)$. The difference of means of $\hat{T}_0$ computed under each strategy is a doubly robust estimator of the average causal effect $\mathrm{E}\left[Y^{a_0=1, a_1=1}\right] - \mathrm{E}\left[Y^{a_0=0, a_1=0}\right]$.

Technical Point 21.3

A doubly robust estimator of $\mathrm{E}\left[Y^{\overline{a}}\right]$ for time-varying treatments. Suppose we are interested in estimating the counterfactual mean $\mathrm{E}\left[Y^{\overline{a}}\right]$ under treatment strategy $\bar{a} = (a_0, a_1, ...a_K)$ assuming that sequential exchangeability and positivity hold at all times $m = 0, 1..K$. Bang and Robins (2005) proposed a recursive method. For a dichotomous treatment and continuous outcome, the method can be implemented as follows:

1. Fit a logistic model $s\left(\bar{A}_{m-1}, \bar{L}_m; \alpha\right)$ for $\Pr\left[A_m = 1|\bar{A}_{m-1}, \bar{L}_m\right]$ with data pooled over all times $m = 0, 1...K$ and all individuals. Obtain the MLE $\hat{\alpha}$ of the vector parameter α. For each person-time, compute both the usual time-varying IP weight estimate $\hat{W}^{\bar{A}_m} = \prod_{k=0}^{t} \frac{1}{\hat{f}\left(A_k|\bar{A}_{k-1}, \bar{L}_k; \hat{\alpha}\right)}$, and the modified IP weight $\hat{W}^{\bar{A}_{m-1}, a_m} = \frac{\hat{W}^{\bar{A}_{m-1}}}{\hat{f}\left(a_m|\bar{A}_{m-1}, \bar{L}_m; \hat{\alpha}\right)}$ for the value a_m in the strategy of interest, with $A_{-1} \equiv 0$ by definition.
2. Set $\hat{T}_{K+1} = Y^{\bar{A}_K} = Y$. Recursively, for $m = K, K-1, ..., 0$,
   (a) specify and fit a parametric linear regression model $h\left(\bar{A}_m, \bar{L}_m; \theta\right)$, with $\hat{W}^{\bar{A}_m}$ as a covariate, for the conditional expectation $\mathrm{E}\left[\hat{T}_{m+1}|\bar{A}_m, \bar{L}_m\right]$. Obtain the MLE $\hat{\theta}$ of the vector parameter θ.
   (b) set $\hat{T}_m^{\bar{A}_{m-1}, a_m ... a_K} \equiv \hat{T}_m$ as the predicted value $\hat{h}\left(\bar{A}_{m-1}, a_m, \bar{L}_m; \hat{\theta}\right)$ computed using the covariate $\hat{W}^{\bar{A}_{m-1}, a_m}$ rather than $\hat{W}^{\bar{A}_m}$.
3. Estimate $\widehat{\mathrm{E}}\left[Y^{\overline{a}}\right] = \mathrm{E}\left[\hat{T}_0\right]$.

If either the model $s\left(\bar{A}_{m-1}, \bar{L}_m; \alpha\right)$ or the model $h\left(\bar{A}_m, \bar{L}_m; \theta\right)$ are correctly specified, then $\mathrm{E}\left[\hat{T}_0\right]$ is consistent for $\mathrm{E}\left[Y^{\overline{a}}\right]$. Confidence intervals can be obtained using the nonparametric bootstrap. Note that, when $\hat{W}^{\bar{A}_m}$ is not used as a covariate, this sequential regression procedure is an alternative, non-doubly robust procedure to estimate the parametric g-formula.

van der Laan and Gruber (2012) proposed an extension of this doubly robust estimator that includes a data adaptive procedure. They called their method longitudinal targeted minimum loss-based estimation (TMLE).

This doubly robust estimator for average causal effects is ready for use in practice, though its widespread implementation has been historically hampered by computational constraints and lack of user-friendly software, especially for hazard-based survival analysis. We anticipate that, in the near future, doubly (or multiply) robust estimators will become more common when studying the effect of complex treatment strategies on failure time outcomes. See Fine Point 21.2 for a description of the different representations of the g-formula and their connections to the above doubly robust estimator.

21.4 G-estimation for time-varying treatments

If we were only interested in the effect of the time-fixed treatment A_1 in Table 21.1, in Chapter 14 we described structural nested mean models for the conditional causal effect of a time-fixed treatment within levels of the covariates. Those models had a single equation because there was a single time point $k = 0$. The extension to time-varying treatments requires that the model specifies as many equations as time points in the data. For the time-varying treatment $\overline{A} = (A_0, A_1)$ at two time points in Table 21.1, we can specify a (saturated)

Fine Point 21.2

Representations of the the g-formula. The g-formula can be mathematically represented in several ways. These different representations of the g-formula are nonparametrically equivalent but lead to different estimators in practice. Throughout this book we have emphasized a representation of the g-formula that is the generalized version of standardization (in the epidemiologic jargon). That is, the g-formula for a mean outcome is $\sum_l \mathrm{E}\left[Y|A=a,L=l\right]\, f\left(l\right)$ for a time-fixed treatment and, as described in this chapter, $\sum_{\bar{l}} \mathrm{E}\left[Y|\bar{A}=\bar{a},\bar{L}=\bar{l}\right] \prod_{k=0}^{K} f\left(l_k|\bar{a}_{k-1},\bar{l}_{k-1}\right)$ for a time-varying treatment. Because a plug-in estimator based on this representation of the g-formula requires estimates of the joint density of the confounders $\prod_{k=0}^{K} f\left(l_k|\bar{a}_{k-1},\bar{l}_{k-1}\right)$ over time, we refer to it as a joint density modeling estimator of the g-formula.

An alternative representation of the g-formula is a conditional expectation. For a time-fixed treatment, we implicitly used this g-formula representation $\mathrm{E}\left[\mathrm{E}\left[Y|A=a,L=l\right]\right]$ in Section 13.3. For a time-varying treatment, the representation is an iterated conditional expectation (ICE) that can be recursively defined. A plug-in estimator based on the ICE representation of the g-formula requires the fitting of sequential predictive algorithms (e.g., regression models). The ICE estimator is described in Section 21.3 and Technical Point 21.3, where we combine it with the estimation of IP weights to construct doubly (or $k+1$) robust estimators.

Another equivalent representation of the g-formula is IP weighting. In fact, as shown in Technical Point 2.3 for time-fixed treatments, the standardized mean and the IP weighted mean are equal under positivity. The same is true for time-varying treatments (Robins, 1986; Young et al, 2014). As described in this chapter, an estimator based on the IP weighting representation of the g-formula requires the estimation of the conditional density of treatment over time given past treatment and covariate history. We refer to these estimators as IP weighted estimators rather than as g-formula estimators.

structural nested mean model with two equations

$$\begin{aligned}&\text{For time } k=0\text{: } \mathrm{E}\left[Y^{a_0,a_1=0}-Y^{a_0=0,a_1=0}\right]=\beta_0 a_0\\&\text{For time } k=1\text{: } \mathrm{E}\left[Y^{a_0,a_1}-Y^{a_0,a_1=0}|L_1^{a_0}=l_1,A_0=a_0\right]=\\&\qquad a_1\left(\beta_{11}+\beta_{12}l_1+\beta_{13}a_0+\beta_{14}a_0l_1\right)\end{aligned}$$

Effect of a_1 when a_0 is set to 0:

- β_{11} in individuals with $L_1^{a_0=0}=0$
- $\beta_{11}+\beta_{12}$ in those with $L_1^{a_0=0}=1$

Effect of a_1 when a_0 is set to 1 :

- $\beta_{11}+\beta_{13}$ in those with $L_1^{a_0=1}=0$
- $\beta_{11}+\beta_{13}+\beta_{14}$ in those with $L_1^{a_0=1}=1$

By consistency, $L_1^{a_0}=L_1$.

The second equation models the effect of treatment at time $k=1$ within each of the 4 treatment and covariate histories defined by (A_0,L_1). This component of the model is saturated because the 4 parameters β_1 in the second equation parameterize the effect of a_1 on Y within the 4 possible levels of past treatment and covariate history. The first equation models the effect of treatment at time $k=0$ when treatment at time $k=1$ is set to zero. This component of the model is also saturated because it has one parameter β_0 to estimate the effect within the only possible history (there is no prior treatment or covariates, so everybody has the same history).

The two equations of the structural nested model are the reason why the model is referred to as *nested*. The first equation models the effect of receiving treatment at time 0 and never again after time 0, the second equation models the effect of receiving treatment at time 1 and never again after time 1, and so on if we had more time points.

Let us use g-estimation to estimate the parameters of our structural nested model with $K=1$. We follow the same approach as in Chapter 14. We start by considering the additive rank-preserving structural nested model for each

individual i

$$Y_i^{a_0,0} = Y_i^{0,0} + \psi_0 a_0$$
$$Y_i^{a_0,a_1} = Y_i^{a_0,0} + \psi_{11} a_1 + \psi_{12} a_1 L_{1,i}^{a_0} + \psi_{13} a_1 a_0 + \psi_{14} a_1 a_0 L_{1,i}^{a_0}$$

(We represent $Y_i^{a_0=0,a_1=0}$ by $Y_i^{0,0}$ to simplify the notation.)

The first equation is a rank-preserving model because the effect ψ_0 is exactly the same for every individual. Thus if $Y_i^{0,0}$ for subject i exceeds $Y_j^{0,0}$ for subject j, the same ranking of i and j will hold for $Y^{1,0}$—the model preserves ranks across strategies. Also, under equation 2, if $Y_i^{1,0}$ for subject i exceeds $Y_j^{1,0}$ for subject j, we can only be certain that $Y_i^{1,1}$ for subject i also exceeds $Y_j^{1,1}$ for subject j, if both have the same values of $L_1^{a_0=1}$. Because the preservation of the ranking is conditional on local factors (i.e., the value $L_1^{a_0=1}$), we refer to the second equation as a conditionally, or locally, rank-preserving model.

As discussed in Chapter 14, rank preservation is biologically implausible because of individual heterogeneity in unmeasured genetic and environmental risks. That is why our primary interest is in the structural nested mean model, which is totally agnostic as to whether or not there is effect heterogeneity across individuals. However, provided the strengthened identifiability conditions hold, g-estimates of ψ from the rank-preserving model are consistent for the parameters β of the mean model, even if the rank-preserving model is misspecified.

The proof can be found in Robins (1994). Note that to fit an unsaturated structural nested mean model by g-estimation, positivity is not required.

The first step in g-estimation is linking the model to the observed data, as we did in Chapter 14 for a time-fixed treatment. To do so, note that, by consistency, the counterfactual outcome Y^{a_0,a_1} is equal to the observed outcome Y for individuals who happen to be treated with treatment values a_0 and a_1. Formally, $Y^{a_0,a_1} = Y^{A_0,A_1} = Y$ for individuals with $(A_0 = a_0, A_1 = a_1)$. Similarly $Y^{a_0,0} = Y^{A_0,0}$ for individuals with $(A_0 = a_0, A_1 = 0)$, and $L_1^{a_0} = L_1$ for individuals with $A_0 = a_0$. Now we can rewrite the structural nested model in terms of the observed data as

$$Y^{A_0,0} = Y - (\psi_{11} A_1 + \psi_{12} A_1 L_1 + \psi_{13} A_1 A_0 + \psi_{14} A_1 A_0 L_1)$$
$$Y^{0,0} = Y^{A_0,0} - \psi_0 A_0$$

(we are omitting the individual index i to simplify the notation).

Table 21.2

A_0	L_1	A_1	Mean $H_1(\psi)$
0	0	0	84
0	0	1	$84 - \psi_{1,1}$
0	1	0	52
0	1	1	$52 - \psi_{11} - \psi_{12}$
1	0	0	76
1	0	1	$76 - \psi_{11} - \psi_{13}$
1	1	0	44
1	1	1	$44 - \psi_{11} - \psi_{12} - \psi_{13} - \psi_{14}$

Table 21.3

A_0	L_1	A_1	Mean $H_0(\psi)$
0	0	0	84
0	0	1	84
0	1	0	52
0	1	1	52
1	0	0	$76 - \psi_0$
1	0	1	$76 - \psi_0$
1	1	0	$44 - \psi_0$
1	1	1	$44 - \psi_0$

The second step in g-estimation is to use the observed data to compute the candidate counterfactuals $H_1(\psi^\dagger)$ and $H_0(\psi^\dagger)$. To do so, we use the structural nested model with the true value ψ of the parameter replaced by some value $\psi^\dagger$:

$$H_1(\psi^\dagger) = Y - \left(\psi_{11}^\dagger A_1 + \psi_{12}^\dagger A_1 L_1 + \psi_{13}^\dagger A_1 A_0 + \psi_{14}^\dagger A_1 A_0 L_1\right)$$
$$H_0(\psi^\dagger) = H_1(\psi^\dagger) - \psi_0^\dagger A_0$$

As in Chapter 14, the goal is to find the value $\psi^\dagger$ of the parameters that is equal to the true value ψ. When $\psi^\dagger = \psi$, the candidate counterfactual $H_k(\psi^\dagger)$ equals the true counterfactual $Y^{\overline{a}_{k-1},\underline{0}_k}$. We can now use sequential exchangeability to conduct g-estimation at each time point. Fine Point 21.3 describes how to g-estimate the parameters ψ of our saturated structural nested model. It turns out that all parameters of the structural nested model are 0, which implies that all counterfactual means $\mathrm{E}[Y^g]$ under any static or dynamic strategy g are equal to 60. This result agrees with those obtained by the g-formula and by IP weighting. G-estimation, like the g-formula and IP weighting, succeeds where traditional methods failed.

Fine Point 21.3

G-estimation with a saturated structural nested model. Sequential exchangeability at $k = 1$ implies that, within any of the four joint strata of (A_0, L_1), the mean of $Y^{A_0,0}$ among individuals with $A_1 = 1$ is equal to the mean among individuals with $A_1 = 0$. Therefore, the means of $H_1\left(\psi^\dagger\right)$ must also be equal when $\psi^\dagger = \psi$.

Consider first the stratum $(A_0, L_1) = (0, 0)$. From data rows 1 and 2 in Table 21.2, we find that the mean of $H_1(\psi)$ is 84 when $A_1 = 0$ and $84 - \psi_{11}$ when $A_1 = 1$. Hence $\psi_{11} = 0$. Next we equate the means of $H_1(\psi)$ in data rows 3 and 4 corresponding to stratum $(A_0, L_1) = (0, 1)$ to obtain $52 = 52 - \psi_{11} - \psi_{12}$. Since $\psi_{11} = 0$, we conclude $\psi_{12} = 0$. Continuing we equate the means of $H_1(\psi)$ in data rows 5 and 6 to obtain $76 = 76 - \psi_{11} - \psi_{13}$. Since $\psi_{11} = \psi_{12} = 0$, we conclude $\psi_{13} = 0$. Finally, equating the means of $H_1(\psi)$ in data rows 7 and 8, we obtain $44 = 44 - \psi_{11} - \psi_{12} - \psi_{13} - \psi_{14}$ so $\psi_{14} = 0$ as well.

To estimate ψ_0, we first substitute the values ψ_{11}, ψ_{12}, ψ_{13}, and ψ_{14} into the expression for the mean of $H_0(\psi)$ in Table 21.2. In this example, all parameters were equal to 0, so the mean of $H_0(\psi)$ was equal to the mean of the observed outcome Y. We then use the first equation of the structural equation model to compute the mean of $H_0(\psi)$ for each data row in the table by subtracting $\psi_0 A_0$ from the mean of $H_1(\psi)$, as shown in Table 21.3. Sequential exchangeability $Y^{0,0} \perp\!\!\!\perp A_0$ at time $k = 0$ implies that the means of $H_0(\psi)$ among the $16,000$ subjects with $A_0 = 1$ and the $16,000$ subjects with $A_0 = 0$ are identical. The mean of $H_0(\psi)$ is $84 \times 0.25 + 52 \times 0.75 = 60$ among individuals with $A_0 = 0$, $(76 - \psi_0) \times 0.5 + (44 - \psi_0) \times 0.5 = 60 - \psi_0$ among individuals with $A_0 = 1$. Hence $\psi_0 = 0$. We have completed g-estimation.

In practice, however, we will encounter observational studies with multiple times k and multiple covariates L_k at each time. In general, a structural nested mean model has as many equations as time points $k = 0, 1...K$. The general form of structural nested mean models is therefore the following: For each time $k = 0, 1...K$

$$\mathrm{E}\left[Y^{\overline{a}_{k-1},a_k,\underline{0}_{k+1}} - Y^{\overline{a}_{k-1},\underline{0}_k} | \overline{L}_k^{\overline{a}_{k-1}} = \overline{l}_k, \overline{A}_{k-1} = \overline{a}_{k-1}\right] = a_k \gamma_k\left(\overline{a}_{k-1}, \overline{l}_k, \beta\right)$$

where $\left(\overline{a}_{k-1}, a_k, \underline{0}_{k+1}\right)$ is a static strategy that assigns treatment $\overline{a}_{k-1}$ between times 0 and $k-1$, treatment a_k at time k, and treatment 0 from time $k = 1$ until the end of follow-up K. The strategies $\left(\overline{a}_{k-1}, a_k, \underline{0}_{k+1}\right)$ and $\left(\overline{a}_{k-1}, \underline{0}_k\right)$ differ only in that the former has treatment a_k at k while the latter has treatment 0 at time k.

The function $\gamma_k\left(\overline{a}_{k-1}, \overline{l}_k, \beta\right)$ satisfies $\gamma_k\left(\overline{a}_{k-1}, \overline{l}_k, 0\right) = 0$ so $\beta = 0$ under the null hypothesis of no effect of treatment.

That is, a structural nested mean model is a model for the effect on the mean of Y of a last blip of treatment of magnitude a_k at k, as a function $\gamma_k\left(\overline{a}_{k-1}, \overline{l}_k, \beta\right)$ of past treatment and covariate history $\left(\overline{a}_{k-1}, \overline{l}_k\right)$. See Technical Point 21.4 for the relationship between structural nested models and marginal structural models.

In our example with $K = 1$, $\gamma_0\left(\overline{a}_{-1}, \overline{l}_0, \beta\right)$ is just β_0 ($\overline{l}_0$ and $\overline{a}_{-1}$ can both be taken to be identically 0) and $\gamma_1\left(\overline{a}_0, \overline{l}_1, \beta\right)$ is $\beta_{11} + \beta_{12} l_1 + \beta_{13} a_0 + \beta_{14} a_0 l_1$. The candidate counterfactuals for models with several time points k, can be compactly defined as

$$H_k\left(\psi^\dagger\right) = Y - \sum_{j=k}^{K} A_j \gamma_j\left(\overline{A}_{j-1}, \overline{L}_j, \psi^\dagger\right)$$

With multiple time points or covariates, we will need to fit an unsaturated structural nested mean model. For example, we might hypothesize that the function $\gamma_k\left(\overline{a}_{k-1}, \overline{l}_k, \beta\right)$ is the same for k. The simplest model would be $\gamma_k\left(\overline{a}_{k-1}, \overline{l}_k, \beta\right) = \beta_1$, which assumes that the effect of a last blip of treatment

Technical Point 21.4

Relation between marginal structural models and structural nested models (Part II). We can now generalize the results in Fine Point 14.1 to time-varying treatments. A structural nested mean model is a semiparametric marginal structural mean model if and only if, for all $\left(\overline{a}_{k-1}, \overline{l}_k, \beta\right)$,

$$\gamma_k\left(\overline{a}_{k-1}, \overline{l}_k, \beta\right) = \gamma_k\left(\overline{a}_{k-1}, \beta\right)$$

Specifically, it is a semiparametric marginal structural mean model with the functional form

$$\mathrm{E}\left[Y^{\overline{a}}\right] = \mathrm{E}\left[Y^{\overline{0}_K}\right] + \sum_{k=0}^{K} a_k \gamma_k\left(\overline{a}_{k-1}, \overline{l}_k, \beta\right),$$

where $\mathrm{E}\left[Y^{\overline{0}_K}\right]$ is left unspecified. However, such a structural nested mean model is not simply a marginal structural mean model, because it also imposes the additional strong assumption that effect modification by past covariate history is absent. In contrast, a marginal structural model is agnostic as to whether there is effect modification by time-varying covariates.

If we specify a structural nested mean model $\gamma_k\left(\overline{a}_{k-1}, \beta\right)$, then we can estimate β either by g-estimation or IP weighting. However the most efficient g-estimator will be more efficient than the most efficient IP weighted estimator when the structural nested mean model (and thus the marginal structural mean model) is correctly specified, because g-estimation uses the additional assumption of no effect modification by past covariates to increase efficiency.

In contrast, suppose the marginal structural mean model is correct but the structural nested mean model is incorrect because $\gamma_k\left(\overline{a}_{k-1}, \overline{l}_k, \beta\right) \neq \gamma_k\left(\overline{a}_{k-1}, \beta\right)$. Then the g-estimates of β and $\mathrm{E}\left[Y^{\overline{a}}\right]$ will be biased, while the IP weighted estimates remain unbiased. Thus we have a classic variance-bias trade off. Given the marginal structural model, g-estimation can increase efficiency if $\gamma_k\left(\overline{a}_{k-1}, \overline{l}_k, \beta\right) = \gamma_k\left(\overline{a}_{k-1}, \beta\right)$, but introduces bias otherwise.

is the same for all times k. Other options are $\beta_1 + \beta_2 k$, which assumes that the effect varies linearly with the time k of treatment, and $\beta_1 + \beta_2 k + \beta_3 a_{k-1} + \beta_4 l_k + \beta_5 l_k a_{k-1}$, which allows the effect to be modified by past treatment and covariate history.

To describe g-estimation for structural nested mean models with multiple time points, suppose the nonsaturated model is $\gamma_k\left(\overline{a}_{k-1}, \overline{l}_k, \beta\right) = \beta_1$. The corresponding rank-preserving model entails $H_k\left(\psi^\dagger\right) = Y - \sum_{j=k}^{K} A_j \psi^\dagger$, which can be computed from the observed data for any value $\psi^\dagger$. We will then choose values ψ_{low} and ψ_{up} that are much smaller and larger, respectively, than any substantively plausible value of ψ, and will compute for each individual the value of $H_k\left(\psi^\dagger\right)$ for each $\psi^\dagger$ on a grid from ψ_{low} to ψ_{up}, say $\psi_{low}, \psi_{low} + 0.1, \psi_{low} + 0.2, ..., \psi_{up}$.

Then, for each value of $\psi^\dagger$, we will fit a pooled logistic regression model

$$\text{logit}\Pr\left[A_k = 1 | , H_k\left(\psi^\dagger\right), \overline{L}_k, \overline{A}_{k-1}\right] = \alpha_0 + \alpha_1 H_k\left(\psi^\dagger\right) + \alpha_2 W_k$$

for the probability of treatment at time k for $k = 0, ..., K$. Here $W_k = w_k\left(\overline{L}_k, \overline{A}_{k-1}\right)$ is a vector of covariates calculated from an individual's covariate and treatment data $\left(\overline{L}_k, \overline{A}_{k-1}\right)$, α_2 is a row vector of unknown parameters, and each person contributes $K + 1$ observations. Under the assumptions of sequential exchangeability and consistency, the g-estimate of ψ, and therefore of β, is the value $\psi^\dagger$ that results in the estimate of α_1 that is closest to 0.

The procedure described above is the generalization to time-varying treat-

Technical Point 21.5

A closed form estimator for linear structural nested mean models. When, as in all the examples we have discussed, $\gamma_k\left(\overline{a}_{k-1}, \overline{l}_k, \beta\right) = \beta^T R_k$ is linear in β with $R_k = r_k\left(\bar{L}_k, \bar{A}_{k-1}\right)$ being a vector of known functions, then, given the model $\text{logit}\Pr\left[A_k = 1|\overline{L}_k, \overline{A}_{k-1}\right] = \alpha^T W_k$, there is an explicit closed form expression for $\widehat{\beta}$ given by

$$\widehat{\beta} = \left\{ \sum_{i=1,k=0}^{i=N,k=K} A_{i,k} X_{i,k}\left(\widehat{\alpha}\right) Q_{i,k} S_{i,k}^T \right\}^{-1} \left\{ \sum_{i=1,k=0}^{i=N,k=K} Y_i X_{i,k}\left(\widehat{\alpha}\right) Q_{i,k} \right\}$$

with $X_{i,k}\left(\widehat{\alpha}\right) = \left[A_{i,k} - \text{expit}\left(\widehat{\alpha}^T W_{i,k}\right)\right]$, $S_{i,k} = \sum_{i=1,j=k}^{i=N,j=K} R_{i,k}$, and the choice of $Q_{i,k} = q_k\left(\bar{L}_{i,k}, \bar{A}_{i,k-1}\right)$ affects efficiency but not consistency. See Robins (1994) for the optimal choice of Q_k.

In fact, when $\gamma_k\left(\overline{a}_{k-1}, \overline{l}_k, \beta\right)$ is linear in β, we can obtain a closed-form doubly robust estimator $\widetilde{\beta}$ of β by specifying a working model $\varsigma^T D_k = \varsigma^T d_k\left(\bar{L}_k, \bar{A}_{k-1}\right)$ for $\text{E}\left[H_k\left(\beta\right)|\bar{L}_k, \bar{A}_{k-1}\right] = \text{E}\left[Y^{\overline{A}_{k-1}, \underline{0}_k}|\bar{L}_k, \bar{A}_{k-1}\right]$ and defining

$$\begin{pmatrix} \widetilde{\beta} \\ \widetilde{\varsigma} \end{pmatrix} = \left\{ \sum_{i=1,k=0}^{i=N,k=K} \begin{pmatrix} A_{i,k} X_{i,k}\left(\widehat{\alpha}\right) Q_{i,k} \\ D_{i,k} \end{pmatrix} \left(S_{i,k}^T, D_{i,k}^T\right) \right\}^{-1} \left\{ \sum_{i=1,k=0}^{i=N,k=K} Y_i \begin{pmatrix} X_{i,k}\left(\widehat{\alpha}\right) Q_{i,k} \\ D_{i,k} \end{pmatrix} \right\}$$

Specifically $\widetilde{\beta}$ will be a consistently asymptotically normal estimator of ψ if either the model $\varsigma^T D_k$ for $\text{E}\left[Y^{\overline{A}_{k-1}, \underline{0}_k}|\bar{L}_k, \bar{A}_{k-1}\right]$ is correct or the model for $\text{logit}\Pr\left[A_k = 1|\overline{L}_k, \overline{A}_{k-1}\right]$ is correct.

The limits of the 95% confidence interval for ψ are the limits of the set of values $\psi^\dagger$ that result in a P-value> 0.05 when testing for $\alpha_1 = 0$.

A 95% joint confidence interval for β_j are the set of values for which the 5 degree-of-freedom score test does not reject at the 5% level. A less computationally demanding approach is to compute a univariate 95% Wald confidence interval as $\widehat{\beta}_j \pm 1.96$ times its standard error.

ments of the g-estimation procedure described in Chapter 14. For simplicity, we considered a structural nested model with a single parameter β_1, which implies that the effect does not vary over time k or by treatment and covariate history. Suppose now that the parameter β is a vector. To be concrete suppose we consider the model with $\gamma_k\left(\overline{a}_{k-1}, \overline{l}_k, \beta\right) = \beta_0 + \beta_1 k + \beta_2 a_{k-1} + \beta_3 l_k + \beta_4 l_k a_{k-1}$ so β is 5-dimensional and l_m is 1-dimensional. Now to estimate 5 parameters one requires 5 additional covariates in the treatment model. For example, we could fit the model $\text{logit}\Pr\left[A_k = 1|H_k\left(\psi^\dagger\right), \overline{L}_k, \overline{A}_{k-1}\right] =$

$$\alpha_0 + H_k\left(\psi^\dagger\right)\left(\alpha_1 + \alpha_2 k + \alpha_3 A_{k-1} + \alpha_4 L_k + \alpha_5 L_k A_{k-1}\right) + \alpha_6 W_k$$

The particular choice of covariates does not affect the consistency of the point estimate of β, but it determines the width of its confidence interval.

The g-estimation procedure then requires a search over a 5-dimensional grid, one dimension for each component β_j of β. So if we had 20 grid points for each component we would have 20^5 different values of β on our 5 dimensional grid. The g-estimate $\widehat{\beta}$ is the β for which the 5 degree of freedom score test that all 5 $(\alpha_1, \alpha_2, \alpha_3, \alpha_4, \alpha_5)$ are precisely zero. However, when the dimension of β is greater than 2, finding the g-estimate $\widehat{\beta}$ by a grid search may be computationally prohibitive. Fortunately, there is a closed form estimator of β that does not require a grid search when, as in all examples discussed in this section, the structural nested mean model is linear. See Technical Point 21.5, which also describes a doubly robust form of the estimator.

After g-estimation of the parameters of the structural nested mean model, the last step is the estimation of the counterfactual mean $\text{E}[Y^g]$ under the strategies g of interest. If there is no effect modification by past covariate

Technical Point 21.6

Estimation of $\mathrm{E}[Y^g]$ after g-estimation of a structural nested mean model. Suppose the identifiability assumptions hold, one has obtained a doubly robust g-estimate $\widetilde{\beta}$ of a structural nested mean model $\gamma_k\left(\overline{a}_{k-1}, \overline{l}_k, \beta\right)$ and one wishes to estimate $\mathrm{E}[Y^g]$ under a dynamic strategy g. To do so, one can use the following steps of a Monte Carlo algorithm:

1. Estimate the mean response $\mathrm{E}\left[Y^{\overline{0}_K}\right]$ had treatment always been withheld by the sample average of $H_0\left(\widetilde{\beta}\right)$ over the N study subjects. Call the estimate $\widehat{\mathrm{E}}\left[Y^{\overline{0}_K}\right]$.
2. Fit a parametric model for $f\left(l_k|\bar{a}_{k-1}, \bar{l}_{k-1}\right)$ to the data, pooled over persons and times, and let $\widehat{f}\left(l_k|\bar{a}_{k-1}, \bar{l}_{k-1}\right)$ denote the estimate of $f\left(l_k|\bar{a}_{k-1}, \bar{l}_{k-1}\right)$ under the model.
3. Do for $v = 1, ..., V$,
   (a) Draw $l_{v,0}$ from $\widehat{f}(l_0)$.
   (b) Recursively for $k = 1, ..., K$ draw $l_{v,k}$ from $\widehat{f}\left(l_k|\bar{a}_{v,k-1}, \bar{l}_{v,k-1}\right)$ with $\bar{a}_{v,k-1} = \overline{g}_{k-1}\left(\overline{l}_{v,k-1}\right)$, the treatment history corresponding to the strategy g.
   (c) Let $\widehat{\Delta}_{g,v} = \sum_{j=0}^{j=K} a_{v,j}\gamma_j\left(\overline{a}_{v,j-1}, \overline{l}_{v,j}, \widetilde{\beta}\right)$ be the v^{th} Monte Carlo estimate of $Y^g - Y^{\overline{0}_K}$, where $a_{v,j} = g_j\left(\overline{l}_{v,j-1}\right)$.
4. Let $\widehat{\mathrm{E}}[Y^g] = \widehat{\mathrm{E}}\left[Y^{\overline{0}_K}\right] + \sum_{v=1}^{v=V} \widehat{\Delta}_{g,v}/V$ be the estimate of $\widehat{\mathrm{E}}[Y^g]$.

If the model for $f\left(l_k|\bar{a}_{k-1}, \bar{l}_{k-1}\right)$, the structural nested mean model $\gamma_k\left(\overline{a}_{k-1}, \overline{l}_k, \beta\right)$, and either the model for treatment $\Pr\left[A_k = 1|\overline{L}_k, \overline{A}_{k-1}\right]$ or the model for $\mathrm{E}\left[Y^{\overline{A}_{k-1}, \underline{0}_k}|\bar{L}_k, \bar{A}_{k-1}\right]$ are correctly specified, then $\widehat{\mathrm{E}}[Y^g]$ is consistent for $\mathrm{E}[Y^g]$. Confidence intervals can be obtained using the nonparametric bootstrap.

Note that $\gamma_k\left(\overline{a}_{k-1}, \overline{l}_k, \widetilde{\beta}\right)$ will converge to 0 if the estimate $\widetilde{\beta}$ is consistent for $\beta = 0$. Thus $\widehat{\Delta}_{g,v}$ will converge to zero and $\widehat{\mathrm{E}}[Y^g]$ to $\widehat{\mathrm{E}}\left[Y^{\overline{0}_K}\right]$ even if the model for $f\left(l_k|\bar{a}_{k-1}, \bar{l}_{k-1}\right)$ is incorrect. That is, the structural nested mean model preserves the null if the identifiability conditions hold and we either know (as in a sequentially randomized experiment) $\Pr\left[A_k = 1|\overline{L}_k, \overline{A}_{k-1}\right]$ or have a correct model for either $\Pr\left[A_k = 1|\overline{L}_k, \overline{A}_{k-1}\right]$ or $\mathrm{E}\left[Y^{\overline{A}_{k-1}, \underline{0}_k}|\bar{L}_k, \bar{A}_{k-1}\right]$.

history, e.g.,

$$\gamma_k\left(\overline{a}_{k-1}, \overline{l}_k, \beta\right) = \gamma_k\left(\overline{a}_{k-1}, \beta\right) = \beta_1 + \beta_2 k + \beta_3 a_{k-1} + \beta_4 a_{k-2} + \beta_5 a_{k-1}a_{k-2}$$

then $\mathrm{E}\left[Y^{\overline{a}}\right]$ under a static strategy $\overline{a}$ is estimated as

$$\widehat{\mathrm{E}}\left[Y^{\overline{a}}\right] = \widehat{\mathrm{E}}\left[Y^{\overline{0}_K}\right] + \sum_{k=0}^{K} a_k\gamma_k\left(\overline{a}_{k-1}, \widetilde{\beta}\right)$$

On the other hand, if the structural nested mean model includes terms for L_k or we want to estimate $\mathrm{E}[Y^g]$ under a dynamic strategy g, then we need to simulate the L_k using the algorithm described in Technical Point 21.6.

21.5 Censoring is a time-varying treatment

You may want to re-read Section 12.6 for a refresher on censoring.

Throughout this chapter we have used an example in which there is no censoring: the outcomes of all individuals in Table 21.1 are known. In practice, however, we will often encounter situations in which some individuals are lost to follow-up and therefore their outcome values are unknown or (right-)censored. We have discussed censoring and methods to handle it in Part II of the book. In Chapter 8, we showed that censoring may introduce selection bias, even under the null. In Chapter 12, we discussed how we are generally interested in the causal effect if nobody in the study population had been censored.

Conditioning on being uncensored ($C = 0$) induces selection bias under the null when C is either a collider on a pathway between treatment A and the outcome Y, or the descendant of one such collider.

However, in Part II we only considered a greatly simplified version of censoring under which we did not specify *when* individuals were censored during the follow-up. That is, we considered censoring C as a time-fixed variable. A more realistic view of censoring is as a time-varying variable $C_1, C_2, ...C_{K+1}$, where C_m is an indicator that takes value 0 if the individual remains uncensored at time m and takes value 1 otherwise. Censoring is a monotonic type of missing data, that is, if an individual's $C_m = 0$ then all previous censoring indicators are also zero ($C_1 = 0, C_2 = 0....C_m = 0$). Also, by definition, $C_0 = 0$ for all individuals in a study; otherwise they would have not been included in the study.

If an individual is censored at time m, i.e., when $C_m = 1$, then treatments, confounders, and outcomes measured after time m are unobserved. Therefore, the analysis becomes necessarily restricted to uncensored person-times, i.e., those with $C_m = 0$. For example, the g-formula for the counterfactual mean outcome $\mathrm{E}\left[Y^{\bar{a}}\right]$ from section 21.1 needs to be rewritten as

$$\sum_{\bar{l}} \mathrm{E}\left[Y|\bar{A} = \bar{a}, \bar{C} = \bar{0}, \bar{L} = \bar{l}\right] \prod_{k=0}^{K} f\left(l_k|\bar{a}_{k-1}, c_{k-1} = 0, \bar{l}_{k-1}\right),$$

with all the terms being conditional on remaining uncensored.

Suppose the identifiability conditions hold with treatment A_m replaced by (A_m, C_m) at all times m. Then it is easy to show that the above expression corresponds to the g-formula for the counterfactual mean outcome $\mathrm{E}\left[Y^{\bar{a},\bar{c}=\bar{0}}\right]$ under the joint treatment $(\bar{a}, \bar{c} = \bar{0})$, that is, the mean outcome that would have been observed if all individuals have received treatment strategy $\bar{a}$ and no individual had been lost to follow-up.

The use of the superscript $\bar{c} = \bar{0}$ makes it explicit the causal contrast that many have in mind when they refer to the causal effect of treatment $\bar{A}$, even if they choose not to use the superscript $\bar{c} = \bar{0}$.

The counterfactual mean $\mathrm{E}\left[Y^{\bar{a},\bar{c}=\bar{0}}\right]$ can also be estimated via IP weighting of a structural mean model when the identifiability conditions hold for the joint treatment $\left(\bar{A}, \bar{C}\right)$. To estimate this mean, we might fit, for example, the outcome regression model

$$\mathrm{E}\left[Y|\overline{A}, \bar{C} = \bar{0}\right] = \theta_0 + \theta_1 cum\left(\overline{A}\right)$$

to the pseudo-population created by the nonstabilized IP weights $W^{\bar{A}} \times W^{\bar{C}}$ where

$$W^{\bar{C}} = \prod_{k=1}^{K+1} \frac{1}{\Pr\left(C_k = 0|\bar{A}_{k-1}, C_{k-1} = 0, \bar{L}_k\right)}$$

We estimate the denominator of the weights by fitting a logistic regression model for $\Pr\left(C_k = 0|\bar{A}_{k-1}, C_{k-1} = 0, \bar{L}_k\right)$.

In the pseudo-population created by the nonstabilized IP weights, the censored individuals are replaced by copies of uncensored individuals with

the same values of treatment and covariate history. Therefore the pseudo-population has the same size as the original study population *before* censoring, that is, before any losses to follow-up occur. The nonstabilized IP weights abolish censoring in the pseudo-population.

Or we can use the pseudo-population created by the stabilized IP weights $SW^{\bar{A}} \times SW^{\bar{C}}$, where

$$SW^{\bar{C}} = \prod_{k=1}^{K+1} \frac{\Pr\left(C_k = 0 | \bar{A}_{k-1}, C_{k-1} = 0\right)}{\Pr\left(C_k = 0 | \bar{A}_{k-1}, C_{k-1} = 0, \bar{L}_k\right)}$$

We estimate the denominator and numerator of the IP weights via two separate models for $\Pr\left(C_k = 0 | \bar{A}_{k-1}, C_{k-1} = 0, \bar{L}_k\right)$ and $\Pr\left(C_k = 0 | \bar{A}_{k-1}, C_{k-1} = 0\right)$, respectively.

Remember:
The estimated IP weights $SW^{\bar{C}}$ have mean 1 when the model for $\Pr\left(C_k = 0 | \bar{A}_{k-1}, C_{k-1} = 0, \bar{L}_k\right)$ is correctly specified.

The pseudo-population created by the stabilized IP weights is of the same size as the original study population *after* censoring, that is, the proportion of censored individuals in the pseudo-population is identical to that in the study population at each time k. The stabilized weights do not eliminate censoring in the pseudo-population, they make censoring occur at random at each time k with respect to the measured covariate history $\bar{L}_k$. That is, there is selection but no selection bias. Regardless of the type of IP weights used, in the pseudo-population there are no arrows from L_k into future C_m for $m > k$. Importantly, under the exchangeability conditions for the joint treatment $\left(\bar{A}, \bar{C}\right)$, IP weighting can unbiasedly estimate the joint effect of $\left(\bar{A}, \bar{C}\right)$ even when some components of $\bar{L}$ are affected by prior treatment.

Finally, when using g-estimation of structural nested models, we first need to adjust for selection bias due to censoring by IP weighting. In practice, this means that we first estimate nonstabilized IP weights $W^{\bar{C}}$ for censoring to create a pseudo-population in which nobody is censored, and then apply g-estimation to the pseudo-population.

Chapter 22
TARGET TRIAL EMULATION

As discussed in Part I, causal inference from observational data can be viewed as an attempt to emulate a hypothetical randomized trial, which we refer to as the target trial. Since we now have all the tools that are needed to tackle causal inferences with time-varying treatments, this chapter generalizes the concept of the target trial to sustained treatment strategies and outlines a unified framework for causal inference, regardless of whether the data arose from a randomized experimental or an observational study.

This chapter also describes a taxonomy of causal effects that may be of interest when emulating a target trial, including intention-to-treat and per-protocol effects. Valid estimation of those causal effects generally requires data on time-varying prognostic factors and treatments, as well as appropriate adjustment for those time-varying factors using g-methods. It is precisely the development of g-methods that makes the concepts discussed here something more than a formal exercise: if data are available, the effects of interest can now be validly estimated.

22.1 The target trial (revisited)

To fix ideas, consider a randomized trial to estimate the effect of antiretroviral therapy on the 5-year risk of death among HIV-positive individuals. Eligible participants—over 18 years of age, no AIDS, no previous use of antiretroviral therapy—are randomly assigned to either treatment strategy g or treatment strategy g' at the start of follow-up $k = 0$ (baseline). Their follow-up starts at the time of assignment and ends at death, loss to follow-up, or 60 months after baseline, whichever occurs earlier. Of course, as in any trial, not all participants adhere to the treatment strategies defined in the trial protocol. That is, there are deviations from protocol.

Our trial is a *pragmatic trial*. In particular, the participants and their treating physicians are aware of the treatment they receive (i.e., the treatment assignment is not blinded), nobody receives a placebo (i.e., both strategies g and g' involve either active treatments or no treatment), and participants are monitored as frequently and intensely as regular patients outside of the study. A pragmatic trial is preferable when the goal is quantifying the effects of treatment strategies under realistic conditions, including that physicians and participants are aware of the care received by the latter.

If conducting this pragmatic randomized trial were not possible, we may attempt to emulate it through the analysis of existing observational data. We then refer to the trial as the *target trial* for our observational analysis.

See Hernán and Robins (2016) for more details about the characteristics of the target trial.

Specifying the protocol of the target trial is a useful device to clarify the causal question of interest that we wish our observational analysis to answer. At the very least, we need to specify the following key components of the protocol: eligibility criteria, start and end of follow-up, treatment strategies, outcomes of interest, causal contrast, and data analysis plan. Note that a precise specification of the protocol of the target trial may require some exploration of the available data. For example, only after having determined that the data included information on HIV diagnosis, we can reasonably propose to emulate a target trial of HIV-positive individuals.

Technical Point 22.1

Controlled direct effects. Consider the average causal effect of a treatment A on an outcome Y when an intermediate variable—or mediator—B is set to a particular value. We refer to this quantity as the *direct effect* of A on Y not through B. If the mediator B could take two values (0 or 1), then we can define the direct effect of A on Y when B is set to 1 and the direct effect of A on Y when B is set to 0. On the additive scale, these two direct effects are defined by the counterfactual differences $\mathrm{E}\left[Y^{a=1,b=1}\right] - \mathrm{E}\left[Y^{a=0,b=1}\right]$ and $\mathrm{E}\left[Y^{a=1,b=0}\right] - \mathrm{E}\left[Y^{a=0,b=0}\right]$, respectively. These direct effects, which are often referred to as *controlled direct effects*, could, in principle, be identified by conducting an experiment with sequential randomization for both treatment A and mediator B, or by emulating such target experiment using observational data. (Technical Point 22.2 describes other types of direct effects for which no target experiment exists.)

Suppose we conduct a randomized experiment in which participants are randomly assigned at baseline to either treatment $A = 1$ or $A = 0$ and one month after baseline to either treatment $B = 1$ or $B = 0$. Thus all individuals will be placed in one of four groups: $(A = 1, B = 1)$, $(A = 1, B = 0)$, $(A = 0, B = 1)$, or $(A = 0, B = 0)$. The outcome of interest Y is measured at 3 months in all individuals (for simplicity, suppose no individuals were lost to follow-up or died). This study design allows us to consistently estimate the controlled direct effects because the randomization of both A and B ensures that the counterfactual quantities $\mathrm{E}\left[Y^{a,b}\right] = \Pr\left[Y^{a,b} = 1\right]$ are consistently estimated by the observed risks $\Pr\left[Y = 1 | A = a, B = b\right]$.

The controlled direct effects can also be validly estimated in observational studies as long as the identifiability conditions of consistency, positivity, and exchangeability hold for both A and B. A precise characterization of these identifiability conditions was actually provided in Chapter 19 because a controlled direct effect is just a particular case of a contrast of treatment strategies sustained over time. To see so, simply replace A and B by A_0 and A_1 in the above expressions. More generally, both the treatment A and the mediator B can be time-varying themselves.

The acronym PICO (Population, Intervention, Comparator, Outcome) has been proposed to summarize some of the components of the target trial (Richardson et al. 1995).

We introduced the concept of the target trial in Chapter 3. However, Parts I and II only referred to simplistic target trials that compared time-fixed treatments. We are now ready to discuss realistic target trials that compare sustained treatment strategies like g_1 "take therapy continuously during the follow-up, unless a contraindication or toxicity arises" and g_0 "refrain from taking therapy during the follow-up". The next section defines causal effects of interest in (real and emulated) randomized trials concerned with sustained treatment strategies. Additional contrasts of sustained strategies—referred to as *direct effects*—are described in Technical Point 22.1.

22.2 Causal effects in randomized trials

Let us review three types of causal effects that may be of interest in a randomized trial. To do so, we need some familiar notation. Let A_k take value 1 if the individual receives therapy at time k and 0 otherwise, and C_k take value 0 if the individual remains uncensored at time k and 1 otherwise, for $k = 0, 1, 2...K$ with $K = 59$. Our trial will assign eligible individuals to either the strategy g_1 "receive treatment $A_k = 1$ continuously during the follow-up unless a contraindication or toxicity arises" or the strategy g_0 "receive treatment $A_k = 0$ continuously during the follow-up". The assignment indicator Z takes value 1 if the individual is assigned to g_1 and 0 if assigned to g_0.

In the previous chapters of Part III, we were interested in the causal effect of treatment on an outcome Y measured at the end of follow-up. Here we extend our description to causal effects on a failure time outcome. That is, the goal of

Technical Point 22.2

Natural direct effects and principal stratum direct effects. Besides the controlled direct effects described in Technical Point 22.1, there exist other definitions of the average direct effect of a treatment A on an outcome Y when a potential mediator B is set to a particular value.

The *natural direct effect* of A on Y not through B is the average causal effect of A on Y if the value of B had been set to the value that B would have taken if A had been set to 0, that is, if B had been set to the value $B^{a=0}$ (which is 1 for some individuals and 0 for others). The natural direct effect, defined by the contrast $\mathrm{E}\left[Y^{a=1,B^{a=0}}\right] - \mathrm{E}\left[Y^{a=0,B^{a=0}}\right]$, is a cross-world quantity because it requires to consider a counterfactual outcome simultaneously indexed by both $a=1$ and $a=0$. Therefore, the natural direct effect cannot be identified in a randomized experiment, not even in principle, and the magnitude of the natural direct effect estimates from observational data cannot be verified. Despite the scientific impossibility of confirming these estimates, natural direct effects are often the goal of causal mediation analyses. This is probably because, under strong assumptions, total treatment effects can be decomposed into natural direct and indirect effects. Natural direct effects were introduced by Robins and Greenland (1992), which referred to them as pure direct effects; Pearl (2001) renamed them as natural direct effects. For a review, see the book by VanderWeele (2015).

The *principal stratum direct effect* of A on Y if the value of B had been set to b is the average causal effect of A on Y in the subset of the population whose value of B would have been equal to b regardless of the value of A, that is, in the subset of the population with $B^{a=0} = B^{a=1} = b$. Then the principal stratum direct effect is defined by the contrast $\mathrm{E}\left[Y^{a=1,b}|B^{a=0} = B^{a=1} = b\right] - \mathrm{E}\left[Y^{a=0,b}|B^{a=0} = B^{a=1} = b\right]$, which is equal to $\mathrm{E}\left[Y^{a=1}|B^{a=0} = B^{a=1} = b\right] - \mathrm{E}\left[Y^{a=0} = 1|B^{a=0} = B^{a=1} = b\right]$. Note that, unlike the other types of direct effects, principal stratum direct effects do not involve joint counterfactuals $Y^{a,b}$, just the counterfactuals Y^a in a subset of the population so, in that sense, they are the total (rather than direct) effect of treatment in that subset of the population. Principal stratum direct effects have little scientific relevance when A affects B in almost all individuals, because then they apply to the very small subset of the population with $B^{a=0} = B^{a=1}$. In practice, B is often coarsened (typically into a binary indicator) to increase the size of the principal stratum, but coarsening itself may make the principal stratum direct effect less scientifically relevant. Principal stratum direct effects were introduced by Robins (1986) and popularized by Rubin (2004). Frangakis and Rubin (2002) used the concept of principal stratum as a tool to handle competing events.

Chapter 9 introduced the concepts of intention-to-treat effect and per-protocol effect for time-fixed treatments.

our trial is to estimate the causal effect on survival (see Technical Point 22.3). Let D_k be an indicator for death (1: yes, 0: no) by month $k = 1, 2...K+1$.

First, let us consider the effect of assignment to the treatment strategy, regardless of treatment actually received. This effect, commonly known as the *intention-to-treat effect*, is defined by a contrast of the outcome distribution under the interventions:

- be assigned to strategy g_1 at baseline and remain under study until the end of follow-up
- be assigned to strategy g_0 at baseline and remain under study until the end of follow-up

The intention-to-treat effect at time k can then be expressed as the contrast of the counterfactual risks of death $\Pr\left[D_k^{z=1,\bar{c}_k=\bar{0}} = 1\right] - \Pr\left[D_k^{z=0,\bar{c}_k=\bar{0}} = 1\right]$ under assignment to strategy g_1 ($z=1$) versus g_0 ($z=0$) if nobody had been lost to follow-up through time k ($\bar{c}_k = \bar{0}$).

In some randomized trials, assignment to and initiation of the treatment strategies occur simultaneously. That is, all individuals assigned to strategy g_1 start to receive treatment at time 0, regardless of whether they continue taking it after baseline, and no individuals assigned to strategy g_0 receive treatment at time 0, regardless of whether they start taking it after baseline. In those cases,

the intention-to-treat effect is not only the effect of assignment but also the effect of initiation of treatment, e.g., $\Pr\left[D_k^{a_0=1,\bar{c}_k=\bar{0}}=1\right]-\Pr\left[D_k^{a_0=0,\bar{c}_k=\bar{0}}=1\right]$.

The intention-to-treat effect is agnostic about any treatment decisions made after baseline, including discontinuation or initiation of the treatments of interest, use of non-approved concomitant treatments, or any other deviations from protocol. This agnosticism implies that the magnitude of the intention-to-treat effect may heavily depend on the particular patterns of deviation from protocol that occur during the conduct of each trial. Two studies with the same protocol but conducted in different settings may have different intention-to-treat effect estimates with neither of them being biased.

Second, let us consider the effect of receiving the interventions as specified in the study protocol. We refer to this effect as the *per-protocol effect*. The per-protocol effect is defined by a contrast of the outcome distribution under the interventions:

- receive treatment strategy g_1 continuously between baseline $k=0$ and end of follow-up
- receive treatment strategy g_0 continuously between baseline $k=0$ and end of follow-up

The per-protocol effect at time k can then be expressed as the contrast of the counterfactual risks of death $\Pr\left[D_k^{g_1,\bar{c}_k=\bar{0}}=1\right]-\Pr\left[D_k^{g_0,\bar{c}_k=\bar{0}}=1\right]$ under full adherence to strategy g_1 versus g_0 if nobody had been lost to follow-up through time k ($\bar{c}_k=\bar{0}$).

Sensible trial protocols will not mandate that treatment be continued no matter what happens to the individual. For example, our strategy g_1 of continuous treatment mandates treatment discontinuation when a contraindication or toxicity arises. That is, the per-protocol effect generally involves the comparison of dynamic strategies ("do this, if X happens then do this other thing") rather than static strategies ("do this, no matter what happens"). Remember that we already made this point in Fine Point 19.2.

Sometimes the study protocol is not explicit about the dynamic nature of the treatment strategies. For example, the protocol may simplify the description of strategy g_1 as "receive treatment $A_k=1$ continuously during the follow-up" without explicitly stating that the therapy must be discontinued "when a contraindication or toxicity arises". This simplified description of strategy g_1 may lead to misunderstandings. Specifically, an individual assigned to g_1 who discontinues therapy because of toxicity should not be labeled as someone who is not adhering to strategy g_1. In fact, that person is perfectly adhering to strategy g_1 as (it should have been) stated in the protocol. When doing otherwise is not an option in the real world, discontinuation of the originally assigned treatment or initiation of other treatments cannot possibly be considered a deviation from protocol. Because the per-protocol effect is defined by a contrast of realistic strategies, it is particularly relevant for causal inference research which seeks to provide evidence for decisions in the real world.

Ideally, to avoid confusions about what should or should not be deemed as nonadherence throughout the follow-up, the protocol would fully specify the treatment strategies of interest. Then the per-protocol effect would be well-defined (Hernán and Robins, 2017).

In fact, the per-protocol effect is often the implicit target of inference. For example, often investigators question the fidelity of the interventions implemented in the study to the interventions described in the protocol, and say that there is "bias". This language indicates that the investigators are really interested in comparing the interventions implemented during the follow-up as specified in the protocol (i.e., the per-protocol effect) and not in the effect of assignment to the interventions at baseline (i.e., the intention-to-treat

effect) because nonadherence after baseline cannot possibly bias the effect of assignment at baseline.

Finally, let us consider the effect of receiving interventions other than the ones specified in the study protocol. Suppose that, while our trial is being conducted, a consensus started to emerge that strategy g_0 "receive treatment $A_k = 0$ continuously during the follow-up" is inferior to strategy g_1. Therefore some physicians began to recommend initiation of therapy when the clinical course worsened, e.g., when the CD4 cell count (L_k) first dropped below 200 cells/μL. As a result, many individuals in the trial who were assigned to strategy g_0 actually followed the modified strategy g_0' "receive treatment $A_k = 0$ continuously during the follow-up but, after $L_k < 200$, switch to treatment $A_k = 1$". The contrast of outcome distributions under the interventions

- receive treatment strategy g_1 continuously between baseline $k = 0$ and end of follow-up
- receive treatment strategy g_0' continuously between baseline $k = 0$ and end of follow-up

corresponds to neither the intention-to-treat effect nor the original per-protocol effect. Rather, it is a question about the per-protocol effect in a hypothetical trial in which individuals are randomized to either strategy g_1 or g_0'.

This example illustrates how causal effects of interest that do not correspond to the original per-protocol effect can be conceptualized as per-protocol effects in target trials that can be emulated using the randomized trial data. Interestingly, if the strategies of interest differ from those in the actual trial, it is actually disadvantageous to have all participants in the actual trial adhere to the strategies specified in the protocol. Specifically, complete adherence implies that the trial data cannot be used to emulate a target trial with a different protocol (because no individuals followed the protocol of the target trial in the actual data). For example, a randomized trial with full adherence in which HIV-positive individuals are assigned to different CD4 cell count thresholds at which to initiate antiretroviral therapy is of little use to emulate a trial in which individuals are assigned to either continuous treatment or no treatment, and vice versa. It is precisely the noncompliance that allows us to use the data from a given randomized trial to emulate other randomized trials that answer different, perhaps more relevant, causal questions.

22.3 Causal effects in observational analyses that emulate a target trial

The causal effects described above for randomized trials can be analogously defined for observational analyses that emulate a target trial.

The observational analog of the intention-to-treat effect is defined by a contrast of the outcome distribution under the hypothetical interventions

- initiate treatment $A_0 = 1$ at baseline and remain under study until the end of follow-up
- initiate treatment $A_0 = 0$ at baseline and remain under study until the end of follow-up

This observational analog of the intention-to-treat effect at time k can then be expressed as the contrast of the counterfactual risks of death $\Pr\left[D_k^{a_0=1,\bar{c}_k=\bar{0}} = 1\right] -$

Technical Point 22.3

Survival analysis with time-varying treatments. Chapter 17 describes g-methods to estimate the effect of point interventions on failure time outcomes. Chapter 21 describes g-methods to estimate the effect of sustained treatment strategies on non-failure time outcomes. In practice, we often need to use g-methods to estimate the effect of sustained strategies on failure time outcomes. To do so, we need to combine the approaches described in Chapters 17 and 21. Below we sketch two approaches, based on the g-formula and on IP weighting, to estimate the counterfactual risk $\Pr\left[D_{k+1}^{\bar{a}}=1\right]$ under treatment strategy $\bar{a}$ if sequential exchangeability, positivity, and consistency hold. We assume no censoring for simplicity.

The risk $\Pr\left[D_{k+1}^{\bar{a}}=1\right]$ is identified by the g-formula

$$\sum_{\bar{l}_k}\sum_{j=0}^{k}\Pr\left[D_{j+1}=0|\bar{A}_j=\bar{a}_j,\bar{L}_j=\bar{l}_j,D_j=0\right]$$
$$\prod_{s=0}^{j}\left\{\Pr\left[D_s=0|\bar{A}_{s-1}=\bar{a}_{s-1},\bar{L}_{s-1}=\bar{l}_{s-1},D_{s-1}=0\right]f\left(l_s|\bar{a}_{s-1},\bar{l}_{s-1},D_s=0\right)\right\}.$$

A plug-in g-formula estimate can then be obtained by fitting models for the discrete-time hazards $\Pr\left[D_{k+1}=1|\bar{A}_k=\bar{a}_k,\bar{L}_k=\bar{l}_k,D_k=0\right]$ and for the conditional density $f\left(l_k|\bar{a}_{k-1},\bar{l}_{k-1},D_k=0\right)$ of the confounders in $\bar{L}$ over time. For example, as described in Chapter 17, a pooled logistic model can be used to adequately approximate the hazards. For details and an application of the method, see Young et al. (2011).

An alternative is to fit a pooled logistic model for the hazards in which each individual receives the time-varying nonstabilized IP weight

$$W_k^{\bar{A}}=\prod_{m=0}^{k}\frac{1}{f\left(A_m|\bar{A}_{m-1},\bar{L}_m\right)}$$

or its corresponding stabilized IP weight at each time k. The parameters of that model estimate the parameters of a marginal structural pooled logistic model (Robins 1998). For details and an application of the method, see Hernán et al. (2001).

$\Pr\left[D_k^{a_0=0,\bar{c}_k=\bar{0}}=1\right]$. That is, it corresponds to the intention-to-treat effect in a target trial in which assignment to and initiation of the strategies occurs simultaneously.

The observational analog of the intention-to-treat effect differs slightly from the intention-to-treat effect in trials in which some individuals assigned to a particular strategy may never initiate it. In our example, we would estimate an observational analog of the intention-to-treat effect by comparing individuals who do and do not initiate antiretroviral therapy at baseline. This observational effect differs from the intention-to-treat effect of a target trial in which some individuals assigned to g_1 do not take any dose of treatment. Yet a hypothetical intervention on initiation, as opposed to assignment, of treatment preserves a key feature of the intention-to-treat effect: interventions are defined solely by events occurring at baseline.

The observational analog of the per-protocol effect is defined identically as that for the target trial. In randomized trials we differentiated between the original per-protocol effect and the per-protocol effects in alternative target trials. In observational studies this difference is unnecessary because, in the absence of a pre-specified protocol, each per-protocol effect corresponds to a particular target trial. In general, we can only use observational data to emulate target trials whose intended interventions are actually followed by at least

some individuals in the study. In some settings, however, investigators may be willing to use modeling, e.g., dose-response structural models, to extrapolate beyond the interventions that are atually present in the data.

An advantage of defining the causal effects in observational studies in reference to those in the target trial is that we are then forced to be explicit about the strategies that are compared. Once we adopt this viewpoint, it is obvious that certain comparisons cannot be translated into a contrast between hypothetical interventions and therefore should be avoided, at least when the goal of the analysis is to help decision makers. Revisit Sections 3.5 and 3.6 if necessary.

Example: The highly publicized discrepancy between the estimates of the effect of postmenopausal hormone therapy on heart disease in observational studies and a randomized trial was partly due to use of a comparison of "current users" vs. "never users" in the observational studies (Hernán et al., 2008). This comparison is rarely, if ever, used in randomized trials because a contrast of "prevalent users" versus "non-users", with prevalent user status changing over the follow-up, does not generally correspond to the contrast of two interventions. Further, such a contrast may be particularly sensitive to selection bias.

Another advantage of an explicit definition of causal effects in observational studies is clarity. As discussed in Fine Point 9.4, there is a widespread view that the intention-to-treat effect measures the effectiveness of treatment (loosely defined: the effect of treatment that would be observed under realistic conditions), whereas the per-protocol effect measures efficacy (loosely defined: the effect of treatment that would be observed under perfect conditions). This view is especially problematic when interested in sustained treatment strategies: it is often difficult to argue that a per-protocol effect of sustained strategies in a realistic setting measures efficacy, or that the intention-to-treat effect in the presence of uncertainty about the benefits (or harms) of treatment measures the effectiveness after those benefits (or harms) are proven. As a result, the labels "effectiveness" and "efficacy" are ambiguous in settings with sustained strategies over long periods. An explicit definition of the treatment strategies that define the causal effect of interest is more informative because decision makers need information about the effect of well-defined causal interventions.

22.4 Time zero

A crucial component of target trial emulation is the determination of the start of follow-up, also referred to as baseline or time zero, in the observational analysis. Eligibility criteria need to be met at that point but not later; study outcomes begin to be counted after that point but not earlier.

In randomized experiments, the time zero for each individual is the time when they are assigned to a treatment strategy while meeting the eligibility criteria. For example, in our randomized trial of antiretroviral therapy, time zero is, the time when the treatment strategies are assigned (the time of randomization), which usually occurs shortly before, or at the same time as, treatment is initiated. We do not start the follow-up, say, 2 years before or after randomization. Starting before randomization would not be reasonable because the treatment strategies had yet to be assigned at that time and the eligibility criteria had not been defined, much less met; starting follow-up after randomization is potentially biased as deaths during the first two years of the trial would thereby be excluded from the analysis. If treatment had a short-term effect on mortality, it would be missed. Even more problematic, if treatment does indeed have a short-term effect, then more susceptible individuals would have died by year 2 in the group assigned to active treatment but not in the other group. This differential proportion of susceptible individuals after two years destroys the baseline comparability achieved by randomization and opens the door to selection bias.

The same rules regarding time zero apply to observational analyses and randomized trials, and for the same reasons. Generally, the follow-up in the

observational analysis should start at the time the follow-up would have started in the target trial. Otherwise the effect estimates may be hard to interpret and biased because of selection affected by treatment. Nonetheless, how to emulate the start of follow-up of the target trial is not always obvious. Consider two main scenarios, depending on how many times the eligibility criteria can be met throughout an individual's lifetime:

Fine Point 22.1 describes the handling of strategies that can be initiated during a grace period after time zero rather than exactly at time zero.

1. Eligibility criteria can be met at a single time. This is the simplest setting. Follow-up starts at the only time the eligibility criteria are met. For example, consider a study to compare immediate initiation of antiretroviral therapy when the CD4 cell count first drops below 500 cells/μL versus delayed initiation in HIV-positive individuals. The follow-up of eligible individuals starts the first time their CD4 cell count drops below 500.

2. Eligibility criteria can be met at multiple times. This is the setting that often leads to confusion. For example, consider a study to compare initiation versus no initiation of hormone therapy among postmenopausal women with no history of chronic disease and no use of hormone therapy during the previous two years. If a woman meets these eligibility criteria continuously between age 51 and 65, when should her follow-up start? At age 51, 52, 53...? In the target trial a woman would be eligible to be recruited at multiple times during her lifetime, i.e., she has multiple eligible times.

In settings with multiple eligibility times, there are several alternatives to choose the time zero of each individual among her eligible times. One could choose as time zero: a) the first eligible time, b) a randomly chosen eligible time, c) every eligible time, etc. Strategy c) requires emulating multiple nested target trials, each of them with a different start of follow-up. The number of nested trials depends on the frequency with which data on treatment and covariates are collected:

- If fixed schedule for data collection at pre-specified times (e.g., every two years, like in many epidemiologic cohorts), then emulate a new trial starting at each pre-specified time.
- If subject-specific schedule for data collection (e.g., electronic medical records), then choose a fixed time unit (e.g., a day, week or month), and emulate a new trial starting at each time unit.

From a statistical standpoint, strategy c) can be more efficient than the previous ones because it uses more of the available data. However, because individuals may be included in multiple target trials, appropriate adjustment of the variance of the effect estimate is required. This can be achieved, for example, via bootstrapping.

22.5 A unified analysis for causal inference

Unifying the causal analysis of randomized and observational studies requires a common language to describe both types of studies. The concept of the target trial provides that common language. Aside from baseline randomization, there are no other necessary differences between analyses of observational

Fine Point 22.1

Grace periods. Consider again the study to compare immediate initiation of treatment when CD4 cell count first drops below 500 cells/μL versus delayed initiation. In the real world, antiretroviral therapy cannot be started exactly on the same day the CD4 cell count is measured. Depending on the health care system, it may take weeks or months until the requisite clinical and administrative procedures are completed and patients are adequately informed. Therefore, investigators need to define a grace period (say, 3 months) after time zero during which initiation is still considered to be immediate. Otherwise the study would be estimating the effect of strategies that do not occur frequently in reality or that could not be successfully implemented in practice.

A consequence of using a grace period is that an individual's observed data is consistent with more than one strategy for the duration of the grace period. For example, in the above study, the introduction of a 3-month grace period implies that the interventions are redefined as "initiate therapy within 3 months after CD4 cell count first drops below 500 cells/μL" versus "initiate therapy more than 3 months after CD4 cell count first drops below 500 cells/μL". Therefore an individual who starts therapy in month 3 after baseline has data consistent with both interventions during months 1 and 2. Had she died during those 2 months, to which arm of the target trial would we have assigned him? One possibility is to randomly assign him to one of the two arms.

Another possibility is to create two exact copies of this individual—clones—in the data and assign each of the two clones to a different arm (Cain et al, 2010). Clones are then censored at the time their data stops being consistent with the arm they were assigned to. For example, if the individual starts therapy in month 3, then the clone assigned to "start after 3 months" would be censored at that time. The potential bias introduced by this likely informative censoring would need to be corrected by adjusting for time-varying factors via IP weighting. Importantly, if the individual had died in month 2, the both clones would have died and therefore the death would have been assigned to both arms. This double allocation of events prevents the bias that could arise if events occurring during the grace period were systematically assigned to one of the two arms only.

When using grace periods with cloning and censoring, the intention-to-treat effect cannot be estimated because almost everyone will contribute a clone to each of the treatment strategies. Because each individual is assigned to all strategies at baseline, a contrast based on baseline assignment (i.e., an "intention-to-treat analysis") will compare groups with essentially identical outcomes. Therefore, analyses with grace period at baseline are geared towards estimating some form of per-protocol effect.

data that emulate a target trial and of true randomized trials. That is, a randomized trial can be viewed as a follow-up study with baseline randomization and observational longitudinal data as a follow-up study without baseline randomization.

In fact, only three things distinguish the data from randomized experiments and observational studies. In randomized experiments, (i) no baseline confounding is expected because of randomization, (ii) the randomization probabilities are known, and (iii) the assignment to a treatment strategy is known for each individual at baseline. An observational analysis can emulate (i) if one measures and appropriately adjusts for a sufficient set of covariates, and (ii) if the model for treatment assignment is correctly specified. Interestingly, (iii) is not necessary for estimating the per-protocol effect in neither randomized experiments nor observational studies because efficient estimators (that are functions of the sufficient statistic) do not use this information.

Robins (1986) showed that, in a randomized trial, you can delete the randomization assignment from the dataset and still estimate a valid per-protocol effect if a sufficient set of confounders was measured.

The similarities between follow-up studies with and without baseline randomization are increasingly apparent in the health and social sciences as a growing number of randomized experiments attempt to estimate the effects of sustained treatment strategies over long periods in real world settings. These studies are a far cry from the short experiments in highly controlled settings that put randomized trials at the top of the hierarchy of study designs in the

early days of clinical research. Randomized experiments of sustained treatment strategies over long periods, with their potential for substantial deviations from protocol (e.g., imperfect adherence to the assigned strategy, loss to follow-up), are subject to confounding and selection biases that we have learned to associate exclusively with observational studies. In particular, when estimating a per-protocol effect, both randomized trials and observational studies may need adjustment for time-varying prognostic factors that predict drop-out (selection bias) and treatment (confounding).

Time-varying confounding in observational studies is a bias with the same structure as nonrandom noncompliance in randomized trials.

In view of these similarities, one might expect that randomized experiments and observational studies would be analyzed similarly, except for the fact that adjustment for baseline confounders is typically necessary in observational studies. In practice, however, the typical analysis of randomized experiments and observational studies differs radically, which is both perplexing and, as we argue below, problematic.

A natural question is whether the "intention-to-treat analysis" and the so-called "per-protocol analysis" commonly used in randomized trials validly estimate the intention-to-treat effect and per-protocol effect, respectively. In general, the answer is no. A typical intention-to-treat analysis compares the distribution of outcomes between randomized groups without any form of adjustment for confounding or selection bias. Lack of adjustment for baseline confounding is justified by randomization: the randomized groups are exchangeable because they are expected to have the same risk of the outcome if both groups had been assigned to the same treatment strategy. No adjustment for post-randomization confounding (e.g., due to nonadherence) is required because, again, there cannot be post-randomization confounding for the effect of baseline assignment.

However, the strategies that define the intention-to-treat effect require that the individuals remain in the study until their outcome variable can be ascertained. Thus the intention-to-treat effect estimate may be affected by post-randomization selection bias if individuals are differentially lost to follow-up, and prognostic factors influence, or are associated with, loss of follow-up. Therefore, valid estimation of the intention-to-treat effect may require an "intention-to-treat analysis" adjusted for post-randomization (time-varying) prognostic factors to eliminate selection bias from loss to follow-up. When the time-varying prognostic factors are affected by prior treatment, an appropriate adjustment will require the use of g-methods. For example, in a randomized trial of antiretroviral therapy among HIV patients, the probability of dropping out of the study may be influenced by the onset of symptoms, which is a consequence of treatment itself.

Because baseline randomization cannot ensure exchangeability between those who are and are not lost to follow-up after randomization, we refer to a naïve intention-to-treat analysis that does not adjust for selection bias as a "pseudo-intention-to-treat analysis".

In addition to the primary "intention-to-treat analysis", many randomized trials also report the results of a so-called "per-protocol analysis". A commonly used form of "per-protocol analysis"—also referred to as "on treatment analysis"—only includes individuals who adhered to the instructions specified in the study protocol. For point interventions, the analysis includes only the subset of trial participants who adhered to their assigned baseline intervention—the per-protocol population. Then the analysis compares the distribution of outcomes between randomized groups in the per-protocol population, typically without any form of adjustment for confounding or selection bias. For sustained treatment strategies, individuals are censored at the first time they deviate from the protocol. That is, the remaining per-protocol population at each time is the set of individuals that are still adhering to the protocol.

This form of "per-protocol analysis" is a "pseudo-intention-to-treat analysis" restricted to the subset of the population who follow the protocol (the per-protocol population) with no adjustment for covariates.

This common approach to "per-protocol analysis" is problematic for two

reasons. First, the analysis, like an "intention-to-treat analysis", needs to consider postrandomization selection bias due to differential loss to follow-up. Second, by restricting to the per-protocol population, the analysis partly disregards the randomized groups and therefore the benefits of randomization: the subset of individuals who remain on protocol under one strategy may not be comparable with the subset on protocol under another strategy. That is, a "per-protocol analysis" is akin to an observational analysis. Therefore, like any observational analysis, a "per-protocol analysis" needs to consider bias due to time-varying prognostic factors that affect the decision to stay on protocol. When these postrandomization factors are affected by the interventions of interest, then g-methods specifically designed to deal with treatment-confounder feedback are needed. Instrumental variable estimation (Chapter 16) can sometimes be used to validly estimate per-protocol effects of point interventions without explicit adjustment for postrandomization factors, but the validity of these methods depends on having a valid instrument and on strong modeling assumptions. Some forms of instrumental variable estimation are a particular case of g-estimation (see Technical Point 16.5).

We often refer to a per-protocol analysis that does not even attempt to adjust for confounding as a *naive per-protocol analysis*.

Analogously to the adjusted analyses for randomized trials, observational analyses need generally be adjusted for both baseline and time-varying prognostic factors using g-methods. The observational analyses are conducted by using the above approaches but now applied to the target trial. The goal is to estimate the observational analog of the intention-to-treat and the per-protocol effect in the target trial.

In summary, the analysis of randomized trials and observational studies should be similar. If we feel compelled to adjust for time-varying confounding and selection bias in the analysis of observational studies, we should feel equally compelled to adjust for post-randomization confounding and selection bias in the analysis of randomized trials. The only necessary difference between follow-up studies with and without baseline randomization is, precisely, baseline randomization. That is, adjustment for baseline confounding will not be generally required in intention-to-treat analyses of randomized trials. However, adjustment for post-baseline (time-varying) factors will generally be necessary for per-protocol analyses of both randomized trials and observational studies. A unified approach to causal inference for sustained treatment strategies is possible based on the target trial concept and on g-methods.

Historically, randomized experiments have been considered far superior to observational studies for the purpose of making causal inferences and aiding decision-making. Unfortunately, randomized experiments are not always available because they may be expensive, infeasible, unethical, or simply untimely to support an urgent decision. Therefore, as much as we may like randomization, many decisions will need to be made in the absence of evidence from randomized trials. When we cannot conduct the randomized experiment that would answer our causal question, we resort to observational analyses. It is therefore important to use a sound approach to design and analyze observational studies. Making the target trial explicit is one step in that direction. When the goal is to assist decision making, the analysis of existing observational data need to explicitly emulate a trial and be evaluated with respect to how well they emulate their target trial.

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